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Improving Indications and Outcomes after Metabolic and Bariatric Surgery

From the Metabolic Changes to the Surgical Aspects

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Improving Indications and Outcomes after Metabolic and Bariatric Surgery

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Á minha família,

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Abbreviations

ADA	American Diabetes Association
AGB	Adjustable Gastric Banding
ASMBS	American Society for Metabolic and Bariatric Surgery
BA	Bile Acid
BI	Billroth I
BII	Billroth II
BMI	Body Mass Index
BOMSS	British Obesity and Metabolic Surgery Society
BPD/DS	Biliopancreatic Diversion with Duodenal Switch
CHUSJ	Centro Hospitalar Universitário de São João
CI	Confidence Interval
CRI-O	Centro de Responsabilidade Integrado de Obesidade
DFS	Disease-Free Survival
eGFR	estimated Glomerular Filtration Rate
EPB	Early Postoperative Bleeding
ERAS	Enhanced Recovery After Surgery
ERCP	Endoscopic Retrograde CholangioPancreatography
ESPEN	European Society for Clinical Nutrition and Metabolism
EWL	Excess Weight Loss
FSG	Fundoplication sleeve gastrectomy
FXR	Farnesoid X receptor
GC	Gastric Cancer
GD	Gallstone Disease
GERD	GastroEsophageal Reflux Disease

GIP	Gastric Inhibitory Polypeptide <i>or</i> Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLP-1 Ras.	Glucagon-Like Peptide-1 Receptor agonists
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
HHR	Hiatal Hernia Repair
IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders
IGB	IntraGastric Balloon
IWL	Insufficient Weight Loss
LDL	Low-Density Lipoprotein
LES	Lower Esophageal Sphincter
LOS	Length Of Stay
MBS	Metabolic and Bariatric Surgery
MD	Mean Differences
MMTT	Mixed Meal Tolerance Test
MT	Medical treatment
NAFLD	Non-Alcoholic Fatty Liver Disease
NIH	National Institutes of Health
OAGB	One-Anastomosis Gastric Bypass
OATB	One-Anastomosis Transit Bipartition
OR	Odds Ratio
OS	Overall Survival
OSA	Obstructive Sleep Apnea
PAL	Preoperative Albumin Level
PBH	Post-Bariatric Hypoglycemia
PNI	Prognostic Nutritional Index

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Risk Ratio
RY	Roux-en-Y
RYGB	Roux-en-Y Gastric Bypass
SADI-S	Single Anastomosis Duodeno–Ileostomy with Sleeve
SASI	Single-Anastomosis Sleeve Ileal bypass
SOS	Swedish Obese Subjects
TALL	Total Alimentary Limb Length
TB	Transit Bipartition
TGR5	Takeda G protein-coupled Receptor 5
TWL	Total Weight Loss
T2DM	Type 2 Diabetes Mellitus
UDCA	UrsoDeoxyCholic Acid
VBG	Vertical Banded Gastroplasty
WHO	World Health Organization
WR	Weight Regain

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I. LIST OF PUBLICATIONS

In accordance with the Doctoral studies regulation of Portuguese Universities (*Ao abrigo do Art.º 8º do Decreto-Lei n.º 388/70*), this Dissertation comprises studies that were presented in several national and international meetings and articles published in peer-reviewed journals. The full-list of publications and presentations is presented below. The articles for evaluation are marked with (*).

A. Improving Indications of Metabolic and Bariatric Surgery (MBS)

1. Comparative Effectiveness of Bariatric Surgeries in Patients with Type 2 Diabetes Mellitus and BMI ≥ 25 kg/m²: a Systematic Review and Network Meta-Analysis. *Obes Surg* 31, 5312–5321 (2021) **[First Author] (*)**
2. Roux-en-Y gastric bypass and sleeve gastrectomy as revisional bariatric procedures after adjustable gastric banding: a retrospective cohort study. *Langenbecks Arch Surg* 408, 411 (2023) **[First Author] (*)**
3. Roux-en-Y Gastric Bypass Vs Sleeve Gastrectomy in Super Obesity: a Systematic Review and Meta-Analysis. *Obes Surg* 32, 170–185 (2022) **[Co-Author]** [Parallel Research Area, co-supervision of PhD thesis of another research team investigator]
4. Risk and Prophylactic Management of Gallstone Disease in Bariatric Surgery: a Systematic Review and A Bayesian meta-analysis. *J Gastrointest Surg* 27, 433–448 (2023) **[First Author] (*)**

5. Incidence of symptomatic gallstones after bariatric surgery: the impact of expectant management. *Langenbecks Arch Surg* 408, 160 (2023) **[First Author] (*)**

B. Improving Outcomes of MBS

6. Preoperative Risk Factors for Early Postoperative Bleeding after Roux-en-Y Gastric Bypass Surgery: A Systematic Review and Meta-Analysis. *Langenbecks Arch Surg* 409, 163 (2024) **[First Author] (*)**
7. Early Postoperative Bleeding After Laparoscopic Roux-En-Y Gastric Bypass: a Single Center Analysis. *Obes Surg* 32, 1902-1908 (2022) *[Co-Author]*
8. Vitamin B Complex Deficiency After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy - a Systematic Review and Meta-Analysis. *Obes Surg* 32, 873–891 (2022) **[First Author] (*)**
9. Assessing Nutritional Deficiencies in Bariatric Surgery Patients: A Comparative Study of Roux-en-Y Gastric Bypass versus Sleeve Gastrectomy. *J Pers Med* 14(6), 650 (2024) **[First Author] (*)**
10. Predictors of Hypoglycemia after Bariatric Surgery: A Systematic Review [*Unpublished data*] [Master Thesis Supervision] [Presented at an International Meeting]

C. From the Metabolic Changes to the Surgical Aspects

11. Efficiency and safety of Single Anastomosis Sleeve Ileal (SASI) bypass in the treatment of obesity and associated comorbidities: A systematic review and meta-analysis. *Langenbecks Arch Surg* 409(1), 221 (2024) **[First Author] (*)**

12. The Role of Fundoplication Sleeve Gastrectomy in Metabolic and Bariatric Surgery: A Systematic Review and Meta-Analysis. [*Unpublished data*] [Master Thesis Supervision] [Presented at an International Meeting]
13. The Impact of Cholecystectomy in Patients with Post-Bariatric Surgery Hypoglycemia. *Obes Surg* 34, 2570–2579 (2024) [*Co-Author*] [Master Thesis Co-supervision]

D. Future perspectives

14. The impact of the prognostic nutritional index (PNI) in gastric cancer. *Langenbecks Arch Surg* 407, 2703–2714 (2022) [**First Author**] (*) [*Associated Research: Bridge between gastric cancer and its nutritional aspects and MBS*]
15. Is there an obesity paradox in gastric cancer patients? Beyond BMI [Invited Presentation at European Gastric Cancer Congress 2018, Leiden, **Unpublished data**] [*Associated Research: Bridge between gastric cancer and its nutritional aspects and MBS*]
16. Oncometabolic Surgery: The Metabolic Effects and Effectiveness of the Different Reconstruction Methods used in Gastric Cancer Surgery. A Systematic Review and Meta-Analysis. *Scientific reports* 14 (1), 23477 (2024) [**First Author**] (*)

Future Research: Insufficient weight loss (IWL) and weight regain (WR) after MBS

17. Roux-en-Y Gastric Bypass Distalization for Insufficient Weight Loss or Weight Regain: a Systematic Review and Meta-Analysis [*Unpublished data*] [Master Thesis Supervision] [Presented at an International Meeting]
18. Predictors of insufficient weight loss and weight regain after bariatric surgery [*Unpublished data*] [Master Thesis Co-supervision] [Presented at an International Meeting]

II. ABSTRACT

Background: Obesity and its associated comorbidities, particularly type 2 diabetes mellitus (T2DM), present a significant public health challenge. MBS has emerged as the most effective treatment for severe obesity and T2DM. Despite its success, key challenges remain, including optimizing patient selection, refining surgical techniques, managing postoperative complications, and understanding the mechanisms underlying metabolic improvements. This thesis aims to address these challenges by evaluating MBS outcomes, exploring innovative surgical techniques, and expanding the application of MBS principles to new patient populations.

Aims: The primary objective of this research was to refine the indications for MBS, enhance patient outcomes, and explore novel surgical techniques that could improve both the safety and metabolic efficacy of MBS procedures. This was achieved through a two-step approach: (1) identifying the limitations of current techniques and their clinical implications, and (2) investigating innovative surgical strategies designed to optimize outcomes and expand the therapeutic potential of MBS. Several critical research questions were addressed to contribute to the understanding and practice of MBS in the context of obesity-related comorbidities, particularly T2DM. These included:

1. *Which bariatric procedure is most effective in achieving long-term T2DM remission?*
2. *What is the most appropriate revisional surgery for patients with suboptimal outcomes after adjustable gastric banding (AGB)?*
3. *Should prophylactic cholecystectomy be performed routinely in MBS patients?*
4. *How can early postoperative bleeding (EPB) after Roux-en-Y gastric bypass (RYGB) be managed effectively?*
5. *What are the long-term implications of nutritional deficiencies following MBS, and how should they be addressed?*

6. *What are the key predictors of post-bariatric hypoglycemia (PBH), and how can personalized evaluation and monitoring optimize outcomes?*
7. *Can novel bariatric surgical techniques overcome the limitations of traditional procedures, particularly by optimizing surgical simplicity, reducing complication rates, and improving long-term outcomes?*
8. *How can MBS principles be applied to gastric cancer (GC) surgery to optimize patient outcomes?*

Methods: The thesis encompasses a cohort study and systematic reviews and meta-analyses to answer critical questions about MBS. The cohort study, part of the "Outcomes of Obesity Surgery" project, retrospectively analyzed 520 patients undergoing MBS at Centro Hospitalar Universitário de São João (CHUSJ). Outcomes assessed included weight loss, comorbidity resolution, and complications. This cohort served as the foundation for the ongoing prospective database of Centro de Responsabilidade Integrado de Obesidade (CRI-O), allowing internal validation of clinical findings, while systematic reviews and meta-analyses provided external validation by integrating evidence from RCTs and international cohorts. Systematic reviews and meta-analyses adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and examined (1) the effectiveness of different bariatric procedures for T2DM remission, (2) the outcomes of single-anastomosis sleeve ileal (SASI) bypass, and (3) the integration of MBS principles into GC surgery.

Results: The findings follow the two-tiered structure of this thesis.

Step 1 – Current Status and Caveats of MBS:

1. *T2DM Remission:* Laparoscopic one-anastomosis gastric bypass (OAGB) emerged as a promising procedure for achieving long-term T2DM remission, demonstrating comparable efficacy to RYGB and advantages over laparoscopic biliopancreatic diversion with duodenal switch (BPD/DS) in terms of lower complication rates and shorter operative times. However, limited long-term data and direct comparisons with procedures such as single anastomosis duodeno-ileostomy with sleeve (SADI-S) underscore the need for further high-quality randomized controlled trials (RCTs).
2. *Revisional Surgery:* Revisional RYGB was found to be the most effective surgical option for managing suboptimal outcomes following AGB. It provided superior weight loss and greater resolution of comorbidities, particularly dyslipidemia, compared to revisional sleeve gastrectomy (SG). While revisional SG was associated with a lower technical complexity, its restrictive mechanism limited its metabolic efficacy. Both procedures

demonstrated comparable safety profiles when performed in high-volume centers by experienced surgeons.

3. *Gallstone Disease (GD) Management:* Routine prophylactic cholecystectomy during MBS was not supported by the findings of this study. Although the risk of developing symptomatic gallstones is higher in MBS patients compared to the general population, the overall incidence remains relatively low. Prophylactic cholecystectomy was associated with longer operative times and increased postoperative complications without any significant improvement in mortality or hospital length of stay (LOS). A selective approach based on risk factors, such as high body mass index (BMI) and preexisting gallstones, was recommended, with symptomatic cases managed conservatively or surgically when necessary.
4. *Early Postoperative Bleeding:* EPB, a significant early complication of RYGB, was associated with older age, male gender, hypertension, revisional surgery, decreased estimated glomerular filtration rate (eGFR), and increased left hepatic lobe diameter. Conservative management proved effective in most cases, with minimal impact on long-term weight loss outcomes. Preoperative optimization, including addressing hepatic size and renal function, was highlighted as critical in reducing EPB risk.
5. *Nutritional Deficiencies:* Nutrient deficiencies remain a significant concern following MBS. RYGB patients exhibited a higher prevalence of deficiencies in vitamin B12, iron, and calcium, while SG patients were more prone to vitamin D and fat-soluble vitamin deficiencies. Gaps in adherence to supplementation protocols were identified, emphasizing the need for standardized and individualized nutritional support regimens. Long-term monitoring and proactive management were deemed essential to prevent complications such as anemia, bone metabolism disturbances, and metabolic syndrome.
6. *Post-Bariatric Hypoglycemia:* Predictors of PBH included younger age, greater weight loss, and metabolic markers such as HbA1c and insulin sensitivity. RYGB was associated with a higher risk of PBH, particularly in patients with prior cholecystectomy. These patients required more aggressive pharmacological interventions, such as higher doses of acarbose, to manage glycemic variability. Personalized evaluation, dietary adjustments, and multidisciplinary care were emphasized as critical components of PBH management.

Step 2 – Emerging Techniques and Expanded Indications:

7. *Innovative Techniques:* The SASI bypass demonstrated significant potential as an alternative to traditional procedures, offering superior weight loss, reduced complication

rates, and improved comorbidity resolution, particularly for T2DM, hypertension, and dyslipidemia. Its simplified surgical approach, preservation of endoscopic access to the duodenum, and mitigation of gastroesophageal reflux disease (GERD) marked it as an important innovation. This procedure exemplifies the evolution toward Sleeve plus concepts, offering balanced restriction and partial hypo/malabsorption for metabolically challenged patients. Further research is needed to standardize the procedure and assess long-term outcomes across diverse patient populations.

8. *Oncometabolic Surgery*: Integrating MBS principles into GC surgery was shown to optimize both oncological and metabolic outcomes. Techniques such as duodenal bypass improved nutritional status and metabolic control, offering a novel approach to treating GC patients with metabolic comorbidities.

Conclusions: This thesis significantly advances the understanding of MBS by addressing key challenges in patient selection, surgical technique optimization, complication management, and the application of MBS principles to new domains such as GC surgery. By adopting a two-tiered approach—first identifying the caveats of existing techniques and then introducing evidence-based innovations such as SASI and oncometabolic surgery—this work provides a comprehensive vision for the future of metabolic surgery. By identifying effective procedures for T2DM remission, refining revisional surgery options, and exploring innovative surgical techniques, this research provides valuable insights into how MBS can be further optimized to improve patient outcomes. The findings emphasize the importance of personalized care, the integration of multidisciplinary approaches, and the need for further research to refine and expand the scope of MBS to benefit a wider range of patients.

Future Research: Future research in MBS should focus on optimizing the management of metabolically challenged patients, particularly those with obesity class IV and V. These patients require personalized approaches to surgery, considering their complex metabolic profiles and higher comorbidity risks. Investigating tailored surgical techniques and postoperative care strategies will be essential to improving their outcomes. Innovative procedures, such as SASI and other Sleeve plus techniques, hold promise for improving efficacy while minimizing complications. Prospective studies from our group, including “Outcomes of SASI in the treatment of patients with BMI over 50 kg/m²”, will provide high-quality evidence to validate these approaches. Additionally, addressing IWL and WR remains a critical area. Refining surgical procedures, exploring revisional surgery options, and

developing better postoperative management strategies will be key to achieving sustainable weight loss and enhancing long-term MBS success.

III. RESUMO

Introdução: A obesidade e as suas comorbilidades associadas, particularmente a diabetes mellitus tipo 2 (DM2), constituem um grande desafio para a saúde pública. A cirurgia metabólica e bariátrica (CMB) tem-se mostrado o tratamento mais eficaz para a obesidade severa e a DM2. Apesar do seu sucesso, permanecem desafios importantes, como otimizar a seleção dos pacientes, aperfeiçoar as técnicas cirúrgicas, gerir as complicações pós-operatórias e compreender os mecanismos subjacentes às melhorias metabólicas. Esta tese visa abordar estes desafios, avaliando os resultados da CMB, explorando técnicas cirúrgicas inovadoras e expandindo a aplicação dos princípios da CMB a novas populações de pacientes.

Objetivos: O objetivo principal desta pesquisa foi refinar as indicações para a CMB, melhorar os resultados dos pacientes e explorar novas técnicas cirúrgicas que possam melhorar tanto a segurança como a eficácia metabólica dos procedimentos de CMB. Este objetivo foi alcançado através de uma abordagem em dois passos: (1) identificar as limitações das técnicas atuais e as suas implicações clínicas e (2) investigar estratégias cirúrgicas inovadoras concebidas para otimizar os resultados e expandir o potencial terapêutico da CMB. Foram abordadas várias questões de investigação de forma a contribuir para a compreensão da CMB no contexto das comorbilidades relacionadas com a obesidade, particularmente a DM2. Estas questões incluíram:

1. *Qual a CMB mais eficaz para alcançar a remissão a longo prazo da DM2?*
2. *Qual é a cirurgia revisional mais apropriada para pacientes com resultados subótimos após a banda gástrica ajustável (BGA)?*
3. *Deve ser realizada colecistectomia profilática por rotina em pacientes de CMB?*
4. *Como pode ser orientada de forma eficaz a hemorragia pós-operatória precoce (HPP) após o bypass gástrico em Y de Roux (BGYR)?*

5. *Quais as implicações a longo prazo das deficiências nutricionais após a CMB e como devem ser tratadas?*
6. *Quais são os principais preditores da hipoglicemia pós-bariátrica (HPB) e como pode a avaliação e monitorização personalizada otimizar os resultados?*
7. *As novas técnicas de CMB podem superar as limitações dos procedimentos tradicionais, particularmente otimizando a simplicidade cirúrgica, reduzindo taxas de complicações e melhorando os resultados a longo prazo?*
8. *Como podem os princípios da CMB ser aplicados à cirurgia de cancro gástrico (CG) para otimizar os resultados dos pacientes?*

Métodos: A tese abrange um estudo de coorte, revisões sistemáticas e meta-análises para responder às questões críticas sobre a CMB. O estudo de coorte, parte do projeto "*Outcomes of Obesity Surgery*", analisou retrospectivamente 520 pacientes submetidos à CMB no CHUSJ. Os resultados avaliados incluíram perda de peso, resolução de comorbidades e complicações. Esta coorte constituiu o alicerce da base de dados prospectiva em curso do Centro de Responsabilidade Integrado de Obesidade (CRI-O), permitindo a validação interna dos achados clínicos, enquanto as revisões sistemáticas e meta-análises forneceram validação externa ao integrar evidência de ensaios clínicos randomizados e coortes internacionais. As revisões sistemáticas e meta-análises seguiram as orientações PRISMA e examinaram (1) a eficácia dos diferentes procedimentos bariátricos para a remissão da DM2, (2) os resultados do bypass sleeve-ileal de anastomose única (SASI) e (3) a integração dos princípios da CMB na cirurgia do cancro gástrico (CG).

Resultados: Os achados seguem a estrutura em dois níveis desta tese.

Passo 1 – Estado Atual e Limitações da CMB:

1. Remissão da DM2: O bypass gástrico de anastomose única laparoscópico emergiu como um procedimento promissor para alcançar a remissão a longo prazo da DM2, demonstrando eficácia comparável ao BGYR e vantagens sobre a cirurgia de switch duodenal laparoscópica em termos de menores taxas de complicações e tempos operatórios mais curtos. No entanto, os dados limitados a longo prazo e as comparações diretas com procedimentos como o SADI-S destacam a necessidade de mais ensaios clínicos randomizados de alta qualidade.
2. Cirurgia Revisional: O BGYR revisional foi o procedimento cirúrgico mais eficaz para gerir os resultados subótimos após a BGA. Proporcionou maior perda de peso e maior resolução das comorbidades, particularmente a dislipidemia, em comparação com a

gastrectomia vertical (SG) revisional. Embora a SG revisional tenha sido associada a uma menor complexidade técnica, o seu mecanismo restritivo limitou a sua eficácia metabólica. Ambos os procedimentos demonstraram perfis de segurança comparáveis quando realizados em centros de grande volume por cirurgiões experientes.

3. Tratamento da litíase biliar: A colecistectomia profilática de rotina durante a CMB não foi apoiada pelos achados deste estudo. Embora o risco de desenvolver cálculos biliares sintomáticos seja mais elevado em pacientes de CMB em comparação com a população geral, a incidência geral permanece relativamente baixa. A colecistectomia profilática foi associada a tempos operatórios mais longos e aumento das complicações pós-operatórias, sem melhoria significativa na mortalidade ou no tempo de internamento hospitalar. Foi recomendada uma abordagem seletiva com base em fatores de risco, como IMC elevado e cálculos biliares pré-existentes, sendo os casos sintomáticos tratados de forma conservadora ou cirúrgica quando necessário.
4. Hemorragia pós-operatória precoce: A HPP, uma complicação precoce significativa do BGYR, foi associada a idade mais avançada, sexo masculino, hipertensão, cirurgia revisional, diminuição da taxa de filtração glomerular estimada (eGFR) e aumento do diâmetro do lobo esquerdo do fígado. O tratamento conservador mostrou-se eficaz na maioria dos casos, com impacto mínimo nos resultados a longo prazo da perda de peso. A otimização pré-operatória, incluindo a melhoria da hepatomegalia e da função renal, foi destacada como crítica para reduzir o risco de HPP.
5. Deficiências Nutricionais: As deficiências nutricionais permanecem uma preocupação significativa após a CMB. Pacientes submetidos a BGYR apresentaram maior prevalência de deficiências em vitamina B12, ferro e cálcio, enquanto os pacientes de SG estavam mais propensos a deficiências de vitamina D e vitaminas lipossolúveis. Foram identificadas lacunas na adesão aos protocolos de suplementação, destacando a necessidade de regimes de suporte nutricional padronizados e individualizados. A monitorização a longo prazo e a orientação proativa foram considerados essenciais para prevenir complicações como anemia, distúrbios no metabolismo ósseo e síndrome metabólica.
6. Hipoglicemia Pós-bariátrica: Os preditores da HPB incluíram idade mais jovem, maior perda de peso e marcadores metabólicos como HbA1c e sensibilidade à insulina. O BGYR foi associado a um maior risco de HPB, particularmente em pacientes com colecistectomia prévia. Estes pacientes necessitaram de intervenções farmacológicas mais agressivas, como doses mais altas de acarbose, para gerir a variabilidade glicêmica. A avaliação

personalizada, ajustes dietéticos e cuidados multidisciplinares foram enfatizados como componentes críticos no tratamento da HPB.

Passo 2 – Técnicas Emergentes e Expansão das Indicações:

7. Técnicas Inovadoras: O bypass SASI demonstrou um potencial significativo como alternativa aos procedimentos tradicionais, oferecendo maior perda de peso, menores taxas de complicações e melhor resolução de comorbidades, particularmente para DM2, hipertensão e dislipidemia. A sua abordagem cirúrgica simplificada, preservação do acesso endoscópico ao duodeno e mitigação da doença do refluxo gastroesofágico (DRGE) marcaram-no como uma inovação importante. Este procedimento exemplifica a evolução para os conceitos *Sleeve plus*, oferecendo restrição equilibrada e hipo/malabsorção parcial para pacientes metabolicamente complexos. São necessários mais estudos para padronizar o procedimento e avaliar os resultados a longo prazo em diversas populações de pacientes.
8. Cirurgia Oncometabólica: A integração dos princípios da CMB na cirurgia de CG demonstrou otimizar tanto os resultados oncológicos como metabólicos. Técnicas como o bypass duodenal melhoraram o estado nutricional e o controle metabólico, oferecendo uma abordagem inovadora no tratamento de pacientes com CG e comorbidades metabólicas.

Conclusões: Esta tese avança significativamente na compreensão da CMB ao abordar desafios chave na seleção de pacientes, otimização das técnicas cirúrgicas, orientação das complicações e aplicação dos princípios da CMB a novos domínios, como a cirurgia do cancro gástrico. Ao adotar uma abordagem em dois níveis — primeiro identificando as limitações das técnicas existentes e depois introduzindo inovações baseadas em evidência, como o SASI e a cirurgia oncometabólica — este trabalho fornece uma visão abrangente para o futuro da cirurgia metabólica. Ao identificar procedimentos eficazes para a remissão da DM2, refinar as opções de cirurgia revisional e explorar técnicas cirúrgicas inovadoras, esta pesquisa oferece valiosos *insights* sobre como a CMB pode ser ainda mais otimizada para melhorar os resultados dos pacientes. Os achados enfatizam a importância dos cuidados personalizados, a integração de abordagens multidisciplinares e a necessidade de mais pesquisa para refinar e expandir o alcance da CMB para beneficiar um maior número de pacientes.

Investigação Futura: A investigação futura em CMB deve focar na otimização da gestão de pacientes metabolicamente desafiantes, particularmente aqueles com obesidade classe IV e V. Estes pacientes requerem abordagens personalizadas para a cirurgia, tendo em conta os

seus perfis metabólicos complexos e maiores riscos de comorbidades. Investigar técnicas cirúrgicas adaptadas e estratégias de cuidados pós-operatórios será essencial para melhorar os seus resultados. Procedimentos inovadores, como o SASI e outras técnicas *Sleeve plus*, mostram potencial para aumentar a eficácia enquanto minimizam complicações. Estudos prospectivos do nosso grupo, incluindo “Resultados do SASI no tratamento de doentes com IMC superior a 50 kg/m²”, fornecerão evidência de alta qualidade para validar estas abordagens. Além disso, abordar a perda insuficiente de peso e o reganho de peso continua a ser uma área crítica. Refinar os procedimentos cirúrgicos, explorar opções de cirurgia revisional e desenvolver melhores estratégias de gestão pós-operatória serão fundamentais para alcançar a perda de peso sustentável e melhorar o sucesso a longo prazo da CMB.

IV. RATIONALE

Obesity and its associated metabolic disorders, particularly T2DM, pose a significant global public health challenge. Despite the implementation of lifestyle interventions and pharmacotherapy, the prevalence of obesity continues to rise, underscoring the need for more effective treatment modalities. MBS has emerged as the most effective long-term solution for severe obesity (*formerly known as morbid obesity*) and its metabolic comorbidities.

While MBS demonstrates notable benefits, the precise metabolic mechanisms underlying its success remain incompletely understood. Additionally, current surgical indications may not be optimized; some patients experience suboptimal results or complications, while others may be undertreated. This knowledge gap necessitates further exploration into the metabolic mechanisms and surgical techniques that could refine patient selection and enhance outcomes.

By deepening our understanding of the metabolic pathways altered by MBS, we can better tailor surgical indications to identify individuals who will benefit most. This research aims to improve patient outcomes by reducing surgical risks and enhancing long-term metabolic benefits.

An important focus of this thesis will be managing both early and late post-operative complications such as post-operative bleeding, nutritional deficiencies, hypoglycemia and GERD. Obesity is also frequently linked with GD, which presents additional management challenges during or after bariatric surgery. Consequently, the surgical approach must effectively address these associated conditions.

Another relevant aspect of this thesis will be examining the growing need for revisional surgeries due to WR or IWL. Given the increasing demand for these procedures, it is essential to determine how existing surgical options can be effectively utilized in such cases.

The ideal surgical approach for obesity should be effective, safe, and personalized. No single method is universally applicable, and the metabolic changes induced by surgery must be carefully considered. In this context, sleeve plus procedures represent a contemporary evolution in MBS, that combine sleeve gastrectomy with varying degrees of intestinal bypass. By combining restrictive and malabsorptive components, these procedures offer the potential to tailor surgical strategies to individual metabolic profiles, particularly in patients with severe obesity or refractory T2DM. Furthermore, sleeve plus approaches may reduce the risk of weight regain and recurrence of metabolic complications, addressing key limitations observed with standalone SG or RYGB. Among these strategies, transit bipartition (TB) has emerged as a promising option, offering an improved safety profile compared to other procedures while achieving strong metabolic outcomes. This is particularly evident through its effects on incretins such as glucagon-like peptide-1 (GLP-1) and its alignment with both the hindgut and foregut theories and the proximal-distal imbalance theory of metabolic improvement after MBS. By modifying nutrient flow through the small bowel, TB promotes hormonal changes that enhance glucose homeostasis, while maintaining a more physiological digestive pathway compared to procedures like RYGB.

Finally, this research will explore the potential to broaden the indications for MBS to include individuals with obesity or metabolic syndrome and GC. The concept of oncometabolic surgery, which combines cancer resection with metabolic improvements, represents an exciting new frontier.

In summary, this thesis seeks to refine the understanding of MBS indications and improve patient outcomes through a dual analytical approach. By first identifying the caveats and unmet needs of current procedures, and subsequently exploring innovative techniques and expanded indications, it aims to build a comprehensive and future-oriented perspective on the evolution of MBS. These insights are expected to contribute to a more effective, safer, and individualized practice of MBS, ultimately extending its benefits to broader patient populations.

V. INTRODUCTION

In this chapter, a review of the literature is presented in four sections, addressing the major topics of this thesis: Improving indications for MBS, including associated comorbidities and pathology as well suboptimal results after previous surgeries (A); Improving outcomes of MBS, based on the most common complications (B); From the metabolic changes to the surgical aspects (C) and Future perspectives (D). For this comprehensive review, we follow two main steps. The first step examines the caveats and limitations of the most commonly performed MBS techniques — SG and RYGB — highlighting the unmet clinical and metabolic needs. The second step focuses on emerging surgical approaches and expanded indications, including the SASI bypass and the concept of oncometabolic surgery, which aim to overcome these limitations and define new directions for MBS.

Obesity is a complex multifactorial disease, whose prevalence is increasing steadily in the last decades [1]. The World Health Organization (WHO) identifies obesity as abnormal or excessive fat accumulation with a BMI of 30 kg/m² or higher, representing a health challenge. It affects almost all physiological functions of the body, and it increases the risk for developing multiple comorbidities, such as T2DM, cardiovascular disease, cancer, osteoarthritis, obstructive sleep apnea (OSA), and poor mental health, thereby contributing to a decline in quality of life (QoL), work productivity as well as to increased healthcare costs [2]. MBS is regarded as the most effective intervention for achieving substantial and long-lasting weight loss and resolution of obesity associated comorbidities, exceeding the results obtained with medical treatment (MT) [3].

Nowadays, RYGB and SG are the two most commonly performed bariatric procedures [4]. RYGB has shown better outcomes regarding the resolution of obesity-related comorbidities

[5]. However, SG is still the most frequent MBS performed because it is technically easier and faster to perform, resulting in fewer postoperative complication and reoperation rates and in similar excess weight reduction [6, 7].

A. IMPROVING INDICATIONS OF MBS

Recent advancements in understanding obesity and its management have led the American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) to issue a joint statement on MBS [8]. The 1991 National Institutes of Health (NIH) Consensus Statement, which set the standard for bariatric surgery criteria, recommended MBS for individuals with a BMI $> 40 \text{ kg/m}^2$ or $> 35 \text{ kg/m}^2$ with co-morbidities [9]. The updated guidelines now suggest MBS for those with a BMI $> 35 \text{ kg/m}^2$, and also for individuals with a BMI of 30-34.9 kg/m^2 if they have metabolic disease [8].

Recognized now as a chronic disease, obesity is linked with a chronic low-grade inflammatory state and immune dysfunction [10, 11]. This prolonged inflammation is suspected to disrupt homeostatic mechanisms, leading to metabolic disorders associated with obesity, mediated through complex pathways involving cytokine production, adipokines, hormones, and acute-phase reactants [11, 12].

Long-term studies have demonstrated that MBS is an effective and durable treatment for severe obesity and its co-morbidities, providing superior weight loss outcomes compared to non-surgical treatments and improving metabolic disease and overall mortality [13-23]. The safety of MBS is well-established, with very low perioperative mortality rates [24]. Modern procedures, such as SG and RYGB, are now predominant, while older techniques like vertical banded gastroplasty (VBG) and AGB are less common [8].

Despite BMI's limitations in assessing future health risks, it remains a key criterion for identifying candidates for MBS. MBS is currently recognized as the most effective evidence-based treatment for obesity across all BMI classes. Class I obesity (BMI 30–34.9 kg/m^2) is known to cause or exacerbate multiple medical and psychological co-morbidities, decrease longevity, and impair QoL [8]. Large prospective and retrospective studies support the notion that MBS should be considered for patients with class I obesity who do not achieve substantial or durable weight loss or co-morbidity improvement with nonsurgical methods. Early findings

have led international diabetes organizations to support the consideration of MBS for patients with BMI < 35 kg/m² and T2DM [25, 26]

Management of associated comorbidities

MBS is a highly effective intervention for the treatment of metabolic syndrome, a cluster of conditions including obesity, insulin resistance, hypertension, dyslipidemia, and increased cardiovascular risk [27]. By inducing significant and sustained weight loss, MBS directly improves the components of metabolic syndrome through mechanisms beyond calorie restriction, such as alterations in gut hormones, bile acid (BA) metabolism, and microbiota [28, 29]. These metabolic changes lead to enhanced insulin sensitivity, improved lipid profiles, and better glycemic control, offering long-term benefits for patients with metabolic syndrome, especially those with obesity-related comorbidities like T2DM [19, 25, 30, 31].

Type 2 Diabetes Mellitus

In 2017, 6.28% of the global population was affected by T2DM, equating to a prevalence of 6,059 cases per 100,000 people. This figure is projected to rise to 7,079 cases per 100,000 by 2030 [32], making T2DM not only an urgent public health concern today but also one of the fastest-growing health challenges worldwide [33].

Obesity management is a crucial step in treating T2DM. Modest, sustained weight loss can improve glycemic control [34] and reduce cardiovascular disease risk [35]. This led the American Diabetes Association (ADA), in 2009, to recommend bariatric surgery as a treatment option for patients with both diabetes and obesity [36].

Previously, MBS was only recommended for individuals with a BMI ≥ 40 kg/m² or adults with a BMI of 35.0–39.9 kg/m² who did not achieve lasting weight loss and improvement in comorbidities, such as hyperglycemia, with MT. However, current guidelines now suggest it may be considered for adults with a BMI of 30.0–34.9 kg/m² if they do not see improvement with MT [8, 37].

The optimal MBS for treating T2DM remains a subject of active research and debate. Among the commonly performed procedures—RYGB, SG, OAGB BPD/DS —each offers different benefits in achieving glycemic control and diabetes remission. RYGB is widely considered the gold standard, known for its robust effects on glucose homeostasis through enhanced incretin

response and modulation of both foregut and hindgut pathways [31, 38-41]. SG, although less invasive, shows substantial T2DM remission, primarily through weight loss and metabolic changes, though its impact on incretin hormones is relatively modest [38-43]. BPD/DS, while more complex and associated with greater nutritional risks, delivers the most dramatic improvements in diabetes outcomes, likely due to significant malabsorption and hormonal alterations [44-46]. OAGB, a newer procedure, is gaining attention for its simplicity and comparable efficacy to RYGB, with promising results in T2DM remission and fewer anastomotic complications [39, 47]. Emerging procedures like TB further add to the landscape by offering potential advantages in T2DM control with fewer side effects [48-50]. Ultimately, the best surgical option depends on individual patient factors, such as BMI, diabetes severity, and balancing metabolic benefits with potential complications [51-53].

Management of metabolic-challenged patients

Metabolically-challenged patients are those with a BMI ≥ 50 kg/m² (obesity class IV and V) or a significant burden of obesity-related conditions, such as T2DM, OSA, hypertension and non-alcoholic fatty liver disease (NAFLD).

Obesity class IV and V (*formerly known as Super obesity*)

The prevalence of patients with class IV-V obesity is increasing more rapidly than that of both class I (BMI 30 – 34.9 kg/m²) and class III obesity (BMI 40 – 49.9 kg/m²) [54-56]. These patients represent a subgroup with more severe obesity, requiring special consideration when determining management strategies.

Metabolically-challenged patients are at an elevated risk of developing or exacerbating obesity-related complications and often experience worse short- and long-term outcomes following MBS [57, 58]. Specifically, having a BMI ≥ 50 kg/m² is an independent risk factor for venous thromboembolism, a leading cause of mortality after MBS [57]. Additionally, this higher BMI is associated with greater risk for postoperative complications and increased mortality [58].

Similar to short-term outcomes, long-term adverse outcomes after MBS are more prevalent among metabolically-challenged patients compared to those with class III obesity [54, 59-62]. While MBS remains an effective treatment for patients with obesity class IV-V, individualized

procedure selection is crucial. Laparoscopic SG is the preferred initial choice for most surgeons [59], particularly for this higher-risk group. However, the risk of weight recurrence (suboptimal clinical response) after both SG and RYGB is significantly higher in patients with class IV-V compared to those with class III obesity [59, 60].

More complex procedures, such as BPD with or without DS, which carry a higher risk for both early and late complications, provide more durable weight loss for metabolically-challenged patients [63, 64].

Performing MBS in patients with BMI ≥ 50 kg/m² presents several challenges. From a technical standpoint, increased thickness of the abdominal wall, increased adipose limiting visualization, excessive torque on the surgeon's hands, and a large liver all add complexity to almost any MBS procedure. From a risk perspective, these patients often have more severe obesity-related complications and comorbidities. In terms of outcomes, they are more susceptible to perioperative and long-term complications and often experience a suboptimal clinical response, including IWL and a higher likelihood of WR.

Despite the increased severity of obesity and the greater likelihood of both short- and long-term complications, this population should not be denied MBS. In fact, the seriousness of their condition underscores the importance of offering them this potentially life-saving intervention.

Management of suboptimal clinical response

Suboptimal clinical response after MBS refers to the less-than-expected improvement in weight loss or resolution of comorbidities, such as T2DM, hypertension, or dyslipidemia [65]. Several factors contribute to this outcome, including patient-specific variables like genetic predispositions [66], poor adherence to dietary and lifestyle recommendations [67], inadequate post-operative follow-up, or pre-existing conditions that limit metabolic improvement [68, 69]. Additionally, variations in surgical technique and the type of procedure performed can influence the efficacy of the surgery [69]. A suboptimal response can manifest as IWL, WR, or limited improvement in metabolic conditions, warranting a comprehensive approach to optimizing patient outcomes through individualized care [65].

Revisional surgery after AGB

The laparoscopic implantation of AGB, introduced in 1993, quickly became a common bariatric procedure due to its safety profile and low initial morbidity [70]. Initially, AGB complications were considered rare, but long-term studies have shown significant late-onset issues leading to revisional surgeries [71]. These complications include hardware failures, esophageal motility disorders, gastrointestinal symptoms, and psychological intolerance, negatively impacting QoL [72, 73]. Additionally, many AGB patients experience IWL or WR, requiring conversion to other procedures [71]. Long-term reoperations are reported in 31–80% of patients [74].

Revisional surgeries have increased due to IWL, WR, and postoperative morbidity [73, 75, 76]. The success of these revisions depends on choosing the most appropriate procedure based on the revision's indication [73]. Despite growing demand, there is still controversy regarding their safety and effectiveness, and insufficient evidence on the best procedure for each patient [76]. RYGB and SG are the most frequently performed revisional procedures from AGB [77].

Management of associated pathology

MBS is commonly performed to address metabolic syndrome and related conditions, but it also has implications for other associated pathologies [78]. Notably, GD is a common concern among MBS patients [79, 80]. Therefore, meticulous preoperative and postoperative management is essential to reduce the likelihood of gallstone formation and its complications. Addressing these additional health concerns is crucial to optimizing overall patient outcomes and ensuring the long-term success of MBS.

Gallstone disease

Rapid weight loss following bariatric surgery can predispose patients to gallstone formation due to increased bile cholesterol saturation and poor gallbladder emptying during early weight loss phases [81–83]. The prophylactic use of ursodeoxycholic acid (UDCA) has been advocated to reduce cholesterol saturation and gallstone incidence during weight loss [84, 85]. However, there is debate about the actual increase in gallstone incidence and its impact on symptomatic gallbladder disease. Bariatric surgery is associated with a 3–28% incidence of

symptomatic GD, with a Swedish cohort study showing a fivefold increased risk compared to the general population [79, 80]. Despite high rates of new gallstone formation, some studies report symptomatic gallstone rates as low as 0.9% post-surgery [86].

Identifying risk factors for GD specific to bariatric surgery patients is crucial for tailored management, as general population risk factors may not apply [87-89]. The varying incidence of symptomatic GD has sparked controversy over whether prophylactic cholecystectomy should be performed alongside bariatric surgery. While current strategies favor conservative approaches like UDCA use or cholecystectomy only in symptomatic cases [90, 91], some advocate for routine prophylactic cholecystectomy [92, 93]. There is no clear consensus on the best approach to prevent symptomatic gallstones. Prophylactic cholecystectomy may prevent complications and future surgeries, but it is a technically demanding procedure, as is cholecystectomy performed after bariatric surgery for symptomatic GD [94, 95].

B. IMPROVING OUTCOMES OF MBS

While MBS offers substantial benefits in weight loss and metabolic improvement, it's crucial to carefully balance efficacy with potential side effects. Ongoing research and advancements in clinical practice are essential to enhancing patient outcomes and minimizing risks.

When selecting a surgical approach, the trade-off between effectiveness and potential complications is key. In this regard, RYGB and BPD/DS generally provide significant weight loss and improvements in metabolic conditions but are associated with higher risks of nutritional deficiencies and surgical complications. On the other hand, SG offers a balance with effective weight loss and lower complication rates, though it may still involve issues such as GERD and nutritional concerns. AGB is a less invasive option with lower immediate risks, but it tends to result in less weight loss and higher reoperation rates.

Early postoperative complications

Postoperative bleeding

Laparoscopic RYGB is a widely performed metabolic procedure known for its effectiveness in managing obesity-related comorbidities and achieving sustained reductions in BMI [96, 97]. Over recent years, the safety of RYGB has improved [3, 98, 99]. However, as the number of procedures rises, the incidence of postoperative complications, despite low rates, remains significant [100, 101].

RYGB is associated with several major early complications, including leaks [102], obstruction, and bleeding [103]. Among these, postoperative bleeding is particularly common [104], occurring in approximately 1.5-3.5% of cases [101, 105]. Although it is usually self-limited, postoperative bleeding can lead to significant morbidity and may escalate into a surgical emergency. Patients who experience bleeding often face extended hospital stays, increased 30-day mortality, and a higher likelihood of further complications [106, 107].

Surgical risk factors, such as the use of a circular stapler for gastrojejunal anastomosis instead of a hand-sewn technique and the lack of staple line reinforcement, have been associated with postoperative bleeding [108, 109]. Despite these findings, there is limited literature on preoperative factors that may predict EPB, including patient demographics and comorbidities

associated with severe obesity. Identifying these risk factors could improve prevention and management strategies, allowing for more vigilant monitoring of at-risk patients.

Late postoperative complications

Nutritional deficiencies

Although bariatric surgery is a safe and effective treatment for obesity, there are some risks, particularly nutritional deficiencies. These deficiencies, especially of micronutrients, can arise postoperatively due to reduced nutrient intake or the exacerbation of pre-existing deficiencies [110]. Obesity itself is associated with a high prevalence of nutritional deficiencies, which can have severe consequences for patients [111].

Postoperative vitamin and mineral deficiencies are influenced by both surgery- and patient-related factors. Common contributors include pre-existing nutritional deficits, altered eating habits, a decreased absorption surface, small intestine bacterial overgrowth, and poor adherence to postoperative dietary recommendations and supplementation [112].

Restriction in food intake, reduced appetite, and alterations in gastrointestinal hormone profiles are common mechanisms contributing to weight loss after RYGB and SG, which also have an impact on nutrient status. In RYGB, the bypass of the stomach and the upper small intestine impairs absorption of essential vitamins and minerals [113]. Although it might be assumed that SG, which maintains the continuity of the small intestine, would result in fewer deficiencies, recent studies show that micronutrient deficiencies occur at similar rates in both RYGB and SG. The effects of SG on gastrointestinal motility, gastric emptying, and decreased acid secretion contribute to these deficiencies [112].

Studies indicate that the most frequently observed deficiencies post-surgery include vitamin B12, folic acid, iron, thiamine (vitamin B1), vitamin D, and calcium. Deficiencies in fat-soluble vitamins (A, E, K), as well as copper, zinc, and selenium, are also reported [112].

Certain vitamins, particularly vitamin B12, require factors produced in the stomach for proper absorption. In SG, part of the stomach is resected, and in RYGB, the stomach is bypassed, both of which impair B12 absorption [114]. The exclusion of the stomach in RYGB is thought to have a greater impact on intrinsic factor production and B12 levels than SG [115].

Folate is absorbed mainly in the upper small intestine, a region bypassed in RYGB, leading to a higher risk of folate deficiency [116]. Similarly, vitamins B1 and B6, absorbed in the

duodenum and jejunum, are more significantly affected by RYGB since these parts of the intestine are excluded from the digestive process [117-119].

These deficiencies can result in a wide range of symptoms and pathologies, some of which are life-threatening. Despite the known prevalence of postoperative deficiencies, there is still limited data on the exact impact of each bariatric procedure on specific nutrient levels.

International guidelines recommend lifelong vitamin and mineral supplementation, along with regular biochemical monitoring, tailored to the specific bariatric procedure performed. Organizations such as the British Obesity and Metabolic Surgery Society (BOMSS) and the Enhanced Recovery After Surgery (ERAS) Society emphasize the importance of personalized supplementation protocols to mitigate the risk of deficiencies [120, 121].

Although several studies have investigated these complications, inconsistencies in methodology, such as variations in nutrient assessments, cut-off values, follow-up periods and supplementation strategies, make it difficult to draw definitive conclusions. Ongoing research is necessary to refine treatment protocols and improve outcomes for patients submitted to MBS.

Post-Bariatric Hypoglycemia

Despite the significant benefits of metabolic surgery, particularly in RYGB, complications such as PBH and dumping syndrome have been increasingly documented [122]. Postprandial hyperinsulinemic hypoglycemia, a common form of PBH, usually arises one to three hours after eating due to an exaggerated insulin response to carbohydrate intake [123-125]. Early dumping syndrome, on the other hand, occurs within 30 minutes of a meal and is caused by rapid gastric emptying, leading to gastrointestinal and vasomotor symptoms [126, 127]. PBH, commonly referred to as postprandial hypoglycemia, can have a profound impact on QoL, often resulting in compensatory overeating and subsequent WR [128]. It is reported that over one-third of metabolic surgery patients experience postprandial hypoglycemia, though severe cases occur in less than 12% of patients [129, 130].

PBH typically manifests several months or even years after surgery, especially in patients that are younger, female, who experience significant postoperative weight loss and have high preoperative insulin sensitivity [127, 128, 131, 132]. Diagnosing PBH is challenging and often requires the presence of Whipple's triad, usually confirmed through provocation testing [128, 132, 133]. Understanding the incidence and risk factors for PBH is crucial for optimizing care

for bariatric surgery patients, highlighting the need for comprehensive preoperative evaluation and ongoing postoperative monitoring.

Gastroesophageal reflux disease

SG has become a widely adopted procedure for severe obesity due to its effective weight loss and improvement in comorbidities [134]. Despite these benefits, SG can significantly impact stomach and esophageal function. Up to 20–60% of patients report GERD symptoms post-SG [135–139], potentially due to the removal of the gastric fundus, reduced stomach volume, and increased pressure in the remaining stomach. This has led to an increase in GERD and Barrett's esophagus cases, possibly linked to biliary duodenogastric reflux [139–143]. Meta-analyses show GERD symptoms in 19%–31.8% of SG patients, with de novo GERD in 23%–31.6% [144], and Barrett's esophagus in 8%–11%, often developing beyond three years without a direct correlation to GERD [144–146].

RYGB is often preferred for obese patients with GERD due to its benefits, such as greater weight loss, disconnection of the gastric body, decreased parietal cell secretion affecting the distal esophagus, bile diversion, and reduced pressure on the lower esophageal sphincter (LES) [147]. However, 24.4%–55.8% of patients may still experience GERD symptoms after RYGB [148, 149], with reasons for persistent GERD not fully understood.

Revisional surgery for GERD is necessary in approximately 3.1%–4.0% of SG patients [144, 150]. Guan *et al.* emphasized the importance of understanding potential revisions [150], and Matar *et al.* found that 30% of patients converting from SG to RYGB did so primarily due to GERD, with 79% achieving symptom resolution after the conversion [151]. Thus, despite the advantages of RYGB, the interplay between GERD symptoms and hiatal hernia remains crucial, even in patients undergoing laparoscopic RYGB [152, 153].

C. FROM THE METABOLIC CHANGES TO THE SURGICAL ASPECTS

Metabolic changes of MBS

MBS induces significant metabolic changes that extend beyond simple weight loss. These changes are largely influenced by alterations in gut hormones, particularly incretins and anti-incretins, which play a pivotal role in glucose metabolism and energy balance. The "Hindgut" and "Foregut" theories attempt to explain these changes in hormonal responses and their subsequent metabolic effects [154].

The role of Incretins and Anti-Incretins

Incretins are a group of hormones that enhance insulin secretion in response to nutrient intake, especially glucose. The two main incretins are GLP-1 and gastric inhibitory polypeptide (also known as glucose-dependent insulintropic polypeptide) (GIP). These hormones stimulate insulin release from the pancreas and help regulate blood glucose levels [155]. After MBS, particularly RYGB, there is a significant increase in the secretion of GLP-1, which leads to improved glycemic control and even the remission of type 2 diabetes [156].

On the other hand, anti-incretins are theorized to oppose the actions of incretins by reducing insulin sensitivity and promoting insulin resistance [157]. The modulation of both incretins and anti-incretins is central to the metabolic effects seen post-surgery.

Hindgut and Foregut theories

The "Hindgut theory" suggests that after procedures like RYGB, the rapid delivery of undigested nutrients into the distal small intestine (hindgut) stimulates the exaggerated secretion of incretins like GLP-1 [158]. This increase in GLP-1 enhances postprandial insulin secretion, suppresses glucagon release, and delays gastric emptying, all of which contribute to improved glucose control and insulin sensitivity [159]. These changes, along with other alterations in gut microbiota and BA metabolism, are thought to be key factors in the improvement of metabolic diseases such as diabetes following surgery [160].

In contrast, the "Foregut theory" posits that bypassing the proximal small intestine (foregut), especially the duodenum, prevents the secretion of anti-incretin hormones that might normally impair insulin sensitivity and glucose metabolism [161]. By excluding the foregut

from nutrient exposure, bariatric surgery may reduce or eliminate the secretion of these anti-incretin factors, leading to improved insulin sensitivity and metabolic function [157].

Interplay between Incretins and Anti-Incretins

The balance between incretin and anti-incretin activity post-bariatric surgery likely contributes to the rapid and sustained improvements in glucose metabolism. This balance explains why metabolic surgery is often more effective than simple caloric restriction in achieving long-term glycemic control. Both the hindgut and foregut mechanisms are important, as they underscore the complexity of hormonal changes triggered by surgical alterations to the gastrointestinal tract [159].

These metabolic changes are crucial in explaining why bariatric surgery is highly effective in resolving conditions like T2DM, even before significant weight loss occurs [162]. Further research into incretin and anti-incretin responses continues to provide insights into optimizing bariatric surgery outcomes and enhancing our understanding of metabolic regulation [163].

Proximal – distal imbalance theory

The proximal-distal imbalance theory, proposed by Santoro, is a central concept behind bipartition surgery [50]. This theory posits that metabolic regulation within the gastrointestinal tract relies heavily on the interaction between the proximal and distal segments of the small intestine. The balance of nutrient flow through these segments significantly influences hormonal responses that govern glucose metabolism, appetite, and energy expenditure.

According to the proximal-distal imbalance theory, modern dietary habits, characterized by refined carbohydrates and high-calorie foods, lead to excessive stimulation of the proximal intestine (duodenum and jejunum), while underutilizing the distal segments (ileum). The proximal gut is responsible for early nutrient absorption and triggers the release of hormones like GIP, which promotes insulin secretion and fat storage. However, in individuals with obesity and metabolic syndrome, chronic stimulation of these pathways contributes to metabolic dysregulation, weight gain, and insulin resistance [164].

Conversely, the distal small intestine, particularly the ileum, plays a key role in secreting GLP-1 and peptide YY, hormones that enhance insulin sensitivity, delay gastric emptying, and

promote satiety. However, in patients with obesity, nutrients often fail to reach the distal segments in sufficient quantities, leading to an imbalance between the hormonal signals from the proximal and distal gut [164].

Bipartition surgery, particularly TB, was developed to correct this imbalance by modifying the route of nutrient passage through the gastrointestinal tract. TB allows part of the ingested food to bypass the proximal intestine and reach the distal ileum directly, while still maintaining partial function of the proximal segments [50]. This dual-path mechanism preserves nutrient absorption in the proximal gut while stimulating the distal intestine.

Bipartition surgery improves metabolic outcomes by rerouting food to the distal gut, which enhances the secretion of incretins like GLP-1 and reduces the overstimulation of GIP in the proximal gut [164]. This hormonal balance improves glucose metabolism, insulin sensitivity, and glycemic control, particularly in patients with T2DM. Unlike more extensive bypass procedures such as RYGB, bipartition surgery maintains nutrient absorption, reducing the risk of malabsorption, dumping syndrome, and nutritional deficiencies.

Hence, this theory highlights the importance of reestablishing the balance between different segments of the small intestine, rather than focusing solely on restricting nutrient intake or absorption [164]. The innovation of bipartition surgery, grounded in this theory, has expanded the potential of MBS, offering an effective option for patients with obesity, T2DM, and other metabolic disorders.

New surgical techniques

New surgical techniques in MBS are evolving to balance efficacy with potential side effects by addressing the complex hormonal changes induced by surgery. These innovations build on our understanding of incretins and anti-incretins, key hormones in glucose metabolism. For example, procedures that enhance the secretion of GLP-1 can significantly improve glycemic control and contribute to the remission of T2DM. However, the increased GLP-1 levels can also raise the risk of PBH, a potential side effect that needs careful management.

Additionally, these techniques incorporate insights from the hindgut and foregut theories. The hindgut theory suggests that stimulating the distal gut can enhance incretin release, improving metabolic outcomes, while the foregut theory proposes that bypassing the proximal gut may reduce hormones that impair insulin sensitivity. Modern surgical approaches aim to optimize these hormonal responses to maximize benefits while minimizing adverse effects. By

strategically targeting these mechanisms, new techniques seek to improve the overall efficacy of MBS while carefully managing potential side effects such as nutritional deficiencies and hypoglycemia.

Sleeve plus procedures

Laparoscopic RYGB has long been regarded as the gold standard procedure for the surgical treatment of severe obesity and T2DM, owing to its well-documented efficacy in achieving sustained weight loss and metabolic improvement. However, despite its effectiveness, RYGB is associated with several long-term complications, including marginal ulceration, dumping syndrome, iron deficiency anemia, osteoporosis, and the need for ongoing endoscopic surveillance, which limit its broader applicability [165]. In contrast, laparoscopic SG is technically simpler and associated with fewer postoperative morbidities, while still providing significant improvements in obesity-related comorbidities. Nonetheless, the long-term durability of SG has been questioned due to the frequent occurrence of weight regain and recurrence of metabolic syndrome typically observed two to five years after surgery. These shortcomings are thought to be related to the progressive dilation of the gastric remnant, undermining the restrictive purpose of the procedure.

Recognizing the need for a surgical approach that combines the metabolic efficacy of RYGB with the safety profile of SG, Huang and Katakwar in 2020 introduced the concept of “sleeve plus” procedures [165]. This concept encompasses a spectrum of operations that integrate sleeve gastrectomy with varying degrees of intestinal bypass — such as the BPD/DS, SADI-S, loop duodenojejunal bypass, or TB — in order to optimize metabolic outcomes while minimizing nutritional deficiencies and procedural morbidity. The rationale behind these approaches reflects a growing understanding that obesity and diabetes are chronic, multifactorial diseases influenced by complex interactions among gut hormones, the microbiota, BA metabolism, and epigenetic mechanisms. Accordingly, sleeve plus procedures represent a contemporary evolution in MBS, aiming to achieve a more physiological and durable balance between efficacy, safety, and long-term metabolic benefit [165].

Transit bipartition

MBS has evolved significantly, with novel techniques emerging to further enhance metabolic outcomes beyond traditional approaches. One such innovative technique is TB, which builds on the physiological principles of altering gut hormone responses to improve obesity treatment and comorbid conditions such as T2DM.

TB was first described by Santoro *et al.* and represents a paradigm shift in surgical intervention by integrating SG with a distinct method of gut partitioning. This approach leverages a physiological and evolutionary rationale by amplifying the nutritive stimulation of the distal gut while attenuating it in the proximal bowel. Unlike other techniques, TB does not exclude the duodenum, aiming to mitigate the risk of nutritional deficiencies commonly associated with other bariatric procedures [166].

In 2014, Mui *et al.* adapted the original TB approach, introducing a refinement known as the SASI bypass. This modification involves performing SG followed by a loop gastroileostomy placed 250 cm from the ileocecal valve. This adaptation simplifies the surgical process by replacing the complex Roux-en-Y anastomosis with a simpler loop configuration, potentially reducing surgical complexity while retaining the benefits for obesity and related metabolic disorders [167].

Further research by Mahdy *et al.* in 2016, which included the first case series of 50 patients with a 1-year follow-up, provided evidence supporting the efficacy of the SASI bypass. This technique demonstrates comparable outcomes to the original TB approach but with a more straightforward surgical execution. The SASI has shown promise in achieving effective weight loss and improvement in comorbid conditions without the complications associated with more complex anastomoses [168].

Several studies have explored the efficacy and safety of the SASI technique, noting variations in the length of the common limb between 200 and 350 cm. This variability in surgical technique has led to various terminologies, including “Laparoscopic sleeve gastrectomy with loop bipartition” [169, 170], “Laparoscopic sleeve gastrectomy with loop gastroileal bypass” [171], and “Laparoscopic sleeve gastrectomy with transit loop bipartition” [172]. These terms reflect the adaptation and evolution of the procedure as it gains wider acceptance and application.

In summary, TB and its adaptations represent a significant advancement in MBS by leveraging the principles of incretin and anti-incretin modulation and the hindgut and foregut theories.

These techniques aim to optimize metabolic outcomes through innovative surgical approaches, enhancing the treatment of obesity and its associated metabolic disorders.

The role of Fundoplication sleeve gastrectomy (FSG) in GERD

Laparoscopic SG is the most frequently performed bariatric surgery globally but is associated with a notable risk of de novo or recurrent GERD. Long-term studies have highlighted an increased incidence of GERD and Barrett's esophagus following LSG [137, 173]. This issue is of particular concern as it can impact the overall QoL and outcomes in patients undergoing SG.

RYGB, the second most common bariatric surgery, is generally preferred for patients with severe obesity and GERD, yet new studies have reported persistent or new GERD cases after RYGB [152, 153]. Conversely, an alternative approach involves performing laparoscopic SG combined with hiatal hernia repair (HHR) [174, 175]. A meta-analysis of 18 studies involving 937 patients showed that laparoscopic SG with HHR significantly reduced GERD symptoms, esophagitis, and improved QoL [176]. A separate study comparing outcomes for patients who underwent concurrent SG with HHR versus those who did not found that while concurrent HHR increased the likelihood of additional abdominal operations and endoscopies, it did not significantly impact the rate of bariatric revisions or conversions [177]. This suggests that while concurrent HHR may lead to increased endoscopy rates, it does not commonly result in bariatric revisions. Consequently, current evidence supports the repair of hiatal hernias irrespective of the surgical approach, highlighting its importance in optimizing surgical outcomes.

Despite its potential benefits, this combined procedure has been criticized for the risk of hiatal hernia recurrence and the return of reflux symptoms [178]. Recent innovations include creating anti-reflux valves during laparoscopic SG to address GERD more effectively.

Accordingly, to address GERD risks after SG and expand its use for patients with mild reflux, several techniques have been proposed, including antireflux sleeve gastropasty [179], laparoscopic partial SG with fundoplication [180], Nissen-SG gastrectomy [181], Rosseti-SG gastrectomy [182], Dor-SG fundoplication [183], and SG with the LINX® system [184].

Hence, despite the potential advantages of fundoplication and HHR, the available evidence is often conflicting or limited, necessitating a careful evaluation of their roles in the context of SG. The integration of these techniques into SG requires a thorough understanding of their mechanisms, benefits, and limitations, as well as a consideration of patient-specific factors.

Associated surgical procedures

The Impact of cholecystectomy in PBH

The exact physiological mechanism behind PBH remains unclear but is believed to involve elevated insulin and GLP-1 levels following metabolic surgery. These are thought to be triggered by rapid gastric emptying, leading to a glycemic spike that overstimulates pancreatic beta cells, causing excessive insulin release and subsequent hypoglycemia [185].

Additionally, the gallbladder, which plays a vital role in BA homeostasis, is frequently removed in patients undergoing metabolic surgery [186]. Cholecystectomy can increase enterohepatic BA recycling, resulting in higher BA concentrations [187]. Postprandial insulin and C4 (a marker of hepatic BA synthesis) levels have been found to be significantly higher in patients who have undergone both metabolic surgery and cholecystectomy [188]. BAs are known to activate intestinal cell receptors like Farnesoid X receptor (FXR) and Takeda G protein-coupled Receptor 5 (TGR5), enhancing GLP-1 release, and increasing fibroblast growth factor 19, which promotes glycogen synthesis [189, 190]. While there is growing interest in the role of cholecystectomy in PBH, the scientific evidence on this topic remains limited.

D. FUTURE PERSPECTIVES

Obesity paradox in GC patients

The obesity paradox refers to the observation that overweight or mildly obese patients with various cancers often have paradoxically better survival outcomes compared to non-overweight patients [191-196], despite obesity being a known risk factor for many malignancies. This paradox highlights a challenge in GC, where obesity may contribute to cancer development while also being associated with improved survival outcomes [197].

This phenomenon has been attributed to several factors, including differences in tumor biology, treatment tolerance and patient's overall performance status [197].

Obesity may influence the progression and management of GC in different ways. Increased adipose tissue can lead to higher levels of circulating hormones and growth factors, which may impact tumor growth and response to treatment. Additionally, obese patients often have a greater nutritional reserve, potentially enabling them to better withstand the physical stress of cancer and its treatment [198].

On the other hand, the obesity paradox presents certain challenges, as excess body fat can aggravate pre-existing conditions like T2DM, cardiovascular disease, and OSA, and these comorbidities may interfere with cancer treatment and impact overall survival (OS) outcomes.

The obesity paradox raises the possibility that MBS could serve as a therapeutic option for GC patients with obesity and metabolic syndrome. Weight loss through MBS may reduce cancer risk and improve metabolic comorbidities. Additionally, the metabolic improvements after surgery, such as enhanced glycemic control, could lead to better post-cancer treatment outcomes and increased survival. However, careful selection of patients and timing of surgery are essential to avoid worsening the nutritional deficits common in both bariatric and cancer patients.

Therefore, the association between BMI and surgical outcomes among patients with GC remain controversial [199]. The preoperative albumin level (PAL) is an inflammation-associated factor, which is related to the OS in various malignancies [200, 201]. It has been postulated that BMI was a prognostic factor in GC patients submitted to curative-intent resectional surgery, probably due to an effect of PAL in the different BMI groups [202, 203]. So, it is possible that the obesity paradox is due to PAL effect in survival rather than the BMI itself.

GC and nutritional status

GC is the fifth most common malignancy globally and the fourth leading cause of cancer-related mortality [204]. The cornerstone of treatment for gastric carcinoma continues to be radical resection, typically involving total or subtotal gastrectomy [205]. While gastrectomy carries significant risks, including perioperative morbidity and mortality, with complication rates ranging from 10% to 46% [206, 207], it remains a potentially curative intervention. Given the global prevalence of this cancer, substantial efforts have been dedicated to identifying modifiable factors that might negatively impact surgical outcomes and overall survival.

Factors such as advanced age, comorbid medical conditions, and late-stage cancer—largely unmodifiable and associated with the patient’s disease status and physical condition—are recognized for their prognostic significance and their influence on surgical complications [208, 209]. However, nutritional status, a potentially modifiable prognostic factor, has long been acknowledged as crucial for optimizing outcomes before surgery. The European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines have recently reinforced the importance of nutritional support, advocating for nutritional optimization in patients at severe nutritional risk, even if it necessitates delaying oncologic surgery [210].

The prognostic nutritional index (PNI), calculated from serum albumin and lymphocyte count [211], is a simple tool for predicting surgical outcomes in various cancers, including GC [212-214], though its optimal cutoff values remain unclear [207, 215].

Oncometabolic surgery

The advent of national screening programs (particularly in East Asia) has enabled the early detection of GC, contributing to a decrease in GC-related mortality rates [216, 217]. As more GC patients survive longer, QoL has become a crucial concern, especially for those with chronic comorbidities like T2DM, hypertension and dyslipidemia [218].

Bariatric surgery, originally designed to treat severe obesity, has shown remarkable success in improving metabolic conditions such as T2DM, hypertension and dyslipidemia, leading to the concept of MBS [3]. Beyond weight loss, these procedures cause significant metabolic improvements, largely due to hormonal and gastrointestinal changes that impact glucose homeostasis.

Recognizing the similarities between MBS and GC surgeries, particularly in gastric resection and foregut bypass, researchers hypothesized that GC surgery could also benefit glycemic control. This led to the development of “Oncometabolic Surgery”, a dual-purpose approach aimed at treating both cancer and chronic metabolic diseases, particularly in patients whose QoL is compromised by these comorbidities [219].

The concept holds promise, as modifications to the gastrointestinal tract may produce beneficial effects on glucose metabolism and appetite through hormonal changes, involving modulation of gut hormones, such as GLP-1, ghrelin, and peptide YY. Early evidence suggests that oncometabolic surgery could enhance both oncologic outcomes and metabolic disease management, offering patients reduced post-operative complications and improved QoL [220].

However, further research is required to optimize and standardize surgical techniques, evaluate long-term metabolic benefits, and validate its safety and efficacy. If successful, oncometabolic surgery could revolutionize the treatment of patients with concurrent GC and metabolic diseases, with potential applications beyond GC alone.

VI. AIMS

The main aim of this thesis was to define the best strategy to optimize MBS by following two main steps: first, identifying the caveats and limitations of current MBS techniques in order to improve patient selection and outcomes; and second, exploring how emerging surgical approaches and new indications, based on the underlying metabolic changes after MBS, can address these limitations and guide the development of novel procedures.

As specific aims, it was intended to:

1. Emphasize the broadening indications to MBS, in order to have the best suitable surgery for each patient, focusing in some subsets of patients (diabetes mellitus, revisional surgery and super obesity) [*Super obesity, parallel research area*]
2. Explore the management of associated pathology in MBS (namely GD)
3. Define strategies to improve outcomes, in the light of safety and efficacy (with emphasis to early postoperative complications, nutritional deficiencies and hypoglycemia)
4. Evaluate the effectiveness and safety of new surgical techniques, based on the metabolic changes of MBS
5. Analyze the impact of associated surgical procedures (focusing in cholecystectomy), in the results and side effects of MBS
6. Identify new fields in which these findings could be applied (particularly GC patients)
7. Give an insight on the predictors and surgical options in IWL and WR after MBS [*Future research*]

VII. METHODS

This thesis is structured into two main components, reflecting a two-step approach. The first step involves a cohort study, providing internal validation by evaluating surgical outcomes in a clinical setting and identifying the real-world limitations and caveats of current MBS techniques. The second step consists of a series of systematic reviews and meta-analyses, offering external validation by integrating evidence from multiple RCTs and cohort studies to compare the effectiveness of several bariatric procedures. Together, these complementary approaches allow for a comprehensive assessment of MBS, combining detailed insights from a single clinical context with broader generalizability from the literature, and ultimately informing the development of novel surgical techniques and expanded indications.

Cohort study (Project “Outcomes of Obesity Surgery”)

This cohort study analyzes patients with obesity who underwent MBS at the Centro de Responsabilidade Integrado de Obesidade (CRI-O), CHUSJ, from 2019 onwards. The study is part of the "Outcomes of Obesity Surgery" project, initiated in 2021, and has received approval from the Institutional Review Board [CES 46–21]. This project established the prospective database currently in use at our unit, for continuous monitoring of surgical outcomes.

This retrospective analysis included 520 patients who met the standard eligibility criteria for bariatric surgery and were recorded in that prospectively maintained institutional database.

The inclusion criteria involved patients with obesity who underwent a range of bariatric procedures (mainly RYGB and SG), including primary and revisional surgeries. All patients underwent comprehensive preoperative evaluations and all procedures followed standardized techniques performed by experienced surgeons. Postoperative care included

regular follow-up visits at 1-month, 3-months, 6-months, and 1-year post-surgery. The follow-up continued annually at least 3-years after surgery.

The primary aims of this study were to:

- Evaluate the outcomes of MBS in terms of weight loss and improvement in obesity-associated comorbidities.
- Assess post-operative complications, including postoperative bleeding, cholelithiasis, and nutritional deficits.
- Analyze specific patient subgroups, particularly those undergoing revisional surgery and superobese (obesity class IV-V) patients. *[The latter represents a parallel research area led by another team investigator (co-supervisor of his PhD thesis)].*
- Compare our institutional results with existing literature to identify trends and variations in surgical outcomes and complications, through a series of systematic reviews and meta-analyses (namely EPB, nutritional deficiencies, GD and superobesity).

Several clinicopathological parameters, such as patient demographics, comorbidities, and perioperative factors, were evaluated to identify potential risk factors and determinants of both surgical outcomes and complications. Short-term outcomes were focused on a 1-year follow-up period to assess weight loss, metabolic improvements, and complication rates. Statistical analyses have included univariate and multivariate approaches to identify significant predictors of outcomes.

Systematic Reviews and Meta-Analyses

Despite providing valuable real-world insights into surgical outcomes, the cohort study was inevitably constrained by the limitations imposed by the COVID-19 pandemic, which affected data collection and follow-up. To overcome these constraints and to strengthen the external validation of the findings, a complementary meta-analytic approach was adopted.

This methodological strategy followed a two-step logic: first, a meta-analysis on T2DM was performed to validate and expand the assessment of current MBS procedures and their metabolic impact; second, two additional meta-analyses were conducted to explore new

surgical techniques and extended indications — namely, the SASI bypass and oncometabolic surgery.

The systematic review and meta-analysis followed PRISMA guidelines [221]. A comprehensive literature search was conducted across major databases (PubMed, Web of Science, Scopus).

Bariatric Surgery in Patients with T2DM and BMI ≥ 25 kg/m²

A systematic review of RCTs with at least 5 years of follow-up was performed. This network meta-analysis evaluated the comparative effectiveness of different bariatric procedures and MT for full remission of T2DM remission, weight loss, micro and macrovascular complications and analytical biomarkers. Statistical analysis was performed using netmeta package of software R. We performed both pairwise meta-analysis for direct comparisons between interventions, and network meta-analysis for obtaining estimates based on both direct and indirect comparisons between interventions. Risk ratios (RR) and mean differences (MD) were calculated to compare outcomes, and heterogeneity across studies was assessed using the I^2 statistic. The quality of evidence was assessed using the Cochrane Risk of Bias Tool [222] and CINeMA [223].

Single Anastomosis Sleeve Ileal Bypass Outcomes

A second systematic review was conducted to assess the outcomes of SASI in terms of safety, weight loss, improvements in comorbidities (such as T2DM, hypertension, dyslipidemia, and OSA), and complication rates. A meta-analysis comparing SASI bypass to SG and OAGB was performed. RR and MD were calculated to compare outcomes, and heterogeneity across studies was assessed using the Cochran's Q statistic p-value and the I^2 statistic. Sources of heterogeneity were studied using leave-one-out sensitivity analysis. The meta package of software R was used to analyze the data for the meta-analysis. The quality of the studies was independently assessed by two reviewers using the NIH quality assessment criteria for Observational studies, and the Cochrane Collaboration Risk of Bias Tool for RCT [222].

Oncometabolic Surgery and GC Reconstruction Techniques

This systematic review aimed to assess the impact of different GC reconstruction techniques on T2DM, hypertension, and BMI reduction rates. A meta-analysis was conducted to compare

the effectiveness of duodenal bypass, Roux-en-Y reconstruction, and residual stomach preservation. RR and MD were used to estimate the effects of these techniques on postoperative metabolic outcomes, with heterogeneity assessed via the I^2 statistic. To explore potential sources of heterogeneity, we performed leave-one-out sensitivity analyses and, for analyses including more than ten primary studies, meta-regression analyses, testing follow-up time, preoperative BMI, and BMI reduction rate as moderator variables. The software and quality assessment methods used were consistent with those employed in the previous systematic review and meta-analysis.

VIII. RESULTS

A. IMPROVING INDICATIONS FOR MBS

Management of associated comorbidities

Type 2 Diabetes Mellitus

Comparative Effectiveness of Bariatric Surgeries in Patients with Type 2 Diabetes Mellitus and BMI ≥ 25 kg/m²: a Systematic Review and Network Meta-Analysis. Obes Surg 31, 5312–5321 (2021) (*) doi: [10.1007/s11695-021-05725-y](https://doi.org/10.1007/s11695-021-05725-y)

Hugo Santos-Sousa and Maria Neves Carmona shared ***First Authorship***

Hugo Santos-Sousa was the ***Corresponding Author***

Cited by **13** articles

(Google Scholar, 2025 October 20)

Scimago Journal Rank (SJR) indicator 0,956 | H Index 152 | Rank 70 of 519 on Surgery journals (**Q1**)

(Scimago Journal & Country Rank, 2021)

Journal Impact Factor (JIF) 3,479 | Rank 57 of 213 on Surgery journals (**Q2**)

Journal Citation Indicator (JCI) 1,27 | Rank 37 of 282 on Surgery journals (**Q1**)

(Thomson-Reuters, Science Citation Index Expanded (SCIE), 2021)



Comparative Effectiveness of Bariatric Surgeries in Patients with Type 2 Diabetes Mellitus and BMI ≥ 25 kg/m²: a Systematic Review and Network Meta-Analysis

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Abstract

Purpose In patients with type 2 diabetes mellitus (T2DM), bariatric surgery appears to be more effective than medical treatment (MT) at improving glycaemic control and decreasing cardiovascular risk. However, long-term effectiveness has not been systematically assessed using randomised controlled trials. In this study, we aimed to systematically assess randomised controlled trials, with at least 5 years of follow-up, on bariatric surgery in patients with T2DM and BMI ≥ 25 kg/m², as well as to compare different bariatric procedures.

Material and Methods PubMed, SCOPUS and Web of Science were searched. We performed a network meta-analysis to evaluate the comparative effectiveness of the different procedures and MT in terms of full T2DM remission, weight loss, complications and cardiometabolic biomarkers. The quality of evidence was assessed using the Cochrane Risk of Bias Tool and CINeMA.

Results We included 11 primary studies. Laparoscopic one-anastomosis gastric bypass (LOAGB) was found to be one of the most effective treatments for full remission of T2DM ($I^2 = 0$, inconsistency p value = 0.9223). Biliopancreatic diversion without duodenal switch was found to be more effective than laparoscopic Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding regarding percent total cholesterol and low-density lipoprotein change. Regarding percent high-density lipoprotein and weight change, all analysed surgical treatments were shown to be more effective than MT. The confidence rating in our results was overall moderate, but most studies had high risk of performance and detection bias.

Conclusion Bariatric surgery seems to be effective for T2DM remission. LOAGB appears to be a good option in this context, and a possible alternative to laparoscopic duodenal switch, but the included primary studies in our review are not sufficiently powered to establish a more definitive conclusion. More studies with longer follow-up times are needed to comprehensively assess bariatric surgery in T2DM.

Keywords Diabetes · Metabolic surgery · Biliopancreatic diversion · Laparoscopic adjustable gastric banding · Laparoscopic one-anastomosis gastric bypass · Laparoscopic Roux-en-Y gastric bypass · Laparoscopic duodenal switch · Laparoscopic sleeve gastrectomy · Vertical banded gastroplasty

Maria Neves Carmona and Hugo Santos-Sousa contributed equally and should be considered first authors.

Key Points

- LOAGB is a good option in terms of T2DM remission.
- Surgical treatments were more effective than medical treatment on HDL control.
- BPD and LRYGB were significantly better than LAGB in lowering DBP.
- No significant differences were found regarding diabetes complications.

Extended author information available on the last page of the article

Introduction

As of 2017, 6.28% of the world's population was affected by type 2 diabetes mellitus (T2DM), corresponding to a prevalence of 6,059 cases per 100,000 persons. This value is expected to increase to 7079 cases per 100,000 persons by 2030 [1], rendering T2DM not only a public health concern at the moment, but also one of the fastest-growing health problems in the world [2].

Obesity management is an important step in the treatment of T2DM. Modest and sustained weight loss can

improve glycaemic control [3] and cardiovascular disease risk [4]. This prompted the American Diabetes Association, in 2009, to add bariatric surgery as an option for the treatment of patients with both diabetes and obesity [5]. Nowadays, bariatric surgery is a recommended option for the treatment of T2DM in patients with BMI ≥ 40 kg/m² and adults with BMI of 35.0–39.9 kg/m² who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with medical treatment (MT). In addition, it may be considered to treat T2DM in adults with BMI of 30.0–34.9 kg/m² if they do not improve with MT [6].

Previous systematic reviews have shown that bariatric surgery in the context of T2DM treatment (often termed “metabolic surgery”) is effective at achieving superior glycaemic control, reduction of cardiovascular disease risk and improvements in micro- and macrovascular complications compared with lifestyle or medical treatment [7, 8]. However, the primary randomised controlled trials (RCT) included in such systematic reviews have follow-up periods of up to 3 years, with longer-term effectiveness of metabolic surgery, and of each surgical approach, not having been yet systematically assessed using RCT.

Therefore, in this study, we aimed to systematically assess all RCT, with at least 5 years of follow-up, on bariatric surgery in patients with BMI ≥ 25 kg/m² and T2DM. We performed a network meta-analysis with the aim of evaluating the comparative effectiveness of the different bariatric procedures and the medical treatment in terms of full T2DM remission, weight loss, micro- and macrovascular complications and analytical biomarkers.

Methods

Search Strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations [9].

PubMed, SCOPUS and Web of Science were searched for RCTs published from database inception to October 6, 2020, with queries using the terms: diabetes, bariatrics, bariatric surgery, biliopancreatic bypass, biliopancreatic diversion, gastrectomy and gastric bypass. Complete queries are available in Supplement 1 (S1).

Eligibility Criteria

We included RCTs with a follow-up of at least five years assessing adults (18 years or older) with T2DM and BMI ≥ 25 kg/m² (studies where only some of the participants had T2DM were included but only the information related to patients with T2DM was extracted) who had been randomised to one bariatric procedure or MT or other bariatric procedure(s). Trials were only included if they provided the baseline number of patients with T2DM and the number of patients with full remission of T2DM at 5 or more years. Nevertheless, we also assessed other outcomes, including the number of patients with diabetes-related complications, and changes in percent weight, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Study Selection

The study selection was composed of two phases. In the screening phase, two authors independently selected records by titles and abstracts. Afterwards, publications of records which were not excluded in the screening phase were fully read and independently selected by the same authors (inclusion phase). Any disagreements were solved by consensus.

Data Collection Process

The data were extracted by two independent authors and discrepancies resolved by consensus. A predesigned data extraction sheet developed according to the Cochrane Handbook [10] was used to extract relevant information such as author name, publication year, study design, participants characteristics (including number of patients with T2DM, mean duration of T2DM, mean age, mean weight, mean BMI and mean HbA1c), interventions, outcome measures, study duration, funding and conflict of interest statements.

Risk of Bias Within Individual Studies and Across Studies

Quality of the studies and risk of bias were assessed using the Cochrane Collaboration Risk of Bias Tool [11] by two independent reviewers (with discrepancies solved by consensus). The risk of selection, performance, detection, attrition, reporting bias and other biases were judged as high, low or unclear. In addition, the quality of evidence obtained through network meta-analysis was assessed using CINeMA [12].

Data Analysis

Statistical analysis was performed using netmeta package of software R. We performed both pairwise meta-analysis for direct comparisons between interventions, and network meta-analysis for obtaining estimates based on both direct and indirect comparisons between interventions.

Network meta-analysis integrates direct evidence (from studies directly comparing two different treatments) and indirect evidence (from paths with one or more intermediate comparators). We opted for this type of analysis, as it allows the extraction of information regarding comparisons between different treatments that have not been directly compared in primary studies, and as it produces more precise relative treatment effects than pairwise meta-analysis [12, 13].

For dichotomous outcomes (full remission of T2DM at 5 years, microvascular complications of T2DM at 5 years—defined as the number of patients with retinopathy, nephropathy or neuropathy and macrovascular complications of T2DM at 5 years—defined as major cardiovascular events), we calculated pooled risk ratios (RRs) with their 95% confidence intervals (CIs). For continuous outcomes (percent total weight, and average TC, LDL, HDL, TG, SBP and DBP change at 5 years), we computed pooled mean differences (MDs). *p* values less than 0.05 were considered statistically significant.

Heterogeneity was assessed using the I^2 statistic. In the presence of low heterogeneity ($I^2 \leq 10\%$), meta-analysis was performed using a fixed-effects model, while a random-effects model was used if moderate or severe heterogeneity was found ($I^2 > 10\%$). For network meta-analysis, in addition to heterogeneity, we assessed inconsistency (i.e., direct and indirect estimates were compared in order to identify possible disagreements), with *p* values < 0.10 indicating substantial heterogeneity.

Results

Study Selection

During the initial search, 10,319 records were identified. After exclusion of duplicates, only 9,622 remained and were analysed. A total of 9,611 records were excluded—9,565 in the screening phase and 46 after full text reading. Therefore, eleven articles were included in this systematic review with network meta-analysis [14–24]. The study selection process is summarised in Fig. 1.

Primary Study Characteristics

HbA1c (%) We included eleven RCT published between 2010 and 2020. The included RCT involved a total of 683 adult subjects with T2DM and BMI ≥ 25 kg/m² [14–24]. In all studies, more than half of the participants were female. Most patients were over 35 and under 50 years old. The main features of the studies are summarised in Table 1 and Tables S2–S3.

The most frequently studied surgical treatments were laparoscopic Roux-en-Y gastric bypass (LRYGB) (8 trials; 234 patients) [14–19, 21, 23] and laparoscopic sleeve gastrectomy (LSG) (4 trials; 158 patients) [14, 17, 18, 20]. Medical treatment was used as the comparator arm in 5 trials (142 participants) [14–16, 19, 24].

The definition of full remission of T2DM displayed small differences (Table S3).

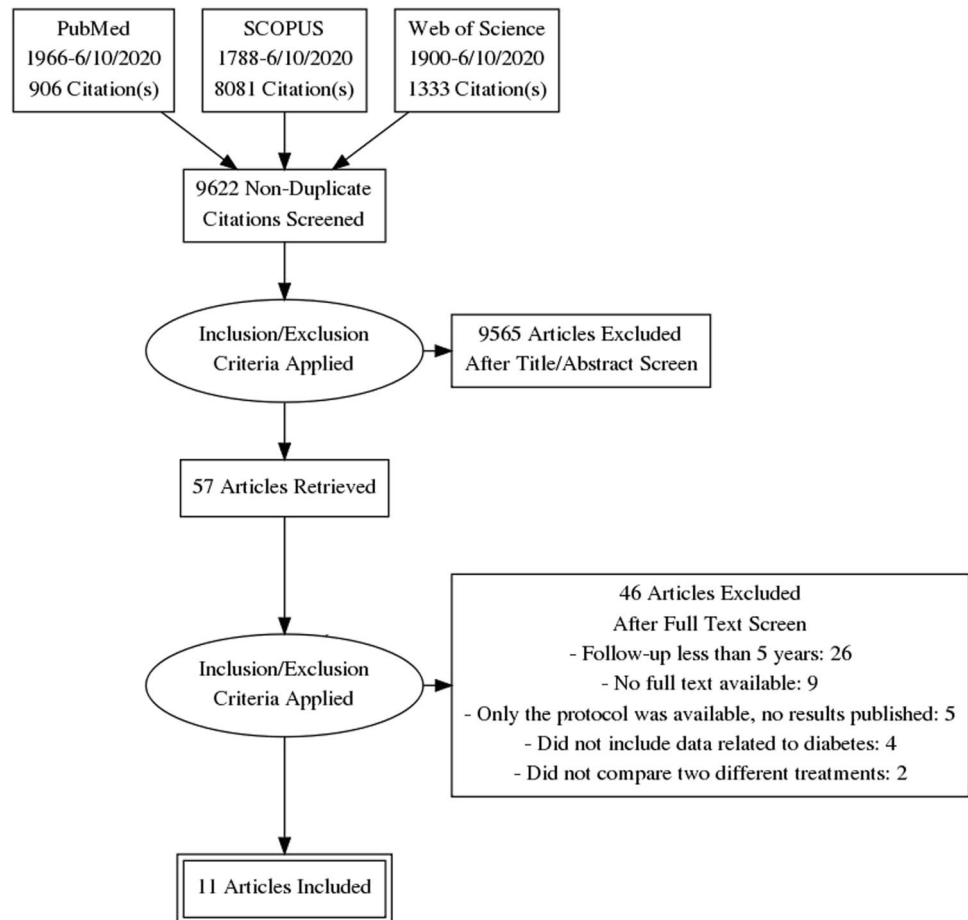
Full T2DM remission rate for biliopancreatic diversion without duodenal switch (BPD) at 5 years was 0% and for laparoscopic duodenal switch (LDS) and vertical banded gastroplasty (VBG) it was 100%. These three treatments were only included in one study each. In terms of MT, full T2DM remission rate at 5 years varied between 0 and 9% with a mean of 3%. For laparoscopic adjustable gastric banding (LAGB), full T2DM remission rate at 5 years varied between 0 and 23% in the different studies, with a mean full T2DM remission rate at 5 years of 8%. For laparoscopic Roux-en-Y gastric bypass (LRYGB), it varied between 0 and 100% with a mean of 40%. In terms of laparoscopic sleeve gastrectomy (LSG), it varied between 12 and 62% with a mean of 32%. For laparoscopic one-anastomosis gastric bypass (LOAGB), it varied between 60 and 100% with a mean of 80%.

Meta-Analyses

Results for pairwise and network meta-analyses are displayed in Table 2 and S4. The network graphs for each outcome are presented in Fig. 2. Not all studies reported data regarding all the outcomes, so the network geometry varies. The most frequent comparisons in terms of remission of T2DM were LRYGB versus LSG and LRYGB versus MT.

Regarding remission of T2DM (Table 2), VBG ($RR_{MTvsVBG} = 0.08$, 95%CI = [0.01;0.72]), LOAGB ($RR_{MTvsLOAGB} = 0.14$, 95%CI = [0.04;0.49]), LDS ($RR_{MTvsLDS} = 0.17$, 95%CI = [0.05;0.55]), LRYGB ($RR_{MTvsLRYGB} = 0.21$, 95%CI = [0.07;0.63]) and LSG ($RR_{MTvsLSG} = 0.26$, 95%CI = [0.08;0.79]) were more effective than MT at maintaining T2DM full remission for 5 years. Laparoscopic one-anastomosis gastric bypass was also found to be more effective than LSG for this outcome ($RR_{LSGvsLOAGB} = 0.55$, 95%CI = [0.31;0.96]). There was no evidence suggesting inconsistency or

Fig. 1 Schematic algorithm for selection of studies in the systematic review and meta-analysis



heterogeneity (Table S4.10.: $I^2 = 0\%$; p value for inconsistency = 0.9223). The rank probability of full remission of T2DM (Table S4.11.) was the highest for VBG and LOAGB (p score_{VBG} = 0.836; p score_{LOAGB} = 0.791) and the lowest for MT (p score = 0.069).

Contrary to full remission, we did not find significant differences in the frequency of macrovascular or microvascular complications (Tables S4.1. and S4.2.).

The analyses of each individual microvascular complication are reported in S2; however, the precision of the estimates was low in all of them.

Regarding the percent total weight change (Table S4.3.), all surgical treatments were found to be more effective than MT. Biliopancreatic diversion without duodenal switch (MD = 15.02, 95%CI = [7.01;23.03]), LRYGB (MD = 10.74, 95%CI = [6.19;15.30]) and LOAGB (MD = 9.65, 95%CI = [0.29;19.02]) were found to be more effective than laparoscopic adjustable gastric banding (LAGB), as well. Biliopancreatic diversion without duodenal switch was also found to be more effective than MT, LAGB and LRYGB in decreasing TC and LDL (Tables S4.4. and S4.5.). However, substantial

heterogeneity and inconsistency were found for all these analyses (Table S4.10.).

In terms of percent HDL change (Table S4.6.), LRYGB was found to be more effective than MT (MD = -25.68; 95%CI = [-29.32; -22.04]), LAGB (MD = -13.36; 95%CI = [-17.33; -9.39]) and BPD (MD = -12.55; 95%CI = [-24.97; -0.13]). Laparoscopic sleeve gastrectomy (MD = -23.19; 95%CI = [-34.52; -11.85]), BPD (MD = -13.13; 95%CI = [-25.35; -0.91]) and LAGB (MD = -12.32; 95%CI = [-16.23; -8.41]) were shown to be more effective than MT for this outcome. Heterogeneity and inconsistency were respectively low and not statistically significant (Table S4.10.: $I^2 = 1.0\%$; p value for inconsistency test = 0.4008).

For percent DBP (Table S4.9.) change, LRYGB was found to be more effective than MT (MD = 4.62; 95%CI = [0.67;8.58]) and LAGB (MD = 8.76; 95%CI = [3.62;13.89]). BPD was also found to be more effective than LAGB (MD = 10.40; 95%CI = [1.08;19.72]). For the remaining outcomes, no significant differences were observed. Heterogeneity and inconsistency were respectively moderate but not statistically significant

Table 1 Characteristics of the included studies

Patients with T2DM, No	Duration of T2DM, (years)	Using insulin, No., (%)	HbA1c (%)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	SBP (mmHg)	DBP (mmHg)	Study	Country	Follow-up (years)	Intervention	Alimentary LL (cm)	Biliopancreatic LL (cm)	Common Patients, LL (cm)	No	Female, No.	Age (years)	BMI (kg/m ²)
20	7.6	10 (50.0)	8.6	200.2	124.3	41.8	115.5 ^a	139.7	81.3	Courcoulas 2020	USA	5	LRYGB	-	-	-	20	16 (80.0)	45.4	35.7
21	6.1	3 (14.3)	7.9	189.5	107.4	40.0	139 ^a	134.5	77.1				LAGB	-	-	-	21	17 (81.0)	47.7	35.6
20	5.7	3 (15.0)	7.0	182.0	105.5	44.1	119.5 ^a	132.0	76.3				MT	-	-	-	20	17 (85.0)	48.9	35.7
60	8.8	35 (61)	9.6	181	102	41	200	127	78	Ikkramuddin 2018	USA, Taiwan	5	LRYGB	150	100	-	60	37 (65)	49	34.9
60	9.1	24 (43)	9.6	186	102	41	211	132	79				MT	-	-	-	60	31 (55)	48	34.4
30	5.8	4 (3.3)	10.0	200.9	137.7	47.9	195.2	130.3	76.4	Lee 2014	Taiwan	5	LOAGB	-	120	-	30	22 (73.3)	44.6	30.2
30	6.9	7 (23.3)	9.9	230.6	142.9	42.8	262.2	128.7	80.1				LSG	-	-	-	30	22 (68.8)	46.4	31
1	-	-	-	-	-	-	-	-	-	Level 2020	Venezuela	5	LOAGB	-	200	-	9	9 (100)	37.5	42.9
2	-	-	-	-	-	-	-	-	-				LRYGB	150	100	-	24	24 (100)	36.8	42.6
20	6.00	- (47)	8.88	5.54 ^b	3.41 ^b	0.99 ^b	2.49 ^b	154.50	95.90	Minigrone 2015	Italy	5	BPD	200	-	50	20	10 (50)	42.75	45.14
20	6.03	- (48)	8.56	4.71 ^b	2.83 ^b	1.13 ^b	1.66 ^b	145.75	91.50				LRYGB	100	75	-	20	12 (60)	43.90	44.85
20	6.08	- (47)	8.51	6.12 ^b	3.99 ^b	0.99 ^b	2.49 ^b	155.20	96.00				MT	-	-	-	20	10 (50)	43.45	45.62
28	-	6 (21.4)	-	-	-	-	-	-	-	Peterli 2018	Switzerland	5	LRYGB	150	50	-	113	79 (71.8)	42.1	44.2
26	-	6 (23.1)	-	-	-	-	-	-	-				LSG	-	-	-	112	77 (72.0)	43.0	43.66
5	-	-	-	-	-	-	-	-	-	Risstad 2015	Norway, Sweden	5	LRYGB	150	50	-	31	23 (74)	35.2	54.8
6	-	-	-	-	-	-	-	-	-				LDS	200	-	100	30	19 (66)	36.1	55.2
49	-	13 (26.5)	-	-	-	-	-	-	-	Salminen 2018	Finland	5	LRYGB	150	50–80	-	119	80 (67.2)	48.4	46.4
52	-	16 (30.8)	-	-	-	-	-	-	-				LSG	-	-	-	121	87 (71.9)	48.5	45.5
50	8.2	22 (44.9)	9.3	-	-	-	-	-	-	Schauer 2017	USA	5	LRYGB	150	50	-	50	29 (58)	48.3	37.0
50	8.5	20 (42.6)	9.5	-	-	-	-	-	-				LSG	-	-	-	50	39 (78)	47.9	36.2
50	8.9	17 (44.7)	8.8	-	-	-	-	-	-				MT	-	-	-	50	31 (62)	49.7	36.8
5	-	-	-	-	-	-	-	-	-	Schouten 2010	Netherlands	7	LAGB	-	-	-	50	40 (80)	39	47
7	-	-	-	-	-	-	-	-	-				VBG	-	-	-	50	40 (80)	37	47
25	2.17	4 (16)	6.9	5.0 ^{b,c}	3.0 ^{b,c}	1.20 ^{b,c}	1.7 ^{b,c}	130	83	Wentworth 2017	Australia	5	LAGB	-	-	-	25	19 (76)	53	29
26	2.75	1 (4)	7.2	5.1 ^{b,c}	2.9 ^{b,c}	1.21 ^{b,c}	2.2 ^{b,c}	131	84				MT	-	-	-	26	17 (65)	53	29

Data regarding mean baseline total cholesterol (TC), mean low-density lipoprotein (LDL), mean high-density lipoprotein (HDL), mean triglycerides (TG), mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) were only extracted for the studies that only included patients with type 2 diabetes mellitus (T2DM). ^aValues correspond to the median, not mean (contrary to the rest of values presented). ^bPresented in mmol/L. ^cData related to the patients with five-year follow-up data. No data was available pertaining the initial group of patients. BPD, biliopancreatic diversion without duodenal switch; LAGB, laparoscopic adjustable gastric banding; LOAGB, laparoscopic one-anastomosis gastric bypass; LRYGB, laparoscopic Roux-en-Y gastric bypass; LDS, laparoscopic duodenal switch; LSG, laparoscopic sleeve gastrectomy; MT, medical treatment; VBG, vertical banded gastroplasty

(Table S4.10.: $I^2 = 45.7\%$; p value for inconsistency test = 0.1177).

Risk of Bias and Evidence Quality Assessment

Figures S5.1. and S5.2. summarise the risk of bias in the studies. In most studies, there was a high risk of performance and detection bias, as blinding of participants, personnel and outcome assessment was not performed. Overall, all studies except that of Lee 2014 present at least one item classified as “high risk of bias”.

Supplement 6 summarises the analysis of confidence in the results for the outcome “Full remission of T2DM” at 5 years. For most comparisons, the degree of confidence is at least moderate. The comparisons between LAGB and VBG and between LDS and LRYGB present a low degree of confidence as both entail major concerns in terms of indirectness and imprecision.

Discussion

Our review found VBG and LOAGB to be the most effective treatments for T2DM full remission at 5 years in patients with T2DM and $\text{BMI} \geq 25 \text{ kg/m}^2$. In terms of microvascular and macrovascular complications, however, we did not find significant differences between treatments. Regarding cardiometabolic outcomes, the only available data concerned BPD, LRYGB, LSG, LAGB and MT. For percent total weight change, all surgical treatments evaluated were found to be more effective than MT. The confidence rating in our results was moderate to high in most comparisons. Nevertheless, it is important to point out the high risk of performance and detection bias in most studies and the major concerns for imprecision in several comparisons.

Only one study presented data on VGB. While this study displayed a 100% remission rate for patients undergoing VGB (thus, explaining its high p score), it only included 12 patients with T2DM (5 in the LAGB group and 7 in the VBG group) [25]. On account of such small sample, the CINeMA confidence level on the comparison between LAGB and VBG was low, despite this being a direct study comparing both treatments. Moreover, nowadays, this procedure is no longer performed due to its high rate of failure and necessity to perform a conversion in case of failure [22].

Previous systematic reviews including studies other than RCTs found LDS to be the most effective surgery for T2DM remission, maintaining remission in more than 95% of subjects for ≥ 2 years [26, 27]. These reviews did not include LOAGB as a comparison. Moreover, in our analysis, we only found one RCT that had 5-year follow-up for LDS [23], having a small sample of T2DM patients. This points to a lack of evidence on long-term effectiveness

of LDS. Therefore, our findings suggest that LOAGB can be a possible alternative for LDS in this context, but more studies are needed comparing the two techniques. It would be beneficial to include the evaluation of cardiometabolic outcomes in these futures studies, as no evidence was available to determine the effect of LOAGB and LDS on these outcomes. This is all the more relevant as LOAGB was shown to have a lower complication rate, to be safer, faster, more effective in terms of weight loss and to have a smaller learning curve than LRYGB [28], which is already a safer technique than LDS [23]. It has also been reported that LOAGB is not inferior to LRYGB in terms of metabolic improvement at 2 years [29, 30]. On the other hand, there has been some criticism regarding this procedure as it seems to predispose to bile reflux and it has a higher rate of marginal ulcers and nutritional deficiencies [31]. The 2020 consensus by Ramos, et al., however, states that concerns regarding an increased risk of gastroesophageal cancer are unfounded [32].

No RCT with 5-year follow-up was found comparing single-anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S) with other procedures in terms of T2DM remission. However, SADI-S has been proposed as an alternative to LDS for these outcomes due to its less dangerous side effect profile [33], so it would be interesting to compare not only LOAGB and LDS, but SADI-S as well.

In terms of microvascular and macrovascular complications, we did not find significant differences between treatments, observing a small number of events associating with each procedure. Studies with longer follow-up showed significant differences between bariatric surgery and MT. The recently published 10-year results of Mingrone et al. show that “Participants in the RYGB and BPD groups had fewer diabetes-related complications than those in the medical therapy group” [34]. These are consistent with the SOS results, a large, non-randomised, case–control study in which bariatric surgery was associated with reduced long-term incidence of microvascular and macrovascular complications. For that study, the median follow-up for diabetes complication was over 17.0 years for the control and the surgery group [35]. It should be noted that the level of evidence in the SOS study is not as high as in the RCTs included in the Mingrone study and in our own review, as it is an observational study and not an experimental one.

In our review, BPD appeared to be more effective than MT, LRYGB and LAGB in terms of percent TC and LDL change at 5 years, and better than LSG for percent LDL change. This technique also appeared to be more effective than LAGB in terms of percent DBP change. In Ding et al. (a similar review with a 3-year follow-up), no significant differences were found between treatments for percent TC, LDL and DBP change [36]. The longer follow-up of our review might explain the differences. Due to the significant level of

Table 2 Net-league table presenting network meta-analyses estimates (grey boxes) and pairwise meta-analyses estimates (white boxes) of risk ratio (RR) of full remission of type 2 diabetes mellitus at 5 years of the different treatments

VBG	--	--	--	--	0.09 [0.01, 1.27]	--	--
0.53 [0.04, 6.53]	LOAGB	--	1.00 [0.39, 2.58]	0.50 [0.27, 0.93]	--	--	--
0.44 [0.04, 5.19]	0.83 [0.40, 1.71]	LDS	0.81 [0.49, 1.34]	--	--	--	--
0.36 [0.03, 4.12]	0.68 [0.37, 1.25]	0.82 [0.55, 1.21]	LRYGB	0.83 [0.60, 1.14]	0.32 [0.01, 7.38]	--	0.16 [0.05, 0.53]
0.29 [0.03, 3.38]	0.55 [0.31, 0.96]	0.66 [0.40, 1.10]	0.81 [0.59, 1.11]	LSG	--	--	0.22 [0.05, 0.95]
0.18 [0.03, 1.07]	0.34 [0.06, 2.02]	0.42 [0.07, 2.32]	0.51 [0.09, 2.71]	0.63 [0.12, 3.40]	LAGB	--	0.38 [0.08, 1.77]
0.15 [0.00, 8.38]	0.27 [0.01, 8.60]	0.33 [0.01, 10.12]	0.41 [0.01, 12.09]	0.50 [0.02, 15.07]	0.80 [0.02, 30.62]	BPD	--
0.08 [0.01, 0.72]	0.14 [0.04, 0.49]	0.17 [0.05, 0.55]	0.21 [0.07, 0.63]	0.26 [0.08, 0.79]	0.42 [0.10, 1.66]	0.52 [0.02, 15.40]	MT

Comparisons between treatments should be read from right to left, and their RR is in the cell in common between the column-defining treatment and the row-defining treatment. RR less than 1 favour the column-defining treatment for the network estimates and the row-defining treatment for the direct estimate. The significant results in the network meta-analysis are presented in bold. *BPD*, biliopancreatic diversion without duodenal switch; *LAGB*, laparoscopic adjustable gastric banding; *LOAGB*, laparoscopic one-anastomosis gastric bypass; *LRYGB*, laparoscopic Roux-en-Y gastric bypass; *LDS*, laparoscopic duodenal switch; *LSG*, laparoscopic sleeve gastrectomy; *MT*, medical treatment; *VBG*, vertical banded gastroplasty

inconsistency and heterogeneity in our networks for these outcomes, these results should be interpreted with caution.

Regarding percent HDL change at 5 years, all surgical treatments analysed were shown to be more effective than MT. LRYGB appeared to be the most effective treatment, with significant differences found between LRYGB and BPD and between LRYGB and LAGB. Previously, LRYGB was found to be superior to both LAGB and MT in controlling HDL levels, but no significant difference was found in comparison with BPD [36].

Our study did not find any statistically significant differences between treatments regarding percent TG and SBP change at 5 years; nevertheless, substantial heterogeneity and inconsistency for these outcomes were found. These results are consistent with the Ding review.

This systematic review has some important limitations worth noting. Only 11 studies were included in the analysis, only six presented data regarding T2DM complications and only five reported information related to cardiometabolic outcomes at 5 years in patients with T2DM and a BMI ≥ 25 kg/m². Moreover, only one RCT had data regarding LDS and no studies were available that reported the effect of LOAGB, VBG and LDS on lipid levels and blood pressure change at 5 years. Also, it was not possible to evaluate the diabetes-related complications, as the number of events was too low, due to a still short follow-up period. Regarding LOAGB, the focus of our discussion, there was only a total of 39 patients in this group, 31 of which had T2DM. All but one of these patients were from a single study. The

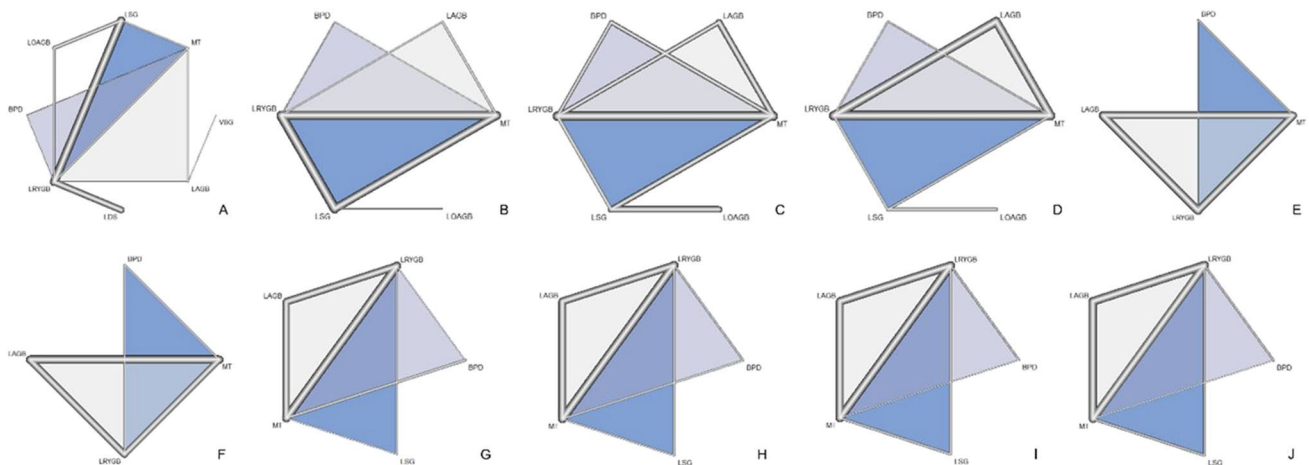


Fig. 2 Networks graphs for: “Full remission of type 2 diabetes mellitus (T2DM) at 5 years” (**2A**); “Microvascular complications of T2DM at 5 years” (**2B**); “Macrovascular complications of T2DM at 5 years” (**2C**); “Percent weight change at 5 years” (**2D**); “Percent total cholesterol change at 5 years” (**2E**); “Percent triglycerides change at 5 years” (**2F**); “Percent low-density lipoprotein change at 5 years” (**2G**); “Percent high-density lipoprotein change at 5 years” (**2H**); “Percent systolic blood pressure change at 5 years” (**2I**); “Percent diastolic blood pressure change at 5 years” (**2J**). Treatments that are compared directly in at least one study are connected by a

straight line. The edge width of each straight line is defined by the inverse of the standard error in the pairwise analysis, reflecting the weight of each comparison in the network meta-analysis. The colours of each triangle do not provide additional information. Biliopancreatic diversion without duodenal switch, BPD; laparoscopic adjustable gastric banding, LAGB; laparoscopic one-anastomosis gastric bypass, LOAGB; laparoscopic Roux-en-Y gastric bypass, LRYGB; laparoscopic duodenal switch, LDS; laparoscopic sleeve gastrectomy, LSG; medical treatment, MT; vertical banded gastroplasty, VBG

population of this specific study had a short duration of T2DM, low BMI and a small number of patients using insulin at baseline, which raises concerns in terms of generalizability. Therefore, even though our review points to LOAGB as a possible alternative to LDS for patients with these characteristics, we need more studies, with longer follow-up times and more diverse populations, comparing these two techniques and evaluating all these outcomes to come to a definitive conclusion. When more data is available, it will also be helpful to perform sub analyses to see whether LOAGB outperforms LDS both in populations with short duration of T2DM and populations with longer duration of the disease. The quality of primary studies included in this systematic review is also an important limitation—the absence of blinding of participants, personnel and outcome assessment in most studies might have led to an overestimation of the impact of surgical treatments on these patients in comparison with the MT. For some analyses, substantial inconsistency and heterogeneity were found, particularly for those concerning cardiometabolic biomarkers. Such across-study differences may be explained by participants' baseline differences or by differences in the assessment. Nevertheless, we were not able to identify a clear pattern (e.g., with specific studies consistently presenting larger or smaller variations). In terms of diabetes-related complications, each study reported these complications using different terms and nomenclatures and not much information was provided

concerning how each complication was defined in each individual study. These differences might be responsible for part of the heterogeneity observed in the analyses of these outcomes and are a limitation in our study. A more systematic approach to the reporting of diabetes-related complications could facilitate this type of analysis in the future. Despite its clinical relevance, the effect of the different procedures on percent HbA1c change at 5 years was not possible to be adequately assessed as several studies did not present baseline and 5-year data regarding that outcome. Therefore, we opted for considering full T2DM remission as our main outcome (even despite the small differences of definitions across studies). Finally, the safety of the different procedures was not analysed, as we focused the analysis solely on effectiveness.

The fact that we searched on three bibliographic databases using no language or date filters is one of the methodological strengths of this study. On the other hand, the ability to compare all the key procedures used for diabetes remission is one of the major strengths of this review. It allowed us to identify LOAGB as a possible alternative to LDS and, if future studies corroborate our findings, this will be clinically useful as it is a simpler and safer technique. Lastly, the 5-year follow-up, despite the previously stated limitation, is another major strength of our review as it suggests that the effect on diabetes remission is, not only immediate, but sustained for long periods of time.

Conclusion

In summary, LOAGB appears to be a good option in terms of T2DM remission, as well as a possible alternative to LDS, but no definitive conclusions can be taken as the included primary studies in our review are underpowered. More RCTs including LDS and LOAGB are needed to better evaluate the difference between the two procedures. No significant differences were found between treatments in terms of diabetes-related complications, but studies with longer follow-up time are needed to truly understand the impact of these surgeries on the development of diabetes complications.

On the other hand, LRYGB seems to be the most effective treatment in terms of controlling HDL levels and BPD in terms of lowering DBP. However, results must be cautiously interpreted on account of observed heterogeneity and inconsistency, as well as limitations in the quality of primary studies.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11695-021-05725-y>.

Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Does not apply.

Competing Interests The authors declare no competing interests.

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Management of suboptimal results of previous surgeries

Revisional surgery after AGB

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RESEARCH



Roux-en-Y gastric bypass and sleeve gastrectomy as revisional bariatric procedures after adjustable gastric banding: a retrospective cohort study

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Abstract

Introduction The frequency of revisional bariatric surgery is increasing, but its effectiveness and safety are not yet fully established. The aim of our study was to compare short-term outcomes of primary (pRYGB and pSG) and revisional bariatric surgeries (rRYGB and rSG).

Methods We performed a retrospective cohort study assessing all patients submitted to primary and revisional (after a failed AGB) RYGB and SG in 2019. Each patient was followed-up at 6 months and 12 months after surgery. We compared pRYGB vs. rRYGB, pSG vs. rSG and rRYGB vs. rSG on weight loss, surgical complications, and resolution of comorbidities.

Results We assessed 494 patients, of which 18.8% had undergone a revisional procedure. Higher weight loss at 6 and 12 months was observed in patients undergoing primary vs. revisional procedures. Patients submitted to rRYGB lost more weight than those with rSG (%EWL 12 months = 82.6% vs. 69.0%, $p < 0.001$). Regarding the resolution of obesity-related comorbidities, diabetes resolution was more frequent in pRYGB than rRYGB (54.2% vs. 25.0%; $p = 0.038$). Also, 41.7% of the patients who underwent rRYGB had dyslipidemia resolution vs. 0% from the rSG group ($p = 0.035$). Dyslipidemia resolution was also more common in pSG vs. rSG (68.6% vs. 0.0%; $p = 0.001$). No significant differences in surgical complications were found.

Conclusion Revisional bariatric surgery is effective and safe treating obesity and related comorbidities after AGB. Primary procedures appear to be associated with better weight loss outcomes. Further prospective studies are needed to better understand the role of revisional bariatric surgery.

Keywords Revisional bariatric surgery · Adjustable gastric band · Roux-en-Y gastric bypass · Sleeve gastrectomy · Obesity

Key points

- Revisional bariatric surgeries are becoming increasingly frequent.
- Revisional RYGB and SG showed poorer weight loss outcomes when compared to primary RYGB and SG, respectively.
- RYGB has better weight loss outcomes than SG when they are used as revisional bariatric procedures.

Hugo Santos-Sousa and Jorge Nogueiro contributed equally and should be considered first authors.

Authors Silvestre Carneiro and Eduardo Lima-da-Costa should both be considered senior authors.

Extended author information available on the last page of the article

Introduction

Obesity is a complex multifactorial disease, whose prevalence is increasing steadily in the last decades [1]. The World Health Organization (WHO) identifies obesity as abnormal or excessive fat accumulation with a body mass index (BMI) of 30 kg/m² or higher, representing a health challenge. It affects almost all physiological functions of the body, and it increases the risk for developing multiple comorbidities, such as diabetes mellitus type 2 (T2DM), cardiovascular disease, cancer, osteoarthritis, obstructive sleep apnea (OSA), and poor mental health, thereby contributing to a decline in quality of life, work productivity as well as to increased healthcare costs [2].

Bariatric surgery is regarded as the most effective intervention for achieving substantial and long-lasting weight loss and resolution of obesity associated comorbidities,

exceeding the results obtained with medical treatment [3]. The laparoscopic implantation of an adjustable gastric banding (AGB) was first described in 1993 and it became one of the most common bariatric procedures in the world [4]. Its popularity was due to the remarkable safety profile and low initial morbidity rate [5]. The AGB has a balloon which can be inflated, constricting the stomach in order to reduce the patient's oral intake [6]. Complications of AGB were initially believed to be minor and rare. However, long-term studies have progressively shown late-onset complications that lead to revisional surgeries [5]. The high complication rate (including hardware malfunctions with the band, tubing, or access port; esophageal motility disorders; adverse gastrointestinal symptoms; and psychological intolerance to the band) negatively impacts patients' satisfaction and quality of life [7, 8]. Moreover, a significant fraction of patients submitted to AGB fail to lose weight or have weight regain, frequently requiring conversion to other bariatric procedures [5]. Recent studies have reported long-term reoperations in 31–80% of patients following failed AGB [9].

Nowadays, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the two most commonly performed bariatric procedures [10]. RYGB has shown better outcomes regarding the resolution of obesity-related comorbidities [11, 12]. However, SG is still the most frequent bariatric surgery performed because it is technically easier and faster to perform, resulting in fewer postoperative complication and reoperation rates and in similar excess weight reduction [13, 14].

Revisional bariatric surgeries are becoming increasingly common due to inadequate weight reduction, weight regain, and postoperative morbidity [8, 15, 16]. The most successful conversion strategy relies on selecting the most appropriate revisional intervention, depending mostly on the indications for revision themselves [8]. Despite the growing demand for revisional procedures, there is still some controversy on their safety and efficacy [16]. Also, there is insufficient evidence on which procedure is more suitable for each patient. Despite the lack of standardized guidelines for the conversion strategy from AGB, RYGB and SG are the most frequent procedures applied [17].

The aim of our study is to compare short-term outcomes of primary (pRYGB and pSG) vs. revisional bariatric surgeries (rRYGB and rSG), and between different types of revisional interventions on weight loss outcomes, surgical complications, and resolution of obesity-related comorbidities.

Materials and methods

Participants and setting

This is a retrospective cohort study assessing a consecutive sample of all adult (age > 18 years) patients submitted to either primary or revisional RYGB or SG between January

to December 2019 in a single tertiary hospital in Northern Portugal. We excluded patients submitted to a revisional surgery whose primary procedure was not the implantation of a laparoscopic AGB.

In our institution, all patients are evaluated multidisciplinary (surgery, endocrinology, nutrition, psychology/psychiatry, and anesthesiology) and per-protocol, all patients are submitted to extensive blood and urine analysis, upper endoscopy and abdominal ultrasonography, and eligibility criteria are defined accordingly to ASMBS and IFSO criteria. Gastric bypass is suggested for individuals dealing with hiatal hernias, GERD, or esophagitis, as well as patients with other comorbidities that will benefit from this procedure, like diabetes or psoriasis. On the other hand, sleeve gastrectomy is proposed to patients with specific diseases, like inflammatory bowel disease, and those with unamenable risk factors for gastric cancer, like persistent *Helicobacter Pylori* infection or familiar history of gastric cancer. Patient opinion and preferences are other important factor to take in account. Challenging cases are discussed in a multidisciplinary meeting held once a week.

Variables

From each patient, we retrieved information on demographic characteristics, obesity-related comorbidities, previous surgeries, and surgical complications. Anthropometric data, metabolic parameters and clinical outcomes, medication, and nutritional supplements from the included patients were retrospectively collected from their electronic medical charts. We reviewed the data from the preoperative period, at the date of the surgery, and postoperatively at 6 and 12 months.

The revision from AGB was a 2-step operation, consisting of band removal followed (at a subsequent date) by a conversion operation, either RYGB or SG. RYGB was performed as a standardized technique with a small gastric pouch, a biliopancreatic limb of 100 cm, and an alimentary limb of 120 cm. SG was performed using a 54-Fr Fouchet tube, sectioning the stomach from the gastric antrum to the angle of His. The choice of bariatric procedure was made individually regarding patient characteristics, comorbidities, previous treatments, preference, and surgeon recommendation.

Weight loss was quantified as the percentage of total weight loss (%TWL) and percentage of excess weight loss (%EWL). Successful weight loss after surgery was defined if patients completed the following criteria at 12 months: %TWL ≥ 20%, %EWL ≥ 50%, and BMI < 35 kg/m². The criteria used to evaluate the resolution of T2DM, dyslipidemia, arterial hypertension (HTN), and OSA were adapted from the American Society for Metabolic and Bariatric Surgery

(ASMBS) consensus statement “Standardized outcomes reporting in metabolic and bariatric surgery” [18]. Improvement of psychiatric disorders, gastroesophageal reflux disease, and osteoarticular pathologies were not evaluated in our series. Postoperative early-onset complications until 90 days after the date of the surgery were also evaluated.

Statistical analysis

Categorical variables are presented with absolute frequencies and percentages and continuous variables are presented with means $\pm$ standard deviations (SD) or with medians and interquartile ranges (IQR), depending on data distribution. The Chi-Square test was used to compare categorical variables. The independent samples t-test was used for the continuous variables with a normal distribution and the Mann–Whitney U test was applied for the continuous variables which do not follow a normal distribution. A p -value < 0.05 was considered statistically significant. IBM SPSS Statistics 26® (SPSS Inc., Chicago, Ill., USA) was used to perform the statistical analysis.

Results

Of the 520 patients submitted to bariatric surgery in 2019 at our hospital, 494 patients met the eligibility criteria and were included in this study (Fig. 1). Ninety-three

(18.8%) of the eligible participants underwent a revisional bariatric surgery after a failed AGB. RYGB was the most common bariatric procedure: 329 (66.6%) patients were submitted to RYGB, 73 (22.2%) of them were patients undergoing rRYGB. Of the 165 patients undergoing SG, 20 (12.1%) had this procedure as a revisional bariatric surgery.

The characteristics of the participants are presented in Table 1. Median age on presentation was 45.0 years for pRYGB and 49.0 for rRYGB ($p = 0.001$). Median age was 44.0 years for pSG vs. 51.0 years for rSG ($p = 0.002$). One pSG was performed as an open surgery, associated to other procedure (bowel reconstruction). As for the remaining bariatric procedures, they were done laparoscopically, not requiring conversion to open surgery. There was no mortality in either group. There were no differences regarding pre-operative BMI and pre-operative comorbidities (30 Clavien-Dindo II; 1 Clavien-Dindo IIIb). Every patient completed the 12-month follow-up of our study.

Figure 2 displays the indications for revisional bariatric surgery. Insufficient weight loss was the main reason for revisional surgery: 65 (69.9%) patients removed the AGB due to inadequate weight loss or weight regain. Slippage and other complications (17 patients; 18.8%), incoercible vomiting (8 patients; 8.6%), and refractory reflux (3 patients; 3.2%) were other indications reported in our series.

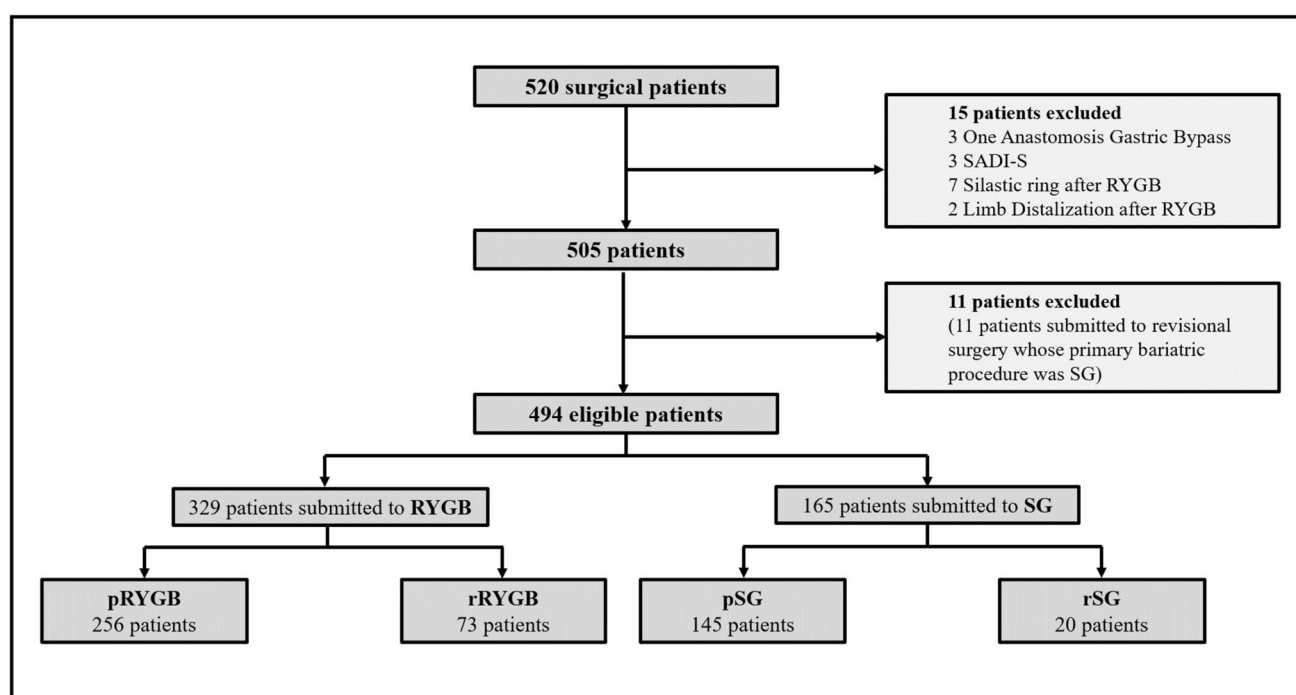


Fig. 1 Flowchart of patients' eligibility

Table 1 Demographic characteristics

	pRYGB (<i>n</i> = 256)	pSG (<i>n</i> = 145)	rRYGB (<i>n</i> = 73)	rSG (<i>n</i> = 20)	<i>p</i> -value	pRYGB vs. rRYGB	pSG vs. rSG	rRYGB vs. rSG
Age (years); median [IQR]	45.00 [IQR 38.25–53.00]	44.00 [IQR 35.50–54.00]	49.00 [IQR 42.00–58.00]	51.00 [IQR 44.00–58.25]	0.001		0.015	0.653
Female; <i>n</i> (%)	224 (87.5%)	103 (71.0%)	67 (91.8%)	17 (85.0%)	0.313		3.189	0.399
Preoperative BMI (kg/m ²); median [IQR]	42.27 [IQR 39.30–45.20]	43.78 [IQR 39.93–49.12]	42.67 [IQR 39.32–45.46]	44.63 [IQR 39.61–49.04]	0.760		0.759	0.180
Preoperative comorbidities								
HTN; <i>n</i> (%)	119 (46.5%)	72 (49.7%)	36 (49.3%)	10 (50.0%)	0.669		0.977	0.957
T2DM; <i>n</i> (%)	74 (28.9%)	33 (22.8%)	21 (28.8%)	3 (15.0%)	0.982		0.570	0.213
Dyslipidemia; <i>n</i> (%)	119 (46.5%)	69 (47.6%)	33 (45.2%)	10 (50.0%)	0.847		0.839	0.102
OSA; <i>n</i> (%)	48 (14.6%)	29 (20.0%)	10 (3.0%)	6 (30.0%)	0.318		0.380	0.703

pRYGB, primary Roux-en-Y gastric bypass; pSG, primary sleeve gastrectomy; rRYGB, revisional Roux-en-Y gastric bypass; rSG, revisional sleeve gastrectomy; BMI, body mass index; HTN, arterial hypertension; T2DM, diabetes mellitus type 2; OSA, obstructive sleep apnea

pRYGB vs. rRYGB

Weight loss outcomes are presented in Table 2. We found significant higher %TWL and %EWL and a lower BMI at 6 and 12 months in the pRYGB group. The frequency of patients reaching the qualitative criteria of %TWL $\geq$ 20%, %EWL $\geq$ 50%, and BMI $<$ 35 kg/m² did not differ between the two groups.

Table 3 presents the results concerning morbidity and mortality. Operative time was shorter in the pRYGB group (median: 90.00 min [IQR 76.00–109.00] vs. 117.00 min [IQR 96.75–145.50], $p < 0.001$). Fourteen (5.5%) patients in the pRYGB group developed postoperative complications vs. 4 (5.5%) patients in the rRYGB group ($p = 1.000$).

Concerning the resolution of obesity-related comorbidities, 32 of the 59 (54.2%) valid cases (with preoperative comorbidities) submitted to pRYGB and 4/ out of 16 (25.0%) patients who underwent rRYGB had a T2DM resolution ($p = 0.038$) (Table 4). No significant differences were observed regarding the resolution of HTN, dyslipidemia, and OSA.

pSG vs. rSG

The %TWL and %EWL at 6 and 12 months were higher in the pSG group than the rSG group. The BMI at 6 months was not statistically different between the two groups, but we found a statistically lower BMI at 12 months in the pSG group when compared to the rSG group (median: 29.45 [IQR 25.98–33.17] vs. 34.16 [IQR 29.38–36.20], $p = 0.012$). Also, at 12 months, 84.6% of the patients submitted to pSG had BMI $<$ 35 kg/m² vs. 60.0% of the rSG patients ($p = 0.033$). No significant differences were observed on the remaining qualitative criteria.

Operative time was longer in the rSG group (62.5 min [IQR 50.75–83.5] vs. 86.0 [IQR 59.00–129.00]; $p = 0.016$). Postoperative complications developed in 11 (7.6%) patients in the pSG group and 2 (10.0%) patients in the rSG group ($p = 0.660$).

Concerning the outcomes of comorbidities, 24 of the 35 (68.6%) valid cases in the pSG group and 0/8 (0.0%) patients in the rSG group had dyslipidemia resolution. No other significant differences were observed.

rRYGB vs. rSG

We found statistically significant higher %TWL and %EWL and a lower BMI at 6 and 12 months in the rRYGB group when compared to the rSG group. Also, 98.3% of the patients submitted to rRYGB had BMI $<$ 35 kg/m² vs. 60% of the rSG patients ($p < 0.001$). No significant differences were observed on the remaining qualitative criteria, even though results tended to favor rRYGB.

Operative time was longer in the rRYGB group (90.00 [IQR 76.00–109.00] vs. 117.00 [IQR 96.75–145.50]

$p=0.020$). Four (5.5%) patients in the rRYGB group and 2 (10.0%) patients in the rSG group developed postoperative complications ($p=0.606$).

Concerning the resolution of obesity-related comorbidities, 10/24 (41.7%) patients submitted to rRYGB and 0/8 (0.0%) patients who underwent rSG had the resolution of dyslipidemia ($p=0.035$). No significant differences were observed regarding the resolution of HTN, T2DM, and OSA.

Discussion

AGB used to be the most common bariatric surgery performed worldwide due to its technical simplicity and low surgical risk [19]. However, it has been associated with high rates of complications requiring revision [5–7, 20]. According to our findings, weight regain, and insufficient weight loss were the most common indications for revisional bariatric surgery, accounting for more than two-thirds of patients submitted to revisional procedures. Other studies report similar findings—in a systematic review, Magouliotis et al. reported that among patients submitted to rRYGB and rSG, two-thirds had the indication of insufficient weight loss after AGB [20].

The present study demonstrates that both rRYGB and rSG are safe procedures. We did not find any significant difference between either the primary and revisional bariatric surgery groups or between the different revisional groups on the frequency of early complications (even though revisional bariatric interventions are technically more demanding and they are usually associated with higher intraoperative and perioperative risks than primary procedures) [9, 21, 22]. The absence of significant differences concerning postoperative complications can be explained by the surgeons' expertise and

the high number of bariatric procedures performed annually at our center. It is consensual in the literature that the experience of the surgical team, as well as the hospital volume, are associated with better outcomes for bariatric surgical procedures [23]. The ASMBS recommends that these revisional procedures should only be done by experienced bariatric surgeons in health care centers with the resources to manage these challenging patients and to provide early treatment to patients who potentially develop postoperative complications [24].

We have also found an increased operation time in the revisional bariatric procedures, which is reported in several studies [21, 22, 25]. rRYGB took longer than rSG, which is in accordance with several studies [20, 26]. This difference may be explained by the fact SG is a technically easier surgical approach [14].

Regarding the weight loss outcomes, we found significant differences at 6 and 12 months between the primary and revisional groups. Patients submitted to pRYGB lost more weight and displayed a better BMI than those who underwent rRYGB. The literature is almost unanimous stating that pRYGB has better weight loss outcomes than rRYGB [27, 28].

Similar conclusions can be drawn when comparing pSG with rSG. pSG group had better weight loss outcomes than rSG. There is insufficient evidence evaluating weight loss outcomes between pSG and rSG after AGB removal, but a few studies report similar weight loss outcomes after rSG when compared to pSG [29].

There is no consensus concerning the weight loss outcomes comparing both revisional procedures. Performing SG after a failed AGB is often criticized because they are both restrictive bariatric procedures, but many others state that the excision of the gastric fundus may have endocrine effects, reducing the ghrelin levels [8, 19]. Many studies report no

Fig. 2 Indications for revisional surgery

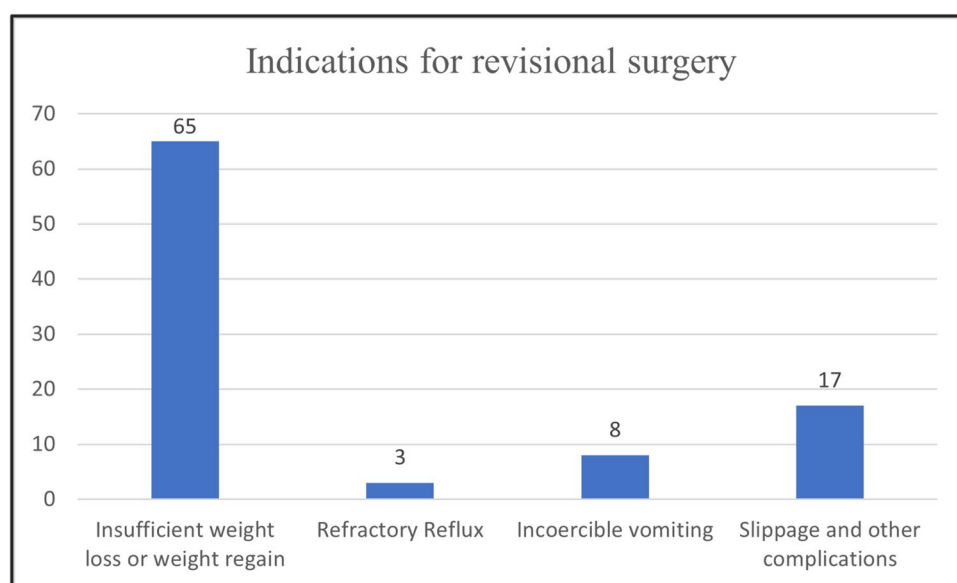


Table 2 Weight loss outcomes

<i>p-value</i>	pRYGB	pSG	rRYGB	rSG	pRYGB vs. rRYGB	pSG vs. rSG	rRYGB vs. rSG
<i>Quantitative parameters</i>							
%EWL at 6 months; median [IQR]	71.69 [IQR 71.40–87.22]	62.56 [IQR 50.69–76.36]	61.12 [IQR 51.99–77.25]	51.21 [IQR 41.93–63.39]	0.004	0.007	0.022
%TWL at 6 months; mean ± SD	28.71 ± 6.09	27.31 ± 6.59	24.80 ± 6.61	21.35 ± 4.74	< 0.001	< 0.001	0.025
BMI at 6 months (kg/m ²); median [IQR]	30.11 [IQR 27.73–32.79]	32.04 [IQR 28.66–35.13]	31.68 [IQR 28.42–34.28]	34.68 [IQR 29.29–38.03]	0.042	0.080	0.035
%EWL at 12 months; median [IQR]	87.50 [IQR 78.08–101.06]	77.16 [IQR 63.80–94.08]	82.64 [IQR 68.01–93.62]	69.01 [IQR 51.20–74.82]	0.040	0.007	< 0.001
%TWL at 12 months; mean ± SD	36.09 ± 7.24	33.55 ± 8.38	32.41 ± 7.33	26.77 ± 6.45	0.001	0.003	0.005
BMI at 12 months (kg/m ²); median [IQR]	27.16 [IQR 24.84–29.20]	29.45 [IQR 25.98–33.17]	28.37 [IQR 25.64–31.15]	34.16 [IQR 29.38–36.20]	0.047	0.012	< 0.001
<i>Qualitative parameters</i>							
BMI < 35 kg/m ² at 12 months; <i>n</i> (%)	209 (97.2%)	88 (84.6%)	59 (98.3%)	9 (60.0%)	1.000	0.033	< 0.001
%EWL > 50% at 12 months; <i>n</i> (%)	211 (98.1%)	96 (92.3%)	56 (93.3%)	12 (80.0%)	0.072	0.143	0.138
%TWL > 20% at 12 months; <i>n</i> (%)	211 (98.1%)	99 (95.2%)	57 (95.0%)	12 (80.0%)	0.178	0.062	0.090

pRYGB, primary Roux-en-Y gastric bypass; pSG, primary sleeve gastrectomy; rRYGB, revisional Roux-en-Y gastric bypass; rSG, revisional sleeve gastrectomy; %EWL, percentage of excess weight loss; %TWL, percentage of total weight loss; BMI, body mass index; bold entries include values of statistically significance

Table 3 Morbidity and mortality

<i>p-value</i>	pRYGB	pSG	rRYGB	rSG	pRYGB vs. rRYGB	pSG vs. rSG	rRYGB vs. rSG
<i>Overall complications</i>							
Early complications; <i>n</i> (%)	14 (5.5%)	11 (7.6%)	4 (5.5%)	2 (10.0%)	1.000	0.660	0.606
Mortality; <i>n</i> (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-
Operative time (minutes); median [IQR]	90.00 [IQR 76.00–109.00]	62.50 [IQR 50.75–83.50]	117.00 [IQR 96.75–145.50]	86.00 [IQR 59.00–129.00]	<0.001	0.016	0.020

pRYGB, primary Roux-en-Y gastric bypass; *pSG*, primary sleeve gastrectomy; *rRYGB*, revisional Roux-en-Y gastric bypass; *rSG*, revisional sleeve gastrectomy; bold entries include values of statistically significance

difference between rRYGB and rSG [26], while other studies conclude that rRYGB has better weight loss outcomes than rSG and is the most appropriate revision procedure if the primary cause for AGB removal was inadequate weight loss [8]. At 6 and 12 months, rRYGB had consistently better weight loss outcomes than rSG. Also, we found that a higher percentage of patients submitted to rRYGB reached BMI < 35 kg/m² compared to those undergoing rSG.

It has been established that revisional bariatric surgery plays a role in the improvement and remission of obesity-related comorbidities [24]. However, whether there are differences in the improvement of comorbidities between procedures is still controversial—most of the studies indicate that pRYGB is associated with higher improvement of comorbidities, [30, 31] but other studies found similar rates between pRYGB and rRYGB regarding obesity-related diseases' resolution [27, 32]. In this study, we found that pRYGB was associated with significantly higher frequency of T2DM resolution, but such was not observed for other comorbidities. Similarly, we observed higher frequency of dyslipidemia resolution with pSG compared to rSG, but no significant differences were observed for other comorbidities. However, these results should be analyzed with caution, given that different indications are used for each procedure.

There is shortage of quality data in the literature comparing revisional procedures concerning resolution of preoperative comorbidities [33]. Although many studies draw recommendations of which revisional surgery is more appropriate based on the primary cause for AGB removal, there are few studies addressing which one is better for the treatment of obesity comorbidities. Our series showed better outcomes regarding the resolution of dyslipidemia in rRYGB patients than those who were submitted to rSG.

The results regarding resolution of obesity-related comorbidities must be interpreted with caution because there is a substantial number of cases missing, since our follow-up period included the COVID-19 pandemic lockdown, with many appointments being done by phone. It was difficult to accurately assess if the patients found the criteria to establish resolution of comorbidities.

Limitations of our work include its retrospective nature. This study was performed in a single institution. Nonetheless, this assures homogeneity in treatment plan, because all patients were evaluated and treated by the same multidisciplinary team. Furthermore, with a short follow-up time, it is difficult to extrapolate long-term outcomes. Also, due to the COVID-19 pandemic, some follow-up consultations were accomplished remotely by telephone. Hence, this study cannot be used to draw conclusions about the long-term expected weight loss or comorbidities' resolution after revisional bariatric surgery without additional longitudinal study.

Table 4 Resolution of comorbidities

<i>p-value</i>							
Obesity-related comorbidity	pRYGB	pSG	rRYGB	rSG	pRYGB vs. rRYGB	pSG vs. rSG	rRYGB vs. rSG
HTN; <i>n/N</i> (%)	37/93 (39.8%)	20/40 (50.0%)	6/28 (21.4%)	1/7 (14.3%)	0.075	0.112	1.000
T2DM; <i>n/N</i> (%)	32/59 (54.2%)	14/21 (66.7%)	4/16 (25.0%)	0/2 (0.0%)	0.038	0.142	1.000
Dyslipidemia; <i>n/N</i> (%)	38/78 (48.7%)	24/35 (68.6%)	10/24 (41.7%)	0/8 (0.0%)	0.545	0.001	0.035
OSA; <i>n/N</i> (%)	16/29 (55.2%)	8/16 (50.0%)	3/6 (50.0%)	0/4 (0.0%)	1.000	0.117	0.200

pRYGB, primary Roux-en-Y gastric bypass; *pSG*, primary sleeve gastrectomy; *rRYGB*, revisional Roux-en-Y gastric bypass; *rSG*, revisional sleeve gastrectomy; *BMI*, body mass index; *HTN*, arterial hypertension; *T2DM*, diabetes mellitus type 2; *OSA*, obstructive sleep apnea, *n*, number of cases who had obesity-related comorbidities' resolution; *N*, number of valid cases; bold entries include values of statistical significance

Conclusion

Revisional bariatric surgery is a safe and effective option to treat obesity and related comorbidities. Our study showed poorer weight loss outcomes of revisional compared to primary RYGB and SG. RYGB was associated with better outcomes compared to SG concerning weight reduction when they are both used as conversion strategies following failed AGB. rSG is less effective than pSG and rRYGB on dyslipidemia's resolution. The choice of the most suitable primary procedure for each patient is of paramount importance. Further clinical studies, with a prospective design and longer follow-up, are necessary to better understand the role of revisional bariatric surgery in the treatment of obesity.

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Author contributions HSS, JN - Data collection; Concept; manuscript writing and revision; Statistical analysis LL; MNC; FAC - Data collection; manuscript revision FR; ACP; JP - Manuscript revision; concept BSP - Manuscript revision SC; ELC - Manuscript revision; concept

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Data Availability All the data supporting the findings of this study are available from the authors upon reasonable request.

Declarations

Ethical approval This study has been approved by the local medical ethics committee (number 46–21); no individual informed consent was necessary.

Competing interests The authors declare no competing interests.

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Management of associated pathology

Gallstone disease

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Risk and Prophylactic Management of Gallstone Disease in Bariatric Surgery: a Systematic Review and A Bayesian meta-analysis

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Abstract

Background The frequency and management of gallstone disease (GD) in bariatric patients, including the role of routine prophylactic concomitant cholecystectomy (CCY), are still a matter of debate. This study aims to assess the risk of de novo GD in patients undergoing bariatric surgery (BS) and their predictive factors, as well as mortality and morbidity in prophylactic CCY compared to BS alone.

Methods We performed a systematic review, searching PubMed, EMBASE, and Web of Science until April 2021. We performed a Bayesian meta-analysis to estimate the risk of GD development after BS and the morbidity and mortality associated with BS alone versus BS + prophylactic CCY. Sources of heterogeneity were explored by meta-regression analysis.

Results The risk of de novo post bariatric GD was 20.7% (95% credible interval [95% CrI] = 13.0–29.7%; $I^2 = 75.4\%$), and that of symptomatic GD was 8.2% ([95% CrI] = 5.9–11.1%; $I^2 = 66.9\%$). Pre-operative average BMI (OR = 1.04; 95% CrI = 0.92–1.17) and female patients' proportion (OR = 1.00; 95% CrI = 0.98–1.04) were not associated with increased risk of symptomatic GD.

BS + prophylactic CCY was associated with a 97% probability of a higher number of postoperative major complications compared to BS alone (OR = 1.74, 95% CrI = 0.97–3.55; $I^2 = 56.5\%$). Mortality was not substantially different between the two approaches (OR = 0.79; 95% CrI = 0.03–3.02; $I^2 = 20.7\%$).

Conclusion The risk of de novo symptomatic GD after BS is not substantially high. Although mortality is similar between groups, odds of major postoperative complications were higher in patients submitted to BS + prophylactic CCY. It is still arguable if prophylactic CCY is a fitting approach for patients with a preoperative lithiasic gallbladder.

Keywords Bariatric surgery · Symptomatic gallstone disease · Prophylactic cholecystectomy, Bayesian meta-analysis

Authors Filipe Amorim-Cruz and Hugo Santos-Sousa contributed equally and should be considered the first authors.

Key points

- The risk of symptomatic GD after BS is not substantially high.
- Gallstone disease predictive factors after BS are not like those of the general population.
- Prophylactic cholecystectomy would have higher postoperative complications.

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Introduction

Bariatric surgery (BS) has been identified as the most effective treatment for clinically severe obesity, resulting in sustained weight loss and significant improvement in obesity-related comorbidities.¹ Despite its benefits, BS is associated with a 3–28% incidence of symptomatic gallstone disease (GD),² which is five times higher than the healthy population³.

Understanding the risk factors associated with GD development may be crucial for risk stratification and distinct patient management, especially since GD risk factors in the general population may not be predictive in patients submitted to BS.^{4, 5, 6}

The varying incidence of symptomatic GD after BS has resulted in controversies regarding whether prophylactic

concomitant cholecystectomy (CCY) should be performed. Currently, there are three approaches on this subject: (i) routine prophylactic cholecystectomy concomitant to BS for all patients (BS + prophylactic CCY), (ii) a selective prophylactic CCY only for those with positive findings on pre-operative ultrasound, and (iii) medical prophylactic treatment with urso-deoxycholic acid (UDCA).^{4,7,8} There may be some arguments in favor or against each of these options—for example, CCY could avoid stone-related complications, including further hospitalization and surgery; however, it is a technically challenging procedure. On the other hand, cholecystectomy after BS, for symptomatic GD, is also a procedure associated with technical difficulties.^{9,10} Despite these controversies, evidence on all of these options has not been systematically assessed.

In this systematic review and meta-analysis, we aimed to (objective i) quantify the risk of de novo asymptomatic or symptomatic GD after BS, (objective ii) identify predictive factors associated with de novo GD after BS, and (objective iii) compare the morbidity and mortality of BS alone versus BS + prophylactic CCY.

Material and Methods

This systematic review with meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines and the recommendations of the Cochrane Handbook for Systematic Reviews.^{11,12}

Eligibility Criteria

We included observational studies assessing BS as an obesity treatment for patients with a BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with weight-related comorbidities. For objectives i and ii (risk of de novo post-bariatric GD and its predictive factors), the outcome to be reported was GD development. It was defined as de novo episodes of symptomatic biliary colic, acute cholecystitis, choledocholithiasis, cholangitis, and acute pancreatitis, or de novo asymptomatic evidence of cholelithiasis on post-operative ultrasound. For objective iii (comparison of the morbidity and mortality of BS alone versus BS + prophylactic CCY), any of the following outcomes needed to be reported: postoperative mortality, duration of surgery, hospital length-of-stay (LOS), and major postoperative complications. BS + prophylactic CCY was defined as cholecystectomy concomitant to bariatric surgery for asymptomatic patients (with no or asymptomatic gallstones confirmed by preoperative ultrasound), who had not been submitted to a previous cholecystectomy.

More detailed inclusion and exclusion criteria, for each specific objective, are shown in Supplementary Table 1.

Search Strategy

We searched three electronic databases (PubMed, EMBASE, and Web of Science) from inception until April 6, 2021 (when our search was performed). Search queries are detailed in Supplementary Table 2. This search was supplemented by a gray literature search (conference papers, clinical trials—ongoing or unpublished), as well as hand-searching references of primary studies and other relevant reviews that were included. No restrictions were set regarding language or publication year.

Study Selection and Data Collection Process

After removing duplicates, each study was independently assessed by two reviewers (F.C and M.R.), first by title and abstract screening and then by full-text reading.

Two reviewers independently extracted data from selected studies using a predefined form purposely built for this systematic review. For each primary study, the following information was retrieved: authors' identification, year of publication, country, study design, number of enrolled patients, type of performed BS, follow-up period, patients' characteristics (distributions of gender, age, and pre-operative and post-operative body mass index (BMI)), frequency of co-morbidities, weight loss after surgery, and preoperative gallbladder status. The latter was classified as alithiasic or lithiasic gallbladder confirmed by ultrasonography. An alithiasic gallbladder was defined as a preoperative gallbladder without gallstones or sludge, and a lithiasic gallbladder was defined as a preoperative asymptomatic gallbladder with gallstones or sludge without being submitted to CCY.

For objectives i and ii (risk of de novo post-bariatric GD and its predictive factors), we also retrieved information on the number of patients: (i) at risk of GD, (ii) at risk of symptomatic GD only (with information retrieved also for the time to symptoms), (iii) who developed GD, (iv) who developed symptomatic GD only, (v) who developed each GD presentation (such as biliary colic, acute cholecystitis, choledocholithiasis, cholangitis, and acute pancreatitis), and (vi) undergoing postoperative cholecystectomy. Both patients with no symptoms of cholelithiasis and either preoperative negative gallstone findings or preoperative positive gallstone findings were at risk of de novo symptomatic GD. In contrast, only patients with preoperative negative gallstone findings and primarily asymptomatic were considered at risk for de novo asymptomatic GD. Whenever provided, we retrieved data separately based on preoperative gallbladder status. Data related to other biliary conditions, such as gallbladder carcinoma or polyps, were not retrieved.

For objective iii (comparison between BS alone versus BS + prophylactic CCY), the additional following

information was concerned: (i) number of patients submitted to BS alone and BS + prophylactic CCY; (ii) reason for prophylactic CCY; (iii) surgery duration; (iv) LOS; (v) major postoperative complications (medical complications—cardiac arrest requiring cardiopulmonary resuscitation (CPR), respiratory failure, pneumonia, sepsis, venous thromboembolism, acute renal failure, and bleeding requiring transfusion; surgical complications—anastomotic leakage, organ space surgical site infection, the conversion rate of laparoscopic surgery, number of reoperations, and hospital readmission within 30 days); and (vii) postoperative mortality.

If distinct eligible publications reported data on the same patient cohort, the more recent and largest cohort was included. Authors were contacted whenever full texts were not available or to provide the relevant missing information. In study selection or data extraction, any disagreements between reviewers were resolved by consulting a third senior reviewer (H.S.S) to reach a final decision.

Quality Assessment

The quality of primary studies was independently assessed by two reviewers (F.C and M.R) using the National Institutes of Health quality assessment criteria for observational studies.¹³ To reach a consensus, divergent opinions regarding quality assessment were discussed with a third reviewer (H.S.S). This tool consists of a form with 14 yes-or-no questions (related to the research question, study population, exposure, outcome, blinding, follow-up, and statistical analysis) and a final quality rating (good, fair, or poor), classifying the study according to its potential risk of bias.¹³ The question about assessors being blinded regarding the exposure status was not possible to assess in any of the included studies.

Synthesis of Results

Given the inclusion of a large number of studies with no occurrence of events, we opted in performing a meta-analysis according to a Bayesian approach following a random-effects model based on a binomial likelihood.¹⁴ Compared to frequentist (“classical”) approaches, Bayesian meta-analysis deals more adequately with proportions equal to zero.

Bayesian methods provide estimations of posterior probability distributions of the parameters of interest, based on prior probability distributions and the observed data. In this study, for the risk of de novo post-bariatric GD, we computed the meta-analytical risk of GD and of symptomatic GD only. To compare outcomes between patients submitted to BS alone as index events versus those submitted to BS + prophylactic CCY, we computed meta-analytical odds ratio (OR) or mean differences (MD) depending on whether outcome variables were categorical or continuous,

respectively. Of these results, we collected information on the mean values and respective 95% credible intervals (95% CrI; a range of values within which the true effect size measure lies, with a 95% probability).

Comparison between concomitant CCY and postoperative cholecystectomy was not quantitatively synthesized, due to the low number of available studies and substantial missing information.

Heterogeneity was assessed through an estimate of the I^2 statistic—an $I^2 > 50\%$ indicated substantial heterogeneity. Heterogeneity sources were explored through univariable meta-regression and subgroup analyses; – in particular, meta-regression allowed for the identification of potential predictive factors for the risk of de novo bariatric GD. Exponentials of the meta-regression coefficients were interpreted as OR. Finally, we also performed a separate meta-analysis for the development of symptomatic GD among patients with preoperative lithiasic versus alithiasic gallbladder.

For both the effect size measure and the τ parameter, we used uninformative prior distributions (dnorm (0, 0.00001) and dgamma (0.00001, 0.00001), respectively). We ran at least 40,000 iterations for each analysis with a burn-in of 15,000 sample iterations. Meta-analysis was performed using the rjags package of software R (version 3.5.0).

Results

Study Selection

The electronic literature search resulted in 5082 articles, of which 1808 were duplicates. After excluding 3184 records in the screening phase, 90 articles were fully read, of which a total of 42 were included in the systematic review (Fig. 1).^{5,7,15–43,45–55} Hand-searching resulted in 23 additional articles, of which 8 were included.^{56–64} Ten authors were asked for additional information, as outcomes of interest were missing. Seven did not answer, and their studies were excluded from objectives i and ii. In total, 50 articles were included—39 for answering objectives i and ii (assessment of the risk of de novo symptomatic or asymptomatic GD and its predictive factors)^{5,7,15,17–24,26–37,39–46,48,49,51,52,55,56,58,62} and 14 for objective iii (comparing BS alone versus BS + prophylactic CCY).^{16,25,38,47,50–54,59–62,64}

Study Characteristics

A summary of included studies is presented in Tables 1, 2, and 3. The remaining characteristics are reported in Supplementary Table 3.1–3.4.

For objectives i and ii, included studies were published between 2004 and 2019, with a cumulative sample size of

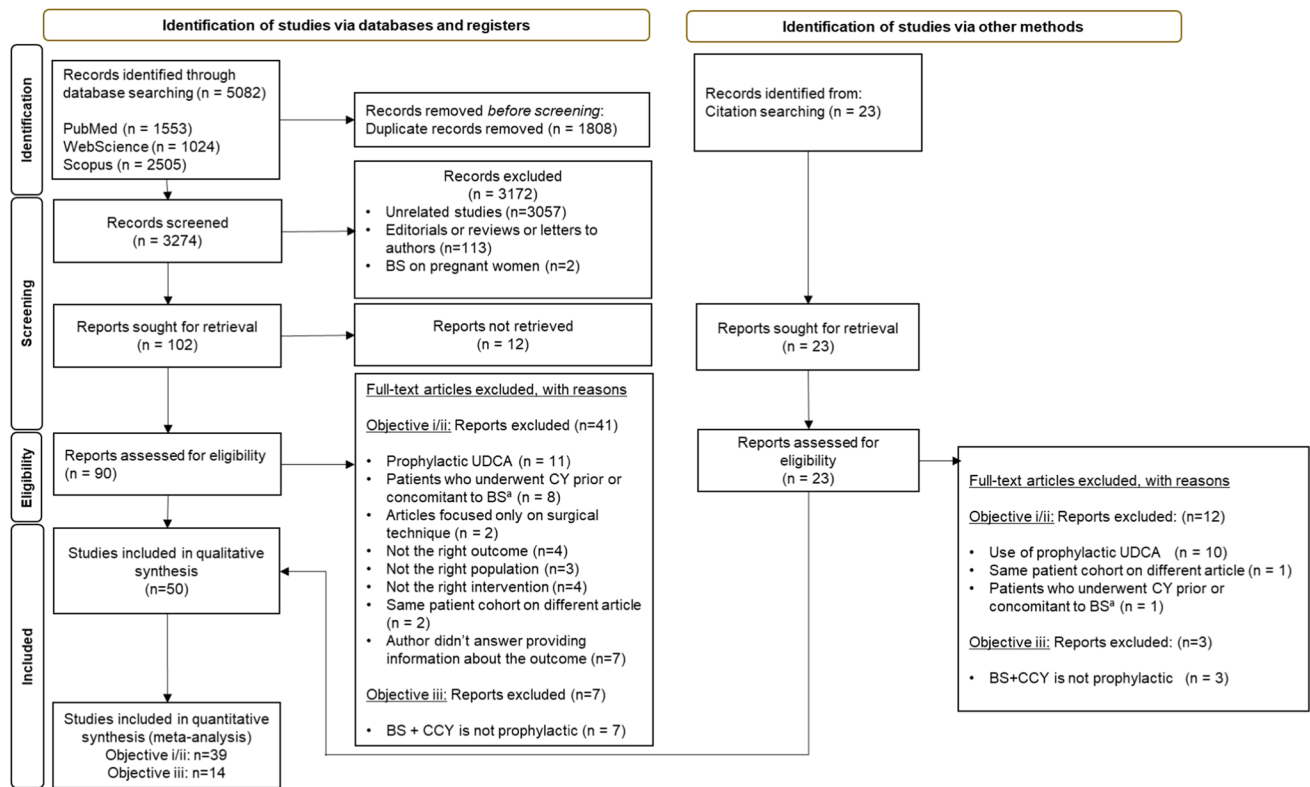


Fig. 1 Flow diagram of study selection. BS, bariatric surgery; UDCA, Ursodeoxycholic acid; BS + CCY, prophylactic cholecystectomy concomitant to bariatric surgery; CY, cholecystectomy. ^aThis exclusion criteria is not applicable if patients with gallbladder in situ were individually reported. Objective i/ii—risk of de novo asymptomatic or symptomatic GD after BS and its predictive factors; objective

iii—comparison of morbidity and mortality of BS alone versus BS + prophylactic CCY. 3 studies (Kim et al.; Tucker et al.; Wanjura et al.) were used for 3 study objectives

64,950 patients. Most were retrospective cohort studies (n = 24, 61.5%). The mean participants' age was 40.9 years (SD = 9.3 years) with a female predominance (74.0%). Laparoscopic Roux-en-Y gastric bypass (LRYGBP) was the most-performed BS type (13 studies, n = 46, 313, 71.3%). The mean follow-up period was of 29.0 months.

For objective iii, included studies were published between 1995 and 2006, with a cumulative sample size of 685,994 patients. Open Roux-en-Y gastric bypass (RYGBP) was the most-performed BS type (5 studies, n = 653, 405, 95.2%). Among patients undergoing prophylactic CCY (n = 26, 461, 4%), 44% had negative findings for GD in pre-operative ultrasonography.

Risk of Developing De Novo Gallstone Disease

A total of 38,210 asymptomatic patients with only pre-operative negative GD findings were at risk of de novo postoperative GD. The Bayesian meta-analysis identified a post-bariatric risk of de novo GD of 20.7% (95% credible interval [95% CrI] = 13.0–29.7%), even though with severe heterogeneity ($I^2 = 75.4\%$). A higher BMI was associated,

– with a 96% probability, – with higher odds of de novo GD ($OR = 1.11$; 95% CrI = 0.99–1.22). Other results of univariable meta-regression are presented in Supplementary Table 4.

A total of 63,938 asymptomatic patients with either pre-operative negative or positive gallstone findings were at risk of de novo symptomatic GD. A total of 3312 developed symptomatic GD, corresponding to a meta-analytical risk of 8.2% (95% CrI = 5.9–11.1%), even though with high heterogeneity ($I^2 = 66.9\%$, Table 4). The three most common clinical presentations were biliary colic (n = 1559, 65.5%), cholecystitis (n = 120, 14.7%), and symptomatic cholelithiasis (n = 37, 4.5%) (Supplementary Table 3.1). Almost all patients required postoperative cholecystectomy (n = 3,179, 96%). The results of univariable meta-regression and subgroup analyses are presented in Table 4. Regarding studies' methodological characteristics, retrospective studies were associated, – with a 94% probability, – with lower odds of de novo symptomatic GD ($OR = 0.60$; 95% CrI = 0.31–1.10).

Pre-operative average BMI ($OR = 1.04$; 95% CrI = 0.92–1.17) and female patients' proportion ($OR = 1.00$;

Table 1 Studies general characteristics

Study	Year publication	Country	Study Design	BS	Preoperative gallbladder status		Quality rating ^a	
					Alithiasic gallbladder (N)	Lithiasic gallbladder (N)	G/F/P	Y/N
Abu Abeid Subhi	2002	Israel	PS	LAGB	134	0	P	7/5
Ahmed AR	2007	USA	RS	LRYGBP	400	0	G	8/4
Aldriweesh MA	2020	Saudi Arabia	RS	LSG (434) LAGB (56)	490	0	G	11/2
Alimogullari M	2020	Turkey	RS	LSG	111	0	G	10/3
Alsaif FA	2020	Saudi Arabia	RS	LSG	711	0	G	10/3
Amstutz S	2015	Switzerland	RS	LRYGBP	64	26	F	9/4
Anveden A	2020	Sweden	PS	OpenRYGBP (236) LAGB (1 519)	NR	NR	G	12/1
Aridi HD	2016	Lebanon	PS	LSG	NR	NR	G	13/0
Bastouly M	2009	Brazil	PS	Open RYGBP	20	0	P	7/4
Brockmeyer JR	2015	USA	RS	Open RYGBP (1 366) LSG (161)	1 111	1	F	7/6
Caruana JA	2005	USA	PS	RYGBP	401	98	F	10/3
Chen JH	2019	Taiwan	RS	Open RYGBP (1 155) LSG (1 156)	NR	NR	G	9/4
Coskun H	2014	Turkey	RS	LSG	32	16	F	9/3
Coupaye M	2015	France	PS	Open RYGBP (117) LSG (43)	160	0	G	11/2
Dakour Aridi HN	2017	Lebanon	RS	LSG	21 137	0	G	11/1
Dhondt M	2011	Belgium	PS	LRYGBP	521	104	G	12/1
de Oliveira CLB	2003	Brazil	RS	Open RYGBP	69	0	F	8/4
Dorman RB	2013	USA	RS	Open RYGBP (4 298) LRYGBP (28 648)	32 946	0	G	11/2
ElHadidi A	2019	Egypt	PS	LSG	755	95	G	11/2
Guzman HM	2019	Chile	RS	Open RYGBP (32) LSG (85) LAGB (59)	176	0	F	9/4
Hasan MY	2017	Singapore	RS	LSG	87	15	F	9/3
Juo YY	2018	USA	RS	Open RYGBP (300 919) LSG (205 315) LAGB (47 406)	536 904	16 755	G	12/1
Karadeniz M	2014	Turkey	RS	LRYGBP	46	0	F	8/4
Kim JJ	2009	USA	RS	Open RYGBP (264) LRYGBP (488)	273	298	G	10/3
Kiewiet RM	2006	Netherlands	RS	LAGB	103	0	G	9/3
Kızılkaya MC	2021	Turkey	RS	LSG	185	0	G	9/4
Lasnibat RJP	2017	Chile	RS	Open RYGBP (107) LAGB (114)	151	0	F	8/5
Li VKM	2009	USA	RS	LRYGBP (496) LSG (52)	548	0	F	10/3
Manatsathit W	2016	USA	RS	LSG	96	0	G	9/3
Melmer A	2015	Austria	PS	LSG (15) LAGB (94)	79	6	G	10/2
Moon RC	2014	USA	RS	LRYGBP (367) LSG (115) LAGB (104)	586	0	G	11/3
Morais M	2016	Portugal	RS	NR	581	72	G	12/1
Nagem R	2012	Brazil	PS	Open RYGBP	38	0	G	9/2
Nougou A	2008	Switzerland	RS	LRYGBP	632	82	F	8/4
OBrien PE	2003	Australia	PS	LAGB	809	0	F	7/5
Ostlund P	2012	Sweden	PS	LRYGBP (6 549) LAGB (6 894)	NR	NR	G	9/3
Santos BF	2014	USA	PS	Open RYGBP	32 041	1 034	F	8/1
Scott DJ	2003	USA	PS	LRYGBP	129	21	F	8/4
Sucandy I	2016	USA	RS	BPDwDS	239	63	F	10/3
Papavramidis S	2003	Greece	PS	NR	84	0	F	9/3

Table 1 (continued)

Study	Year publication	Country	Study Design	BS	Preoperative gallbladder status		Quality rating ^a	
					Alithiasic gallbladder (N)	Lithiasic gallbladder (N)	G/F/P	Y/N
Patel JA	2009	USA	RS	LRYGBP	NR	NR	F	10/3
Patel KR	2009	USA	PS	LRYGBP	NR	NR	G	10/3
Pineda O	2017	Mexico	PS	NR	97	49	G	10/3
Portenier DD	2007	England	RS	LRYGBP	406	110	F	9/2
Sakcak I	2011	Turkey	PS	LAGB	137	0	F	10/3
Sioka E	2014	Greece	RS	LSG	106	32	G	11/2
Taha MIA	2006	Brazil	RS	LRYGBP	103	0	G	11/2
Tarantino I	2011	Switzerland	RS	LRYGBP	140	0	G	10/2
Tucker ON	2008	USA	RS	LRYGBP	1 462	82	F	7/5
Wanjura V	2018	Sweden	RS	LRYGBP	33 573	152	G	11/2
Wood SG	2019	USA	RS	LSG	4 048	0	G	11/2
Wood SG	2019	USA	RS	LRYGBP	2 820	0	G	11/2
Zilberstein B	2004	Brazil	PS	LAGB	263	17	F	8/4

RS, retrospective study; PS, prospective study; BS, bariatric surgery; *OpenRYGBP*, laparotomy Roux-en-Y gastric bypass; *LRYGBP*, laparoscopic Roux-en-Y gastric bypass; *LAGB*, laparoscopic adjustable gastric banding; *LSG*, laparoscopic sleeve gastrectomy; *BPDwDS*, biliopancreatic diversion with duodenal switch; NR, not reported

^aNIH (National Institutes of Health) quality assessment criteria for observational studies—it is based on a quality rating of G (good), F (fair), and P (poor), and 14 questions of yes/no/not applicable/not reported/cannot determine. Y/N is the ratio of questions with positive answers (Y=yes) and negative answers (N=no)

Alithiasic gallbladder: a preoperative gallbladder without gallstones or sludge, confirmed by ultrasonography

Lithiasic gallbladder: a preoperative asymptomatic gallbladder with gallstones or sludge confirmed by ultrasonography, without being submitted to concomitant cholecystectomy

In included studies, Wood et al. provided separate data of laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y Gastric Bypass (LRYGBP) with concomitant cholecystectomy (CCY), so we included these data as two individual studies

95% CrI = 0.98–1.04) did not impact the risk of de novo symptomatic GD. Although none of the assessed bariatric surgery types had a strong impact on GD risk, laparoscopic gastric banding (LAGB) was associated, – with an 82% probability,—with lower odds of de novo symptomatic GD. Insufficient data on co-morbidities and weight loss after surgery did not allow meta-regression analysis models to include these variables.

Comparison between bariatric surgery alone versus prophylactic cholecystectomy concomitant to bariatric surgery

Bayesian meta-analysis identified that postoperative mortality was not substantially different between BS alone versus BS + prophylactic CCY ($OR = 0.79$; 95% CrI = 0.03–3.02; $I^2 = 20.7\%$). BS + prophylactic CCY was associated with 97% probability of a higher number of postoperative major complications compared to BS alone ($OR = 1.74$, 95% CrI = 0.97–3.55; $I^2 = 56.5\%$). The odds of organ space surgical site infection were similar between groups ($OR = 0.97$, 95% CrI = 0.05–4.71; $I^2 = 52.8\%$) (Table 5). Insufficient

data on some complications, namely the conversion rate of laparoscopic surgery and hospital readmissions within 30 days did not allow such outcomes to be analyzed through meta-analysis.

Univariable meta-regression results are presented in Table 6. Neither age ($OR = 1.22$, 95% CrI = 0.87–1.68) nor female patients' proportion ($OR = 0.95$, 95% CrI = 0.87–1.04) were associated with a relevant impact on the association between BS alone versus BS + prophylactic CCY on the occurrence of postoperative major complications. Although any type of bariatric surgery had no strong impact on postoperative major complications, they slightly changed through bariatric procedures—laparoscopic gastric banding (LAGB) was the one associated with lower chances (87%) of postoperative major complications between BS + prophylactic CCY versus BS alone ($OR = 0.42$, 95% CrI = 0.04–1.97). Moreover, prophylactic cholecystectomy concomitant to laparoscopic sleeve gastrectomy (LSG), compared to prophylactic cholecystectomy concomitant laparoscopic Roux-en-Y gastric bypass (LRYGBP) ($OR = 0.66$, 95% CrI = 0.16–2.59 versus $OR = 2.33$, 95% CrI = 0.28–10.27), had a tendentially lower

Table 2 Studies' Clinical Characteristics for risk of de novo post-bariatric gallstone disease and its predictive factors

Study	Patients (N)	Age (mean $\pm$ SD, years)	Female (%)	Preoperative BMI (mean $\pm$ SD, kg/m ²)	Follow-up (mon)	Asymptomatic + symptomatic de novo GD	Patients at risk (N)	Patients with GD (N)	Symptomatic de novo GD	Patients at risk (N)	Patients with GD (N)	Time to event (mon)	PosCY (N)
Abu Abeid Subhi	134	38.0	87.3	43.6	9.0	134	10	10	134	10	10	8.0	NR
Aldriweesh MA	490	36.8 $\pm$ 11.4	61.4	46.2 $\pm$ 6.9	27.0	490	32	32	490	32	32	48.0	NR
Alimogullari M	111	38.9	81.1	45.9 $\pm$ 6.1	20.6	111	41	41	111	41	41	13.8	41
Alsaif FA	711	34.6 $\pm$ 12.0	57.8	45.0 $\pm$ 10.3	12.0	NR	NR	NR	711	25	25	12.4	NR
Amstutz S	64	NR	73.4	43.8	44.0	64	33	33	64	22	22	25.43	16
Anveden A	1 755	47.2 $\pm$ 5.9	32.0	42.4 $\pm$ 4.5	254.4	NR	NR	NR	1755	307	307	NR	230
Aridi HD	319	30.2 $\pm$ 7.4	61.4	42.9 $\pm$ 7.1	24.0	NR	NR	NR	319	24	24	14.0	24
Bastouly M	20	39.3	80.0	46.1 $\pm$ 5.2	35.0	20	13	13	20	6	6	6.0	0
Brockmeyer JR	1 527	44.6	NR	47.7	140.0	NR	NR	NR	1111	91	91	20.4	91
Chen JH	2 317	32.8 $\pm$ 8.6	57.4	NR	71.4	NR	NR	NR	2317	67	67	33.89	NR
Coupaye M	160	41.7 $\pm$ 11.1	90.6	44.9 $\pm$ 6.0	24.0	160	52	52	160	20	20	14.96	23
de Oliveira CLB	103	39.0	NR	54.1	12.0	36	19	19	36	19	19	12.0	NR
Dhonit M	625	38.1	69.0	41.5	51.0	521	34	34	625	43	43	17.4	39
ElHadidi A	850	35.3 $\pm$ 7.7	70.8	39.5 $\pm$ 1.0	19.83	755	218	218	850	235	235	11.67	NR
Guzman HM	176	37.8 $\pm$ 10.5	54.5	37.5	12.0	176	65	65	176	NR	NR	NR	NR
Hasan MY	102	43.0	58.8	41.7 $\pm$ 6.5	28.4	NR	24	24	101	1	1	NR	1
Karadeniz M	46	39.1 $\pm$ 10.0	89.1	47.8 $\pm$ 7.0	28.6	46	10	10	46	6	6	18.0	5
Kim, Jin-Jo	454	42.6 $\pm$ 9.3	NR	54.2 $\pm$ 10.4	30.6	273	9	9	273	9	9	14.7	NR
Kiewiet RM	103	42.3 $\pm$ 9.1	90.3	44.2 $\pm$ 5.6	56.1	103	31	31	103	7	7	37.0	7
Kizilkaya MC	185	36.4 $\pm$ 9.5	81.6	44.2 $\pm$ 5.0	6.0	185	27	27	185	3	3	NR	NR
Lasnibat RJP	221	44.9	NR	39.7 $\pm$ 39.7	12.0	141	6	6	141	1	1	0.0	6
Li VKM	548	42.7 $\pm$ 74.8	74.8	48.0	26.1	NR	NR	NR	548	45	45	10.11	NR
Manatsathit W	96	44.5 $\pm$ 12.0	79.2	49.1 $\pm$ 7.9	14.3	96	48	48	96	22	22	353.17	17
Melmer A	109	55.3 $\pm$ 10.5	NR	NR	125.5	79	19	19	79	12	12	21.6	12
Moon RC	586	43.4 $\pm$ 11.7	76.1	45.9 $\pm$ 7.2	14.9	NR	NR	NR	586	28	28	12.64	28
Morais M	653	42.0 $\pm$ 10.6	85.0	44.8 $\pm$ 5.4	26.0	NR	NR	NR	653	24	24	16.5	9
Nagem R	38	41.7	89.5	48.1	36.0	38	11	11	38	6	6	NR	11
O'Brien PE	809	NR	NR	NR	42.0	NR	NR	NR	809	55	55	NR	55
Ostlund M	13 443	40.0	74.4	NR	88.1	NR	NR	NR	13,443	722	722	15.0	1,149
Papavramidis S	84	33.7 $\pm$ 9.2	61.9	52.6 $\pm$ 10.0	24.0	NR	NR	NR	84	34	34	16.0	34
Patel JA	1 050	43.4	75.2	49.3	32.3	NR	NR	NR	1050	52	52	10.9	52
Patel KR	199	43.0	85.9	50.1	14.7	NR	NR	NR	199	12	12	9.5	12
Pineda O	146	38.5	80.8	NR	24.0	97	31	31	146	5	5	NR	5
Portenier DD	1 057	NR	NR	49.0	30.0	903	66	66	984	80	80	11.2	80
Sakcak I	137	29.6 $\pm$ 6.1	78.8	46.8 $\pm$ 6.6	23.8	NR	NR	NR	137	7	7	7.4	7
Sioka E	150	NR	NR	46.1	26.0	106	8	8	138	8	8	NR	7
Taha MIA	103	NR	82.5	48.6 $\pm$ 7.2	12.0	103	48	48	103	22	22	6.2	NR

Table 2 (continued)

Tucker ON	1 544	NR	NR	NR	30.5	NR	NR	1544	85
Wanjura V	33 725	40.7 ± 11.0	78.3	42.5 ± 5.4	24.0	33,573	1133	33,573	1,133

BMI, body index mass (kg/m²); *GD*, gallstone disease; *PosCY*, postoperativecholecystectomy; *SD*, standard deviation; *mon*, months; *NR*, not reported

probability of postoperative major complications. Regarding Roux-en-Y gastric bypass, comparing open and laparoscopic approaches, the probability of postoperative major complications was not too dissimilar ($OR = 1.64$, 95% CrI = 0.33–4.80 versus $OR = 2.33$, 95% CrI = 0.28–10.27).

Patients submitted to BS + prophylactic CCY had a longer operative time—more than 29.2 min (95% CrI = 17.9–40.7), even though there was severe heterogeneity found ($I^2 = 89.3\%$). There were no relevant differences in hospital LOS (MD = −0.1 days; 95% CrI = −1.0–0.5; $I^2 = 74.3\%$) (Table 5).

Risk of Bias of Individual Studies

The results of the risk of bias assessments for included primary studies are presented in Table 1, and a detailed description is reported in Supplementary Table 5.1 and Table 5.2. Most studies ($n = 47$, 94%) did not justify the sample size, and 39 studies (78%) did not adjust for any potential confounding variables. For the remaining parameters, most studies were associated with a low risk of bias. Bastouly et al.⁵⁶ were considered to have a high risk of bias, namely selection bias since patients were selectively invited.

In fact, when considering only high-quality studies, the risk of symptomatic GD is of 7.5% (95% CrI = 5.2–10.6%; $I^2 = 59.1\%$). Such a trend was not observed for asymptomatic or symptomatic GD. Having a high risk of bias was also related,—with 93% probability,—with a weak association between BS alone versus BS + prophylactic CCY on the occurrence of postoperative major complications (OR 0.49; 95% CrI = 0.16–1.27).

Discussion

The main findings of our study were the following: (1) the risk of developing de novo symptomatic gallstone disease after BS is not substantially high (8.2%), although three times higher than the healthy population; (2) GD predictive factors after BS are not similar to those of the general population, except for preoperative average of BMI in asymptomatic or symptomatic GD; and (3) patients who underwent prophylactic CCY had a longer operative time and a higher rate of postoperative complications than those who underwent BS alone, but mortality and hospital LOS were similar.

Some of the pathogenic mechanisms that can explain why patients after BS are at risk of developing GD include an increased biliary cholesterol concentration following rapid weight loss, gallbladder hypomotility secondary to vagal nerve resection and a decreased cholecystokinin secretion, an increased secretion of calcium and biliary mucin, and a disturbed enterohepatic circulation of biliary salts.^{5,6,37,65} Our meta-analysis showed that the risk of developing symptomatic GD is 8.2%, in a mean follow-up of 29.0 months. Warschkow et al.⁸ reported a similar percentage (6.8%),

Table 3 Studies' clinical characteristics for comparison of the morbidity and mortality of bariatric surgery alone versus prophylactic cholecystectomy concomitant to bariatric surgery

Study	Patients (N)	Age (mean $\pm$ SD, years)	Female (%)	Preop- erative BMI (mean $\pm$ SD, kg/m ²)	Follow-up (days)	BS + CCY (N)	BS alone (N)	Reason for BS + CCY	
								US – (N)	US + (N)
Ahmed AR	400	43.0 $\pm$ 18.5	84.8	NR	30	200	200	200	0
Coskun H	48	35.5 $\pm$ 10.7	72.9	51.0 $\pm$ 5.47	3	16	32	0	16
Dakour-Aridi HN	21 137	44.8 $\pm$ 11.3	78.2	46.3 $\pm$ 8.1	30	422	20,715	422	0
Dorman RB	32 946	NR	79.3	NR	30	1731	31,215	1731	0
Juo, Yen-Yi	553 659	NR	78.1	NR	182	18,268	535,391	5 261	13,007
Kim, Jin-Jo	752	42.6 $\pm$ 9.3	79.8	54.2 $\pm$ 10.4	949	298	273	0	298
Nougou A	772	39.8	75.9	45.6	NR	655	59	576	79
Santos BF	33 075	44.0 $\pm$ 11.0	NR	47.0 $\pm$ 8.0	3	1034	32,041	0	1034
Sucandy I	361	44.8 $\pm$ 10.1	73.1	50.5 $\pm$ 20.9	961	63	239	0	63
Tarantino I	274	41.8 $\pm$ 27.2	73.7	46.9 $\pm$ 6.1	986	134	140	34	100
Tucker ON	1 669	NR	NR	NR	946	123	1464	0	122
Wanjura V	33 725	40.7 $\pm$ 11.0	78.3	42.5 $\pm$ 5.4	730	67	33,573	0	67
Wood SG	4 048	45.3 $\pm$ 12.0	84.7	44.9 $\pm$ 8.1	30	2 024	2024	2024	0
Wood SG	2 820	45.6 $\pm$ 11.9	80.2	46.3 $\pm$ 8.7	30	1410	1410	1410	0
Zilberstein B	308	36.4 $\pm$ 23.6	72.4	41.6	558	17	290	0	17
Study	Operative time (mean $\pm$ SD, minutes)			Hospital of stay (mean $\pm$ SD, days)		Postoperative complications		Postoperative mortal- ity (N)	
	BS + CCY	BS alone	Difference	BS + CCY	BS alone	Total N (%)		BS + CCY	BS alone
						BS + CCY	BS alone		
Ahmed AR	125.0 $\pm$ 28.0	96.0 $\pm$ 23.0	29.0	2.0 $\pm$ 0.2	2.0 $\pm$ 0.3	17 (8.5)	17 (8.5)	0	0
Coskun H	157.2 $\pm$ 40.0	95.7 $\pm$ 26.2	61.5	3.6 $\pm$ 0.9	3.4 $\pm$ 0.8	2 (6.3)	3 (18.8)	0	0
Dakour-Aridi HN	128.2 $\pm$ 53.9	95.3 $\pm$ 47.3	32.9	2.1 $\pm$ 6.0	2.3 $\pm$ 4.4	24 (5.7)	820 (4.0)	19	1
Dorman RB	NR	NR	NR	NR	NR	114 (6.6)	1 528 (5.0)	60	6
Juo, Yen-Yi	NR	NR	NR	2 $\pm$ 1	2.0 $\pm$ 1.0	1 115 (6.2)	20 345 (3.8)	NR	NR
Kim, Jin-Jo	198.4 $\pm$ 61.9	177.7 $\pm$ 57.7	20.7	3.3 $\pm$ 5.5	2.9 $\pm$ 6.1	NR	NR	5	3
Nougou A	142.6	158.5	– 15.6	4.0	4.0	1 (0.002)	0	NR	NR
Santos BF	NR	NR	NR	2.6	2.5	60 (5.8)	1615 (5.0)	51	3
Sucandy I	302.8 $\pm$ 62.8	290.8 $\pm$ 67.8	12.0	3.0	3.5	NR	NR	0	0
Tarantino I	220.7 $\pm$ 58.4	234.8 $\pm$ 70.7	– 14.1	7.3 $\pm$ 4.7	10.8 $\pm$ 6.0	NR	NR	NR	NR
Tucker ON	NR	NR	NR	2.8	2.6	4 (3.2)	0	0	0
Wanjura V	145.0 $\pm$ 53.0	74.2 $\pm$ 36.3	70.8	NR	NR	26 (38.8)	2 865 (8.5)	NR	NR
Wood SG	103.7 $\pm$ 46.2	76.7 $\pm$ 40.6	27.0	1.9 $\pm$ 1.8	1.8 $\pm$ 3.0	69 (3.4)	51 (2.5)	2	0
Wood SG	149.6 $\pm$ 60.8	121.9 $\pm$ 59.8	27.7	2.4 $\pm$ 3.3	2.2 $\pm$ 2.7	100 (7.1)	84 (6.0)	2	0
Zilberstein B	86.0 $\pm$ 17.0	58.0 $\pm$ 19.0	28.0	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1	0	14 (4.8)	0	0

BMI, body mass index (kg/m²); *SD*, standard deviation; *US* –, preoperative negative ultrasonography findings for gallstone disease; *US* +, preoperative positive ultrasonography findings for gallstone disease; *BS*, bariatric surgery; *BS* + *CCY*, prophylactic cholecystectomy concomitant to bariatric surgery; *NR*, not reported

although the cumulative sample size was lower and only LRYGBP was performed. Our risk might be slightly underestimated since a clear decrease in the risk of de novo symptomatic GD was observed for retrospective studies, which might be explained by information bias. In fact, considering only prospective studies, this risk rises to 11.2%. Therefore, our findings, regarding the risk of developing symptomatic

GD after BS, may call into question the pertinence of prophylactic CCY. Theoretically, one of the reasons to routinely perform cholecystectomy concomitant to BS concerns the prevention of later biliary complications (symptomatic choledocholithiasis, acute cholangitis, and biliary pancreatitis), mainly because endoscopic retrograde cholangiopancreatography (ERCP) is routinely impossible to perform after

Table 4 Results of metaregression and subgroup analyses for the risk of de novo post-bariatric symptomatic gallstone disease after bariatric surgery

	Number of studies	Number of patients	Subgroup analyses	I^2	Univariable metaregression—OR (95% CrI) [% iterations with OR < 1]
			Percent of risk of de novo symptomatic GD (95%CrI)		
All	39	63 938	8.2 (5.9–11.1)	66.9	
Year of publication	39	63 938	a	a	0.99 (0.99–1.00) [99%]
Study design					
Prospective design	15	18 798	11.2 (6.9–16.7)	61.3	b
Retrospective design	23	45 140	6.6 (4.1–10.4)	70.7	0.60 (0.31–1.10) [94%]
Average of Age	27	58 656	a	a	0.99 (0.92–1.06) [59%]
Female Patients' Proportion	29	58 823	a	a	1.00 (0.98–1.04) [37%]
Pre-operative Average BMI	26	42 917	a	a	1.04 (0.92–1.17) [26%]
Follow-up	31	61 176	a	a	1.00 (1.00–1.01) [25%]
Preoperative gallbladder status					
Lithiasic gallbladder	7	37 492	6.1 (1.6–14.2)	76	b
Alithiasic gallbladder	22	4 601	10.2 (6.0–15.6)	70.3	2.24 (0.72–5.23) [9%]
Type of BS					
No RYGBP subgroup	25	57 726	7.7 (5.6–10.3)	56.9	b
RYGBP subgroup	10	6 212	8.2 (2.5–22.0)	82.7	1.10 (0.47–2.52) [40%]
No LRYGBP subgroup	23	10 900	8.3 (5.0–12.5)	69.1	b
LRYGBP subgroup	13	53 038	7.5 (4.8–11.7)	60.7	0.93 (0.47–1.87) [59%]
No LSG subgroup	21	55 960	8.8 (5.4–13.1)	68	b
LSG subgroup	15	7 978	7.1 (4.4–13.0)	64.4	0.84 (0.40–1.67) [69%]
No LAGB subgroup	25	46 085	9.1 (5.8–13.2)	69	b
LAGB subgroup	10	17 853	6.5 (3.8–10.6)	52.6	0.69 (0.32–1.44) [82%]
Quality rating					
Poor/fair quality	16	40 558	9.6 (4.5–16.9)	77	b
High quality	22	23 380	7.5 (5.2–10.6)	59.1	0.60 (0.30–1.14) [94%]

BMI, body mass index (kg/m²); *OpenRYGBP*, laparotomy Roux-en-Y gastric bypass; *LRYGBP*, laparoscopic Roux-en-Y gastric bypass; *LAGB*, laparoscopic adjustable gastric banding; *LSG*, laparoscopic sleeve gastrectomy; *GD*, gallstone disease; *OR*, odds ratio; *CrI*, credible intervals

^aNo subgroup analysis was performed, as this is a continuous variable (we were only able to perform meta-regression analysis)

^bReference category

LRYGBP.^{8,66} In the present study, similar to other meta-analyses,^{8,67} symptomatic choledocholithiasis occurred in 37 patients (4.5%) and acute pancreatitis in 23 (2.8%). As a rare event, it does not uphold a prophylactic CCY.

Understanding predictive factors for gallstone formation after BS could influence distinct patient management, including a selective approach for BS + prophylactic CCY. To the best of our knowledge, this is the first meta-analysis exploring this topic. Through meta-regression and subgroup analyses, we found that neither higher pre-operative BMI, nor female patients' proportion appear to be risk factors. However, we were only able to assess data at the study level. Assessing whether having a high BMI or being a female as risk factors for GD development would require an assessment of individual participant data. In our study, LAGB was

associated with lower odds of de novo symptomatic GD. This could be explained by the fact that this restrictive bariatric procedure does not alter gastrointestinal transit, biliary contraction mechanisms, and enterohepatic circulation.^{36,68} On the contrary, in the RYGBP procedure, the altered anatomy, the division of the vagus nerve, and reduced cholecystokinin may lead to gallbladder dysmotility.^{18,69} It was not possible to understand the association between symptomatic GD and excessive weight loss. Although rapid weight loss is classically pointed to as the main predictive factor,⁷ it is not consensual across individual studies.^{4,6,26,27,36}

We performed a separate meta-analysis to understand the impact of preoperative gallbladder status (lithiasic versus alithiasic) in the development of symptomatic GD. There is a 30% probability of symptomatic GD being more

Table 5 Outcomes measured in the comparison between bariatric surgery alone versus prophylactic cholecystectomy concomitant to bariatric surgery

	Number of studies	Number of patients	OR (95% CrI)	I^2	MD (95% CrI)	I^2
Total of major complications	13	684 607	1.74 (0.97–3.55)	56.5%		
Pneumonia	4	60 951	1.26 (0.23–5.34)	58.4%		
Venous thromboembolism	3	39 814	0.34 (0.04–1.40)	25.3%		
Bleeding transfusion	7	61 351	1.05 (0.28–2.09)	33.5%		
Organ space surgical site infection	5	60 951	0.97 (0.05–4.71)	52.8%		
Postoperative mortality	11	97 564	0.79 (0.03–3.02)	20.7%		
Surgery duration	13	619 323			29.2 (17.9–40.7)	89.3%
Hospital length-of-stay	11	64 645			–0.1 (–1.0–0.5)	74.3%

OR, odds ratio; MD, mean differences; CrI, credible intervals

Table 6 Results of metaregression for postoperative major complications between bariatric surgery alone versus prophylactic cholecystectomy concomitant to bariatric surgery

	Number of studies	Number of patients	Univariable metaregression—OR (95% CrI) [% iterations with OR < 1]
Year of publication	13	684 607	1.00 (1.00–1.00) [62%]
Study design (retrospective)	13	651 224	3.77 (0.51 – 5.945) [9%]
Mean age	9	96 333	1.22 (0.87 – 1.68) [25%]
Female patients' proportion	10	649 863	0.95 (0.87 – 1.04) [80%]
Preoperative average BMI	8	95 933	0.80 (0.68 – 0.98) [99%]
Follow-up	11	683 835	1.00 (1.00 – 1.00) [0%]
OpenRYGBP	5	653 405	1.64 (0.33 – 4.80) [36%]
LRYGBP	7	38 607	2.33 (0.28 – 10.27) [33%]
LSG	4	578 892	0.66 (0.16 – 2.59) [74%]
LAGB	2	553 967	0.42 (0.04 – 1.97) [87%]
Quality rating	13	615 010	0.49 (0.16 – 1.27) [93%]

OR, odds ratio; MD, mean differences; CrI, credible intervals

BMI, body mass index (kg/m²); OpenRYGBP, laparotomy Roux-en-Y gastric bypass; LRYGBP, laparoscopic Roux-en-Y gastric bypass; LAGB, laparoscopic adjustable gastric banding; LSG, laparoscopic sleeve gastrectomy; OR, odds ratio; CrI, credible intervals

common in patients with preoperative lithiasic gallbladder than with preoperative alithiasic gallbladder ($OR = 1.51$; 95% CrI = 0.31–3.77). Moreover, according to the literature, severe biliary complications after bariatric surgery (symptomatic choledocholithiasis, acute cholangitis, and biliary pancreatitis) are more common in patients with asymptomatic preoperative gallstones.^{70,71} These arguments might reinforce a more selective approach, where patients with asymptomatic GD would undergo prophylactic CCY, given that, after RYGBP, ERCP is impossible to perform. However, from an expectant management perspective, surgery would be avoided in 88% of these patients and, consequently morbidity of a concomitant procedure. Furthermore, as ultrasound has a low sensibility in patients with obesity, there is no ideal screening method for patient selection. In meta-regression, studies enrolling only patients with alithiasic gallbladders were associated with higher odds of de novo

symptomatic GD compared to studies enrolling patients with alithiasic and lithiasic gallbladders. These two approaches (separate meta-analysis versus meta-regression) may seem to contradict each other. However, the first approach evaluates individual participant data, whereas the second evaluates data at a study level, aiming to measure covariable impact in heterogeneity.

Regarding safety, we observed similar results in postoperative mortality and hospital LOS in patients submitted to BS + prophylactic CCY in comparison to BS alone. On the other hand, operative time and odds of postoperative major complications were higher in patients submitted to BS + prophylactic CCY. Concomitant cholecystectomy is a technically challenging procedure, which could account for these findings. Gallbladder position, often embedded in a steatosis liver, the inadequate position of the trocars, and operator fatigue are some issues to be pointed out.^{4,66,72} It is

worth mentioning that there could be a selection bias present, when assessing the outcome operation BS + prophylactic CCY. In some studies,^{38,51,62} patients had an indication for prophylactic CCY, but the procedure was abandoned due to insufficient exposure of the right upper quadrant, patients' comorbidities, surgeon preference, or technical difficulties. Other meta-analyses reached identical results,^{10,67,70,73} but it is worth noting that these authors studied cholecystectomy concomitant to bariatric surgery for both prophylactic and symptomatic management.

Our results should be interpreted with caution, owing to the observed heterogeneity, which suggests important differences between studies.

Through meta-regression, covariates such as age and the proportion of females did not have a relevant impact on the association between BS alone versus BS + prophylactic CCY in concern to postoperative major complications. We also found that no type of bariatric surgery had a strong impact on postoperative major complications. In the open RYGBP era, prophylactic concomitant cholecystectomy was advocated due to the higher risk of symptomatic gallstone disease, technical difficulties in re-operation, and low morbidity with concomitant cholecystectomy. With current minimally invasive procedures, postoperative major complications seem to outdo the relatively low incidence of symptomatic gallstone.^{7,51} There are only a few studies and no systematic reviews comparing postoperative complications between LSG and LRYGBP with prophylactic CCY. Based on our data, the addition of prophylactic CCY either to LSG or LRYGBP was not associated with an increase in major complications.

Postoperative cholecystectomy safety could modify the perspective regarding prophylactic CY. While it would have been interesting to explore the morbidity and mortality of BS + prophylactic CCY versus postoperative cholecystectomy, we were not able to perform a meta-analysis due to a limited number of studies. Reduced intra-abdominal fat and liver size after BS²⁶ make delayed cholecystectomy technically easier to perform. Warschkow et al.⁸ found that the risk of suffering a complication during subsequent cholecystectomy is only 0.1%. Randomized controlled studies are still needed to assess surgical complications, operative time, LOS, and mortality associated with subsequent cholecystectomy.

This systematic review has some limitations worth noting. First, severe heterogeneity was found, explained by different study designs and eligibility criteria. To explore possible sources of heterogeneity, meta-regression and subgroup analysis were preformed, even though they did not account for all heterogeneity. The impact of distinct exclusion criteria, mainly in objectives i and ii (risk of de novo post-bariatric GD and its predictive factors), might be an explanation—some authors^{18,32,58} excluded patients with preoperative positive findings for GD in ultrasonography, while others^{20,23,29} did not, leading to a possible overestimation of GD development.

Second, this systematic review lacks randomized controlled trials to provide strong evidence to support our findings. Third, almost half of the included studies did not have a low risk of bias, which could impact our results on the risk of de novo GD and postoperative complications rate, particularly, as the quality of the primary studies' was found to be a moderator variable of heterogeneity.

There are also strengths in our study. The main methodological strength of this study is its meta-analytical approach to quantitative synthesis. The main advantage of Bayesian meta-analysis is its use of exact methods, dealing more adequately with zero-cells. Second, we performed a comprehensive search, encompassing three different electronic bibliographic databases and not using exclusion criteria based on the date or language of publication. Third, regarding eligibility criteria, to estimate the risk of post-bariatric de novo GD, studies that included prophylactic treatment with UDCA after BS or patients submitted to cholecystectomy prior or concomitant to BS, were excluded avoiding the risk of underestimation. Finally, meta-regression and subgroup analysis allowed the identification of predictive factors for gallstone formation.

In conclusion, after BS, the risk of developing GD is not substantially high, and severe biliary complications are extremely rare. Although there were no substantial differences in postoperative mortality or hospital length-of-stay, the determined risk of symptomatic GD and the higher risk of postoperative complications do not seem to justify performing prophylactic CCY in patients with lithiasic gallbladder. Doubts remain if a selective approach is advantageous since patients with preoperative gallbladder pathology have some increased risk of symptomatic GD. Randomized controlled studies might be considered to further clarify the role of prophylactic CCY as a selective approach. For future studies, we make the following recommendations: (i) postoperative cholecystectomy versus prophylactic CCY safety should be further explored; (ii) excess weight loss should be reported more consistently since findings are still not consensual regarding its lithogenic influence.

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Author Contribution All authors were involved in the conception and design. F. Amorim-Cruz, H. Santos-Sousa, M. Ribeiro, A. Costa-Pinho and B. Sousa-Pinto were involved in the acquisition, analysis, and interpretation of the data. F. Amorim-Cruz, H. Santos-Sousa and B. Sousa-Pinto were involved in the drafting of the article. All authors were involved in the critical revision of the article. All authors approved

the final version to be published and agreed to be accountable for all aspects of the work.

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Data Availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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RESEARCH



Incidence of symptomatic gallstones after bariatric surgery: the impact of expectant management

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Abstract

Background Bariatric surgery is the most effective treatment for sustained weight reduction and obesity-related comorbidities. The development of gallstones as a result of rapid weight loss is a well-known consequence of bariatric procedures. It remains unclear, if there is an increased risk of these gallstones becoming symptomatic.

Methods A retrospective analysis of 505 consecutive patients submitted to either Roux-en-Y Gastric Bypass or Sleeve Gastrectomy between January and December 2019 was performed. The aim of our study was to determine the incidence of symptomatic cholelithiasis in asymptomatic patients with their gallbladder in situ after bariatric surgery and to identify potential risk factors for its development.

Results Of the 505 patients included, 79 (15.6%) underwent either previous cholecystectomy ($n=67$, 84.8%) or concomitant cholecystectomy during bariatric surgery ($n=12$, 15.2%). Among the remaining 426 (84.4%) patients, only 8 (1.9%) became symptomatic during the 12-month follow-up period. When compared with patients who remained asymptomatic, they had a higher median preoperative BMI (47.0 vs. 42.8, $p=0.046$) and prevalence of cholelithiasis on preoperative ultrasound (62.5% vs. 10.7%, $p=0.001$). Multivariate analysis revealed preoperative BMI and cholelithiasis on preoperative ultrasound as independent risk factors for symptomatic biliary disease (OR 1.187, 95%CI 1.025–1.376, $p=0.022$ and OR 10.720, 95%CI 1.613–71.246, $p=0.014$, respectively).

Conclusion Considering a low incidence of symptomatic gallstones after bariatric surgery, concomitant cholecystectomy should only be performed in symptomatic patients undergoing bariatric surgery. Preoperative factors, such as a higher BMI and positive ultrasound for cholelithiasis, may be related to the development of symptomatic gallstones.

Keywords Bariatric surgery · Gallstones · Symptomatic · Cholecystectomy

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Introduction

The prevalence of overweight and obesity is increasing and some reports estimate that 57.8% of world population will have overweight or obesity by 2030 [1, 2].

Bariatric surgery is the most effective treatment for sustained weight reduction and for obesity-related

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comorbidities, especially for patients with clinically severe obesity [3]. The two most common bariatric surgeries worldwide are Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG), being laparoscopy the gold-standard approach [4].

Rapid weight loss as a result of bariatric surgery can, however, predispose to the development of gallstones [5]. During early weight loss after the procedure, patients are at increased risk for gallstones due to an increased bile cholesterol saturation and poor gallbladder emptying [6, 7]. It has been advocated that the prophylactic use of ursodeoxycholic acid (UDCA) decreases cholesterol saturation and therefore gallstone incidence during weight loss [8, 9].

Doubts emerge over this increased incidence of gallstones and its influence on developing symptomatic gallbladder disease. A population-based cohort study in Sweden demonstrated a fivefold increased risk of symptomatic gallstone disease after bariatric surgery compared with that in the general population [10]. On the other hand, rates of symptomatic gallstones postbariatric surgery as low as 0.9% have been reported, despite a high incidence of new onset gallstones [11].

Distinct approaches to this issue have been proposed. While, currently, conservative options, such as the use of UDCA or performing cholecystectomy concomitantly with bariatric surgery only in the presence of symptomatic gallstones, appear to be superior [12, 13], others advocate routine prophylactic cholecystectomy [14, 15]. Consequently, to date there is no definitive answer as to what approach to prevent symptomatic cholelithiasis should be used.

The aim of this study was to determine the incidence of symptomatic cholelithiasis after SG and RYGB and identify potential risk factors for developing symptomatic cholelithiasis after bariatric surgery. Perhaps there is no clear answer to the dilemma of performing or not performing a cholecystectomy concomitantly with bariatric surgery. Most importantly may be stratifying patients by their risk factors for symptomatic cholelithiasis and, individually, decide for a more aggressive or conservative approach.

Methods

From January 2019 to December 2019, 520 patients were submitted to a bariatric procedure in our institution. Among them, 15 patients underwent a bariatric procedure other than RYGB or SG and were excluded. Therefore, we performed a retrospective analysis of 505 consecutive patients who underwent either RYGB or SG. The study was approved by the Institutional Review Board (CES 46–21).

Patients were considered eligible for bariatric surgery according to the National Institutes of Health Consensus Conference guidelines (body mass index (BMI) ≥ 35 kg/

m² associated with obesity-related co-morbidities or a BMI ≥ 40 kg/m²). The choice of bariatric procedure was made individually regarding patient characteristics, comorbidities, previous treatments, preference and surgeon recommendation. In the context of preoperative evaluation, an ultrasonography was conducted for evaluation of hepatobiliary abnormalities, including the presence of fatty liver disease and gallstones.

Concurrent cholecystectomy was only performed in patients who had symptoms consistent with biliary disease. Data concerning demographic and laboratory evaluations were obtained by consultation of medical records. No gallstone-lowering prophylaxis was used for those with gallbladder in situ. In our institution postoperative visits are done at 1, 6, 12 and 18 months and annually thereafter. Due to the COVID-19 pandemic when face-to-face consultation was not possible, patients were interviewed by telephone.

Our primary aim was to define the risk of symptomatic gallstones after SG and RYGB. For this purpose, patients with previous cholecystectomy or with concomitant cholecystectomy during bariatric surgery, despite having their characteristics analyzed at the time of bariatric surgery, were not considered for subsequent analysis. Only asymptomatic patients with their gallbladder in situ remained, and the occurrence of symptomatic biliary disease was sought.

Symptomatic cholelithiasis is defined as gallbladder pain in the presence of gallstones and, when uncomplicated (i.e., biliary colic), is frequently vague or mild and may be limited to nausea or gastric reflux symptoms [16]. In order to minimize missing cases, a comprehensive definition was used, and symptomatic cholelithiasis after bariatric procedures was defined by the presence of biliary symptoms (typical biliary colic, nonspecific upper quadrant abdominal pain, nausea and vomiting) in the follow-up or emergency department visits, the necessity of any hospital admission for biliary complications (acute cholecystitis, biliary pancreatitis, cholangitis or symptomatic choledocholithiasis) or the performance of cholecystectomy for such complications.

Our secondary objective was to identify potential risk factors for developing symptomatic gallstones after bariatric surgery. With that in mind, we compared patients who developed symptomatic cholelithiasis with those with gallbladder in situ who remained asymptomatic during the follow-up period. Preoperative characteristics such as age, gender, preoperative BMI, gallstones or severe steatosis on preoperative ultrasound, and obesity related disorders namely diabetes and dyslipidemia, as well as factors related to the bariatric procedure, such as the type of surgery and its effectiveness (i.e., %EWL at 6 and 12 months) were considered for comparison. We further compared asymptomatic patients at the time of bariatric surgery with those requiring concurrent cholecystectomy to find additional factors to stratify the risk for symptomatic cholelithiasis.

Statistical analysis was performed using SPSS® 26.0 for Mac (IBM Co., Armonk, NY,

USA). Significance was assumed for p-values inferior to 0.05. Non-parametric Mann–Whitney.

U-test was used to compare the distribution of continuous variables. Chi-square or Fisher's exact test were used to compare proportions, as appropriate. Considering statistically significant variables on univariate analysis and clinically relevant variables, a multivariate analysis was performed. Logistic regression was used for multivariate analysis.

Results

From January 2019 to December 2019, 505 patients underwent either RYGB ($n = 340$, 67.3%) or SG ($n = 165$, 32.7%). Among them, median age was 45 years (range 20–67), 422 (83.6%) were female and median preoperative BMI was 42.7 kg/m² (IQR 39.5–46.1). Only 1 (0.02%) patient was submitted to an open procedure for concomitant intestinal

transit reconstruction. One-hundred and three (20.4%) patients were submitted to RYGB or SG as a revisional surgery (mostly after laparoscopic adjustable gastric banding (LAGB)). There was no post-operative mortality. A follow-up period of 12 months was possible for all patients. Baseline cohort demographic parameters are shown in Table 1.

Sixty-seven (13.3%) patients had had prior cholecystectomy, and 12 (2.4%) patients with symptomatic cholelithiasis underwent concomitant cholecystectomy during bariatric procedure. Therefore, 426 (84.4%) patients remained with their gallbladders in situ. Of these patients, 8 (1.9%) eventually developed symptomatic gallstones during the 12-month follow-up (Fig. 1). Complicated symptomatic cholelithiasis was found in only 1 (12.5%) patient who presented with biliary pancreatitis.

Considering the existence of gallstones in the preoperative ultrasound ($n = 59$) and those who underwent previous ($n = 67$) or concomitant cholecystectomy ($n = 12$), preoperative gallbladder disease was found in 128 (25.3%) patients.

Regarding patients with preoperative asymptomatic gallstones versus patients with no evidence of preoperative gallstones (Table 2), previously bariatric surgery was the only risk factor identified for having gallstones (30.6% vs 14.8%, $p = 0.013$).

Univariate analysis revealed that patients who developed symptomatic gallstones had a higher median preoperative BMI (47.0 vs. 42.8 kg/m², $p = 0.046$) and prevalence of gallstones on preoperative abdominal ultrasound (62.5% vs. 10.7%, $p = 0.001$) when compared with patients who remained asymptomatic during follow-up (Table 3). Multivariate analysis was then performed and denoted preoperative BMI (OR 1.187, 95% CI 1.025–1.376) and gallstones on preoperative ultrasound (OR 10.720, 95% CI 1.613–71.246) as independent risk factors for

Table 1 Population baseline parameters

	All $n = 505$
Age at surgery (years), median (range)	45 (20–67)
Female, n (%)	422 (83.6)
DM, n (%)	131 (25.9)
Dyslipidemia, n (%)	233 (46.1)
RYGB, n (%)	340 (67.3)
SG, n (%)	165 (32.7)
Revisional surgery, n (%)	103 (20.4)

BMI: body mass index, IQR: interquartile range, DM: diabetes mellitus, RYGB: Roux-en-Y gastric bypass, SG: sleeve gastrectomy

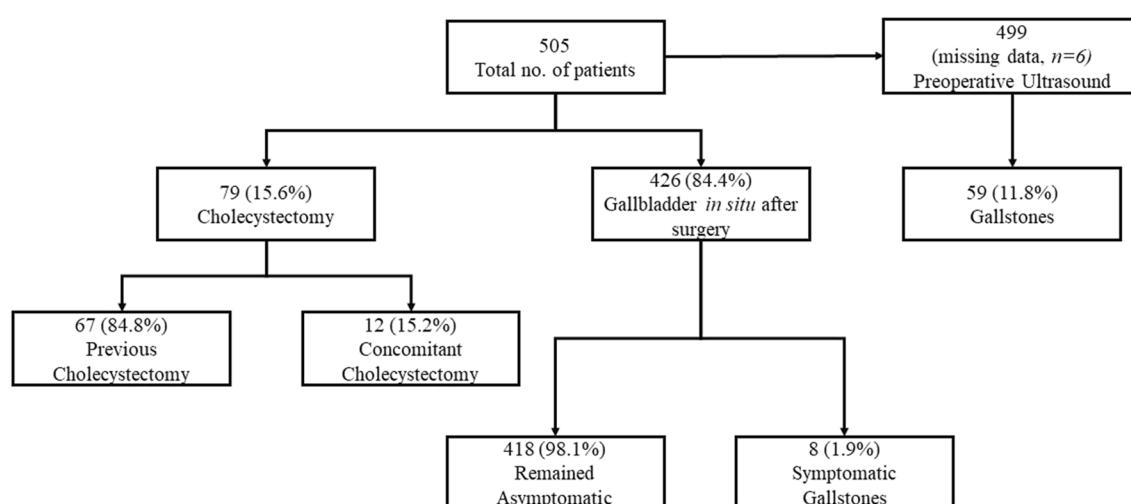


Fig. 1 Flow chart of patients who underwent RYGB or SG

Table 2 Comparison between patients with and without preoperative evidence of gallstones

	Preoperative asymptomatic gallstones <i>N</i> = 49	No evidence of preoperative gallstones <i>N</i> = 371	<i>P</i> value
Age (years), median (range)	45 (33–67)	45 (20–67)	0.392
Female, <i>n</i> (%)	41 (83.7)	300 (88.0)	0.846
Type of surgery (%)			0.338
RYGB, <i>n</i> (%)	29 (59.2)	247 (66.6)	
SG, <i>n</i> (%)	20 (40.8)	124 (33.4)	
Revisional surgery, <i>n</i> (%)	15 (30.6)	55 (14.8)	0.013
Preoperative BMI (kg/m ²), median (IQR)	42.3 (39.2–46.8)	42.9 (39.4–46.2)	0.791
DM, <i>n</i> (%)	11 (22.4)	91 (24.5)	0.860
Glucose (mg/dL), median (IQR)	97 (84.5–113)	95 (87–108.25)	0.575
HbA1c (%), median (IQR)	5.5 (5.3–5.9)	5.6 (5.3–6.0)	0.661
Dyslipidemia, <i>n</i> (%)	21 (42.9)	157 (42.3)	1.000
Total cholesterol (mg/dL), median (IQR)	187 (164–220)	184 (161–209)	0.407
Severe steatosis, <i>n</i> (%)	10 (23.2)	88 (25.7)	0.853

RYGB Roux-en-Y gastric bypass, SG sleeve gastrectomy, BMI body mass index, IQR interquartile range, DM diabetes mellitus, HbA1c hemoglobin A1c

Table 3 Comparison between asymptomatic and symptomatic patients who remained with their gallbladder in situ after bariatric surgery

	Asymptomatic gallbladder in situ <i>N</i> = 418	Symptomatic gallstones <i>N</i> = 8	<i>P</i> value
Age (years), median (range)	45 (20–67)	37.5 (29–61)	0.062
Female, <i>n</i> (%)	340 (81.3)	7 (87.5)	1.000
Type of surgery (%)			1.000
RYGB, <i>n</i> (%)	276 (66)	5 (62.5)	
SG, <i>n</i> (%)	142 (34)	3 (37.5)	
Revisional surgery, <i>n</i> (%)	75 (17.9)	1 (12.5)	1.000
Preoperative BMI (kg/m ²), median (IQR)	42.8 (39.5–46.1)	47.0 (42.4–53.3)	0.046
Gallstones on preoperative abdominal US, <i>n</i> (%)	44 (10.7)	5 (62.5)	0.001
DM, <i>n</i> (%)	102 (24.4)	2 (25)	1.000
Glucose (mg/dL), median (IQR)	95 (86.3–109)	93.5 (81.3–107.8)	0.760
HbA1c (%), median (IQR)	5.6 (5.3–6.0)	5.8 (5.5–5.9)	0.366
Dyslipidemia, <i>n</i> (%)	197 (47.1)	3 (37.5)	0.728
Total cholesterol (mg/dL), median (IQR)	184 (162–212)	186 (158.3–223.5)	0.823
LDL-c (mg/dL), median (IQR)	111 (91–137)	112.5 (82–148.8)	0.970
HDL-c (mg/dL), median (IQR)	48 (41–55)	54 (45–59)	0.312
Triglycerides (mg/dL), median (IQR)	111 (82–146)	100 (78.8–211.8)	0.941
Severe steatosis, <i>n</i> (%)	96 (25.2)	2 (28.6)	1.000
Postoperative, 6 m %EWL, median (IQR)	66.7 (55.6–81.3)	55.4 (46.3–64.3)	0.055
Postoperative, 12 m			
BMI (kg/m ²), median (IQR)	27.9 (25.4–30.6)	29.7 (23.3–36.2)	0.493
%EWL, median (IQR)	84.6 (70.2–97.8)	79.3 (61.7–105.9)	0.638

RYGB Roux-en-Y gastric bypass, SG sleeve gastrectomy, BMI body mass index, IQR interquartile range, DM diabetes mellitus, HbA1c hemoglobin A1c, LDL-c low density lipoprotein cholesterol, HDL-c high density lipoprotein cholesterol, %EWL percentage of excess weight loss

developing symptomatic biliary disease after bariatric surgery (Table 4).

At the time of bariatric surgery, symptomatic patients who required concomitant cholecystectomy (*n* = 12) were

Table 4 Multivariate analysis for factors related to symptomatic gallstones

	OR (95% CI)	P value
Age	0.931 (0.846–1.024)	0.142
Gender	0.999 (0.093–10.721)	0.999
Type of bariatric surgery	0.720 (0.098–5.309)	0.747
Preoperative BMI	1.187 (1.025–1.376)	0.022
Gallstones on preoperative abdominal US	10.720 (1.613–71.246)	0.014
Dyslipidemia	1.621 (0.267–9.847)	0.600
%EWL, 6 m	0.995 (0.976–1.015)	0.639

OR odds ratio, CI confidence interval, BMI body mass index, %EWL percentage of excess weight loss

not significantly different from those who were asymptomatic ($n = 440$) (Table 5).

Discussion

Obesity is a well-known risk factor for cholelithiasis [17]. In our cohort we found a prevalence of preoperative gallbladder disease of 25.3%. Similar results were found in other studies, with a prevalence of cholelithiasis in bariatric population being estimated at 20.8 to 36.7% [15, 18–23].

Early after bariatric surgery there is a greater incidence of gallstones. An increased bile saturation of cholesterol and crystallization-promoting proteins, such as mucin [24], along with defective gallbladder emptying, result in cholesterol crystal formation and gallstone development [6, 7, 24]. Some authors suggest that rapid weight loss is the main element leading to gallstone formation after either RYGB or SG [25] and that gallstone formation during active weight

loss seems to increase in an exponential fashion [26]. Nonetheless, the type of bariatric procedure may also play an important role in the overall risk for symptomatic cholelithiasis. Sneineh et al. reported that a change in BMI after bariatric surgery could not explain the significantly increased incidence of symptomatic cholelithiasis following RYGB (14.5%) compared to SG (4.4%), LAGB (4.1%) and one anastomosis gastric bypass (OAGB) (7.5%). The lack of interference with the biliary contraction mechanisms and enterohepatic circulation in SG and LAGB was in part considered responsible for this discrepancy [27].

In our cohort we found an incidence of symptomatic cholelithiasis after bariatric surgery of 1.9% during a 12-month follow-up period, with 87.5% of patients presenting with uncomplicated gallbladder disease (i.e., biliary colic). Several studies with a similar study design, in which no gallstone-lowering prophylaxis was used, reported an incidence of 0.9% to 6.2% [11, 21–23, 27]. When focusing on the need for subsequent cholecystectomy, Swartz et al. reported that 14.7% of patients with prior RYGB required later cholecystectomy [28], while Altieri et al. found that 9.7% of patients underwent cholecystectomy after RYGB and 10.1% after SG [29].

A nationwide Swedish multiregister study found that, while prior to RYGB patients with obesity were already at an increased risk for cholecystectomy, this risk was even higher after RYGB, and only returning to baseline after 36 months [30]. Alternatively, a cohort study by Chen et al. reported that, even though the bariatric surgery group had a significantly higher rate of gallstone disease than the general population (2.89% vs. 1.15%, $p < 0.001$), there were no significant differences between the bariatric surgery group when compared with patients with obesity that did not undergo a bariatric procedure. Hence, they concluded

Table 5 Comparison between asymptomatic patients and patients who underwent concomitant cholecystectomy at the time of bariatric surgery

	Asymptomatic gallbladder in situ $N = 426$	Concomitant cholecystectomy $N = 12$	P value
Age, (years), median (range)	45 (20–67)	44 (26–62)	0.726
Female, n (%)	347 (81.5%)	12 (100)	0.136
Preoperative BMI (kg/m^2), median (IQR)	42.9 (39.5–46.2)	39.2 (37.4–48.8)	0.537
DM, n (%)	104 (24.4)	3 (25)	1.000
Glucose (mg/dL), median (IQR)	95 (86.3–109)	101 (84–110)	0.481
HbA1c (%), median (IQR)	5.6 (5.3–6.0)	5.6 (5.2–6.0)	0.913
Dyslipidemia, n (%)	200 (46.9%)	5 (41.7)	0.718
Total cholesterol (mg/dL), median (IQR)	184 (162–213)	182 (160–198.5)	0.672
LDL-c (mg/dL), median (IQR)	111 (91–137)	114 (86–120.5)	0.659
HDL-c (mg/dL), median (IQR)	48 (41–55)	48 (46–55)	0.470
Triglycerides (mg/dL), median (IQR)	111 (82–146)	110 (78.5–136)	0.809
Severe steatosis, n (%)	101 (25.3)	3 (25)	1.000

BMI body mass index, IQR interquartile range, DM diabetes mellitus, HbA1c hemoglobin A1c, LDL-c low density lipoprotein cholesterol, HDL-c high density lipoprotein cholesterol

that the risk of symptomatic cholelithiasis did not increase after bariatric surgery, despite being higher than the general population [31]. On the other hand, our results on the incidence of symptomatic cholelithiasis (1.9%) are comparable to the risk of symptomatic gallstones in the general population with asymptomatic gallstones, which is 1 to 4% per year [32]. In the general population, treatment of asymptomatic gallstone patients is not routinely recommended, and most patients are treated by elective laparoscopic cholecystectomy when they become symptomatic [33]. Considering the low incidence of gallstone disease after bariatric procedures, the same expectant approach appears appropriate [13, 22, 28].

In order to find particular patients where a more aggressive approach could be used, we sought risk factors for symptomatic cholelithiasis. In our series we noted that patients who developed symptomatic gallstones had higher preoperative BMI than patients that remained asymptomatic (47.0 vs. 42.8 kg/m², $p = 0.046$), and higher rates of gallstones on preoperative abdominal ultrasound (62.5% vs. 10.7%, $p = 0.001$). These two risk factors remained as independent risk factors for developing symptomatic gallstones after multivariate analysis (OR 1.187, 95% CI 1.025–1.376; OR 10.720, 95% CI 1.613–71.246; respectively). These results may indicate that preoperative characteristics, namely high BMI and cholelithiasis, are probably more important for the development of symptomatic cholelithiasis than factors more intrinsically related to bariatric surgery, such as the type of surgery used or its effectiveness (i.e., %EWL). Prospective studies are needed in order to validate these findings and to accurately identify patients which might benefit to be submitted to cholecystectomy in same surgical time.

Age, gender and obesity related disorders, notably diabetes, dyslipidemia and severe steatosis were not considered significantly different between the two groups in our population. We further compare those who had concomitant cholecystectomy with patients that left the operating room with their gallbladders in situ, but did not find any significant difference between them.

Other studies indicated that a weight loss of more than 25% of original weight [20], rapid weight loss [21], restrictive procedures [31], female gender [21, 31] and increased age [34] were associated with an increased risk of symptomatic gallstones. Noteworthy, a recent study reported that patients who had another bariatric procedure in the past were at an increased risk for gallstone formation and cholecystectomy [27]. Conversely, some studies failed to find any predictors of symptomatic cholelithiasis [22, 35]. As new studies emerge some of these risk factors may be further supported and others identified.

Postoperative administration of UDCA, for a period of 6 months, was considered effective for reducing the rate of gallstone formations after bariatric surgery [36, 37] and reduced the need for urgent cholecystectomy [37].

Nonetheless, its cost-effectiveness [38] and compliance [28] are questionable. Therefore, in our institution, we do not routinely use UDCA for gallstone prevention. To clarify the role of UDCA, prospective trials regarding this issue should provide better evidence on this matter.

Despite a clear shift towards a more conservative approach, with several studies concluding that concomitant cholecystectomy should only be performed in symptomatic patients [13, 22, 23, 28, 35, 39, 40], there is still evidence supporting prophylactic cholecystectomy [14, 41]. In fact, a large study by Weiss et al. reported that in comparison with RYGB alone, patients who underwent concomitant cholecystectomy had improved survival and long-term outcomes. Additionally, cholecystectomy patients who had undergone prior RYGB had higher risk of conversion to open cholecystectomy, post-operative complications, and death, when compared with cholecystectomy patients without any prior bariatric procedure [41].

Limitations of our work include its retrospective nature. This study was performed in a single institution; nonetheless, this assures homogeneity in treatment plan, because all patients were evaluated and treated by the same multidisciplinary team. The rate of symptomatic cholelithiasis after bariatric surgery may have been underestimated for two reasons. Firstly, due to the COVID-19 pandemic, several follow-up consultations were accomplished remotely by telephone, and that may have resulted in omitted symptoms. Secondly, despite our comprehensive definition for symptomatic cholelithiasis, unspecific or vague upper abdominal pain and nausea from gallstones, most likely, have been attributed to another cause than the other way around. As postoperative abdominal ultrasound is not routinely performed after bariatric surgery, we could not identify what proportion of patients developed asymptomatic gallstones.

Further studies, multicentric and prospective in nature, with longer follow-up period should be the key to definitively establish risk factors for development of symptomatic gallstones after bariatric surgeries and identify patients who might benefit the most with concomitant cholecystectomy.

Conclusion

In line with recent available evidence, our results on the incidence of symptomatic gallstones after bariatric surgery support the performance of cholecystectomy concomitantly with bariatric surgery only in symptomatic patients. Higher BMI and preoperative ultrasound for cholelithiasis were independent risk factors for development of symptomatic gallstones after SG and RYGB. Further prospective studies are needed in order to accurately clarify the role of these risk factors. In the future, predictive modeling taking in consideration BMI and preoperative ultrasound may assist in the

decision-making process of identifying patients that could benefit from concomitant cholecystectomy.

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Declarations

Competing interests The authors declare no competing interests.

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Conflict of Interest The authors declare that they have no conflict of interest.

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B. IMPROVING OUTCOMES OF MBS

Early postoperative complications

Early postoperative bleeding

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(**Q1**)

(Scimago Journal & Country Rank, 2023)

Journal Impact Factor (JIF) 2,1 | Rank 98 of 290 on Surgery journals (**Q2**)

Journal Citation Indicator (JCI) 0,95 | Rank 77 of 290 on Surgery journals (**Q2**)

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SYSTEMATIC REVIEW



Preoperative risk factors for early postoperative bleeding after Roux-en-Y gastric bypass surgery: a systematic review and meta-analysis

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Abstract

Purpose Although bariatric surgery is an effective intervention for obesity, it comes with risks such as early postoperative bleeding (EPB). Identifying preoperative risk factors for this complication can help patients' risk stratification and optimization. We performed a systematic review and meta-analysis to find predictors for early postoperative bleeding after Roux-en-Y gastric bypass (RYGB).

Methods We conducted a systematic review, searching PubMed, Cochrane Library, and Web of Science until November 2023. We performed a random-effects meta-analysis to explore preoperative risk factors associated with early postoperative bleeding after RYGB. Sources of heterogeneity were explored by leave-one-out analyses.

Results 23 studies were included, comprising 232,488 patients. Male gender (meta-analytical RR = 1.42, 95%CI = 1.21–1.66, I^2 = 18%, Q Cochran test p -value = 0.29) and revisional surgery (meta-analytical RR = 1.35, 95%CI = 1.12–1.62, I^2 = 22%, Q Cochran test p = 0.21) were associated with higher risk of EPB. On average, patients with EPB were older than the remainder (MD for the mean age = 2.82 years, 95%CI = 0.97–4.67, I^2 = 0.00%, Q Cochran test p = 0.46). Except for hypertension (meta-analytical RR = 1.33, 95%CI = 1.02–1.73, I^2 = 66%, Q Cochran test p < 0.0001), comorbidities were not associated with a higher risk of EPB.

Conclusion Preoperative risk factors, including age, gender, hypertension, and revisional bariatric surgery, are associated with early postoperative bleeding after RYGB. Further primary studies, with higher methodological quality, are required to detail more risk factors.

Keywords Bariatric surgery · Obesity · Roux-en-Y gastric bypass · Risk factors · Hemorrhage

Hugo Santos-Sousa and Filipe Amorim-Cruz have contributed equally to this work, and should both be considered first authors.

Silvestre Carneiro and Bernardo Sousa-Pinto have contributed equally to this work, and should both be considered the last authors.

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Introduction

Obesity is a complex multifactorial disease, whose prevalence has been increasing steadily in the last decades [1]. Bariatric surgery has been identified as the most effective treatment for clinically severe obesity, resulting in substantial and sustained weight loss and improvement in obesity-related comorbidities [2]. Considering its metabolic impact, Roux-en-Y gastric bypass (RYGB) remains one of the most performed metabolic procedures [3]. Although the safety profile of RYGB has improved over the past few decades [4], as the number of procedures performed continues to increase, it is important to acknowledge that the risk of major early complications is not inexistent.

Postoperative bleeding is one of the most common complications in the early postoperative period after RYGB [5], leading to longer hospital stays, higher reoperation rates, and higher mortality rates. Understanding the risk factors associated with early postoperative bleeding might be important for better preoperative optimization of modifiable risk factors and individual risk stratification aiming for closer surveillance in the early postoperative period. During RYGB, intraoperative and technical risk factors associated with EPB had already been systematically studied – for instance, performing a mechanic gastrojejunal anastomosis with a circular stapler instead of a hand-sewn and not reinforcing the staple line increases the risk of bleeding [6, 7]. On the other hand, in contrast to intraoperative risk factors, there is no systematic evidence of preoperative clinical factors, even though there is growing evidence that patient illness severity, demographic characteristics, and specific preoperative comorbidities may increase the likelihood of postoperative bleeding. Therefore, in this systematic review and meta-analysis, we aimed to identify preoperative predictors of early postoperative bleeding in patients undergoing RYGB.

Materials and methods

This systematic review with meta-analysis follows the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement guidelines and the recommendations of the Cochrane Handbook for Systematic Reviews [8, 9].

Literature search and eligibility criteria

We searched MEDLINE, Scopus, and Web of Science from inception to November 2023 using a pre-defined search strategy (Supplementary Table 1). Through Tripdatabase (<https://www.tripdatabase.com>), this search was supplemented by gray literature search as well as by hand-searching

references of primary studies that were included. No restrictions were set regarding language or publication year.

Original studies were included if (i) RYGB was an obesity treatment for patients with a BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with weight-related comorbidities, and (ii) incidence of early postoperative bleeding was reported, in combination with evaluation of preoperative risk factors, comparing patients with and without EPB. Early postoperative bleeding was defined as bleeding occurring in a period of up to 30 days after RYGB surgery. More details on the adopted inclusion and exclusion criteria are available in Supplementary Table 2.

Study selection and data extraction

After removing duplicates, each study was independently assessed by two reviewers (H.S.S and F.C), first by title and abstract screening, and then by full-text reading. Any disagreements were resolved by consulting a third reviewer to reach a final decision.

Two reviewers independently extracted data from selected studies using a predefined spreadsheet purposely built for this systematic review. For each primary study, the following information was retrieved: authors' identification, the year of publication, country, study design, timing and surgical technique (ORYGB, LRYGB, RRYGB), frequency of co-morbidities, total number of patients with EPB after RYGB, and number of patients with (and without) EPB according to the presence or absence of potential preoperative risk factors.

Quality of reporting analysis

The quality of primary studies was independently assessed by two reviewers (H.S.S and F.C) using the Methodological Index for Non-Randomized Studies (MINORS) [10]. To reach a consensus, divergent opinions regarding quality assessment were discussed with a third reviewer. This tool consists of a form with 12 items - the first eight being specifically for non-comparative studies (related to the research question, study population, exposure, outcome, blinding, follow-up, and statistical analysis) [10]. For this review and meta-analysis, a score of < 8 was considered to be poor quality, 9–14 moderate quality, and 15–16 good quality for noncomparative studies. Cutoff points were < 14 , 15–22, and 23–24, respectively, for comparative studies [10].

Synthesis of results

We performed a random-effects meta-analysis using the DerSimonian-Laird method, computing pooled meta-analytical values for the association between each potential

preoperative risk factor and postoperative bleeding. We calculated pooled risk ratios (RR) for categorical variables and pooled mean differences (MD) for continuous variables. If a risk factor was pooled in two or more primary studies, a meta-analysis was performed, assuring that if only two primary studies were included, they could be meaningfully pooled and provided sufficiently 'similar' results. Heterogeneity was assessed using the Q-Cochran test statistic p-value and the I^2 statistic. For the Q-Cochran test statistic, p-values < 0.10 were considered to indicate significant heterogeneity. For the I^2 statistic, we considered 0% to correspond to the absence of detected heterogeneity, 0–10% to be low heterogeneity, 10–50% to be moderate heterogeneity, and above 50% to be high heterogeneity [8]. Heterogeneity sources were explored through leave-one-out sensitivity analyses. Statistical analysis was performed using R statistical software (version 4.3.2), with the use of the "meta" [11] and "gtsummary" packages [12].

Results

Study selection and characteristics

The electronic literature search yielded 4,593 articles, of which 886 were duplicates. After excluding 3,474 records in the screening phase, 373 articles were fully read, of which a total of 22 were included in the systematic review (Fig. 1). Hand-searching resulted in 55 additional articles, of which 1 was included. In total, 23 articles were included [13–35].

A summary of included studies is presented in Table 1. A more detailed presentation of the studies' characteristics is reported in Supplementary Table 3. Studies were published between 2009 and 2023, with a cumulative sample size of

232,488 patients. Most studies [13–18, 20–22, 24–33, 35] were retrospective cohort studies ($n = 21$, 91.30%), with the remaining being prospective observational studies [19, 23]. The mean participants' age was 45.2 years (SD = 10.8 years) with a female predominance (79.30%). Laparoscopic Roux-en-Y gastric bypass (LRYGB) was the most performed RYGB type ($n = 211,723$, 91.10%) and 204,952 (88.0%) of patients were submitted to a primary surgery.

Preoperative risk factors for early postoperative bleeding after RYGB

Our meta-analysis showed that the cumulative incidence of early postoperative bleeding after RYGB was 2.60% (95% CI 2.1–3.1%), $I^2 = 97\%$; Q Cochran test p-value < 0.01; Fig. 2). We were able to do a meta-analysis on the following risk factors (Table 2): average participants' age, gender, patients with a BMI > 50 kg/m², patients' comorbidities (diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea (OSA), gastroesophageal reflux disease (GERD)), prophylaxis for thromboembolism (heparin versus enoxaparin) and previous bariatric surgery requiring revisional RYGB (rRYGB). Male gender (meta-analytical RR = 1.42, 95%CI = 1.21–1.66, $I^2 = 18\%$, Q Cochran test p-value = 0.29; Supplementary Fig. 2) and revisional RYGB (meta-analytical RR = 1.35, 95%CI = 1.12–1.62, $I^2 = 22\%$, Q Cochran test $p = 0.21$; Supplementary Fig. 9) were significantly associated with higher risk of early postoperative bleeding after RYGB. For gender, in leave-one-out sensitivity analysis, omitting Rabl et al. [28], there was a decrease from 18 to 0% in I^2 (Supplementary Table 6). On average, patients with EPB were older (MD for the mean participants' age = 2.82 years, 95%CI = 0.97–4.67, $I^2 = 0.00\%$, Q Cochran test $p = 0.46$; Supplementary Fig. 1). Compared with

Fig. 1 PRISMA flow chart of the study

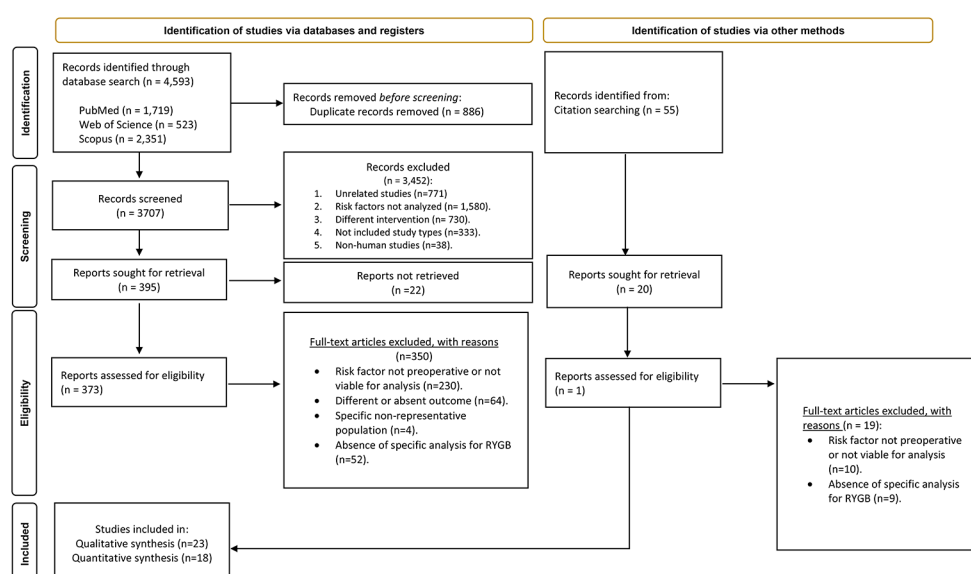


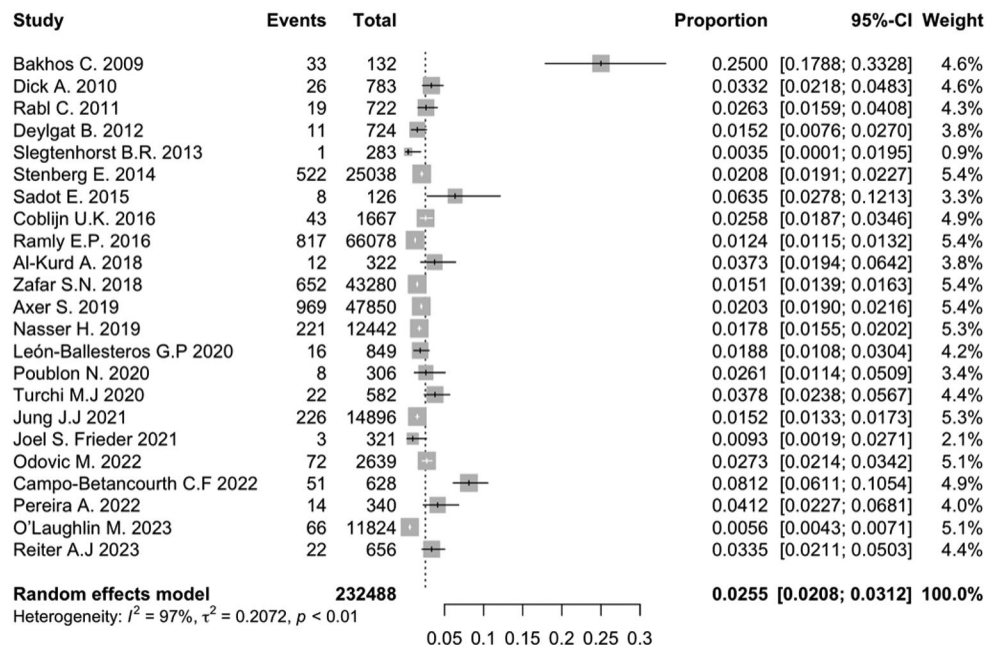
Table 1 Studies general characteristics

Study	Yr	Study Design	Sample Size	Follow up (month)	Patients with EPB (n)	Presence of Risk Factor in Bleeding Patients (n)	Presence of Risk Factor in non-bleeding Patients (n)	Average age in patients with bleeding (years)	Average age in patients without bleeding (years)
Bakhos C.	2009	RS	132	1	33	Male gender: 7 Superobesity: 15 DVT P. Heparin: 16 DVT P. Enoxaparin: 15	Male gender: 18 Superobesity: 48 TVP P. Heparin: 69 TVP P. Enoxaparin: 25	47.5 ± 8.7	42.8 ± 10.8
Dick A.	2010	PS	783	1	26	Male gender: 5 Diabetes mellitus: 7 Hypertension: 13 Dyslipidemia: 6 OSA: 9 GERD: 9 Revisional Surgery: 0	Male gender: 135 Diabetes mellitus: 288 Hypertension: 497 Dyslipidemia: 301 OSA: 261 GERD: 324 Revisional Surgery: 13	47 ± 12	44 ± 11.6
Rabl C.	2011	RS	722	20.9	19	Male gender: 1 Diabetes mellitus: 11 Hypertension: 12 OSA: 5 Revisional Surgery: 3	Male gender: 134 Diabetes mellitus: 227 Hypertension: 439 OSA: 250 Revisional Surgery: 66	44.9 ± 9.4	44.8 ± 10.6
Deylgat B.	2012	RS	724	45	11	Revisional Surgery: 3	Revisional Surgery: 69	NR	NR
Slegtenhorst B.R.	2013	RS	283	NR	1	Revisional Surgery: 0	Revisional Surgery: 66	NR	NR
Stenberg E.	2014	RS	25,038	1	522	Male gender: 174 Diabetes mellitus: 120 Hypertension: 194 Dyslipidemia: 88 OSA: 72 Cardiovascular Disease: 194	Male gender: 5,874 Diabetes mellitus: 3640 Hypertension: 6127 Dyslipidemia: 2452 OSA: 2373 Cardiovascular Disease: 6127	NR	NR
Sadot E.	2015	RS	126	72	8	Revisional Surgery: 3	Revisional Surgery: 41	NR	NR
Coblijn U.K.	2016	RS	1667	96	43	Revisional Surgery: 10	Revisional Surgery: 298	NR	NR
Ramly E.P.	2016	RS	66,078	60	817	Revisional Surgery: 17	Revisional Surgery: 1195	NR	NR
Al-Kurd A.	2018	RS	322	12	12	Revisional Surgery: 4	Revisional Surgery: 2	NR	NR
Zafar S.N.	2018	RS	43,280	1	652	Age ≥ 60 years: 114 Male gender: 156 Superobesity: 171 Diabetes mellitus: 396 Hypertension: 398 Dyslipidemia: 228 OSA: 287 GERD: 277 Cardiovascular Disease: 70 Revisional Surgery: 90	Age ≥ 60 years: 5714 Male gender: 8483 Superobesity: 11,200 Diabetes mellitus: 28,134 Hypertension: 22,623 Dyslipidemia: 12,446 OSA: 17,676 GERD: 16,221 Cardiovascular Disease: 2127 Revisional Surgery: 3591	NR	NR
Axer S.	2019	RS	47,850	60	969	Revisional Surgery: 52	Revisional Surgery: 917	NR	NR
Nasser H.	2019	RS	12,442	1	221	Revisional Surgery: 221	Revisional Surgery: 12,221	NR	NR
León-Ballesteros G.P.	2020	RS	849	12	16	Age ≥ 60 years: 0	Age ≥ 60 years: 57	NR	NR
Poublon N.	2020	RS	306	36	8	Revisional Surgery: 8	Revisional Surgery: 298	NR	NR
Turchi M.J.	2020	RS	582	60	22	Age ≥ 60 years: 2	Age ≥ 60 years: 51	NR	NR
Jung J.J.	2021	RS	14,896	1	226	Revisional Surgery: 25	Revisional Surgery: 1115	NR	NR
Joel S. Frieder	2021	RS	321	24	3	Age ≥ 60 years: 3	Age ≥ 60 years: 318	NR	NR

Table 1 (continued)

Study	Yr	Study Design	Sample Size	Follow up (month)	Patients with EPB (n)	Presence of Risk Factor in Bleeding Patients (n)	Presence of Risk Factor in non-bleeding Patients (n)	Average age in patients with bleeding (years)	Average age in patients without bleeding (years)
Odovic M.	2022	RS	2639	1	72	Male gender: 27 Superobesity: 10 Diabetes mellitus: 47 Hypertension: 43 Dyslipidemia: 44 OSA: 39 Revisional Surgery: 5	Male gender: 607 Superobesity: 449 Diabetes mellitus: 1715 Hypertension: 1182 Dyslipidemia: 1734 OSA: 1437 Revisional Surgery: 146	44.9 ± 12.4	42.1 ± 12.4
Campo-Betan-courth C.F	2022	RS	628	1	51	Revisional Surgery: 1	Revisional Surgery: 50	NR	NR
Pereira A.	2022	RS	340	1	14	Male gender: 3 Diabetes mellitus: 4 Hypertension: 5 Dyslipidemia: 5 OSA: 1 GERD: 5 Revisional Surgery: 5	Male gender: 35 Diabetes mellitus: 91 Hypertension: 153 Dyslipidemia: 149 OSA: 57 GERD: 58 Revisional Surgery: 78	47	46
O'Laughlin M.	2023	PS	11,824	1	66	Revisional Surgery: 33	Revisional Surgery: 5879	NR	NR
Reiter A.J	2023	RS	656	120	22	DVT P. Heparin: 7 DVT P. Enoxaparin: 15	DVT P. Heparin: 379 DVT P. Enoxaparin: 255	NR	NR

Yr: Year of publication, n: number of patients, EPB: Early (<30 days) Postoperative Bleeding, SD: Standard Deviation; Cardiovascular Disease includes Ischemic heart disease (Acute coronary syndrome, Stable coronary artery disease, history of arterial revascularization), Stroke or Transient Ischemic Attack, Peripheral artery disease, Aortic aneurysm; GERD: Gastroesophageal reflux disease, OSA: Obstructive sleep apnea; DVT P. – Deep Vein Thrombosis Prophylaxis; NR: Not reported

Fig. 2 Forest plot representing the cumulative incidence of post-operative bleeding after RYGB in the first 30 days

patients with BMI < 50 kg/m², patients with BMI > 50 kg/m² had no statistically significant increased risk of EPB after RYGB (meta-analytical RR = 0.97, 95%CI = 0.83–1.15, $I^2 = 0\%$, Q Cochran test $p = 0.73$; Supplementary

Fig. 3). Comorbidities were not significantly associated with increased risk of EPB, except for hypertension (meta-analytical RR = 1.33, 95%CI = 1.02–1.73, $I^2 = 66\%$, Q Cochran test $p < 0.0001$; Supplementary Fig. 5). Even

Table 2 Preoperative risk factors for early postoperative bleeding

Preoperative Risk Factor for EPB	Studies (n)	Total Patients (n)	Patients with EPB (n)	Random effects model	I ²	Q Cochran test p
Age	4	4616	164	MD = 2.82, 95%CI = 0.97–4.67	0%	0.46
Gender	7	72,934	373	RR = 1.42, 95%CI = 1.21–1.66	18%	0.29
BMI > 50 kg/m ²	3	45,825	754	RR = 0.97, 95%CI = 0.83–1.15	0%	0.73
Diabetes Mellitus	6	72,802	585	RR = 1.13, 95%CI = 0.72–1.76	87%	< 0.01
Arterial Hypertension	6	72,802	665	RR = 1.33, 95%CI = 1.02–1.73	66%	< 0.01
Dyslipidemia	5	72,080	371	RR = 1.07, 95%CI = 0.74–1.55	79%	< 0.01
Obstructive Sleep Apnea	6	72,802	413	RR = 1.15, 95%CI = 0.94–1.40	32%	0.2
GERD	3	44,403	692	RR = 1.19, 95%CI = 0.76–1.85	40%	0.19
Revisional RYGB Surgery	14	191,440	248	RR = 1.35, 95%CI = 1.12–1.62	22%	0.21
Prophylaxis for thromboembolism	2	728	53	RR = 0.37, 95%CI = 0.23–0.58	0%	0.68

n: number of patients, EPB: Early (<30 days) Postoperative Bleeding, MD: Mean Difference, RR: Risk Ratio, RYGB: Roux-en-Y gastric bypass, BMI: Body Mass Index, GERD: Gastroesophageal reflux disease

though a leave-one-out sensitivity analysis was performed, we observed that no primary study was a significant source of heterogeneity for diabetes mellitus (Supplementary Table 8), dyslipidemia (Supplementary Table 10), and GERD (Supplementary Table 12). For hypertension, in leave-one-out sensitivity analysis, omitting Dick et al. [19], there was a decrease from 66 to 46.4% in I² and a stronger association was found (meta-analytical RR = 1.50, 95%CI = 1.23–1.83, Supplementary Table 9). Preoperative administration of unfractionated heparin was associated with a lower risk of EPB after RYGB compared to enoxaparin (RR = 0.37, 95%CI = 0.23–0.58, I² = 0.00%, Q Cochran test p = 0.68; Supplementary Fig. 10).

Quality of reporting analysis

The results of the MINORS risk of bias assessments for included primary studies are presented in Supplementary Table 4. Most studies (n = 17, 73.9%) were classified as having a moderate quality study, with the remaining [16–18, 20, 22, 27] being poor quality studies. Most studies (n = 19, 82.60%) did not mention an established protocol before the beginning of the study. A total of 8 (34.8%) studies had a reported loss to follow-up up less than 5%. The main difference between moderate and poor quality studies was reporting baseline equivalence of the groups and/or adequate statistical analysis (with the calculation of confidence intervals or relative risk).

Discussion

In this study, we systematically reviewed the literature on preoperative risk factors associated with EPB, having identified five factors that were significantly associated with a higher risk of this complication - older age, male gender,

hypertension, revisional RYGB, and preoperative administration of enoxaparin.

Gastrointestinal bleeding after gastric bypass surgery, although rare (with an estimated incidence of 1.1–4%), is one of the most common early complications after RYGB. It most commonly occurs at the anastomotic staple lines and presents within 12–24 h after surgery [36]. It is usually self-limited, but it can present as a life-threatening condition. It is crucial to identify the risk factors for early bleeding after bariatric surgery to prevent and manage this complication effectively. Surgical teams, being aware of this information, could take the necessary precautions and closely monitor patients who may be at higher risk of EPB, ensuring a safe and successful postoperative period.

Our meta-analysis showed that the risk of EPB was significantly associated with being of the male gender, which is in line with the recent literature [37–39]. Male gender has been associated with a higher incidence of overall postoperative complications or mortality after bariatric surgery, specifically, in RYGB. This could be explained by the more complicated male anatomy, such as the central distribution of adipose tissue, a higher prevalence of massive steatosis, and an increased liver size [37, 40]. In our meta-analysis, four retrospective studies [15, 19, 24, 25, 28] analyzed the effect of age, as a continuous variable, demonstrating that, on average, patients with EPB tend to be older, possibly due to the increased pre- and post-operative comorbidities. For older patients, Xu et al. [41] and Kermansaravi et al. [42] suggest that sleeve gastrectomy is safer than RYGB, despite RYGB being more effective in reducing obesity-related diseases and weight loss outcomes.

Revisional RYGB surgery is technically challenging due to altered anatomy and the presence of adhesions. Thus, it has a higher complication rate, including postoperative bleeding [22]. In our meta-analysis, this preoperative risk factor was the most well-studied variable, being reported

by 14 primary studies [13, 14, 16–19, 21, 23–25, 29, 31, 32, 35]. In line with the literature, we found a significant association between revisional RYGB surgery and early postoperative bleeding.

Prophylaxis for thromboembolism after bariatric surgery is a delicate balance between reducing venous thromboembolism rates (0.3–1.5%) [30] and avoiding bleeding complications after the surgery. Our study found that the use of unfractionated heparin for thromboembolism chemoprophylaxis before surgery is associated with a lower risk of EPB compared to using enoxaparin. Given the low number of studies [15, 30] on this matter, this result should be interpreted with caution, and more primary studies are needed to draw conclusive evidence.

In our meta-analysis, except for hypertension, we did not find traditional hemorrhage-associated comorbidities to be associated with a higher risk of bleeding. Hypertension had previously been shown to be a risk factor for mortality after RYGB, due to an abnormal response to injury [40]. In our study, hypertension was found to be statistically significantly associated with an increased risk of EPB, with a stronger association when Dick et al. [19], inducing significant heterogeneity, was omitted in leave-one-out sensitivity analyses. We found a trend between OSA and postoperative bleeding, but it did not reach statistical significance. Neither diabetes mellitus, dyslipidemia nor GERD were shown to be preoperative risk factors for early postoperative bleeding. The role of diabetes as a risk factor for postoperative complications after RYGB is not completely established. Diabetes is associated with a pro-inflammatory state and slower wound healing, being a risk factor for cardiovascular, respiratory, infectious, and renal complications [43]. In our meta-analyses, the included studies with the largest samples reached opposite conclusions about the role of diabetes in early postoperative bleeding [33, 35]. Our findings should be interpreted with caution and require further investigation. Although a higher BMI has been identified as a risk factor for morbidity and mortality after bariatric surgery [44], our study did not find any association between a BMI greater than 50 kg/m² and bleeding risk. However, it is important to interpret this result with caution since the effect of BMI was not possible to be analyzed as a continuous variable; and the literature [45] shows that extremes of BMI are associated with increased risk of early postoperative bleeding.

This systematic review has some limitations worth noting. An important limitation concerns the severe heterogeneity found, mainly in comorbidities' patients' risk factors, mirroring not only the nature of this meta-analysis (i.e. a quantitative synthesis of risk factors of a rare and unreported event such as early postoperative bleeding after RYGB) but also the differences in eligibility criteria across primary studies. To explore possible sources of heterogeneity, we

performed leave-one-out analyses, although severe heterogeneity did not cease. Second, in part due to the characteristics of primary studies, during the selection process, 230 studies were excluded for not reporting preoperative risk factors for EPB; and, during data extraction, some variables, such as total weight loss and pre- and pos-bariatric BMI, were not computed due to lack of information. Finally, the assessment of the quality of some studies is hampered by the lack of follow-up of less than 5% and unreported criteria on the methods of participant selection or data collection. These limitations raise the need for subsequent studies to be performed with rigorous study designs and validated methods.

There are also strengths in our study. To the best of our knowledge, this is the first systematic review and meta-analysis to examine preoperative risk factors associated with early postoperative bleeding. Hence, we believe that the generated information is relevant to the field and to conduct future studies. Second, we performed a comprehensive search, encompassing three different electronic bibliographic databases and not applying exclusion criteria based on the date or the language of publication.

In conclusion, our results suggest that, after RYGB, patients with some preoperative risk factors, including age, gender, hypertension, revisional bariatric surgery, and preoperative administration of enoxaparin may need to be more judiciously monitored for early bleeding, as they are at increased risk of developing such event. Preoperative optimization of hemorrhagic risk factors is an essential step in the preoperative assessment of these patients. Further research on more preoperative risk factors could allow the building of a clinical tool to predict early postoperative bleeding risk.

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Declarations

Competing interests The authors declare no competing interests.

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Late postoperative complications

Nutritional deficiencies

Vitamin B Complex Deficiency After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy - a Systematic Review and Meta-Analysis. *Obes Surg* 32, 873–891 (2022) (*) doi: [10.1007/s11695-021-05783-2](https://doi.org/10.1007/s11695-021-05783-2)

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Hugo Santos-Sousa was the ***Corresponding Author***

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Journal Impact Factor (JIF) 2,9 | Rank 63 of 213 on Surgery journals (**Q2**)

Journal Citation Indicator (JCI) 1,22 | Rank 41 of 286 on Surgery Journals (**Q1**)

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Vitamin B Complex Deficiency After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy—a Systematic Review and Meta-Analysis

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Abstract

Bariatric surgery, although an effective method, still has complications, like nutritional deficiencies. Our aim was to summarize the evidence on the frequency of complex B vitamin deficiencies in studies comparing Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). We included 25 studies for qualitative synthesis and 21 studies for quantitative synthesis. Relevant data was extracted, including proportion of patients with deficiency and mean serum vitamin values in 3 different timeframes. B12 and folate were the most prevalent deficiencies. B12 deficiency was more common after RYGB and folate serum mean levels were higher after RYGB. SG causes less nutrient deficiency and is therefore a better technique from this point of view. More studies are needed on B2, B3, and B6 vitamins to draw better conclusions.

Keywords Obesity · Vitamin B complex deficiencies · Bariatric surgery · Roux-en-Y gastric bypass · Sleeve gastrectomy

Key Points

- Bariatric surgery is associated with vitamin deficiency.
- RYGB is associated with higher B12 deficiency and folate serum levels (vs. SG).
- Patients who underwent SG have more vitamin B6 deficiency (vs. SG).
- It is vital to monitor vitamin deficiencies before and after bariatric surgery.

Authors Rita Nunes and Hugo Santos-Sousa have contributed equally to this work and should both be considered first authors.

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Introduction

Obesity is a chronic metabolic disease that has acquired epidemic proportions. According to the World Health Organization (WHO), in 2016, 39% of adults were considered overweight and 13% had obesity [1].

Overweight and obesity are a risk factor for the development of an array of other health issues, such as cardiovascular disease, type 2 diabetes, musculoskeletal disorders, and some types of cancer, having a major impact on life expectancy. Additionally, it is responsible for markedly expanding health and social-economic burden.

A body mass index (*BMI*) ≥ 25 kg/m² is considered overweight and a *BMI* ≥ 30 kg/m² is considered obese. Having a *BMI* ≥ 25 kg/m² was defined as being the sixth biggest risk factor for the overall burden of disease [2].

Obesity is an intricate multifactorial disease, caused by several biological, genetic, social, environmental, and behavioral determinants [3]. Nevertheless, one of its main causes is a disproportion between calorie intake and calorie expenditure [3].

One of the available treatments is bariatric surgery, which has proven to be effective in the treatment of obesity, and consequently improved the quality of life of these patients [4].

Although worldwide heterogeneous national criteria for patient selection can be observed, it is widely accepted that

a person is considered eligible for bariatric surgery in the presence of a $BMI \geq 40 \text{ kg/m}^2$ or $BMI \geq 35 \text{ kg/m}^2$ with one or more coexisting obesity-related comorbidities [5].

Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) have become two of the trendiest and most common bariatric surgery procedures in recent years [6].

In 2018, there were 696,191 bariatric surgeries performed worldwide. SG was the most commonly used technique comprising 55.4% of all surgeries followed by RYGB with 29.3% [7].

According to the American Society for Metabolic and Bariatric Surgery (ASMBS), the most common method in the United States of America is, by far, sleeve gastrectomy, accounting in 2017 for 59.4% of all bariatric surgeries. The second most performed method was Roux-en-Y gastric bypass, constituting 17% of all surgeries [8].

Although bariatric surgery is considered safe, some risks must be considered. One common complication of bariatric surgery is nutritional deficiencies caused by inadequate nutrient intake, especially of micronutrients [9].

Additionally, these vitamins, particularly vitamin B12, have complex mechanisms of absorption, requiring factors produced in the stomach, which can be partially resected, in the case of SG or bypassed, in the case of RYGB [10]. This would lead us to believe a RYGB procedure would have a greater impact on the levels of vitamin B12 since the exclusion of the stomach leads to a decrease of stimulation of the gastric tissue and hypoacidity, which reduce the production of intrinsic factor in a greater level than a SG procedure does [11].

Folate is absorbed mainly in the upper third of the small intestine [12]. Since in the RYGB procedure, this area is bypassed, we would expect that this technique would lead to a higher risk of folate deficiency.

Vitamin B1 and vitamin B6 are absorbed in the proximal parts of the small intestine. Vitamin B1 is absorbed in the duodenum and proximal jejunum, [13] while vitamin B6 is absorbed mainly in the upper jejunum, as well as in the ileum, [14] leading us to believe a RYGB procedure would have a greater impact in the absorption of these vitamins since it excludes duodenum and part of the proximal jejunum [15].

These nutritional deficiencies can cause a wide array of symptoms and pathologies that can sometimes be life threatening.

The aim of this systematic review and meta-analysis is to compare the effect of RYGB and SG on vitamin B complex deficiencies in patients with obesity. Although it is certain that nutritional deficiencies are prevalent after bariatric surgery, there is still little evidence regarding the impact each technique has on these deficiencies. This study could not only help establish a more accurate postoperative nutritional supplementation regime, adequate to the type of surgery the patient will be subjected to, as well as aid in deciding between these two common surgical techniques.

Methods

Search Strategy

Literature of the effects of bariatric surgery on vitamin deficiency was extracted from three databases: PubMed, Scopus, and the Cochrane Central Register of Controlled Trials. The search was conducted using five queries: [((“gastric bypass”[MeSH Terms] OR (“gastric”[All Fields] AND “bypass”[All Fields])) OR “gastric bypass”[All Fields]) OR “roux en y gastric bypass”[All Fields]] AND [(((“sleeve”[All Fields] OR “sleeved”[All Fields]) OR “sleeves”[All Fields]) OR “sleeving”[All Fields]) AND ((“gastrectomy”[MeSH Terms] OR “gastrectomy”[All Fields]) OR “gastrectomies”[All Fields]))] AND [((“avitaminosis”[MeSH Terms] OR “avitaminosis”[All Fields]) OR (“vitamin”[All Fields] AND “deficiency”[All Fields])) OR “vitamin deficiency”[All Fields]], and [avitaminosis [all fields] AND obesity [all fields] AND bariatric surgery [all fields]] for pubmed; ALL (“gastric bypass”OR “roux en y gastric bypass”) AND ALL (“sleeve”OR “sleeved”OR “sleeves”OR “sleeving”) AND ALL (“gastrectomy”OR “gastrectomies”) AND ALL (“avitaminosis”OR “vitamin”) AND ALL (“deficiency”OR “vitamin deficiency”) for Scopus; [(gastric bypass) AND (sleeve gastrectomy) AND (vitamin deficiency)], and [(bariatric surgery) AND (vitamin deficiency) AND (obesity)] for the Cochrane Central Register of Controlled Trials. All articles up to November 2020 were considered.

Selection Criteria

In order to be included, studies had to meet the following criteria:

- (1) Comparison of SG and RYGB; (2) evaluation of the effects of RYGB and SG on the deficiency of any of the B-complex vitamins; (3) original data was available.

Studies were excluded if:

- (1) The population was not adult (2); the population included only patients with diabetes mellitus; (3) the article was a review, letter, article of opinion, editorial, or animal study.

The search was conducted, independently, by two researchers who selected relevant studies based on their titles and abstracts and detected duplicate studies.

On a second phase, selected full text articles were examined and included if they met all criteria. Any disagreements were discussed. Concomitantly, the reference lists of relevant articles were searched.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used [16].

Quality Assessment and Data Extraction

We used the Cochrane's Collaboration Tool [17] and the Methodological Index for Non-randomized Studies (MINORS) [18] to assess the quality of the randomized controlled trials (RCT) (Fig. 1) and the observational studies (OBSs) (Table 1), respectively. Discrepancies were discussed with a third researcher.

Two independent authors extracted pre-defined study characteristics into a structured excel spreadsheet (author, publication year, country, study design, sample size, patient inclusion criteria, follow-up time, reference ranges for deficiency, baseline age, *BMI*, % of women and B-complex vitamin proportion of deficiency and mean values at baseline and in the three timeframes after RYGB and SG) from each included article.

Statistical Analysis

Review manager 5.4 was used to analyze the data for the meta-analysis. Data was grouped into short-term (< 1 year), mid-term (≥ 1 year and < 3 years), and long-term results (≥ 3 years) and we conducted sub-group and pooled analysis. For continuous data, we calculated mean differences (MD), and for dichotomous data, we calculated odds ratios (OR). A 95% confidence interval (CI) and a random effects model were used for every outcome. $P < 0.05$ was considered

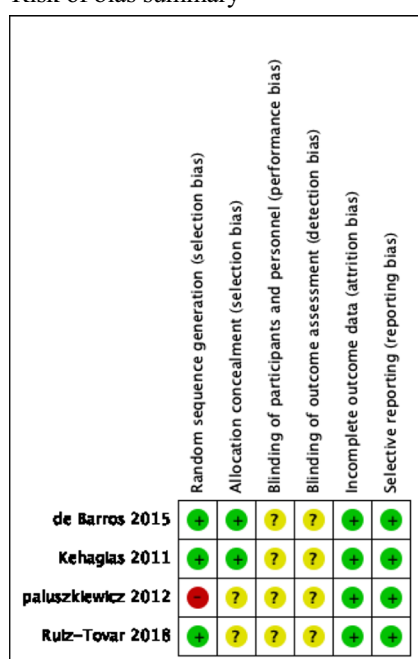
statistically significant. Heterogeneity was assessed using the Q test and I^2 statistic.

Results

A total of 3174 studies were identified through database searching and an additional 5 articles through manual screening of relevant articles. After detection of duplicates, we obtained 2832 articles, and after screening titles and abstracts, a total of 55 articles were left. After reading the full-text articles, 25 studies were eligible for inclusion in the qualitative synthesis. For the meta-analysis, 21 studies were included. Figure 2 shows the flow diagram describing the steps followed.

Table 2 shows the characteristics of all studies included in the systematic review. Of the 25 studies eligible, 6 were randomized controlled trials (RCTs), 12 retrospective observational studies (OBSs), and 7 prospective observational studies (OBSs). Articles were published between 2009 and 2020 and conducted in Australia, Brazil, China, Finland, France, Greece, India, Iran, Italy, Poland, Spain, Switzerland, and the USA. The shortest follow-up time was 3 months and the longest was 72 months. Data from 5729 patients was extracted to be included in the meta-analysis, including 3191 patients submitted to RYGB surgery and 2538 patients submitted to SG surgery. We extracted proportion of deficiency, mean and

Risk of bias summary



Risk of bias graph

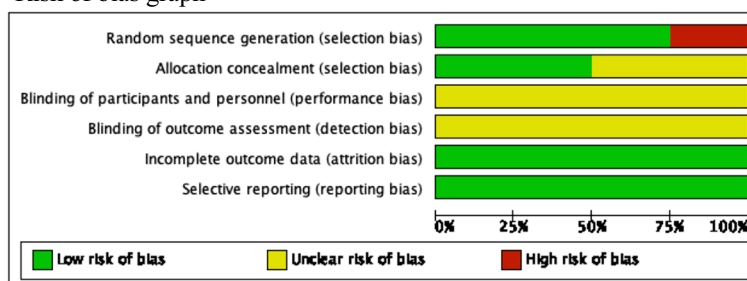


Fig. 1 Risk of bias summary and graph for the RCTs included in the meta-analysis

Table 1 Methodological Index for Non-randomized Studies

Study	1)	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)	Total
Toh, 2009 [46]	2	2	2	2	0	2	2	2	-	-	-	-	14
Gehrer, 2011 [22]	2	2	2	2	0	2	2	2	2	2	1	2	21
Moizé, 2013 [35]	2	2	2	2	0	2	1	2	2	2	1	2	20
Alexandrou, 2014 [19]	2	2	2	2	0	2	2	2	2	2	1	2	21
Coupaye, 2014 [26]	2	1	2	2	0	2	1	2	2	2	2	2	20
Verger, 2015 [52]	2	2	2	2	0	2	1	2	2	2	1	2	20
Ferraz, 2016 [53]	2	2	2	2	0	2	1	2	2	2	1	2	20
Nassour, 2017 [29]	2	2	2	1	0	2	2	0	2	2	0	2	17
Guan, 2018 [20]	2	2	2	2	0	2	1	2	2	2	1	2	20
Javanainen, 2018 [27]	2	2	2	2	0	2	2	2	2	2	1	2	21
Antoniewicz, 2019 [10]	2	2	2	2	0	2	2	2	2	2	1	2	21
Bhandari, 2019 [54]	2	2	2	2	0	2	1	2	2	2	1	2	20
Johnson, 2019 [55]	2	2	2	2	0	2	1	2	2	2	1	2	20
Lombardo, 2019 [56]	2	1	2	2	0	2	2	2	-	-	-	-	13
Vinolas, 2019 [57]	2	2	2	2	0	2	1	1	2	2	1	2	19
Hosseini-Esfahani, 2020 [34]	2	2	2	2	0	2	2	2	2	2	1	2	21
Ledoux, 2020 [21]	2	0	2	2	0	2	1	2	2	2	1	2	18
Misra, 2020 [30]	2	2	2	2	0	2	1	2	2	2	1	2	20
Souza, 2020 [28]	2	0	2	2	0	2	1	2	2	2	1	2	18

0 – not reported; 1 – reported but inadequate; 2 – reported and adequate

median values of vitamin B12, folate, B6, B1, and B2. Table 3 shows the reference range for deficiency used in each study. Table 4 shows the preoperative characteristic of the patients included in the meta-analysis. Tables 5, 6, 7, and 8 show the proportion of deficiency and serum values of vitamin B12, folate, B1, and B6, which were used in the meta-analysis.

We grouped results from every article into short-term (< 1 year), mid-term (≥ 1 year and < 3 years), and long-term results (≥ 3 years) and conducted sub-group and pooled analysis. Ledoux et. al considered two timeframes, one of which ≤ 1 year, which we considered in our short-term group. When there was more than one measurement for one of these time frames, the latest measurement was chosen. As long as there were two or more data in each time frame, a forest plot was created. Forest plots were created for vitamin B12, folate, B1, and B6 using dichotomous data and continuous data. In the continuous data, we chose to use results from articles presented as mean serum vitamin and standard deviation (SD) as there was more data available.

Vitamin B12

Figure 3 shows the continuous and dichotomous data for vitamin B12. In the dichotomous data, we found that there was a significantly greater number of patients who presented with deficiency after RYGB, when comparing with SG in the short-term period (12 studies; $OR=1.47$, 95% CI (1.04, 2.08); $P=0.03$; $I^2=0\%$), the long-term period (10 studies; $OR=2.22$, 95% CI (1.22, 4.04); $P=0.009$; $I^2=62\%$) as well

as in the pooled analysis ($OR=1.66$, 95% CI (1.29, 2.15); $P=0.0001$; $I^2=27\%$). In the mid-term analysis, deficiency was also more frequent after RYGB, albeit not significant.

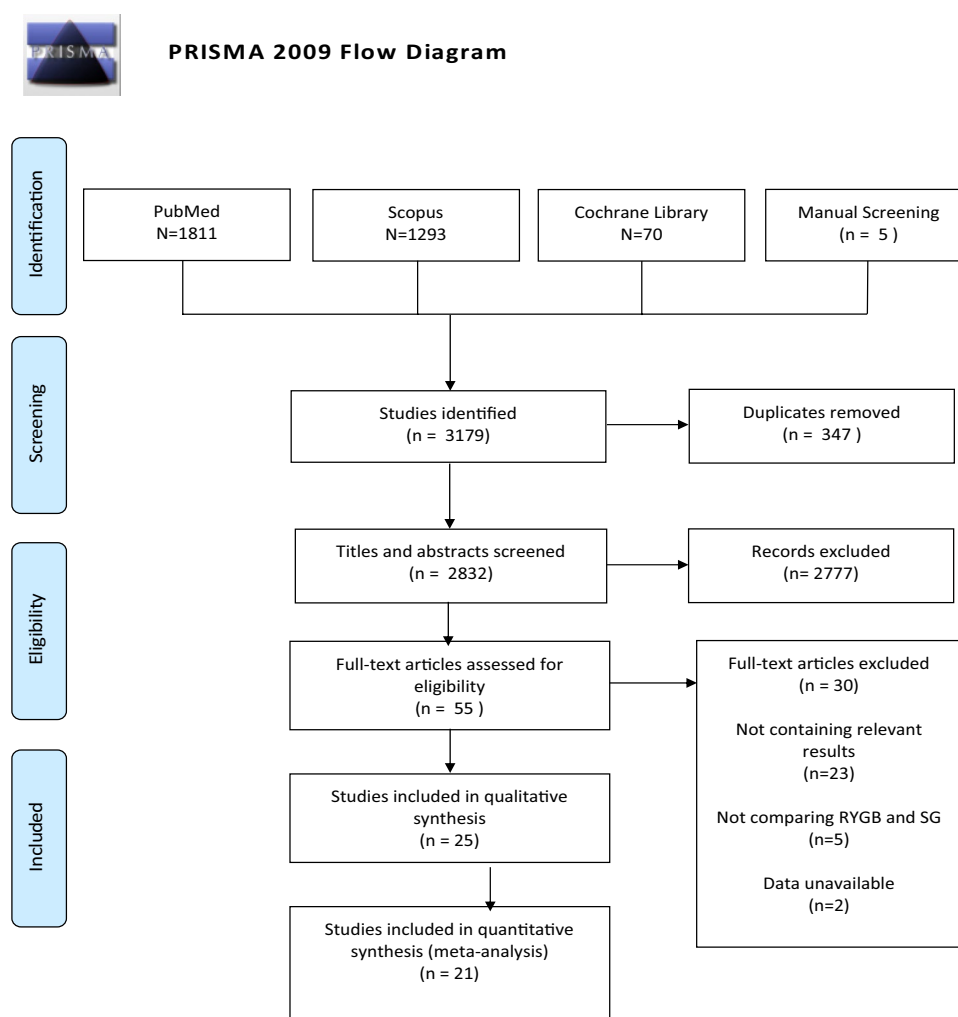
The continuous data revealed significantly higher serum B12 mean levels after SG, in the long-term (3 studies; $MD=-50.17$, 95% CI (-71.27, -29.08); $P<0.00001$; $I^2=0\%$) and in the pooled analyses ($MD=-44.78$, 95% CI (-67.54, -22.02); $P=0.0001$; $I^2=44\%$). In the short and mid-term, mean values were higher after SG but not significantly. This supports our findings in the dichotomous data, since there were more deficiencies after RYGB and therefore, lower vitamin mean values.

Folate

On the other hand, the dichotomous analysis for the proportion of folate deficiency (Fig. 4) showed no statistically significant differences between the two surgical techniques, although the forest-plots show a tendency for higher proportion of deficiency after SG in the 3 timeframes as well as in the pooled analysis.

Contrastingly, there were significantly higher values of mean serum folate after RYGB, in the mid-term (3 studies; $MD=3.04$, 95% CI (0.95, 5.12); $P=0.004$; $I^2=15\%$) and in the pooled analysis ($MD=2.56$, 95% CI (0.89, 4.24); $P=0.003$; $I^2=31\%$). The analysis on the long-term was not possible, seeing as only one study, Alexandrou et al. [19] reported data on this timeframe. This study found a higher mean folate value after RYGB, but there was no statistically significant difference

Fig. 2 PRISMA flow diagram for selection of studies in the systematic review and meta-analysis



($P=0.093$). In the short-term analysis, there were higher folate levels after RYGB, but it was not significant.

Vitamin B1

Figure 5 shows the continuous and dichotomous analysis for vitamin B1. Although there is a tendency for more proportion of deficiency after SG, no significant differences were found between the two techniques in any of the time frames regarding the dichotomous data.

Similarly, we found no significant differences for the continuous data, albeit there being a tendency for higher mean B1 levels after RYGB. We did not find any study that reported data on the long-term for the continuous analysis.

Vitamin B6

Figure 6 shows the data for vitamin B6 deficiency. We did not find any significant differences between the two techniques in the dichotomous analysis in any of the timeframes, but there was a tendency for a higher proportion of patients

with deficiency after SG and the pooled analysis showed significant difference in that sense ($OR=0.60$, 95% CI (0.37, 0.95); $P=0.03$; $I^2=44\%$).

Regarding the continuous analysis, there was a tendency for higher mean values after RYGB, but there were not statistically significant differences between the techniques. Furthermore, we did not find any articles with data in the long-term; hence, this analysis was not possible.

Vitamin B2

Only one article reported data on the proportion of vitamin B2 deficiency after RYGB and SG. Although, preoperatively, there was a percentage of 1.4% and 0.8% of deficiency, in a subgroup of patients later submitted to RYGB and SG, respectively, Guan et al. [20] did not find any deficiency in the post-operative analysis. Regarding mean vitamin levels, there was no statistically significant difference found in any of the post-operative analysis. Further studies would be necessary to draw any type of conclusion on the effect of these type of surgeries on this vitamin.

Table 2 Included studies in the systematic review and characteristics

Author, year	Country	Study design	Sample size, no	Patient inclusion criteria	Follow-up (months)
Randomized controlled studies					
Kehagias, 2011 [25]	Greece	RCT	30/30	$BMI \leq 50 \text{ kg/m}^2$	36
Paluszkievicz, 2012 [58]	Poland	RCT	36/36	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity, age between 18 and 65	12
de Barros, 2015 [47]	Brazil	RCT	25/25	$BMI \geq 40 \text{ kg/m}^2$, age between 18 and 65	3
Peterli, 2017 [15]	Switzerland (multicenter)	RCT	110/107	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity. Failure of conservative treatment for > 2 years	36
Ruiz-Tovar, 2018 [42]	Spain	RCT	200/200	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity. > 18 years old	60
Salminen, 2018 [59]	Finland (multicenter)	RCT	119/121	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity, age between 18 and 65 and failure of conservative treatment	60
Non-randomized studies					
Toh, 2009 [46]	Australia	Retrospective	121/64	NR	12
Gehrer, 2010 [22]	Switzerland	Prospective	86/50	NR	36
Moizé, 2013 [35]	Spain	Prospective	294/61	NR	60
Coupaye, 2013 [26]	France	Prospective	43/43	NR	12
Alexandrou, 2014 [19]	Greece	Retrospective	55/40	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity. Failure of conservative treatment and expected adherence to postoperative care	12
Verger, 2015 [52]	France	Prospective	22/30	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity	12
Nassour, 2017 [29]	USA	Retrospective	141/97	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity	48
Ferraz, 2018 [53]	Brazil	Prospective	238/338	NR	24
Guan, 2018 [20]	China	Retrospective	120/149	$BMI \geq 32.5 \text{ kg/m}^2$ or $\geq 27.5 \text{ kg/m}^2$ with uncontrolled T2DM and at least one other metabolic disease. Age between 18 and 65	12
Javanainen, 2018 [27]	Finland	Retrospective	253/142	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity, age between 18 and 65 and failure of conservative treatment	24
Antoniewicz, 2019 [10]	Poland	Retrospective	47/51	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity, age between 18 and 65	12
Bhandari, 2019 [54]	India	Prospective	95/98	NR	72
Johnson, 2019 [55]	USA	Retrospective	110/358	NR	NR
Vinolas, 2019 [57]	France	Retrospective	28/29	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity	1, 3, 6, 12
Lombardo, 2019 [56]	Italy	Prospective	16/36	Age between 18 and 65	36,30

Table 2 (continued)

Author, year	Country	Study design	Sample size, no	Patient inclusion criteria	Follow-up (months)
Hosseini-Esfahani, 2020 [34]	Iran	Retrospective	58/122	$BMI \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ with comorbidity, age between 18 and 65, and failure of conservative treatment	12
Ledoux, 2020 (short-term) [21]	France	Retrospective	275/280	NR	12
Ledoux, 2020 (long-term) [21]			383/111	NR	> 36
Misra, 2020 [30]	India	Retrospective	132/258	According to the IFSO-APC guidelines	24
Souza, 2020 [28]	Brazil	Retrospective	582/109	NR	12

Note: All data is presented by the order of RYGB and SG

BMI body mass index, *T2DM* type 2 diabetes mellitus, *RCT* randomized controlled trial, *NR* not reported

Table 3 Reference range for deficiency

Study	Vitamin B12	Folate	Vitamin B1	Vitamin B6
Randomized controlled trials				
Kehagias, 2011 [25]	< 200 pg/mL	< 1.5 ng/mL	-	-
Paluszkiwicz, 2012 [58]	NR	-	-	-
De Barros, 2014 [47]	< 200 pg/dL	< 3 ng/mL	-	-
Ruiz-Tovar, 2018 [42]	NR	-	-	-
Non-randomized studies				
Toh, 2009 [46]	< 145 pmol/L	< 7.0 nmol/L	-	-
Gehrer, 2010 [22]	< 150 pmol/L	< 6 nmol/l	< 66 nmol/l	< 35 nmol/l
Moizé, 2013 [35]	< 250 pg/mL	< 250 ng/mL ^a	< 66 nmol/l	< 15 ng/mL
Coupaye, 2013 [26]	< 190 ng/L or pg/mL	< 3 ng/mL	< 126 nmol/L	< 20 nmol/l
Alexandrou, 2014 [19]	< 200 pg/mL	< 4 ng/mL	-	-
Verger, 2015 [52]	< 140 pmol/l = 189.75 pg/mL	< 945 nmol/L ^a	< 126 nmol/L	-
Ferraz, 2016 [53]	< 200 pg/mL	-	-	-
Guan, 2018 [20]	< 211 pg/mL	< 4.6 ng/mL	< 50 nmol/l	< 14.6 nmol/L
Javanainen, 2018 [27]	< 138 pmol/L = 187.04 pg/mL	-	-	-
Antoniewicz, 2019 [10]	NR	NR	-	-
Bhandari, 2019 [54]	< 200 ng/mL	-	-	-
Johnson, 2019 [55]	< 210 pg/ml	-	< 70 nmol/l	-
Lombardo, 2019 [56]	< 200 pg/mL	-	-	-
Vinolas, 2019 [57]	< 180 ng/mL	< 3 ng/mL	< 66.5 nmol/l	< 66.5 nmol/l
Ledoux, 2020 [21]	< 190 ng/l	< 3 ug/l	< 126 nmol/L	< 20 nmol/l
Misra, 2020 [30]	< 220 pg/dL	-	-	-
Souza, 2020 [28]	< 200 pg/mL	-	-	-

NR not reported

^aIntraerythrocyte folic acid

Vitamin B3

Only Ledoux et al. [21] reported data on B3 deficiency after RYGB and SG. This study reported two timeframes, short-term, which reported data in ≤ 1 year post-operatively, and the long-term, which reported data in ≥ 3 years

post-operatively. In the short-term, 13.1% and 10.7% of patients had vitamin B3 deficiency after RYGB and SG, respectively. In the long-term, 19.8% and 20.7% of patients had deficiency after RYGB and SG. In spite of there not being any statistically significant difference between the two surgical methods in either of the time frames, the percentage

Table 4 Preoperative characteristics of the studies included in the meta-analysis

Author, year	Country	Surgery	Sample size, no	Baseline mean age, (SD), year	Baseline mean BMI (SD) (kg/m ²)	Baseline % of women	Baseline B12 proportion of deficiency (%)	Baseline B12 mean serum values	Baseline folate proportion of deficiency (%)	Baseline folate serum levels	Baseline B1 proportion of deficiency (%)	Baseline B1 serum levels	Baseline B6 proportion of deficiency (%)	Baseline B6 serum levels
Randomized controlled studies														
Kehagias, 2011 [25]	Greece	RYGB	30	36 (8.4)	45.8(3.7)	73.3	1/30 (3.3)	—	0/30 (0)	—	—	—	—	—
		SG	30	33.7 (9.9)	44.9(3.4)	73.3	1/30 (3.3)	—	0/30 (0)	—	—	—	—	—
Paluszkievicz, 2012 [58]	Poland	RYGB	36	43.9(10.8)	48.6(5.4)	63.9	ND	—	—	—	—	—	—	—
		SG	36	44.9(10.6)	46.1(5.9)	72.2	ND	—	—	—	—	—	—	—
De Barros, 2014 [47]	Brazil	RYGB	25	35.20 (10.83)	49.24 (7.99)	92	3/25 (12)	—	0/25 (0)	—	—	—	—	—
		SG	25	38.24 (9.51)	45.62 (6.51)	92	1/25 (4)	—	0/25 (0)	—	—	—	—	—
Ruiz-Tovar, 2018 [42]	Spain	RYGB	200	45(11.3)	45.3(3.2)	75	ND	—	ND	—	—	—	—	—
		SG	200	43.9(10.9)	46.5(3.4)	75	ND	—	ND	—	—	—	—	—
Non-randomized studies														
Toh, 2009 [46]	Australia	RYGB	121	48(10)	43.1(5.2)	63.64	1/88 (1)	374 (166.7)	0/65 (0)	—	—	—	—	—
		SG	64	46(12)	51.0(11.2)	57.8	2/46 (4)	305 (110.5)	0/32 (0)	—	—	—	—	—
Gehrer, 2010 [22]	Switzerland	RYGB	86	43.5(23–66)	44.2(35–56)	71	ND	—	ND	—	ND	—	ND	—
		SG	50	41.9(21–64)	46.5(38–58)	74	ND	—	ND	—	ND	—	ND	—
Moizé, 2013 [35]	Spain	RYGB	294	45.2(10.6)	47.4(6.0)	77	5/294 (1.8)	—	5/294 (1.8)	—	16/294 (5.5)	—	33/294 (11.3)	—
		SG	61	46.4(11.6)	51.6(6.7)	67.2	2/61 (2.7)	—	0/61 (0)	—	0/61 (0)	—	46/61 (75)	—
Coupaye, 2013 [26]	France	RYGB	43	44(9)	48.6(7.8)	72.1	3/43 (7)	433.6 (229.2)	3/43 (7)	6.2+–2.7	15/43 (35)	139.8±34.6	15/43 (35)	25.6±17.8
		SG	43	45(11)	48.5(9.6)	72.1	1/43 (2)	462.9 (152.3)	3/43 (7)	6.6+–3.2	16/43 (37)	139.3±40.3	8/43 (19)	35.7±22.8
Alexandrou, 2014 [19]	Greece	RYGB	55	44.8(9.9)	49.1(6.1)	72.7	ND	ND	ND	ND	—	—	—	—
		SG	40	43.4(11.2)	51.5(7.2)	90	ND	ND	ND	ND	—	—	—	—
Verger, 2015 [58]	France	RYGB	22	43.5(38.0–51.0)	45.5(41.6–49.1)	68.2	1/22 (5)	284(209–334) ^a	4/22 (18)	1287 (1023–1429) ^a	2/22 (9)	157 (150–174) ^a	—	—
		SG	30	41.0(36.0–49.0)	43.2(39.0–47.7)	66.7	1/30 (3)	293 (248–358) ^a	5/30 (17)	1234 (1036–1377) ^a	5/30 (17)	147 (134–175) ^a	—	—
Ferraz, 2016 [53]	Brazil	RYGB	238	41.9(11.1)	42.7(5.9)	67.6	9/238 (3.7)	482.7 (320.9)	—	—	—	—	—	—
		SG	338	37.2(11)	39.4(2.6)	85.8	10/338 (2.9)	451.4 (17)	—	—	—	—	—	—
Guan, 2018 [20]	China	RYGB	120	33.46(9.89)	43.73(11.03)	42.5	4/120 (3.3)	424.5 (309.0)	39/120 (32.5)	5.7 (4.9)	36/120 (30)	63.5 (18.2)	29/120 (24.3)	25.7 (22.0)
		SG	149	30.23(10.72)	37.18(7.07)	73.8	5/149 (3.4)	398.0 (211.0)	33/149 (22.1)	6.6 (4.9)	62.58/149 (42)	51.4 (18.5)	45/149 (30.3)	20.0 (15.2)
Javanainen, 2018 [27]	Finland	RYGB	253	47.0(41.5–54.0)	47.5(43.7–52.6)	66.8	ND	ND	—	—	—	—	—	—
		SG	142	48.0(40.0–57.0)	47.9(43.8–54.7)	71.8	ND	ND	—	—	—	—	—	—
Antoniewicz, 2019 [10]	Poland	RYGB	47	44.29(8.97)	49.78(46.25–55.63)	70.21	3/47 (6.4)	245.02 (174.19–329.15) ^a	6/47 (12.8%)	18.58 (14.73–25.61) ^a	—	—	—	—
		SG	51	43.93(11)	44.11(41.27–49.12)	65.96	3/51 (5.9)	256.68 (194.46–319.55) ^a	0/51 (0%)	19.48 (15.86–25.27) ^a	—	—	—	—
Bhandari, 2019 [54]	India	RYGB	95	45.40(12.57)	45.25(6.04)	53.7	37/95 (38.94)	—	—	—	—	—	—	—
		SG	98	40.21(13.78)	45.39(8.44)	52.1	35/98 (35.71)	—	—	—	—	—	—	—
Johnson, 2019 [55]	USA	RYGB	110	45.6(13.0)	44.3(7.2)	89	1/110 (1.6)	578 (403)	—	—	—	126±34	—	—
		SG	358	41.0(11.8)	47.2(7.6)	84	3/358 (1.3)	549 (336)	—	—	—	120±36	—	—
Lombardo, 2019 [56]	Italy	RYGB	16	41.4(8.6)	48(8.1)	93.75	13/16 (81.25)	—	—	—	—	—	—	—
		SG	36	43.5(11.5)	49.5(7.8)	72.22	20/36 (55.56)	—	—	—	—	—	—	—
Vinolas, 2019 [57]	France	RYGB	28	42.9(11)	46.8(6.9)	ND	4/28 (16)	286.4 (126.7)	0/28 (0)	8.2±5.6	0/28 (0)	135.8±20.25	6/28 (24)	46.5±71.3
		SG	29	45.2(9.2)	44.1(9.4)	ND	1/29 (4.3)	370.7 (170)	0/29 (0)	8.4±8.3	1/29 (3.8)	122.9±40.5	3/29 (11.5)	45.2±36.1

Table 4 (continued)

Author, year	Country	Surgery	Sample size, no	Baseline mean age, (SD), year	Baseline mean BMI (SD) (kg/m ²)	Baseline % of women	Baseline B12 proportion of deficiency (%)	Baseline B12 mean serum values	Baseline Folate proportion of deficiency (%)	Baseline folate serum levels	Baseline B1 proportion of deficiency (%)	Baseline B1 serum levels	Baseline B6 proportion of deficiency (%)	Baseline B6 serum levels
Ledoux, 2020 (Short-term) [21]	France	RYGB	275	43.5(18.8)	33.5(9.2)	86	ND	—	ND	—	ND	—	ND	—
		SG	280	42.1(11.0)	32.7(5.4)	86	ND	—	ND	—	ND	—	ND	—
Ledoux, 2020 (Long-term) [21]		RYGB	383	48.2(10.7)	31.5(6.2)	88	ND	—	ND	—	ND	—	ND	—
		SG	111	46.3(10.3)	34.0(8.5)	90	ND	—	ND	—	ND	—	ND	—
Misra, 2020 [30]	India	RYGB	132	40.09(10.2)	42.49(5.78)	59.09	0/132 (0)	440.46 (87.94)	—	—	—	—	—	—
		SG	258	38.26(11.35)	44.64(8.12)	55.81	12/258 (4.7)	449.87 (108.38)	—	—	—	—	—	—
Souza, 2020 [28]	Brazil	RYGB	582	37.6(9.3)		75.1	ND	—	—	—	—	—	—	—
		SG	109				ND	—	—	—	—	—	—	—

All serum vitamin values are expressed in means (standard deviation) except the ones identified with ^avalues expressed in median and Interquartile range (IQR) (All units are accessible in Table 3)

of deficiency was still high, especially in the long-term. Therefore, more research would be beneficial.

Discussion

Vitamin deficiencies are common in individuals with obesity and bariatric surgery may exacerbate them [22]. According to the ASMBS nutritional guidelines, [23] routine pre-surgery screening of vitamin B12 and folate (Grade B evidence), as well as vitamin B1 (Grade C evidence), should be conducted to identify potential nutritional deficiencies. However, failure to test for vitamin deficiencies pre- and post-surgery is still high [24].

In regard to vitamin B12, we found a significantly higher proportion of patients with deficiency after RYGB when compared to SG, particularly in the short- and long-term. A total of 9 studies found that, at any time, there were significantly higher numbers of patients with deficiency after RYGB [10, 19, 20, 22, 25–29]. Misra et al. found that 3 years after RYGB surgery, 36.4% of patients had presented with vitamin B12 deficiency [30]. Regarding the mean vitamin level, we found that in the pooled analyses, there were significantly higher means after SG, which supports the results previously described. Furthermore, the statistical significance was greater in the long-term, for the proportion of deficiency and the mean values, suggesting a more pronounced vitamin B12 deficiency after RYGB in the late stages post-surgery. This can be due to an insufficient supplementation of these patients in the long-term by health care services or an inadequate compliance of the patient.

This propensity for vitamin B12 deficiency after RYGB is greatly explained by the complex mechanism of its absorption. The absorption of this vitamin is affected due to the bypass of structures in RYGB, leaving a lower absorption surface as well as a lower secretion from the stomach of the factors needed for absorption, such as intrinsic factor and gastric acid [10, 31–33]. Additionally, studies have shown that in the first year after bariatric surgery, patients consumed less than the recommended dose of daily protein intake [34, 35]. SG, being a restrictive procedure, does not bypass the duodenum and is less associated with this type of vitamin deficiency. Vitamin B12 storage lasts up to 3 years, which means that clinical deficiency can take several years after surgery to manifest [36]. Therefore, deficiencies presenting in the short-term period after bariatric surgery, as we see in this meta-analysis, may indicate that a deficiency was already present pre-surgery.

Despite regular supplementation, Peterli et al. found a high prevalence of B12 deficiency, supporting the need for prolonged supplementation and close monitoring of deficiencies regardless of which technique is performed [15].

Table 5 Vitamin B12 proportion of deficiency and serum values

Author, year	Surgery	Post-op B12 proportion of deficiency (%)			Post-op B12 mean (SD) serum values (N)		
		Short-term	Mid-term	Long-term	Short-term	Mid-term	Long-term
Randomized controlled studies							
Kehagias, 2011 [25]	RYGB	NR	NR	7/29 (24.1)	-	-	-
	SG	NR	NR	1/28 (3.57)	-	-	-
Paluszkiewicz, 2012 [58]	RYGB	11/36 (30.6)	NR	NR	-	-	-
	SG	5/36 (13.8)	NR	NR	-	-	-
De Barros, 2014 [47]	RYGB	2/25 (8)	NR	NR	-	-	-
	SG	1/25 (4)	NR	NR	-	-	-
Ruiz-Tovar, 2018 [42]	RYGB	NR	17/184 (9.5)	18/184 (10)	-	-	-
	SG	NR	15/182 (8.5)	13/182 (7)	-	-	-
Non-randomized studies							
Toh, 2009 [46]	RYGB	NR	6/56 (11)	NR	NR	429 (323.3) (56)	NR
	SG	NR	0/9 (0)	NR	NR	323 (102.5) (9)	NR
Gehrer, 2010 [22]	RYGB	13/86 (15.12)	2/86 (2.3)	0/86 (0)	-	-	-
	SG	5/50 (10)	0/50 (0)	2/50 (4)	-	-	-
Moizé, 2013 [35]	RYGB	9/294 (2.9)	14/259 (5.5)	7/138 (5)	-	-	-
	SG	2/61 (3.7)	3/51 (5.9)	3/21 (12.5)	-	-	-
Coupaye, 2013 [26]	RYGB	5/43 (12)	5/30 (17)	NR	355.8 (172.2) (43)	334.9 (160.4) (30)	NR
	SG	2/43 (5)	2/30 (7)	NR	426.3 (155.5) (43)	430.5 (194.6) (30)	NR
Alexandrou, 2014 [19]	RYGB	NR	NR	23/55 (42.1)	NR	NR	278.4 (183.9) (55)
	SG	NR	NR	2/40 (5)	NR	NR	380.7 (206.7) (40)
Verger, 2015 [52]	RYGB	1/22 (5)	0/14 (0)	NR	252 (227–345) ^a (22)	221 (195–278) ^a (14)	NR
	SG	0/30 (0)	0/19 (0)	NR	311 (224–464) ^a (30)	311 (216–432) ^a (19)	NR
Ferraz, 2016 [53]	RYGB	NR	8/129 (6.2)	7/80 (8.7)	476.0 (214.1) (111)	437.7 (202.4) (129)	422.9 (194.1) (80)
	SG	NR	9/78 (11.5)	3/45 (6.6)	527.1 (309.9) (100)	443.2 (207.7) (78)	459.1 (222.8) (45)
Guan, 2018 [20]	RYGB	4/50 (8)	8/50 (16)	NR	302.0 (115.6) (50)	255.0 (147.6) (50)	NR
	SG	4/43 (9.3)	4/37 (10.8)	NR	345.8 (234.0) (43)	370.0 (210.2) (37)	NR
Javanainen, 2018 [27]	RYGB	NR	8/253 (3)	NR	NR	65.0 (56.0–77.3) ^a (253)	NR
	SG	NR	1/142 (1)	NR	NR	65.0(55.0–77.5) ^a (142)	NR
Antoniewicz, 2019 [10]	RYGB	1/47 (2.3)	12/47 (25.5)	NR	302.80 (207.82–387.15) ^a (47)	169.08 (140.22–230.92) ^a (47)	NR
	SG	1/51 (2.3)	4/51 (7.8)	NR	319.59 (233.10–461.36) ^a (51)	262.51 (206.20–352.54) ^a (51)	NR
Bhandari, 2019 [54]	RYGB	NR	NR	13/95 (13.68)	-	-	-
	SG	NR	NR	3/98 (3.06)	-	-	-
Johnson, 2019 [55]	RYGB	1/85 (1.2)	1/63 (1.4)	NR	832 (555) (85)	1142 (1342) (63)	NR
	SG	2/255 (0.9)	0/94 (0)	NR	1062 (1047) (255)	989 (1007) (94)	NR
Lombardo, 2019 [56]	RYGB	NR	Z	13/16 (81.25)	-	-	-
	SG	NR	NR	15/36 (41.67)	-	-	-
Vinolas, 2019 [57]	RYGB	0/25 (0)	4/26 (16)	NR	319 (128) (25)	288 (97) (26)	NR
	SG	2/25 (8.3)	4/28 (14.3)	NR	295 (135) (25)	327 (169) (28)	NR
Ledoux, 2020 [21]	RYGB	35/275 (12.7)	NR	45/383 (11.8)	-	-	-
	SG	21/280 (7.5)	NR	8/111 (7.2)	-	-	-
Misra, 2020 [30]	RYGB	NR	NR	38/105 (36.4)	NR	316.93 (104.08) (114)	282.18 (89.03) (105)
	SG	NR	NR	38/204 (18.8)	NR	359.41 (149.63) (210)	329.37 (110.22) (204)
Souza, 2020 [28]	RYGB	117/229 (51.1)	98/172 (57)	NR	-	-	-
	SG	16/30 (53.3)	8/16 (50)	NR	-	-	-

NR not reported

^aResults reported in median and IQR

Table 6 Folate proportion of deficiency and serum values

Author, year	Surgery	Post-op folate proportion of deficiency (%)			Post-op folate mean (SD) serum values (N)		
		Short-term	Mid-term	Long-term	Short-term	Mid-term	Long-term
Randomized controlled studies							
Kehagias, 2011 [25]	RYGB	NR	NR	0/29 (0)	-	-	-
	SG	NR	NR	0/28 (0)	-	-	-
De Barros, 2014 [47]	RYGB	0/25 (0)	NR	NR	-	-	-
	SG	0/25 (0)	NR	NR	-	-	-
Ruiz-Tovar, 2018 [42]	RYGB	NR	20/184 (11)	22/184 (12)	-	-	-
	SG	NR	15/182 (8)	9/182 (5)	-	-	-
Non-randomized studies							
Toh, 2009 [46]	RYGB	NR	0/22 (0)	NR	-	-	-
	SG	NR	0/5 (0)	NR	-	-	-
Gehrer, 2010 [22]	RYGB	3/86 (3.49)	1/86 (1,16)	0/86 (0)	-	-	-
	SG	3/50 (6)	2/50 (4)	1/50 (2)	-	-	-
Moizé, 2013 [35]	RYGB	3/294 (0.9)	19/259 (7.5)	11/138 (7.9)	-	-	-
	SG	8/61 (13.6)	3/51 (6.1)	3/21 (12.5)	-	-	-
Coupaye, 2013 [26]	RYGB	0/43 (0)	1/30 (3)	NR	15.6 (7.5) (43)	14.0 (7.4) (30)	NR
	SG	4/43 (9)	2/30 (7)	NR	11.9 (9.5) (43)	11.0 (7.5) (30)	NR
Alexandrou, 2014 [19]	RYGB	NR	NR	10/55 (18.4)	NR	NR	8.3 (5.2) (55)
	SG	NR	NR	8/40 (20)	NR	NR	5.5 (1.9) (40)
Verger, 2015 [52]	RYGB	2/22 (9)	0/14 (0)	NR	1760 (1457–1961) ^a (22)	1940 (1421–2169) ^a (14)	NR
	SG	0/30 (0)	0/19 (0)	NR	1411 (1246–1806) ^a (30)	1540 (1366–1804) ^a (19)	NR
Guan, 2018 [20]	RYGB	11/50 (22)	2/50 (4)	NR	8.3 (10.3) (50)	11.3 (11.0) (50)	NR
	SG	5/43 (11.6)	4/37 (10.8)	NR	9.6 (8.7) (43)	11.2 (10.3) (37)	NR
Antoniewicz, 2019 [10]	RYGB	5/47 (11.4)	3/47 (6.4)	NR	19.03 (14.16–23.23) ^a (47)	21.30 (13.60–29.00) ^a (47)	NR
	SG	1/51 (2.3)	7/51 (13.7)	NR	19.48 (16.52–23.34) ^a (51)	21.52 (12.60–26.29) ^a (51)	NR
Vinolas, 2019 [57]	RYGB	0/25 (0)	1/26 (4.2)	NR	9.9 (5.6) (25)	10.6 (5.5) (26)	NR
	SG	2/25 (8.3)	1/28 (3.6)	NR	6.4 (5.3) (25)	6.5 (3.17) (28)	NR
Ledoux, 2020 [21]	RYGB	1/275 (0.4)	NR	7/383 (1.8)	-	-	-
	SG	11/280 (3.9)	NR	17/111 (15.3)	-	-	-

NR not reported

^aResults reported in median and IQR

Vitamin B12 deficiency can lead to macrocytic anemia [37]. Neurological symptoms, such as paresthesia of the limbs and numbness, and psychiatric symptoms of B12 deficiency usually manifest months or even years before macrocytic anemia [13].

Nowadays, the broader use of techniques with more sensitivity and specificity such as assays for the metabolites methylmalonic acid (MMA) and homocysteine has made the identification of lesser degrees of vitamin B12 deficiency possible [38]. This poses the question of what is in fact a clinically relevant deficiency or a subclinical deficiency and when and if these individuals with slightly higher levels of

MMA and homocysteine and lower levels of transcobalamin bound B12 will progress to a clinically relevant deficiency accompanied by symptoms of anemia or if they will remain with stable chronic low levels of this vitamin [39].

Iron deficiency anemia is also common in patients submitted to bariatric surgery, due to the exclusion of the duodenum and proximal jejunum where iron is absorbed, particularly after RYGB. Gastric hypoacidity, which leads to iron malabsorption; a disequilibrium between iron demands, which surpass absorption; and diminished intake of red meats are also factors for iron deficiency anemia [37]. A meta-analysis found that patients were more likely

Table 7 Vitamin B1 proportion of deficiency and serum values

Author, year	Surgery	Post-op vitamin B1 proportion of deficiency (%)			Post-op vitamin B1 mean (SD) serum values (N)		
		Short-term	Mid-term	Long-term	Short-term	Mid-term	Long-term
Non-randomized studies							
Gehrer, 2010 [22]	RYGB	0/86 (0)	NR	NR	-	-	-
	SG	0/50 (0)	NR	NR	-	-	-
Moizé, 2013 [35]	RYGB	25/294 (8.4)	5/259 (1.8)	8/138 (5.9)	-	-	-
	SG	3/61 (4.8)	13/51 (25)	0/21 (0)	-	-	-
Coupaye, 2013 [26]	RYGB	16/43 (37)	7/30 (23)	NR	141.2 (36.1) (43)	167.9 (60.7) (30)	NR
	SG	16/43 (37)	7/30 (23)	NR	140.65 (42.6) (43)	165.0 (53.0) (30)	NR
Verger, 2015 [52]	RYGB	1/22 (5)	0/14 (0)	NR	193 (155–193) ^a (22)	197 (174–215) ^a (14)	NR
	SG	1/30 (3)	0/19 (0)	NR	177 (158–191) ^a (30)	181 (149–218) ^a (19)	NR
Guan, 2018 [20]	RYGB	6/50 (12.5)	8/50 (16.1)	NR	65.1 (19.0) (50)	60.7 (32.1) (50)	NR
	SG	6/43 (14.7)	6/37 (16.7)	NR	70.4 (21.6) (43)	63.8 (29.7) (37)	NR
Johnson, 2019 [55]	RYGB	-	-	-	112 (37) (85)	129 (40) (63)	NR
	SG	-	-	-	113 (33) (255)	120 (36) (94)	NR
Vinolas, 2019 [57]	RYGB	0/25 (0)	0/26 (0)	NR	148.2 (34.3) (25)	163.4 (38.3) (26)	NR
	SG	0/25 (0)	1/28 (3.6)	NR	118 (21.5) (25)	128.9 (39.2) (28)	NR
Ledoux, 2020 [21]	RYGB	31/275 (11.3)	NR	24/383 (6.3)	-	-	-
	SG	42/280 (15)	NR	26/111 (23.4)	-	-	-

NR not reported

^aResults reported in median and IQR**Table 8** Vitamin B6 proportion of deficiency and serum values

Author, year	Surgery	Post-op vitamin B6 proportion of deficiency (%)			Post-op vitamin B6 mean (SD) serum values (N)		
		Short-term	Mid-term	Long-term	Short-term	Mid-term	Long-term
Non-randomized studies							
Gehrer, 2010 [22]	RYGB	0/86 (0)	NR	NR	-	-	-
	SG	0/50 (0)	NR	NR	-	-	-
Moizé, 2013 [35]	RYGB	18/294 (6)	10/259 (3.9)	6/138 (4.2)	-	-	-
	SG	16/61 (26.3)	0/51 (0)	0/21 (0)	-	-	-
Coupaye, 2013 [26]	RYGB	7/43 (16)	3/30 (10)	NR	42.5 (20.2) (43)	40.4 (20.1) (30)	NR
	SG	7/43 (16)	5/30 (17)	NR	37.6 (24.6) (43)	49.4 (31.7) (30)	NR
Guan, 2018 [20]	RYGB	13/50 (25)	11/50 (22.6)	NR	20.9 (13.2) (50)	21.1 (20.4) (50)	NR
	SG	11/43 (26.2)	10/37 (26.7)	NR	18.8 (13.1) (43)	18.9 (7.5) (37)	NR
Vinolas, 2019 [47]	RYGB	2/25 (8)	0/26 (0)	NR	79.3 (67.6) (25)	92.4 (62.0) (26)	NR
	SG	3/25 (12)	1/28 (3.6)	NR	70.5 (85.3) (25)	50.2 (19.9) (28)	NR
Ledoux, 2020 [21]	RYGB	15/275 (5.4)	NR	28/383 (7.3)	-	-	-
	SG	18/280 (6.4)	NR	20/111 (18)	-	-	-

NR not reported

^aResults reported in median and IQR

to have anemia after RYGB compared to SG. The same study also found significant higher levels of serum iron after SG [40].

Folate, on the other hand, is mainly absorbed in the upper third, and sometimes throughout the rest of the small intestine, and therefore not as affected by the changes in

anatomy caused by bariatric surgery [12]. Deficiency is mainly caused by an insufficient intake of folate-rich food. Nonetheless, vitamin B12 aids in the activation of folate and the deficiency of one can affect the other [41].

This meta-analysis showed no significant differences between the two techniques regarding the proportion of individuals who developed folate deficiencies. Ruiz-Tovar et al. [42] concluded that 5 years after surgery, patients submitted to RYGB had significantly greater need for folic acid supplementation. In contrast, it was shown that in the patients who underwent SG, there was a statistically significantly higher proportion of patients with folate deficiency, at 6 months, in Moizé et al. [35] and up to the year following surgery as well as 3 years post-surgery, in Ledoux et al. [21] Regarding the mean folate level analyses, we found there was a statistically higher folate mean level after RYGB in the mid-term as well as in the pooled analysis.

Folate deficiency can also lead to megaloblastic anemia, a type of macrocytic anemia. However, a meta-analysis conducted by Weng et al. found that the presence of anemia 1 year after RYGB was better related to vitamin B12 deficiency rather than folate deficiency, seeing as folate deficiency was not frequent in this study [43]. Other complications of folate deficiency are growth retardation and neural tube defects [13].

In contrast to vitamin B12, folate storage levels run out only a few months after the intake of this vitamin halts [44]. Therefore, it is expected that folate deficiency occurs in earlier stages after bariatric surgery when compared to vitamin B12 deficiency.

It is important to keep in mind that, due to folic acid fortification programs in several countries, deficiency in these populations might be much less accentuated than in countries where fortification is not general practice [45]. This fact can create a bias when analyzing the data of patients from different countries.

These findings come as a surprise considering the anatomy of folate's absorption.

To our knowledge, the only studies included in our meta-analysis which were conducted in a country where folic acid fortification is mandatory were by Toh et al. [46] and de Barros et al. [47]. Toh et al. [46] was a study conducted in Australia which has a folic acid fortification program in place. However, it was only introduced in September 2009 and the study was published in March 2009 [48]. This study did not find any patients with deficiency in the RYGB and SG group in pre-operative or 1 year post-op times [46].

De Barros et al. [47] conducted their study in Brazil which has a folic acid fortification program in action since 2004 [49]. This study conducted analysis in the pre-operative time and 3 months post RYGB and SG and there were no deficiencies found [47]. This may be due to the folic acid fortification program implemented.

We could think that, in the countries with no such programs in place, the notion that a RYGB procedure leads to more vitamin deficiencies would prompt a more rigorous supplementation regime. This could explain the tendency for more folate deficiency post SG in our meta-analysis.

Vitamin B1 is absorbed in the duodenum and proximal jejunum [13]. Deficiency can occur in patients with frequent vomiting, fast weight loss, and poor intake of thiamin-rich foods [32]. Small intestinal bacterial overgrowth (SIBO) may also be responsible for B1 deficiencies, as well as vitamin B12 deficiencies [50].

Common presentation of B1 deficiency is neuropathy ("dry" beriberi), high-output cardiovascular disease ("wet" beriberi), neuropsychiatric symptoms (Wernicke encephalopathy/korsakoff syndrome), and gastrointestinal beriberi (nausea, vomiting, constipation, and megajejunum) [51].

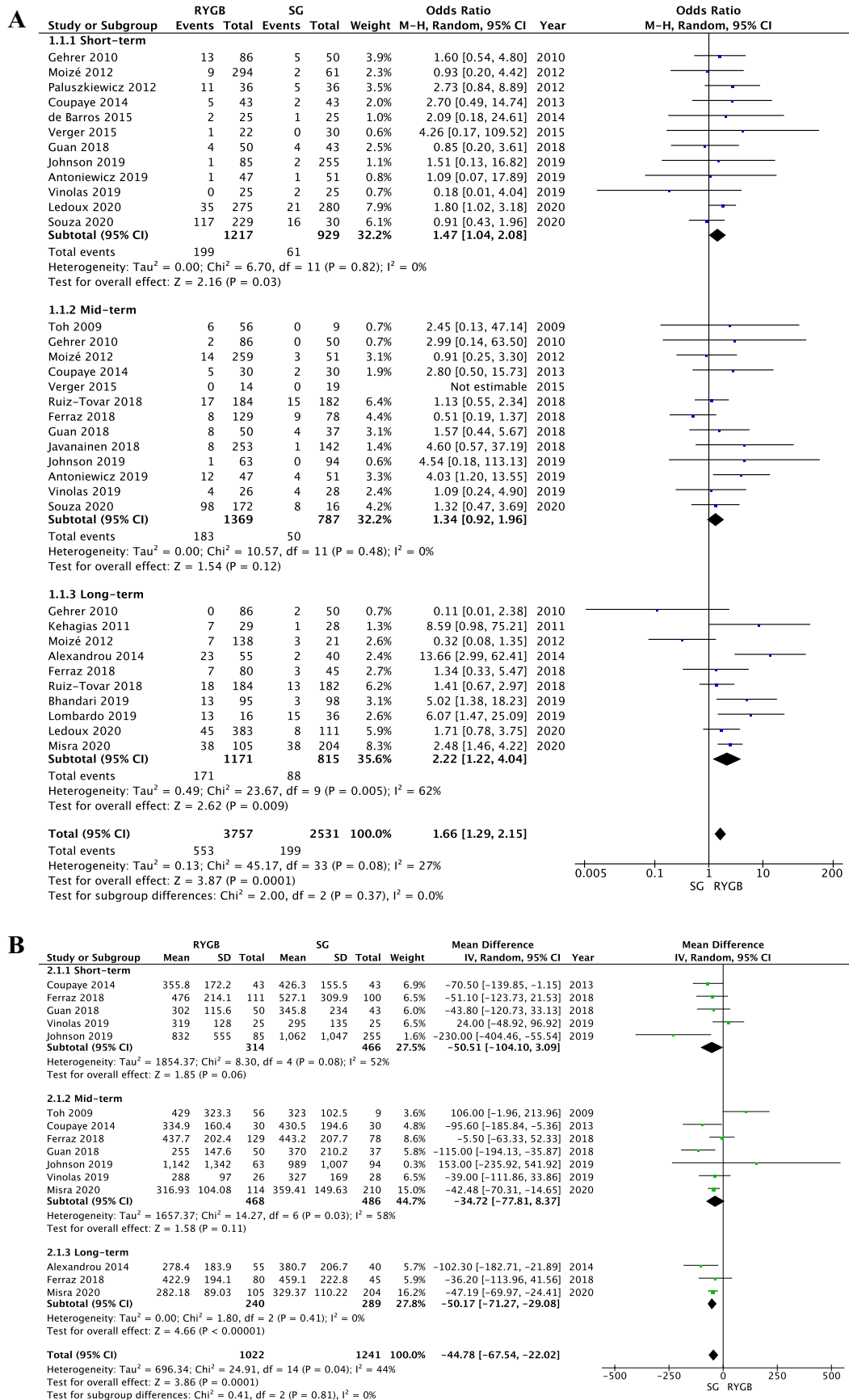
We did not find any significant difference between RYGB and SG for B1 continuous or dichotomous data in our meta-analysis. Two studies, Moizé et al. [35] and Ledoux et al. [21], did reveal a significantly higher proportion of deficiencies after SG at 24 months post-op and after 3 years post-operatively, respectively.

While none of the timeframes showed a significant difference in terms of techniques for vitamin B6, the pooled analysis showed a higher prevalence of this deficiency after SG. Moizé et al. [35] and Ledoux et al. [21] found significant higher prevalence of deficiency after SG at 6 months and after 3 years post-surgery, respectively.

Vitamin B6 is absorbed mainly in the upper jejunum, as well as in the ileum. Deficiency is rarely associated with insufficient dietary intake, since this vitamin is present in various foods and it is normally accompanied with deficiency of other B-complex vitamins. B6 deficiency may also cause microcytic anemia [14].

Only one article studied vitamin B2 and B3. Despite having described 1.4% and 0.8% of deficiencies pre-operatively in the RYGB and SG group, respectively, Guan et al. [20] found no B2 deficiencies post-surgery. Ledoux et al. [21] found that in the first year post-surgery, more patients had vitamin B3 deficiency after RYGB (13.1%) than in SG (10.7%). On the other hand, 3 years post-surgery, more patients had deficiency after SG, with 20.7% compared to 19.8%, in the RYGB group. None of these differences was statistically significant and more evidence is needed to make a conclusion of the effects of bariatric surgery on this vitamin.

In order to better comprehend the impact of RYGB and SG on complex B vitamin deficiencies, more studies should be conducted, especially regarding vitamin B1, B6, B2, and B3. A better knowledge of this topic could have an impact in the decision of which type of surgery to perform and prevent vitamin deficiencies.

**Fig. 3** Forest plots showing B12 proportion of deficiency (A) and mean serum levels (B)

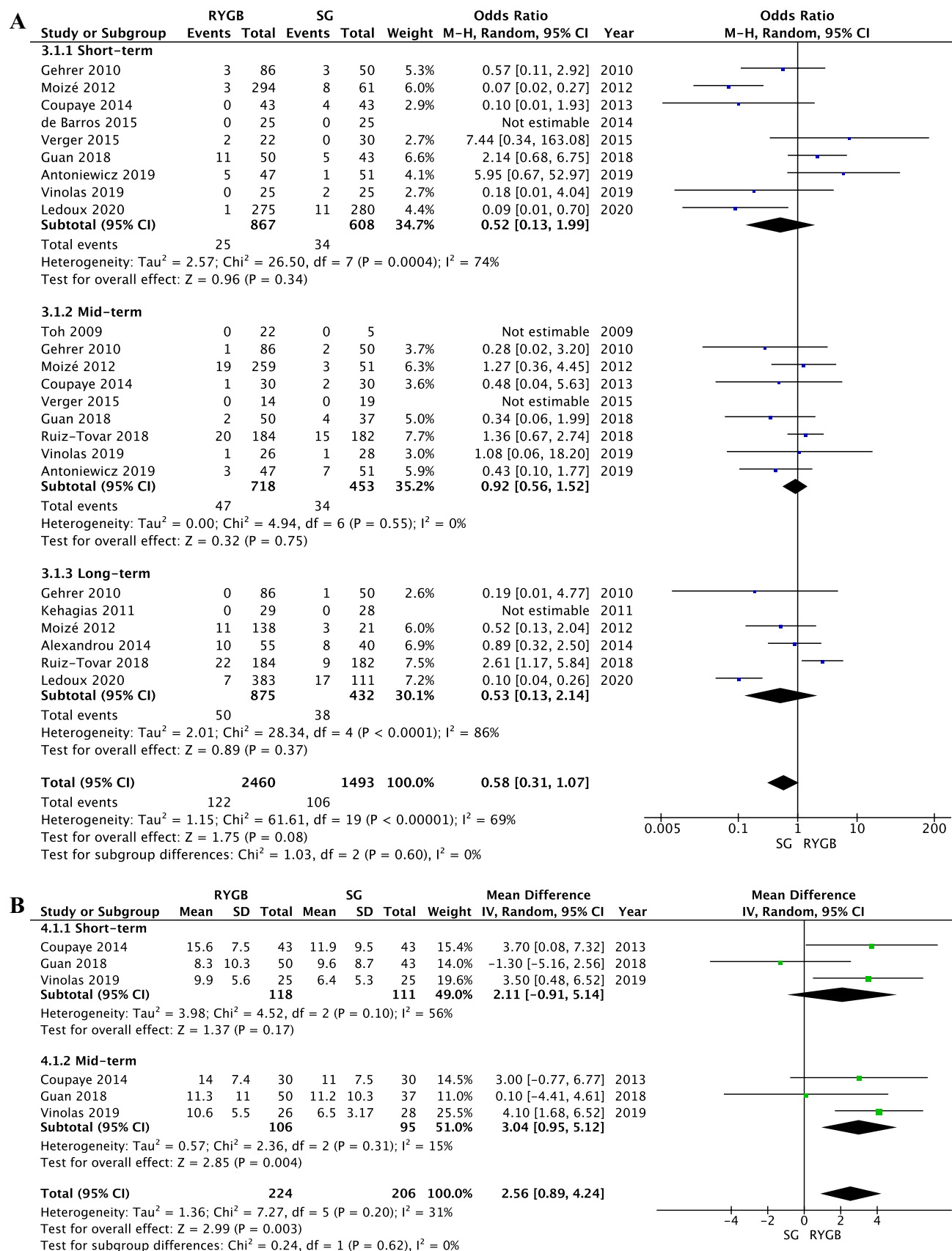


Fig. 4 Forest plots showing folate proportion of deficiency (A) and mean serum levels (B)

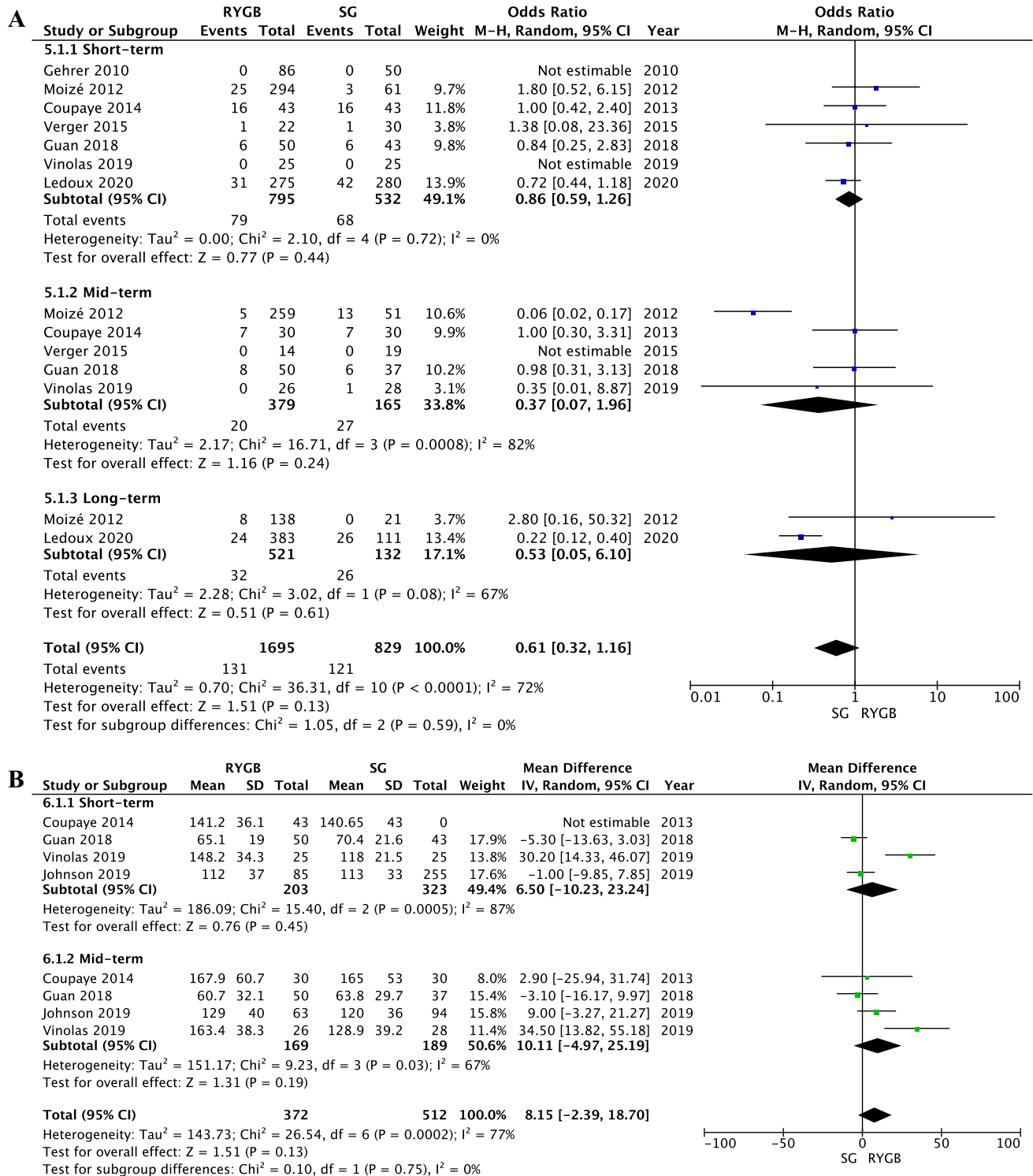


Fig. 5 Vitamin B1 proportion of deficiency (A) and mean serum levels (B)

There are some limitations to this study. First of all, this meta-analysis consists mostly of observational studies. We think an effort to create more multicenter RCTs on this topic would be beneficial. Secondly, characteristics like supplementation, reference values for deficiency, and different measurements from

different laboratories may create bias. This being said, study protocols vary a lot, and we should proceed cautiously when drawing conclusions. Lastly, we believe an effort should be made to uniformize measures such as means/medians, standard deviations/interquartile ranges, in order to make reviewing data easier.

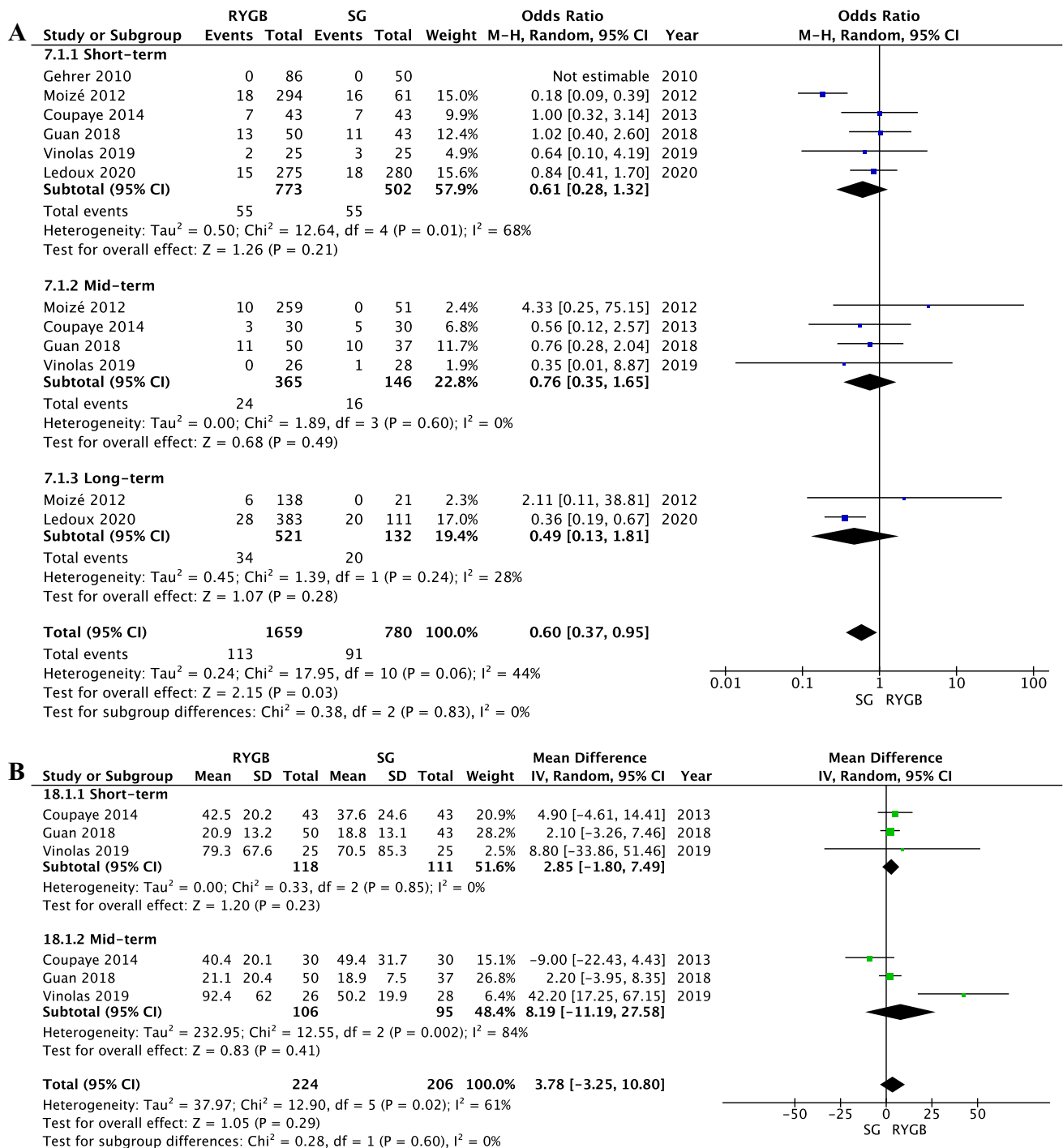


Fig. 6 Forest plots showing vitamin B6 proportion of deficiency (A) and mean serum levels (B)

Conclusion

Although both RYGB and SG are great surgical techniques, which improve greatly the quality of life and comorbidities of patients with obesity, they are not free of complications, such as nutrient deficiencies. This meta-analysis found that LSG had less probability of vitamin B12 deficiency. On the other hand,

RYGB had better results regarding folate mean levels and B6 proportion of deficiency. Nevertheless, it is imperative to tightly follow guidelines regarding screening and supplementation. It is also important to sensitize patients early on to the possibility of vitamin deficiencies post-surgery and the necessity for long-term, and in some cases, life-long supplementation, while instilling the importance of protocol follow-up.

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Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent does not apply.

Competing Interests The authors declare no competing interests.

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Article

Assessing Nutritional Deficiencies in Bariatric Surgery Patients: A Comparative Study of Roux-en-Y Gastric Bypass versus Sleeve Gastrectomy

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Abstract: Obesity is a worldwide epidemic, and bariatric surgery is considered the primary treatment for long-term weight loss and managing obesity-related health issues. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most performed procedures. Nutritional deficiencies are a significant concern following bariatric surgery and can have serious consequences. This study aims to compare the incidence of nutritional deficiencies in patients undergoing RYGB and SG. A retrospective analysis was conducted on the nutritional status of 505 consecutive patients who underwent either RYGB or SG between January and December 2019. Data were collected regarding vitamin B12, folic acid, vitamin D, calcium, PTH, magnesium, hemoglobin, iron, ferritin, and transferrin at preoperative, 6-month, and 12-month intervals post-surgery. The RYGB group showed significantly higher excess weight loss. Vitamin B12, hemoglobin, and ferritin levels were consistently higher in the SG group throughout the study. Vitamin D deficiency was prevalent, with no significant difference between the groups. Vitamin B12 deficiency was significantly more common in the RYGB group (6 months: 17.46% vs. 4.69%, $p < 0.001$; 12 months: 16.74% vs. 0.93%, $p < 0.001$). Despite differences in their mechanisms, bariatric surgeries were associated with nutritional deficiencies. It is crucial to efficiently assess, prevent, and manage these deficiencies tailored to each surgical procedure.

Keywords: obesity; nutritional deficiencies; bariatric surgery; Roux-en-Y gastric bypass; sleeve gastrectomy



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1. Introduction

Obesity has emerged as a significant global healthcare challenge in recent decades, now recognized as an epidemic of the twenty-first century [1]. By 2022, 43% of the adults worldwide were classified as overweight and 16% as obese, with a higher prevalence among women than men [2]. In Europe, the prevalence of obesity among adults ranges from 10% to 30% [3].

The increase in obesity can be linked to various factors contributing to an “obesogenic” environment: industrialization and fast economic growth, the increasingly sedentary

lifestyle, and the consumption of low-cost processed foods high in calories but low in nutrients [4,5].

Overweight and obesity are major risk factors for numerous diseases, such as cardiovascular conditions [6], diabetes [7], and even some cancers [8], leading to substantial morbidity and mortality. Consequently, effective treatment is crucial, with bariatric surgery recognized as the most effective intervention [9–11]. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the two most performed techniques [12–14], both proving similarly effective in reducing weight [13,15].

As the obese population continues to grow, the number of bariatric surgeries performed worldwide has also increased. In 2019, an estimated 256,000 bariatric surgeries were performed in the United States of America [12], while in Europe, data from The International Federation for the Surgery of Obesity and Metabolic Disorders (2019) reported 381,627 surgeries from 2014 to 2019 [14].

Despite being an essential tool in combating obesity, bariatric surgery is not without its complications. One of the most significant side effects of this technique is the development of nutritional deficiencies or the exacerbation of preexisting ones. This is particularly critical as obesity itself is associated with a high prevalence of nutritional deficiencies, potentially leading to devastating consequences for patients [16].

The underlying variables associated with postoperative vitamin and mineral deficiencies are surgery- and patient-related. Preoperative nutritional deficits, altered eating habits, decreased absorption surface, small intestine bacterial overgrowth, and poor compliance with the postoperative recommendations for diet optimization and nutritional supplementation are associated with the nutrient-deficient state [17]. Food intake restriction, decreased appetite, and gastrointestinal hormone profile changes are common mechanisms for weight loss reported after RYGB and SG, affecting nutrient status as well. The malabsorptive aspect of RYGB impairs vitamin and mineral absorption because the remnant stomach and the upper part of the small intestine are excluded from the gastrointestinal transit [18]. The degree of malabsorption is related to the length of the common channel rather than the lengths of the Roux limb. Since the small bowel remains intact after surgery, one would expect the report of fewer micronutrient deficiencies after SG than RYGB. However, several recent reports show that micronutrient deficiencies may occur to the same extent after both types of surgery despite intact intestinal absorptive surface area in SG. SG impacts micronutrient status by altering gastrointestinal motility, accelerating gastric emptying and gastro-duodenal transit time, and decreasing hydrochloric acid and intrinsic factor secretion [17].

Although there are already some studies in this area, the results remain heterogeneous due to variations in assessed nutrients, cut-off values, follow-up periods, and supplementation strategies across institutions. The most common micronutrient deficiencies after RYGB and SG are vitamin B12, folic acid, iron, thiamine (vitamin B1), vitamin D, and calcium. Other reports on nutritional deficiencies after weight loss surgery mention fat-soluble vitamins (vitamins A, E, and K), as well as copper, zinc, and selenium [17].

Several studies are aligned with this finding, reporting that *de novo* deficiency is uncommon, and only identifying a higher risk for deficiency in some key nutrients. Although prophylactic micronutrient supplementation is still required, these findings question the need for a high dose of all ten nutrients contained in the prophylactic multivitamin prescriptions after SG or RYGB, especially where the limb length is ≤ 150 cm and patients are supported in a multidisciplinary postoperative setting [19]. International guidelines recommend lifelong vitamin and mineral supplementation and nutritional biochemical monitoring post-surgery, tailored to the specific bariatric procedure. For instance, guidelines from the British Obesity and Metabolic Surgery Society (BOMSS) and the Enhanced Recovery After Surgery (ERAS) Society emphasize comprehensive supplementation and frequent monitoring to prevent deficiencies [20,21]. These guidelines highlight the importance of individualizing supplementation protocols based on patient needs and surgical variables.

Therefore, our study aimed to compare the incidence of nutritional deficiencies in obese patients undergoing SG and RYGB at our institution to improve patient management and mitigate the risk of deficiencies in the future.

2. Materials and Methods

2.1. Study Design and Participants

This study is a retrospective analysis of 505 consecutive patients who underwent bariatric surgery at our institution between 1 January 2019 and 31 December 2019. Our hospital serves as a referral center for bariatric patients and performed 580 surgeries in 2019. We excluded the patients who underwent gastric band removal surgeries, complications-related surgeries ($n = 60$), as well as those who underwent single anastomosis duodeno-ileal bypass with sleeve gastrectomy, one anastomosis gastric bypass, silastic ring gastric bypass, and the revision of RYGB with limb distalization ($n = 15$).

Thus, we reviewed the electronic medical records of 165 patients submitted to SG and 340 patients who underwent RYGB. Table 1 provides a comparison of the characteristics of the RYGB and SG groups.

Table 1. Comparison of demographic characteristics, clinical parameters, and comorbidities between Roux-en-Y gastric bypass and sleeve gastrectomy patients.

Characteristics	Roux-en-Y Gastric Bypass $n = 340$	Sleeve Gastrectomy $n = 165$	p -Value
Gender, n (%)			<0.001
Female	302 (88.82%)	120 (72.73%)	
Male	38 (11.18%)	45 (27.27%)	
Age at surgery (years), median (IQR ¹)	46.00 (40.00–54.00)	45.00 (36.00–54.50)	0.400
Body mass index (kg/m ²), median (IQR ¹)			
Before surgery	42.31 (39.25–45.34)	43.82 (39.80–49.12)	0.005
6 months post-surgery	30.55 (27.85–33.15)	32.21 (28.72–35.31)	<0.001
12 months post-surgery	27.41 (25.23–29.76)	29.78 (26.22–33.67)	<0.001
Percentage of excess weight loss ¹ , median (IQR ²)			
6 months post-surgery	67.66 (56.82–82.32)	61.77 (49.27–74.16)	0.001
12 months post-surgery	86.07 (75.12–98.34)	74.82 (62.80–92.90)	<0.001
Comorbidities, n (%)			
Diabetes mellitus	95 (27.94%)	36 (21.82%)	0.141
Arterial hypertension	158 (46.47%)	82 (49.70%)	0.496
Dyslipidemia	143 (42.06%)	70 (42.42%)	0.938

¹ the percentage of excess weight loss (%EWL) is a common metric for reporting weight loss after bariatric surgery. %EWL is one of the most accepted criteria for evaluating the success of bariatric surgery. It is calculated by the difference between the baseline weight and weight after surgery, divided by the difference between the baseline weight and the ideal weight, and expressed as a percentage: (initial weight – follow-up weight)/(initial weight – ideal weight for BMI 25) $\times$ 100 [22,23]. ² IQR—interquartile range.

The eligibility criteria for bariatric surgery include patients between 18 and 65 years old with BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity-related comorbidities [13,24]. The exclusion criteria for surgery include the absence of one year of conservative treatment, the inability to follow-up, psychiatric disorders, drug or alcohol abuse, short-term fatal diseases, and patients incapable of self-care or lacking social support.

2.2. Surgical Techniques

This study compared RYGB and SG, with both the procedures standardized and uniformly performed throughout the study period.

RYGB involved creating a calibrated gastric pouch (using a 36-Fr Fouchet's bougie), positioning the roux limb 100 cm distally to the ligament of Treitz, and performing the jejunojejunostomy 120 cm distally to the gastroduodenostomy.

In the SG technique, stomach resection was performed with an Echelon™ 60 mm, with calibration achieved using a 54-Fr Fouchet's bougie.

2.3. Follow-Up

The patients in our institution undergo follow-up every six months during the initial two years after surgery, followed by annual visits thereafter. Each follow-up visit evaluates weight loss, comorbidities, and nutritional status.

This study analyzed the values of vitamin B12, folic acid, vitamin D, calcium, parathormone (PTH), magnesium, hemoglobin, iron, ferritin, and transferrin at three different intervals: preoperatively, and 6 and 12 months after surgery. Deficiency thresholds (or excess in the case of PTH and transferrin) were determined according to the hospital laboratory reference ranges, listed in Table 2. Vitamin D deficiency is defined as a 25(OH)D level of less than 20 ng/mL, while vitamin D insufficiency is recognized as a 25(OH)D level of 21–29 ng/mL. The recommended goal is to maintain 25(OH)D levels above 30 ng/mL to take full advantage of all the health benefits that vitamin D provides [25].

Table 2. Nutrient reference range values and deficiency/excess cut-off values.

Nutrient	Reference Range	Deficiency/Excess Cut-Off
Vitamin B12 (pg/mL)	187–883 pg/mL	<187 pg/mL
Folic acid (ng/mL)	2.2–17.5 ng/mL	<2.2 ng/mL
Vitamin D (ng/mL)	>30 ng/mL	<20 ng/mL
Calcium (mEq/L)	4.2–5.1 mEq/L	<4.2 mEq/L
PTH (pg/mL)	10–65 pg/mL	>65 pg/mL
Magnesium (mEq/L)	1.55–2.05 mEq/L	<1.55 mEq/L
Hemoglobin (g/dL)	12–16 g/dL	<12 g/dL
Iron (µg/dL)	49–151 µg/dL	<49 µg/dL
Ferritin (ng/mL)	Pre-menopause: 10–120 ng/mL Post-menopause: 10–250 ng/mL	<10 µg/dL
Transferrin (mg/dL)	200–360 mg/dL	>360 mg/dL

After the surgery, the patients were advised to take daily multivitamin supplementation (1 to 2 tablets of Centrum®: 800 µg of vitamin A, 15 mg of vitamin E, 100 mg of vitamin C, 30 µg of vitamin K, 1.4 mg of thiamine, 1.75 mg of riboflavin, 2 mg of vitamin B6, 2.5 µg of vitamin B12, 5 µg of vitamin D, 62.5 µg of biotin, 200 µg of folic acid, 162 mg of calcium, 125 mg of phosphorus, 100 mg of magnesium, 5 mg of iron, 100 µg of iodine, 500 µg of copper, 2 mg of manganese, 40 µg of chromium, 50 µg of molybdenum, 30 µg of selenium, and 5 mg of zinc).

2.4. Statistical Analysis

Statistical analysis was performed using SPSS® version 26.0 for Mac (IBM Co., Armonk, NY, USA). Continuous variables were presented as median values with interquartile range, while categorical variables were expressed as percentages.

To compare the two techniques, we applied the chi-squared test and the independent samples Mann–Whitney U test. The statistical significance level was set at p -values < 0.05.

3. Results

Table 1 displays the anthropometric characteristics of the two groups, totaling 505 patients, who were followed for 12 months. Most participants in both the groups were women, accounting for 88.82% and 72.73% of the RYGB and the SG samples, respectively. At the baseline, the median age of the patients was 46 years in the RYGB group and 45 years in the SG group.

The BMI was significantly higher in the SG group both preoperatively and throughout the entire 12-month follow-up period compared to the RYGB group. Similarly, the RYGB group exhibited significantly higher excess weight loss at 6 and 12 months after surgery.

There were no significant differences in comorbidities between the groups, with diabetes mellitus being more prevalent in the RYGB group, while hypertension and dyslipidemia predominated in the SG group.

When comparing the median value of the measured parameters (Table 3), vitamin B12, hemoglobin, and ferritin were the only ones that showed significant differences between the two groups throughout the study period. Additionally, differences in the nutrient levels were observed at various points during the study: folic acid and transferrin were significantly higher in the RYGB group at 12 months of follow-up, calcium was higher in the SG patients throughout the postoperative period, and PTH and iron levels were higher in the RYGB and the SG groups, respectively, at 6 months after surgery.

Table 3. Nutrient levels at the preoperative period and during the 12-month follow-up after RYGB and SG.

Nutrient/Type of Surgery	Before Surgery, Median (IQR)	<i>p</i> -Value	6 Months Post-Surgery, Median (IQR)	<i>p</i> -Value	12 Months Post-Surgery, Median (IQR)	<i>p</i> -Value
Vitamin B12 (pg/mL)		0.008		<0.001		<0.001
RYGB	348.00 (264.50–454.00)		270.50 (204.25–355.50)		271.00 (214.00–353.00)	
SG	407.00 (311.50–541.50)		372.50 (273.25–459.25)		382.00 (288.25–496.50)	
Folic acid (ng/mL)		0.434		0.357		0.022
RYGB	5.05 (3.90–7.20)		10.50 (7.00–15.10)		11.15 (6.30–15.28)	
SG	5.60 (4.00–7.90)		10.40 (5.95–14.35)		9.70 (5.00–14.10)	
Vitamin D (ng/mL)		0.597		0.329		0.696
RYGB	18.00 (12.00–24.00)		25.00 (19.00–31.00)		27.00 (21.00–33.00)	
SG	16.50 (13.00–21.00)		26.70 (21.00–30.00)		26.00 (20.00–33.75)	
Calcium (mEq/L)		0.218		0.002		0.001
RYGB	4.60 (4.50–4.80)		4.70 (4.60–4.90)		4.70 (4.60–4.90)	
SG	4.70 (4.60–4.80)		4.80 (4.70–4.90)		4.80 (4.70–4.90)	
PTH (pg/mL)		0.367		0.020		0.118
RYGB	49.80 (38.10–68.08)		45.20 (33.85–57.80)		44.10 (34.30–56.40)	
SG	51.30 (42.95–70.60)		40.70 (31.00–52.90)		40.05 (32.90–54.03)	
Magnesium (mEq/L)		0.849		0.064		0.863
RYGB	1.62 (1.54–1.69)		1.63 (1.54–1.71)		1.63 (1.55–1.70)	
SG	1.63 (1.52–1.69)		1.65 (1.57–1.74)		1.64 (1.56–1.71)	
Hemoglobin (g/dL)		0.001		0.010		0.005
RYGB	13.50 (12.90–14.20)		13.20 (12.60–13.90)		13.10 (12.43–13.98)	
SG	13.95 (12.90–15.00)		13.50 (12.80–14.40)		13.60 (12.70–14.23)	
Iron (µg/dL)		0.154		<0.001		0.137
RYGB	74.00 (58.75–95.00)		78.00 (61.00–93.00)		91.00 (69.00–113.00)	
SG	88.00 (63.75–105.50)		91.50 (70.75–111.25)		96.00 (73.00–118.00)	
Ferritin (ng/mL)		0.011		<0.001		<0.001
RYGB	81.00 (39.30–141.70)		91.25 (48.48–179.60)		79.70 (33.38–153.68)	
SG	135.80 (60.80–276.00)		148.40 (71.95–258.95)		142.20 (67.90–243.70)	
Transferrin (mg/dL)		0.182		0.298		0.008
RYGB	274.00 (244.00–317.75)		235.50 (211.00–266.00)		251.00 (220.50–291.00)	
SG	269.00 (235.50–290.75)		230.00 (207.00–261.00)		237.00 (214.00–268.00)	

RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; IQR: interquartile range.

The deficiencies of each nutrient are outlined in Table 4. Notably, vitamin D deficiencies were prevalent preoperatively in both groups, with no significant difference between them: 62.05% in the RYGB and 74.24% in the SG group. In the postoperative period, these deficiencies became more prevalent in the RYGB patients at 6 months after surgery (29.64% vs. 24.03%), and in the SG group at 12 months (31.48% vs. 22.41%).

Table 4. Prevalence of nutrient deficiencies/excess before surgery and in the 12-month follow-up period after surgery (RYGB vs. SG).

Nutrient/Type of Surgery	Before Surgery, n (%)	p-Value	6 Months Post-Surgery, n (%)	p-Value	12 Months Post-Surgery, n (%)	p-Value
Vitamin B12 (pg/mL)		0.684		<0.001		<0.001
RYGB	7 (5.60%)		44 (17.46%)		39 (16.74%)	
SG	2 (4.08%)		6 (4.69%)		1 (0.93%)	
Folic acid (ng/mL)		0.897		^a		0.425
RYGB	3 (2.27%)		0 (0.00%)		2 (0.86%)	
SG	1 (1.96%)		0 (0.00%)		2 (1.87%)	
Vitamin D (ng/mL)		0.078		0.247		0.073
RYGB	103 (62.05%)		75 (29.64%)		52 (22.41%)	
SG	49 (74.24%)		31 (24.03%)		34 (31.48%)	
Calcium (mEq/L)		0.809		0.189		0.090
RYGB	10 (3.62%)		7 (2.79%)		6 (2.58%)	
SG	4 (3.15%)		1 (0.76%)		7 (6.31%)	
PTH (pg/mL)		0.546		0.039		0.528
RYGB	35 (26.12%)		41 (16.40%)		36 (15.86%)	
SG	15 (30.61%)		11 (8.66%)		14 (13.21%)	
Magnesium (mEq/L)		0.700		0.120		0.892
RYGB	85 (30.47%)		72 (28.35%)		58 (25.00%)	
SG	36 (28.57%)		28 (21.05%)		27 (24.32%)	
Hemoglobin (g/dL)		0.393		0.378		0.095
RYGB	25 (7.55%)		31 (11.79%)		39 (15.73%)	
SG	9 (5.49%)		12 (8.89%)		11 (9.32%)	
Iron (µg/dL)		0.620		0.119		0.318
RYGB	17 (12.69%)		28 (11.07%)		15 (6.41%)	
SG	6 (15.79%)		8 (6.15%)		4 (3.74%)	
Ferritin (ng/mL)		0.445		0.374		0.252
RYGB	2 (1.48%)		5 (1.97%)		10 (4.27%)	
SG	0 (0.00%)		1 (0.78%)		2 (1.83%)	
Transferrin (mg/dL)		0.075		0.149		0.017
RYGB	11 (9.17%)		4 (1.60%)		12 (5.15%)	
SG	0 (0.00%)		0 (0.00%)		0 (0.00%)	

RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy. ^a no statistics were computed because the values were constant.

Statistically significant differences between the two types of surgery were observed in vitamin B12 deficiency post-surgery, with a higher prevalence in the RYGB patients (17.56% vs. 4.96% at 6 months and 16.74% vs. 0.93% at 12 months). Additionally, the RYGB group exhibited higher levels of excess PTH at six months post-surgery (16.40% vs. 8.66%) and excess transferrin at 12 months post-surgery (5.15% vs. 0%) compared to the other group.

Calcium deficiencies were more prevalent in the RYGB group before and 6 months after surgery, shifting to a higher prevalence in the SG group after 12 months (although this difference was not significant).

Magnesium deficiencies were relatively prevalent in both groups, although the difference between the groups was not significant. Magnesium deficiencies were slightly more common in the RYGB group throughout the entire follow-up period. Conversely, folic acid deficiencies were rare.

Anemia, iron, and ferritin deficiencies, as well as transferrin excess, were more prevalent in the RYGB group, except for iron deficiency, which was higher in the SG group preoperatively (15.79% vs. 12.69%).

Moreover, it is noteworthy that before surgery, 73.82% of the RYGB patients and 78.18% of the SG patients were under some supplementation to correct specific deficiencies.

4. Discussion

The study results revealed several nutritional deficiencies in bariatric patients, either in the pre- or postoperative periods.

4.1. Vitamin B12

The most considerable difference between the patients who underwent RYGB or SG was observed in relation to vitamin B12, particularly after the surgery. The RYGB group demonstrated a 17.46% and 16.74% prevalence of vitamin B12 deficiency at 6 and 12 months, respectively, while the SG group exhibited lower rates of 4.69% and 0.93%, respectively. Consistent with our findings, systematic reviews by Alexandrou et al., Antoniewicz et al., and Kwon et al. showed that SG carries a lower risk of postoperative vitamin B12 deficiency compared to RYGB [26–28]. On the other hand, Ferraz et al. did not find any significant difference between the two surgical techniques concerning vitamin B12 deficiency [29]. Preoperative vitamin B12 deficiency in our study population aligned with the reports from the American Society for Metabolic and Bariatric Surgery [16].

Vitamin B12 absorption involves a complex series of metabolic steps within the gastrointestinal tract. Humans require a dietary source of vitamin B12 due to the complexity of its biosynthesis, which is limited to prokaryotes [17]. The intrinsic factor (IF), synthesized by the parietal cells of the stomach, plays a crucial role in cobalamin absorption [30,31]. In RYGB patients, there are several potential mechanisms that may contribute to vitamin B12 malabsorption and deficiency: (1) the decreased acid and pepsin digestion of protein-bound cobalamins from food, (2) the incomplete release of vitamin B12 from R proteins due to inadequate mixing of nutrients with pancreatic secretions, and (3) the decreased availability of IF [17]. Increased intolerance to certain foods, such as meat, was also identified as a potential exacerbating factor for these deficiencies [32]. Furthermore, Majumder et al. also noted that bacterial overgrowth could contribute to the vitamin B12 deficit [33].

Changes in the architecture of the gastrointestinal tract secondary to gastric fundus resection result in decreased hydrochloric acid and pepsin secretion by the functional remnant segment [30,34,35]. This leads to the inadequate capture of vitamin B12 from dietary sources and the lack of food contact with the IF-producing cells, thus causing cobalamin malabsorption and deficiency. The small pouch constructed from the gastric cardia in the RYGB procedure is virtually devoid of acid secretion, causing food-bound vitamin B12 to be maldigested and subsequently malabsorbed [17].

A small study showed a decreased gastric production of transcobalamin 1 (TCN1) after RYGB, affecting B12 intestinal transport. Cobalamin preferentially binds to TCN1 in the low acidic gastric environment and attaches to IF only in the small upper bowel. Despite indirect improvements in cobalamin absorption following bariatric procedures, studies show a higher incidence of vitamin B12 deficiency after RYGB than SG. The authors argue that after restrictive bariatric surgery, TCN1 synthesis might be inhibited; however, food exposure to the entire intestinal surface area leads to local IF production and IF-mediated B12 gut transport is less affected [28].

Recommendations for preventing vitamin B12 deficiency after bariatric surgery include the oral intake of 350–500 mg per day or the intramuscular administration of 1000 mg per month [16,36]. Vitamin B12 is a complex biomolecule that plays a vital role in key biochemical reactions. As a water-soluble vitamin derived from dietary sources such as eggs, red meat, and dairy, it is not stored in large quantities, and excess amounts are rapidly eliminated from the body. Both oral and intramuscular (IM) vitamin B12 are common routes for treating B12 deficiency, with several studies evaluating their efficacy. Deficiency is mainly caused by inadequate dietary intake. Severe clinical abnormalities require intensive treatment with B12, such as cyanocobalamin or hydroxocobalamin. Following an intramuscular injection of 1000 µg of cyanocobalamin, approximately 150 µg is retained in

the body, primarily stored in the liver, although retention variability is high across studies. Hydroxocobalamin, commonly used in Europe, is often administered at intervals of 2 to 3 months due to its better retention than cyanocobalamin. High-dose oral supplementation is an effective alternative to parenteral treatment. Studies have shown that 0.5–4% of an oral B12 dose is absorbed; thus, high-dose tablets of 1000 µg provide, on average, 5–40 µg of B12. Randomized studies have demonstrated that the daily oral doses of 1000–2000 µg are equivalent or superior to injected B12 in maintaining adequate levels. In summary, while the parenteral administration of 1000 µg of B12 monthly may not provide a consistent supply due to the rapid excretion of excess amounts, the daily oral administration of 350–500 µg, or even higher doses, is more effective in maintaining stable and adequate vitamin B12 levels. This approach is particularly beneficial for patients with compromised absorption capacities, such as those who have undergone bariatric surgery [37].

In our center, the current supplement prescribed to our patients contains less than the recommended dose for this patient population. Therefore, it is imperative to consider developing specialized supplementation tailored to the specific needs of bariatric patients based on the type of surgery they undergo. This approach aims to mitigate the prevalence of vitamin B12 deficiencies, particularly in the RYGB group.

4.2. Folic Acid

Our study revealed that folic acid deficiency was negligible at 6 months post-surgery and remained rare at 12 months, consistent with the findings from other reported studies [35]. This can be attributed to the adaptive mechanisms of folate absorption in the entire small bowel following the bariatric surgery, rather than being absorbed in the proximal segment as usual [26,30].

4.3. Vitamin D

This study reveals that vitamin D was the most common nutrient deficiency both before and after surgery, with prevalence rates of 62.05% and 74.24% in the RYGB and SG groups, respectively. This is consistent with previous research on the Mediterranean population [38]. The high deficiency rates may be due to the body storing lipid-soluble vitamins in adipose tissue, reduced sunlight exposure, and the low intake of dairy products [5,35,39]. After surgery, the deficiency rates decreased significantly, with fluctuations between the RYGB and SG groups at 6 and 12 months post-surgery. The altered anatomy in the RYGB procedure can lead to the decreased absorption of fat-soluble proteins because of the delayed blend of the food with bile and pancreatic enzymes [40]. In our study, the high prevalence of hypovitaminosis D before surgery may help explain the lack of significant differences between the groups after surgery.

4.4. Calcium and PTH

Calcium deficiency was rare in our study and did not show any significant difference between the RYGB and SG groups. It was more common in the RYGB group before and at 6 months after surgery, but after 12 months it became more frequent in the SG patients. This can be explained by the fact that procedures like RYGB create a bypass to the duodenum and jejunum, which are the preferential sites for calcium absorption. Additionally, insufficient levels of vitamin D can limit the transcellular vitamin D-dependent active transport of calcium. Therefore, the increase in the calcium deficiency at 12 months in the SG group may be related to the simultaneous increase of the vitamin D deficiency in this same group [36,40]. Furthermore, the intolerance of dairy products might contribute to this deficiency [32].

We also assessed the levels of PTH, which is a crucial indicator of calcium metabolism [41]. After undergoing RYGB surgery, the patients showed a significant increase in PTH levels, with 16.40% of these patients having a value above the normal range (vs. 8.66% in the SG group) at 6 months of follow-up. In this same period, calcium and vitamin D deficiencies were also more prevalent in the RYGB group, revealing an intensification in bone

metabolism due to the development of secondary hyperparathyroidism [42,43]. As this can lead to bone mineralization issues (such as osteopenia or osteoporosis), it is essential to maintain the long-term screening and supplementation of vitamin D and calcium [43–46].

4.5. Magnesium

Regarding magnesium, the study found that the RYGB patients experienced more deficiencies throughout the study, although without statistical difference. Hypomagnesemia has been linked to insulin resistance and metabolic syndrome, so addressing this deficiency could be an essential step to improve patients' health [47].

4.6. Hemoglobin, Iron, Ferritin, and Transferrin

The prevalence of anemia in our study increased after surgery in both the groups, with a higher prevalence in the RYGB patients, as demonstrated by Antoniewicz et al. [27] and Ferreira et al. [48]. However, there was no significant difference between the two surgical techniques. Although vitamin B12 deficiency can lead to changes in erythropoiesis, iron deficiency remains one of the most frequent causes of anemia [49], as seen in our patients throughout the study period (Table 4). Before surgery, the constant inflammatory state of obesity with the elevated production of hepcidin, along with poor dietary intake, led to a reduction in iron absorption, which may justify the iron deficiency in these patients [26,35,50,51].

The inflammatory state also explains the lower prevalence of ferritin deficiency compared to iron deficiency, as ferritin is a positive acute-phase protein [52]. Also, we found a lower prevalence of iron deficiency in the postoperative period compared to pre-surgery, along with an increase in ferritin deficiencies, likely due to reduced inflammation because of weight loss.

After surgery, the RYGB group showed a higher prevalence of iron and ferritin deficiencies and transferrin excess. This could be attributed to factors such as bypassing the major sites of the absorption of iron (duodenum and proximal jejunum), reduced stomach acid, and decreased meat consumption [26,32,35,52,53]. Additionally, our sample consisted mostly of women of reproductive age, which could exacerbate iron deficiency, especially after surgery, as weight loss can help resolve potential menstrual irregularities in obese women [52].

The study findings indicate that nutrient deficiencies were more prevalent before surgery, except for vitamin B12, hemoglobin, and ferritin. This could be attributed to the patient's pre-surgery diet, which was high in energy but lacking in various nutrients, as well as the use of restrictive diets that may contribute to rapid metabolic changes and exacerbate these deficiencies [35,54]. After surgery, the patients received more rigorous follow-up care and were supplemented with a multivitamin, leading to a decrease in the prevalence of deficiencies in the postoperative period.

Although there are no strict guidelines for correcting pre-surgery deficiencies, our center emphasized the assessment and correction of nutritional deficiencies before surgery due to evidence suggesting that surgery may exacerbate these deficiencies [26,55,56]. In our sample, 73.82% of the RYGB patients and 78.18% of the SG patients received supplementation before surgery. It is important to note that obesity itself can cause nutritional deficiencies, especially in iron and vitamin D, due to the inflammatory process associated with excess weight. Higher levels of ferritin have been observed in obese subjects than in non-obese individuals. This is probably related to the low-grade chronic inflammation that characterizes obesity. However, despite the higher levels of ferritin, the obese subjects present lower serum iron (Fe) concentrations and reduced percentage of transferrin saturation compared with the non-overweight subjects, and therefore the prevalence of iron deficiency is significantly higher in the obese individuals. The reduction in serum Fe is partially explained by chronic inflammation accompanying obesity, which sets in motion a series of pathological mechanisms. Moreover, the liver is frequently affected by lipid accumulation, called non-alcoholic fatty liver disease (NAFLD), which contributes to

the disturbance of iron balance by increasing cytokine production and developing insulin resistance [57]. A meta-analysis concluded that obesity is associated with an increased risk of vitamin D insufficiency or deficiency, independent of latitude, age, and conditions of human development. It has been suggested that excess body fat retains vitamin D metabolites, sequestering cholecalciferol produced through the skin or diet before it reaches the liver for hydroxylation. The elevated levels of the vitamin D activation enzyme 1- α -hydroxylase in the adipose cells of obese individuals may explain the increased local utilization of 25(OH)D. Variations in serum 25(OH)D and vitamin D reserves are related to the amount of subcutaneous fat. Wortsman et al. reported that, following sunlight exposure, the serum concentration of 25(OH)D increased by 53% less in obese individuals than non-obese individuals [58,59].

In our practice, RYGB is the preferred procedure. However, in patients at the extremes of age and BMI, SG is performed. Because our department has a super obesity rate of 10–15%, the SG group will statistically have a higher baseline BMI than the RYGB group, thus possibly introducing a selection bias. In super-obese patients, SG is preferred because of the technical challenges of performing RYGB in these patients. Also, SG is frequently used as a bridge procedure, allowing the patients to reduce weight initially, thus making other procedures safer and more effective later.

Proton pump inhibitors are known to increase the risk for vitamin and mineral deficiencies and to affect vitamin B12, vitamin C, calcium, iron, and magnesium metabolism. Although the risk is low in the general population with the use of these medications, it may be considerable in the elderly and malnourished patients [60]. All the patients received PPIs for the first 2 months following surgery, up to the time of their first follow-up visit. After 6 months, PPIs were discontinued if no symptoms of reflux were present [20].

However, the study had several limitations, such as its retrospective nature, single-center design, challenges in accurately assessing post-surgery supplementation compliance, and the impact of the COVID-19 pandemic, which led to the cancellation of many follow-up visits and laboratory evaluations. Additionally, the study used serum vitamin B12 instead of serum methylmalonic acid to identify deficiencies [16]. Likewise, we did not study the mean corpuscular volume in the patients with anemia to establish potential correlations with vitamin B12 and iron deficiencies. As this study was conducted in a high-volume specialized center with experienced surgeons and more complex cases, its applicability to other contexts may be limited.

The study emphasized the importance of patient adherence to supplementation, with all the patients being encouraged to take multivitamins and their adherence closely monitored. Continuous efforts were made to enhance patient adherence during each follow-up, conducted every six months in the first year and annually after that. Additionally, at each follow-up appointment, supplementation was adjusted based on signs or symptoms of nutritional deficits and analytical changes. However, a limitation of this study is the lack of objective data on adherence levels and on the patients who developed signs or symptoms of nutritional deficit, representing a limitation of our study.

Nonetheless, a strength of our study lies in the analysis of a large sample of 505 patients over three different time points, providing comprehensive insights into changes in nutritional status throughout the follow-up period across ten different analytical parameters. We recognize that the follow-up period in this study was relatively short. However, we chose to conduct this study over this period to emphasize the early and short-term postoperative outcomes of the surgery on nutrition. This approach allows us to closely monitor the initial impact of the surgery and the early occurrence of nutritional deficiencies. Future studies with longer follow-up periods are planned to comprehensively assess the long-term outcomes of the surgical procedures.

The fact that our study was limited to RYGB and SG procedures and that we excluded other less standardized techniques in our center might reduce potential bias.

5. Conclusions

Consistent with other findings, our research revealed that the patients with obesity who undergo bariatric surgery develop a range of nutritional deficiencies, reflecting the intricate interplay between nutrient metabolism and specific surgical procedures. Notably, vitamin D deficiency is common in bariatric surgery patients, and vitamin B12 deficiency is higher in the patients undergoing RYGB.

Healthcare professionals working with obese patients should be mindful of these issues, as they can have far-reaching effects. The assessment of nutritional status before surgery and rigorous postoperative monitoring of these patients is mandatory, along with tailored supplementation strategies based on individual needs and the type of surgery performed.

Further research is needed to develop comprehensive guidelines that address these complexities.

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C. FROM THE METABOLIC CHANGES TO THE SURGICAL ASPECTS

New surgical techniques

Efficiency and safety of Single Anastomosis Sleeve Ileal (SASI) bypass in the treatment of obesity and associated comorbidities: A systematic review and meta-analysis. Langenbecks Arch Surg 409(1), 221 (2024) (*) doi: [10.1007/s00423-024-03413-w](https://doi.org/10.1007/s00423-024-03413-w)

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SYSTEMATIC REVIEW



Efficiency and safety of single anastomosis sleeve ileal (SASI) bypass in the treatment of obesity and associated comorbidities: a systematic review and meta-analysis

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Abstract

Introduction The Single Anastomosis Sleeve Ileal (SASI) bypass is a new bariatric surgery corresponding to an adaptation of the Santoro approach, consisting of a sleeve gastrectomy (SG) followed by loop gastroileostomy. Therefore, we aimed to systematically assess all the current literature on SASI bypass in terms of safety, weight loss, improvement in associated comorbidities, and complications.

Methods Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations, we conducted a systematic review and meta-analysis by searching three databases (PubMed, Scopus, and Web of Science). We performed a meta-analysis of risk ratios and mean differences to compare surgical approaches for excessive weight loss, improvement/remission in type 2 diabetes mellitus (T2DM), hypertension (HT), dyslipidemia (DL), obstructive sleep apnea (OSA), and complications. Heterogeneity was assessed using the I^2 statistic.

Results Eighteen studies were included in the qualitative analysis and four in the quantitative analysis, comparing SASI bypass with SG and One-Anastomosis Gastric Bypass (OAGB). A comparison between Roux-en-Y Gastric Bypass (RYGB) and SASI bypass could not be performed. Compared to SG, the SASI bypass was associated with improved weight loss (MD=11.32; 95% confidence interval (95%CI) [7.89;14.76]; $p<0.0001$), and improvement or remission in T2DM (RR=1.35; 95%CI [1.07;1.69]; $p=0.011$), DL (RR=1.41; 95%CI [1.00;1.99]; $p=0.048$) and OSA (RR=1.50; 95%CI [1.01;2.22]; $p=0.042$). No statistically significant differences in any of the assessed outcomes were observed when compared with OAGB. When compared to both SG and OAGB, the complication rate of SASI was similar.

Conclusion Although studies with longer follow-up periods are needed, this systematic review and meta-analysis showed that SASI bypass has a significant effect on weight loss and metabolic variables. Variations in outcomes between studies reinforce the need for standardization.

Keywords Obesity · Bariatric surgery · SASI bypass · Single anastomosis sleeve ileal bypass · Systematic review · Meta-analysis

Carolina Rodrigues Oliveira and Hugo Santos-Sousa contributed equally and should be considered first authors.

Bernardo Sousa-Pinto and Silvestre Carneiro should both be considered senior authors.

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Introduction

With the growing prevalence of obesity, it has become a major public health concern [1]. Conservative treatment typically fails to provide satisfactory results. However, bariatric surgery has proven to be the most effective treatment [2].

The most common procedure is the Sleeve Gastrectomy (SG) followed by Roux-en-Y Gastric Bypass (RYGB) [3].

In 2014, Mui et al. described a new technique that was adapted from the Santoro approach, which consisted of SG followed by loop gastroileostomy 250 cm proximal of the ileocecal valve [4]. In 2016, Mahdy et al. presented the first case series of 50 patients with 1-year follow-up and named it the Single Anastomosis Sleeve Ileal (SASI) bypass [5]. By changing the Roux-en-Y anastomosis of Santoro to a simple loop, the SASI bypass appears to be a simpler and safer technique without losing benefits in the treatment of obesity and its comorbidities.

Several studies evaluated the efficacy and safety of this technique. The common limb length varied between 200 and 350 cm. Due to this variation, some authors referred to this technique as “Laparoscopic sleeve gastrectomy with loop bipartition” [6, 7], “Laparoscopic sleeve gastrectomy with loop gastroileal bypass” [8] and “Laparoscopic sleeve gastrectomy with transit loop bipartition” [9].

Therefore, we aimed to systematically assess the current literature on SASI bypass in terms of safety, weight loss, improvement in associated comorbidities, and complications. Additionally, we aimed to establish a comparison with other bariatric surgeries. To the best of our knowledge, this is the first meta-analysis comparing this technique with other bariatric procedures. This study will contribute to a better understanding of this technique and will allow standardization for improved outcomes in the future.

Methods

This systematic review and meta-analysis was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines [10].

Eligibility of primary studies

We included studies assessing adult patients with obesity who underwent SASI bypass. We included both single-arm studies and experimental or observational studies comparing SASI bypass with other bariatric surgeries.

The following outcomes were considered: weight loss and change in body mass index (BMI), improvement in comorbidities such as type 2 diabetes mellitus (T2DM),

hypertension (HT), dyslipidemia (DL), gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), and complications.

We excluded animal studies, unrelated articles, editorials, correspondence, video reports, reviews, and meta-analyses. In addition, we excluded studies assessing less than 10 participants.

Search strategy

In October 2022, a systematic review of the available literature was conducted using three search databases - PubMed, Scopus, and Web of Science. The search queries are listed in Supplementary Table 1. In addition, reference lists of the primary articles were hand-searched.

We considered only studies published after 2013, as this technique was first described in 2014 by Mui et al. [4].

Study selection

After removing the duplicates, study selection was conducted independently by two authors (C.O. and M.O.) in two separate phases. Firstly, the articles were searched by title and abstract. Subsequently, articles not excluded were selected based on their full-text reading. Any disagreements were discussed between the reviewers and a third author (H.S.S.).

Data collection process

Data were independently extracted by two authors (C.O. and M.O.) into a predesigned data extraction form that was developed according to the Cochrane Handbook [11] to extract relevant information such as author name, publication year, country and journal of the publication, study design, duration of follow-up, sample size, PICO, patient inclusion and exclusion criteria, participants characteristics (mean age, percentage of each gender, mean BMI, number of patients with T2DM, HT, DL, GERD and OSA), interventions, specific measures of the SASI bypass, outcomes measures (weight loss and improvement in comorbidities), and every kind of complications after surgery.

Quality assessment

The quality of the studies was independently assessed by two reviewers (M.C. and C.O.) using the National Institutes of Health quality assessment criteria for Observational studies [12], and the Cochrane Collaboration Risk of Bias Tool for randomized control trials (RCT) [13].

The first tool is 14 questions of yes or no, resulting in a final rating (Good, Fair, or Poor). Because exposure is

a surgical procedure that can't be quantified or measured more than once, questions assessing these parameters were considered not applicable.

The second tool classifies each study as having a high, low, or unclear risk bias, based on selection, performance, detection, elimination, reporting, and other bias factors.

Quantitative synthesis of results

We performed a random-effects meta-analysis (using the restricted maximum likelihood approach) of mean differences (MD) for the continuous outcome (percentage of excess weight loss, %EWL) and relative risks (RR) for dichotomous variables (improvement or remission of T2DM, HT, DL, OSA, and complications).

Heterogeneity was evaluated using Cochran's Q statistic p-value and the I^2 statistic. Heterogeneity was considered high if $I^2 > 50\%$ or Cochran's Q test p-value < 0.10 . Sources of heterogeneity were studied using leave-one-out sensitivity analysis.

A p-value lower than 0.05 was considered statistically significant. The meta package of software R was used to analyse the data for the meta-analysis.

%EWL is a measured that is calculated as $[(\text{preoperative weight} - \text{weight on follow-up}) / (\text{preoperative weight} - \text{ideal weight})] \times 100$, with an ideal weight corresponding to an BMI of 25 kg/m².

Results

Study selection

After the search in the databases, a total of 840 studies were found, of which 409 were duplicates. After the screening phase, 15 articles were fully read, and all were included. Hand searching resulted in 3 additional articles. A total of 18 articles were included in the qualitative synthesis and 4 in the quantitative synthesis. The study selection process is summarized in Fig. 1 [10].

Study characteristics

Table 1 shows the characteristics of studies included in the systematic review. Of the 18 articles included 13 were retrospective observational studies [5, 7, 9, 14–23], 4 prospective observational studies [8, 24–26], and 1 RCT [6].

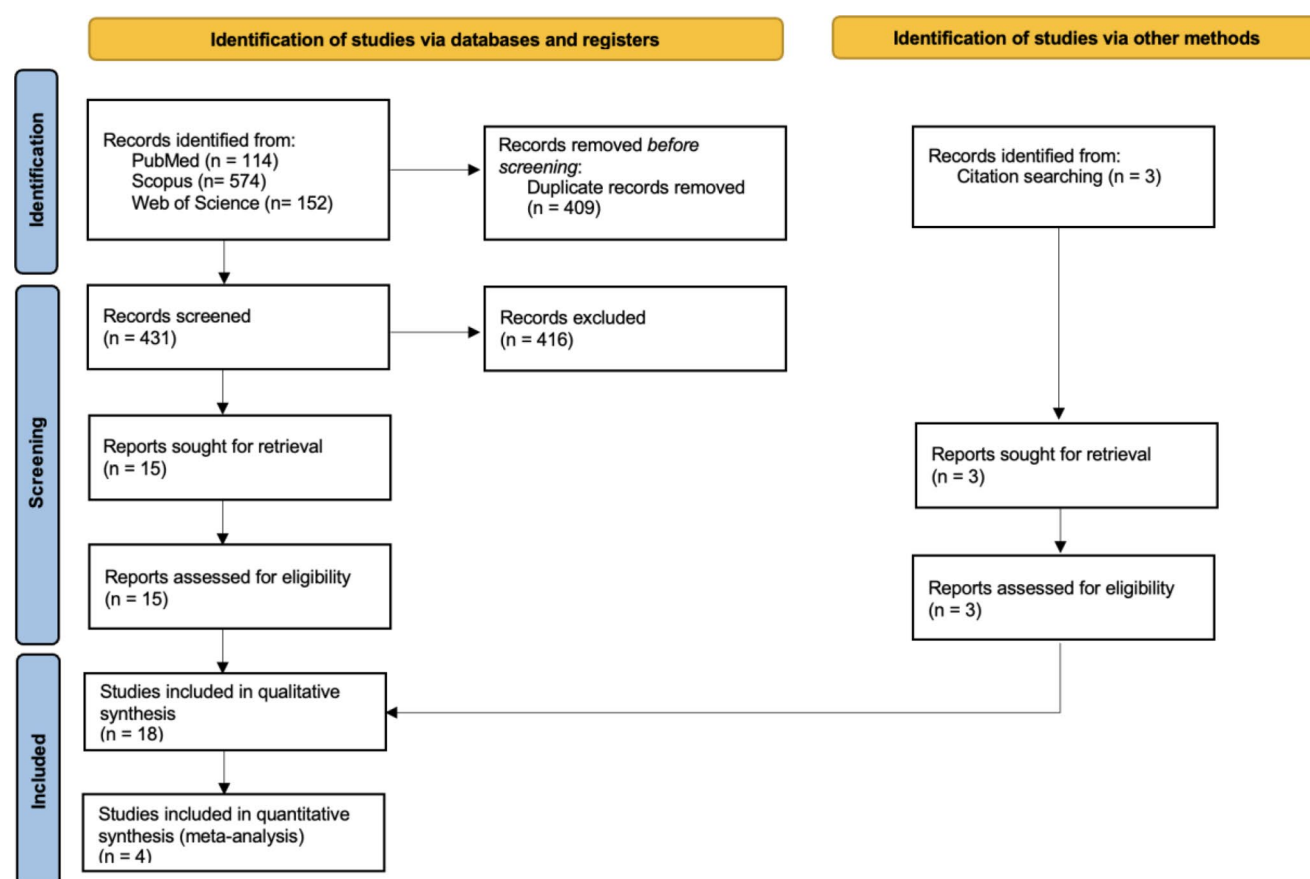


Fig. 1 Flow diagram of study selection

Table 1 Studies included in the systematic review and characteristics of patients who underwent SASI bypass

Author, year	Country	Study Design	Sample size, n°	Female (%)	Preoperative BMI (kg/m ²), mean $\pm$ SD	Follow-up (months)	Common limb, cm	Compares with (n°)
Mahdy et al. [5]	Egypt	Retrospective cohort	50	66	48.7 $\pm$ 7.6	12	250	-
Salama et al. [24]	Egypt	Prospective cohort	45	75.5	43.2	12	300	-
Vennapusa et al. [8]	India	Prospective cohort	113	41.6	43.48 $\pm$ 7.57	12	250, 300 or 350*	-
Arslan et al. [7]	Turkey	Retrospective cohort	15	46.7	35.05 $\pm$ 4.15	3	300	-
Abouzeid et al. [25]	Egypt	Prospective cohort	20	80	45.80 $\pm$ 7.60	12	250	-
Khalil et al. [6]	Egypt	Randomized control trial	26	73.1	45.5 $\pm$ 7.1	12	250	SG (25)
Mahdy et al. [18]	Multicenter	Retrospective cohort	551	70.8	43.2 $\pm$ 12.5	12	250	-
Mohamed et al. [9]	Bahrain	Retrospective cohort	34	-	58.3	12	250	SG (104) and OAGB (39)
Kermansaravi et al. [22]	Iran	Retrospective cohort	24	79.2	44.2 $\pm$ 4.3	12	250	-
Madyan et al. [26]	Egypt	Prospective cohort	20	85	53.7 $\pm$ 5.9	12	300	SG
Khalaf et al. [20]	Egypt	Retrospective cohort	322	61.5	50.1 $\pm$ 7.7	24	250 or 300 **	-
Romero et al. [23]	Mexico	Retrospective cohort	83	63.8	40.9 $\pm$ 7.1	12	300	-
Mahdy et al. [17]	UAE	Retrospective cohort	46	50	44.4 $\pm$ 9.8	12	300	RYGB (46)
Mahdy et al. [19]	UAE	Retrospective cohort	74	70.3	42.1 $\pm$ 14.5	12	300	SG (99) and OAGB (91)
Emile et al. [16]	Multicenter	Retrospective cohort	58	77.6	48.9 $\pm$ 16.9	12	250	SG (58)
Tarnowski et al. [21]	Poland	Retrospective cohort	19	94.7	40.3 $\pm$ 3.74	12	300	-
Hosseini et al. [15]	Iran	Retrospective cohort	116	84.5	43.54 $\pm$ 3.88	36	300	-
Hosseini et al. [14]	Iran	Retrospective cohort	138	84.8	45.35 $\pm$ 4.61	12	$\geq$ 200	SASJ (24)

SD – Standard deviation; SASJ – Single anastomosis sleeve jejunal bypass

a - NIH (National Institutes of Health) quality assessment criteria for observational studies: it is based on a quality rating of G (good), F (fair), and P (poor), and 14 questions that can be answered with yes/no/not applicable/not reported/cannot determine. Y/N is the ratio of questions with positive answers (Y=yes) and negative answers (N=no)

*Common channel length was 250 cm in 18 patients, 300 cm in 88 patients, and 350 cm in 7 patients

**The length of the CL was determined according to the total bowel length (TBL). If the TBL was $\leq$ 6 m, the CL length was 250 cm. The CL length was 300 cm if the TBL was more than 6 m. 250 cm was performed 36% (116) of the time and 300 cm 64% of the time (206)

Five studies made a comparison with SG (3 retrospective, 1 prospective, 1 RCT) and 2 retrospective studies made a comparison with OAGB (Table 1).

These studies were published between 2016 and 2022 and were conducted in Iran [14, 15, 22], United Arab Emirates (UAE) [17, 19], Egypt [5, 6, 20, 24–26], Poland [21], Mexico [23], India [8], Bahrain [9], and Turkey [7]. Two of the studies were multicentric, one was conducted in 7 countries (UAE, Kuwait, Egypt, Germany, Norway, Portugal, and Turkey) [18], and the other was in 2 countries (Egypt and UAE) [16].

A total of 1714 patients were studied, with sample sizes ranging from 19 to 551. The follow-up time ranged between 3 months and 36 months.

Risk of bias of individual studies

The risk of bias in the observational studies is demonstrated in the Supplementary Table 2. Most studies failed to justify the sample size, and none ensured that the assessors were blinded to the exposure status. Only two studies had a loss of follow-up after baseline higher than 20%. For the other criteria, most studies showed a low risk of bias. Therefore, all studies were considered good or fair.

The results of the quality assessment of RCT are shown in Supplementary Table 3 [27]. Overall, this study was considered to have a low risk of bias since only two parameters were considered unclear.

Comparison between SASI bypass and SG

Percentage of excess weight loss

A total of 329 patients were analysed in three studies on %EWL after 12 months (Fig. 2a). SASI was found to be significantly better than SG in the meta-analytical %EWD MD (MD=11.32; 95%CI[7.89;14.76]; $p<0.0001$), with a moderate heterogeneity ($I^2=11\%$; $p=0.33$). Heterogeneity ceased to be observed after removing the study by Madyan et al. (Supplementary Table 4).

Type 2 diabetes mellitus

A total of 124 patients were analysed in four studies that compared SASI versus SG on the partial or complete remission of T2DM after 12 months.

Compared with SG, SASI bypass was associated with 1.35 times more probability of improvement or resolution of T2DM, and this difference was significant (RR=1.35; 95%CI[1.07; 1.69]; $p=0.011$). No heterogeneity was detected ($I^2=0\%$; $p=0.96$) (Fig. 2b).

Hypertension

Four studies compared SASI and SG on the improvement or resolution of HT in these two techniques (101 patients) after 12 months. The results presented in Fig. 2c show no significant difference (RR=1.10; 95%CI[0.82;1.46]; $p=0.532$) between the two approaches, and no heterogeneity was detected ($I^2=0\%$; $p=0.95$).

Dyslipidemia

A total of 68 patients were analysed in two studies that compared partial or complete remission of DL after 12 months.

Compared to SG, a patient who underwent SASI bypass was associated with 1.41 times more probability of improvement or resolution of DL (RR=1.41; 95%CI[1.00;1.99]; $p=0.048$). No heterogeneity was detected ($I^2=0\%$; $p=0.91$) (Fig. 2d).

Obstructive sleep apnea

A total of 34 patients were analysed in two studies that compared partial or complete remission of OSA after 12 months.

Compared to SG, a patient who underwent SASI bypass was associated with 1.5 times greater chance of improvement or resolution of OSA (RR=1.50; 95%CI[1.01;2.22]; $p=0.042$). No heterogeneity was detected ($I^2=0\%$; $p=0.32$) (Fig. 2e).

Complications

A total of 467 patients were analysed in four studies after 12 months (Fig. 2f). No significant differences between techniques (RR=2.81; 95%CI[0.3;20.61]; $p=0.310$) were observed, and high heterogeneity was detected ($I^2=86\%$; $p<0.01$). Heterogeneity decreased (albeit remaining high – 67.1%) with the exclusion of the Emile et al. study (Supplementary Table 5).

Comparison between SASI bypass and OAGB

In the comparison between SASI bypass and OAGB, it was not possible to establish a comparison regarding weight loss due to the lack of data.

Comorbidities

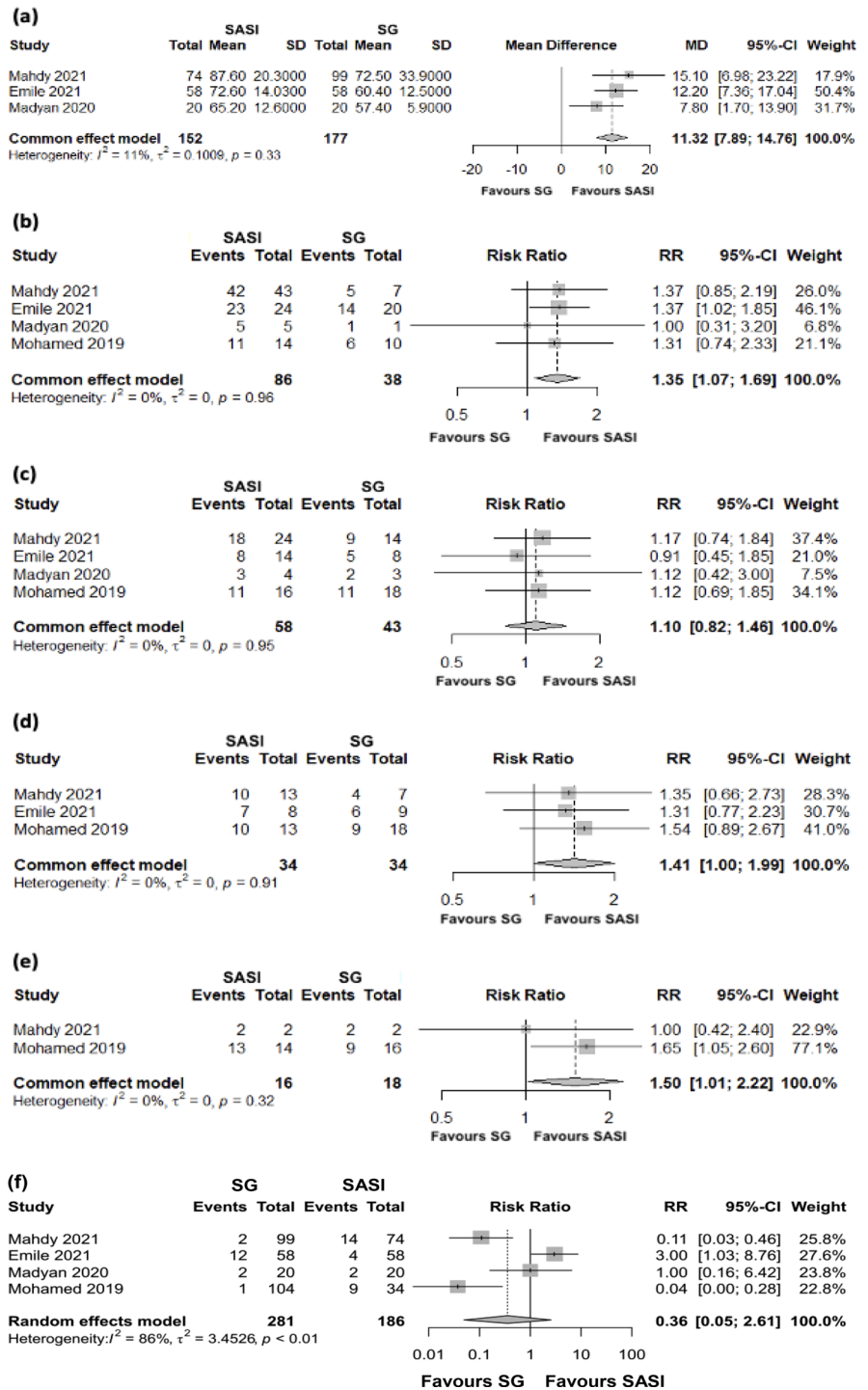
Two studies evaluated the improvement or remission of T2DM (110 patients), HT (81 patients), DL (50 patients), and OSA (33 patients) after 12 months. No significant differences between techniques were observed in T2DM (RR=1.08; 95%CI[0.94;1.24]; $p=0.257$), HT (RR=0.87; 95%CI[0.69;1.11]; $p=0.266$), DL (RR=1.03; 95%CI[0.75;1.41]; $p=0.854$), and OSA (RR=1.14; 95%CI[0.85; 1.52]; $p=0.3789$). No heterogeneity was detected in any of these.

Complications

Four studies evaluated the complications in 283 patients after 12 months (Fig. 3e). No significant differences were observed between techniques (RR=2.47; 95%CI[0.3;20.61]; $p=0.31$), although moderated heterogeneity was observed ($I^2=42\%$; $p=0.19$).

The effectiveness of SASI bypass, in terms of weight reduction and improvement in comorbidities, was associated with a favourable safety profile. In this review, complications were observed in 11.7% of patients, which is comparable to the rate reported in previous studies for SG [28]. Concerns regarding the need for reversal surgery were mainly due to excessive weight loss or hypoalbuminemia. However, in this review, the rates of excessive weight loss and hypoalbuminemia were 1.03% and 1.5%, respectively. Other complications reported were: 33 vomiting (~0,02%) [17, 18], 21 bleeding (~0,01%) [5, 6, 14–23, 25], 16 diarrhea (~0,01%) [18, 21], 10 leakage (~0,01%) [5, 6, 14, 15, 25], 8 stomal ulcer (~0,01%) [5, 6, 9, 18], 5 intestinal obstruction (<0,01%) [5, 16–19], 4 pulmonary embolism (<0,01%) [5, 15, 17, 18], 4 pneumonia (<0,01%) [6, 16, 26], 4 dumping syndrome (<0,01%) [6], 3 worsening symptoms of GERD (<0,01%) [6, 20],

Fig. 2 Forest plots of the comparison between SASI and SG; (a) %EWL, (b) T2DM, (c) HT, (d) DL, (e) OSA, and (f) complications



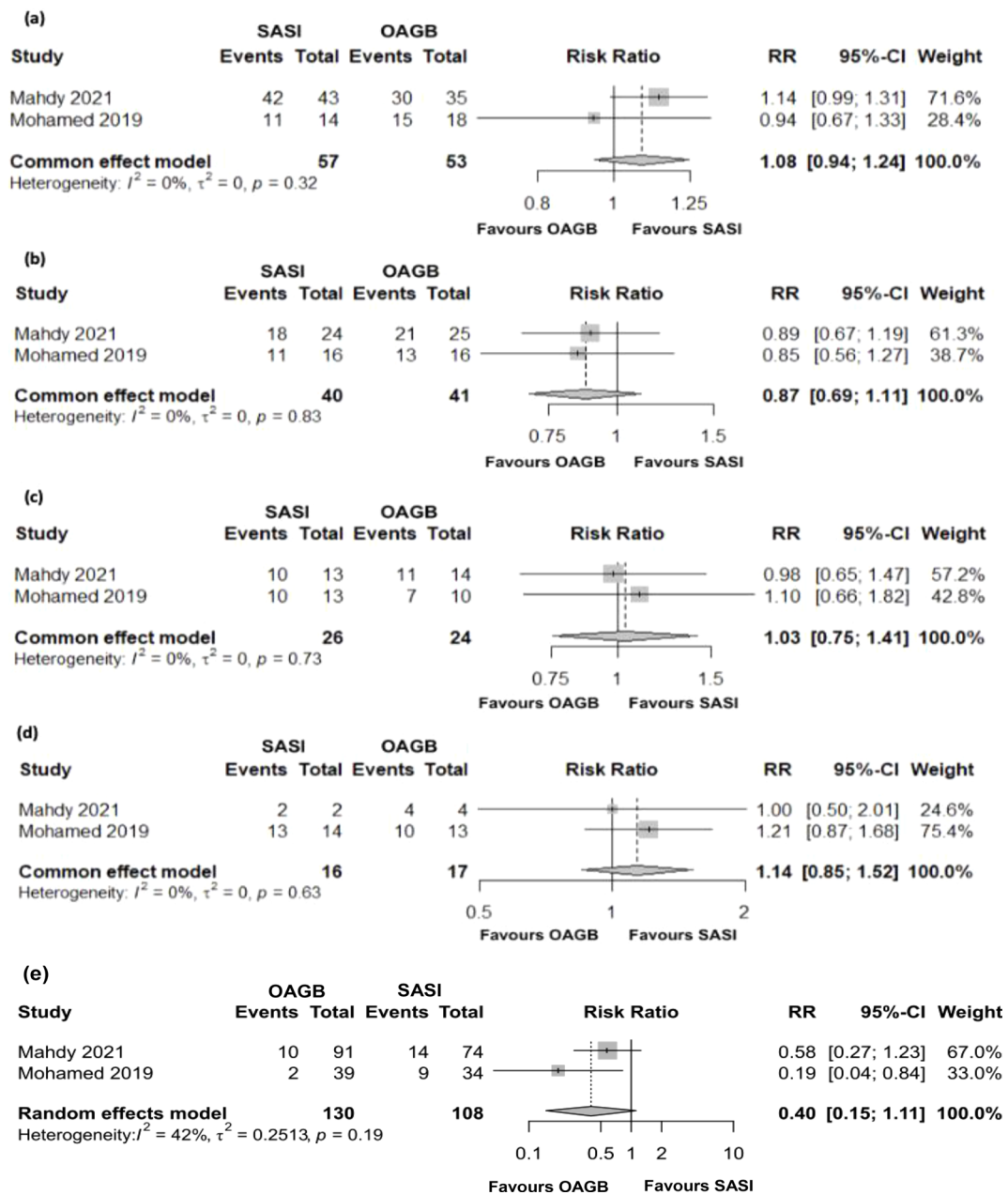


Fig. 3 Forest plots of the comparison between SASI and OAGB; (a) T2DM, (b) HT, (c) DL, (d) OSA, and (e) complications

2 dysphagia (<0,01%) [21, 23], 2 thrombosis (<0,01%) [14], 2 wound infection (<0,01%) [23], 2 peripheral neuropathy (<0,01%) [19], 2 calcium deficiency (<0,01%) [24], 2 internal hernia (<0,01%) [6, 23], 2 calcular obstructive jaundice (<0,01%) [18], 1 urinary tract infection (<0,01%) [6], 1 ileal perforation (<0,01%) [18], 1 ileus (<0,01%) [26], 1 twisting of the biliopancreatic limb at the gastroileal anastomosis site (<0,01%) [23], 1 biliary gastritis (<0,01%) [23], 1 acute cholecystitis (<0,01%) [23] and 1 trocar site hernia (<0,01%) [22].

Discussion

Summary of evidence

The ideal bariatric surgery should be safe, technically simple, and successful in reducing weight and treating comorbidities [29]. The Santoro technique [30] was the foundation for SASI bypass, which had the goals of facilitating the procedure and try to lower the risk of complications, by reducing the number of anastomoses [5].

Most studies (14) used the %EWL to evaluate the impact of SASI bypass on the weight of participants [5, 6, 8, 14–23, 26]. The median %EWL at 12 months was 87.14%, which was nearly the same as in the initial report by Mahdy et al. (90%) [5]. A wide variation in the values was registered within the studies, varying between 63.9% and 94.33%. This deviation may be attributed to distinct patients' characteristics, or a lack of technical standardization. Studies with a lower %EWL had a higher preoperative BMI. This is consistent with previous studies that showed that patients with a higher BMI had a lower %EWL after bariatric surgery. [31]. Comparing these results with a systematic review by Emile et al., which demonstrated that SG had a %EWL of 67.3% after 12 months [28], we can verify that SASI bypass has a better %EWL (87.14%), demonstrating a reasonable weight loss. These results are concordant with those in the comparison of SASI bypass with SG, indicating a clear superiority of SASI bypass. Due to a lack of data, we were unable to compare SASI bypass and OAGB in the meta-analysis. Two studies reported results after two years of follow-up, showing even better results (90.7% [15] and 96.7% [20]). Additionally, one study [15] had a three-year follow-up that had a mean %EWL of 80.6%.

In total, 713 patients were studied for the improvement or remission of T2DM after 12 months in 16 studies. The results ranged between 78.6% and 100%, with a median of 96.35% [5, 6, 8, 9, 14–23, 25, 26], which is higher than the results reported in previous studies for SG, RYGB, and OAGB [28, 32]. Although there was a wide range of results, only four studies had a rate lower than 90%. These results are concordant with those of our meta-analysis, which demonstrated that patients who underwent SASI bypass had better chances of improvement or resolution than those who underwent SG. Additionally, when compared with the OAGB, the SASI bypass had similar results.

Regarding HT, 15 studies evaluated the rate of complete remission and improvement, in 514 patients after 12 months [5, 8, 9, 14–23, 25, 26]. With a median of 75.8%, the findings were between 36.1% and 100%, with only five studies reporting an outcome under 75%. In our analysis, we determined that the SASI bypass had similar results compared to SG and OAGB.

In 11 studies, 340 patients with DL were evaluated after one year to calculate the proportion of full remission and improvement [5, 9, 14–19, 22, 23, 25]. The findings ranged from 65 to 100%, with a median of 87.5%, and only one study had a median under 75%.

According to our analysis, SASI bypass had higher chances of DL improvement or resolution than SG but had similar results compared to OAGB.

OSA was evaluated in eight studies that demonstrated an improvement or remission between 20% and 100%, with a median of 89.3% [14, 15, 17–20, 22]. Although the range of

values was considerable, only three studies had a rate lower than 75%, and this difference could result from the distinct features between patients. The study that reported a value of 20% had a sample size of five patients with OSA, which can also explain the results. According to our meta-analysis, SASI bypass had better results than SG and similar results to OAGB.

Six studies evaluated GERD and reported a median improvement or remission rate of 84.1%, ranging from 75 to 100% [16, 18–20, 23, 26].

Owing to the limited sample size and lack of research, we were unable to establish a comparison for the meta-analysis of this outcome.

Two studies reported results regarding complete remission of non-alcoholic fatty liver disease (NAFLD) after 12 months. Kermansanavi et al. reported a rate of approximately 73% [22], and Hosseini et al. reported a rate of 90% [14]. Although these results are promising, further studies are needed to evaluate the efficiency of SASI bypass in NAFLD remission. In both studies, abdominal ultrasonography was performed to assess improvement in NAFLD.

Regarding the occurrence of biliary reflux, only one article reported a patient with evidence of severe biliary reflux on upper endoscopy, and he was managed by conversion to RYGB bypass [20]. No other evidence was found in any of the remaining articles. Nonetheless, biliary reflux should be addressed in future studies.

This review verified that technical variations in SASI bypass could induce different rates of weight loss, improvement in comorbidities and complications [28].

These variations included the length of the common limb, which varied between 200 and 350 cm; the size of the gastro-ileal anastomosis, which was 3–4 cm; and the gastro-ileal anastomosis proximal to the pylorus, which ranged between 3 and 6 cm.

Hosseini et al. demonstrated that a longer biliopancreatic limb was associated with greater improvement in HT, the cause of which is not clear. It may be related to alterations in the levels of ghrelin and GLP-1 hormones with respect to the length of the common limb, but further research is needed to better understand this mechanism [14].

On the other hand, a larger anastomosis size was associated with higher weight loss and a decrease in HT due to food diversion from the gastric pouch to the ileum, leading to an increase in the malabsorptive effect [14].

Recently, a world consensus meeting was held in India, resulting in a statement suggesting standardization of numerous bariatric surgeries, including SASI bypass. Recommendations to standardise the SASI bypass method included a width of the residual sleeve of 3 cm, the gastric pouch between 150 and 250 cc, separating the gastroileal anastomosis from the pylorus by 2–6 cm, an anastomosis size of 3 cm, and a common limb length of 300 cm [33].

Throughout the studies, there were many advantages of the SASI bypass. The single anastomosis of SASI bypass has many advantages over a double anastomosis in the Santoro procedure (SG + TB), including being a simpler procedure, shorter operative time, and a lower risk of anastomosis complications and internal hernia.

Another advantage of this procedure is that it allows endoscopic inspection of the duodenum and biliary tract due to the preservation of natural endoscopic access.

Improvement in GERD symptoms after SASI bypass, compared to SG, can be explained by the addition of the anastomosis, which will reduce intragastric pressure and help drain gastric acidity, thus contributing to the improvement of symptoms [16, 17].

After some bariatric surgeries, patients have an excluded part of the stomach (i.e., RYGB, OAGB). This means that the detection of gastric lesions is challenging, and diagnosis and treatment may be delayed [34]. This is not a problem in SASI bypass, because it is a sleeve without an excluded stomach.

SASI bypass can be considered a technique between SG and SADI-S. Removing the anastomosis converts the SASI bypass to SG, and sectioning the duodenum converts the SASI bypass into a modified SADI-S. Therefore, it can be converted to SG in cases of malnutrition or excessive weight loss or modified to SADI-S if the bariatric and metabolic outcomes are considered unsatisfactory [35].

Limitations

One of the main limitations of this review was the fact that only two studies [15, 20] had more than 12 months of follow-up, so there is a need for more studies with a longer follow-up period to evaluate mid-term and long-term outcomes. Additionally, a longer follow-up period is needed to guarantee that long-term complications such as malnutrition, hypoalbuminemia, and excessive weight loss will not develop.

Secondly, given that this technique is relatively recent, most studies had a limited number of participants. Therefore, most of the existing studies consist of small or medium-sized cohorts.

Owing to the small number of studies included in the SASI and OAGB meta-analyses, there are insufficient data to establish a significant comparison between these techniques.

A meta-analysis comparing SASI bypass and RYGB, the main bypass technique used, could not be established because only one of the selected studies compared these techniques.

There was not a common definition between studies in the definition of improvement/remission in comorbidities,

which may cause some variation in results between studies and limits the conclusions presented related to comorbidities.

The high statistical heterogeneity obtained in some of the analyses, can be potentially explained by distinctive patient features, or lack of technical standardization.

Lastly, observational studies, which are more susceptible to bias and confounding variables, constituted nearly all the included studies. Consequently, determining a more effective technique can be more challenging. Therefore, more RCT are required.

Conclusions

SASI bypass has a significant effect on weight loss, and remarkable metabolic control. Additionally, this new technique seems to be a safe bariatric surgical procedure. Nevertheless, there is a need for mid and long-term studies, comparing SASI to other better known and used choices (namely RYGB), in order to ascertain the true clinical advantage of SASI and determine the most robust factors for selecting patients for this procedure.

In conclusion, SASI bypass could be an important tool in the future, but there is a need for studies with longer follow-up periods (> 12 months) to confirm the efficiency and safety of this surgical technique.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00423-024-03413-w>.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Carolina Rodrigues Oliveira, Hugo Santos-Sousa, Maria Pinho Costa, and Bernardo Sousa-Pinto. The first draft of the manuscript was written by Carolina Rodrigues Oliveira and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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D. FUTURE PERSPECTIVES

GC and nutritional status

The impact of the prognostic nutritional index (PNI) in gastric cancer. Langenbecks Arch Surg 407, 2703–2714 (2022) (*) doi: [10.1007/s00423-022-02627-0](https://doi.org/10.1007/s00423-022-02627-0)

[Associated Research: Bridge between GC and its nutritional aspects and MBS]

Hugo Santos-Sousa and Jorge Nogueiro shared **First Authorship**

Cited by **54** articles

(Google Scholar, 2025, October 20)

Scimago Journal Rank (SJR) indicator 0,721 | H Index 86 | Rank 118 of 512 on Surgery journals (**Q1**)

(Scimago Journal & Country Rank, 2022)

Journal Impact Factor (JIF) 2,3 | Rank 97 of 213 on Surgery journals (**Q2**)

Journal Citation Indicator (JCI) 0,95 | Rank 74 of 286 on Surgery journals (**Q2**)

(Thomson-Reuters, Science Citation Index Expanded (SCIE), 2022)



The impact of the prognostic nutritional index (PNI) in gastric cancer

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Abstract

Background Regarding the assessment of patients' immune and nutritional status, prognostic nutritional index (PNI) has been reported as a predictive marker for surgical outcomes in various types of cancer. The aim of our study was to evaluate the effect of PNI in prognosis of gastric cancer patients submitted to curative-intent resectional surgery.

Material and methods A retrospective analysis with 637 gastric cancer cases submitted to curative-intent surgery, between 2010 and 2017, in an upper GI surgery unit. We analyzed 396 patients that met the inclusion criteria for this study. The median follow-up was 37 (0–113) months.

Results According to Youden's method, the optimal PNI cutoff for OS was 41.625 (sensitivity 89.3% and specificity 41.3%). OS was significantly shorter in the lower-PNI group of patients when compared to the higher-PNI group (40.26 vs 77.49 months; $p < 0.001$). Higher PNI had a positive impact on OS in univariable analysis. When adjusted to pStage, higher PNI was still significantly associated with better OS (HR 0.405; CI 95% 0.253–0.649; $p < 0.001$). Regarding DFS, higher PNI was associated with better DFS (HR 0.421; CI 95% 0.218–0.815; $p = 0.010$). Higher-PNI group had a protective effect regarding postoperative morbidity and mortality.

Conclusions In this cohort, PNI was disclosed to significantly impact GC patients' OS and DFS, including in multivariable analysis when adjusting for classical prognostic features. PNI can be used to predict patients at increased risk of postoperative morbidity and mortality. This index may be of use in identifying candidate patients who would benefit from perioperative nutritional support to improve surgical outcomes.

Keywords Gastric cancer · Nutrition · Prognosis · Survival

Introduction

Gastric cancer (GC) is the 5th most incident and the 3rd most deadly cancer worldwide, with age standardized incidence and mortality rates of 11.1/100,000 and 8.2/100,000, respectively, in 2018. Incidence is increasing, with 1,758,810 new estimated cases expected in 2040 [1]. In the USA, around 1% of men and women will be diagnosed with GC during their lifetime. Only 31.5% of patients survive after 5 years. Solely 28% of patients are diagnosed with localized disease,

and survival of disseminated disease is very poor, rounding 5% [2].

A successful gastrectomy is an essential part of a successful treatment. While this surgery harbors the risk of perioperative morbidity and mortality, with perioperative complication rates that can range from 10 to 46% [3, 4], it can also potentially cure the disease. As one of the most common malignancies worldwide, efforts have been made to identify potentially amenable factors that can adversely influence surgical outcomes and survival prognosis.

Advanced age, medical comorbidities, and advanced stage, among other mainly unamenable factors related to disease status or patients' physical status, hold prognostic significance and are related to surgical complications [5, 6].

Assessment of patients' nutritional status has been identified for a long time as a potentially prognostic factor that can be corrected prior to surgery. The importance of patient nutritional support has been recently advocated by ESPEN

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Guidelines, as a patient with severe nutritional risk should be optimized even if oncologic surgeries have to be delayed [7].

Despite the existence of several tools to assess nutritional status, including nutrition risk index [8] and nutritional risk screening 2002 [9], these are difficult to use in daily practice, with some parameters not always available.

The prognostic nutritional index (PNI), calculated with the following equation — $[(10 \times \text{serum albumin (g/dL)}) + (0.005 \times \text{total lymphocyte count})]$ [10] — has emerged as an easily calculated index, with routinely evaluated parameters in daily practice. PNI has been referred to as a prognostic factor in several gastrointestinal cancers, including colorectal, esophageal, and liver cancer [11–13]. There are some reports regarding the prognostic significance of PNI in GC, but controversy remains regarding the optimal cutoff values in predicting surgical outcomes [4, 14].

The aim of this study was to validate the PNI as a prognostic marker in a well-defined cohort of GC patients from a tertiary center, looking for clinicopathological correlations and impact on patient outcome, namely survival.

Material and methods

Patient sample

In this study, we retrospectively reviewed and analyzed data in a prospectively maintained database of 637 consecutive patients with gastric cancer treated in an upper GI surgery

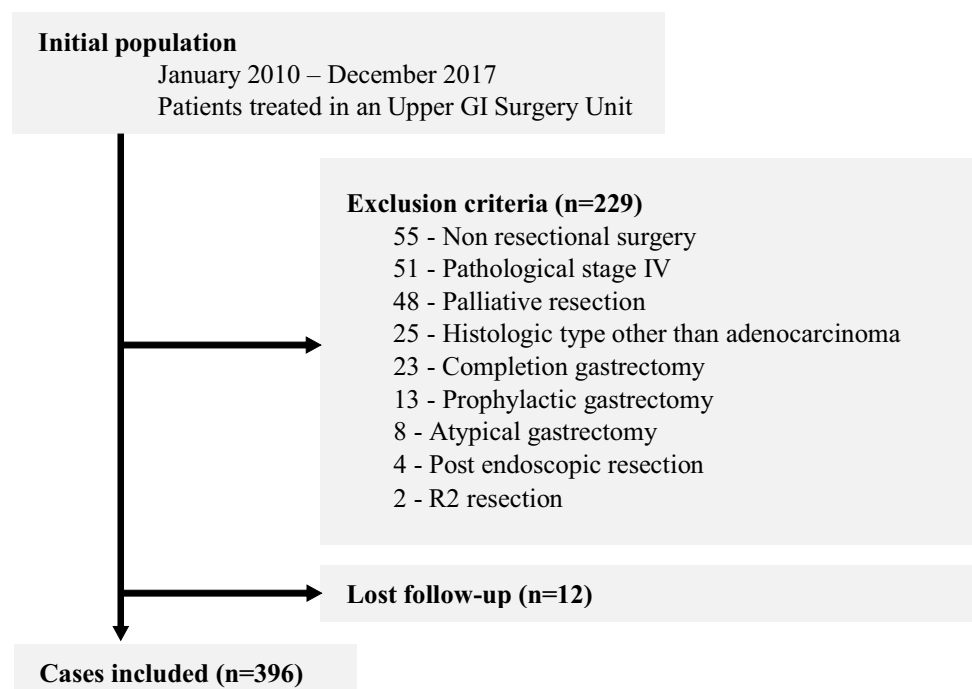
unit of a tertiary hospital between January 2010 and December 2017.

For this study, only curative-intent surgeries for gastric adenocarcinoma were considered. The exclusion criteria were non-resectional surgery, palliative and prophylactic gastrectomies, completion gastrectomies, atypical resections, pathological stage IV carcinomas, histologic types other than adenocarcinoma, and R2 resections. Patients lost for follow-up were not included in this analysis. A total of 396 patients fulfilled these criteria and were enrolled in this study (Fig. 1).

Data collection

Baseline characteristics were collected from each patient, in order to characterize the population. The following demographic parameters were collected: age at time of surgery, gender, American Society of Anesthesiologists (ASA) physical status classification, body mass index (BMI), and comorbidities. The presence of comorbidities was characterized as having at least one of the following: hypertension was assigned to patients who were taking antihypertensive drugs or according to American Heart Association guidelines; dyslipidemia was assigned to patients who were taking any anti-dyslipidemia drugs; ischemic heart disease was annotated in patients diagnosed with angina or myocardial infarction, or having undergone stent placement, bypass surgery, or medical therapy for coronary disease; cerebrovascular disease was similarly acknowledged in patients diagnosed with cerebral infarction or cerebral hemorrhage; diabetes mellitus

Fig. 1 Flow chart of the study design



was defined as the use of oral hypoglycemic drugs or insulin; and pulmonary disease was conceded in patients diagnosed with chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA). Any other comorbidity was evaluated case by case. In order to describe the clinico-pathological profile, tumor location and size (cm), macroscopic appearance, histologic type (Laurén classification), growth pattern (Ming classification), TNM staging (7th edition, 2010), pathological stage (pStage), resected lymph node (LN) ratio, venous, perineural, and lymphatic invasions were evaluated. The surgery approach, type of resection (R), and the presence of neoadjuvant therapy were used to characterize the therapeutic approach. Resection was defined as curative (R0) when the tumor was completely removed with negative margins; and incomplete resection was defined as residual gross disease (R2) or positive surgical margins [(R1), tumor less than 1 mm from any margin].

For short-term complications analysis, the following parameters were evaluated: postoperative morbidity (less than 30 days after surgery) and postoperative mortality.

In survival analysis, overall survival (OS) and disease-free survival (DFS) were evaluated. OS was defined as the period between the day of surgery and death of patient. Patients who had survived until the end of the observation period were censored at their last follow-up visit. DFS was considered the period between the end of primary therapy and the first evidence of disease recurrence. Clinical, radiologic, or endoscopic signs of disease were used in order to diagnose recurrence.

Median (range) follow-up was 37 (0–113) months and patient follow-up review was completed in September 2019, for the entire study population.

Perioperative management and surgical procedure

As a diagnostic procedure for GC, all the patients were submitted to upper endoscopy with biopsy and computerized tomography (CT). Staging was established according to clinical, radiological (CT), or endoscopic (endoscopic ultrasonography) features, and staging laparoscopy when considered necessary (mainly in local advanced tumors, when resectability was uncertain).

All laparoscopic resections were performed by surgeons with considerable experience in upper GI minimally invasive surgery, namely advanced laparoscopic procedures for morbid obesity.

For diffuse and proximally located tumors, the surgery performed was a total gastrectomy with Roux-en-Y reconstruction. Additionally, for distally located tumors, the surgery performed was a subtotal distal gastrectomy, using Billroth II and sporadically Roux-en-Y reconstruction, according to age and comorbidities of the patient.

All patients were routinely managed in post-surgical intensive care unit for the immediate postoperative period, with postoperatively early extubation, pain control, vigorous respiratory therapy, early mobilization, and ambulation as goals. According to clinical evolution, food intake was permitted. Patients were followed up at 3- and 6-month intervals, during the first and second year after the surgery, respectively, and annually afterwards.

PNI assessment

Patients' preoperative blood samples and laboratory measurements collected up to 2 weeks prior to the date of surgery were considered for inclusion in the PNI assessment. When patients had multiple samples that were available during this period, the one closest to the surgery was used.

The PNI was determined, as previously described, with the following equation: $[(10 \times \text{serum albumin (g/dL)}) + (0.005 \times \text{total lymphocyte count})]$.

Statistical analysis

Non-parametric Mann-Whitney *U*-test was used to compare the distribution of continuous variables among categories. Chi-square and Fisher's exact tests were used to compare proportions, as appropriate. Logistic regression was computed for assessing association with morbi-mortality, with respective odds ratios (ORs).

To evaluate the sensitivity and specificity for the 2-year OS, receiver operating characteristic (ROC) curve was calculated, and the Youden index was estimated to determine the optimal cutoff value for the PNI.

Cumulative survival curves for OS and DFS were computed using the Kaplan-Meier (KM) method, and log rank test was used to assess differences between groups. Hazard ratio (HR) and respective 95% confidence intervals (CIs) were calculated by Cox regression model. Univariable and multivariable analyses were performed.

Statistical analysis was performed using SPSS® 26.0 for Mac (IBM Co., Armonk, NY, USA). Significance was assumed for *p* values inferior to 0.05. All *p* values given are results of 2-sided tests.

Results

We included 396 patients in our study with only 203 eligible with completed analytical data. The mean age was 66 (range: 54–78) years and 59.6% were males.

In order to categorize patients according to PNI value, a cutoff value was determined. Using the 2-year survival as an endpoint, the area under the ROC curve for the PNI was 0.644 (CI 95% 0.555–0.734; *p* = 0.001). The Youden

index was maximal when the PNI was 41.625 (sensitivity 89.3%; specificity 41.3%). Therefore, the cutoff value of the PNI was set at 41.625. Then, 41 patients (20.2%) with PNI of 41.625 or lower and 162 patients (79.8%) with PNI > 41.625 were classified into a PNI-low and PNI-high group, respectively. Population demographics and clinico-pathologic characteristics are described in Table 1.

PNI groups differed significantly regarding the mean age, ASA score, tumor size, pathological P stage and N stage, lymphatic permeation, venous invasion, perineural invasion, and pathological stage (Table 1).

Regarding survival outcomes, in our cohort, the mean OS was 70.04 months and the mean DFS was of 86.38 months. OS was significantly shorter in the lower-PNI group of patients when compared to the higher-PNI group (40.26 vs 77.49 months). Furthermore, when stratifying the analysis to pathological stage, OS was still significantly shorter within stages I and III patients with lower PNI (Fig. 2). Also, DFS was significantly poorer in the lower PNI patients when compared to the high PNI patients (Fig. 3) (Table 2).

Higher PNI had a positive impact on OS (HR 0.325; CI 95% 0.207–0.511; $p < 0.001$) in univariable analysis. When adjusted to pStage, higher PNI was still significantly associated with better OS (HR 0.405; CI 95% 0.253–0.649; $p < 0.001$). Regarding DFS, higher PNI was also associated with better DFS (HR 0.421; CI 95% 0.218–0.815; $p = 0.010$), but this was not maintained when adjusting for pStage (Table 3).

In univariable analysis, both age, postoperative complications, surgery approach, tumor size, the presence of lymphatic, venous and perineural invasion, pathological stage, and PNI were significantly associated with OS. The multivariable analysis demonstrated that the PNI, pathological stage, age, postoperative complications, and surgery approach were prognostic factors for the OS (Table 4).

Regarding DFS, both surgery approach, the presence of lymphatic, venous and perineural invasion, pathological stage, and PNI were significantly associated with DFS in the univariable analysis. Only pathological stage revealed to be an independent prognostic factor for DFS in multivariable analysis (Table 5).

Postoperative complications developed in 48 patients (23.6%); 28 (13.8%) of them being *Clavien-Dindo* IIIa or higher (Table 6). The lower-PNI group patients had significantly higher postoperative complications than higher-PNI group (26.6% vs 20.4%; $p = 0.029$). Postoperative mortality was also significantly associated with PNI with higher mortality in the lower-PNI group (14.6% vs 3.1%; $p = 0.004$) (Table 7). Logistic regression analysis revealed that the higher-PNI group had a protective effect regarding

postoperative morbidity and mortality with OR 0.443; CI 95% 0.211–0.931; $p = 0.032$ and OR 0.186; CI 95% 0.054–0.643; $p = 0.008$, respectively (Table 8).

Discussion

GC is a widespread cancer, and incidence is increasing worldwide. Treatment is primarily surgical, and may be curative; in fact, recurrence is largely dependent on the adequacy of surgical resection and success of lymph node dissection. However, also equally important, the success rate depends on the patient health status, and on the ability to endure frequent side effects and morbidity associated with the surgery and with eventual systemic treatments. In this context, the nutritional status of the individual patient (with GC and overall with any other neoplasm) is of paramount importance. In fact, the European Society of Clinical Nutrition and Metabolism Guidelines on clinical nutrition in surgery recommend to administer nutritional therapy prior to major surgery in patients with severe nutritional risk even if neoplastic surgery have to be delayed [7].

In spite of this, our ability to ascertain the nutritional status of patients in the routine clinical setting is to the best limited. On one end of the spectrum, clinicians rely on limited tools like serum albumin on a day-to-day basis, which is logically suboptimal for considering the whole profile of the patient. On the other hand, nutritionists often rely on complex scores, which are cumbersome and difficult to apply on a daily basis on admission, including variables that are not often available or repeated shortly to allow for monitoring of the patient. There is a need for an objective, practical, and simple method for assessing the nutritional status of the surgical patient, specific per pathology (given the peculiarities of each disease and surgical strategy).

In the recent years, a lot of attention and research effort has been directed to PNI. This has proved to be a practical tool that accurately and globally assesses the nutritional profile of patients, relying on the addition of total lymphocyte count to serum albumin, reflecting the relevance of inflammation and related signaling pathways on nutrition and metabolism [15]. In healthy individuals, more than 50% of the serum proteins comprise albumin which is produced by hepatocytes [16]. It is regulated by proinflammatory cytokines, produced by the host or by the tumor, and plays crucial roles in cancer progression and neo-angiogenesis [17]. Hence, low serum albumin is associated with the prognosis of several malignancies and is correlated with an increased inflammatory response to the tumor. Lymphocytes, as fundamental components of the cytotoxic immune response, play a key role in suppressing tumor cell

Table 1 Baseline demographics and correlation between PNI and clinicopathologic parameters

		PNI		
	All <i>n</i> = 203 (%)	< 41.625 (<i>n</i> = 41)	> 41.625 (<i>n</i> = 162)	<i>p</i> value
Demographics				
Age at surgery (years), mean ± SD	66.09 ± 12.45	72.93 ± 8.53	64.36 ± 12.71	< 0.001
Gender, <i>n</i> (%)				0.841
Male	121 (59.6)	25 (61.0)	96 (59.3)	
Female	82 (40.4)	16 (39.0)	26 (40.7)	
Comorbidities, <i>n</i> (%)				0.263
Absence	37 (18.2)	5 (12.2)	32 (19.8)	
Presence	166 (81.8)	36 (87.8)	130 (80.2)	
ASA, <i>n</i> (%)				0.007
I	29 (14.3)	5 (12.2)	24 (14.8)	
II	110 (54.2)	14 (34.1)	96 (59.3)	
III	59 (29.1)	20 (48.8)	39 (24.1)	
IV	5 (2.5)	2 (4.9)	3 (1.9)	
BMI (kg/m²), mean ± SD	25.65 ± 4.35	25.19 ± 5.63	25.74 ± 4.05	0.361
Therapeutic approach				
Surgery approach, <i>n</i> (%)				0.012
Open	113 (55.7)	30 (73.2)	83 (51.2)	
Laparoscopic	90 (44.3)	11 (26.8)	79 (48.8)	
Neoadjuvant therapy, <i>n</i> (%)				0.272
Absence	172 (84.7)	37 (90.2)	135 (83.3)	
Presence	31 (15.3)	4 (9.8)	27 (16.7)	
R classification, <i>n</i> (%)				0.065
R0	197 (97.0)	38 (92.7)	159 (98.1)	
R1	6 (3.0)	3 (7.3)	3 (1.9)	
Clinicopathological profile				
Tumor size (cm), mean ± SD	4.59 ± 2.82	6.00 ± 3.19	4.23 ± 2.61	0.001
Tumor location, <i>n</i> (%)				0.511
Proximal third (fundus)	4 (2.0)	0 (0.0)	4 (2.5)	
Middle third (body)	56 (28.4)	13 (32.5)	43 (27.4)	
Distal third (antrum/pylorus)	137 (69.5)	27 (67.5)	110 (70.1)	
Macroscopic type, <i>n</i> (%)				0.051
Fungating	32 (17.0)	8 (21.1)	24 (16.0)	
Ulcerated	54 (28.7)	7 (18.4)	47 (31.3)	
Infiltrative	22 (11.7)	1 (2.6)	21 (14.0)	
Ulcerofungating	21 (11.2)	4 (10.5)	17 (11.3)	
Ulceroinfiltrative	59 (31.4)	18 (47.4)	41 (27.3)	
Histologic type (Laurén), <i>n</i> (%)				0.757
Intestinal	88 (45.1)	19 (47.5)	69 (44.5)	
Diffuse	27 (13.8)	3 (7.5)	24 (15.5)	
Unclassified of solid structure	6 (3.1)	1 (2.5)	5 (3.2)	
Unclassified of mixed structure	51 (26.2)	12 (30.0)	39 (25.2)	
Unclassified NOS	23 (11.8)	5(12.5)	18 (11.6)	
Growth pattern (Ming), <i>n</i> (%)				0.122
Expansive	43 (21.9)	9 (22.5)	34 (21.8)	
Infiltrative	138 (70.4)	31 (77.5)	107 (68.6)	
Unclassified	15 (7.7)	0 (0.0)	15 (9.6)	
pT (7th ed. 2010), <i>n</i> (%)				< 0.001
pT1-2	106 (53.3)	11 (27.5)	95 (59.7)	

Table 1 (continued)

	All <i>n</i> = 203 (%)	PNI		<i>p</i> value
		< 41.625 (<i>n</i> = 41)	> 41.625 (<i>n</i> = 162)	
pT3-4	93 (46.7)	29 (72.5)	64 (40.333)	0.006
pN (7th ed. 2010), <i>n</i> (%)				
pN–	108 (53.2)	14 (34.1)	94 (58.0)	
pN+	95 (46.8)	27 (65.9)	68 (42.0)	
LN ratio, <i>n</i> (%)				0.081
≤ 0.2	159 (78.3)	28 (68.3)	131 (80.9)	
> 0.2	44 (21.7)	13 (31.7)	31 (19.1)	
Pathological stage, <i>n</i> (%)				0.001
I	91 (45.0)	9 (22.0)	82 (50.9)	
II	49 (24.3)	11 (26.8)	38 (23.6)	
III	62 (30.7)	21 (51.2)	41 (25.5)	
Lymphatic permeation, <i>n</i> (%)				0.010
Absence	96 (48.2)	12 (30.0)	84 (52.8)	
Presence	103 (51.8)	28 (70.0)	75 (47.2)	
Venous invasion, <i>n</i> (%)				0.014
Absence	132 (66.3)	20 (50.0)	112 (70.4)	
Presence	67 (33.7)	20 (50.0)	47 (29.6)	
Perineural invasion, <i>n</i> (%)				0.003
Absence	134 (67.3)	19 (47.5)	115 (72.3)	
Presence	65 (32.7)	21 (52.5)	44 (27.7)	

Bold entries include values of statistically significance

proliferation and invasion via cytokine-mediated cytotoxicity [18]. Therefore, the PNI, taking into account both these variables, may represent a comprehensive indicator of the long-term prognosis of cancer patients. This score has been proved to risk-stratify cancer patients, which may allow for timely identification of high-risk patients that should be actively optimized nutritionally before surgery, in order to achieve the best survival outcome.

In this work, we aimed to assess the prognostic impact of PNI in a well-defined GC cohort, looking specifically for impact on survival and postoperative complication events.

Our study findings indicate that low preoperative PNI values in GC patients submitted to curative-intent surgery are predictive of poor prognosis even when adjusted to classical prognostic factors, such as the pathological stage. The OS and DFS rates of the low-PNI group were significantly lower than those of the high-PNI group. Regarding OS, long-term outcomes of patients with stage I disease were poorer in patients with worse nutritional status. Preoperative PNI may be a valid prognostic factor in this group of patients, implying that lower PNI prior to surgical resection is predictive of poor survival, even if survival expectations as determined by staging are high.

The multivariable analysis performed demonstrates that, in addition to conventional prognostic factors, the PNI was a predictor for the OS.

Our results also indicate that low preoperative PNI values are an indicator of worse postoperative outcome, with patients with PNI < 41.625 suffering higher rates of morbidity in the short postoperative period.

One of the most arguable issues within the PNI (and one reason impeding its translation to the clinic) has been the establishment of a consensus cutoff. In our work, we used a ROC curve analysis adjusted to 2-year survival for establishing the most clinically relevant cutoff value, based on impact on survival in our specific population. A PNI cutoff of 43.8 has been cited by Sakurai et al. [19] as predicting poor survival in patients with GC. In fact, as demonstrated in a meta-analysis by Li et al. [15], several cutoff values ranging from 40 to 51 have been used to stratify patients.

Limitations of our work include its retrospective nature, which is also seen in most published works on this topic. Importantly, the recent Multi-Centre NOURISH Point Prevalence Study [20–24] provided a prospective analysis and initiated prospective intervention studies, which contribute to improve the awareness of this issue in clinical

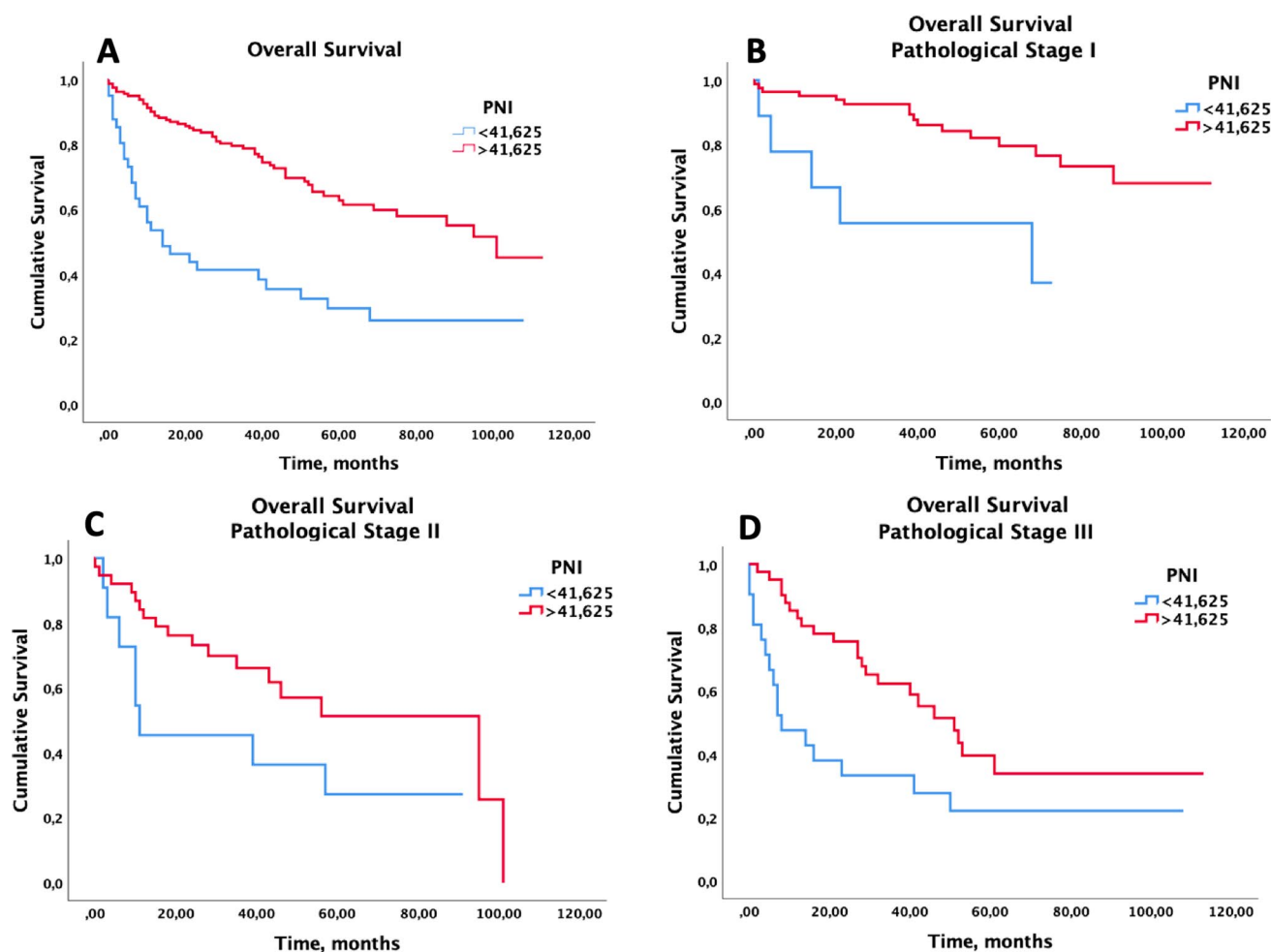


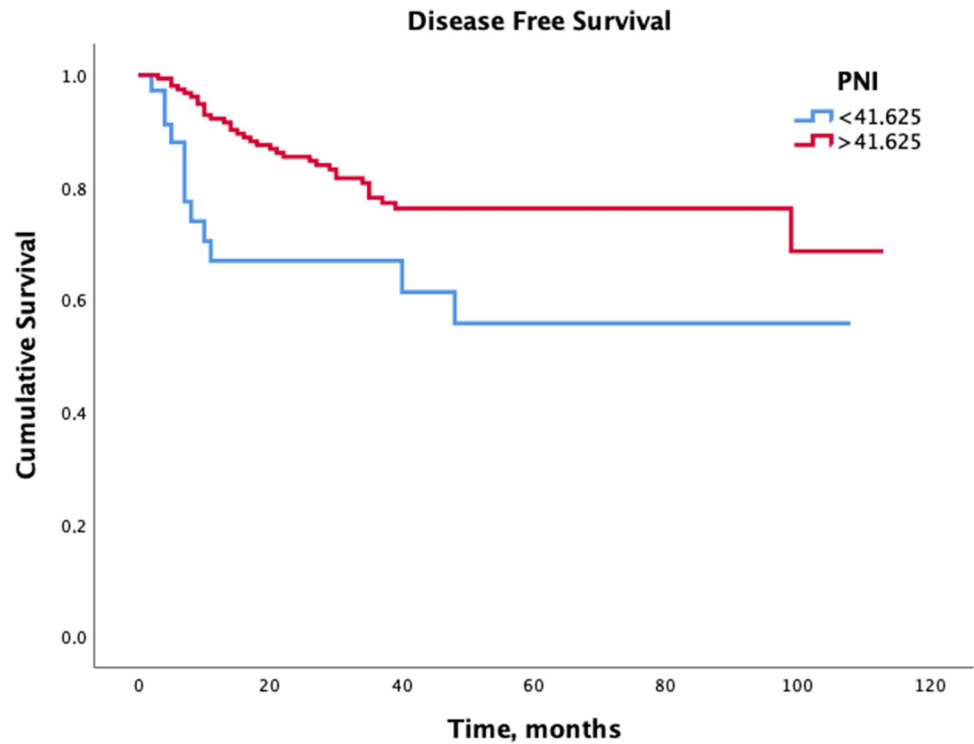
Fig. 2 A KM survival curves for OS in relation to PNI; B, C, D KM survival curves for OS in relation to PNI adjusted to pStage (I, II, and III, respectively)

practice and may provide more robust data. Also, not all patients could be included in the study due to lack of complete clinical information. The study was performed in a single institution; however, this also assures homogeneity in treatment strategies, as all patients were treated by the same multidisciplinary team. Moreover, additional data on metabolic background of the patients, namely chronic conditions such as diabetes mellitus and others, were missing. However, our data has replicated several other studies, strengthening the role of PNI as a clinically useful marker for GC patients.

Despite not being the aim of this work, we intend to make a statement about the fact that open surgery was associated with worse survival outcomes in our cohort. The surgical approach was selected case by case and according to surgeon experience. The retrospective nature of the study, along with the higher prevalence of advanced gastric

cancer patients being submitted to open procedure (68.5% vs 50.0%), might explain this finding, since there are some recent randomized clinical trials showing the non-inferiority of laparoscopic approach when compared to open surgery [25–27].

In conclusion, PNI was disclosed to significantly impact GC patients' OS and DFS, including in multi-variable analysis when adjusting for classical prognostic features. Also, it was shown to accurately predict postoperative complications. Further studies, multicentric and prospective, should be the key to definitively establish PNI as a relevant marker for the clinical approach to GC patients, to determine the optimal cutoff point in this population, and to facilitate its implementation in the clinic. Based on our results, as a simple and useful marker, we suggest that PNI should be included in the routine assessment of GC patients.

Fig. 3 KM survival curves for DFS in relation to PNI**Table 2** Comparative analysis between PNI groups: survival analysis–Kaplan–Meier

	All (<i>n</i> = 203)	PNI		<i>p</i> value
		< 41.625	> 41.625	
OS (months), mean ± SD	70.04 ± 3.46	40.36 ± 6.93	77.49 ± 3.71	< 0.001
OS (months) stratified for pStage, mean ± SD				
I	88.29 ± 4.40	44.07 ± 10.34	92.05 ± 4.34	0.002
II	57.10 ± 6.29	37.36 ± 10.99	62.63 ± 7.21	0.076
III	51.05 ± 6.04	33.58 ± 9.27	58.98 ± 7.34	0.014
DFS (months), mean ± SD	86.38 ± 3.38	67.31 ± 9.09	89.84 ± 3.49	0.008

Bold entries include values of statistical significance

Table 3 Survival analysis–Cox regression, crude, and adjusted HR for pathological stage

	Crude			pStage adjusted		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Overall survival (OS)						
PNI < 41.625	1			1		
PNI > 41.625	0.325	0.207–0.511	< 0.001	0.405	0.253–0.649	< 0.001
Disease-free survival (DFS)						
PNI < 41.625	1			1		
PNI > 41.625	0.421	0.218–0.815	0.010	0.685	0.350–1.342	0.271

Bold entries include values of statistical significance

PNI, prognostic nutritional index; HR, hazard ratio; CI 95%, confidence interval 95%; OS, overall survival; DFS, disease-free survival; pStage, pathological stage

Table 4 Prognostic factors for OS, univariable, and multivariable analysis.

	Univariable analysis			Multivariable analysis		
	HR	CI 95%	<i>p</i> value	HR	CI 95%	<i>p</i> value
Age	1.037	1.022–1.052	< 0.001	1.026	1.003–1.050	0.025
Complications						
Absence	1			1		
Presence	2.545	1.630–3.974	< 0.001	2.649	1.680–4.177	< 0.001
Tumor size	1.130	1.084–1.178	< 0.001			
Surgery approach						
Laparoscopic	1			1		
Open	1.953	1.422–2.682	< 0.001	1.869	1.148–3.039	0.012
Lymphatic permeation						
Absence	1					
Presence	2.699	1.924–3.785	< 0.001			
Venous invasion						
Absence	1					
Presence	2.268	1.667–3.085	< 0.001			
Perineural invasion						
Absence	1					
Presence	2.186	1.612–2.966	< 0.001			
Pathological stage						
I	1			1		
II	2.540	1.659–3.890	< 0.001	2.590	1.423–4.715	0.002
III	4.439	3.043–6.474	< 0.001	3.168	1.802–5.570	< 0.001
PNI						
< 41.625	1			1		
> 41.625	0.325	0.207–0.511	< 0.001	0.544	0.333–0.889	0.015

Bold entries include values of statistically significance

PNI, prognostic nutritional index; LN, lymph node; HR, hazard ratio; CI 95%, confidence interval 95%

Table 5 Prognostic factors for DFS, univariable, and multivariable analysis.

	Univariable analysis			Multivariable analysis		
	HR	CI 95%	<i>p</i> value	HR	CI 95%	<i>p</i> value
Age	1.009	0.991–1.027	0.348			
Complications						
Absence	1					
Presence	1.098	0.530–2.277	0.801			
Tumor size	1.203	1.142–1.268	< 0.001			
Surgery approach						
Laparoscopic	1					
Open	1.539	1.008–2.349	0.046			
Lymphatic permeation						
Absence	1					
Presence	5.489	3.147–9.573	< 0.001			
Venous invasion						
Absence	1					
Presence	3.338	2.154–5.172	< 0.001			
Perineural invasion						
Absence	1					
Presence	4.354	2.794–6.783	< 0.001			
Pathological stage						
I	1			1		
II	9.175	3.718–22.638	< 0.001	8.058	2.623–24.748	< 0.001
III	24.309	10.477–56.403	< 0.001	14.673	5.136–41.924	< 0.001
PNI						
< 41.625	1					
> 41.625	0.421	0.218–0.815	0.010			

Bold entries include values of statistically significance

PNI, prognostic nutritional index; LN, lymph node; HR, hazard ratio; CI 95%, confidence interval 95%

Table 6 Complications according to Clavien-Dindo classification

	All <i>n</i> = 203 (%)
Clavien-Dindo grade	<i>n</i> (%)
None	155 (76.4)
II	20 (9.9)
IIIa	4 (2.0)
IIIb	9 (4.4)
IVa	2 (1.0)
IVb	2 (1.0)
V	11 (5.4)

Table 7 Outcome analysis and correlation with PNI

	All <i>n</i> = 203 (%)	<i>PNI</i>		<i>p</i> value
		< 41.625	> 41.625	
Postoperative morbidity, <i>n</i> (%)				0.029
Absence	155 (76.4)	26 (63.4)	129 (79.6)	
Presence	48 (23.6)	15 (36.6)	33 (20.4)	
Postoperative mortality, <i>n</i> (%)				0.004
Absence	192 (94.6)	35 (85.4)	157 (96.9)	
Presence	11 (5.4)	6 (14.6)	5 (3.1)	

Bold entries include values of statistically significance

Table 8 Complications analysis—logistic regression, crude OR

	OR	95% CI	<i>p</i> value
Postoperative morbidity			
PNI < 41.625	1		
PNI > 41.625	0.443	0.211–0.931	0.032
Postoperative mortality			
PNI < 41.625	1		
PNI > 41.625	0.186	0.054–0.643	0.008

Bold entries include values of statistically significance

PNI, prognostic nutritional index; *OR*, odds ratio; *CI* 95%, confidence interval 95%

Declarations

Conflict of interest The authors declare no competing interests.

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Oncometabolic surgery

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Scimago Journal Rank (SJR) indicator 0,9 | H Index 315 | Rank 15 of 175 on Multidisciplinary journals (**Q1**) (**Percentile 10**)

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OPEN The Metabolic Effects and Effectiveness of the Different Reconstruction Methods used in Gastric Cancer Surgery: A Systematic Review and Meta-Analysis

Maria Pinho Costa^{1,2,9}, Hugo Santos-Sousa^{1,2,3,5,9✉}, Carolina Rodrigues Oliveira^{1,4}, Filipe Amorim-Cruz^{2,5}, Raquel Bouça⁶, Elisabete Barbosa^{1,2,5}, Silvestre Carneiro^{1,2,5,10} & Bernardo Sousa-Pinto^{1,7,8,10}

Gastric Cancer (GC) is the fifth most common cancer worldwide. Early stages of GC began being detected, giving rise to a new concern, Quality of Life. This study aimed to systematically assess the effects of different GC reconstruction techniques on postoperative type 2 diabetes mellitus (T2DM), hypertension (HBP), and body mass index (BMI) reduction rate and to provide an overview of recent research on oncometabolic surgery (OS). We performed a systematic review and meta-analysis by searching three databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We performed a meta-analysis of risk ratios and mean differences to estimate the impact of duodenal bypass, Roux-en-Y reconstruction, and residual stomach on T2DM, HBP, and BMI reduction rate. Heterogeneity was assessed using the I^2 statistics. At the end of the follow-up, the duodenal bypass group compared to Billroth I had a significantly higher postoperative remission of T2DM and HBP, with a relative risk (RR) of 1.43 (95% confidence interval (95% CI) [1.27; 1.62]) and 1.3 (95% CI [1.00; 1.69]), respectively. Compared with the Billroth II group, Roux-en-Y reconstruction had significantly greater T2DM remission after gastrectomy (RR = 1.19; 95% CI [1.08; 1.31]), while HBP showed no significant differences. Regarding the improvement of HBP, total gastrectomy was significantly superior to subtotal gastrectomy (95% CI [1.01; 2.64]). A trend towards Roux-en-Y Esophagojejunostomy as the best option for T2DM remission was observed (95% CI [0.98; 2.77]; $p = 0.06$). Gastrectomy with Roux-en-Y reconstruction appears to be the most effective treatment for T2DM remission. Further research is needed to assess the impact of OS on metabolic diseases.

Keywords Oncometabolic surgery, Gastric cancer, Gastrectomy, Gastric bypass, Metabolic diseases, Metabolic syndrome

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Gastric Cancer (GC) is the fifth most common cancer worldwide and the fourth leading cause of cancer-related deaths¹. The standard treatment for gastric carcinoma remains radical resection with total or subtotal gastrectomy^{2,3}.

The implementation of national screening programs made it possible to identify patients in the early stages of the disease, leading to a decline in GC mortality rates^{4,5}. With the rise in life expectancy of patients with GC, a new health factor has emerged: Quality of Life. This topic is particularly important for patients with concurrent chronic diseases such as type 2 diabetes mellitus (T2DM), hypertension (HBP), and dyslipidaemia⁶.

Traditionally, bariatric surgery has been used to treat morbid obesity. However, it rapidly became clear its effectiveness in treating chronic comorbidities in obese patients, such as T2DM, dyslipidaemia, and HBP. These conclusions gave rise to the concept of Metabolic Surgery⁷.

Recently, based on the similarities between GC and bariatric surgery (including gastric resection and foregut bypass), surgeons have hypothesized that GC surgery could have beneficial effects on glycemic control. These findings led to the emergence of “Oncometabolic Surgery”⁸, a dual-purpose surgery with the potential to treat oncologic conditions while simultaneously improving patients’ quality of life by ameliorating chronic metabolic diseases with debilitating consequences⁹.

The primary purpose of this systematic review and meta-analysis was to provide an overview of recent research findings on oncometabolic surgery (OS). The second goal was to evaluate whether GC surgery helps oncologic patients improve their metabolic status. Additionally, we sought to assess the most suitable reconstructive technique for achieving the best metabolic profile.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁰.

Eligibility criteria

We included all observational studies and randomized controlled trials analyzing patients that underwent gastrectomy for GC with concurrent metabolic diseases (T2DM, HBP, visceral fat, and dyslipidaemia).

We included studies assessing the outcomes of complete or partial remission of T2DM and HBP, body mass index (BMI) reduction rate, visceral and subcutaneous fat reduction rate, changes in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG).

We excluded studies with small sample sizes (i.e., less than ten patients) or those that did not specify the reconstruction method used. All the reports identified as animal trials, editorials, correspondence, video reports, reviews, or meta-analyses were excluded. We did not apply a language restriction.

Information sources and search strategy

We searched three databases (PubMed, Scopus, and Web of Science) through December 2023. This search was conducted using the following Query: ((Bariatric Surgery) AND (Gastric Cancer)) OR (Oncometabolic). This Search Query was reinforced by a Grey Literature.

Study selection and data collection process

The study selection was divided into two phases. In the screening phase, after duplicate removal, each study was independently assessed and selected by title and abstract reading by two reviewers (MC, CO). In the second phase, study selection was based on full-text reading. Any disagreements were resolved by a third researcher (HSS).

Regarding the data collection process, both reviewers (MC, CO) extracted data from the selected articles separately using a predesigned data extraction sheet developed according to the Cochrane Handbook¹¹. For each study, the following information was extracted: authors’ identification, year of publication, country, study design, number of participants, follow-up, participants’ inclusion and exclusion criteria, general characteristics of the participants (age, gender, mean duration T2DM, mean BMI, mean weight, mean hemoglobin A1c (HbA1c), mean fasting plasma glucose (FPG), mean systolic and diastolic blood pressure, TC, LDL, HDL, TG, and visceral and subcutaneous fat area), the metabolic diseases evaluated by the study (T2DM, HBP, adiposity, and dyslipidaemia), GC type and stage, neoadjuvant or adjuvant therapy, type of surgery (total or partial gastrectomy), reconstruction method (Roux-en-Y, Billroth I, and Billroth II) and outcome measures.

Quality assessment

The quality of the articles was independently analyzed by two reviewers (MC, CO) using the National Institutes of Health quality assessment criteria for observational studies¹², and the Cochrane risk of bias tool for randomized control trials¹³.

The first tool consists of a form with 14 yes-or-no questions (related to research question, study population, exposure, outcome, blinding, follow-up, and statistical analysis), obtaining a final quality rating (ranging from good to poor) to classify the study according to its potential risk of bias (Supplementary Table 1).

The second tool includes stratification of the risk of selection, performance, detection, attrition, reporting bias, and other sources biases and the classification of the studies as high, low, or unclear (Supplementary Fig. 1).

Quantitative synthesis of results

We performed meta-analyses of relative risks for dichotomous variables (complete and partial remission of T2DM and HBP), and mean differences for continuous variables (BMI reduction rate). BMI reduction rate is a measure that is calculated as $[(\text{preoperative BMI} - \text{postoperative BMI}) \div (\text{preoperative BMI})] \times 100$.

For each outcome, the pooled meta-analytical measure, and the respective 95% confidence interval (95% CI) were obtained. We performed a random-effects meta-analysis using the restricted maximum likelihood approach.

Heterogeneity was assessed using Cochran's Q test p -value and I^2 statistic. Heterogeneity was considered high for p -values of the Cochran's Q test lower than 0.10 or I^2 above 50%. To explore potential sources of heterogeneity, we performed leave-one-out sensitivity analyses and, for analyses including more than ten primary studies, meta-regression analyses, testing follow-up time, preoperative BMI, and BMI reduction rate as moderator variables.

A p -value lower than 0.05 was considered statistically significant. This meta-analysis was performed using meta package of software R.

Results

Study selection

During the initial search, 2799 records were identified. After excluding duplicates, 1529 articles remained. After the screening phase, 31 articles were fully read, of which 25 were included. Through Grey Literature, 7 articles arose, and 6 of them were included. The quantitative synthesis comprised 18 papers out of the 31 included in the qualitative synthesis (Fig. 1)¹⁰.

Study characteristics

A summary of the study's characteristics is presented in Table 1. The 18 articles included in the meta-analysis comprised of 3453 patients. Of the 31 eligible studies, 18 were retrospective studies^{8,14–30}, 11 were prospective studies^{31–41}, and 2 were randomized controlled trials^{42,43}. The articles were published between 2012 and 2022 and were conducted in Korea, Japan, Taiwan, China, and Brazil. The minimum follow-up time of the included studies was 3 months (Zhang et al.³⁷), with five studies having a follow-up period lower than 12 months, fourteen studies between 12 and 24 months and twelve studies higher than 24 months.

Two types of gastrectomy (subtotal and total) and three different reconstruction methods were studied: Billroth I (BI), Billroth II (BII), and Roux-en-Y (RY; conventional and long-limb).

Although the definition of complete remission and improvement of T2DM and HBP demonstrated small differences between studies, all of them used the reduction or absence of medication as complete or partial remission criteria.

Risk of bias of individual studies

Supplementary table and Fig. 1 display the findings of the risk of bias assessments of the included studies.

Regarding observational studies, none of the studies justified their sample size, nor was the participants' level of exposure hidden from the outcome assessors. Concerning the eighth and tenth parameters related to the level and assessment of exposure in observational studies, we considered them not applicable to all articles.

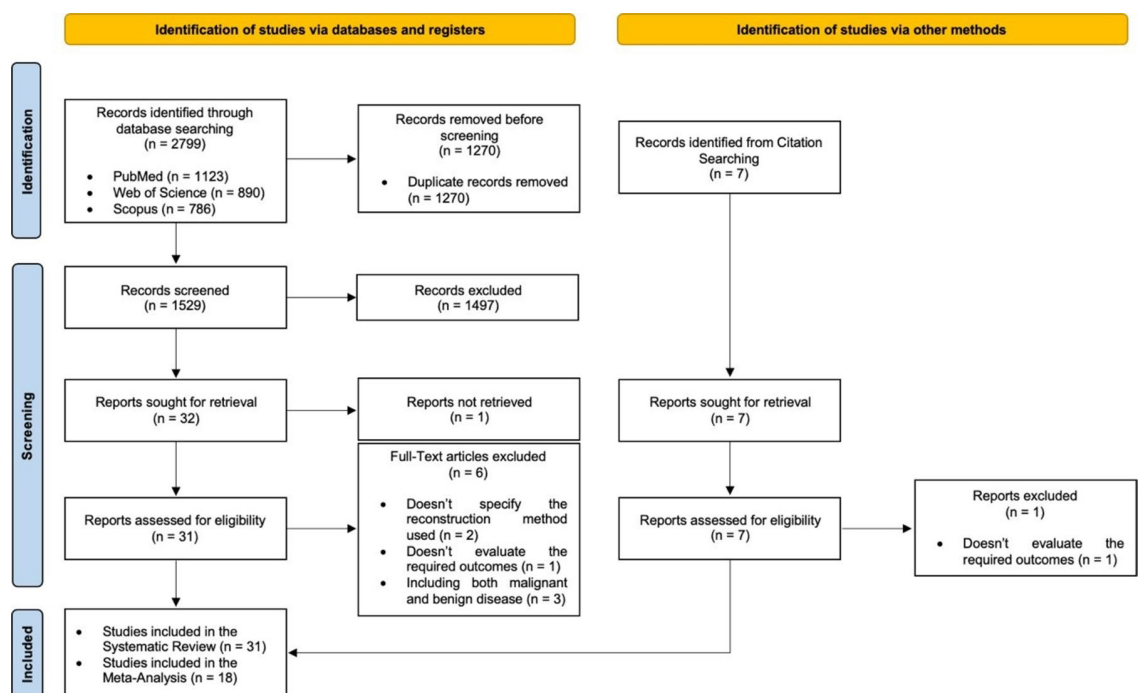


Fig. 1. Flow diagram of study selection.

Study, year	Country	Study design	N° patients	Mean Age (years)	Male (%)	Mean follow-up (months)	GC staging	Neoadjuvant or adjuvant therapy	Intervention type	Mean BMI (kg/m ²)	BMI reduction ratio (%)	Mean HbA1c (%)	Mean FPG (mg/dL)	Mean duration of T2DM (months)	Mean SBP (mmHg)	Mean DBP (mmHg)	Mean TC (mg/dL)	Mean LDL (mg/dL)	Mean HDL (mg/dL)	Mean TG (mg/dL)	Mean SFA (cm ²)	Mean VFA (cm ²)
Lee et al. ²⁴	Korea	RS	220	64.5	77.8	12	I, II, III	Adjuvant Therapy	BI, BII, RYGI, RYEJ	23.9	7.82	-	150.9	-	-	-	-	-	-	-	-	-
Kang et al. ²⁵	Korea	RS	75	67	72	35	-	Adjuvant Therapy	BI, BII, RYEJ	23.8	8.03	7.4	-	-	-	-	176.77	-	-	-	-	-
Kim et al. ²⁶	Korea	RS	403	63.8	76.2	33.7	-	-	RYEJ, BI, BII	24.7	9.8	-	-	-	-	-	-	-	-	-	-	-
Zhang et al. ²⁷	China	PS	21	55.3	83.33	3	I, II, III	No	BII	22.4	-	7	140.0	-	-	-	-	-	-	-	-	-
Hayashi et al. ²⁸	Brazil	PS	164	68.3	57.2	36	-	-	RYEJ, RYGI	25.85	8.5	-	116.25	-	-	-	179.65	-	-	-	-	-
An et al. ²⁹	Korea	PS	64	62.7	67.2	12	I	No	BI, BII, RYEJ	24.7	10.22	7.2	149.63	6.6	-	-	-	102.6	43.17	138.13	-	-
Kim et al. ³⁰	Korea	PS	15	62.1	66.67	12	I, II, III	Neoadjuvant and Adjuvant Therapy	LRYGJ, LRYEJ	< 30	13.89	-	-	136.9	-	-	-	-	-	-	-	-
Tanaka et al. ³¹	Japan	RS	152	62.8	69.74	6	I, II, III	Adjuvant Therapy	BI, RYGI	22.6	9.36	-	-	-	-	-	-	-	-	-	118.15	77.9
Wei et al. ³²	China	RS	67	65.7	70	57.4	I, II, III, IV	Adjuvant Therapy	BII, RYEJ	-	14.53	-	-	-	-	-	-	-	-	-	-	-
Wang et al. ³³	Taiwan	RS	69	70.3	76.8	67.8	-	-	RYGI, RYEJ, BI, BII	24.8	15.7	-	149.2	-	-	-	-	-	-	-	-	-
Xiong et al. ³⁴	China	RS	54	52.2	68.52	6	I, II, III, IV	-	LRYGJ, LRYEJ	-	-	10.6	102.6	105.6	-	-	-	-	-	-	-	-
Tanaka et al. ³⁵	Japan	RCT	221	64.1	67.9	12	-	Adjuvant Therapy	BI, RYGI	22.55	9.22	-	-	-	-	-	-	-	-	-	121.5	88.25
Kwon et al. ³⁶	Korea	RS	49	65.2	82.3	24	I, II, III	Adjuvant Therapy	BI and BII	25.07	7.58	7.3	145	-	120	75	162	-	-	-	-	-
Zhu ³⁷	China	RS	292	64.9	69.5	24	-	No	BI, BII, RYEJ	22.4	10	-	102.6	97.2	-	-	-	-	-	-	-	-
Liu ³⁸	China	PS	93	59	50.54	12	-	-	BI, RYGI, RYEJ	29.31	-	9.27	184.86	-	-	-	-	-	-	-	-	-
Pak ³⁹	Korea	RS	90	65.4	70	24	I, II, III	-	BI, BII, RYEJ	24.8	11	7.1	151.0	25.6	119	-	-	-	-	-	-	-
Kim et al. ⁴⁰	Korea	PS	30	63.9	46.7	12	I, II, III, IV	Adjuvant Therapy	LRYGJ	26.8	15.25	7.6	144.7	100.8	-	-	-	-	-	-	-	-
Ho et al. ⁴¹	Taiwan	RS	579	57	67.7	47.1	-	-	RYEJ	-	-	-	-	-	-	-	-	-	-	-	-	-
Choi ⁴²	Korea	RCT	40	62.6	65	12	I, II, III	No	RYGJ, BI	25.65	-	7.4	135.15	-	-	-	-	-	-	-	-	-
Guner et al. ⁴³	Korea	RS	238	62.9	75	24	I, II	No	BI, BII	24.3	-	7.2	137	96	-	-	-	-	-	-	-	-
Lee et al. ⁴⁴	Korea	RS	42	68.7	68.6	60	I, II, III	-	BI, BII, RYEJ	25.1	-	6.9	139.6	152.4	-	-	-	-	-	-	-	-
Min Jeong Park ⁴⁵	Korea	PS	52	65	73.08	12	I, II, III	Adjuvant Therapy	BI, BII, RYGI, RYEJ	24.94	-	-	-	-	-	-	-	-	-	-	144.70	128.18
Lin et al. ⁴⁶	China	RS	455	69.4	56.76	99	I	No	BII, RYGI	21.6	-	-	-	100	123	74	163	-	54	81	-	-
Kim et al. ⁴⁷	Korea	PS	66	62	65.3	12	Ia, Ib	No	BI, BII, RYGI, RYEJ	25.5	-	-	-	-	125	82	178	111	45	110	-	-
Park et al. ⁴⁸	Korea	PS	40	60	80	12	I	Adjuvant Therapy	LRYGJ, RYGI	29.6	9.63	5.8	-	-	136	84.25	-	-	-	-	-	-
Kim et al. ⁴⁹	Korea	RS	1305	58.55	65.4	12	Ia, Ib, IIa	No	BI, BII, RYGI	23.63	-	-	-	-	-	-	182	-	-	-	-	-
Kim et al. ⁵⁰	Korea	RS	226	63.05	77	12	I	No	LRYGJ, BII	25.59	11	7.25	149.55	-	-	-	-	-	-	-	-	-

Continued

Study, year	Country	Study design	N° patients	Mean Age (years)	Male (%)	Mean follow-up (months)	GC staging	Neoadjuvant or adjuvant therapy	Intervention type	Mean BMI (kg/m ²)	BMI reduction ratio (%)	Mean HbA1c (%)	Mean FPG (mg/dL)	Mean duration of T2DM (months)	Mean SBP (mmHg)	Mean DBP (mmHg)	Mean TC (mg/dL)	Mean LDL (mg/dL)	Mean HDL (mg/dL)	Mean TG (mg/dL)	Mean SFA (cm ²)	Mean VFA (cm ²)
Peng et al. ¹⁸	China	RS	143	65.1	63.6	6	-	-	BI, BII, RYEJ, RYGJ	23.4	12.82	-	-	-	-	-	-	-	-	-	-	-
Park et al. ³³	Korea	PS	20	60.1	70	6	I, II	No	BI, LBII, LRYGJ	25.8	8.91	7.8	121.4	36	-	-	-	-	-	-	-	-
Lee et al. ³⁹	Korea	PS	41	62.4	80.5	12	Ia, Ib	No	BI, BII, RYGJ, RYEJ	24.5	6.45	7.3	132.5	81.6	-	-	-	-	-	-	-	-
Choi et al. ¹⁴	Korea	RS	48	60.73	83.1	12	I, II	No	LRYGJ, LRYEJ	23.77	11.34	7.45	122.21	-	-	-	-	-	-	-	-	-

Table 1. General characteristics of the included studies. *GC* gastric cancer, *BMI* body mass index, *HbA1c* hemoglobin A1c, *FPG* fasting plasma glucose, *T2DM* type 2 diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TG* triglycerides, *SFA* subcutaneous fat area, *VFA* visceral fat area, *RS* retrospective study, *PS* prospective study, *BI* Billroth I, *BII* Billroth II, *RYGJ* Roux-en-Y Gastrojejunostomy, *RYEJ* Roux-en-Y Esophagojejunostomy, *LRYGJ* Long-limb Roux-en-Y Gastrojejunostomy, *LRYEJ* Long-limb Roux-en-Y Esophagojejunostomy.

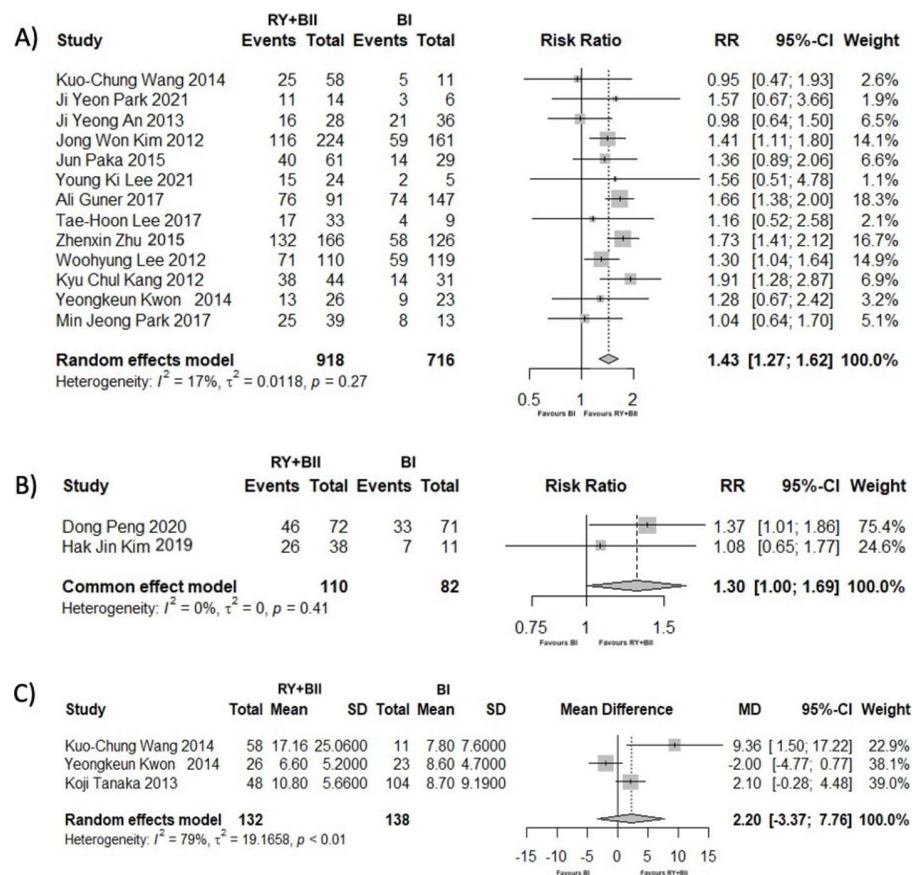


Fig. 2. (A) Forest Plot showing the outcomes of complete or partial remission of T2DM after gastrectomy, comparing duodenal bypass to BI reconstruction, at the end of the follow-up period. (B) Forest Plot showing the outcomes of complete or partial remission of HBP after gastrectomy, comparing duodenal bypass to BI reconstruction, at the end of the follow-up period. (C) Forest Plot showing the outcomes of BMI reduction rate after gastrectomy, comparing duodenal bypass to BI reconstruction, at the end of the follow-up period.

Most studies had a low risk of bias for the evaluated parameters. Twenty-three (79.31%) articles were classified as good, and six (20.69%) as fair.

Five studies (17.24%) with a follow-up duration of < 12 months did not have a sufficient timeframe to identify potential associations between exposure and outcomes, as their follow-up duration was judged inadequate to properly assess the outcomes.

The two randomized controlled trials included in the qualitative synthesis were considered to have an overall low risk of bias. Only one parameter, the random sequence generation, in Tanaka et al.⁴², was recognized as having high risk of selection bias.

Comparison of the duodenal bypass reconstruction techniques (Roux-en-Y and Billroth II) with Billroth I

Type 2 diabetes mellitus

The frequency of patients who achieved diabetic remission at the end of follow-up period was evaluated in 13 studies^{8,15,17,20,22–25,28,33,34,39,41}.

Patients who underwent gastrectomy with duodenal bypass reconstruction had 1.43 times more probability of T2DM improvement or remission compared to the BI reconstruction (RR = 1.43; 95% CI [1.27; 1.62]; $p < 0.001$). The heterogeneity between studies was moderate but not significant ($I^2 = 16.90\%$; $p = 0.27$) (Fig. 2A).

Heterogeneity ceased to be observed using leave-one-out sensitivity analyses by omitting An et al.³⁴ (Supplementary Table 2). To further explore the potential sources of heterogeneity, a meta-regression analysis was performed. None of the variables analyzed (follow-up time, preoperative BMI, and BMI reduction rate) were identified as heterogeneity moderators (Supplementary Table 3).

Hypertension

Two studies^{18,38} including 192 patients examined partial or complete HBP remission after duodenal bypass or BI reconstruction.

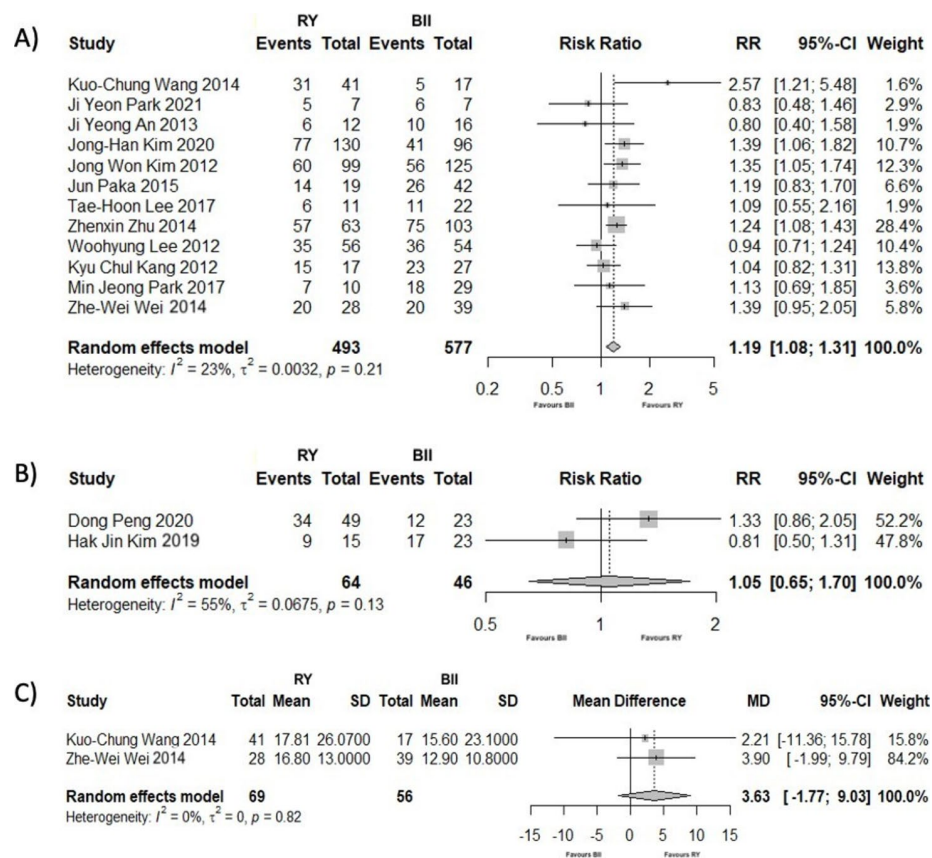


Fig. 3. (A) Forest Plot showing the outcomes of complete or partial remission of T2DM after gastrectomy, comparing RY to BII reconstruction, at the end of the follow-up period. (B) Forest Plot showing the outcomes of complete or partial remission of HBP after gastrectomy, comparing RY to BII reconstruction, at the end of the follow-up period. (C) Forest Plot showing the outcomes of BMI reduction rate after gastrectomy, comparing RY to BII reconstruction, at the end of the follow-up period.

After gastrectomy, patients who received RY or BII reconstruction had a 1.3 higher likelihood of improving or having their HBP resolved (RR = 1.30; 95% CI [1.00; 1.69]; $p = 0.048$), with no heterogeneity being detected ($I^2 = 0\%$; $p = 0.41$) (Fig. 2B).

BMI reduction rate

Three studies^{15,28,30} (270 patients) compared surgical techniques regarding their BMI reduction rate after gastrectomy at the end of follow-up. There were no significant differences between BI and duodenal bypass reconstruction techniques in this parameter (MD = 2.20; 95% CI [-3.37; 7.76]; $p = 0.44$). In addition, there was a high degree of heterogeneity within studies ($I^2 = 79.20\%$; $p < 0.01$) (Fig. 2C).

Comparison of the two duodenal bypass procedures, Roux-en-Y and Billroth II

Type 2 diabetes mellitus

Twelve studies^{8,15-17,20,23-25,29,33,34,41} assessed the frequency of patients who had T2DM remission or improvement at the end of the follow-up period. The patients to whom gastrectomy with RY was performed had a 1.19 times greater chance of partial or complete remission compared to those with BII reconstruction (RR = 1.19; 95% CI [1.08; 1.31]; $p < 0.001$). The degree of heterogeneity was moderate, although not statistically significant ($I^2 = 23.40\%$; $p = 0.21$) (Fig. 3A).

Using leave-one-out sensitivity analyses, the heterogeneity decreased significantly ($I^2 = 3.60\%$) by omitting Wang et al.¹⁵ (Supplementary Table 4). None of the variables analyzed in meta-regression (follow-up time and preoperative BMI) were identified as heterogeneity moderators (Supplementary Table 5).

Hypertension

Two studies^{18,38} (110 patients) analyzed HBP remission or improvement at the end of the follow-up period. There were no significant differences between the RY and BII groups (RR = 1.05; 95% CI [0.65; 1.70]; $p = 0.84$), with heterogeneity being substantial ($I^2 = 55.40\%$; $p = 0.13$) (Fig. 3B).

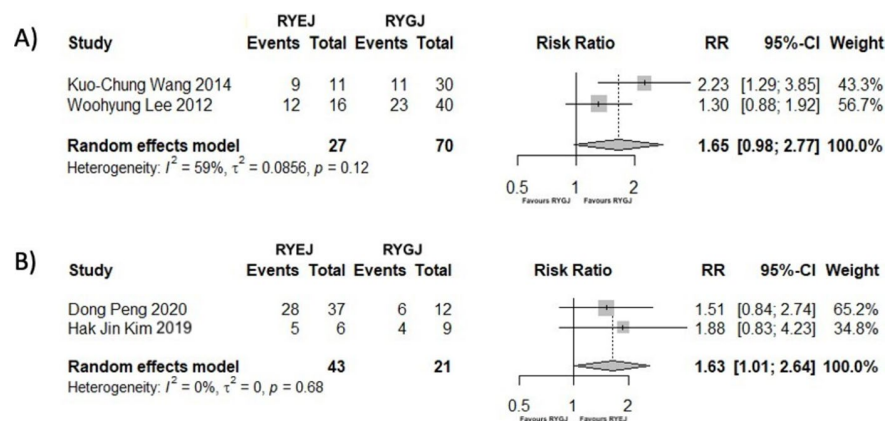


Fig. 4. (A) Forest Plot showing the outcomes of complete or partial remission of T2DM, comparing RYEJ to RYGJ, at the end of the follow-up period. (B) Forest Plot showing the outcomes of complete or partial remission of HBP, comparing RYEJ to RYGJ, at the end of the follow-up period.

BMI reduction rate

At the end of the follow-up period, the BMI reduction rates from two studies^{15,29} were compared (125 patients). No significant differences were observed between RY and BII reconstruction techniques (MD = 3.63; 95% CI [−1.77; 9.03]; $p = 0.19$; $I^2 = 0\%$) (Fig. 3C).

Comparing Roux-en-Y between total gastrectomy and subtotal gastrectomy

Type 2 diabetes mellitus

To determine the impact of the residual stomach on T2DM remission, we compared RY reconstruction between total and subtotal gastrectomy, Roux-en-Y Esophagojejunostomy (RYEJ) and Roux-en-Y Gastrojejunostomy (RYGJ).

After total or subtotal gastrectomy with RY reconstruction, two studies^{15,24} (97 patients) evaluated complete or partial remission of T2DM. Figure 4A shows a trend favouring total gastrectomy, although no significant difference was observed (RR = 1.65; 95% CI [0.98; 2.77]; $p = 0.06$; $I^2 = 59.40\%$).

Hypertension

We examined Roux-en-Y reconstruction between total and subtotal gastrectomy to explore the impact of residual stomach on remission of HBP.

Two studies^{18,38} (64 patients) assessed the improvement or remission of HBP who underwent RYEJ or RYGJ. After RYEJ, patients had a 1.63 higher probability of improving their HBP (RR = 1.63; 95% CI [1.01; 2.64]; $p = 0.046$), with no heterogeneity detected ($I^2 = 0\%$; $p = 0.68$) (Fig. 4B).

Discussion

Summary of evidence

The mechanism underlying GC surgery as a metabolic surgery shares many similarities with bariatric Roux-en-Y Gastric Bypass (RYGB). Both rely on reduction of gastric volume and anatomical reconstruction of the stomach²². BI reconstruction preserves gastric tract continuity. In contrast, in reconstruction techniques that involve duodenal bypass, BII or RY, food bypasses the duodenum and proximal jejunum, reaching the distal ileum earlier. These two reconstruction techniques resemble bariatric surgery more than BI¹⁴.

Bariatric and Oncometabolic Surgery share many concepts, yet they also exhibit significant differences. One major drawback is their substantially different target population, candidate patients for OS tend to be older, frailer, and lighter⁹. Consequently, in contrast to obese individuals receiving bariatric surgery, inferior outcomes are to be anticipated in oncological patients undergoing gastrectomy. Patients with GC are less likely to be obese. Therefore, the effect of weight loss is smaller than what is expected in bariatric patients. Another disparity is their age: oncological patients are generally older. Ageing exponentially increases surgical morbidity and mortality, leading to higher and more severe preoperative comorbidities and postoperative risks⁴⁴. Lastly, in conventional GC surgery, the bypass length is usually shorter than in bariatric RYGB, leading to a weaker enteric effect¹⁴.

Therefore, GC surgical techniques can be adjusted, thoroughly evaluated, and tailored to optimize therapeutic benefits without sacrificing oncological safety⁴⁵ for a particular and cautiously selected patient group. OS involves adapting and choosing the best surgical method available for optimal oncologic and metabolic control.

To the best of our knowledge, this is the first meta-analysis exploring the impact of duodenal bypass (RY or BII), residual stomach, and the various GC reconstruction techniques on postoperative T2DM, HBP, and BMI reduction rate in patients with GC.

Duodenal Bypass demonstrated a significantly higher efficiency in the improvement of T2DM compared to BI reconstruction. For BII, the remission rate ranged from 13 to 83.5%, and for RY, it ranged from 30.7 to 90.5%. This wide variability may be attributed to distinct patient characteristics, different follow-up periods, lack of technical

standardization, different lengths of the biliopancreatic and alimentary limbs, or the fact that almost all included studies, the primary goal was the resection of the tumor rather than the improvement of glycemic control.

The mechanism underlying T2DM remission after gastrectomy is similar to that in bariatric surgery. Two theories have been developed to explain this phenomenon: Foregut and Hindgut Hypotheses⁴⁶. According to the Foregut Hypothesis, bypass of the duodenum alters levels of postprandial hormones, improving glucose control by enhancing insulin release and sensitivity. On the other hand, the Hindgut Hypothesis suggests that early contact of nutrients with the distal small intestine induces an antidiabetic effect by increasing GLP-1, which enhances insulin release and reduces postprandial hyperglycemia by slowing gastric emptying. Lastly, we must highlight the essential role of gut hormones in remission, not only in T2DM but also in HBP, dyslipidaemia, and cardiovascular events. Studies have demonstrated that, independent of weight loss, proximal intestinal bypass promotes T2DM improvement via incretins/anti-incretins, gut hormones, alteration in the gut microbiome, or altered bile acid signaling^{28,47,48}.

According to several studies, the most significant independent predictors were the duration and severity of T2DM^{8,14,15,20–22,25,28,34,36,40,41} (preoperative diabetes duration, insulinogenic index, and HbA1c level) and weight loss^{8,17,20,22,34,36,40} (preoperative BMI, and BMI reduction rate). Several previous bariatric and gastrectomy studies have reported pancreatic β cell function as having an important role in T2DM remission^{49,50}. Patients with shorter T2DM duration have greater β cell activity¹⁵. Therefore glycemic control would be more effective in GC patients with a shorter diabetes diagnosis time, not requiring insulin therapy, and with lower preoperative HbA1c levels^{8,20,21,25,28,36,41}. Weight loss, higher preoperative BMI, and higher BMI reduction rate, even in nonobese patients, were also important factors in the improvement of glucose metabolism^{8,17,20,22,36,38}.

Hypertension is a modifiable risk factor that is intimately linked to cardiovascular and cerebrovascular diseases and can affect the quality of life of cancer survivors³⁸. Three articles^{18,31,38} from this qualitative synthesis evaluated the influence of gastrectomy and its different reconstruction methods on blood pressure control in patients with a BMI < 30 kg/m². Remission and improvement of HBP after gastrectomy ranged from 53.1 to 67.4%. Two studies^{18,38} included in this quantitative synthesis showed significant superiority of duodenal bypass reconstruction over BI. However, no discernible difference was established between RY and BII. A statistically significant difference was observed in the extent of gastrectomy, demonstrating the superiority of RY Esophagojejunostomy. These findings were consistent with those in Peng et al., that reported that total gastrectomy was associated with a greater remission rate of HBP, and that no noticeable superiority was seen among the three reconstructive techniques for subtotal gastrectomy¹⁸. Both studies acknowledge that additional factors such as lifestyle modifications may play an important role.

The effect of GC surgery on metabolic control has been evaluated in several studies involving oncologic patients with BMI < 30 kg/m². In fact, most have shown that T2DM, HBP, and dyslipidaemia improve following gastrectomy in non-obese patients^{23,25,28,31,38,41}. However, although it has been proven that weight loss plays a crucial role in the metabolic status of patients with GC, suggesting that patients with a lower BMI are less likely to benefit from metabolic surgery, it is not the only contributing factor, nor is it statistically significant on its own²⁰. Weight loss and the effects of duodenal bypass appear to work synergistically to improve metabolic control after gastrectomy, even in non-obese patients²². This suggests that while weight loss plays a role, other mechanisms, also significantly contribute to metabolic outcomes.

Cerebrovascular, cardiac, and respiratory diseases are common causes of death in patients with early GC⁵². One of the main findings of Lee et al. was that patients who underwent gastrectomy for early GC had a similar overall mortality as the general Korean population, but a significantly lower cardiovascular mortality⁵³. Multiple studies included in this systematic review showed a significant lowering of TC, TG, and LDL levels and a rise of HDL after gastrectomy^{25–28,31,34,38}.

Lin et al.²⁶ states that GC patients who had undergone subtotal gastrectomy (BII and RY reconstruction) had significantly lower TC and TG levels, BMI, decreased waist circumferences, and occurrence of T2DM and Metabolic Syndrome. Lee et al. reinforced the correlation between weight loss and patients' lipid profiles. After gastrectomy, a significant reduction in body weight and visceral fat might improve lipid metabolism and prevent atherosclerotic changes, leading to a reduction in cardiovascular mortality⁵³.

One retrospective study and one randomized controlled trial (373 patients)^{30,42} evaluated the influence of RY and BI on visceral fat reduction after gastrectomy. Visceral fat accumulation has been identified as an underlying cause of metabolic syndrome⁵⁴. These two studies showed that both duodenal bypass and gastrectomy promoted significant visceral fat loss.

Long-limb RY reconstruction has recently emerged as an option in GC surgery. Studies have suggested that increasing the length of biliopancreatic and alimentary limbs leads to better metabolic outcomes after gastrectomy⁴³. Currently, no consensus on the optimal limb length has been established. Long-limb RY reconstruction typically refers to a modification of the standard procedure where the lengths of the anastomosis limbs exceed the traditional measurements. In conventional RY reconstruction surgery for gastric cancer, the length of the alimentary limb ranges from 40 to 50 cm, and the biliopancreatic limb is generally about 30–40 cm in length⁹.

Seven studies (433 patients)^{14,16,19,31,33,36,40} investigated the effect of long-limb RY reconstruction on T2DM improvement, ranging from 50.8 to 85%. These studies showed that a longer modification of RY resulted in better outcomes for T2DM, HBP, and dyslipidaemia. Kim et al. reported a statistically significant superiority of long-limb RY over the conventional BII in a multicenter retrospective cohort of 226 patients for up to 1 year after surgery¹⁶. Choi et al. found that the results of long-limb Roux-en-Y gastrojejunostomy (LRYGJ) in oncologic, diabetic, nonobese patients were similar to that of metabolic surgery in obese diabetic patients¹⁴. A prospective study of 40 patients compared long-limb RY with conventional RY for T2DM and HBP. It disclosed that the complication rate of OS group did not differ from the conventional group. Although no significant difference was observed between the two methods, the results showed higher remission rates for both T2DM (LRYGJ 77.8% and RYGJ 50%) and HBP (LRYGJ 68.8% and RYGJ 41.2%). Lastly, it reported an improvement in dyslipidaemia

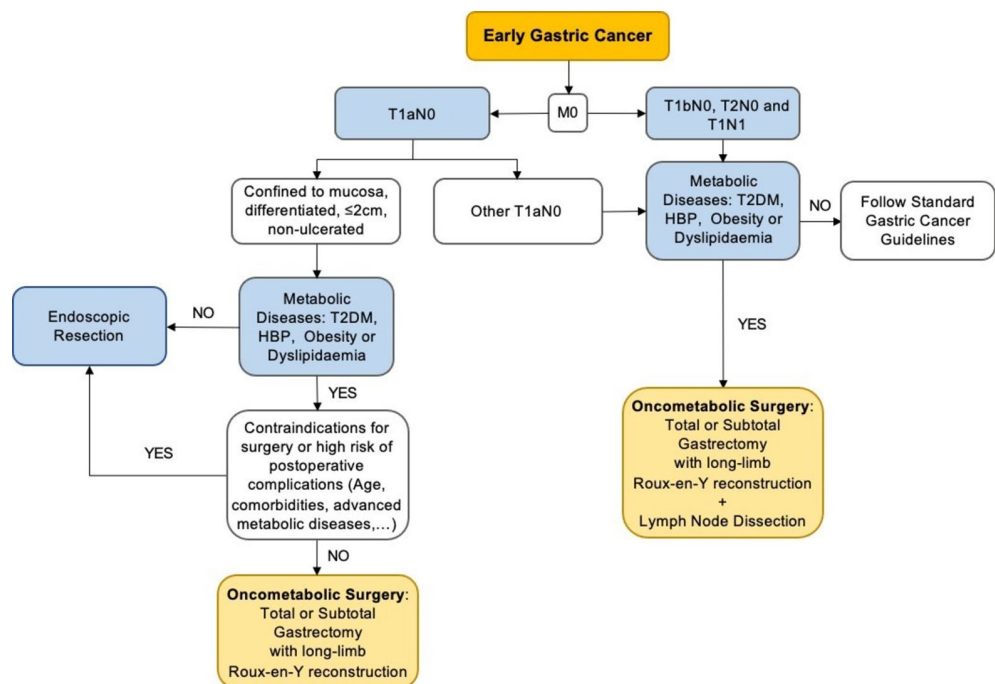


Fig. 5. Potential treatment algorithm for early gastric cancer patients with metabolic diseases. (Adapted from Kim et al.³³ and ESMO Clinical Practice Guidelines⁵⁵).

in 61.5% of patients in the OS group. However, this study had a small sample size, and its primary endpoint was nutritional safety not OS efficacy³¹.

Who would benefit from OS? Patients with longer life expectancies, with localized early-stage GC, who would require ongoing care for their metabolic comorbidities: younger oncologic patients with shorter duration of T2DM, HBP, and dyslipidaemia, especially those who cannot adequately control their comorbidities by optimal lifestyle modification or pharmacotherapy. Although numerous studies have shown excellent outcomes in individuals with normal BMI, this surgery would be particularly favorable for patients with obesity. Figure 5 shows a potential treatment algorithm for patients with early GC and concomitant metabolic diseases, based on the ESMO Clinical Practice Guidelines⁵⁵.

Limitations

Most included studies were based in Asia, specifically Korea, China, Japan, and Taiwan, except for Hayashi et al.³⁵, which was from Brazil. The characteristics of Asian patients are distinct from those observed in other regions. There is a higher percentage of GC and less obesity in East Asia. This might be due to several risk factors, such as dietary patterns and the high prevalence of *Helicobacter pylori* infection⁵⁶.

Second, most studies employed different criteria for remission and improvement of T2DM. Nevertheless, all studies used one common criterion: reduction or cessation of medication as indicators of partial or complete remission, respectively. In regard to T2DM, the majority of these studies adhered to the American Diabetes Association (ADA) criteria for defining complete and partial remission. According to the ADA, complete remission is characterized by a fasting blood glucose (FBS) level of less than 100 mg/dL and an HbA1c level below 6.0%, maintained for 1 year without the use of antidiabetic medication. Partial remission, on the other hand, is defined as a fasting blood glucose level between 100 and 125 mg/dL and an HbA1c level below 6.5%, which was maintained for 1 year in the absence of antidiabetic medication^{8,14,16,20,24,29,33,43}. For HBP, both studies used reduction or cessation of medication as the criteria for determining partial or complete remission^{18,38}.

Another limitation was the inability to analyze other key outcomes such as dyslipidaemia, visceral fat reduction, and other metabolic diseases. Data on such outcomes were not presented in the primary studies.

The influence of neoadjuvant and adjuvant therapy on glycemia, hypertension, and dyslipidemia in these patients was not deeply explored in the included studies, it is important to note that only one study briefly addressed the impact of adjuvant therapy. Lee et al. states that adjuvant chemotherapy in advanced stages could potentially influence glucose management. The most prevalent side effects are diminished appetite, nausea, vomiting, and growth hormone deficiency post-chemotherapy, which can impact insulin secretion²⁴. Further research is needed to explore the influence of neoadjuvant and adjuvant therapies on glycemia, HBP, and dyslipidemia in gastric cancer patients. This area of study is crucial to better understand the comprehensive impact of these therapies on metabolic parameters and to optimize treatment outcomes.

Patients with GC and concurrent HBP after gastrectomy have rarely been reported. Further investigation is required on this subject as well as studies with larger sample sizes and longer follow-up times.

Most of the included studies reported weight reduction primarily using BMI reduction rates, which are commonly used in gastric cancer surgery, rather than the standard metrics used in bariatric surgery, such as %TWL, %EWL, or %EBMIL.

Further research on the efficiency of long-limb RY reconstruction with larger sample sizes and long-term outcomes is needed to compare its results with those of traditional BII and RY gastrectomy. In addition, a standard biliopancreatic limb length should be established to obtain optimal results.

All the outcomes analyzed in this meta-analysis were evaluated at the end of the follow-up period. Such periods ranged between 6 and 67.8 months. Three studies^{18,30,33} had a follow-up of 6 months, and four studies^{8,15,17,25} had follow-ups over 24 months. At both extremes, we observed significant improvements in the metabolic status. To evaluate whether this variation influenced heterogeneity, a meta-regression analysis was performed, which showed that this variable was not a heterogeneity moderator.

Lastly, some of our results demonstrated low to high heterogeneity. This heterogeneity might be due to disparity in patient characteristics, lack of standardization of biliopancreatic and alimentary limb lengths, and outcomes not being the primary goal of the study.

Conclusion

Our systematic review and meta-analysis demonstrated that both conventional and modified gastrectomy were effective in the improvement of metabolic diseases. However, RY reconstruction after gastrectomy is the most effective method for altering GC patients' metabolic status.

The concept of OS could change the surgical oncology paradigm. Its future lies in surgeons actively selecting patients with specific characteristics (T2DM, obesity, HBP, dyslipidaemia, GC, and younger age) and modifying the traditional GC operation based on the principles of metabolic and bariatric surgery.

Future perspectives

Research on OS has mainly focused on T2DM rather than cardiovascular diseases or other metabolic comorbidities such as HBP, dyslipidaemia, obesity, and non-alcoholic fatty liver disease.

Further research with longer follow-up periods is needed to reflect the impact of OS on survival rates, quality of life and the safety of this procedure.

OS provides a glimmer for the prospective widening of the criteria for metabolic and bariatric surgery in the treatment of T2DM in non-obese, non-oncologic patients.

In future GC guidelines, OS should be considered as an option for patients with obesity or metabolic diseases.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Author contributions

Study concepts: M.P.C., H.S.S. Study design: M.P.C., H.S.S., B.S.—Pinto Data acquisition: M.P.C., Carolina Rodrigues Oliveira Quality control of data and algorithms: M.P.C., C.O., H.-S.S., B.S.-P. Data analysis and interpretation: M.P.C., C.O., H.-S.S., B.S.-P. Statistical analysis: M.P.C., B.S.-P. Manuscript preparation: M.P.C. Manuscript editing: M.P.C., C.O., H.-S.S., B.S.-P. Manuscript review: M.P.C., C.O., H.-S.S., B.S.-P., F.A.-C., R.B., E.B., S.C.

Competing interests

The authors declare no competing interests.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

For this type of study, formal consent is not required.

Additional information

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IX. DISCUSSION

In the Results section we have included the articles relevant for this thesis.

In the Discussion, we aim to interpret and integrate these findings within a structured two-tiered framework. The first step provides a comprehensive overview of the current status and limitations of MBS, highlighting the caveats and unmet needs associated with widely used procedures such as SG and RYGB. This analysis identifies areas where existing surgical strategies may lead to suboptimal outcomes or complications, thereby establishing the rationale for the development of novel techniques.

The second step extends this analysis by examining emerging surgical approaches and expanded indications, including the SASI bypass and oncometabolic surgery, designed to overcome the limitations highlighted in the first phase and enhance the therapeutic scope of MBS.

Based on this two-tiered framework, the Discussion further addresses the main findings of our work and explores several research questions across the following key topics:

Step 1 – Current status and caveats of MBS techniques

1. ***Obesity and metabolic disorders:*** Obesity and its related metabolic disorders, especially T2DM, are growing public health concerns. Despite the widespread use of lifestyle interventions and pharmacotherapy, the prevalence of obesity continues to rise, underscoring the need for more effective treatments like MBS.
2. ***Metabolic mechanisms and surgical indications:*** There is still limited understanding of the metabolic mechanisms behind the success of MBS. Current surgical indications may not be optimized for all patients, leading to suboptimal results or complications in some, while others may be undertreated.

3. **Improving patient selection:** By better understanding the metabolic pathways altered by MBS, surgical indications can be refined to identify patients who would benefit the most, reducing risks and improving long-term outcomes.
4. **Complications and management:** A key focus of this thesis is addressing early and late postoperative complications such as bleeding, nutritional deficiencies, hypoglycemia, GERD, and gallstones. Optimizing surgical techniques to address these will improve patient outcomes.
5. **Revisional surgeries:** With increasing demand for revisional surgeries due to WR or IWL, determining how to effectively utilize existing surgical options for these cases is critical.

Step 2 – Emerging techniques and expanded indications

6. **Personalized surgical approaches:** There is no one-size-fits-all approach to obesity surgery. Procedures like TB show promise in terms of safety and metabolic benefits, and could be an essential tool in optimizing glucose homeostasis while maintaining a more physiological digestive pathway.
7. **Expanding Indications to other populations:** The concept of combining cancer resection with metabolic surgery (oncometabolic surgery) represents a groundbreaking frontier, particularly for patients with obesity or metabolic syndrome and GC.

Building on these seven key points, the following research questions are addressed to provide a deeper understanding of the effectiveness, limitations and potential of MBS. These questions focus on both the current challenges identified in widely used procedures and the opportunities offered by emerging surgical techniques, aiming to guide evidence-based decisions for patient selection, optimization of outcomes, and expansion of surgical indications.

Improving obesity-associated comorbidities: which surgery is the most effective in achieving long-term remission of T2DM?

Our systematic review identified VBG and laparoscopic OAGB as the most effective surgical treatments for achieving full remission of T2DM at 5 years in patients with a BMI ≥ 25 kg/m². However, significant limitations temper these findings. For instance, the high remission rate

observed with VBG (100%) was based on a single study of only 12 patients, and VBG is no longer performed due to its high failure and revision rates [224, 225].

The review also highlighted laparoscopic OAGB as a potential alternative to other procedures, particularly laparoscopic BPD/DS. Previous systematic reviews, which included non-randomized studies, identified laparoscopic BPD/DS as the most effective surgery for T2DM remission, maintaining remission in over 95% of patients for at least two years [30, 226]. However, these reviews did not include laparoscopic OAGB as a comparator. Moreover, the current review found only one RCT with a 5-year follow-up for laparoscopic BPD/DS [227], involving a small number of T2DM patients, indicating a lack of evidence for laparoscopic BPD/DS's long-term effectiveness. These findings suggest that laparoscopic OAGB could be a viable alternative to laparoscopic BPD/DS, particularly given its advantages, such as a lower complication rate, shorter surgical time, and comparable metabolic improvements to laparoscopic RYGB at two years [228-230]. However, concerns about bile reflux, marginal ulcers, and nutritional deficiencies with laparoscopic OAGB remain [231].

No RCT with a 5-year follow-up was available comparing SADI-S to other procedures for T2DM remission. Despite the absence of direct comparisons, SADI-S has been proposed as a viable alternative to laparoscopic BPD/DS due to its lower risk of complications [232]. Future research should focus on comparative evaluations of laparoscopic OAGB, BPD/DS and SADI-S, with particular attention to long-term outcomes, diabetes remission rates and cardiometabolic benefits. This is especially important as laparoscopic OAGB has shown promise in being simpler, safer and faster than laparoscopic BPD/DS, though its long-term effects on cardiometabolic outcomes and its safety profile require further investigation.

In terms of other outcomes, the review found no significant differences in microvascular and macrovascular complications across procedures, largely due to the small number of events and short follow-up periods. Longer-term studies, such as the 10-year results by Mingrone *et al.* and the Swedish Obese Subjects (SOS) study, have demonstrated a reduction in diabetes-related complications with bariatric surgery compared to MT [233, 234]. These findings are consistent with the benefits of surgical interventions in reducing long-term complications, although the level of evidence from these studies is lower than that of the RCTs included in this review.

BPD/DS was identified as more effective than MT, laparoscopic RYGB, and AGB for percent total cholesterol and low-density lipoprotein (LDL) changes at 5 years, while no significant differences were found in triglyceride and systolic blood pressure changes across procedures.

For high-density lipoprotein (HDL) levels, laparoscopic RYGB appeared to be the most effective treatment, surpassing both BPD/DS and laparoscopic AGB. However, substantial heterogeneity and inconsistency in the data were noted, limiting the interpretation of these findings [235].

Despite its comprehensive methodology, including a broad search strategy and the inclusion of various procedures, the review faced several limitations. These include the small number of studies, inconsistent reporting of outcomes, and limited data on diabetes-related complications and safety profiles. Additionally, only six studies reported data on T2DM complications, and only five provided information on cardiometabolic outcomes at 5 years. For laparoscopic OAGB, the analysis was based on data from 39 patients, 31 of whom had T2DM, raising concerns about generalizability. The lack of a systematic approach to reporting diabetes-related complications and varying definitions across studies further complicated the analysis. Moreover, the absence of blinding in most studies may have led to performance and detection biases, potentially overestimating the benefits of surgical treatments compared to MT.

This review underscores the need for more high-quality RCTs with longer follow-up periods, consistent reporting of outcomes, and direct comparisons of laparoscopic OAGB, BPD/DS, and SADI-S. Such studies could clarify laparoscopic OAGB's role as a simpler and potentially safer alternative to BPD/DS while providing more robust evidence on its long-term effects on diabetes remission and cardiometabolic outcomes.

Management of suboptimal clinical response after MBS: what is the most appropriate revisional surgery after AGB?

Our retrospective cohort study evaluated the outcomes of revisional bariatric surgery, focusing on revisional RYGB and revisional SG following the failure of AGB, comparing with primary surgery results.

AGB, once the most commonly performed bariatric procedure, is associated with high complication rates, especially WR and IWL, leading to the need for revision [71, 72, 236-238]. Our findings confirm this trend, with over two-thirds of patients undergoing revisional surgery for these reasons.

Regarding safety, we found no significant difference in early complication rates between primary and revisional groups, supporting other studies that suggest revisional surgeries,

despite being more technically challenging, do not increase complication rates when performed by experienced surgeons in high-volume centers [74, 239-241]. The expertise of the surgical team and the center's high volume likely contributed to our favorable outcomes. The ASMBS recommends that revisional procedures be performed in specialized centers with the resources to manage complex cases [242].

The study also observed increased operation time for revisional procedures, particularly revisional RYGB, which took longer than revisional SG, a result consistent with the literature [238, 243]. This is likely due to the more complex nature of revisional RYGB compared to revisional SG [7].

In terms of weight loss, our study showed significant differences at 6 and 12 months, with primary RYGB resulting in greater weight loss and better BMI outcomes compared to revisional RYGB. This supports existing evidence that primary RYGB generally leads to better weight loss than revisional RYGB [244, 245]. Similarly, primary SG demonstrated better weight loss outcomes than revisional SG, although there is limited direct comparison between the two procedures following AGB removal [246]. While some studies report no significant difference in outcomes between revisional RYGB and revisional SG, our findings suggest that revisional RYGB provides better weight loss results, with more patients achieving a BMI below 35 kg/m². Performing SG after a failed AGB is often criticized because they are both restrictive bariatric procedures, but many others state that the excision of the gastric fundus may have endocrine effects, reducing the ghrelin levels [73, 237].

Regarding comorbidities, we found that primary RYGB was associated with significantly higher rates of T2DM resolution, while primary SG showed better outcomes for dyslipidemia resolution than revisional SG. These findings should be interpreted cautiously, as the different indications for each procedure may influence outcomes. Notably, revisional RYGB was more effective than revisional SG in resolving dyslipidemia, which is not consistently reported in the literature.

Our study also highlights the need for further research, as the literature remains divided on the comparative efficacy of revisional RYGB and revisional SG for resolving obesity-related comorbidities [247-249]. While primary RYGB is often favored for T2DM resolution, revisional RYGB may provide better outcomes for certain comorbidities, like dyslipidemia. Further studies are needed to clarify the long-term benefits of revisional procedures on both weight loss and comorbidity resolution.

In the optimal management strategy for GD in MBS patients, should prophylactic cholecystectomy be performed routinely?

Our systematic review and Bayesian meta-analysis provides important insights into the management of GD in MBS patients:

1. *Risk of de novo symptomatic GD:* The risk of developing symptomatic GD after MBS was found to be relatively low (8.2%), though it is still three times higher than in the general population. This suggests that while the risk is increased post-surgery, it remains a rare event [250-253].
2. *Predictive factors for GD:* The predictive factors for GD after MBS differ from those in the general population. Preoperative BMI was the only factor related to both asymptomatic and symptomatic GD in the bariatric surgery population. The study did not find higher preoperative BMI or a higher proportion of females to be significant risk factors for developing GD post-surgery. This finding challenges the common belief that rapid weight loss is the primary predictive factor [250, 251, 254, 255].
3. *Prophylactic cholecystectomy:* The study casts doubt on the routine performance of prophylactic cholecystectomy during MBS. Although prophylactic cholecystectomy was associated with a longer operative time and higher rates of postoperative complications, mortality and hospital LOS were similar to patients undergoing MBS alone. The study suggests that the low incidence of serious biliary complications (such as choledocholithiasis and acute pancreatitis) does not justify routine cholecystectomy, especially given that endoscopic retrograde cholangiopancreatography (ERCP) is difficult to perform after laparoscopic RYGB [90, 256, 257].
4. *Mechanisms of GD post-surgery:* The pathogenic mechanisms contributing to an increased risk of GD after MBS are multifactorial, including increased biliary cholesterol concentration due to rapid weight loss, gallbladder hypomotility caused by vagal nerve resection, decreased cholecystokinin secretion, altered enterohepatic circulation, and increased secretion of calcium and biliary mucin [250-253].
5. *Impact of bariatric procedure type:* The study found that patients undergoing laparoscopic AGB had a lower incidence of symptomatic GD. This is likely due to the fact that laparoscopic AGB does not alter gastrointestinal transit, biliary contraction, or enterohepatic circulation, unlike procedures such as RYGB, which disrupt these physiological mechanisms and increase the risk of gallbladder dysmotility [83, 258, 259].

6. *Preoperative gallbladder status:* The study examined the impact of preoperative gallbladder status (lithiasic vs. alithiasic) on the development of symptomatic GD. It found a 30% higher probability of developing symptomatic GD in patients with preoperative lithiasic gallbladders. This suggests that patients with asymptomatic gallstones may benefit from prophylactic cholecystectomy, especially since ERCP is not feasible after RYGB [260, 261].
7. *Safety of prophylactic cholecystectomy:* The study found that patients undergoing MBS with prophylactic cholecystectomy experienced higher operative times and a higher incidence of major postoperative complications. However, there was no difference in mortality or hospital LOS between the two groups. Prophylactic cholecystectomy is technically challenging, with issues such as gallbladder position and liver steatosis making the procedure more difficult. It is also suggested that the reduced intra-abdominal fat and smaller liver size post-surgery could make delayed cholecystectomy safer and easier to perform [87, 257, 262].

Building on the insights from the meta-analysis, our cohort study further explores the incidence and management of symptomatic gallstones following MBS.

Obesity is a well-established risk factor for cholelithiasis, and in our cohort, we found a preoperative prevalence of GD of 25.3%, which is consistent with other studies where the prevalence of cholelithiasis in bariatric populations ranges from 20.8% to 36.7% [88, 251, 255, 263-266].

Our results also indicate that the incidence of symptomatic gallstones after MBS is elevated in the early postoperative period. Factors such as increased bile cholesterol saturation and crystallization-promoting proteins, as well as defective gallbladder emptying, contribute to the formation of cholesterol crystals and gallstones [82, 83, 267]. Rapid weight loss has been proposed as the primary factor behind gallstone formation post-bariatric surgery, particularly after RYGB and SG, with the risk of gallstone formation reportedly increasing in an exponential fashion during active weight loss [268, 269]. However, some studies suggest that the type of bariatric surgery also plays a significant role in the risk of developing symptomatic cholelithiasis. For instance, a study by Sneineh *et al.* found that the incidence of symptomatic cholelithiasis was significantly higher after RYGB (14.5%) compared to SG (4.4%), AGB (4.1%), and OAGB (7.5%) [259]. The difference was attributed to the lack of interference with biliary contraction mechanisms and enterohepatic circulation in SG and AGB.

In our cohort, we found an incidence of symptomatic cholelithiasis of 1.9% during a 12-month follow-up period, with 87.5% of patients presenting with uncomplicated gallbladder disease. This incidence is comparable to the 1%–4% annual risk of symptomatic gallstones seen in the general population with asymptomatic gallstones [270]. In line with these findings, the treatment of asymptomatic gallstones in the general population is not routinely recommended, and most patients are treated with elective laparoscopic cholecystectomy once symptoms occur [271]. Therefore, a conservative, expectant approach to managing gallstones following MBS appears to be appropriate, as suggested by several studies [91, 265, 272].

Our cohort analysis also identified risk factors for developing symptomatic cholelithiasis. Patients who developed symptomatic gallstones had a significantly higher preoperative BMI (47.0 vs. 42.8 kg/m², $p = 0.046$) and were more likely to have preoperative gallstones (62.5% vs. 10.7%, $p = 0.001$). These two factors remained independent predictors of symptomatic gallstone development in multivariate analysis (BMI: Odds Ratio (OR) 1.187, 95% Confidence Interval (CI) 1.025–1.376; preoperative gallstones: OR 10.720, 95% CI 1.613–71.246). These findings suggest that preoperative characteristics, particularly high BMI and the presence of gallstones, are likely more important in predicting symptomatic cholelithiasis than factors related to the type of MBS or its effectiveness (such as % Excess Weight Loss (EWL)). Interestingly, age, gender, and obesity-related disorders like diabetes, dyslipidemia, and severe steatosis did not show significant differences between symptomatic and asymptomatic patients in our cohort.

We also compared patients who underwent concomitant cholecystectomy with those whose gallbladders were left in situ and found no significant difference in outcomes between the two groups. This further supports the notion that a conservative approach to gallstone management is appropriate in most cases.

Postoperative administration of UDCA for 6 months has been shown to reduce the incidence of gallstone formation after MBS and the need for urgent cholecystectomy [273, 274]. However, at our institution, UDCA is not routinely used for gallstone prevention, as the cost-effectiveness and patient compliance with this treatment remain questionable. Despite the shift toward a more conservative approach, with most studies advocating for prophylactic cholecystectomy only in symptomatic patients [91, 261, 265, 266, 272, 275, 276], there is still some evidence supporting prophylactic cholecystectomy [187, 277]. Thus, further prospective

trials are needed to clarify the role of UDCA and prophylactic cholecystectomy in this population.

Management of early postoperative complications after RYGB: how can preoperative risk factors for bleeding be identified and mitigated to improve surgical outcomes?

Our systematic review and meta-analysis identified five preoperative risk factors significantly associated with EPB following RYGB: older age, male gender, hypertension, revisional RYGB, and preoperative administration of enoxaparin. Gastrointestinal bleeding, though rare (estimated incidence: 1.1–4%), is one of the most common early complications after RYGB, typically occurring at anastomotic staple lines within 12–24 hours postoperatively. While often self-limited, it can be life-threatening, underscoring the importance of identifying risk factors to enhance prevention and management strategies.

Male gender was significantly associated with an increased risk of EPB, consistent with prior literature. Factors such as central adipose distribution, higher prevalence of massive steatosis, and larger liver size in men may contribute to this risk [100, 278–280]. Older age was also associated with EPB, likely due to increased comorbidities and the physiological changes accompanying aging. Alternative surgical approaches, such as sleeve gastrectomy, may be safer for older patients, although RYGB provides superior weight loss and metabolic outcomes [105, 107, 281–285].

Revisional RYGB emerged as a prominent risk factor due to its technical complexity stemming from altered anatomy and adhesions. This finding aligns with previous studies, where revisional procedures were shown to carry higher complication rates [106, 107, 283, 284, 286–296]. Regarding pharmacologic prophylaxis, the study found that unfractionated heparin was associated with a lower risk of EPB compared to enoxaparin. However, due to limited data, these findings require cautious interpretation and further research [105, 297].

Hypertension was another significant risk factor, corroborating its known association with higher morbidity and mortality after RYGB. Other traditional comorbidities such as diabetes, dyslipidemia, GERD, and OSA showed no significant association with EPB. Notably, diabetes, despite its pro-inflammatory state and impaired wound healing, demonstrated inconclusive evidence regarding its role in EPB [280] [101, 106, 107, 281, 282, 298].

Interestingly, no association was found between a BMI > 50 kg/m² and EPB risk, contrasting with the general literature that links extremes of BMI to higher complication rates [299, 300].

While the study's strengths include being the first systematic review and meta-analysis, to the best of our knowledge, to evaluate EPB risk factors comprehensively, limitations such as severe heterogeneity, lack of data on certain variables, and methodological issues in primary studies were noted. These findings emphasize the need for rigorous future research to validate the results and develop predictive clinical tools for EPB risk stratification.

To summarize, the study highlights the importance of preoperative optimization and closely monitoring patients with identified risk factors, including age, gender, hypertension, revisional surgery, and enoxaparin administration, to minimize EPB risk and improve surgical outcomes.

Expanding on the findings from the meta-analysis, our cohort study (*co-author*) delves the incidence and risk factors associated with EPB after laparoscopic RYGB in a high-volume MBS center. We identified several patient-related predictors of EPB, notably severely decreased eGFR and an increased diameter of the left hepatic lobe, which may serve as early indicators of potential hemorrhagic complications. These findings align with prior studies, while also introducing novel insights regarding the relationship between hepatomegaly and EPB, warranting further investigation and preoperative management strategies aimed at mitigating this risk.

In our cohort, EPB occurred in 4.1% of patients, with 85.7% of the bleeding events happening within the first 48 hours after surgery. Melena and hematochezia were the most common presentations, and 92.9% of cases were managed conservatively [106].

Our study showed that EPB after laparoscopic RYGB is associated with a longer hospital stay, higher reintervention rates, and increased 30-day readmission rates. These findings align with other studies, which reported similar bleeding incidences [106, 107, 301, 302]. However, our definition of EPB was broader, including all clinically significant hemorrhagic events, regardless of the need for transfusions or reintervention, which minimized selection bias [106].

We found no significant differences in demographic factors, including BMI, between patients with and without EPB. Traditional hemorrhage-associated comorbidities, such as diabetes, hypertension, and anticoagulation therapy, did not show a significant association with EPB in our cohort. However, we observed that patients with severely decreased eGFR were more likely to experience EPB. This finding is consistent with previous reports linking end-stage renal disease to higher complication rates after MBS, as renal insufficiency is associated with several

hemorrhagic risk factors, such as prolonged bleeding times and platelet dysfunction [106, 303, 304].

A novel finding in our study was the association between an increased left hepatic lobe diameter and EPB. This may be due to the difficulty in liver retraction during laparoscopic RYGB in patients with hepatomegaly, which could complicate critical surgical steps [305]. As hepatomegaly has not been previously reported as a risk factor for EPB, this finding warrants further investigation, and preoperative management of liver size, including dietary modifications (for instance, preoperative low-carbohydrate diet), may help mitigate this risk [302].

We also observed that patients with prior cholecystectomy or previous bariatric procedures had a higher prevalence of EPB. Given that revisional surgery and technically challenging procedures are known risk factors for EPB, these patients should be carefully evaluated preoperatively for potential bleeding risks [106].

In terms of EPB management, our center's approach to diagnosis relied on clinical assessment, including evaluation of gastrointestinal bleeding symptoms, hemoglobin and hematocrit levels, and abdominal drainage characteristics. In contrast to some studies that advocate for endoscopic intervention [306], no patient in our cohort required endoscopic treatment for EPB. This suggests that conservative management is often sufficient for most cases.

Despite the increased morbidity associated with EPB, including longer hospital stays and reinterventions, we found that early bleeding did not significantly affect total weight loss (TWL) or EWL 6- and 12-months post-surgery, indicating that laparoscopic RYGB's efficacy is not compromised by early hemorrhagic events [306].

What are the implications of nutrient deficiencies after RYGB and SG for long-term patient care?

Vitamin deficiencies are common in individuals with obesity, and bariatric surgery may exacerbate these deficiencies [307]. The ASMBS nutritional guidelines recommend routine pre-surgery screening for vitamin B12 and folate (Grade B evidence) and vitamin B1 (Grade C evidence) to identify potential deficiencies, although adherence to these guidelines remains suboptimal [111, 308].

1. *Vitamin B12*: Our meta-analysis revealed a higher prevalence of vitamin B12 deficiency after RYGB compared to SG, particularly in the short and long term [307] [309-316]. This is likely due to the bypassed structures in RYGB, which reduce intrinsic factor secretion and absorption surface [309, 317-319]. Despite supplementation, B12 deficiency was common, emphasizing the need for prolonged monitoring and adherence to supplementation [320]. Deficiency can lead to macrocytic anemia and neurological or psychiatric symptoms, which may manifest years before anemia [321, 322]. Improved diagnostic techniques, such as measuring methylmalonic acid and homocysteine, allow earlier detection of subclinical deficiencies, though their clinical significance remains unclear [323, 324].
2. *Iron and Folate*: Iron deficiency anemia was more prevalent after RYGB due to the exclusion of the duodenum and proximal jejunum, gastric hypoacidity, and reduced red meat intake [322]. Conversely, folate deficiency showed no significant differences between RYGB and SG, although trends varied between studies depending on regional folic acid fortification programs [116, 325-327]. Folate deficiency is associated with megaloblastic anemia, growth retardation, and neural tube defects [321, 328]. Unlike B12, folate storage depletes within months, causing deficiencies to manifest earlier post-surgery [329].
3. *Other B-Complex Vitamins*: Vitamin B1 deficiency, often linked to frequent vomiting, rapid weight loss, or small intestinal bacterial overgrowth, showed no significant differences between RYGB and SG, though some studies indicated higher deficiencies in SG at later stages [325, 330, 331]. Deficiencies in vitamins B6, B2, and B3 were less commonly studied, with limited evidence suggesting occasional differences between RYGB and SG [118, 311, 325].

The study highlighted the need for standardized protocols, consistent supplementation regimens, and uniform diagnostic criteria across studies to improve the understanding of B-complex vitamin deficiencies after bariatric surgery. It recommended further multicenter RCTs to address these gaps and better inform surgical decision-making and long-term patient care.

Leveraging the results from the meta-analysis, the cohort study compared nutritional deficiencies in patients undergoing RYGB versus SG in our center, revealing significant differences in the prevalence and types of deficiencies. While deficiencies were observed pre-

and postoperatively, rigorous follow-up and supplementation reduced their prevalence post-surgery. However, specific deficiencies remained prevalent, particularly in RYGB patients.

1. *Vitamin B12*: Vitamin B12 deficiency was significantly higher in the RYGB group (17.46% at 6 months and 16.74% at 12 months) compared to SG (4.69% and 0.93%, respectively). This aligns with systematic reviews [114, 310, 332], though some studies, such as Ferraz *et al.*, found no significant difference [333]. The deficiency arises from altered gastrointestinal architecture in RYGB, which impairs the release and absorption of vitamin B12 due to reduced acid, intrinsic factor, and pepsin production, exacerbated by food intolerances and bacterial overgrowth [112, 334, 335]. The study emphasized the necessity of tailored supplementation, as current regimens in our center fell short of recommended doses [111, 117].
2. *Folic Acid*: Folic acid deficiency was rare post-surgery, attributed to adaptive absorption mechanisms in the small intestine [310, 318].
3. *Vitamin D*: Vitamin D deficiency was the most common deficiency pre- and postoperatively, with higher prevalence in SG patients (74.24%) compared to RYGB (62.05%). Postoperative deficiency rates declined but remained high due to factors such as adipose tissue storage of vitamin D, low sunlight exposure, and reduced dairy intake [336-338]. The study emphasized the role of altered anatomy in RYGB in reducing fat-soluble vitamin absorption [339].
4. *Calcium and Parathyroid Hormone*: Calcium deficiency was initially more frequent in RYGB patients but became more prevalent in SG patients at 12 months, correlating with vitamin D deficiency. Secondary hyperparathyroidism was observed in RYGB patients (16.40% vs. 8.66% in SG at 6 months), indicating intensified bone metabolism and the need for long-term monitoring and supplementation [340-343].
5. *Magnesium*: Magnesium deficiency was more common in RYGB patients, though not statistically significant. Addressing magnesium deficiency is critical due to its association with metabolic syndrome and insulin resistance [344].
6. *Hemoglobin, Iron, Ferritin, and Transferrin*: Anemia prevalence increased post-surgery, with higher rates in RYGB patients, consistent with other studies [114, 345]. Iron deficiency remained the leading cause of anemia, exacerbated by bypassing iron absorption sites in RYGB and reduced dietary intake [310, 334, 337, 346, 347]. Postoperative weight loss and inflammation resolution partially mitigated ferritin and iron deficiencies.

Preoperative nutritional deficiencies, often linked to obesity-related inflammation and poor diets, were common. The study emphasized correcting deficiencies preoperatively to prevent exacerbation post-surgery [310, 348, 349]. Most patients received pre-surgery supplementation (73.82% RYGB and 78.18% SG), reflecting the importance of proactive management.

The study was limited by its retrospective design, single-center scope, and challenges in assessing supplementation adherence and compliance. However, its strengths included a large sample size (505 patients) and comprehensive analysis over multiple time points, providing valuable insights into early postoperative outcomes.

Longer follow-up studies are needed to evaluate the long-term impact of RYGB and SG on nutritional status. Tailored supplementation regimens based on surgical techniques and patient characteristics, particularly in high-risk populations, are essential for optimizing outcomes.

What are the key predictors of PBH, and how can personalized evaluation and monitoring optimize outcomes, particularly in patients with prior cholecystectomy?

The systematic review (*unpublished data, master thesis supervision*) highlights the wide range of hypoglycemia occurrences post-bariatric surgery, with rates varying from 9.1% to 61.7%. Younger age, lower pre-surgery BMI, greater weight loss, and specific metabolic markers [such as hemoglobin A1c (HbA1c) and insulin sensitivity] were identified as predictors of PBH. The type of bariatric procedure also plays a significant role, with procedures like RYGB exhibiting the highest rates of hypoglycemia [350].

Preoperative assessment, including the identification of risk factors for PBH and the presence of preoperative hypoglycemic symptoms, is crucial [125, 351]. PBH can significantly impact QoL, increase the risk of accidents, and contribute to psychological distress, making effective prevention and management strategies essential [352]. Identifying modifiable and non-modifiable predictors of PBH allows for targeted interventions. Non-modifiable factors include age at surgery and baseline metabolic parameters, while modifiable factors such as dietary habits, physical activity, and weight loss rate can be addressed both pre- and post-surgery. This underscores the need for thorough preoperative evaluation and postoperative monitoring to ensure early diagnosis and management of at-risk patients [351].

Education on symptom recognition and adjustments to nutrition plans, such as controlling carbohydrate intake and favoring low-glycemic options, are essential for improving patient outcomes post-surgery [350]. However, there are gaps in PBH management, such as the lack of standardized diagnostic criteria and screening protocols, which hinders early intervention. Personalized approaches to preoperative evaluation and postoperative monitoring are crucial to optimize patient outcomes, highlighting the need for a multidisciplinary approach involving bariatric surgeons, endocrinologists, dietitians, psychologists, and primary care physicians [125, 353]. Further research is needed to better understand the incidence, pathophysiological mechanisms, and predictors of PBH, as well as the impact of different surgical techniques, to improve management strategies.

Our retrospective cohort study (*co-author*) investigates the impact of cholecystectomy on PBH by exploring hormonal alterations related to BA metabolism. BA, through the activation of FXR and TGR5, stimulates GLP-1 production, which affects glucose metabolism [125, 189, 354]. The study hypothesizes that cholecystectomy alters BA kinetics, influencing the onset and treatment of PBH. The results show that patients with prior cholecystectomy had higher insulin and C-peptide levels at 60 and 90 minutes after a mixed meal tolerance test (MMTT), indicating greater glycemic variability. However, no significant differences were found in time to diagnosis of PBH between the two groups, despite the altered BA kinetics in the cholecystectomy group [188].

The study emphasizes hyperinsulinism as the central mechanism of PBH, with the BA-GLP-1-insulin axis playing a key role [355-357]. While GLP-1 receptor antagonism can reduce PBH episodes, its exact role remains unclear. GLP-1 receptor agonists (GLP-1 RAs) have shown both inhibitory and stimulatory effects on glucagon secretion during hyperglycemia and hypoglycemia, respectively [358, 359]. Furthermore, GLP-1 RAs can reduce small bowel motility, potentially exacerbating hypoglycemic events [360, 361]. The role of BA in GLP-1 and insulin secretion, particularly after cholecystectomy, was also examined. Despite these hormonal changes, the study did not find that cholecystectomy shortened the time to PBH diagnosis, although it might have contributed to earlier glycemic fluctuations.

Dietary modifications remain the primary treatment for PBH, emphasizing meals with balanced macronutrients and avoiding foods with a high glycemic index [125, 362-365]. In some cases, pharmacological therapy, such as acarbose, is required. The study found that a higher proportion of patients with prior cholecystectomy required acarbose doses of 150

mg/day or more, suggesting heightened glycemic variability and the need for a more aggressive pharmacological approach [366]. Acarbose slows glucose absorption and attenuates insulin peaks, making it effective in managing PBH symptoms [367].

Limitations of the study include its small sample size, retrospective design, and potential confounding variables. The cohort was drawn from a single medical center, and the lack of dietary restrictions prior to the MMTT could have influenced the results. Despite these limitations, the study provides valuable insights into the pharmacological treatment and hormonal responses of PBH patients with and without prior cholecystectomy. Further studies with larger sample sizes and prospective designs are needed to validate these findings.

Can a new bariatric surgical technique overcome the limitations of traditional procedures by optimizing surgical simplicity, reducing complication rates, and improving long-term weight loss and comorbidity resolution?

TB and SASI: reviving and innovating old techniques to overcome the limitations of traditional bariatric surgeries

The ideal bariatric procedure must effectively address weight loss and comorbidity resolution while being safe and technically straightforward [368]. The SASI bypass, also known as one-anastomosis transit bipartition (OATB), derived from the Santoro technique [166], attempts to meet these criteria by simplifying the surgical approach and reducing complications through a reduction in anastomoses [168]. This procedure has garnered attention for its promising results in both weight loss and the management of obesity-related comorbidities.

Studies evaluating SASI bypass outcomes primarily focus on the %EWL. The median %EWL across 14 studies at 12 months was 87.14%, aligning closely with the initial report by Mahdy *et al.* (90%) [168]. However, %EWL varied significantly, ranging from 63.9% to 94.33%. This variation is likely due to differences in patient characteristics, such as preoperative BMI, as well as the lack of standardized surgical techniques. Higher preoperative BMI was associated with lower %EWL, consistent with existing literature suggesting that greater BMI negatively impacts weight loss outcomes post-surgery [369]. Compared to SG, which reported a 12-month %EWL of 67.3% [370], SASI bypass demonstrated superior weight loss outcomes, suggesting its potential as a more effective bariatric option.

In terms of comorbidity resolution, SASI bypass showed encouraging outcomes. For T2DM, the median improvement rate across 16 studies was 96.35%, which is higher than the

resolution rates observed for SG, RYGB and OAGB [370, 371]. This suggests that SASI bypass may be more effective than other bariatric procedures in resolving T2DM. Additionally, SASI bypass showed favorable outcomes for hypertension and dyslipidemia, with 12-month improvement rates of 75.8% for hypertension and 87.5% for dyslipidemia, outperforming SG and achieving comparable results to OAGB.

OSA outcomes were more variable, with a wide range of improvements (20%-100%) and a median improvement rate of 89.3%. Despite this variability, SASI bypass outperformed SG and was comparable to OAGB.

GERD was assessed in six studies, reporting a median improvement rate of 84.1%. However, the small sample sizes and limited research prevented a more comprehensive meta-analysis of GERD outcomes.

Regarding NAFLD, two studies found remission rates between 73% and 90%, indicating that SASI bypass may help manage this condition, although further research is needed. The incidence of biliary reflux was minimal, with only one case of severe reflux managed by conversion to RYGB [372]. This suggests that while biliary reflux is a potential concern, it is rare and can be addressed in selected cases.

Technical variations in the SASI bypass procedure, such as the length of the common limb (ranging from 200 to 350 cm) and the size of the gastro-ileal anastomosis (typically 3-4 cm), were found to influence outcomes. Longer biliopancreatic limbs were associated with improved hypertension outcomes, potentially due to hormonal changes, such as altered ghrelin and GLP-1 levels, although the underlying mechanisms require further study. A larger gastro-ileal anastomosis was associated with better weight loss and improved hypertension, possibly due to enhanced malabsorptive effects [373].

A key advantage of SASI bypass is its procedural simplicity and shorter operative time compared to double anastomosis procedures like the Santoro technique (TB). The single anastomosis reduces the risk of complications such as internal hernias. Moreover, SASI bypass preserves natural endoscopic access to the duodenum and biliary tract, unlike other procedures like RYGB and OAGB, which exclude parts of the stomach and may complicate the detection of gastric lesions, delaying diagnosis and treatment [374].

The anastomosis in SASI bypass may also help alleviate GERD symptoms by reducing intragastric pressure and promoting gastric acid drainage, improving symptoms compared to SG, where the lack of an anastomosis may increase intragastric pressure and worsen GERD.

[375, 376]. Additionally, the flexibility of SASI bypass allows for conversion to SG in cases of malnutrition or excessive weight loss, or to a modified SADI-S for improved metabolic and bariatric outcomes [377]. This adaptability makes SASI bypass a promising option for addressing diverse patient needs and optimizing long-term bariatric and metabolic outcomes.

Hence, SASI bypass presents a promising alternative to traditional bariatric procedures, offering benefits in weight loss, comorbidity resolution, and technical simplicity. However, further research is needed to standardize the procedure, investigate the mechanisms behind its success, and evaluate its long-term effectiveness in several patient populations.

GERD: Overcoming an Achilles' Heel of MBS and addressing a cardinal factor in its decision-making algorithms

Obesity is a well-established risk factor for GERD, with epidemiological studies indicating a 2-2.5 times higher risk of GERD in obese patients [378]. Additionally, bariatric surgery and weight reduction through lifestyle changes have been shown to significantly improve GERD symptoms [379, 380]. Despite the benefits of weight loss, the development or exacerbation of GERD remains an “Achilles’ Heel” in MBS [381], particularly following SG, which can lead to a post-operative GERD incidence of up to 25-30% [382, 383].

Several factors contribute to the development or worsening of GERD after SG. These include decreased gastric compliance, increased gastric pressure, lower LES pressure, and alterations in the gastroesophageal junction [6, 135, 378, 384]. These changes can aggravate reflux symptoms, limiting the procedure's applicability for patients with pre-existing GERD. While RYGB is traditionally considered the procedure of choice for obese patients with severe GERD due to its ability to divert gastric and bile contents away from the esophagus, it is associated with complications such as nutritional deficiencies and anastomotic issues.

FSG has emerged as a potential solution to mitigate GERD risk while preserving SG's weight loss benefits. Our systematic review and meta-analysis (*unpublished data, master thesis supervision*) found that FSG resulted in significant weight loss, with %EWL ranging from $58 \pm 23\%$ to $83.3 \pm 28.5\%$ at 12 months, which is comparable to traditional SG outcomes [181, 183, 385-391]. These findings suggest that adding fundoplication does not diminish the weight loss efficacy of SG. FSG demonstrated a significantly lower postoperative GERD prevalence (RR = 0.08; 95% CI: 0.01–0.47) and greater GERD resolution (RR = 1.86; 95% CI: 0.80–4.20), but higher complication (RR = 2.95; 95% CI: 1.02–8.50) and reoperation rates (RR = 4.39; 95% CI:

1.47–13.12). Nevertheless, the limited number of studies and the heterogeneity in surgical techniques and patient populations make it difficult to draw definitive conclusions.

Concerns about the FSG technique itself remain, particularly regarding the amount of gastric fundus left behind for the fundoplication. Leaving too much fundus could compromise the weight loss effect of the procedure, as it may reduce gastric capacity. The variation in fundoplication techniques (e.g., Nissen, Dor, or Toupet fundoplication) also introduces a degree of heterogeneity that complicates comparisons across studies. Moreover, the small sample sizes and observational study designs in the included studies limit the strength of the evidence.

In comparison to RYGB, FSG may offer a more targeted approach for patients with GERD, addressing the reflux component without the more complex risks associated with RYGB. However, direct comparisons between FSG and RYGB are scarce. Future studies should focus on comparing the two procedures to evaluate their relative benefits and risks in GERD management. Moreover, additional research comparing different variations of FSG is crucial to determine the optimal technique for minimizing GERD while maximizing weight loss.

Ultimately, GERD is a critical factor in MBS decision-making, as it can affect clinical outcomes and patient satisfaction. FSG offers a potential solution by reducing GERD risk while maintaining effective weight loss. Although current evidence supports its safety and efficacy, further long-term studies are needed. By addressing GERD, FSG could improve patient outcomes and expand the applicability of bariatric procedures, advancing the field of MBS.

Can MBS principles be expanded to GC surgery to optimize patient outcomes?

The importance of nutritional status in GC outcomes

GC is a prevalent malignancy with rising global incidence. Surgical treatment is the primary intervention, aiming for curative resection. However, the success of surgery is contingent not only on the adequacy of tumor resection and lymph node dissection but also on the patient's health status and ability to tolerate the side effects and morbidity associated with surgery and systemic treatments. In this regard, the nutritional status of the patient plays a critical role. The ESPEN guidelines recommend nutritional therapy prior to major surgery for patients at severe nutritional risk, even if it delays the surgical procedure [210].

Despite this, assessing the nutritional status of patients in routine clinical practice remains challenging. Clinicians often rely on basic markers like serum albumin, which are insufficient to capture the complexity of the patient's nutritional profile. On the other hand, nutritionists use more complex scoring systems that may be difficult to apply consistently, especially when key variables are not readily available. Thus, there is a need for a simple, objective, and practical method for assessing nutritional status tailored to specific pathologies.

The PNI has gained attention as a practical tool for evaluating the nutritional status of cancer patients. PNI combines serum albumin with the total lymphocyte count, reflecting both the nutritional state and the inflammatory response, which are crucial factors in cancer progression and recovery. Albumin, produced by hepatocytes, is influenced by proinflammatory cytokines from the host or tumor and plays a significant role in cancer progression [392]. Lymphocytes, vital components of the immune response, help suppress tumor cell proliferation and invasion [393]. Therefore, PNI serves as a comprehensive indicator of prognosis. The PNI has been shown to risk-stratify cancer patients effectively, allowing for the identification of those at high risk, who would benefit from nutritional optimization before surgery.

In GC, studies have demonstrated that low preoperative PNI values predict poor prognosis, even when adjusted for conventional prognostic factors such as cancer stage. Patients with low PNI scores had lower OS and disease-free survival (DFS) rates, even in early-stage GC. This suggests that poor nutritional status may adversely affect survival outcomes, even when stage I disease would otherwise indicate a favorable prognosis. Furthermore, low PNI values are associated with worse postoperative outcomes, including higher rates of complications and mortality in the short term.

A challenge with PNI is determining a universally accepted cutoff value. Studies have used various cutoff points, ranging from 40 to 51, to predict outcomes. While our study utilized a cutoff of 41.625, further prospective studies are needed to refine these thresholds and validate PNI's clinical utility across different populations [394].

The obesity paradox in GC outcomes

The relationship between BMI and GC prognosis has been the subject of ongoing debate, with recent research suggesting a phenomenon known as the "obesity paradox." This paradox refers to the observation that overweight and obese patients may experience better

outcomes than those with normal or lower BMI, particularly in terms of survival after surgical treatment. The objective of our study "Is there an obesity paradox in gastric cancer patients? – Beyond BMI" [*Invited Presentation at European Gastric Cancer Congress 2018, Leiden, Unpublished data*] was to explore the role of BMI and PAL in the prognosis of GC patients undergoing curative resectional surgery.

In this cohort of 267 GC patients, BMI was categorized into three groups: underweight (<18.5), normal weight (18.5–25), and overweight/obese (≥ 25 kg/m²). The study found that, overall, patients with underweight status had the worst OS compared to those in the normal weight or overweight/obese groups. Notably, the obesity paradox emerged when the analysis adjusted for PAL, as no significant survival differences were observed between normal and overweight/obese patients. In fact, PAL was significantly associated with both OS and DFS, suggesting that the impact of obesity on GC outcomes might be largely mediated through its effect on PAL, rather than BMI alone.

PAL, an inflammation-associated factor, was found to be lower in underweight patients and significantly associated with worse outcomes, including higher rates of postoperative complications. The data implied that nutritional status, as reflected by PAL, may be a more critical predictor of survival and postoperative recovery than BMI itself. This aligns with previous studies indicating that poor nutritional status exacerbates the risk of complications and decreases survival in cancer patients.

Given that obesity may have a protective effect on GC outcomes through its influence on nutritional reserves, it raises the question: *Can MBS principles be expanded to GC surgery to optimize patient outcomes?*

Oncometabolic surgery: an emerging concept

The metabolic mechanisms of GC surgery align closely with MBS as RYGB, relying on gastric volume reduction and anatomical reconstruction [395]. Reconstruction techniques such as Billroth II (BII) and Roux-en-Y (RY), which bypass the duodenum and proximal jejunum, resemble bariatric surgery more closely than Billroth I (BI), which preserves gastric continuity [396].

Despite shared principles, bariatric and oncometabolic surgeries differ significantly. GC surgery targets a distinct, older, frailer, and less obese population, resulting in inferior outcomes compared to bariatric surgery [220]. For instance, weight loss in GC patients is less

pronounced, and shorter bypass lengths in conventional GC surgery diminish the enteric effect seen in bariatric procedures [397]. Tailoring GC surgical techniques to balance oncological safety and metabolic benefits is essential [398].

This meta-analysis is the first to explore how duodenal bypass (RY and BII), residual stomach, and GC reconstruction methods affect T2DM, hypertension, and BMI in GC patients. Duodenal bypass proved more effective than BI for T2DM remission, with BII and RY achieving remission rates of 13–83.5% and 30.7–90.5%, respectively. This variability is attributed to differences in patient characteristics, surgical techniques, and the primary oncological goal of the procedures [396].

The T2DM remission mechanisms are rooted in the Foregut and Hindgut Hypotheses [399]. The Foregut Hypothesis suggests that bypassing the duodenum alters hormone levels, enhancing insulin sensitivity and release. The Hindgut Hypothesis posits that early nutrient delivery to the distal intestine increases GLP-1 secretion, improving glycemic control. Gut hormones, incretins/anti-incretins, BA signaling, and microbiome alterations also contribute to metabolic improvements [400-402].

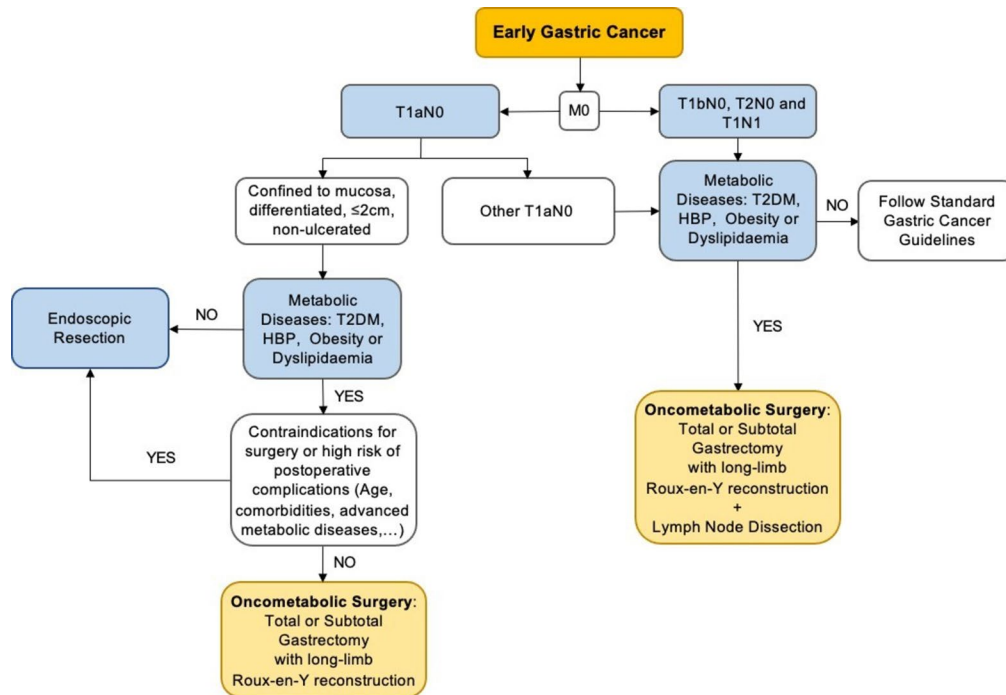
Key predictors of T2DM remission include shorter diabetes duration, better β -cell function, lower preoperative HbA1c levels, and greater weight loss [395, 403-407]. GC patients with shorter diabetes duration and higher preoperative BMI are more likely to achieve glycemic control, even in non-obese individuals [405].

Hypertension remission after gastrectomy ranged from 53.1% to 67.4%, with duodenal bypass techniques showing greater efficacy than BI [405, 408]. However, no significant difference was observed between RY and BII reconstructions. Factors such as lifestyle modifications may also influence outcomes.

Gastrectomy improves lipid profiles, reducing total cholesterol, triglycerides, and LDL levels while increasing HDL, which may contribute to reduced cardiovascular mortality [400, 408-414]. Additionally, visceral fat reduction, achieved through both gastrectomy and duodenal bypass, is critical in mitigating metabolic syndrome [415].

Long-limb RY reconstruction has shown promise for better metabolic outcomes in T2DM, hypertension, and dyslipidemia, with superior results compared to standard BII reconstructions [416]. Studies suggest that extending biliopancreatic and alimentary limbs improves metabolic outcomes, but no consensus exists on optimal limb length [417].

Candidates for oncometabolic surgery include younger patients with early-stage GC and metabolic comorbidities inadequately managed by lifestyle or pharmacotherapy. While beneficial for normal-BMI individuals, this approach is particularly advantageous for obese patients, offering a tailored treatment algorithm for early GC patients with metabolic diseases [418].



Potential treatment algorithm for early gastric cancer patients with metabolic diseases.

(Adapted from Kim et al. [414] and ESMO Clinical Practice Guidelines) [418].

Integrating the Two-Tiered Framework: From Caveats to Innovation

The analysis of the seven key topics highlights the dynamic and multidimensional nature of MBS. When viewed through the lens of the two-tiered framework, the first part—focused on the current status and caveats of MBS—reveals that, despite remarkable progress over the last decades, current procedures such as SG and RYGB still present important limitations. Although these operations remain the cornerstone of MBS, issues such as suboptimal long-term weight loss, recurrence of metabolic disease, postoperative complications, and nutritional deficiencies continue to affect a significant proportion of patients. These caveats underscore the need to refine patient selection criteria, optimize perioperative management, and individualize surgical strategy according to metabolic profile, comorbidity burden, and anatomical factors.

Furthermore, the analysis of metabolic mechanisms and surgical outcomes demonstrates that no single technique can address the full spectrum of obesity and its related metabolic disorders. The variability in hormonal response, nutrient flow, and absorptive function after MBS partly explains the heterogeneity of results observed across patient populations. This reinforces the importance of understanding the physiological foundations of each procedure and tailoring the surgical plan accordingly. The findings discussed in this thesis also highlight the critical role of multidisciplinary care and long-term follow-up, not only for early detection of complications but also for sustaining weight loss and metabolic benefits.

The second part of the discussion, centered on emerging techniques and expanded indications, provides a natural continuation of this reasoning. Innovative approaches such as Sleeve plus procedures — including the SASI — represent an evolution of traditional MBS, aiming to balance metabolic efficacy with nutritional safety. These techniques combine the restrictive and hormonal benefits of the sleeve with a partial intestinal bypass, offering improved glycemic control and weight loss, while mitigating the risks of malabsorption. Likewise, the concept of oncometabolic surgery expands the role of MBS into the oncologic domain, offering dual metabolic and curative benefits for patients with obesity and gastric cancer.

Integrating the findings from both tiers of analysis, this thesis reinforces a central concept: the future of MBS lies in personalization and physiological balance. The identification of caveats in current techniques provides the scientific foundation for innovation, while the development and assessment of new procedures, such as SASI and oncometabolic surgery, represent the practical translation of this knowledge. By bridging the gap between clinical

need and surgical evolution, these approaches pave the way toward a more precise, patient-centered, and metabolically oriented practice of bariatric surgery.

X. CONCLUSION

Obesity and its associated metabolic disorders, particularly T2DM, remain a significant global health challenge. While MBS has emerged as the most effective long-term treatment for severe obesity and its comorbidities, key challenges persist, including optimizing patient selection, understanding metabolic mechanisms, and addressing complications and suboptimal outcomes.

This thesis aimed to refine MBS indications, enhance patient outcomes, and explore surgical techniques to improve safety and metabolic efficacy. To achieve these goals, it addressed several critical research questions to advance the understanding and practice of MBS.

Improving obesity-associated comorbidities: which surgery is the most effective in achieving long-term remission of T2DM?

Laparoscopic OAGB is a promising surgical option for achieving long-term remission of T2DM, showing comparable metabolic outcomes to laparoscopic RYGB and potential advantages over laparoscopic BPD/DS, including lower complication rates and shorter surgical times. However, while laparoscopic OAGB has shown promise, the lack of long-term data and direct comparisons with other procedures such as laparoscopic BPD/DS and SADI-S means that further high-quality, long-term RCTs are needed to definitively establish the most effective surgical approach for T2DM remission. This study underscores the importance of refining patient selection and surgical techniques to optimize outcomes for individuals with obesity and T2DM.

Management of suboptimal clinical response after MBS: what is the most appropriate revisional surgery after AGB?

The management of suboptimal clinical responses after AGB often necessitates revisional bariatric surgery. Based on our findings, revisional RYGB appears to be the most effective option, achieving superior weight loss and greater resolution of obesity-related comorbidities, particularly dyslipidemia, compared to revisional SG. While revisional SG may be a viable alternative, especially when a less complex procedure is preferred, its restrictive mechanism and lower efficacy in weight loss and metabolic improvement limit its utility following AGB failure. Both procedures, however, demonstrated comparable safety profiles when performed in specialized, high-volume centers by experienced surgeons. Ultimately, the choice of revisional surgery should be individualized, considering patient-specific factors, comorbidities, and the expertise of the surgical team, with revisional RYGB emerging as the preferred approach for most cases.

In the optimal management strategy for GD in MBS patients, should prophylactic cholecystectomy be performed routinely?

No, the optimal management strategy for GD in MBS patients does not support routine prophylactic cholecystectomy. While the risk of developing symptomatic gallstones after MBS is higher than in the general population, it remains relatively low. The study suggests that prophylactic cholecystectomy is associated with longer operative times and increased postoperative complications, without significant benefits in mortality or hospital LOS. A conservative approach, reserving cholecystectomy for symptomatic cases, is recommended. Preoperative factors, such as high BMI and the presence of gallstones, are more significant predictors of symptomatic GD than the type of MBS procedure performed. Further prospective trials are needed to clarify the role of prophylactic cholecystectomy and other preventive measures, such as UDCA.

Management of early postoperative complications after RYGB: how can preoperative risk factors for bleeding be identified and mitigated to improve surgical outcomes?

The management of EPB after RYGB can be optimized by identifying preoperative risk factors and implementing targeted strategies to mitigate these risks. Our systematic review and cohort study highlighted several key factors associated with increased EPB risk, including older

age, male gender, hypertension, revisional surgery, and preoperative enoxaparin use. Additionally, novel findings such as decreased eGFR and increased left hepatic lobe diameter may offer further insights into predicting hemorrhagic complications. Preoperative optimization, such as managing liver size and carefully evaluating patients with renal insufficiency or revisional surgery, is crucial for minimizing EPB risk. Conservative management of EPB proves effective in most cases, and although EPB can increase morbidity, it does not significantly impact long-term weight loss outcomes. Future research should aim to validate these findings and further refine preoperative risk stratification tools to improve surgical outcomes in RYGB patients.

What are the implications of nutrient deficiencies after RYGB and SG for long-term patient care?

The implications of nutrient deficiencies after RYGB and SG for long-term patient care are significant and highlight the need for tailored and ongoing nutritional management. Our research confirmed that while both procedures lead to deficiencies in critical nutrients, the nature and prevalence of these deficiencies differ. RYGB patients are particularly vulnerable to vitamin B12, iron, and calcium deficiencies, which may require long-term supplementation and monitoring. Despite similar recommendations for supplementation, the study revealed gaps in adherence and the need for standardized protocols across centers. Furthermore, deficiencies in fat-soluble vitamins, such as vitamin D, remain prevalent, particularly in SG patients, due to factors like reduced intake and low sunlight exposure. Addressing these deficiencies preoperatively, coupled with rigorous follow-up care post-surgery, is crucial to preventing long-term complications such as anemia, bone metabolism disturbances, and metabolic syndrome. This study underscores the importance of personalized, evidence-based supplementation regimens and continuous monitoring to optimize long-term outcomes for bariatric surgery patients.

What are the key predictors of PBH, and how can personalized evaluation and monitoring optimize outcomes, particularly in patients with prior cholecystectomy?

This research identifies key predictors of PBH, such as younger age, lower pre-surgery BMI, greater weight loss, and specific metabolic markers like HbA1c and insulin sensitivity. The type of bariatric procedure, particularly RYGB, also plays a significant role in PBH incidence. The

study underscores the importance of personalized preoperative evaluation and postoperative monitoring, especially for patients with prior cholecystectomy. While cholecystectomy may influence BA metabolism and glycemic variability, it did not significantly affect the timing of PBH diagnosis in our cohort. The study also provides valuable insights into the pharmacological treatment and hormonal responses of PBH patients with and without prior cholecystectomy. Notably, patients with prior cholecystectomy required more aggressive pharmacological interventions, such as higher doses of acarbose, to manage glycemic variability. These findings highlight the importance of targeting modifiable factors, such as dietary habits and weight loss rate, and reinforcing patient education on symptom recognition and dietary adjustments. Multidisciplinary collaboration is essential for optimizing PBH management and patient outcomes. Further research with larger cohorts and prospective designs is needed to refine treatment strategies and gain a deeper understanding of the hormonal mechanisms underlying PBH.

Can a new bariatric surgical technique overcome the limitations of traditional procedures by optimizing surgical simplicity, reducing complication rates, and improving long-term weight loss and comorbidity resolution?

The SASI bypass (also known as OATB) emerges as a promising alternative to traditional bariatric procedures, addressing several limitations of older techniques. Its simplified surgical approach and reduced complication risk, such as internal hernias, are associated with superior weight loss outcomes and a remarkable resolution of obesity-related comorbidities, including T2DM, hypertension, and dyslipidemia. Additionally, the SASI bypass preserves natural endoscopic access to the duodenum and biliary tract, which is important for managing GD. In contrast, procedures like RYGB and OAGB exclude parts of the stomach, potentially complicating gastric lesion detection and delaying diagnosis and treatment. The anastomosis in SASI bypass may also help alleviate GERD symptoms by reducing intragastric pressure and promoting gastric acid drainage, offering improvements over SG, which can exacerbate GERD due to increased intragastric pressure. The procedure's technical simplicity, shorter operative time, and flexibility for future conversions further enhance its advantages. While promising results have been observed, further research is crucial to standardize the technique, investigate the underlying mechanisms, and assess its long-term efficacy across different patient populations.

GERD, often considered the Achilles' Heel of MBS and a cardinal factor in its decision-making algorithms, remains a significant challenge, particularly following SG, where it can develop or worsen in a substantial proportion of patients. While RYGB has traditionally been favored for patients with severe GERD, the associated complications, such as nutritional deficiencies, highlight the need for alternative solutions. FSG shows promise as a technique that could mitigate GERD risk while preserving SG's benefits in weight loss. Although the evidence is still emerging, FSG achieves weight loss comparable to SG and may reduce postoperative GERD prevalence, but carries an increased complication and reoperation risk. Future studies are crucial to standardize the procedure, compare it directly with RYGB, and identify the most effective variations of fundoplication. Addressing GERD effectively could expand the indications for bariatric surgery, improving long-term outcomes and patient satisfaction.

Can MBS principles be expanded to GC surgery to optimize patient outcomes?

Yes, MBS principles can be expanded to GC surgery to optimize patient outcomes. By integrating nutritional optimization, particularly through preoperative nutritional support and the use of surgical techniques like duodenal bypass (BII and RY), GC surgery can potentially improve both oncological and metabolic outcomes. This approach, which aligns with the benefits seen in MBS, could particularly benefit GC patients with metabolic comorbidities, offering a more holistic treatment strategy. Further research is needed to refine these techniques and identify the most suitable patient populations, but the integration of MBS principles holds promise for improving GC surgery outcomes.

This thesis integrates clinical evidence, systematic reviews, and meta-analyses to advance the understanding of MBS within a two-tiered conceptual framework. The first tier, focused on the current status and caveats of MBS, identified persistent challenges associated with conventional procedures such as SG and RYGB. Despite their proven effectiveness in weight loss and metabolic improvement, these operations still present limitations, including nutritional deficiencies, postoperative complications, and variable long-term outcomes. Moreover, the analysis of indications and patient selection highlighted the unmet needs of metabolically challenged populations—particularly those with class IV and V obesity—underscoring the importance of a more individualized approach.

The second tier explored innovative surgical strategies and expanded indications that aim to address these limitations. Sleeve plus procedures, particularly the SASI bypass, emerged as promising alternatives that combine the benefits of restriction and partial malabsorption while maintaining physiological continuity. Similarly, the concept of oncometabolic surgery broadens the scope of MBS, integrating metabolic and oncologic goals in selected patients with obesity and gastric cancer. Together, these approaches represent a paradigm shift towards more physiological, tailored, and multidisciplinary models of care.

By integrating these findings, this thesis emphasizes that the future of MBS lies in precision, balance, and personalization. Continuous refinement of patient selection, surgical techniques, and postoperative management will be essential to optimize safety and long-term efficacy. The ongoing prospective studies within our research group, including the prospective study on SASI outcomes in patients with BMI > 50 kg/m², will further contribute to the generation of high-quality evidence and to the validation of innovative procedures. Ultimately, this work aims to bridge the gap between clinical needs and surgical innovation, paving the way for a new generation of MBS focused on individualized treatment and sustainable metabolic health.

XI. FUTURE RESEARCH

In the evolving field of MBS, future research is pivotal in refining both the indications for surgery and the strategies to improve long-term outcomes. One key area of focus is the management of metabolically challenged patients, particularly those with obesity class IV and V (*formerly known as super obesity*). These patients often face complex metabolic profiles and higher risks of comorbidities, which demand personalized, tailored approaches to surgery. Investigating optimal patient selection, surgical techniques, and postoperative care for this group will be crucial in enhancing their outcomes and minimizing complications.

Another critical area for future research is improving MBS outcomes, particularly in addressing IWL and WR. Despite the effectiveness of MBS, many patients experience suboptimal weight loss or regain weight over time. Exploring the underlying mechanisms, refining surgical procedures, and developing better postoperative management strategies will be essential in achieving sustainable weight loss and improving the long-term success of MBS. This chapter will outline the future directions for research aimed at optimizing both the indications and outcomes of MBS, with a focus on these two high-priority areas.

A. IMPROVING INDICATIONS OF MBS

Management of metabolic-challenged patients

Obesity class IV and V (*formerly known as Super obesity*)

[Parallel Research Area, co-supervision of PhD thesis of a research team investigator]

Metabolically-challenged populations, particularly those with obesity class IV (BMI ≥ 50 kg/m²) and obesity class V (BMI ≥ 60 kg/m²), present unique challenges in the context of MBS. These patients often exhibit a higher burden of obesity-related comorbidities, such as T2DM, hypertension, and NAFLD, which complicate both the surgical process and postoperative recovery. The two-step approach to bariatric surgery has emerged as a promising strategy for these high-risk individuals, involving an initial weight loss procedure followed by a more definitive surgery.

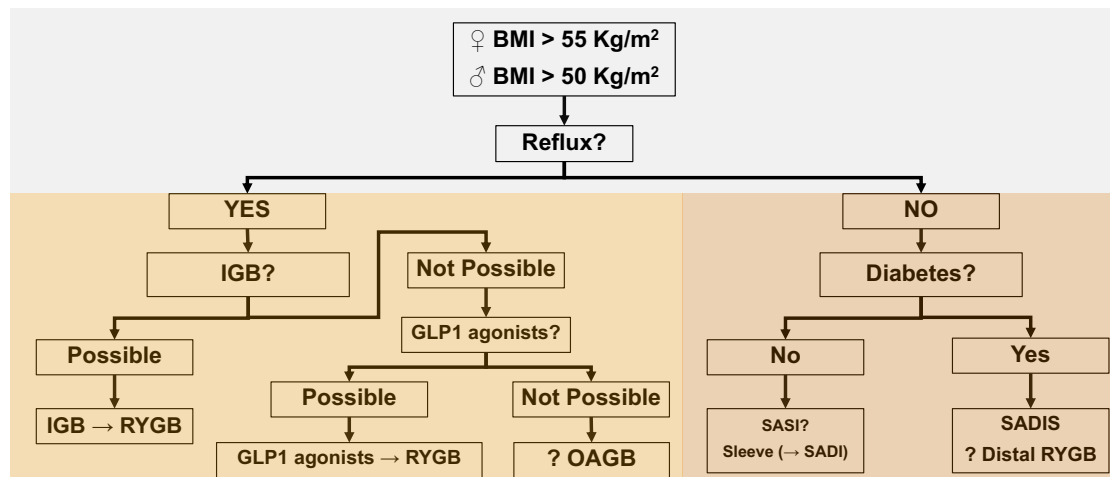
Sleeve plus procedures, including the SASI, are increasingly relevant for these metabolically challenged patients. By combining the restrictive effects of sleeve gastrectomy with an additional intestinal component, these approaches enhance metabolic outcomes, including improved glycemic control and greater weight loss, while maintaining a more physiological nutrient flow and minimizing severe malabsorption. Their application in obesity class IV-V patients addresses the limitations of conventional procedures, such as suboptimal weight loss, persistent T2DM, and higher complication rates. Future research should focus on prospective studies evaluating not only weight loss and metabolic improvements, but also safety, nutritional status, and quality of life, providing evidence-based guidance for the use of these innovative techniques in high-risk populations.

Our meta-analysis *“Roux-en-Y Gastric Bypass Vs Sleeve Gastrectomy in Super Obesity: a Systematic Review and Meta-Analysis”*, emphasizes that RYGB demonstrated significantly better weight loss at 6 and 12 months compared to SG, with superior dyslipidemia resolution at 1 year. However, after 24 months, differences in weight loss between the two procedures were not significant. The study did not find significant differences in the resolution of other comorbidities.

Building on the results of our meta-analysis, future research by our investigation team will explore the particularities of treating obesity class IV and V patients, focusing on the tailored

surgical approaches required to address their complex metabolic profiles and minimize risks. It will also examine the role of the two-step approach in improving outcomes, ensuring safety, and enhancing long-term success in this challenging patient population.

Decision-making algorithm proposal



Courtesy of André Costa-Pinho with permission

In addition to the findings presented in this thesis, our research group is currently conducting a prospective study titled *“Outcomes of SASI in the treatment of patients with BMI over 50 kg/m² – prospective study”*. This study evaluates 40 patients aged 30–60 years submitted to SASI (October 2024 – September 2025) and aims to provide comprehensive prospective data on its safety, efficacy, and metabolic outcomes in metabolic-challenged patients. Key outcomes include %TWL, postoperative complications (Comprehensive Complication Index), operative time, length of hospital stay, readmissions, nutritional deficiencies, and improvement of major comorbidities such as T2DM, hypertension, dyslipidemia, and OSA. Additional assessments involve quality of life (Moorehead-Ardelt questionnaire), comprehensive outcome (SF-Bari Score), postoperative dumping (Sigstad score), GERD (GERD-HRQL questionnaire), and analysis of ileal versus duodenal effluent. Patients are carefully selected according to standard inclusion and exclusion criteria and evaluated by a multidisciplinary team following national guidelines for MBS. The study will include a three-year follow-up and comparative analysis with patients undergoing other MBS procedures in the same period. My role as co-supervisor contributes to the ongoing guidance of this project, which complements the findings of this thesis and addresses the need for prospective evidence on innovative bariatric procedures within our research group.

B. IMPROVING OUTCOMES OF MBS

IWL and WR after MBS

[Master Thesis Supervision and Co-supervision]

IWL and WR are common challenges following MBS, often impacting long-term success.

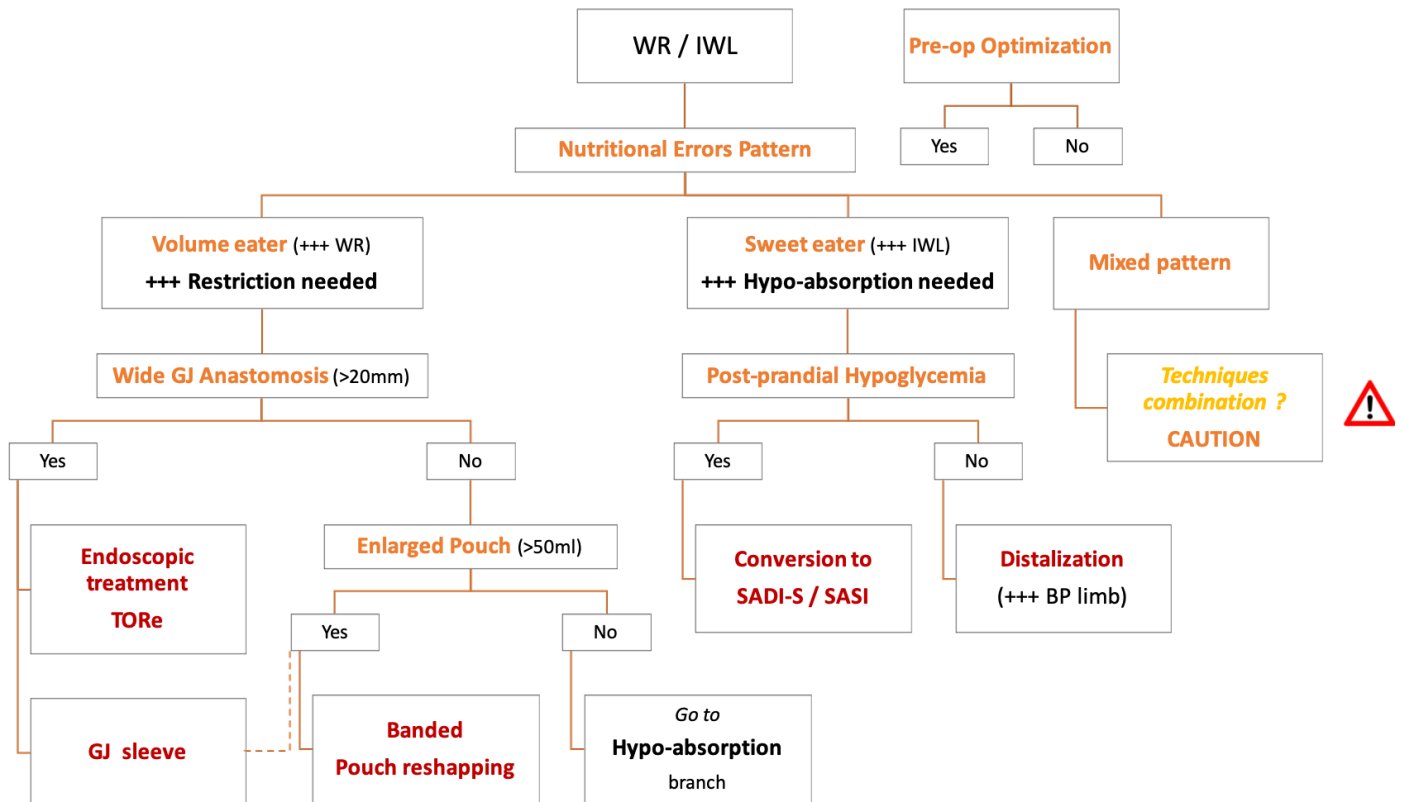
Our study *“Predictors of inadequate weight loss and weight regain after bariatric surgery” (unpublished data, master thesis co-supervision)* found that weight nadir typically occurs within the first-year post-surgery, aligning with prior research. WR begins two years post-surgery, peaking in the third year. Factors associated with IWL include older age, lower educational levels, and psychotropic drug use, likely due to metabolic effects and adherence challenges. Younger age correlated with WR, potentially linked to fewer comorbidities and less medical oversight. Comorbidities like hypertension and metabolic syndrome appeared protective against WR.

Additionally, the role of RYGB distalization as a strategy to address IWL and WR will be explored, highlighting its potential in improving outcomes for patients experiencing suboptimal results after initial surgery.

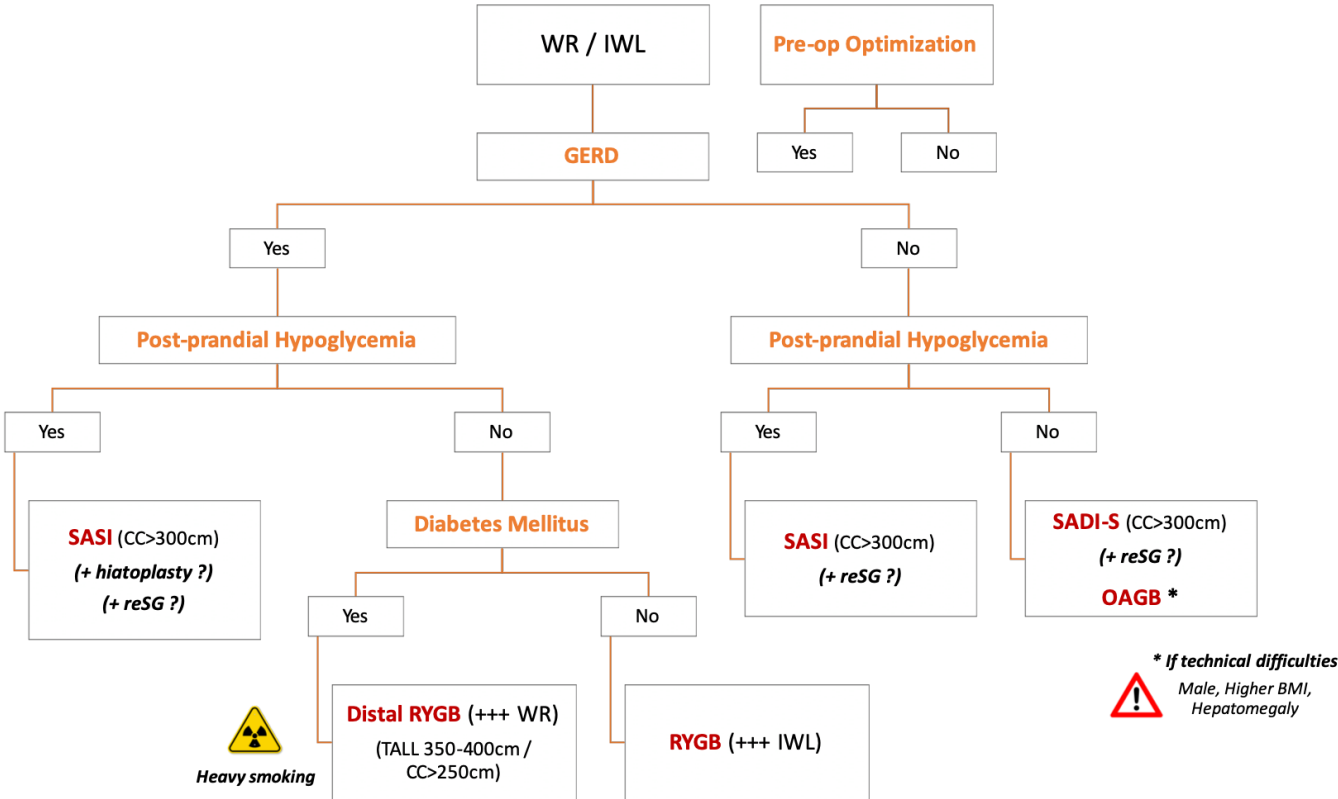
Our systematic review and meta-analysis *(unpublished data, master thesis supervision)* found that RYGB distalization shows promise as an effective revisional surgery for WR or IWL, with %EWL exceeding 50% and % TWL above 20%. However, the optimal limb lengths [Total Alimentary Limb Length (TALL), common limb, biliopancreatic limb] and techniques (Type I-IV) remain undefined, and severe protein-energy malnutrition poses a significant risk. The study emphasizes standardizing surgical practices, success criteria, and predictors to enhance comparability and outcomes. Further research is needed to refine techniques and mitigate nutritional complications.

Decision-making algorithm proposal

WR/IWL after RYGB



WR/IWL after SG



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XIII. APPENDICES

PUBLICATIONS EVALUATION

Journal Rank according Scimago and Thomson-Reuters Science Citation Index Expanded

#	Publication	Authorship	PHD Thesis Evaluation	Journal	Year	Scimago	Rank	Category	Quartile	Percentile 10	JIF	Rank	Category	Quartile	Percentile 10	JCI	Rank	Category	Quartile	Percentile 10						
1	Comparative Effectiveness of Bariatric Surgeries in Patients with Type 2 Diabetes Mellitus and BMI ≥ 25 kg/m2: a Systematic Review and Network Meta-Analysis	First	Yes	Obes Surg	2021	0.956	70	519	13,49%	Surgery	Q1	No	3,479	57	213	26,76%	Surgery	Q2	No	1,27	37	282	13,12%	Surgery	Q1	No
2	Roux-en-Y gastric bypass and sleeve gastrectomy as revisional bariatric procedures after adjustable gastric banding: a retrospective cohort study	First	Yes	Langenbecks Arch Surg	2023	0.758	117	549	21,31%	Surgery	Q1	No	2,1	98	290	33,79%	Surgery	Q2	No	0,95	77	290	26,55%	Surgery	Q2	No
3	Roux-en-Y Gastric Bypass Vs Sleeve Gastrectomy in Super Obesity: a Systematic Review and Meta-Analysis	Co	No	Obes Surg	2022	1,127	49	512	9,57%	Surgery	Q1	Yes	2,9	63	213	29,58%	Surgery	Q2	No	1,22	41	286	14,34%	Surgery	Q1	No
4	Risk and Prophylactic Management of Gallstone Disease in Bariatric Surgery: a Systematic Review and A Bayesian meta-analysis	First	Yes	J Gastrointest Surg	2023	0.941	79	549	14,39%	Surgery	Q1	No	2,2	90	290	31,03%	Surgery	Q2	No	0,85	96	290	33,10%	Surgery	Q2	No
5	Incidence of symptomatic gallstones after bariatric surgery: the impact of expectant management	First	Yes	Langenbecks Arch Surg	2023	0.758	117	549	21,31%	Surgery	Q1	No	2,1	98	290	33,79%	Surgery	Q2	No	0,95	77	290	26,55%	Surgery	Q2	No
6	Preoperative Risk Factors for Early Postoperative Bleeding after Roux-en-Y Gastric Bypass Surgery: A Systematic Review and Meta-Analysis	First	Yes	Langenbecks Arch Surg	2024	0.758	117	549	21,31%	Surgery	Q1	No	2,1	98	290	33,79%	Surgery	Q2	No	0,95	77	290	26,55%	Surgery	Q2	No
7	Early Postoperative Bleeding After Laparoscopic Roux-En-Y Gastric Bypass: a Single Center Analysis	Co	No	Obes Surg	2022	1,127	49	512	9,57%	Surgery	Q1	Yes	2,9	63	213	29,58%	Surgery	Q2	No	1,22	41	286	14,34%	Surgery	Q1	No
8	Gastric Bypass and Sleeve Gastrectomy - a Systematic Review and Meta-Analysis	First	Yes	Obes Surg	2022	1,127	49	512	9,57%	Surgery	Q1	Yes	2,9	63	213	29,58%	Surgery	Q2	No	1,22	41	286	14,34%	Surgery	Q1	No
9	Nutritional deficiencies in bariatric surgery patients: a comparison between Roux-en-Y Gastric Bypass and Sleeve Gastrectomy	First	Yes	J Pers Med	2024	0.736	809	2495	32,42%	Medicine, General and Internal	Q2	No	3	58	325	17,85%	Medicine, General and Internal	Q1	No	1,05	48	329	14,59%	Medicine, General and Internal	Q1	No
10	Predictors of Hypoglycemia after Bariatric Surgery: A Systematic Review	Unpublished	No																							
11	Efficiency and safety of Single Anastomosis Sleeve Ileal (SASI) bypass in the treatment of obesity and associated comorbidities: A systematic review and meta-analysis	First	Yes	Langenbecks Arch Surg	2024	0.758	117	549	21,31%	Surgery	Q1	No	2,1	98	290	33,79%	Surgery	Q2	No	0,95	77	290	26,55%	Surgery	Q2	No
12	Role of Fundoplication Sleeve Gastrectomy in Metabolic and Bariatric Surgery: A Systematic Review and Meta-Analysis	Unpublished	No	Obes Surg	2024	1,083	55	549	10,02%	Surgery	Q1	No	2,9	49	290	16,90%	Surgery	Q1	No	1,24	42	290	14,48%	Surgery	Q1	No
13	The Impact of Cholecystectomy in Patients with Post - Bariatric Surgery Hypoglycemia	Co	No	Obes Surg	2024	1,083	55	549	10,02%	Surgery	Q1	No	2,9	49	290	16,90%	Surgery	Q1	No	1,24	42	290	14,48%	Surgery	Q1	No
14	The impact of the prognostic nutritional index (PNI) in gastric cancer	First	Yes	Langenbecks Arch Surg	2022	0.721	118	512	23,05%	Surgery	Q1	No	2,3	97	213	45,54%	Surgery	Q2	No	0,95	74	286	25,87%	Surgery	Q2	No
15	Is there an obesity paradox in gastric cancer patients? Beyond BMI	Unpublished	No																							
16	Oncometabolic Surgery: The Metabolic Effects and Effectiveness of the Different Reconstruction Methods used in Gastric Cancer Surgery - A Systematic Review and Meta-Analysis	First	Yes	Scientific reports	2024	0,9	15	175	8,57%	Multidisciplinary Sciences	Q1	Yes	3,8	25	134	18,66%	Multidisciplinary Sciences	Q1	No	1,05	23	135	17,04%	Multidisciplinary Sciences	Q1	No
17	Roux-en-Y Gastric Bypass Disatization for Insufficient Weight Loss or Weight Regain: a Systematic Review and Meta-Analysis	Unpublished	No																							
18	Predictors of insufficient weight loss and weight regain after bariatric surgery	Unpublished	No																							
Q1 / Percentile 10										9	2								2	0			4	0		
Q2										1									8				6			
Total										10									10				10			

OUTPUTS OF RELATED STUDIES

A. IMPROVING INDICATIONS FOR MBS

Management of metabolic-challenged patients

Obesity class IV and V (*formerly known as Super obesity*)

Roux-en-Y Gastric Bypass Vs Sleeve Gastrectomy in Super Obesity: a Systematic Review and Meta-Analysis. Obes Surg 32, 170–185 (2022) doi: [10.1007/s11695-021-05745-8](https://doi.org/10.1007/s11695-021-05745-8)

Hugo Santos-Sousa was **Co-Author**

[Parallel Research Area, co-supervision of PhD thesis of a research team investigator]

Cited by **47** articles

(Google Scholar, 2025, October 20)

Scimago Journal Rank (SJR) indicator 1,127 (2022) H Index 152 | Rank 49 of 512 on Surgery journals (**Q1; Percentile 10**)

(Scimago Journal & Country Rank, 2022)

Journal Impact Factor (JIF) 2,9 | Rank 63 of 213 on Surgery journals (**Q2**)

Journal Citation Indicator (JCI) 1,22 | Rank 41 of 286 on Surgery Journals (**Q1**)

(Thomson-Reuters, Science Citation Index Expanded (SCIE), 2022)



Roux-en-Y Gastric Bypass Vs Sleeve Gastrectomy in Super Obesity: a Systematic Review and Meta-Analysis

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Abstract

Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are safe procedures that may present sub-optimal results in superobesity (SO). A meta-analysis was performed aiming to summarize the available evidence on weight loss (primary outcome) and comorbidities resolution of LRYGB and LSG in patients with SO (BMI ≥ 50 kg/m²). From the 16 included studies, 7 integrated the meta-analysis. LRYGB showed a significantly higher weight loss at 6 to 12-months, but not after 24 months and a higher dyslipidemia resolution at 12 months. When compared with LSG, LRYGB achieved better weight loss after 6 and 12 months and higher dyslipidemia resolution after 1 year. There were no significant differences for resolution of the other co-morbidities studied.

Keywords Bariatric surgery · Laparoscopic Roux-en-Y gastric bypass · LRYGB · Laparoscopic sleeve gastrectomy · LSG · Super obesity · Weight loss · Comorbidity resolution · Meta-analysis

Introduction

Obesity is a major worldwide health issue associated with several comorbid conditions, namely, diabetes mellitus (DM), hypertension (HTN), dyslipidemia (DL), cardiovascular diseases (CVD), and obstructive sleep apnea

(OSA) [1–5]. Super obesity (SO), i.e., a body mass index (BMI) ≥ 50 kg/m², represents the extreme severity of the disease which results in substantial morbidity, mortality, and poorer quality of life. In SO, bariatric surgery is proven to exceed medical treatment regarding long-term weight loss and comorbidity resolution [6–8]. The conventional methods—laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG)—may present sub-optimal results in SO, when compared with the milder forms of the disease, due to the increased operative risks and technically challenging approach. However, these procedures may also be safer than more complex techniques such as two-step approaches [9]. Balancing the risks and benefits of obesity surgery in patients with SO can be quite difficult and controversial; therefore, we aimed to summarize and critically appraise the available evidence on the effects of LRYGB and LSG in these patients.

Key Points LRYGB and LSG are safe procedures with a debatable role in SO.

LRYGB had a greater weight loss at 6 and 12 months, but not at 2 years.

From the studied comorbidities at 1 year, LRYGB only had a greater resolution of DL.

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Methods

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines statement [10].

Search Strategy

A comprehensive electronic literature search was performed on PubMed, Cochrane Library, and Scopus databases, from their inception to October 2020, using a pre-defined search strategy (Appendix) designed by the authors. A manual screening of the references lists of relevant papers was also performed to supplement our literature search. Two authors (S.R., C.N.) independently screened abstracts obtained from the database search. The full-texts of potentially relevant articles were retrieved for further assessment and disagreements were resolved by consensus-based discussion or by consultation with a third reviewer (A.P.).

Study Selection

Eligible articles for this review comprised original observational studies comparing the effects of primary LRYGB and LSG in weight loss outcomes and comorbidity resolution. Studies had to be performed in adults (18–65 years old) with SO ($\text{BMI} \geq 50 \text{ kg/m}^2$). No restriction regarding control group, language, or temporal limits were imposed. Reviews, letters, editorials, articles of opinion, animal studies, and studies on other bariatric techniques were excluded (Table 1).

Data Extraction

Relevant data were extracted onto a structured excel spreadsheet and reviewed by two authors, independently. Four pre-defined domains of items were extracted: study characteristics (author's name, year of publication, journal, country

of study, study design, sample size, and duration of follow-up), sample characteristics (age, gender, BMI), post-surgery weight loss outcomes (expressed in postoperative BMI, percent of excess weight loss (%EWL), BMI loss (BMIL), percent total weight loss (%TWL), and absolute weight loss), and comorbidities outcomes (frequency, therapeutic interventions, improvement/resolution of analytical parameters related to DM, HTN, DL, and OSA).

Data Analysis

We summarized characteristics using frequencies and percentages. We used the Review Manager software (V.5.4) for pooled mean difference (MD) and odds ratio (OR) and the 95% confidence interval (CI). Heterogeneity was assessed using the Q test and I^2 statistic, a random-effects model was used to pool all outcomes, and a P value of <0.05 was considered to be statistically significant. The primary outcome was weight loss after bariatric surgery and the secondary outcomes were the effect, presumably remission or improvement, of the procedures in obesity-related comorbidities (DM, HTN, DL, OSA), assessed for 12 months as defined according to the ASMBS, SOARD outcome reporting standards [11]. We conducted a subanalysis of the primary and secondary outcomes regarding the time of follow-up.

Quality Assessment

Methodological quality assessment of included studies was performed independently by 2 authors (S.R. and C.N.) and disagreements were resolved by consensus-based discussion or by consultation with a third reviewer (A.P.). The level of evidence of each article was assessed using the SORT “Strength of Recommendation Taxonomy.” The journal's quartile was defined according to the “Scimago Journal and Country Rank” regarding the year 2019. The methodological scale for nonrandomized studies (MINORS) was used to assess the methodological quality of our studies (Fig. 1) [12]. Included papers were assessed on 12 items, each item

Table 1 Inclusion/exclusion criteria for identified studies

	Inclusion criteria	Exclusion criteria
Population	Humans $\text{BMI} \geq 50 \text{ kg/m}^2$ Age [18–65] years old Undergoing bariatric surgery	
Intervention	Primary RYGB and primary SG	Revisional or conversion procedures
Control group	Any	
Outcome	Weight loss Co-morbidity resolution or improvement	Unobtainable outcome
Study design	Any	Reviews, letters, editorials, articles of opinion
Follow-up	Any	

BMI, body mass index; *RYGB*, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy

Methodological items for non-randomized studies	Score [†]
1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature 2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion) 3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study 4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis. 5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated 6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events 7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint 8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes <i>Additional criteria in the case of comparative study</i> 9. An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data 10. Contemporary groups: control and studied group should be managed during the same time period (no historical comparison) 11. Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results 12. Adequate statistical analyses: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

[†]The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Fig. 1 MINORS scale

being scored from 0 to 2; hence, the maximum total score is 24 in controlled studies, such as the ones included, and a high-quality score defined as ≥ 16 .

Results

The search returned 1271 records: 636 from PubMed, 91 from Cochrane Library, 541 from Scopus and 3 from a manual screening of the reference lists of relevant papers. Full-text assessment for eligibility resulted in 16 studies being included [13–28]. The PRISMA statement guideline's flow-chart of this process is shown in Fig. 2 [10]. From these, 7 were used in the meta-analysis. Overall, the main reasons for exclusion were absence of an analysis of the subgroup with SO, no comparison between LRYGB and LSG and sample outside the age range. We summarized data comprising 53,858 patients for weight outcomes and comorbidity resolution after LSG and LRYGB in patients with SO.

Weight Loss Outcome

Although LRYGB may be a predictor of weight loss in the first 2 years of follow-up [15], having obesity within the second year of follow-up ($P < 0.0001$), female gender ($P = 0.041$) or SG and RYGB procedures ($P = 0.008$) may predict a 3 year BMI ≥ 30 kg/m², but not failure of

bariatric surgery (%EWL $< 50\%$ or %TWL $< 20\%$) [25]. Bhandari M et al. showed a higher failure rate (BMI ≥ 35) at 2 and 3 years after LSG (16.2% and 67.9%, respectively) than RYGB (15.9% and 29.2%, respectively) [25]. LRYGB commonly showed a longer duration of stay [19, 24] and longer mean operative times [17, 21, 24, 26, 28] of, for example, 124 ± 49 min versus 98 ± 51 min in LSG ($P < 0.005$) [28]. Minimum weight was achieved around 12–24 months after surgery [15, 17, 21, 23, 24, 26]. For the LSG group, the %EWL dropped earlier, at 30 months [24] and only at 36 months for the LRYGB group [24, 26], whose tendency of greater weight loss weakened at 3 years and beyond [15, 18, 23, 24]. Two studies compared the success rate, i.e., reaching a %EWL $\geq 50\%$, at 2 years with results of up to 80% and 85% following LRYGB and of less than 60% and 74.6% after LSG, respectively [13, 15]. Additionally, patient stratification by obesity category showed that a higher baseline BMI was associated with a lower %EWL [18, 28]. Regarding complications, most studies exposed no difference in the 30-day analysis [15–17, 24, 26, 27]. One study reported significantly higher major adverse events [28] and another higher adjusted rates of mortality after LRYGB [16]. Moreover, Jain D et al. reported that 25–35% of patients required reoperation due to weight gain or gastroesophageal reflux disease (GERD) after LSG [18].

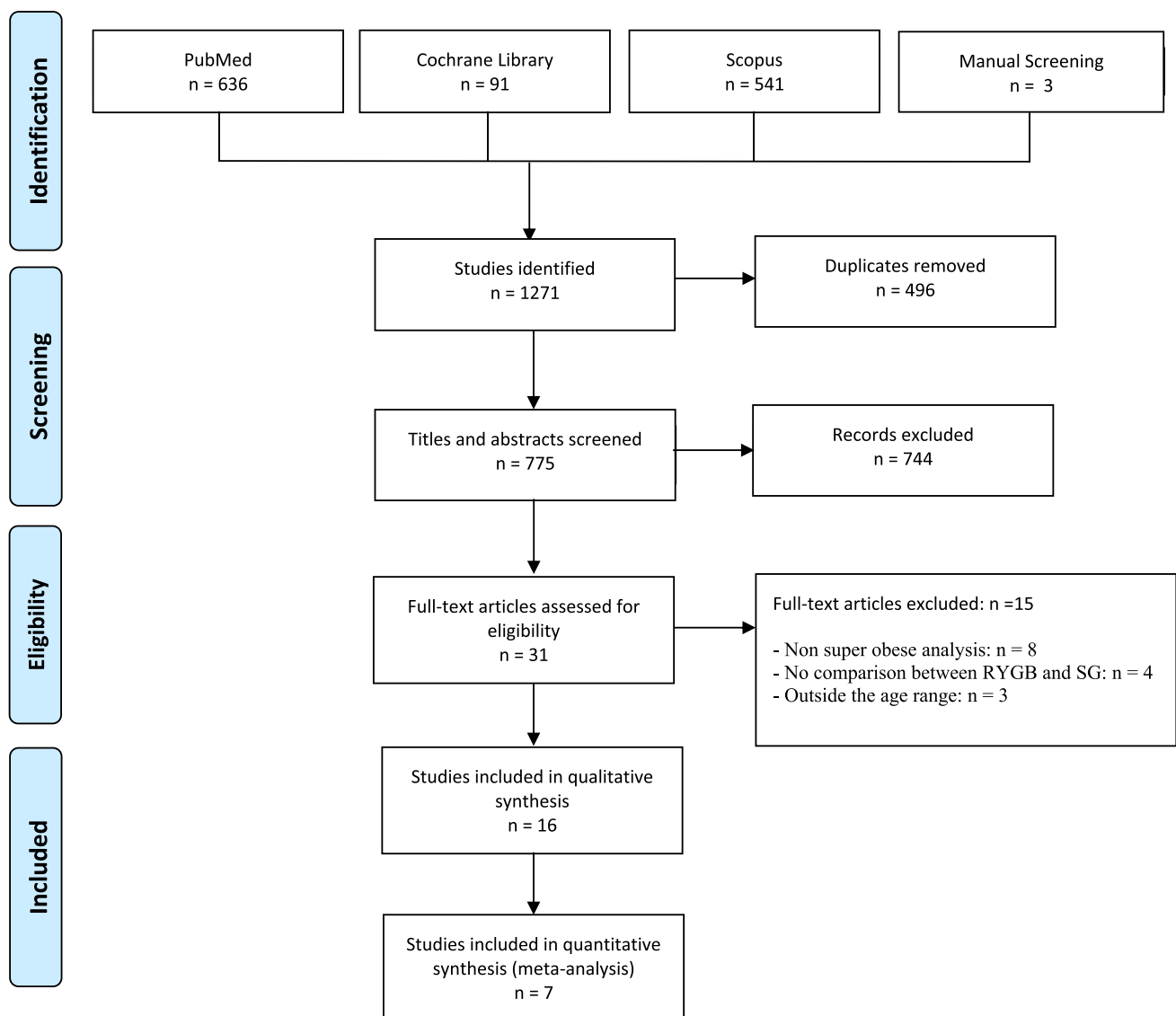


Fig. 2 Flow diagram regarding the selection of articles, according to the preferred reporting items for systematic reviews and meta-analyses statement. (Moher D, Liberati A, Tetzlaff J, Altman DG, The

PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. <https://doi.org/10.1371/journal.pmed1000097>)

%EWL and %TWL

We conducted a subanalysis of the primary outcome according to the time of follow-up: 6, 12, and 24 months after surgery. As seen in Fig. 3, two studies (24,740 patients) comparing %EWL after 6 months showed a significant difference between techniques ($MD=4.90$; 95%CI [4.59–5.11]; $P<0.00001$), with a weighted average of 42.82 and 37.95%EWL after LRYGB and LSG, respectively. However, Hariri K et al. presented no difference in %TWL during this period. After 12 months, 5 studies described a significant %EWL difference ($MD=10.15$; 95%CI [6.55; 13.76]; $P<0.00001$) with a significant moderate heterogeneity between studies ($I^2=68\%$, $P=0.01$). The results of

a pooled analysis of %TWL were concordant during this period ($MD=4.51$; 95%CI [2.02; 6.99]; $P=0.0004$) and the mean weighted average at 1 year was of 59.73%EWL and 36.06%TWL for LRYGB and of 49.34%EWL and 35.98%TWL for LSG.

There was, however, no significant difference in the %EWL between the 4 studies (1241 patients) at 2 years, even though Bettencourt-Silva R et al. stated a significantly higher %TWL after LRYGB, and a high heterogeneity between studies ($I^2=80\%$, $P=0.002$) was seen. Compiling this information, the pooled analysis of %EWL until 2 years revealed a significant difference between procedures ($MD=7.06$; 95%CI –4.15 to 13.15; $P<0.00001$) and a high heterogeneity ($I^2=93\%$, $P<0.00001$) (Fig. 3). Additionally, Hong J et al.

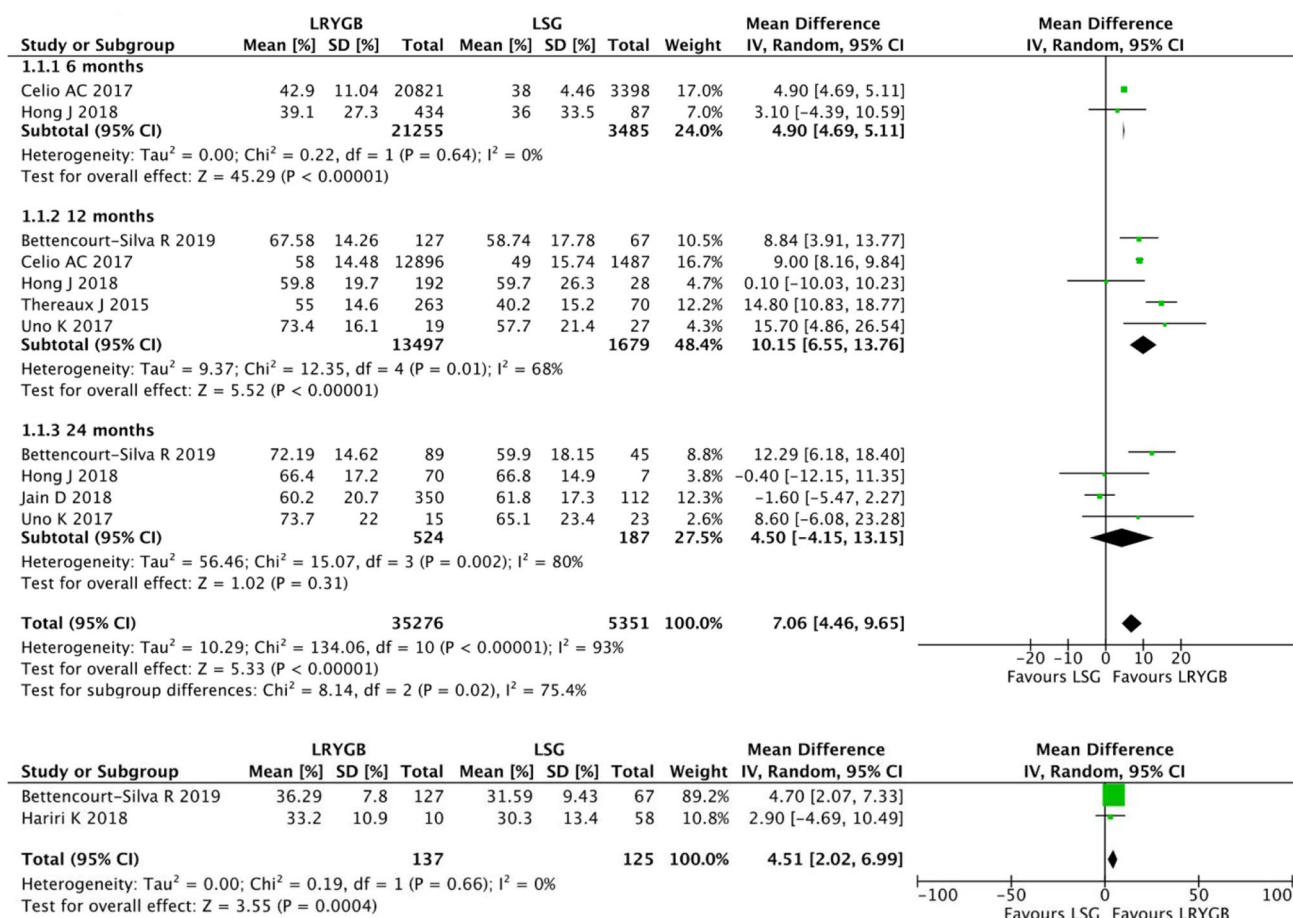


Fig. 3 Comparison of pooled short-term outcomes between laparoscopic Roux-en-y gastric bypass and laparoscopic sleeve gastrectomy patients (from above to below: %excess weight loss and %total weight loss)

presented a higher mean %EWL at 36 months after LSG, but without any statistically significant difference.

Comorbidity Improvement and Resolution

Some studies presented higher rates of comorbidities resolution after LRYGB, namely, DL [15], DM, OSA, asthma, and improved exercise tolerance [22] or even joint pain [17]. Celio et al., in particular, reported that this procedure provides greater improvement of all examined comorbidities and resolution of all but OSA [16]. In addition, two studies revealed a significant improvement in HbA1c with no statistical difference between the two techniques [23, 28] and Hong et al. found that patients from both groups had a 100% resolution of type 2 diabetes (T2D) after 18 months.

Diabetes

The pooled results at 12 months verified a non-significant difference in OR of DM resolution with a nonsignificant moderate heterogeneity between studies (Fig. 4) and a

weighted average of DM resolution of 69.26% after RYGB and 42.57% after LSG. At 24 months, Samuel et al. stated that complete diabetes remission was significantly higher in patients undergoing LRYGB treatment, while Hong J et al. showed no significant difference.

Hypertension

After 12 months, there was no significant difference in HTN resolution between techniques and a high heterogeneity was found within the included studies ($I^2 = 87\%$, $P = 0.0005$) (Fig. 4). The weighted average HTN resolution was 44.10% after LRYGB and 27.22% after LSG. Additionally, Samuel N et al. reported a significantly higher remission of HTN 24 months after LRYGB, and Arapis K et al. after 6 years.

Dyslipidemia

The pooled results yielded a significant difference of DL resolution after LRYGB and LSG at 1 year (OR = 3.57; 95%CI [2.30; 8.52]; $P < 0.00001$) and an insignificant low

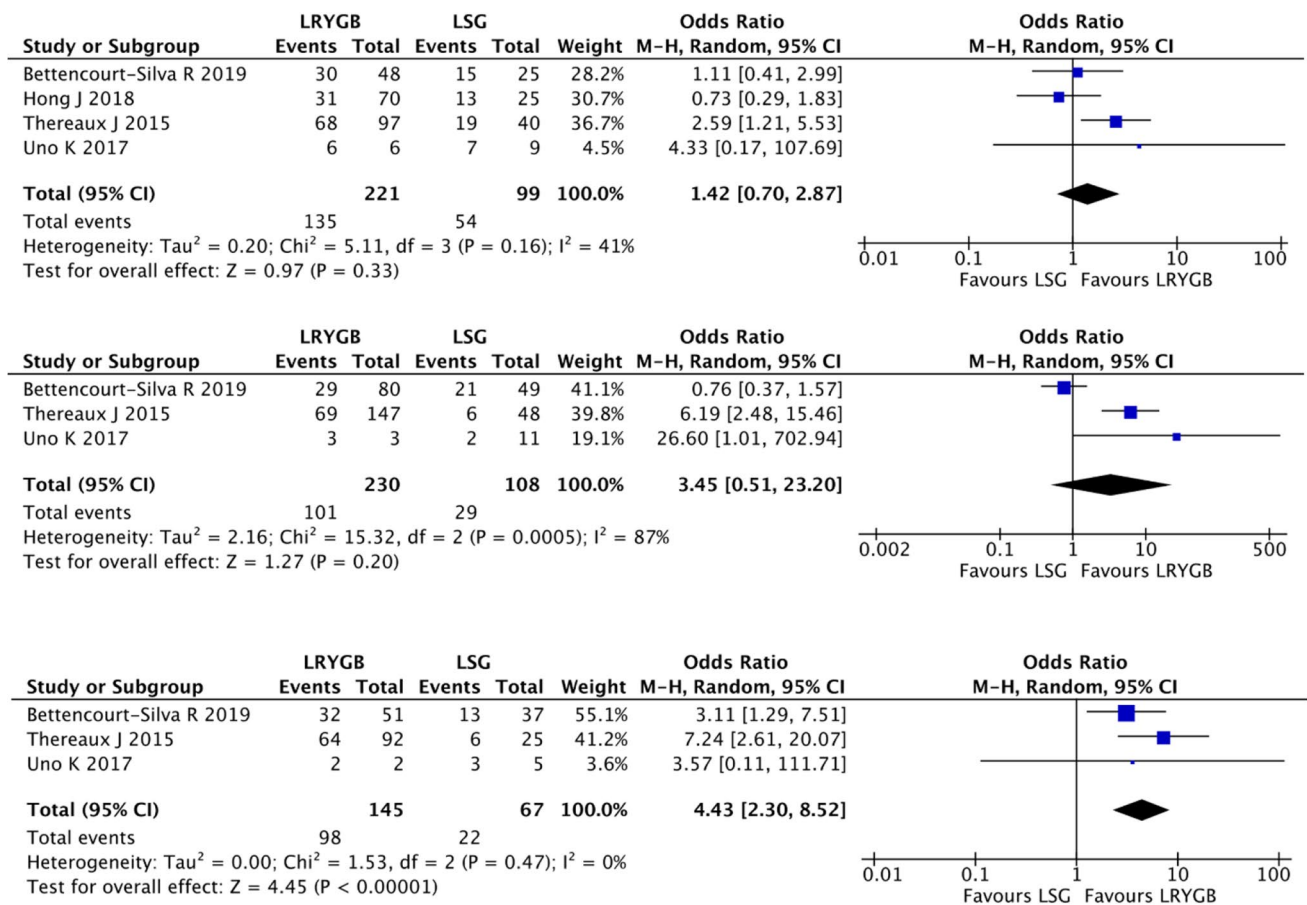


Fig. 4 Comparison of pooled 12 months comorbidity resolution between laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy patients (from above to below: diabetes resolution, hypertension resolution, dyslipidemia resolution)

heterogeneity within studies (Fig. 4). Comparing both techniques, 67.47% of patients had DL resolution after LRYGB and only 32.82% after LSG. Moreover, Samuel N et al. found this tendency still present at 24 months.

Obstructive Sleep Apnea

While Samuel N et al. and Thereaux J et al.'s patients undergoing LRYGB had a significant greater OSA resolution than LSG after 1 year, Arapis K et al. showed all differences in comorbidity resolution were significant after 6 years, except for OSA.

Study Characteristics

All 16 studies included in the review were observational comparative studies (14 retrospective and 2 prospective). There were no RCTs fulfilling our eligibility criteria. The main characteristics of the included studies are depicted in

Table 1 and Table 2. Study publication dates ranged from 2014 to 2020, with an increase in publication numbers since 2001, peaking in 2020. Sample sizes ranged from 30 to 50,987 participants and only one study exclusively evaluated patients with BMI ranging from 50 to 60 kg/m² [21].

Quality Assessment and Level of Evidence

The included studies are nonrandomized observational studies with variable methodological quality. Most studies collected their data retrospectively and the level of evidence of the included studies was mostly II. The MINORS scores of the included studies ranged from 17 to 21/24, presenting a high-quality score (Table 2.). Common weaknesses were unblinded assessment of outcome, retrospective nature of data collection, low sample size with lack of power calculation, group characteristics imbalance, and lack of adjustment for confounding factors. No studies reported conflict of interest.

Table 2 Study characteristics

Author (year)	Type of study	Quar- title	Level of evi- dence SORT	Coun- try	Journal	Patients' char- acteristics	Num- ber of patients (LRYGB vs LSG)	Age (M(SD)) (LRYGB vs LSG)	%females (LRYGB vs LSG)	BMI at baseline (M(SD)) (LRYGB vs LSG)	Time to follow-up (months)	Evaluated comor- bidities	Weight out- come	Other out- comes	Minors scale
Uno K et al. (2017)	Retro- spec- tive	Q1	Level 2, A	Japan	Obesity Surgery	BMI ≥ 50 kg/ m ² (until 79 kg/m ²)	48 (20 vs 28)	32.6 (6.6) vs 37.9 (9.2)	60 vs 21.4	55.7 (4.2) vs 57.1 (5.1)	12, 24	DM, HTN, DL	BMI Weight (kg) %EWL	Weight loss, Operative time, Com- plications, Conversion to open surgery, Metabolic profile changes	18/24 1/2; 2/2; 3/2; 4/2; 5/0; 6/2; 7/0; 8/1; 9/2; 10/2; 11/1; 12/2
Onyewu SC et al. (2017)	Retro- spec- tive	Q1	Level 2, A	USA	The Ameri- can Journal of Sur- gery	BMI ≥ 50 kg/ m ² ; Black patients	87 (70 vs 17)	42.3 (10.5) vs 40.9 (9.3)	90 vs 76	57.1 (6.5) vs 55.7 (6.0)	1, 6, 12	DM, HTN, DL	%EWL BMI	Weight loss, Coexisting conditions changes	17/24 1/2; 2/2; 3/2; 4/2; 5/0; 6/1; 7/1; 8/1; 9/2; 10/2; 11/1; 12/1
Betten- court- Silva R et al (2019)	Retro- spec- tive	Q1	Level 2, A	Portu- gal	Obesity Surgery	BMI ≥ 50 kg/ m ²	194 (127 vs 67)	42.09 (10.67) vs 44.70 (13.21)	85 vs 64.2	54.32 (4.28) vs 54.73 (4.89)	12, 24	DM, HTN, DL	BMI %EWL %TWL	Weight loss, Coexisting conditions changes	19/24 1/2; 2/2; 3/2; 4/2; 5/0; 6/2; 7/1; 8/1; 9/2; 10/2; 11/1; 12/2

Table 2 (continued)

Author (year)	Type of study	Quar- title	Level of evi- dence SORT	Coun- try	Journal	Patients' char- acteristics	Num- ber of patients (LRYGB vs LSG)	Age (M(SD)) (LRYGB vs LSG)	%females (LRYGB vs LSG)	BMI at baseline (M(SD)) (LRYGB vs LSG)	Time to follow-up (months)	Evaluated comor- bidities	Weight out- come	Other out- comes	Minors scale
Celio AC et al. (2017)	Retro- spec- tive	Q1	Level 2, A	USA	Surgical Endos- copy	BMI ≥ 50 kg/ m ²	50,987 (42,119 vs 8868)	43.7 vs 43.9	72.9 vs 70.9	57.3 vs 57.8	3, 6, 12	DM, HTN, DL, OSA, GERD	%TWL %EBWL BMIL	Weight loss, Compli- cations, Coexisting conditions changes	19/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)1; 7)1; 8)1; 9)2; 10)2; 11)2; 12)2
Thereaux J et al. (2015)	Pro- spec- tive	Q1	Level 2, A	USA	Surgery for Obesity and Related Dis- eases	BMI ≥ 50 kg/ m ²	359 (285 vs 74)	40.9 (12.2) vs 45.5 (13.7)	73.7 vs 64.9	56.7 (5.5) vs 57.2 (7.1)	12	DM, HTN, DL, OSA, Joint pain	BMI %EWL %WL	Weight loss, Operative time, Hos- pital length of stay, Complica- tions, Conversion to open surgery, Coexisting conditions changes	19/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)1; 7)1; 8)1; 9)2; 10)2; 11)2; 12)2
Jain D et al. (2018)	Retro- spec- tive	Q1	Level 2, B	USA	Surgery for Obesity and Related Dis- eases	BMI ≥ 50 kg/ m ²	462 (350 vs 112)	44.2 (10.7) vs 43.3 (11.1)	79 vs 81	NR	24	NR	%EWL BMI	Weight loss	20/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)2; 7)2; 8)1; 9)2; 10)2; 11)1; 12)2

Table 2 (continued)

Author (year)	Type of study	Quar- title	Level of evi- dence	Coun- try	Journal	Patients' char- acteristics	Num- ber of patients (LRYGB vs LSG)	Age (M(SD)) (LRYGB vs LSG)	%females (LRYGB vs LSG)	BMI at baseline (M(SD)) (LRYGB vs LSG)	Time to follow-up (months)	Evaluated comor- bidities	Weight out- come	Other out- comes	Minors scale
Rajan R et al. (2019)	Retro- spec- tive	Q3	level 2, B	Malay- sia	Journal of Mini- mal Access Surgery	BMI ≥ 50 kg/ m ² with T2DM	30 (3 vs 27)	49.7 (14.7) vs 39.2 (11.2)	56% vs 67%	52.6 (2.5) vs 60.9 (9.3)	3, 6, 12	DM, HTN, DL, GERD	Weight BMI %EBMIL %TBWL	Mean opera- tive time, Hospital length of stay, Conversion to open surgery, 30-day morbidity, 30-day mortality, Coexisting conditions changes	18/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)1; 7)1; 8)2; 9)2; 10)2; 11)1; 12)1
Hariri K et al. (2018)	Retro- spec- tive	Q1	Level 2, A	USA	Surgery for Obesity and Related Dis- eases	BMI ≥ 50 kg/ m ²	171 (20 vs 151)	49.3 (11.4)	678 (72.9)	43.9 $\pm$ 7.5	6, 12	NR	%TBWL $\pm$ SD BMI $\pm$ SD	Weight loss, Coexisting conditions changes	18/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)1; 7)1; 8)1; 9)2; 10)2; 11)1; 12)2
Zerrweck C et al. (2013)	Retro- spec- tive	Q1	Level 2, A	Méx- ico	Obesity Surgery	BMI 50–59.9 kg/m ²	77 (32 vs 45)	35.4 (7.6) vs 35.4 (7.6)	31 (96) vs 25 (55)	52.7 (2.1) vs 53.87 (2.8)	1, 3, 6, 9, 12	NR	BMI %EWL	Weight loss, Early com- plications (< 30 days)	17/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)1; 7)1; 8)1; 9)2; 10)2; 11)1; 12)1

Table 2 (continued)

Author (year)	Type of study	Quar- tile	Level of evi- dence SORT	Coun- try	Journal	Patients' char- acteristics	Num- ber of patients (LRYGB vs LSG)	Age (M(SD)) (LRYGB vs LSG)	%females (LRYGB vs LSG)	BMI at baseline (M(SD)) (LRYGB vs LSG)	Time to follow-up (months)	Evaluated comor- bidities	Weight out- come	Other out- comes	Minors scale
Samuel N et al. (2019)	Pro- spec- tive	Q3	Level 2, A	UK	Annals	BMI 50–59.9 kg/m ² & BMI > 60 kg/m ²	153: 134 SO 101 (46.3%) vs 33 (47.1%); 19 SSO 13 (5.9%) vs 6 (8.5%)	Median: SO 41.9 vs 46.8; SSO 39.7 vs 40.2	SO 78 (77.2%) vs 23 (69.7%); SSO 12 (92.3%) vs 4 (66.7%)	SO 101 (46.3%) vs 22 (47.1%); SSO 13 (5.9%) vs 6 (8.5%)	1 week, 6 weeks, 3, 6, 12, 24 months	DM, HTN, DL, OSA, GERD, Asthma, Exercise tolerance	Weight (Kg) %EWL BMI	Weight loss, Perioperative morbidity, Coexisting conditions changes	21/24 1/2; 2/2; 3/2; 4/2; 5/0; 6/2; 7/2; 8/1; 9/2; 10/2; 11/2; 12/2
Hong J et al. (2018)	Retro- spec- tive	Q1	Level 2, A	USA	Surgery for Obesity and Related Dis- eases	BMI ≥ 50 kg/m ²	607 (501 vs 106)	44.58 (11.94) vs 43.65 (16.08)	67.3 vs 44.3	57.7 (9.27) vs 55.21 (7.90)	6, 12, 18, 24, and 36	DM, HTN, DL, OSA, GERD	%EWL BMI	Weight loss, Diabetes remission	20/24 1/2; 2/2; 3/2; 4/2; 5/0; 6/2; 7/1; 8/1; 9/2; 10/2; 11/2; 12/2
Arapis K et al. (2018)	Retro- spec- tive	Q1	Level 2, A	France	Surgery for Obesity and Related Dis- eases	BMI ≥ 60 kg/m ²	87 (70 vs 17)	42.3 (10.5) vs 40.9 (9.3)	90 vs 76	57.1 (6.5) vs 55.7 (6.0)	1, 6, 12	DM, HTN, DL	%EWL BMI	Weight loss; Coexisting conditions changes	17/24 1/2; 2/2; 3/2; 4/2; 5/0; 6/1; 7/1; 8/1; 9/2; 10/2; 11/1; 12/1

Table 2 (continued)

Author (year)	Type of study	Quar- tile	Level of evi- dence SORT	Coun- try	Journal	Patients' char- acteristics	Num- ber of patients (LRYGB vs LSG)	Age (M(SD)) (LRYGB vs LSG)	%females (LRYGB vs LSG)	BMI at baseline (M(SD)) (LRYGB vs LSG)	Time to follow-up (months)	Evaluated comor- bidities	Weight out- come	Other out- comes	Minors scale
Bhandari M et al (2019)	Retro- spec- tive	Q1	Level 2, A	India	Obesity	BMI ≥ 50 kg/ m ²	329 (102 vs 227)	Total: 44.39 (11.9); 42.99 (11.7) vs LSG 45.85 (12.2)	59 (57.8) vs 127 (55.9)	54.64 (4.56) vs 56.39 (6.11)	24, 36	NR	%TBWL %EBWL BMI	Weight loss, Opera- tive time, Estimated blood loss, Postopera- tive compli- cations	19/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)2; 7)1; 8)1; 9)2; 10)2; 11)1; 12)2
Gonzalez R et al. (2016)	Retro- spec- tive	Q1	Level 2, A	USA	Surgical Endos- copy	BMI ≥ 60 kg/ m ²	89 (12 vs 77)	44.4 (9.9) vs 38.1 (10.1)	NR	64.2 (2.5) vs 64.9 (4.2)	1, 3, 6, 12, 24, and 36	NR	%EWL %WL	Weight loss, Length of stay, Mean operative time, Com- plications	20/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)2; 7)1; 8)2; 9)2; 10)2; 11)2; 12)1
Marti- natis L et al (2018)	Retro- spec- tive	Q2	Level 2, A	Spain	The Spanish Jour- nal of Gastro- enterol- ogy	BMI ≥ 50 kg/ m ² ; Sub- group of Age $\geq$ 60 years	43 (29 vs 14)	44.6 (42.6– 46.7) vs 42.5 (38.4– 47.6)	72 (74.2%) vs 15 (62.5%)	47.2 (45.9– 48.1) vs 53.5 (49.2– 59.2)	1, 6, 12, 24, 36, 60	NR	Total weight loss change in BMI, %EBMIL, BF% FFM	Weight loss, Length of stay, Com- plications, Reop- erations, Coexisting conditions changes	18/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)2; 7)1; 8)1; 9)2; 10)2; 11)1; 12)1

Table 2 (continued)

Author (year)	Type of study	Quar-tile	Level of evi-dence SORT	Coun-try	Journal	Patients' char-acteristics	Num-ber of patients (LRYGB vs LSG)	Age (M(SD)) (LRYGB vs LSG)	%females (LRYGB vs LSG)	BMI at baseline (M(SD)) (LRYGB vs LSG)	Time to follow-up (months)	Evaluated comor-bidities	Weight out-come	Other out-comes	Minors scale
Serrano OK et al. (2015)	Retro-spec-tive	Q1	Level 2, A	USA	Surgical Endos-copy	BMI ≥ 60 kg/m ²	135 (93/42)	33.1 (11.5) vs 38.2 (11.3)	71 vs 52	66.3 (5.4) vs 68.4 (7.9)	1, 3, 6, and 12	NR	%EWL BMI	Weight loss, Mean opera-tive time, Length of stay, Com-plications, Diabetes remission	18/24 1)2; 2)2; 3)2; 4)2; 5)0; 6)1; 7)1; 8)1; 9)2; 10)2; 11)2; 12)1

BF% body fat percentage, *BMI* body mass index, *BMIL* BMI loss, *DM* diabetes mellitus, *DL* dyslipidemia, *FFM* fat-free mass, *FPG* fasting plasma glucose, *GERD* gastroesophageal reflux disease *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein cholesterol, *HTN* hypertension, *LDL* low-density lipoprotein cholesterol, *M* mean, *NR* no report, *OSA* obstructive sleep apnea, *%EWL* percent excess weight loss, *%TWL* percent total weight loss, *%WL* percent weight loss *RYGP* Roux-en-Y gastric bypass, *SD* standard deviation, *SG* sleeve gastrectomy, *SO* super obese, *SSO* super super obese, *TC* total cholesterol, *TG* triglycerides

Discussion

As seen in other diseases, patients with SO are more challenging to manage and may present suboptimal results after LRYGB or LSG [29] since higher BMI independently increases the risk of complications and mortality [18, 28, 30]. These vulnerabilities have guided some surgeons to offer an intermedium procedure, such as the intra gastric balloon, to downgrade the patients BMI to an acceptable range before offering a more definitive procedure [22]. This may be an interesting option, but beyond the possible benefits, this two-step approach presents considerable risks associated with the invasive nature of its deployment and retrieval. Additional studies should be carried in order to clarify its role in patients with SO. Presently, LRYGB and LSG are considered to achieve sub-optimal results in SO patients [23]. Although LRYGB is one of the leading interventions for surgical treatment of morbid obesity, its role in the treatment of SO may not be as well-defined, yet some studies show it might still be an independent predictor of weight loss in patients with BMI ≥ 50 kg/m² [15]. In its turn, LSG, known for a technical simplicity, reproducibility and less demanding follow-up regarding hipo-absorptive issues, has a much shorter operative time [17, 21, 24, 26, 28] and fewer post-operative complications. [14]. However, it also presents poorer long-term weight loss outcomes and comorbidities improvement than other techniques. It is also important to keep in mind that an initial sleeve procedure in this group of patients allows revision surgery in case of inadequate weight loss whereas there is no definitive revision procedure for an anatomically correct LRYGB accomplishing an inadequate weight loss [24].

Studies defend that more complex techniques such as duodenal switch, single anastomosis duodeno-ileostomy with sleeve gastrectomy (SADI-S), or even one-anastomosis gastric bypass may achieve improved results at the eventual expense of increased risk of perioperative and long-term complications [25, 31–33]. For example, bilio-pancreatic diversion with duodenal switch (BPD-DS) achieved a higher %EWL at 1 year (69% versus 55%) [34, 35] and more sustained weight loss than LRYGB [29], with lower proportion of failures (%EWL < 50%) [36] but with discordant findings regarding comorbidities resolution [29, 37]. In the common practice, BPD-DS is rarely offered to patients with obesity mainly because of technical complexity, long-term nutritional deficiencies and diarrhea. Therefore, other techniques, such as SADI-S, which is derived from BPD-DS, focused on achieving the same outcomes while minimizing side effects and possible complications, may be preferred.

Weight Loss Outcome

Studies reported that most weight loss was achieved within the first 12–24 months with both procedures, but both also presented a slight weight increase after long-term follow-up. This emphasizes the need to maintain a healthy lifestyle, performing daily physical activity and to carry out dietary recommendations in order to achieve a sustainable result [27]. Considerable weight loss was recorded following both procedures, but LRYGB accomplished a higher %EWL (mean = 59.73%) and %TWL (mean = 36.06%) at 12 months. Although this tendency was already present at 6 months, there was no difference after 24 months, which may be explained by the lack of data and loss of follow-up. Additionally, one study showed the success rate was considerably better after LRYGB at 2 years [13] and another showed a higher weight loss failure rate (BMI ≥ 35) at 2 and 3 years after LSG [25].

Resolution of Comorbidities

We performed a meta-analysis for all comorbidities mentioned above except for OSA, given the lack of data. Although multiple studies suggested LRYGB to be more successful in controlling obesity-related comorbidities than LSG [15–17, 22, 38], our main findings state a non-significant difference for most comorbidities at 12 months except for dyslipidemia, which favored LRYGB. Nevertheless, it is important to keep in mind that the small amount of available data may have impaired these results. Interestingly, some studies suggest that patients with higher BMI may rely more on weight loss to achieve T2D remission than in milder obesity ranges. That being said, patients with SO may benefit more from a technique able to achieve greater weight loss results, therefore supporting the use of LRYGB over LSG [23, 39, 40]. Additionally, studies defend that in patients in whom GERD poses a significant health burden, LRYGB is the best option to treat both obesity and GERD [28]. Additionally, perioperative complications were shown to be similar between the two groups, but LRYGB patients had more reoperations and readmissions [16] and one study defended that age alone should not preclude older patients from getting the best bariatric procedure [27]. Therefore, proven a satisfactory weight loss and comorbidities resolution, clinicians should regard these two techniques as viable options in SO, aside from more complex procedures.

Limitations, Publication Bias, and Heterogeneity

This review had some limitations that should be addressed. There was an important clinical diversity shown across the included studies. Key data were not adequately reported in some of the included studies, with inconsistencies in

reporting weight loss outcomes and follow-up losses. Regarding study design, some studies had a small sample size or a disproportionate number of patients for each intervention. This can also contribute to the meta-analysis heterogeneity and may limit the conclusions that can be drawn. Additionally, we could not stratify the selected studies based on age, race, %females, which may affect the weight loss effect. There was a lack of mid- and long-term outcomes in our study, which is a major limitation. Furthermore, most of the included studies were designed retrospectively, and there was no randomization of performed technique in the different groups, which can cause a possible selection bias. Even though we recognize how challenging it must be to design and perform studies with long-term follow-up, our systematic review appeals for a comparative analysis of the available data on long-term effects in SO. We believe an analysis of the percentage of patients achieving both a > 50% weight loss and a resolution of their co-morbidities would provide a wider perspective onto the effects of the analyzed procedures and measure success.

Conclusion

In conclusion, our results revealed that both procedures are effective single standing measures for short-term obesity management in patients with SO. While certain factors such as better weight loss outcomes, DL resolution, or GERD may favor LRYGB, a higher BMI, no significant difference in the resolution of the remaining analyzed comorbidities, technical simplicity and the chance of, towards unsuccessful weight loss, carrying out a revisional procedure strongly favor LSG. Given the satisfactory weight loss and comorbidities resolution of these procedures, clinicians should also regard them as viable options in SO, aside from more complex procedures. This is a challenging disease demanding a tailored approach and in which the patient's thoroughly informed personal choices should be regarded as a major determinant. Our results emphasize the need for more studies analyzing the effect of these techniques in SO so that we can offer the best surgical and non-surgical treatments for these patients.

Appendix

In October 2020, a comprehensive electronic literature search was performed on PubMed, Cochrane Library, and Scopus databases. On Pubmed, the following search was carried out: ("bariatric surgery"[Title/Abstract] OR "gastric bypass"[Title/Abstract] OR "laparoscopic gastric bypass"[Title/Abstract] OR "laparoscopic sleeve gastrectomy"[Title/Abstract] OR "sleeve gastrectomy"[Title/

Abstract] OR "laparoscopic Roux-en-Y gastric bypass"[Title/Abstract] OR "open Roux-en-Y gastric bypass"[Title/Abstract] OR "Roux-en-Y gastric bypass"[Title/Abstract] OR "vertical banded gastroplasty-Roux-en-Y gastric bypass"[Title/Abstract] OR "gastric bypass"[MeSH Terms]) AND ("superobes*"[Title/Abstract] OR "super obes*"[Title/Abstract] OR "super super obes*"[Title/Abstract] OR "BMI ≥ 50"[Title/Abstract]). On Cochrane Library, an advanced search (Title Abstract Keyword) was conducted for: ("bariatric surgery" OR "gastric bypass" OR "laparoscopic gastric bypass" OR "laparoscopic sleeve gastrectomy" OR "sleeve gastrectomy" OR "laparoscopic Roux-en-Y gastric bypass" OR "open Roux-en-Y gastric bypass" OR "Roux-en-Y gastric bypass" OR "vertical banded gastroplasty-Roux-en-Y gastric bypass") AND ("superobese" OR "super obese" OR "super super obese" OR "BMI ≥ 50"). On Scopus, we also performed an advanced search with the following: TITLE-ABS-KEY(("bariatric surgery" OR "gastric bypass" OR "laparoscopic gastric bypass" OR "laparoscopic sleeve gastrectomy" OR "sleeve gastrectomy" OR "laparoscopic Roux-en-Y gastric bypass" OR "open Roux-en-Y gastric bypass" OR "Roux-en-Y gastric bypass" OR "vertical banded gastroplasty-Roux-en-Y gastric bypass") AND ("superobese" OR "super obese" OR "super super obese" OR "BMI ≥ 50")).

Declarations

Consent to Participate For this type of study, formal consent is not required.

Informed Consent Informed consent does not apply.

Competing Interests The authors declare no competing interests.

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B. IMPROVING OUTCOMES OF MBS

Early postoperative complications

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Scimago Journal Rank (SJR) indicator 1,127 (2022) H Index 152 | Rank 49 of 512 on Surgery journals (**Q1; Percentile 10**)

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Journal Impact Factor (JIF) 2,9 | Rank 63 of 213 on Surgery journals (**Q2**)

Journal Citation Indicator (JCI) 1,22 | Rank 41 of 286 on Surgery Journals (**Q1**)

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Early Postoperative Bleeding After Laparoscopic Roux-En-Y Gastric Bypass: a Single Center Analysis

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Abstract

Purpose Early postoperative bleeding is a common complication after laparoscopic Roux-en-Y gastric bypass (LRYGB) and is associated with significant morbidity. We aimed to identify predictors of early postoperative bleeding after LRYGB and characterize hemorrhagic events and 30-day postoperative outcomes.

Material and Methods We conducted a retrospective cohort study regarding all patients submitted to LRYGB in 2019 at a high-volume obesity center. Early postoperative bleeding was defined as any clinically significant evidence of hemorrhage in the early postoperative period. Demographic, preoperative, and intraoperative factors were evaluated for associations with postoperative bleeding. Postoperative outcomes were compared between patients with and without hemorrhage.

Results Of 340 patients submitted to LRYGB, 14 (4.1%) had early postoperative bleeding. Patients with bleeding had an increased preoperative left hepatic lobe diameter (8.4 vs. 7.3 cm, $p = 0.048$). Prior cholecystectomy (28.6 vs. 14.5%) and previous bariatric surgery (35.7 vs. 23.9%) tended to be more prevalent among these patients. Bleeding occurred at a median time of 31.2 [IQR 19.7–38.5] h. Thirteen patients presented with intraluminal bleeding and one with extraluminal bleeding. Melena was the most common symptom. All hemorrhages were clinically diagnosed, and 92.9% were managed conservatively. Postoperative bleeding was associated with longer hospital stay (3.5 vs. 2.0 days), higher reintervention (7.1 vs. 0%), and readmission (14.3 vs. 0%), all $p < 0.05$.

Conclusions Bleeding was the most frequent early complication after LRYGB. Patients with hepatomegaly and prior surgeries may have technically challenging LRYGB and should be carefully assessed. Perioperative strategies should be encouraged in high-risk patients to prevent bleeding.

Keywords Obesity · Bariatric surgery · Laparoscopic Roux-en-Y Gastric Bypass · Risk factors · Postoperative complications · Bleeding

Key Points

- Bleeding was the most frequent complication after LRYGB, with an incidence of 4.1%.
- Patients with bleeding had an increased preoperative left hepatic lobe diameter.
- Bleeding was conservatively managed in 92.9% of the patients.
- Bleeding resulted in longer hospital stay, higher reintervention, and readmission.

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Introduction

Laparoscopic Roux-en-Y gastric bypass (LRYGB) is one of the most commonly performed metabolic procedures worldwide [1] given its effectiveness in preventing or improving obesity-related comorbidities and its capability of promoting a sustained reduction of the body mass index (BMI) [2]. The safety of LRYGB has improved in recent years [3, 4]. Nevertheless, as the number of performed procedures continues to increase, the number of patients presenting with complications in the postoperative period cannot be overlooked, even with low complication rates [5, 6].

Postoperative bleeding is one of the most common complications in the early postoperative period after LRYGB [7]. Though usually self-limited, it may lead to significant

morbidity and even present as a surgical emergency. Patients with postoperative hemorrhage are more likely to have adverse outcomes, such as a longer hospital stay, higher 30-day mortality, and higher rates of additional postoperative complications [8].

Therefore, the identification of risk factors for early postoperative bleeding may enhance the prevention and treatment of this complication. Also, the recognition of these predictors enables the surgical team to foresee which patients will need more active and close surveillance in the early postoperative period.

Hence, our objectives are to identify potential predictors of early postoperative bleeding after LRYGB and characterize early postoperative hemorrhagic events and 30-day postoperative outcomes.

Materials and Methods

Study Design

We conducted a cohort study that included patients who underwent LRYGB from January 1 to December 31 of 2019 at a specialized high-volume obesity center.

The inclusion criteria were adult patients (> 18 years old) submitted to primary or revisional LRYGB during 2019. The number of eligible patients determined the sample size. For all participants, we retrospectively reviewed the electronic records regarding demographic, preoperative, intraoperative, and postoperative outcomes.

Demographic data included age, sex, BMI, and waist and hip circumference before surgery. Preoperative variables included coexisting comorbidities, medication history, laboratory data, abdominal ultrasound findings, and prior surgeries. Intraoperative variables included concurrent procedures, gastric remnant resection, conversions to open surgery, intraoperative complications, and surgery duration. For the postoperative analysis, we evaluated the length of hospital stay, postoperative complications, surgical reintervention, readmission, and mortality in the early postoperative period, defined as 30 days after LRYGB. Weight outcomes at 6 and 12 months after surgery were also collected.

All obesity-related comorbidities and postoperative complications were defined according to ASMBS and SOARD outcome reporting standards [9].

All patients were screened for bleeding and clotting disorders with a pre-operative analytical study that included, among other parameters, an hemogram with platelet count and a coagulation study. No patients with abnormal parameters were found or included in our study. Only patients with postoperative hemorrhage did complete blood count and coagulation testing after surgery.

Postoperative bleeding was defined as any clinical evidence of hemorrhage — hematemesis, hematochezia, melena, or significant hematic abdominal drainage associated with signs of hemodynamic compromise — in the early postoperative period.

In the group of patients with postoperative bleeding, further clinical details were collected: interval from surgery to evidence of bleeding, clinical symptoms and signs presented, postoperative hematocrit, hemorrhagic source (intraluminal or extraluminal), the volume of blood drainage (abdominal drain was placed per-protocol) and performed treatments.

LRYGB Procedure

LRYGB was performed as a standardized technique, with a small gastric pouch (30 cc), calibrated 36 Fr gastro-jejunal anastomosis, biliopancreatic limb of 100 cm, and alimentary limb of 120 cm. Both anastomoses were performed with an automatic stapler device (blue color recharge, 1.5-mm height), tested for leaks using methylene blue dye, and the mesenteric defects were closed. Reinforcement of the stapler line was not routinely used.

Systematically, it was placed an abdominal drain at the end of the procedure. The drain was removed in the second day after surgery if there was no evidence of active bleeding, non-hematic drainage, and drainage volume < 150 cc/24 h.

Venous Thromboembolism (VTE) Prevention

All patients received a single dose of prophylactic (40 mg) low molecular weight heparin (LMWH) in the day before surgery. After the procedure, LMWH was administered once a day, for 2 weeks. On the admission, all patients were instructed to put elastic compression socks. They were also encouraged to wander in the ward during the peri-operative period.

Statistical Analysis

Categorical variables were presented as absolute values and percentages (%), and continuous variables were expressed as means $\pm$ standard deviation (SD) or medians and interquartile range [IQR] if not normally distributed. In the case of missing values, given percentages relate to the effective total number of available data. Variables with more than 30% of missing values were marked and the total number of patients analyzed was reported.

All demographic, preoperative, and intraoperative variables were evaluated for potential associations with early postoperative bleeding, and postoperative outcomes were compared between patients with and without bleeding. Categorical variables were compared using Pearson's chi-squared and Fisher's exact test. For continuous variables, we used

Mann–Whitney *U* test if non-normally distributed and Student's *t*-test if normally distributed. $P < 0.05$ was considered significant. All statistical analyses were performed using the IBM® SPSS version 26.0 software package for macOS.

Results

In 2019, 520 patients underwent metabolic surgery at our obesity center. A total of 340 (65.4%) patients underwent LRYGB and were included in this study. Early postoperative complications occurred in 19 (5.6%) patients. Early postoperative bleeding (EPB) was the most common complication, present in 14 patients (4.1%). Other complications included surgical site infection, systemic infections, and acute kidney injury.

Baseline Characteristics

The median age of the participants was 46 (*IQR* 40–54) years. The median BMI was 42.3 (*IQR* 39.2–45.3) kg/m², and 302 (88.8%) patients were female. Eighty-three (24.4%) were submitted to revisional LRYGB. There were no conversions to open surgery. Table 1 summarizes the baseline demographic, preoperative, and intraoperative variables. Demographics and relevant preoperative risk factors were not significantly different between patients with and without EPB. One patient with end-stage renal disease (ESRD) experienced EPB, making estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m² significantly associated with bleeding (1 vs. 0, $p = 0.043$). Among intraoperative factors, the left hepatic lobe diameter was significantly increased (8.4 vs. 7.3 cm) in patients with EPB. Prior cholecystectomy (28.6 vs. 14.5%) and previous bariatric surgery (35.7 vs. 23.9%) tended to be more prevalent among patients with hemorrhage.

Early Postoperative Bleeding Events

EPB occurred at a median time of 31.2 (*IQR* 19.7–38.5) h after surgery. Thirteen out of the 14 patients presented with typical gastrointestinal bleeding symptoms and were classified as intraluminal bleedings. Melena was the most common symptom (57.1%), followed by hematochezia (50%). Three patients (21.4%) presented with both hematochezia and melena. Table 2 compiles the clinical presentation and management of the bleeding events. A clinical diagnosis was established in all EPB, supported by serial laboratory assessments of hemoglobin and hematocrit. Conservative measures were successful in the management of 92.9% of the patients. General supportive measures included nil per os, withholding of prophylactic antithrombotic agents, volume resuscitation, proton pump inhibitors, and anti-emetics

if hematemesis was present. Coagulation tests and platelet count were re-evaluated. Six (42.9%) patients needed aminocaproic acid or vitamin K in addition to the general supportive measures. Other six (42.9%) patients received a median of 2.5 ± 2.0 units of packed red blood cells. No patient required endoscopic procedures for diagnosis or treatment. Only the patient with extraluminal bleeding required surgical reintervention. This patient had a BMI of 51.7 kg/m², underwent primary LRYGB, and presented 23 h after surgery with a high volume of hematic drainage and hemodynamic compromise. For detailed information about all EPB events, see supplementary Table 2.

Postoperative Outcomes

EPB was associated with a longer median postoperative length of stay (3.5 vs. 2.0 days), a higher reintervention (7.1 vs. 0%), and higher readmission (14.3 vs. 0%) in the early postoperative period (Table 3). No patient died during the 30-day follow-up period.

Total weight loss (TWL) and excess weight loss (EWL) at 6 and 12 months were not significantly different between patients with and without postoperative bleeding.

Discussion

Here, we report data on early postoperative bleeding after LRYGB in a high-volume center exclusively dedicated to metabolic surgery. Patient-related predictors statistically associated with hemorrhage were severely decreased eGFR and increased diameter of the left hepatic lobe, whereas several other factors were found to be more prevalent among patients with EPB, although a significant association could not be found. We reviewed post-LRYGB bleeding events in detail: 85.7% of the patients presented with hemorrhage within the first 48 h after surgery, melena and hematochezia were the most common presentation, all hemorrhagic events were clinically diagnosed, and 92.9% of the events were conservatively managed. Postoperative outcomes analysis revealed that bleeding after LRYGB was associated with a longer hospital stay, a higher reintervention, and higher readmission in 30 days after surgery.

Early postoperative bleeding after LRYGB occurred in 4.1% of all patients. Zafar et al. found a hemorrhage incidence of 1.51% in their series of 43,280 patients [8], and Susmallian et al. reported a bleeding incidence of 3.05% [10]. Unlike these studies, our definition of EPB is more liberal and includes all hemorrhagic events regardless of the severity and treatment performed, without exclusion of EPB that did not result in transfusion or reintervention. With this approach, we report all clinically significant EPB, minimizing selection bias. When the same definition was

Table 1 Baseline demographic, preoperative, and intraoperative factors among patients with and without early postoperative bleeding

	All patients <i>N</i> (%) = 340 (100)	Patients with bleeding <i>N</i> (%) = 14 (4.1)	Patients without bleeding <i>N</i> (%) = 326 (95.9)	<i>P</i> -value
Demographics				
Age, y	46 [40–54]	47 [40–52]	46 [40–54]	0.921
Sex				0.197
Female	302 (88.8)	11 (78.6)	291 (89.3)	
Male	38 (11.2)	3 (21.4)	35 (10.7)	
BMI, kg/m ²	42.3 [39.2–45.3]	41.7 [38.9–44.8]	42.4 [39.3–45.4]	0.479
Waist-hip ratio (<i>n</i> = 210) ^a	0.92 [0.87–0.98]	0.95 [0.88–0.99]	0.92 [0.87–0.98]	0.552
Preoperative factors				
Coexisting comorbidities				
Diabetes	95 (27.9)	4 (28.6)	91 (27.9)	1.000
Hypertension	158 (46.5)	5 (35.7)	153 (46.9)	0.410
Dyslipidemia	154 (45.3)	5 (35.7)	149 (45.7)	0.462
Obstructive sleep apnea	58 (17.1)	1 (7.1)	57 (17.5)	0.525
GERD	63 (19.7)	5 (35.7)	58 (19.0)	0.162
Esophagitis	42 (13.3)	3 (23.1)	39 (12.9)	0.393
Severe hepatic steatosis	78 (25.8)	4 (33.3)	74 (25.5)	0.514
Gallstone disease	36 (10.8)	1 (7.1)	35 (10.9)	1.000
Arrhythmia	15 (4.4)	0	15 (4.6)	1.000
Prior deep vein thrombosis	5 (1.5)	0	5 (1.5)	1.000
Active smoking	39 (13.2)	3 (21.4)	36 (12.8)	0.408
Depression	109 (32.1)	5 (35.7)	103 (31.6)	0.765
Medication history				
Therapeutic anticoagulation	4 (1.2)	0	4 (1.2)	1.000
Acetylsalicylic acid	15 (4.4)	1 (7.1)	14 (4.3)	0.476
Chronic Glucocorticoid	2 (0.6)	0	2 (0.6)	1.000
Weight-loss pharmacotherapy	34 (10.4)	0	34 (10.9)	0.377
Laboratory results				
Hematocrit				0.334
Female	40.1 ± 2.6	41.1 ± 2.4	40.1 ± 2.6	
Male	43.0 ± 3.5	41.8 ± 7.6	43.1 ± 3.1	
PT > UNL, seconds (<i>n</i> = 112) ^a	13 (11.6)	1 (12.5)	12 (11.5)	1.000
aPTT > UNL, seconds (<i>n</i> = 113) ^a	3 (2.7)	0	3 (2.9)	1.000
eGFR, mL/min/1.73m ²	98.9 [80.5–119.2]	95.4 [87.3–120.7]	98.9 [80.5–119.1]	0.952
Intraoperative factors				
Left Hepatic lobe diameter, cm	7.3 [6.6–8.5]	8.4 [8.0–9.0]	7.3 [6.5–8.4]	0.048*
Prior cholecystectomy	51 (15.1)	4 (28.6)	47 (14.5)	0.241
Prior bariatric surgery	83 (24.4)	5 (35.7)	78 (23.9)	0.343
AGB	73 (21.5)	4 (28.6)	69 (21.2)	
SG	10 (2.9)	1 (7.1)	9 (2.8)	
Concurrent procedure	11 (3.2)	1 (7.1)	10 (3.1)	0.375
Cholecystectomy	10 (2.9)	1 (7.1)	9 (2.8)	
Other	1 (0.3)	0	1 (0.3)	
Gastric remnant resection	8 (2.4)	0	8 (2.5)	1.000
Intraoperative complications	4 (1.2)	0	4 (1.2)	1.000
Surgery duration, min	95.0 [79.5–117.0]	93.0 [72.0–113.0]	95.0 [80.0–117.0]	0.743

Values for categorical variables are given as number (percentage); values for continuous variables as mean ± standard deviation if normally distributed or median [interquartile range] if non-normally distributed. Categorical variables were compared using Pearson's chi-squared and Fisher's exact test. Continuous variables were compared using Mann–Whitney *U* test if non-normally distributed and Student's *t*-test if normally distributed. *P* < 0.05 was considered significant

*Statistically significant result

^aMissing values superior to 30%

Abbreviations: y years, *BMI* body mass index, *GERD* gastroesophageal reflux disease, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *UNL* upper normal limit; *eGFR* estimated glomerular filtration Rate (Cockcroft-Gault equation using ideal body weight), *cm* cen-

Table 1 (continued)timeters, *AGB* adjustable gastric banding, *SG* sleeve gastrectomy, *min* minutes**Table 2** Clinical presentation and management of patients with post-operative bleeding

Characteristics	<i>N</i> (%) = 14 (4.1)
Time to bleeding, hours	
< 24	6 (42.9)
24–48	6 (42.9)
> 48	2 (14.3)
Symptoms/signs ^a	
Hematochezia and/or melena	12 (85.7)
Hematemesis	3 (21.4)
Tachycardia	3 (21.4)
Hypotension	4 (28.6)
Abdominal pain	5 (35.7)
Others (acid–base disturbances, fever or acute kidney injury)	3 (21.4)
Diagnostic modality	
Clinical diagnosis	14 (100)
Decrease in hematocrit	13.4 ± 3.0
Bleeding site	
Intraluminal	13 (92.9)
Extraluminal	1 (7.1)
Treatment ^a	
General supportive measures only	5 (35.7)
Drug therapy to stop bleeding	6 (42.9)
Blood transfusion	6 (42.9)
Endoscopic treatment	0
Reintervention	1 (7.1)
Severity	
Minor	8 (57.1)
Major	6 (42.9)

^aSeveral patients presented with more than one clinical feature and/or required multiple therapies

used, Dick et al. reported a bleeding incidence of 3.3% [11] and Bellorin et al. 3.86% [12], similar to our incidence of 4.1%. However, we must say that for the American College of Surgeons, only hemorrhages requiring transfusions should be considered [13, 14].

We hypothesized that demographic, preoperative, and intraoperative risk factors could predict bleeding after LRYGB. In our analysis, demographic factors were not significantly different between patients with and without EPB. Noteworthy, median BMI was similar between the two groups of patients, coincident with previous studies that reported that an increased BMI was not associated with more bleeding [10, 15].

We did not find traditional hemorrhage-associated comorbidities and medication to be more prevalent in the bleeding group. These conditions have previously been associated with EPB, including diabetes [15], hypertension [16], history of deep vein thrombosis [8], therapeutic anticoagulation [8], chronic glucocorticoid treatment [17], and prolonged partial thromboplastin time [18]. In our center, all patients received a preoperative evaluation for optimal control of high-risk comorbidities. Our findings could reflect how adequate perioperative comorbidities management impacts bleeding risk reduction.

Only one patient in our series had ESRD and its postoperative period was complicated by bleeding. For this reason, the association found between EPB and severely decreased eGFR must be carefully analyzed. Nevertheless, ESRD has been associated with a higher risk of post-bariatric surgery complications [19], and renal insufficiency has already been reported as an independent risk factor for bleeding [8]. Decreased eGFR reflects global decreased kidney function, which is associated with well-established hemorrhagic risk

Table 3 Outcome data analysis of patients with and without postoperative bleeding

	All patients <i>N</i> (%) = 340 (100)	Patients with bleeding <i>N</i> (%) = 14 (4.1)	Patients without bleeding <i>N</i> (%) = 326 (95.9)	<i>P</i> -value
Length of stay, days	2.0 [2.0–2.0]	3.5 [3.0–4.0]	2.0 [2.0–2.0]	< 0.001*
Reintervention within 30 days	1 (0.3)	1 (7.1)	0	0.041*
Readmission within 30 days	2 (0.6)	2 (14.3)	0	0.002*
TWL at 6 months, %	28.2 [23.0–32.4]	26.3 [23.3–28.7]	28.3 [23.0–32.4]	0.393
TWL at 12 months, %	35.7 [30.6–40.5]	33.2 [27.7–40.3]	35.8 [30.6–40.5]	0.360
EWL at 6 months, %	69.6 ± 19.4	67.9 ± 23.9	69.7 ± 19.2	0.729
EWL at 12 months, %	87.8 ± 21.3	87.1 ± 30.6	87.8 ± 20.9	0.903

TWL total weight loss, EWL excess weight loss

*Statistically significant result

factors, especially in later stages of the disease [20]. Lower hematocrit levels, prolonged bleeding time, and platelet dysfunction are all present in ESRD. Therefore, we must acknowledge the elevated risk of postoperative bleeding in these patients.

We found that the median left hepatic lobe diameter, measured preoperatively by abdominal ultrasound, was significantly increased in patients with EPB. To our knowledge, no previous studies have reported the relationship between hepatomegaly and post-LRYGB bleeding. We believe that the mechanism underlying this association is mainly related to the surgical technique. Retraction of the liver's left lobe is an essential step in LRYGB to ensure good operating exposure and an adequate working space [21]. An increased diameter of the left hepatic lobe can hinder liver retraction and compromise several steps of the LRYGB procedure: the stomach division, the creation of the gastrojejunostomy, and the closure of the staple line of the gastric remnant. Hence, a larger left hepatic lobe could increase the technical difficulty of the LRYGB procedure and be associated with more EPB events. We may speculate that strategies to reduce hepatomegaly, such as preoperative low-carbohydrate diets, may reduce this EPB risk factor. Also, patients with severe hepatomegaly may benefit from evaluation by gastroenterologists/hepatologists to exclude chronic liver disease or portal hypertension.

Other preoperative factors that foresee a technically challenging LRYGB tended to be more prevalent among patients with postoperative bleeding. Prior cholecystectomy had been performed in 28.6% of patients with EPB vs. 14.5% of the patients without EPB. Also, in the EPB group, 35.7% of patients had already undergone a previous bariatric procedure against 23.9% of the patients without bleeding. Revisional surgery is a well-known predictor of EPB [8], and our results support the hypothesis that patients with predictable technically difficult LRYGB should be carefully assessed because of their risk of EPB.

On the other hand, intraoperative concomitant procedures and complications were not more prevalent nor statistically different between the two groups of patients, concurring with previous studies [8].

Analyzing post-LRYGB bleeding events, we conclude that EPB always occurred in the first 3 days after surgery, coinciding with previous reports [22]. This 3-day interval should be considered the maximum risk time interval for suspicion of EPB. All patients should be evaluated for: [1] typical gastrointestinal bleeding clinical features and hemodynamic stability, [2] hemoglobin and hematocrit levels, and [3] volume and characteristics of abdominal drainage. In our center, all patients with EPB were diagnosed through these three simple steps, and we believe that additional diagnostic studies are usually unnecessary. Bellorin et al. reported that even when bleeding was extraluminal, it was clinically

confirmed by a sizeable bloody drain output and drop in hematocrit level [12]. This strengthens our view that the initial approach of EPB can be made only by clinical assessment and that our approach effectively distinguishes between intraluminal and extraluminal bleeding if drain is placed per protocol.

Regarding EPB management, all intraluminal bleedings were approached conservatively, with supportive care and blood transfusions, and only the patient with extraluminal hemorrhage needed reintervention. Endoscopy has been described as an effective therapeutic tool and has been included in treatment algorithms for patients with severe intraluminal EPB [23]. Yet, no patient required endoscopic treatment in our center, and Heneghan et al. [22] reported the same in their series. Thus, our opinion is that, though effective, endoscopic treatment plays a limited role in most EPB patients.

Hospitalization of patients with EPB was, in median, more than one and a half days longer, and only patients with EPB had to be reoperated and readmitted in the early postoperative period. These findings demonstrate that EPB is an important cause of morbidity and is associated with several adverse outcomes. Still, TWL and EWL at 6 and 12 months after surgery were not significantly different between the two groups, indicating that the efficacy of LRYGB is not affected by an early hemorrhagic event.

Our analysis has some limitations. Firstly, the preoperative variables were collected by reviewing the preoperative surgery, endocrinology, and psychiatry appointments undertaken by all patients submitted to LRYGB. The accuracy of gathered data was dependent on what was reported in medical records, and we present a retrospective analysis of data that different clinicians collected. Also, the time interval from preoperative assessment to surgery was not equal between participants, with a risk of information bias. Secondly, we assumed that all patients with early postoperative complications after the discharge date were evaluated at our center. This could have underestimated the number of complications. However, 6-month postoperative appointment records were reviewed to confirm any unreported complication. Thirdly, the effect of over suture, glues, clips, or buttress staple line reinforcement was not evaluated since these were not routinely performed. We must reinforce that this is an important issue debated in literature [11, 22, 24]. Nevertheless, we were able to identify relevant risk factors and presented EPB impact in the early postoperative outcomes from a high-volume obesity center. Our outcomes analysis concurred with multicentric studies reports on EPB in LRYGB, acknowledging the generalizability of our postoperative findings.

To conclude, early postoperative bleeding was the most common complication after LRYGB, with a significant 4.1% incidence. Postoperative bleeding events are associated

with increased morbidity and a costly postoperative period. Patients with severely decreased eGFR and predictable technically complex LRYGB must be judiciously evaluated to prevent early bleeding. Preoperative optimization of hemorrhagic risk factors is an essential step in the preoperative assessment of these patients. If postoperative bleeding still occurs, astute clinical observation is the diagnosis hallmark, and the presence of early hemorrhagic events does not reduce LRYGB efficacy.

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Declarations

Ethics Approval This study was approved by the Health Ethics Committee of our hospital (deliberation no. 46/2021).

Informed Consent Informed consent does not apply.

Conflict of Interest The authors declare no competing interests.

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C. FROM THE METABOLIC CHANGES TO THE SURGICAL ASPECTS

Associated surgical procedures

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Scimago Journal Rank (SJR) indicator 1,083 | H Index 159 | Rank 55 of 549 on Surgery journals (**Q1**)

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Journal Impact Factor (JIF) 2,9 | Rank 49 of 290 on Surgery journals (**Q1**) Journal Citation Indicator (JCI) 1,24 | Rank 42 of 290 on Surgery journals (**Q1**) (Thomson-Reuters, Science Citation Index Expanded (SCIE), 2023)



The Impact of Cholecystectomy in Patients with Post-Bariatric Surgery Hypoglycemia

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Abstract

Background Metabolic surgery is the foremost treatment for obesity and its associated medical conditions. Nonetheless, post-bariatric hypoglycemia (PBH) emerges as a prevalent complication. PBH pathophysiology implicates heightened insulin and glucagon-like peptide 1 (GLP-1) levels, with bile acids (BA) contributing to GLP-1 release. A plausible association exists between cholecystectomy and PBH, which is attributed to alterations in BA metabolism and ensuing hormonal responses. The objective of this retrospective cohort study was to evaluate the impact of cholecystectomy on PBH pharmacological treatment, diagnostic timelines and metabolic parameters.

Materials and methods Patients diagnosed with PBH after bariatric surgery were evaluated based on their history of cholecystectomy. Demographic, anthropometric and clinical data were collected. Mixed meal tolerance tests (MMTT) results were compiled to assess metabolic responses.

Results Of the 131 patients with PBH included in the study, 29 had prior cholecystectomy. The time to PBH diagnosis was similar across groups. Patients with prior cholecystectomy required higher doses of acarbose ($p = 0.046$), compared to those without prior cholecystectomy. Additionally, MMTT revealed higher insulin ($t = 60$ min: $p = 0.010$ and $t = 90$ min: $p = 0.034$) and c-peptide levels ($t = 60$ min: $p = 0.008$) and greater glycemic variability in patients with prior cholecystectomy ($p = 0.049$), highlighting the impact of cholecystectomy on glucose metabolism.

Conclusion Our study offers novel insights into PBH pharmacotherapy, indicating that PBH patients with a history of cholecystectomy require elevated doses of acarbose for symptom control than PBH patients without such surgical history. Furthermore, our findings underscore the pivotal role of hyperinsulinism in PBH aetiology, emphasizing the significance of the BA-GLP-1-insulin axis.

Key Points

Patients with post-bariatric hypoglycemia (PBH) post-cholecystectomy need higher acarbose doses for symptom control. Cholecystectomy impacts glucose metabolism, emphasizing BA-GLP-1-insulin axis.

Patients with PBH post-cholecystectomy exhibit elevated insulin and glycemic variability.

Cholecystectomy influences glucose control in PBH.

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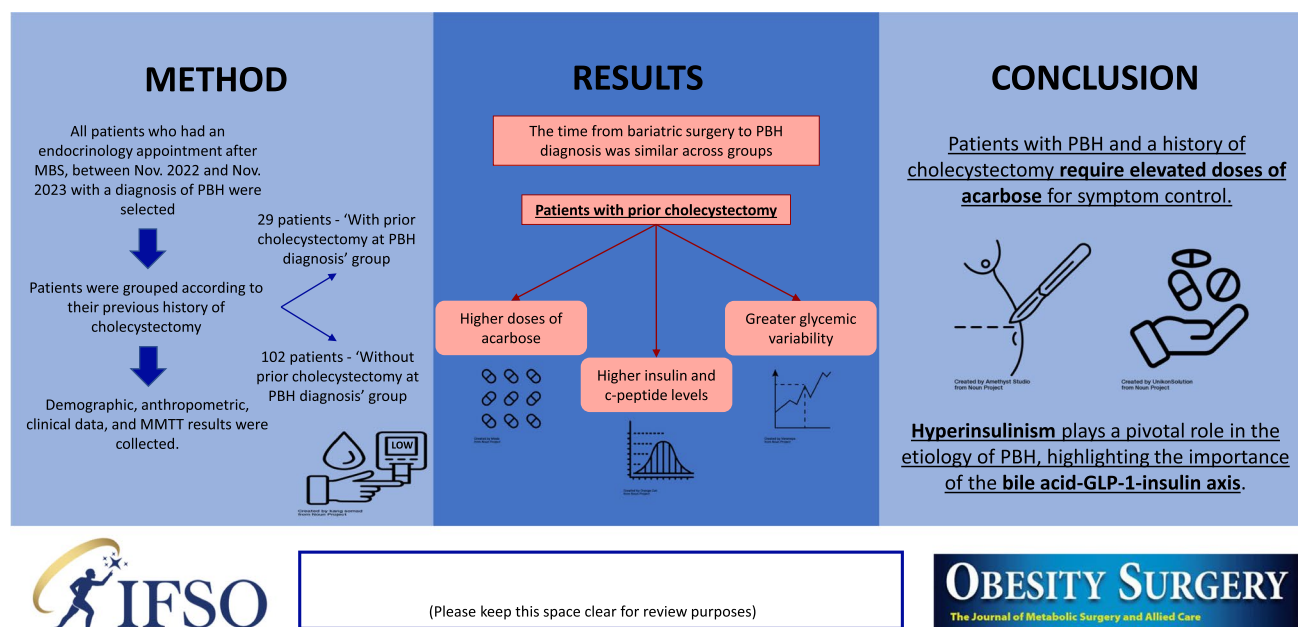
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Graphical Abstract

The impact of cholecystectomy in patients with post-bariatric surgery hypoglycemia



Keywords Post-bariatric hypoglycemia · Cholecystectomy · Bariatric surgery · Acarbose · Glucose metabolism · Bile acids · Glucagon-like peptide 1

Introduction

Metabolic and bariatric surgery (MBS), which encompasses a wide range of possible techniques, the main ones being Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), has proven to be the most effective and long-lasting treatment for obesity and its associated medical conditions [1]. However, despite the many advantages of this procedure, patients undergoing metabolic surgery, particularly RYGB, can develop some complications, such as post-bariatric surgery hypoglycemia (PBH) and dumping syndrome [2].

The definition of PBH is controversial. Nevertheless, most definitions include a symptomatic hypoglycemic event one to three hours after a meal [3]. This condition has a substantial impact on quality of life and can lead to overeating, thus increasing patients' weight [4]. More than a third of patients undergoing MBS report symptoms of postprandial hypoglycemia [5]. Nonetheless, severe hypoglycemic episodes occur in less than 12% of patients [6]. PBH is thought to occur several months or even years after metabolic surgery [7].

The physiology of PBH is not yet fully understood, but seems to be explained by the high levels of insulin and glucagon-like peptide 1 (GLP-1) that occur after metabolic surgery. This increase is presumed to be triggered by rapid

gastric emptying, leading to an acute glycemic peak. The beta cells of the pancreatic islets are hyperstimulated and consequently release insulin, causing a marked decrease in plasma glucose [8].

The gallbladder plays a crucial role in bile acid (BA) homeostasis. However, cholecystectomy is a procedure performed with high frequency in patients undergoing metabolic surgery, both before and after surgery [9]. One of the consequences of cholecystectomy is an increase in the enterohepatic recycling of BA, increasing their plasma concentration [10]. Following cholecystectomy in patients with history of MBS, postprandial levels of insulin and C4 (a marker of hepatic BA synthesis) are two to three times higher than those of patients with history of MBS who did not undergo cholecystectomy [11]. The metabolism of BA after MBS is not fully known, but it is recognised that they act on cells in the intestinal wall by activating the farnesoid x receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), which potentiates the release of GLP-1 [12]. BA also induce an increase in the fibroblast growth factor (FGF19) concentration, which in turn enhances glycogen synthesis [13].

There is a paramount importance to understand the significance of cholecystectomy in patients diagnosed with PBH; however, there is very little scientific evidence on this subject.

The objective of this study was to assess the impact of cholecystectomy in patients with PBH. To do this, we sought to evaluate possible differences in the time interval between MBS and the onset of PBH, in the results of mixed-meal tolerance tests (MMTT) and also the requirement and dose of pharmacologic interventions to control hypoglycemic symptoms in patients with PBH, with or without cholecystectomy at the diagnosis of PBH.

Materials and Methods

Patients

All patients who had an endocrinology appointment after MBS at our centre, between November 2022 and November 2023, were screened, and those with a diagnosis of PBH were selected ($N=131$).

We considered a diagnosis of PBH to be the existence of a history of autonomic and/or neuroglycopenic symptoms at least 6 months after MBS, concomitantly associated with a plasma glucose level <55 mg/dL 1 to 3 h after a meal. Symptoms subside upon restoration of plasma glucose concentration to physiological levels [3]. Plasma glucose levels during symptomatic episodes were reported by patients ($n=32$) or objectified during MMTT ($n=65$) with a standardised liquid meal (Fresubin Energy Drink, 200 ml, 300 kcal [50E% carbohydrate, 15E% protein and 35E% fat]; Fresenius Kabi Deutschland, Bad Homburg, Germany), based on macronutrient composition in accordance with post-bariatric surgery nutritional recommendations [14, 15]. Additionally, hyperinsulinemia (plasma insulin levels >50 μ U/L) during the MMTT was one of the criteria used to support the diagnosis of PBH [16]. On the one hand, headaches, muscle weakness, difficulty concentrating, confusion, convulsions, slurred speech, coma, or altered state of consciousness were all considered to be neuroglycopenic symptoms. On the other hand, sweating, tremors, palpitations, paresthesia and hunger were considered to be autonomic symptoms [16–18]. All patients reported at least one of the above-mentioned symptoms.

Inclusion criteria included a history of previous MBS (RYGB [$n=120$] or SG [$n=11$]), stable weight (defined as a change of less than 10% over the last 6 months), HbA1c $<6.5\%$ and fasting plasma glucose <126 mg/dL at the time of diagnosis of PBH. Exclusion criteria were ongoing pregnancy, taking antidiabetics (except in the case of PBH treatment), diagnosis of diabetes after MBS, history of gastrointestinal surgery (except in the case of MBS and cholecystectomy), chronic kidney disease, or previous diagnosis of any medical condition that could lead to postprandial hypoglycemia.

This was a retrospective cohort study. The study protocol was reviewed and approved by the local Ethics Committee (403–2023).

The following data was acquired from the electronic medical records for all the patients: demographics, anthropometrics, clinical presentation of symptomatic hypoglycemic episodes, history of cholecystectomy, laboratory data, information of MBS and also the time interval between surgery and the onset of hypoglycemia and therapy.

Study Groups

Patients were selected and grouped according to their previous history of cholecystectomy. Those patients who had undergone cholecystectomy before the diagnosis of PBH were allocated to the ‘With prior cholecystectomy at PBH diagnosis’ group ($n=29$; a total of 21 patients had prior cholecystectomy to MBS [the median time between cholecystectomy and MBS was 15.9 months] and 8 patients who had undergone cholecystectomy after MBS [the median time between MBS and cholecystectomy was 63.4 months]), and the remaining patients, including those who had undergone cholecystectomy after diagnosis of PBH ($n=7$), were allocated to the ‘Without prior cholecystectomy at PBH diagnosis’ group ($n=102$).

Calculations

The percentage of total weight loss (%TWL) was calculated as [(preoperative weight – weight at PBH diagnosis) $\div$ (weight at PBH diagnosis) $\times 100$] and the percentage of excess body mass index (BMI) loss (%EBMI) was determined as [(preoperative BMI – BMI at PBH diagnosis) $\div$ (preoperative BMI – 25) $\times 100$], with 25 kg/m² as the target BMI.

Homeostasis model assessment indexes (HOMA2) were determined using the HOMA Calculator version 2.2.3 (<http://www.dtu.ox.ac.uk>, accessed January 2024), which measures beta cell function (HOMA2-B), peripheral insulin sensitivity (HOMA2-S) and insulin resistance (HOMA2-IR).

The nadir corresponds to the minimum value during the MMTT, and the peak corresponds to the maximum value during the MMTT.

The maximum-to-minimum glucose ratio (MMGR) was calculated to evaluate plasma glucose variation (maximum glycemic value $\div$ minimum glycemic value, during the MMTT).

Statistical Analysis

All analyses were carried out using Stata® IC 15.1 (Stata Corp, College Station, TX, USA).

Continuous data were summarised as being mean $\pm$ standard deviation if the variables were normally

distributed or median and interquartile ranges if the variables did not follow a normal distribution. Normality of continuous variables was assessed using the Shapiro–Wilk test. In the case of continuous variables that follow a normal distribution, the two groups were compared using Student's *t*-test and for those who did not follow a normal distribution, we used Kruskal–Wallis test. Categorical data were presented as counts and proportions and were compared using Pearson χ^2 .

All *p* values < 0.05 were considered to be statistically significant.

Results

The characteristics of patients with and without prior cholecystectomy at PBH diagnosis are summarised in Table 1. The age at PBH diagnosis and the age at MBS in patients with prior cholecystectomy was slightly higher than those of patients without prior cholecystectomy ($p=0.008$ and $p=0.029$, respectively). No statistically significant differences were found in the other demographic or anthropometric parameters. A total of 21 individuals had been diagnosed with type 2 diabetes prior to MBS. The levels indicating beta cell function (HOMA2-B), insulin sensitivity (HOMA2-S) and peripheral insulin resistance (HOMA2-IR) were not

significantly different between the two groups ($p=0.832$, $p=0.703$ and $p=0.741$, respectively).

Metabolic Responses During MMTT

Fasting glucose levels, peak and nadir during the MMTT were similar between the two groups ($p=0.692$, $p=0.400$ and $p=0.109$, respectively, Table 2). No differences were observed at minutes 30, 60, 90 and 120 (Fig. 1A). However, glycemic variability showed statistically significant differences between the two groups, with the MMGR being 24% higher in the group 'with prior cholecystectomy' ($p=0.049$, Table 2).

The 'with prior cholecystectomy' group had significantly higher insulin levels ($t=60$ min: $p=0.010$ and $t=90$: $p=0.034$) (Fig. 1B). However, despite this, there were no differences in fasting and peak insulin levels ($p=0.653$ and $p=0.446$, respectively, Table 2).

C-peptide levels showed a similar trend to insulin, with significantly higher levels in the 'with prior cholecystectomy' group at minute 60 ($p=0.008$, Fig. 1C). At minutes 30, 90 and 120, the levels of c-peptide were also higher in the 'with prior cholecystectomy' group, although the differences were not statistically significant ($p=0.758$, $p=0.063$ and $p=0.406$, respectively, Fig. 1C). C-peptide parameters, such as fasting levels, peak and nadir, were comparable

Table 1 Patient characteristics, overall and according to prior cholecystectomy at PBH diagnosis

	Total [n = 131]	Without prior cholecystectomy at PBH diagnosis [n = 102]	With prior cholecystectomy at PBH diagnosis [n = 29]	<i>p</i> value
Female, <i>n</i> (%)	120 (91.6)	92 (90.2)	28 (96.6)	0.276
Age at MBS, years	40.41 ± 9.57	39.44 ± 9.30	43.83 ± 9.88	0.029
RYGB, <i>n</i> (%)	120 (91.6)	92 (90.2)	28 (96.6)	0.521
History of T2DM before MBS, <i>n</i> (%)	21 (16.0)	16 (15.7)	5 (17.2)	0.840
BMI before MBS (Kg/m ²) ^a	42.00 (38.65, 45.34)	41.91 (38.57, 45.31)	42.32 (39.45, 46.20)	0.797
BMI at PBH diagnosis (Kg/m ²)	27.00 (25.02, 30.50)	27.15 (24.77, 30.80)	26.90 (25.85, 29.70)	0.896
Age at PBH diagnosis, years	43.18 ± 9.68	42.00 ± 9.26	47.34 ± 10.14	0.008
%EBMIL (%) ^a	83.99 ± 24.65	84.32 ± 24.95	82.81 ± 23.98	0.773
%TWL (%) ^a	53.34 ± 22.47	53.72 ± 21.91	52.00 ± 24.66	0.719
HOMA2-B (%) ^b	97.70 (76.20, 129.70)	97.40 (75.90, 130.00)	98.20 (77.60, 114.60)	0.832
HOMA2-S (%) ^b	128.60 (89.20, 202.30)	128.60 (89.20, 202.30)	127.55 (94.50, 188.30)	0.703
HOMA2-IR ^b	0.78 (0.49, 1.12)	0.78 (0.49, 1.12)	0.79 (0.53, 1.06)	0.741

Data are presented as means ± SD or median (25th percentile, 75th percentile) or number (%). Statistically significant differences (*p* value < 0.05) are highlighted in bold

PBH, post-bariatric surgery hypoglycemia; MBS, metabolic and bariatric surgery; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus; BMI, body mass index; EBMIL, excess BMI loss; TWL, total weight loss; HOMA2-B, homeostasis model assessment for β -cell function; HOMA2-S, homeostasis model assessment for insulin sensitivity; HOMA-IR, homeostasis model assessment for insulin resistance

^aBMI before MBS was unknown for one patient in the 'Without prior cholecystectomy at PBH diagnosis' group, and therefore it was not possible to calculate %EBMIL and %TWL for this particular patient

^bHOMA2-B, HOMA2-S and HOMA2-IR were not calculated in 32 patients ($n=11$ in the 'With prior cholecystectomy at PBH diagnosis' group, and $n=21$ in the 'Without prior cholecystectomy at PBH diagnosis' group) who had not undergone a mixed-meal tolerance test (MMTT)

Table 2 Metabolic responses to mixed meal tolerance tests

	Total [<i>n</i> = 99]	Without prior cholecystectomy at PBH diagnosis [<i>n</i> = 81]	With prior cholecystectomy at PBH diagnosis [<i>n</i> = 18]	<i>p</i> value
Glucose				
Fasting (mg/dL)	81.90 (76.86, 86.94)	81.90 (76.86, 85.86)	82.44 (76.86, 87.84)	0.692
Peak (mg/dL)	166.68 ± 46.62	164.70 ± 45.90	174.96 ± 49.86	0.400
Nadir (mg/dL)	50.04 (39.96, 52.96)	50.94 (39.96, 54.94)	45.00 (41.94, 50.94)	0.109
MMGR	3.24 (2.55, 4.15)	3.07 (2.47, 4.10)	3.81 (3.44, 4.30)	0.049
Insulin				
Fasting (μU/mL)	6.10 (3.90, 8.90)	6.10 (3.90, 8.90)	6.15 (4.40, 8.20)	0.653
Peak (μU/mL)	224.40 (137.70, 308.20)	224.60 (121.60, 307.10)	217.80 (171.00, 315.50)	0.446
C-peptide				
Fasting (ng/mL)	1.98 (1.59, 2.41)	1.93 (1.58, 2.35)	2.16 (1.73, 2.50)	0.291
Peak (ng/mL)	15.46 (12.06, 19.14)	15.39 (11.59, 19.39)	16.12 (14.24, 16.98)	0.272
Nadir (ng/mL)	1.60 (1.28, 2.04)	1.59 (0.99, 1.99)	1.92 (1.55, 2.12)	0.062

Data are presented as means ± SD or median (25th percentile, 75th percentile). Statistically significant differences (*p* value < 0.05) are highlighted in bold

PBH, post-bariatric surgery hypoglycemia; MMGR, minimum-to-maximum glucose ratio

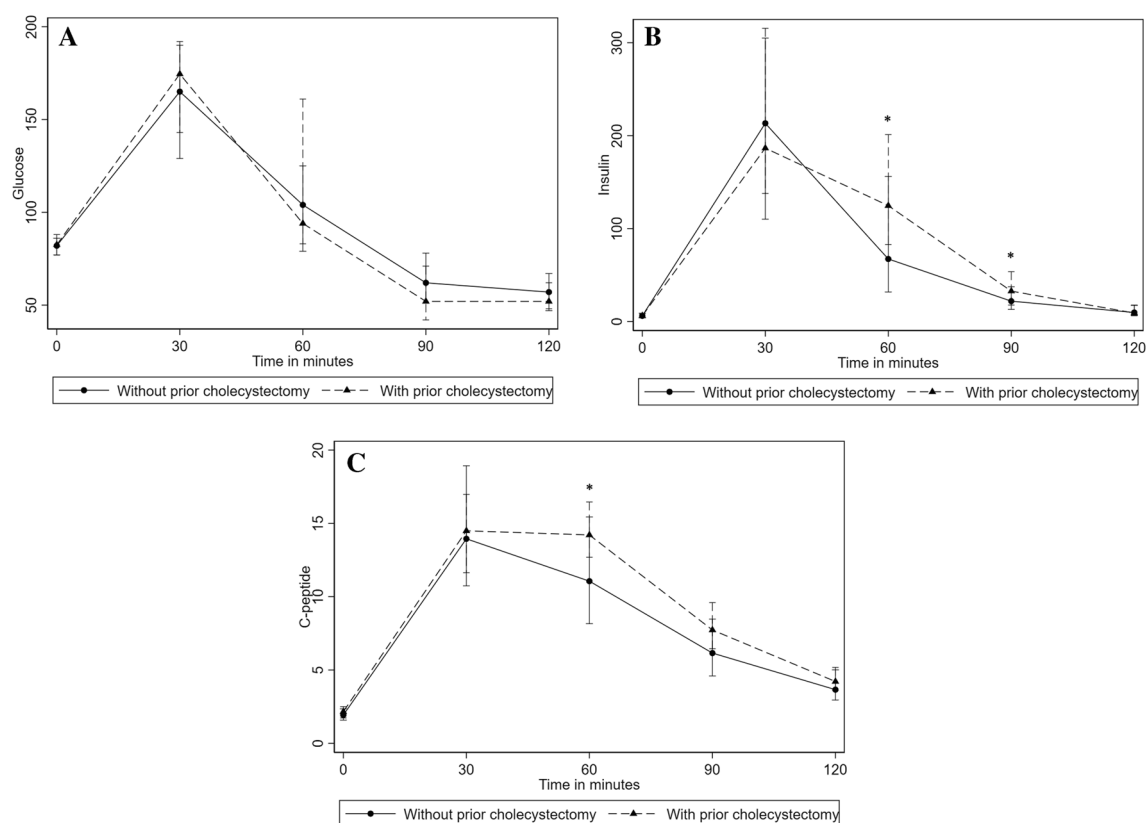


Fig. 1 Glucose (A), insulin (B) and c-peptide peripheral levels (C) during MMTT, according to prior cholecystectomy at PBH diagnosis. Data are presented as median (25th percentile, 75th percentile). Statistically significant differences are marked as **p* < 0.05

between the groups ($p = 0.291$, $p = 0.272$ and $p = 0.062$, respectively, Table 2).

Pharmacological Treatment and Time from MBS to Diagnosis of PBH

The median time to diagnosis of PBH (time interval between MBS and PBH diagnosis) of all patients was 25 months (2 years and 1 month). There were no differences between the groups with and without prior cholecystectomy ($p = 0.167$, Table 3). A total of 62.8% of the patients in the ‘without prior cholecystectomy’ group required acarbose associated with dietary modifications to control hypoglycemic episodes, and in the cases of the ‘with prior cholecystectomy’ group, the percentage of patients who required acarbose was higher (79.3% vs 62.8%, respectively), albeit the difference was not statistically significant ($p = 0.096$, Table 3). The proportion of patients in the ‘with prior cholecystectomy’ group who required medication with a dose greater than or equal to 150 mg/day to control hypoglycemic symptoms was significantly higher than in the ‘without prior cholecystectomy’ group (69.6% vs 45.3%, respectively, $p = 0.046$, Table 3). A sensitivity analysis was conducted and showed no differences related to sex or type 2 diabetes prior to MBS in the need for pharmacological therapy or the requirement for medication with a dose greater than or equal to 150 mg/day. Insufficient weight loss has been previously defined as %TWL < 20 [19, 20]. Thus, setting a cutoff point at 20% of TWL, no significant differences were observed. When the analysis was restricted to patients who had undergone RYGB, significant differences were verified, consistent with the overall results (the data are not shown).

Discussion

This study provides support for hypothesis that hormonal alterations caused by cholecystectomy have an impact on the diagnosis and pharmacological treatment of patients with PBH. It is known that BA, through the activation of FXR and TGR5, stimulate the production of GLP-1, an insulinotropic hormone, and hence induce changes in glucose metabolism [12, 18, 21]. Alterations in the kinetics of the BA enterohepatic cycle play a role in the development of PBH [22]. Accordingly, we theorise that the absence of the gallbladder in patients with PBH could alter the kinetics of BA and consequently the respective time from MBS to the diagnosis of PBH and its treatment. One previous study showed that patients with history of MBS and cholecystectomy had higher postprandial levels of insulin and C4 (a marker of hepatic BA synthesis) than patients with history of MBS who did not undergo cholecystectomy [11]. Considering this finding, we grouped patients with PBH according to their previous history of cholecystectomy and assessed the dynamics of glucose, insulin and c-peptide during MMTT. A cut-off value of 55 mg/dL was established to define hypoglycemia, in line with previous studies [14, 23, 24]. Postprandial hypoglycemia depends on the characteristics of the meal [25]; however, despite the use of a standardised meal, there is no assurance it can replicate the symptoms that led to the diagnosis of PBH for each patient. In line with a previous study [11], the results showed higher insulin and c-peptide levels in the ‘with prior cholecystectomy’ group, particularly at minutes 60 and 90. However, there were no differences at fasting, peak, and nadir. In turn, MMGR was significantly higher in the ‘with prior cholecystectomy’ group. In both groups, the highest glucose levels were recorded at minute

Table 3 Time from metabolic and bariatric surgery to diagnosis of post-bariatric hypoglycemia and pharmacological therapy

	Total [$n = 131$]	Without prior cholecystectomy at PBH diagnosis [$n = 102$]	With prior cholecystectomy at PBH diagnosis [$n = 29$]	p value
Time interval between MBS and PBH diagnosis, months	25 (15, 41)	24 (14, 40)	36 (17, 46)	0.167
Need of pharmacological therapy—acarbose, n (%) ^a	87 (66.4)	64 (62.8)	23 (79.3)	0.096
≥ 150 mg/day (%) ^b	45 (51.7)	29 (45.3)	16 (69.6)	0.046

Data are presented as median (25th percentile, 75th percentile) or number (%). Statistically significant differences (p value < 0.05) are highlighted in bold

MBS, metabolic and bariatric surgery; PBH, post-bariatric surgery hypoglycemia

^aAll patients controlled hypoglycemic symptoms either through dietary modifications alone, or in conjunction with the use of acarbose

^bThe dose of acarbose that was considered for grouping patients at ≥ 150 mg/day was the minimum effective dose for controlling hypoglycemic episodes

30, the lowest being at minute 90. The ‘with prior cholecystectomy’ group had higher glucose values at minute 30, and lower ones at minute 90 than the ‘without prior cholecystectomy’ group, reflecting the significantly higher insulin levels at minutes 60 and 90, which thus explains the larger degree of glycemic variability in this group. No clinical differences between the groups could explain the different responses in the MMTT to the same stimulus. The age at MBS and at diagnosis of PBH in the ‘with prior cholecystectomy’ group was slightly higher. However, there is no evidence that a difference of 5 years in itself causes different responses to the MMTT [26]. Our findings therefore reinforce the role of hyperinsulinism as the central mechanism of PBH and the importance of the BA-GLP-1-insulin axis [27–29]. Indeed, a previous study has shown that blocking the GLP-1 receptor can reduce episodes of PBH [24], while others have described that GLP-1 does not play an essential role in the development of PBH [23, 30]. GLP-1 receptor agonist analogs (GLP-1 RA) have been observed to improve hypoglycemic episodes; however, the entire mechanism remains incompletely understood [30–33]. While endogenous GLP-1 acts as an inhibitor of glucagon secretion during hyperglycemic episodes, some studies indicate that exogenous GLP-1 exerts a stimulatory effect on glucagon secretion during hypoglycemia in healthy individuals [34, 35]. The beneficial effect of GLP-1 on PBH may be biphasic, initially inhibitory and later becoming stimulatory of glucagon secretion during hypoglycemia. Additionally, GLP-1 RA has been shown to reduce small intestine motility and delay intestinal transit, potentially enhancing hypoglycemic episodes [36, 37]. Another conceivable mechanism is that long-term treatment with GLP-1 RA could mitigate the effect of postprandial endogenous GLP-1 [30, 31].

The gallbladder is essential for BA homeostasis. Cholecystectomy has been associated with an increase in postprandial BA synthesis and C4, which is a biomarker of synthesis [38]. Considering the increase in GLP-1 and FGF19, which consequently leads to an increase in insulin induced by BA in patients with history of MBS, our aim was to see whether the time interval until the diagnosis of PBH was shorter in patients who had undergone cholecystectomy. Indeed, to the best of our knowledge, this is the first study to describe the early onset of the diagnosis of PBH in patients with prior cholecystectomy versus those who had not undergone cholecystectomy previously. We found no significant differences in the time to diagnosis; however, the time interval to diagnosis was longer in the cases of the ‘with prior cholecystectomy’ group. The median age at PBH diagnosis of all patients was 43 years, and the median time to diagnosis of PBH was 25 months. This is in line with a previous study that reported a median age at PBH diagnosis of 46 years and a longer median time to diagnosis of PBH, 40.6 months [39]. PBH onset and severity are highly diverse. Based on

our findings, these alterations do not seem enough to shorten the time from MBS to the development of PBH, even though cholecystectomy induces hypoglycemic kinetic changes in BA.

Modifying dietary habits is the primary treatment for PBH. The nutritional composition of meals impacts glucose and insulin dynamics, depending on the glycemic index, which influences the glycemic peak and insulin secretion [17, 18, 40–42]. Nutritional requirements for patients after MBS vary according to their height, weight, age, and type of bariatric intervention. A daily macronutrient distribution of 45% carbohydrates, 25% proteins and 30% fats is recommended [43, 44]. Hypoglycemic episodes are more likely to be triggered by meals that are low in protein and high in sugar content [45]. Indeed, according to the Society for Endocrinology guidelines for the diagnosis and management of PBH [46], it is recommended to consume at least 60 g/day of protein, although higher intake may be necessary. When consumed concomitantly with carbohydrates, there is a decrease in gastric emptying and intestinal motility, thereby reducing hypoglycemic episodes. Patients with history of MBS are advised to consume fibre to reduce carbohydrate absorption, limit foods with a high glycemic index, prefer complex carbohydrates, and have a diet fractioned in frequent small meals [44, 47–49]. Additionally, maintaining a food diary that includes records of hypoglycemic episodes and the foods consumed prior to these episodes can be beneficial [47]. Nonetheless, these dietary measures may only provide limited benefits for patients with severe symptoms, necessitating the addition of pharmacological therapy [50].

Pharmacological therapy for PBH consists of acarbose, diazoxide, octreotide, GLP-1 RA and pasireotide [51]. The patients included in this study controlled their hypoglycemic episodes either through dietary modifications alone or in conjunction with the use of acarbose, and none required surgical treatment. Considering the metabolic alterations outlined above resulting from cholecystectomy, we aimed to investigate whether a higher proportion of patients in the ‘with prior cholecystectomy’ group required acarbose than those ‘without prior cholecystectomy’. In addition, we studied whether those patients in the ‘with prior cholecystectomy’ group who were medicated with acarbose required a higher dose to control symptoms. According to the international consensus on diagnosing and managing dumping syndrome [52], the minimum dose of acarbose indicated for maintenance therapy is 150 mg/day. However, in this study, several patients required a dose lower than 150 mg/day to control their symptoms, which aligns with a previous study [53]. Therefore, we found that the proportion of patients in the ‘with prior cholecystectomy’ group who required a dose of 150 mg/day or more was significantly higher than the other group. Acarbose, an α -glucosidase inhibitor, lowers glucose, insulin and GLP-1 levels [54]. It blocks the

hydrolysis of polysaccharides, oligosaccharides and disaccharides into monosaccharides, thus delaying and attenuating the glucose and insulin peak [53]. The observed disparity in doses between the two groups aligns with the heightened glycemic variability described during the MMTT in individuals with a history of cholecystectomy. This study was a pioneer in comparing the dose of acarbose required to reduce hypoglycemic episodes in patients with and without prior cholecystectomy at diagnosis of PBH. The overactivation of the BA-GLP-1-insulin axis can partly explain the difference found in the acarbose dose. Therefore, considering the potential association between cholecystectomy and PBH, it may be prudent to initiate treatment with acarbose at higher doses in patients with a history of cholecystectomy.

This study presents some limitations that must be acknowledged. We recognise that the number of patients with history of cholecystectomy was relatively small and therefore future studies should contemplate larger samples, which would be important to validate our findings. This study conducted a retrospective analysis on a cohort from a single medical centre in northern Portugal, and thus caution should be exercised when generalising the findings to other populations. Additionally, the patients in our study had no dietary restrictions in the days before the MMTT, which may influence the research outcome. Due to the retrospective design, bias and confounding may have been introduced, representing a scenario which is less likely in a prospective study design. Considering the retrospective design, certain data points are lacking, as they were originally documented for clinical monitoring purposes rather than for the explicit intent of this study. Nevertheless, this study was carried out in a teaching hospital that is recognised as being a reference centre for bariatric surgery in Portugal. The greatest strength of this study is that it provides insights into the differences in pharmacological treatment and hormonal responses during MMTT in PBH patients with and without prior cholecystectomy at PBH diagnosis.

Conclusion

Our study provides new insights into the pharmacological treatment of PBH by showing that PBH patients with prior cholecystectomy require higher doses of acarbose to control hypoglycemic symptoms when compared to PBH patients who had not undergone prior cholecystectomy. Additionally, our research reinforces the role of hyperinsulinism as being the main mechanism of PBH and also the importance of the BA-GLP1-insulin axis.

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Data Availability All the data supporting the findings of this study are available from the authors upon reasonable request.

Declarations

Competing Interests The authors declare no competing interests.

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