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FACULDADE DE DESPORTO
UNIVERSIDADE DO PORTO

Associação da severidade da fragilidade com o risco de complicações pós-cirúrgicas em doentes oncológicos: revisão sistemática e meta-análise

Dissertação apresentada com vista à obtenção do 2º ciclo em Atividade Física e Saúde, da Faculdade de Desporto da Universidade do Porto, ao abrigo do Decreto-Lei nº 74/2006, de 24 de março, na redação dada pelo Decreto-Lei nº 65/2018 de 16 de agosto.

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PALAVRAS-CHAVE: FRAGILIDADE; COMPLICAÇÕES PÓS-CIRÚRGICAS; CANCRO; REVISÃO SISTEMÁTICA; META-ANÁLISE.

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Resumo

Introdução: A população tem vindo a envelhecer drasticamente nos últimos anos. As consequências deste fenómeno são visíveis na saúde dos cidadãos, nomeadamente através do aumento o número de casos de cancro. A intervenção cirúrgica corresponde à opção terapêutica com maior potencial curativa para os tumores sólidos. No entanto, não é isenta de eventos adversos, particularmente em indivíduos idosos vulneráveis, onde causam morbilidade e mortalidade. A fragilidade e a sua severidade são reconhecidas como fatores preditores de complicações no pós-operatório. Neste sentido, tem vindo a ser reconhecida a importância da avaliação da fragilidade no momento pré-cirúrgico, com o intuito identificar os doentes mais suscetíveis a complicações pós-cirúrgicas e, consequentemente, auxiliar a decisão terapêutica. De modo a esclarecer a relação entre fragilidade e a sua severidade com o risco de complicações pós-cirúrgicas em doentes oncológicos, propusemo-nos a realizar uma revisão sistemática e meta-análise.

Metodologia: A pesquisa foi realizada entre janeiro e março de 2019 e foram incluídos para análise um total de 19 estudos (7 prospetivos e 12 retrospetivos). Para a avaliação da qualidade dos artigos foi utilizada a *Newcastle-Ottawa Quality Assessment Scale*. A análise estatística foi realizada com recurso ao *ReviewManager 5.3; Copenhagen: the Nordic Cochrane Centre, Cochrane Collaboration*.

Resultados: Verificamos que o doente oncológico frágil apresenta um risco acrescido e significativo de ter complicações após a cirurgia (OR= 2.23, 95% IC: 1.91-2.60; $p<0.00001$; $I^2=88\%$). O risco manteve-se elevado mesmo após realizadas sub-análises, exceto para o tipo de cancro, onde verificamos que a fragilidade não se encontrou associada a complicações pós-cirúrgicas no contexto do cancro ginecológico.

Conclusão: Os nossos resultados alertam para o impacto da fragilidade e a respetiva severidade no desenvolvimento de complicações pós-cirúrgicas em doentes oncológicos, reforçando a importância da sua avaliação em contexto clínico.

PALAVRAS-CHAVE: FRAGILIDADE; COMPLICAÇÕES PÓS-CIRÚRGICAS; CANCRO; REVISÃO SISTEMÁTICA; META-ANÁLISE.

Abstract

Introduction: The population has been aging dramatically in recent years. The consequences of this phenomenon are visible in population's health, namely, in the increased number of cancer cases. Surgical intervention corresponds to the therapeutic option with the greatest curative potential for solid tumors. However, it is not adverse events free, particularly in vulnerable elderly individuals, where they cause marked morbidity and mortality. Frailty and its severity are recognized as predictors of postoperative complications. In this sense, the relevance of assessing frailty in the preoperative period has been recognized, in order to identify the most susceptible patients to postoperative complications and, consequently, to assist the therapeutic decisions. In order to clarify the relationship between frailty and its severity with risk of postoperative complications in cancer patients, we proposed to develop a systematic review and meta-analysis.

Methods: The research was conducted between January and March 2019 and a total of 19 studies were included (7 prospective and 12 retrospective). To evaluate the quality of the studies, the Newcastle-Ottawa Quality Assessment Scale was used. Statistical analysis was performed using ReviewManager 5.3; Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration.

Results: We found that frail cancer patients have an increased and significant risk of complications after surgery (OR= 2.23, 95% IC: 1.91-2.60; $p<0.00001$; $I^2=88\%$). The risk remained high even after sub-analyzes, except for the type of cancer, where we found that frailty was not associated with postoperative complications in gynecological cancer.

Conclusion: Our results highlight the impact of frailty and its severity on the development of postoperative complications in cancer patients, reinforcing the relevance of their evaluation in clinical context.

KEY-WORDS: FRALITY; POSTOPERATIVE COMPLICATIONS; CANCER; SYSTEMATIC REVIEW; META-ANALYSIS.

1. Introdução

1.1. A saúde da população: o envelhecimento

Os indicadores demográficos mundiais evidenciam que a população mundial cresceu significativamente até ao ano 1927 e atingiu os 2 bilhões de pessoas em 1974 (Housman & Dorman, 2005). Em apenas 25 anos, de 1974 até 1999, a população aumentou o dobro atingindo um total de 4 bilhões de pessoas (Cohen, 2003). Este aumento da população é um acontecimento nunca antes vivido (Cohen, 2003). Segundo a *United Nations Population Fund* estima-se que em 2050 o número de pessoas com mais de 60 anos ultrapasse os 2 bilhões (Figura 1).

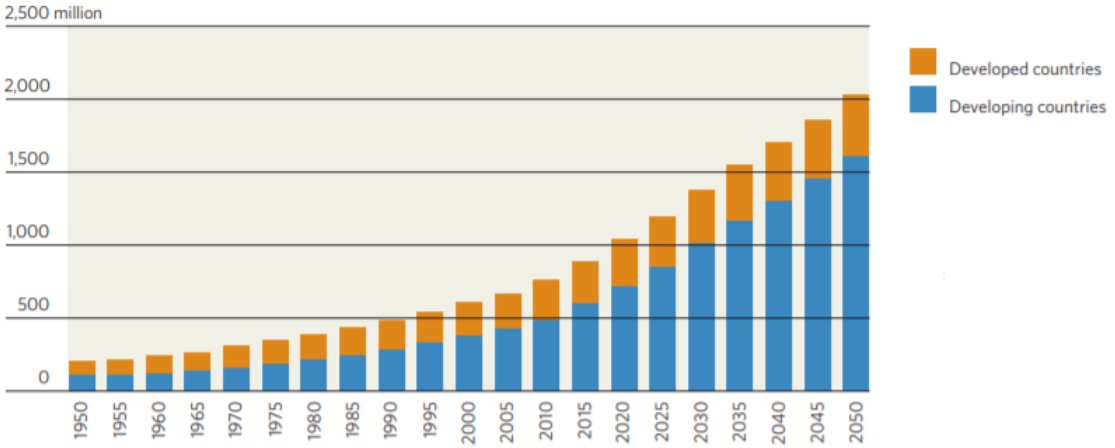

Figura 1 – Crescimento global do envelhecimento da população (United Nations Population Fund, 2011).

Portugal, segue esta tendência e os seus habitantes vivem cada vez mais anos. Estima-se que 21% dos portugueses têm 65 ou mais anos, enquanto 14% têm menos de 15 (Ministério da Saúde, 2018). Esta realidade evidencia uma melhoria nas condições de vida, no entanto, traz consigo inúmeros problemas, como por exemplo, o baixo índice de fecundidade, a emergência de novos problemas de saúde e o aumento da prevalência de doenças crónicas (Ministério da Saúde, 2018). No mesmo sentido, estudos refletem sobre a associação positiva entre o envelhecimento populacional e o aumento do número de casos de cancro (National Services Scotland, 2019; Office for National Statistics, 2019) (Figura 2).

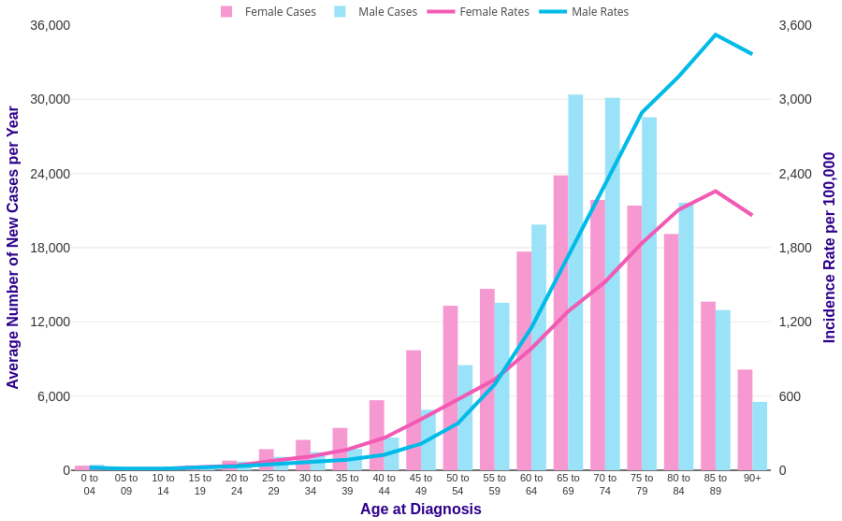

Figura 2 – Número médio de novos casos de cancro por ano e taxas de incidência, por idade, por 100.000 habitantes, Reino Unido, 2014-2016 (Cancer Research UK, 2019).

1.2. Cancro

Segundo a Organização Mundial de Saúde (OMS), cancro é definido como um crescimento descontrolado de células que pode afetar qualquer parte do corpo humano.

Dados disponibilizados, em 2018, pelo *International Agency for Research on Cancer* apontam para um aumento de 63,1% no número de casos incidentes de cancro no mundo, entre 2018 e 2040 (Figura 3).

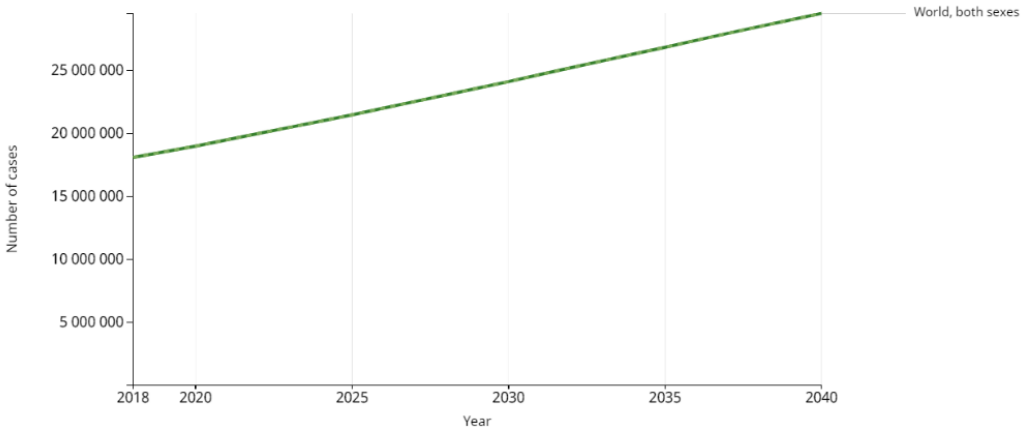

Figura 3 -Número estimado de casos incidentes desde 2018 a 2040, todos os cancros, ambos os sexos, todas as idades, no mundo (Global Cancer Observatory, 2019)

No panorama português, estima-se que entre 2018 e 2040 a incidência de cancro aumente de 58 199 para 69 565 novos casos, correspondendo a um aumento de 19,0% (Figura 4). Neste sentido, compreende-se que a mortalidade e letalidade associadas a esta doença a tornem um problema central de saúde pública mundial.

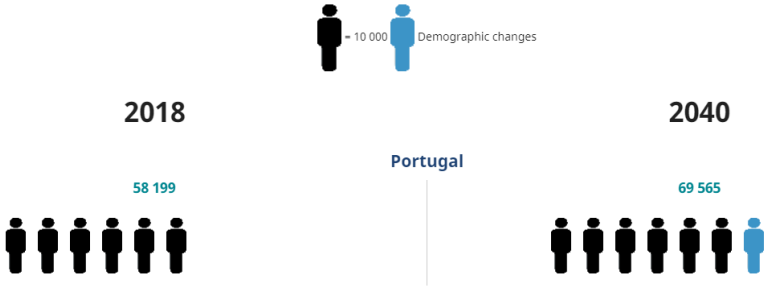

Figura 4 - Número estimado de casos incidentes desde 2018 a 2040, todos os cancros, ambos os sexos, todas as idades, em Portugal (Global Cancer Observatory, 2019).

Esta realidade, fez aumentar o número de tratamentos de radioterapia e/ou quimioterapia, em Portugal, tanto em sessões de hospital de dia como em internamento, assim como, o número de cirurgias oncológicas realizadas (Nuno Miranda et al., 2016) (Figura 5).

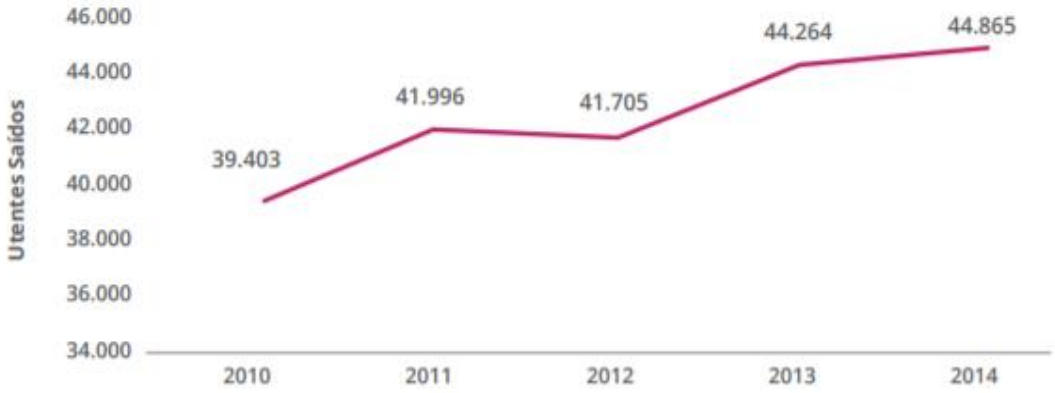

Figura 5 - Evolução do número de cirurgias a neoplasias malignas, Portugal Continental (2010-2014). (Doenças Oncológicas em Números, 2015)

Dados mundiais demonstram uma tendência para o aumento do número de cirurgias oncológicas realizadas nos próximos anos (Figura 6).

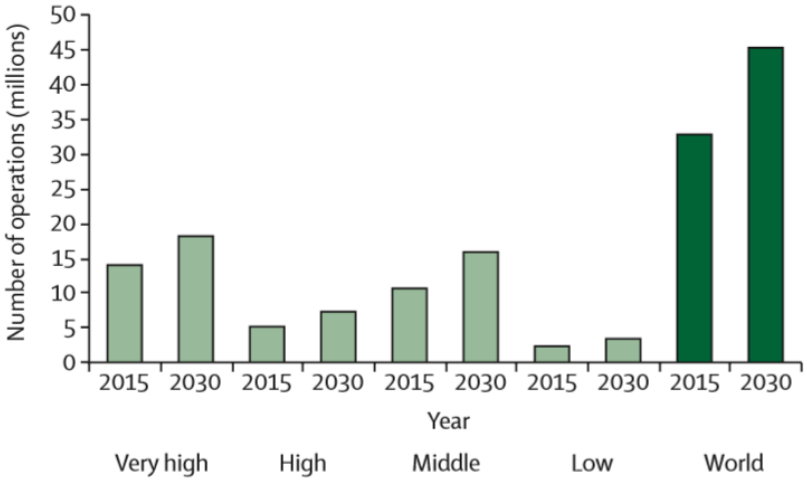

Figura 6 – Número estimado de cirurgias oncológicas realizadas entre 2015 e 2030 (GLOBOCAN, 2012).

A cirurgia é um dos principais tratamentos do cancro e desempenha um papel relevante no prolongamento da vida do doente oncológico (Holland, 2003). No entanto, esta intervenção revela-se um evento de grande *stress* para o doente e com riscos inerentes. São várias as possíveis complicações pós-cirúrgicas, nomeadamente, hemorragias, danos nos tecidos, infeções, entre outras, que: i) implicam uma maior utilização dos recursos de saúde (Scarborough et al., 2017); ii) interferem nos tratamentos subsequentes (Hendren et al., 2010); iii) poderão levar à morte prematura e perda de independência funcional (Booka et al., 2018; Lawrence et al., 2004) e; iv) têm impacto económico (para os doentes e/ou hospitais) (Zogg et al., 2018).

Neste sentido, compreende-se a necessidade de serem desenvolvidas estratégias que diminuam as complicações pós-operatórias e, consequentemente, potenciem a qualidade de vida do doente após estas intervenções. Destaca-se, por exemplo, da avaliação da fragilidade do doente oncológico antes da intervenção cirúrgica.

1.3. Fragilidade

A fragilidade tem sido reconhecida como uma condição clinicamente diagnosticável e caracteriza-se pela diminuição das reservas fisiológicas e funcionais em diversos sistemas e maior vulnerabilidade proporcionando menor tolerância fisiológica e psicológica para responder a um evento de grande *stress*

ou exposição a risco elevado de eventos adversos à saúde física e mental, como é o caso da cirurgia (Lu et al., 2016).

É consensual na literatura que a avaliação da fragilidade: i) reflete a idade biológica do individuo (que é mais discriminativa do risco de comorbilidade e mortalidade do que a idade cronológica) (Morley et al., 2013); ii) é potencialmente reversível ou atenuada por intervenções específicas (Morley et al., 2013); iii) o seu conhecimento é útil para o planeamento e realização de cuidados de saúde (Chen et al., 2014). Adicionalmente, a fragilidade e a sua severidade são reconhecidas como fatores preditores de complicações no pós-operatório (Brahmbhatt et al., 2016; Ehlert et al., 2016; Fang et al., 2017; Hewitt et al., 2015; Karam et al., 2013; O'Neill et al., 2016). Neste sentido, torna-se pertinente a sua avaliação previamente à realização de cirurgias a neoplasias, de modo a reduzir os riscos e complicações resultantes destes procedimentos. A aplicação de ferramentas de avaliação da fragilidade permitirá: i) analisar o estado (físico, psicológico, social) do doente oncológico; ii) delinear estratégias adequadas para otimizar o estado do doente oncológico antes da intervenção (pré-habilitação e redefinição alimentar por exemplo) (Mogal et al., 2017). Neste sentido, é compreensível e necessário que se investa na melhor compreensão da relação entre a fragilidade e os efeitos adversos da cirurgia, bem como no tipo de instrumentos com maior eficácia de predição, aplicável em contexto clínico, que facilite os processos de tomada de decisão no que concerne ao encaminhamento dos doentes oncológicos para intervenções cirúrgicas, podendo o doente ser direcionado para programas de otimização como por exemplo a preabilitação com exercício físico (Morley et al., 2013).

2. Objetivos

De modo a contribuir para o esclarecimento da relação entre fragilidade e eventos adversos pós-cirúrgicos, realizou-se uma revisão sistemática e meta-análise, com o objetivo de avaliar a associação da severidade da fragilidade com o risco de complicações pós-cirúrgicas.

3. Revisão sistemática e meta-análise

Association of frailty severity with the risk of postoperative complications in oncologic patients: systematic review and meta-analysis

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ABSTRACT

Background: Frailty is a biological syndrome characterized by a reduction of physiological reserves and decreased tolerance to stressful stimuli like a disease or a surgery. The prevalence of frailty increases with age and its incidence among older patients with cancer is especially high. Because cancer itself as well as anti-cancer therapies can impose a significant additional stress that challenges the patient's physiologic reserve, it is anticipated that frailty will cause a significant burden to cancer patients. Multiple studies have shown an important association between preoperative frailty with poor post-operative health outcomes in older cancer patients under surgery. However, it is still unclear what is the impact of pre-frailty on adverse outcomes after surgery.

Aim: This work aims to study the association between the severity of frailty and the development of postoperative complications in cancer patients undergoing surgery.

Methods: Potential studies were systemically searched through the Pubmed/Medline, Cochrane Library and Academic Google, using the keywords "frail OR frailty" AND "cancer OR oncology OR oncologic" AND "postoperative complications OR postsurgical/post-surgery complications" OR "postoperative outcomes OR postsurgical/post-surgery outcomes", between January and March 2019. All possible definitions of frailty were considered. The first author, year of publication, study design, country of research, study population, age and gender of participants, sample size, type of cancer, frailty tool, type of surgery (elective or emergency), type of surgical procedure (open and laparoscopic), postoperative complication (type/severity and timing of occurrence) and inclusion and exclusion criteria were extracted. Quality of the studies was assessed with the Newcastle-Ottawa quality assessment scale for non-randomized studies. Statistical analysis was performed in Revman (Review manager V5.3). The random-effects model was used to calculate the Odds Ratios (OR) and the 95% confidence interval (CI). PRISMA guidelines were followed. We explored the sources of heterogeneity by performing sub analysis. Funnel plots were used to

visually inspect for publication bias. Sensitivity analysis was performed by omitting every single study.

Results: From a total of 91 423 articles, 19 (7 prospective and 12 retrospective) were eligible for the meta-analysis, with a total of 247 328 participants, 41.8% male and mean age 63.6 years. Compared to patients classified as “non-frail”, “frail” patients had an increased risk of postoperative complications (OR = 2.40, 95% CI 2.08-2.77; p <0.00001; I2 = 89%). When sub analysis for frailty severity was performed, there was a high risk of postoperative complications in the “frail” individuals (OR = 4.2, 95% CI 2.86-6.19; p <0.00001; I2 = 86%) and “pre-frail” (OR = 2.24, 95% CI 1.76-2.86; p <0.00001; I2 = 81%) compared to the “robust” ones. It was also found that the "frail" had a higher risk of complications compared to the "pre-frail" (OR = 2.55, 95% CI 2.09-3.11; p <0.0004; I2 = 80%).

Conclusions: Frailty and pre-frailty seems to be a major risk factor for postoperative complications in cancer patients. Pre-surgical assessment of frailty level may be useful in identifying individuals who could benefit from optimization interventions for surgery, such as pre-habilitation.

Key-words: Frailty, Postoperative complications, Oncologic.

INTRODUCTION

Cancer incidence and mortality are rapidly growing worldwide, with the 14 million new cancer cases in 2012 expected to rise to 24 million new cancer cases in 2035 (1). The reasons for these trends are complex but are thought to reflect changes in the prevalence and distribution of the main risk factors for cancer, including the aging and growth of the population (1). Indeed, the world's population is expected to grow from 6.3 billion to 8.9 billion until just 2050 and the fraction of people aged 60 years and older are projected to increase more than double by the year 2050 (2). In 2012, 47.5% of all new cancer cases worldwide were diagnosed among adults aged ≥65 and this number is estimated to increase to 70% by 2030 (3). Moreover, elderly cancer patients account for approximately 80% of cancer deaths each year (4). The growing cancer burden at older ages is likely to result in major challenges in the provision of clinical and health services that adequately meet these needs over the coming decades (5). For instance, this segment of the population is characterized by the presence of multiple comorbidities, polypharmacy and physiologic age-related changes, that may condition whether or not a certain treatment is offered (6). This is particularly worrying regarding surgery, which is a fundamental method for both curative and palliative treatment of most solid cancers (7). In fact, older cancer patients are often denied standard surgical management as they are believed to be have poor tolerance to surgical stress and thus, to be at increased risk of postoperative morbidity and mortality (7). However, this conservative attitude is not supported by the current evidence as long-term outcomes after surgical treatment do not differ according to the patient's age (8). The truth is that the older population is very heterogeneous with regard to health, functional, psychological, social, cultural and economic status, and all these factors may ultimately influence the surgical risk in this patient group (9). Thus, in order to provide optimal care and improve health outcomes, the decision of whether or not an older patient will tolerate a surgical procedure should be based on a more objective and individualized preoperative risk assessment.

There are several instruments used to assess preoperative risk, but they are highly biased by chronological age and do not take into account the patient's

physiologic reserve or biological age (10). In order to better understand the functional and physiologic heterogeneity among the elderly, the concept of frailty has been introduced. Frailty is defined as a dynamic status (which means it can improve or worsen) of vulnerability to endogenous and exogenous stressors, characterized by a reduction in the physical, psychological and/or social functions, exposing the individual to a higher risk of negative health-related outcomes (11) (12). The condition can be described as a vicious cycle responsible for the onset of negative health-related outcomes and a transition phase between successful aging and disability (12). The prevalence of frailty in the general population was shown to be around 10% in people aged 65 and over, rising to between 25% and 50% in those aged 85 and over (13). In community-dwelling older people, frailty was shown to be a significant predictor of falls (14), fractures (14), hospitalization (15), disability (15), poor quality of life (16), dementia (17) and mortality (18). Frailty has also been recognized as an important risk factor for adverse postoperative outcomes in older patients submitted to vascular (19), cardiac (20) and orthopedic surgery (21). Regarding cancer, more than 50% of older cancer patients are thought to be pre-frail or frail, placing them at greater risk of chemotherapy intolerance, postoperative complications and mortality (22). Thus, given the growing number of patients presenting for surgical procedures, frailty may be a valuable tool in perioperative assessment of older cancer patients by helping clinicians to tailor treatment options, facilitating shared decisions making, improving patient selection and helping to optimize patients preoperatively so as to reduce surgical complications (23).

Despite the potential clinical utility of frailty assessment, clinicians will find difficulties in the moment of choosing the instrument to assess it, as there are dozens of options, representing different definitions of frailty (24). These definitions vary in their conceptual foundations (there is no universal definition of frailty), clinical practicality (some are more time-consuming), domains (single vs. multi-domains), and assessment items (25), which compromise their comparability. Moreover, there are no consensus on which frailty assessment instrument is appropriate to a specific purpose (e.g. risk of fall, hospitalization,

morbidity, and mortality), context (e.g. community, primary or secondary care) (25). Specifically, in the context of cancer patients, while it has been shown that frail patients are at greater risk of postoperative complications than non-frail, it is not clear if the severity of frailty (robust vs. pre-frail vs. frail) plays a role. It also remains to be explored what frailty instruments better predict postoperative complications and if frailty similarly impacts postoperative outcomes all types of cancer.

The purpose of this systematic review and meta-analysis is to evaluate the association between frailty status and postoperative complications. By defining a priori sub-analysis by the type of frailty assessment instrument and type of cancer, we hope to better clarify how these important factors could impact the relation between frailty and postoperative complications.

METHODS

This review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (26).

Protocol and registration

A protocol for this review has not been published separately.

Eligibility criteria

Type of studies

Only published observational (retrospective and prospective) studies, reporting crude or sufficient raw data to allow calculation of the association between frailty and post-operative complications, published in English in the last 10 years were considered eligible for inclusion in the review.

Type of participants

We included studies that recruited adult patients aged 18 or older, of both sexes and any ethnicity, diagnosed with cancer and scheduled to surgery for tumor resection with and without neoadjuvant therapy. In addition, studies had to stratify and compare participants by frailty status, assessed before any treatment. Given the absence of a standard consensus on the ideal frailty metric, all possible author descriptions for inclusion were considered, with no limitations on the number of items and domains used for frailty assessment.

Type of interventions

The search was limited to studies comparing the risk of postoperative complications between frail versus non-frail or frail versus pre-frail versus robust.

Types of outcome measures

The primary outcome for this review was to compare the risk of postoperative complications according to frailty status in oncologic patients. There was no minimum length of follow-up for the studies that were eligible for inclusion in the review, but they had to report the timing and type/severity of complications.

Information source and search strategy

One author (RR) performed a systematic search in the electronic databases PUBMED, Cochrane online databases and Google Academic, using the following terms: “frail OR frailty” AND “cancer OR oncology OR oncologic” AND “postoperative complications OR postsurgical/post-surgery complications” OR “postoperative outcomes OR postsurgical/post-surgery outcomes”. The search happened between January and March 2019, limited to articles written in English and published in the last ten years. The reference lists of the selected articles were also reviewed to identify relevant articles.

Study Selection

One author (RR) independently screened the titles and abstracts of the articles to identify potentially relevant studies. Whenever an article was considered relevant, the full text was reviewed. Finally, to identify potentially eligible studies, all the reference list of the included studies was also reviewed. Any disagreement was resolved by discussion and consensus with the participation of a second person (DMG).

Data Extraction

The following data was extracted by one person (RR) from selected articles: first author, year of publication, study design, country of research, study population, age and gender of participants, sample size, type of cancer, frailty tool, type of surgery (elective or emergency), type of surgical procedure (open and laparoscopic), postoperative complication (type/severity and timing of occurrence) and inclusion and exclusion criteria. The information was subsequently verified by a second person (DMG). If the data was insufficient in the original manuscript, the corresponding author was contacted for additional information.

Data items

Only numerical values reported by the studies (e.g. percentages, counts, means) were used to calculate frailty prevalence and risk of postoperative complications. We anticipated the use of different frailty instruments and different classifications of frailty (e.g. frail and non-frail; frail, pre-frail and robust; cumulative frailty). Thus, and in order to include the greatest number of articles in this review and/or to perform analysis by frailty status, we dichotomized (frail and non-frail) or trichotomized (frail, pre-frail and robust) frailty classification, following established cut-off points. Regarding dichotomization, “pre-frail” and “robust” patients were merged and considered “non-frail”; for studies using cumulative frailty (from 0 to 1), we considered “non-frail” those with a frailty index <0.2 and “frail” those ≥0.2 (27). For trichotomization, we considered “robust”, “pre-frail” and “frail” those with a frailty index ≤0.10, 0.10 to 0.21 and >0.21, respectively (28). In studies that categorized the patients in “frail, intermediate frail or moderately frail and not frail or robust”, we combined “intermediate frail” or “moderately frail” and “not frail” or “robust” in a “not frail group” and frail in a “frail group” (29).

Study quality assessment

We used the Newcastle-Ottawa quality assessment scale for non-randomized studies to assess the quality of studies (30). This instrument evaluates three domains of nonrandomized studies: i) *selection,* encompassing representativeness of the exposed group, selection of the non-exposed group, ascertainment of exposure, and demonstration that the outcome of interest was not present at the beginning of the study; ii) *comparability*, evaluating whether confounders were adjusted for; and iii) *outcome*, assessing the adequacy of the follow-up period, cohort retention and the ascertainment of outcome data (30).

We appraised the quality of the studies by adding stars in each domain: The maximum total grade was 9, and a higher grade represented a better study quality. Any disagreement regarding the assessment of the quality of a study was discussed and resolved during a consensus meeting.

Summary of measures

Postoperative complications were expressed as Risk Ratio (RR) with 95% confidence intervals (CI).

Synthesis of results

Data synthesis was performed according to recommendations in the Cochrane Handbook for Systematic Reviews of Interventions, using the Review Manager software (*RevMan 5.3; Copenhagen: the Nordic Cochrane Centre, Cochrane Collaboration*). The meta-analysis of binary outcomes used study-specific frequency of events (presence or absence of postoperative complication) as outcome data and the resulting pooled estimates and confidence intervals were converted to odds ratios (OR). We calculated pooled OR and 95% confidence intervals (95% CI) using the Mantel – Haenszel method.

The random-effects mode was used because we assume that the true effect size varies from one study to the next, and that the studies in our analysis represent a random sample of effect sizes that could have been observed. Only unadjusted data was pooled. Since the binary outcomes were all adverse events, a positive OR indicated that frailty is associated with worse patient outcomes.

Assessment of heterogeneity

Heterogeneity of the effect size between studies was tested for each outcome to describe the extent of the between-study heterogeneity by using a standard Chi^2 value with a significance cut off level of $P < 0.10$ and by the I^2 statistic. An I^2 estimate greater than or equal to 50% with a significant value for Chi^2, was interpreted as evidence of statistical heterogeneity (31).

Assessment of reporting biases

Funnel plots were used to visually inspect for publication bias.

Subgroup analysis

We established a priori subgroup analysis of postoperative complications by frailty severity, type of frailty instrument and type of cancer. After collecting all the information from the included studies, the following subgroup analysis were also performed: study design (prospective, retrospective), location (USA, Europe, Asia), sample size (>1000, <1000), age (>65 years), follow-up time (<30, more than 1 year, not reported).

Sensitivity analysis

Sensitivity analysis was performed by calculating the effect size after omitting every single study.

RESULTS

Selected Studies

A PRISMA flow diagram summarizing the review process is presented in **Figure 1**. A total of 91 423 articles were found. Of these. 73 were duplicates and were removed. After screening the titles and abstracts, 91 278 studies were excluded, and 52 relevant articles were assessed for eligibility. After reading the full texts, 33 articles were excluded. Reasons for exclusion are listed in **Table 1**. In total, 19 studies were selected for qualitative and quantitative evaluation.

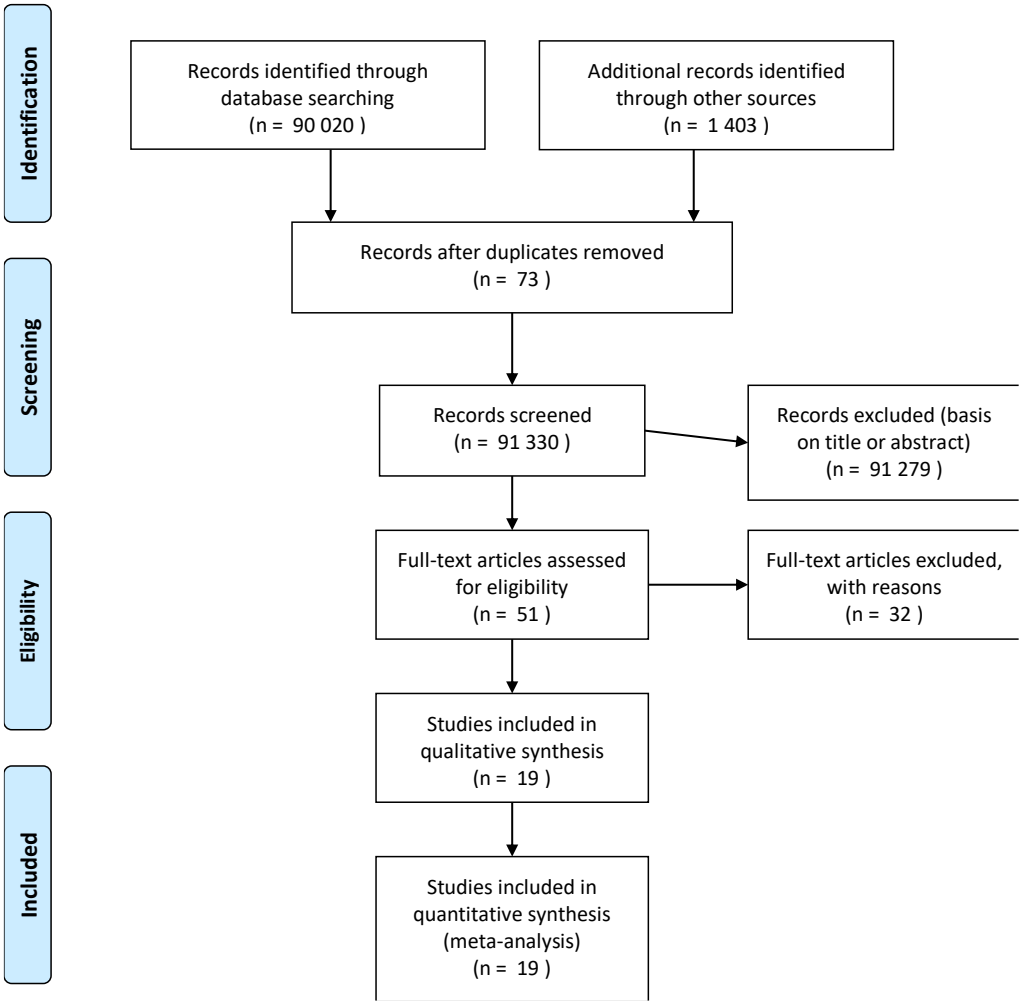

Figure 1: PRISMA Flow diagram of articles included in the present study.

Table 1: Reasons for exclusion

Study	Exclusion
Chappidi et al. 2016 (32)	Did not include post-operative complications
Fitzmaurice et al. 2017 (33)	Did not include post-operative complications
Uppal et al. 2015 (34)	Did not include post-operative complications
Nishida et al. 2016 (35)	Did not include frailty tool, exclusion criteria, post-operative complications
Ommundsen et al. 2018 (36)	Did not include post-operative complications
Ommundsen et al. 2014 (37)	Did not include post-operative complications
Abt et al. 2017 (38)	Did not include post-operative complications
Revenig et al. 2014 (39)	Did not include post-operative complications
Revenig et al. 2015 (40)	Did not include country, post-operative complications
Huisman et al. 2015 (41)	Did not include country
Revenig et al. 2013 (42)	Did not include country
Lin Hui-San, et al. 2016 (43)	It was a systematic review
Ronning et al. 2010 (44)	Irrelevant
Augustin et al. 2016 (45)	Irrelevant
LA van Vugt et al. 2014 (46)	Irrelevant
Pearl et al. 2017 (47)	Irrelevant
Kuroki et al. 2015 (48)	Did not include post-operative complications
Choe et al. 2017 (49)	Did not include post-operative complications
Landi et al. 2013 (50)	Did not include post-operative complications
Nieman et al. 2018 (51)	Irrelevant
Fagard et al. 2016 (52)	It was a systematic review
Shin Hyuk Yoo et al. 2016 (53)	Did not include study design, frailty tool
Wagner et al. 2018 (54)	Did not include country
Rinkinen et al. 2016 (55)	Irrelevant
Finlayson et al. 2012 (56)	Did not include frailty tool, post-operative complications
Salvi et al. 2016 (57)	Did not include country post-operative complications
Sunghye Kim et al. 2017 (58)	Irrelevant
Ugolini et al. 2014 (59)	Irrelevant
Jun Lu et al. 2017 (60)	Study design
Chen et al. 2016 (61)	Did not include post-operative complications
Dong-Dong Huang 2016 (62)	Did not have participants age, frailty tool
Roman Mayr 2018 (63)	Did not include country, frailty tool

Study characteristics

The detailed characteristics of the 19 studies are presented in **Table 2**. From the 19 studies, 7 were prospective (64-70) and 9 were retrospective (11, 23, 71-80). Overall, we included data from 243 328 patients, 41.8% (n=101 719) were male and 58.2% (n=141 609) were female, with an average of 63.6 years old.

Thirteen studies were conducted in the USA (America) (11, 23, 64, 66, 69, 71, 73-76, 78-80); 3 were from Europe (65, 67, 72), while the other 3 were from Asia (68, 70, 77). The reported data included those from gastrointestinal (11, 23, 67, 68, 70, 80), gynecologic (64, 74, 75), urologic (78, 79), head and neck (72, 76), abdominal (65, 66), pulmonary (77), neurologic (73), column cancer (71) and cancer in general (69).

Thirty-day post-operative complications were reported in 8 studies (23, 64, 66, 74-76, 79, 80), 1 year in 4 studies (65, 67, 69, 72), more than 1 year in 2 studies (68, 77) and not reported in 4 studies (11, 70, 71, 73, 78). Regarding the type of surgery, all the studies reported elective surgery.

A total of 8 different tools was used for evaluation of frailty: 9 studies used modified frailty index (mFI) (11, 23, 66, 68, 73, 75, 76, 78, 80), 3 used Fried phenotype (FP) (64, 69, 70), 2 used comprehensive geriatric assessment (CGA) (65, 67), 1 used simplified frailty index (SFI) (79), one used unintentional weight loss (74), one used Groningen frailty index (72), one used L3 muscle index (77) and one used spinal tumor frailty index (71). Irrespective of the frailty assessment method, the average prevalence of frailty was 17.5% (range 0.5%–41%). Overall, prevalence of postoperative complications was 38.58% (range 3.06%–76.32%) in frail patients and 19.77% (range 2.39%–48.04%) in non-frail patients.

Table 2: Characteristics of included studies.

.Author, published year	Location	Study design	Type of surgery	Cancer	Sample size
Sathianathen, 2018 (79)	USA	Retrospective	Elective	Bladder	5516
Konstantinidis, 2017 (66)	USA	Prospective	Elective	Intraperitoneal	1171
Vermillion, 2017 (80)	USA	Retrospective	Elective	Gastrointestinal	41 455
A Karim Ahmed, 2017 (71)	USA	Retrospective	Elective	primary spinal tumors	1589
Kim E. Y., 2017 (77)	Korea	Retrospective	Elective	Lung	272
Cloney, 2016 (73)	USA	Retrospective	Elective	Glioblastoma	319
Erin M. George, 2015 (75)	USA	Retrospective	Elective	Uterine, cervical, ovarian	66 105
Bras, 2015 (72)	Netherland	Retrospective	Elective	Head and neck	90
Danny Lascano, 2015 (78)	USA	Retrospective	Elective	Urologic	41 681
Tan, 2012 (70)	Asia	Prospective	Elective	Colorectal	83
Courtney Brooks, 2012 (64)	USA	Prospective	Elective	Gynecologic	37
Erekson, 2011 (74)	USA	Retrospective	Elective	Gynecologic	22 214
Kristjansson, 2010 (67)	Norway	Prospective	Elective	Colorectal	185
Pandit, 2018 (11)	USA	Retrospective	Elective	Colon	53 652
Hodari, 2013 (76)	USA	Retrospective	Elective	Esophageal	2095
Mogal, 2017 (23)	USA	Retrospective	Elective	Pancreatic	9986
Makary, 2010 (69)	USA	Prospective	Elective	General	594
Jun Lu, 2018 (68)	China	Prospective	Elective	Gastric	119
Kenig, 2018 (65)	Poland	Prospective	Elective	Abdominal	165

Table 2: Characteristics of included studies *(continued).*

Author, published year	Age	Male (%)	Type of complication	Frailty tool	Frailty criteria definition
Sathianathen, 2018 (79)	median 69 (62-76)	4228 (76.7)	Surgical complications which defined by NSQIP, Clavien dindo classification grade III-V	symplified Frailty Index (5 items)	0 robust, 1 mild frailty, 2 moderate frailty, 3+ frailty
Konstantinidis, 2017 (66)	≥ 70	521 (44.5)	Surgical complications which defined by NSQIP, Clavien Dindo classification grade IV	MFI (11 items)	Non frail, midly frail, severely frail
Vermillion, 2017 (80)	mean 72.4	Overall- 21840 (52.7) No frailty- 19247 (51.6), frailty- 2593 (61.7)	Surgical complications which defined by NSQIP and Clavien Dindo classification	MFI 11 items	≤0.27 Non frail, >0.27 frail
A Karim Ahmed, 2017 (71)	median 47 (21-61)	823 (51,8)	Surgical complications which defined by NSQIP	STFI (9 items)	No frailty, mild, frailty, moderate frailty, severe frailty
Kim E. Y., 2017 (77)	mean age 62.9 (dp 9.6 yr)	164 (60.3)	Overall, respiratory, cardiac	L3 muscle index	Sarcopenia, no sarcopenia
Cloney, 2016 (73)	≥ 65	N/A	overall, systemic, regional, neurological	MFI (11 items)	0 Least frail, 1 or 2 moderately frail, ≥3 most frail
Erin M. George, 2015 (75)	≥ 60	0 (women)	Surgical complications which defined by NSQIP, Clavien dindo classification grade IV	MFI (11 items)	0 non frail, 0-0.09, 0.1-0.19 , 0.2-0.29, 0.3-0.49, ≥0.5 Frail
Bras, 2015 (72)	≥ 65	67 (74,4)	Clavien dindo classification	GFI (15 items)	≥4 frail, <4 non frail
Danny Lascano, 2015 (78)	Mean age 62 (prostatectomy, radical nephrectomy, nephroureterectomy); mean age 59 (partial nephrectomy, cystectomy)	23 350 (100) prostatectomy; 3 466 (60.8) partial nephrectomy; 4 760 (61.1)- radical nephrectomy; 883 (61,3)- nephroureterectomy; 2 722 (80,4)- cystectomy	Clavien dindo classification grade IV	MFI (11 items)	0–0.05 non frail, 0.05–0.10, 0.10–0.15, 0.15–0.20, >0.20 Frail

Table 2: Characteristics of included studies *(continued).*

Author, published year	Age	Male (%)	Type of complication	Frailty tool	Frailty criteria definition
Tan, 2012 (70)	≥ 75	N/A	Clavien dindo classification grade II or above	Fried (5 items)	No frailty, frailty
Courtney Brooks, 2012 (64)	≥ 65	N/A	Surgical complications which defined by NSQIP	Fried (5 items)	Not frail, intermediately frail, frail
Erekson, 2011 (74)	≥ 16	0 (women)	Surgical complications which defined by NSQIP	Unintentional wheight loss	no frailty, frailty
Kristjansson, 2010 (67)	≥ 70	83 (43)	Clavien dindo classification	CGA (6 items)	Fit, intermediate, frail
Pandit, 2018 (11)	≥ 65	33 264 (62)	In-hospital complications, hospital LOS, adverse discharge disposition, mortality	MFI (9 items)	>27 frail, ≤27 non frail
Hodari, 2013 (76)	≥ 65	N/A	The clavien-dindo classification grade IV (Respiratory and cardiovascular)	MFI (11 items)	0 non frail , 0.09 , 0.18, 0.27, 0.36, 0.45 frail
Mogal, 2017 (23)	mean 64.1 (+ - 12.4)	5121 (51.2)	Surgical complications which defined by NSQIP and the clavien dindo classification grade III and IV	MFI (11 items)	<0.27 non frail, ≥ 0.27 frail)
Makary, 2010 (69)	≥ 65	Overall 236 (40) No frailty 112 (32.4), moderate frailty 88 (47.3), frailty 36 (58.1)	Surgical complications which defined by NSQIP	Fried (5 items)	No frailty, moderate frailty, frailty
Jun Lu, 2018 (68)	≥ 80	HPMFI 39 (90.7) LPMFI 58 (76.3)	The clavien dindo classification	MFI (8 items)	Low preoperative modified frailty index (LPMFI)- Frail, High preoperative modified frailty index (HPMFI)- Non frail
Kenig, 2018 (65)	≥ 70	94 (57)	The clavien dindo classification	CGA (10 items)	No frailty, frailty

Table 2: Characteristics of included studies *(continued).*

Author, published year	Inclusion criteria	Exclusion criteria	Follow-up	Results (events/total)	Results (events/total)
Sathianathen, 2018 (79)	Patients concomitant bladder cancer diagnosis bases on international classification of diseases	Patients with metastatic disease or not elective	30 days after surgery	0=140/1817, 1=254/2469, 2=167/1101, 3+=33/123	No frailty 140/1817, moderate frailty 421/3570, frailty 32/123
Konstantinidis, 2017 (66)	Age fo 70 years or older and albumin level of 3 or lower	N/A	30 days after surgery	Non frail 716/48, midly frail 449/49, severely frail 6/2	No frailty 716/48, midly frail 449/49, severely frail 6/2
Vermillion, 2017 (80)	N/A	Patients who were ASA 5, diagnosed with preoperative sepsis, undergoing emergency surgery, or missing at least one of the 11 variables used to determine mFI	30 days after surgery	≤0.27 9296/3725, >0.27 1548/4203	No frailty 9296/3725, frailty 1548/4203
A Karim Ahmed, 2017 (71)	Primary discharge diagnosis of benign neoplasm, vertebral column, benign neoplasm of sacrum and coccyx, malignant neoplasm of sacrum and coccyx	Spinal decompression and/or fusion	N/A	No Frailty 65/1139, mild frailty 60/319, moderate frailty 28/95, severe frailty 15/35	No Frailty 65/1139, mild frailty 60/319, moderate frailty 28/95, frailty 15/35
Kim E. Y., 2017 (77)	N/A	Patients in whom their baseline positron emission tomography/computed tomography images were unavailable for evaluation	26.3 months	Overall Sarcopenia 61/18 No sarcopenia 211/44	Sarcopenia 61/18 No sarcopenia 211/44

Table 2: Characteristics of included studies *(continued).*

Author, published year	Inclusion criteria	Exclusion criteria	Follow-up	Results (events/total)	Results (events/total)
Cloney, 2016 (73)	patients with lobar glioblastioma who underwent craniotomy	Patients with a history of lower grade glioma or recurrent disease at the time of presentation	N/A	Least frail 0= 45/3, moderately frail 1 or 2= 151/34, most frail ≥3= 47/15	No frailty 45/3, moderate frail 151/34, Frail 47/15
Erin M. George, 2015 (75)	N/A	N/A	30 days after surgery	Clavian IV 0=44045/432 , 0-0.09=9341/145 , 0.1-0.19=2555/76 , 0.2-0.29=7930/161 , 0.3-0.49=2110/79 , ≥0.5=124/9; Any complication 0=44045/1634 , 0-0.09=9341/447 , 0.1-0.19=2555/171 , 0.2-0.29=7930/404 , 0.3-0.49=2110/169 , ≥0.5=124/18	Clavian IV No frailty 53386/576, moderate frail 2555/76, frail 10164/249; Any complication. No frailty 53386/2081, moderate frailty 2555/171, frail 10164/591
Bras, 2015 (72)	patients suitable for surgical treatment, patients with both mucosal head and neck cancer and those with skin cancer of the head and neck cancer	Patients with histological different malignant tumour types and malignancies of the thyroid gland	1 month after surgery	frail (GFI≥4) 36/9 not frail (GFI<4) 54/9	Frailty 36/9, Non frail 54/9

Table 2: Characteristics of included studies *(continued).*

Author, published year	Inclusion criteria	Exclusion criteria	Follow-up	Results (events/total)	Results (events/total)
Danny Lascano, 2015 (78)	N/A	Nononcological cases	N/A	**Radical prostatectomy** 0–0.05=81/11,312 0.05–0.10=109/9,256 0.10–0.15=24/1,656 0.15–0.20=19/637 >0.20= 13/219; **Radical and partial nephrectomy** 0–0.05=66/4,390/ 0.05–0.10=169/5,546 0.10–0.15=61/1,534 0.15–0.20=82/1,349 >0.20= 57/681; **Nephroureterectomy** 0–0.05=5/410 0.05–0.10=32/634 0.10–0.15=13/181 0.15–0.20=15/130 >0.20= 11/88; **Radical cystectomy** 0–0.05=73/1,108 0.05–0.10=122/1,330 0.10–0.15=60/423 0.15–0.20=37/351 >0.20= 30/176;	**Radical prostatectomy**: No frailty 190/20838, moderate frailty 43/2293, frailty 13/219. **Radical and partial nephrectomy**: No frailty 235/9936, moderate frailty 143/2883, Frailty 57/681. **Nephroureterectomy**: No frailty 37/1044, moderate frailty 28/311, frailty 11/88. **Radical cystectomy**: No frailty 195/2438, moderate frailty 97/774, frailty 30/176.
Tan, 2012 (70)	N/A	Patients who declined data collection and with parkinsonism or taking levodopa or antidepressants	30 days after surgery	No frailty 11/60, frailty 11/23	No frailty 11/60, frailty 11/23

Table 2: Characteristics of included studies *(continued).*

Author, published year	Inclusion criteria	Exclusion criteria	Follow-up	Results (events/total)	Results (events/total)
Courtney Brooks, 2012 (64)	65 years or greater and a planned surgical procedure by a gynecologic oncologist	History of parkinson's disease, a history of prior stroke, a mini-mental state exam score of ≤18, either cardibopa/levodopa, or donezepil hydrochloride as a current medication, an inability to walk 15ft or a known neurologic disorder affecting grip strength.	30 days after surgery	Not frail 21/5, intermediately frail 10/1, Frail 6/4	No frailty 21/5, intermediately frail 10/1, Frail 6/4
Erekson, 2011 (74)	N/A	Classification of male sex with gynecolgic procedures, current pregnancy, Previous operation within 30 days of current procedures, CPT-4, code inconsistent with gynecologic procedure.	30 days after surgery	unintentional wheight loss of more than 10% in past 6 mo functional status (dependent for activities of daily living) No frailty 21397/792, frailty 817/25	No frailty 21397/792, frailty 817/25

Table 2: Characteristics of included studies *(continued).*

Author, published year	Inclusion criteria	Exclusion criteria	Follow-up	Results (events/total)	Results (events/total)
Kristjansson, 2010 (67)	Patients aged 70 years or older who were planned for surgery of a confirmed or suspected colorectal cancer	N/A	30 days after surgery	Fit=10/21 Intermediate 39/81 Frail 58/76	Fit=10/21 Intermediate 39/81 Frail 58/76
Pandit, 2018 (11)	N/A	emergent surgery, rectal cancer	N/A	>27=5400/18241 ≤27=6586/35411	Frailty 5 400/18 241 Non-frailty 6586/35 411
Hodari, 2013 (76)	Demographics, surgical profiles, comorbidities and preoperative and intraoperative variables	N/A	surgery after 30 days (chemoterapy), surgery after 90 days (radiotherapy)	0=795/142, 0.09=710/178, 0.18=401/126, 0.27=140/48, 0.36=36/16, 0.45=13/8	No frailty 1505/320, intermediate frailty 401/126 , Frailty 189/72
Mogal, 2017 (23)	Lower risk patients who were operative candidates	N/A	30 days after surgery	mFI < 0.27=9349/3364 ≥ 0.27=637/309	No frailty 3364/9349, frailty 309/637
Makary, 2010 (69)	N/A	Patients with parkinson disease, previous stroke, a mini mental status examination score and those taking carbidopa/levodopa, donepezil hydrochloride or antidepressants.	30 days after surgery	No frailty 80/346, moderate frailty 77/186, frailty 34/62	No frailty 80/346, moderate frailty 77/186, frailty 34/62

Table 2: Characteristics of included studies.

Author, published year	Inclusion criteria	Exclusion criteria	Follow-up	Results (events/total)	Results (events/total)
Jun Lu, 2018 (68)	Patients with na age than 80 years; a diagnosis of primary gastric cancer based on a pathology report, without without evidence of distant metastases; an R0 resection and no preoperative chemoradiotherapy.	The presence of other malignancies; a preoperative or intraoperative examination showuing distant metastasis; T4b tumours; lack of a pathologically confirmed diagnosis and conversion to laparotomy	Median 37 months	HPMFI (frail) vs CVd grade I= 2/43, LPMFI (non frail) vs CVd grade I= 1/76, HPMFI (frail) vs CVd grade II= 18/43, LPMFI (non frail) vs CVd grade II= 17/76, HPMFI (frail) vs CVd grade IIIa= 2/43, LPMFI (non frail) vs CVd grade IIIa= 3/76, HPMFI (frail) vs CVd grade IIIb= 1/43, LPMFI (non frail) vs CVd grade IIIb= 0/76, HPMFI (frail) vs CVd grade IV= 1/43, LPMFI (non frail) vs CVd grade IV= 2/76, HPMFI (frail) vs CVd grade V= 0/43, LPMFI (non frail) vs CVd grade V= 0/76	HPMFI (frail) vs CVd grade I= 2/43, LPMFI (non frail) vs CVd grade I= 1/76, HPMFI (frail) vs CVd grade II= 18/43, LPMFI (non frail) vs CVd grade II= 17/76, HPMFI (frail) vs CVd grade IIIa= 2/43, LPMFI (non frail) vs CVd grade IIIa= 3/76, HPMFI (frail) vs CVd grade IIIb= 1/43, LPMFI (non frail) vs CVd grade IIIb= 0/76, HPMFI (frail) vs CVd grade IV= 1/43, LPMFI (non frail) vs CVd grade IV= 2/76, HPMFI (frail) vs CVd grade V= 0/43, LPMFI (non frail) vs CVd grade V= 0/76
Kenig, 2018 (65)	Elective abdominal cancer surgery	Patients with distant metastases, peritoneal carcinomatosis and underwent laparoscopy/laparotomy	30 days after surgery	No frailty 102/34 Frailty 63/ 48	No frailty 102/34 Frailty 63/ 48

Risk of bias and applicability

The total score regarding quality assessment of the 19 included articles in shown in **Table 3**. The scores ranged from 7 to 9 with, a mean value of 8. The overall classification of the 19 articles was “good quality”.

Table 3: Quality assessment tool.

Quality Assessment Criteria	Acceptable (*)	Sathianathen et al. (2018) (79)	Konstantinidis et al. (2017) (66)	Jun Lu et al. (2018) (68)	Kenig et al. (2018) (65)	Kristjansson et al. (2010) (67)
Selection						
Representativeness of exposed cohort?	Representative of average adult in community (age/sex/being at risk of disease)	*	*	*	*	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*	*	*	*	*
Ascertainment for exposure?	Secured records, Structured interview	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Only incident cases of CRC	*	*	*	*	*
Comparability						
Study controls for age/sex?	Yes	*	*	*	*	*
Study controls for at least 3 additional risk factors?	BMI, ethnicity, family H/O CRC, smoking, alcohol, physical activity, dietary factors (red meat, fat intake, fruits and vegetables), DM duration/severity, aspirin/NSAID, station use, Vitamin D/Calcium intake, hormone replacement therapy	*	*	*	*	*
Outcome						
Assessment of outcome?	Independent blind assessment, record linkage	*	*	*	*	*
Was follow-up long enough for outcome to occur?	Follow-up= 30 days	*	*	/	/	/
Adequacy of follow-up of cohorts?	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	*	*	*	*	*
Overall Quality Score (Maximum=9)		9	9	8	8	8

Table 3: Quality assessment tool *(continued).*

Quality Assessment Criteria	Acceptable (*)	Cloney et al. (2015) (73)	Tan et al. (2012) (70)	Makary et al. (2010) (69)	Courtney-Brooks, et al. (2012) (64)	Vermillion et al. (2017) (80)
				Selection		
Representativeness of exposed cohort?	Representative of average adult in community (age/sex/being at risk of disease)	*	*	*	*	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*	*	*	*	*
Ascertainment for exposure?	Secured records, Structured interview	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Only incident cases of CRC	*	*	*	*	*
				Comparability		
Study controls for age/sex?	Yes	*	*	*	*	*
Study controls for at least 3 additional risk factors?	BMI, ethnicity, family H/O CRC, smoking, alcohol, physical activity, dietary factors (red meat, fat intake, fruits and vegetables), DM duration/severity, aspirin/NSAID, station use, Vitamin D/Calcium intake, hormone replacement therapy	*	*	*	*	*
				Outcome		
Assessment of outcome?	Independent blind assessment, record linkage	*	/	*	*	*
Was follow-up long enough for outcome to occur?	Follow-up= 30 days	/	/	/	*	*
Adequacy of follow-up of cohorts?	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	*	*	/	*	*
Overall Quality Score (Maximum=9)		8	7	7	9	9

Table 3: Quality assessment tool *(continued).*

Quality Assessment Criteria	Acceptable (*)	Erekson et al. (2011)	Erin M. George et al. (2016)	A Karim Ahmed et al. (2017)	Bras et al. (2015)	Danny Lascano, B.A. (2015)
		Selection				
Representativeness of exposed cohort?	Representative of average adult in community (age/sex/being at risk of disease)	*	*	*	*	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*	*	*	*	*
Ascertainment for exposure?	Secured records, Structured interview	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Only incident cases of CRC	*	*	*	*	*
		Comparability				
Study controls for age/sex?	Yes	*	*	*	*	*
Study controls for at least 3 additional risk factors?	BMI, ethnicity, family H/O CRC, smoking, alcohol, physical activity, dietary factors (red meat, fat intake, fruits and vegetables),hormone replacement therapy	*	*	*	*	*
		Outcome				
Assessment of outcome?	Independent blind assessment, record linkage	*	*	*	*	*
Was follow-up long enough for outcome to occur?	Follow-up= 30 days	*	*	/	*	/
Adequacy of follow-up of cohorts?	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	*	*	/	*	*
Overall Quality Score (Maximum=9)		9	9	7	9	8

Table 3: Quality assessment tool *(continued).*

Quality Assessment Criteria	Acceptable (*)	Pandit et al. (2018) (11)	Hodari et al (2013) (76)	Mogal et al (2017) (23)	Jun Lu (2018) (68)
		Selection			
Representativeness of exposed cohort?	Representative of average adult in community (age/sex/being at risk of disease)	*	*	*	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*	*	*	*
Ascertainment for exposure?	Secured records, Structured interview	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Only incident cases of CRC	*	*	*	*
		Comparability			
Study controls for age/sex?	Yes	*	*	*	*
Study controls for at least 3 additional risk factors?	BMI, ethnicity, family H/O CRC, smoking, alcohol, physical activity, dietary factors (red meat, fat intake, fruits and vegetables),hormone replacement therapy	*	*	*	*
		Outcome			
Assessment of outcome?	Independent blind assessment, record linkage	*	*	*	*
Was follow-up long enough for outcome to occur?	Follow-up= 30 days	/	*	*	/
Adequacy of follow-up of cohorts?	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	*	*	*	*
Overall Quality Score (Maximum=9)		8	9	9	8

Synthesis of the results

Frailty and postoperative complications

The risk of post-operative complications between frail and non-frail was possible to obtain in 19 studies (11, 23, 64-80). In 10 studies (64, 66, 67, 69, 71, 73, 75, 76, 78, 79), we had to dichotomize the data, while in 9 studies (11, 23, 65, 68, 70, 72, 74, 77, 80), the data was already presented accordingly. Of these, 5 showed no increased risk (66, 72-74, 77). The cumulative analysis showed a significant association of frailty with postoperative complications (OR= 2.23, 95% CI: 1.91-2.60; p<0.00001) but the heterogeneity was found to be high (I^2=88%; p<0.00001) (**Figure 2**). In order to explore the sources of heterogeneity, we performed several sub-analyses.

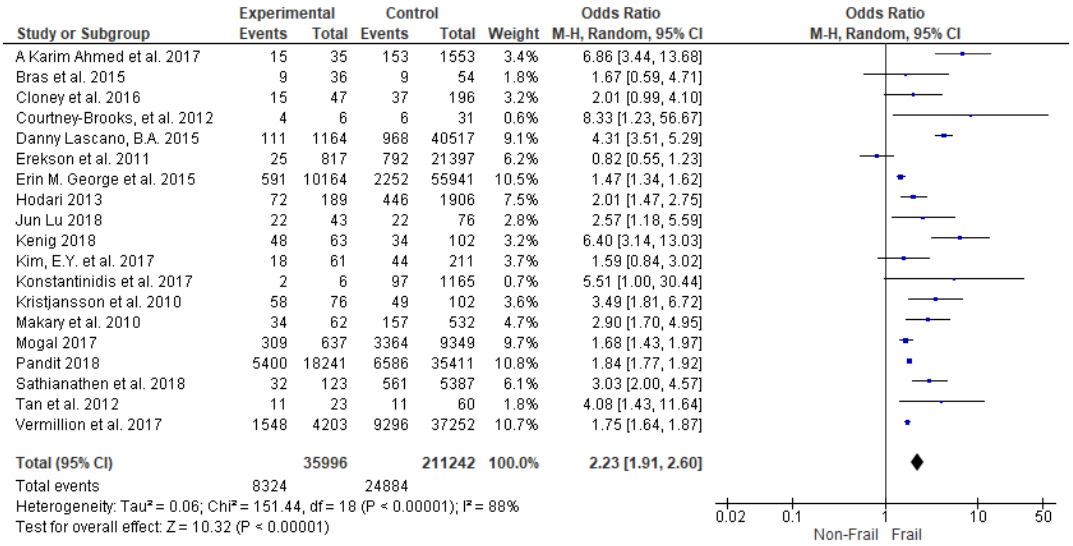

Figure 2: Forest plot for the association between frailty and postoperative complications.

Priori-defined sub-analysis

Frailty severity and postoperative complications

In order to analyze the risk of post-operative complications by frailty severity (frail versus pre-frail versus robust), the data was trichotomized in 10 studies (64, 66, 67, 69, 71, 73, 75, 76, 78, 79) while in 9 studies (11, 23, 65, 68, 70, 72, 74, 77,

80) the data was already presented accordingly. Frail patients were shown to be at greater risk than prefrail patients in 5 studies (64, 67, 71, 78, 79) and then robust patients in 9 studies (66, 67, 69, 71, 73, 75, 76, 78, 79). The pooled analysis showed that the risk of postoperative complications in the frail group was significantly higher than the pre-frail (OR: 1.96; 95% CI: 1.33-2.89; I^2=86%; p<0.00001) and robust group (OR: 4.20; 95% CI: 2.45-7.21; I^2=95%; p<0.00001). The risk of postoperative complications in the pre-frail group was also significantly higher than the robust group (OR: 2.09; 95% CI: 1.65-2.64; I^2=83%; p<0.00001) (**Figure 3**).

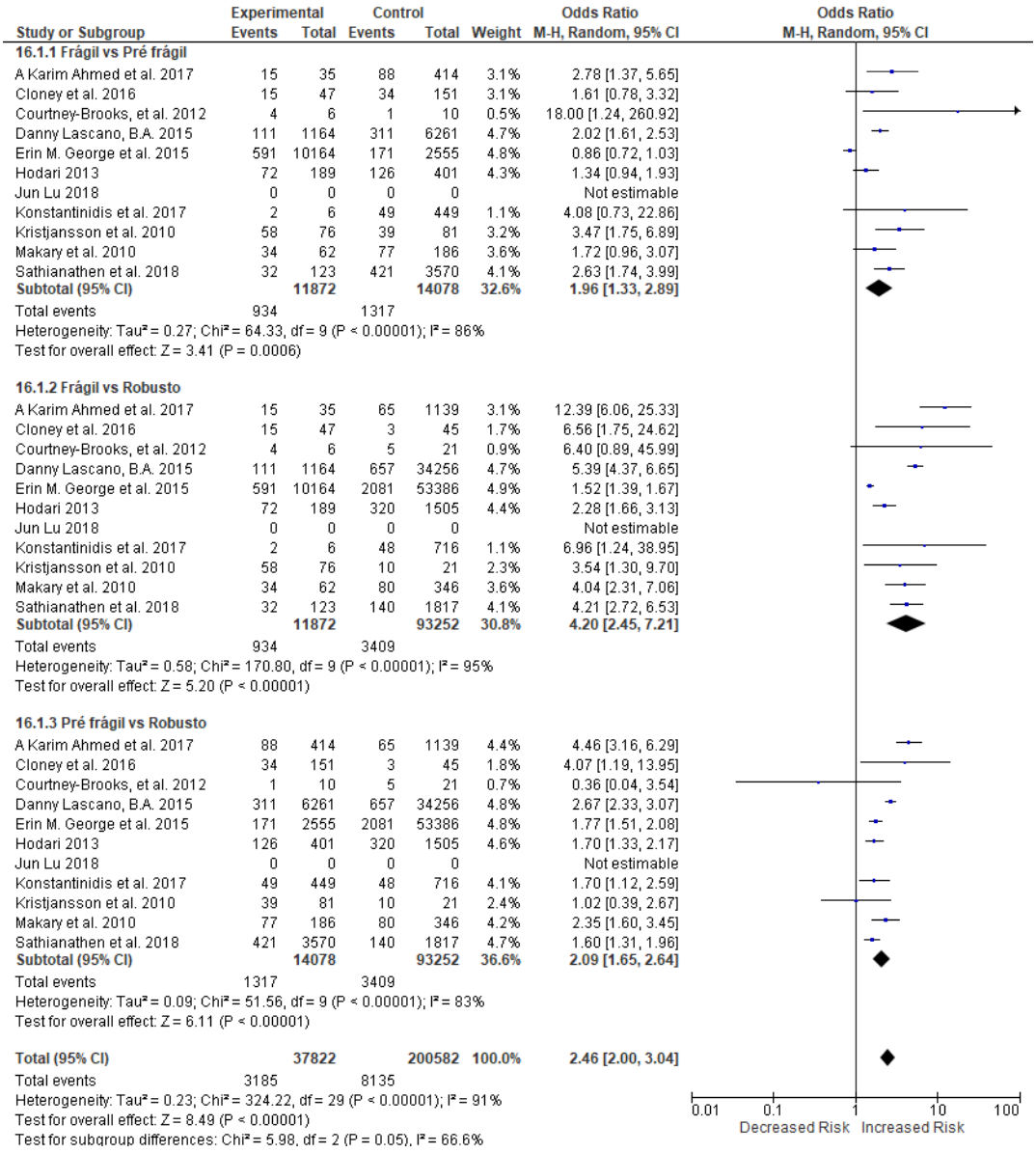

Figure 3: Forest plot for sub-analysis of postoperative complications by frailty severity.

Frailty instrument and postoperative complications

The association of frailty and postoperative complications was determined in 9 articles (11, 23, 66, 68, 73, 75, 76, 78, 80) with mFI, 3 with FP (64, 69, 70), 2 with CGA (65, 67) and 5 with others frailty tools (71, 72, 74, 77, 79). The cumulative analysis showed that frail patients had an OR of 2.02 as defined by the mFI (95% CI: 1.72-2.37; I^2=91%, p<00001), OR of 3.30 as defined by FP (95% CI: 2.08-5.23; I^2=0%, p<0.00001) and an OR of 4.65 as defined by the CGA (95% CI: 2.56-8.42; I^2=34%, p<0.00001) **(Figure 4).**

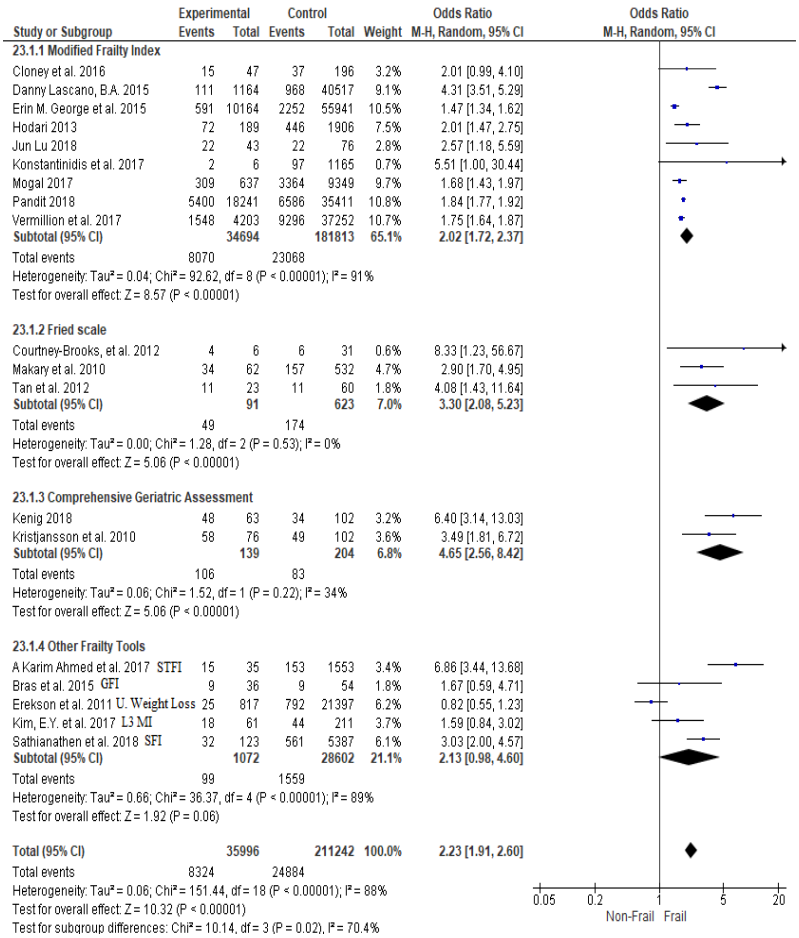

Figure 4: Forest plot for sub-analysis of postoperative complications by frailty instrument.

Type of cancer and postoperative complications

The association of frailty and postoperative complications was reported in 6 studies (11, 23, 67, 68, 70, 80) for gastrointestinal cancer, 3 studies (64, 74, 75) for gynecologic cancer, 2 studies (78, 79) for urologic cancer, 2 studies (72, 76)

for head and neck cancer, 2 studies (65, 66) for abdominal cancer, 1 study (71) for column cancer, 1 study (73) for neurologic cancer, 1 study (77) for pulmonary cancer and 1 study (69) for cancer in general. Pooled data suggests a significant OR of frailty with postoperative complications in the setting of gastrointestinal (OR=1.81; 95% CI: 1.68-1.95; I^2=46%, p<0.00001), urologic (OR=3.78; 95% CI: 2.70-5.29; I^2=56%, p<0.00001), head and neck (OR=1.98; 95% CI: 1.47-2.67; I^2=0%, p<0.00001) and abdominal cancer (OR=6.26; 95% CI: 3.25-12.07; I^2=0%, p<0.0007), but not for gynecologic (OR=1.34; 95% CI: 0.73-2.46; I^2=82%, p<0.35) (**Figure 5**).

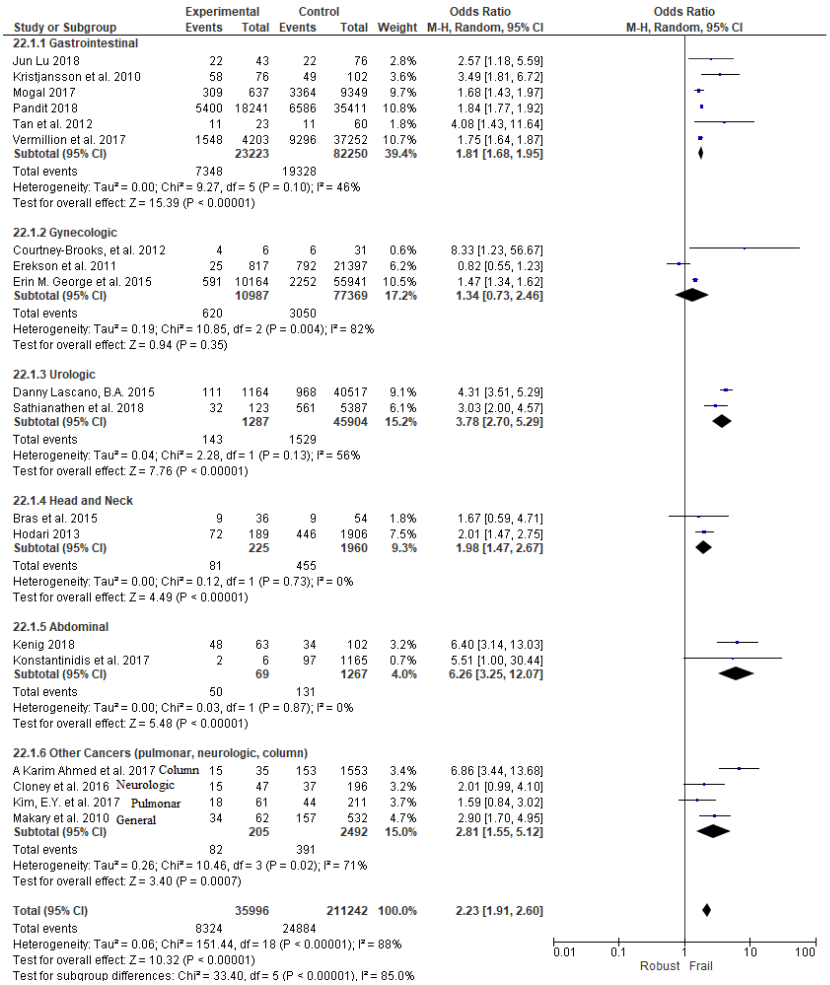

Figure 5: Forest plot for sub-analysis of postoperative complications in frail patients by type of cancer.

Subgroup analysis defined after data collection

Sub-analysis by severity of postoperative complications (Clavien-Dindo)

The severity of post-operative complications by Clavien-Dindo (CD) was reported 10 studies. Seven studies (23, 66, 75, 76, 78-80) reported data regarding CD class III and IV complications and 3 studies (67, 70, 72) included all the classes (I to IV). One study (66) did not show increased risk of CD class III and IV in frail patients (OR=5.51; 95% CI: 1.00-30.44) and another one (72) for CV I-IV (OR=1.67; 95% CI: 0.59-4.71) (**Figure 6**). Cumulative analysis showed that frail patients have an increased risk of postoperative complications with CD classification of III-IV (OR=2.40; 95% CI: 1.88-3.06; I^2=91%, p<0.0001) or CD I-IV (OR=3.96: 95% CI: 1.60-9.82; I^2=64%, p<0.003).

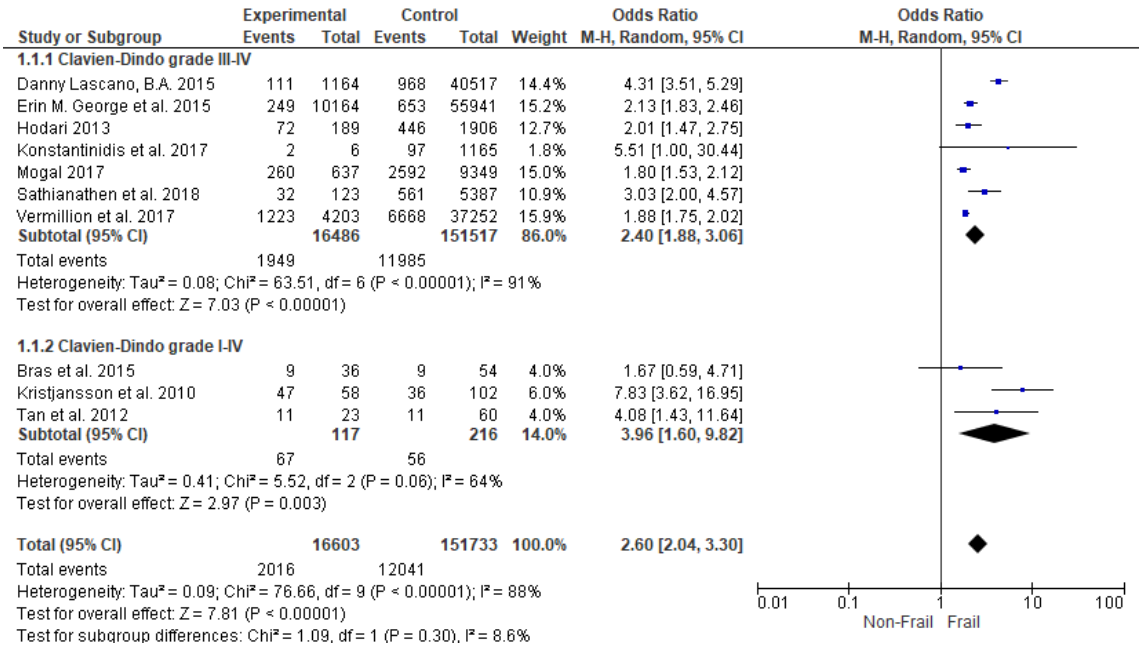

Figure 6: Forest plot for postoperative complications in frail patients as stratified by Clavien-Dindo III-IV or I-V.

Sub-analysis by study design

The association of frailty and occurrence of any postoperative complications was reported in 7 prospective studies (64-70) and 12 retrospective studies (11, 23, 71-80). Only 1 prospective (66) and 4 retrospective studies (72, 73) (74) (77) did not show a significant increased risk in frail patients. The cumulative analysis

showed an OR of 3.68 (95% CI: 2.72-4.97; I^2=0%; p<0.00001) for prospective studies, while retrospective studies showed an OR of 1.99 (95% CI: 1.70-2.33; I^2=88%; p<0.00001) (**Figure 7**).

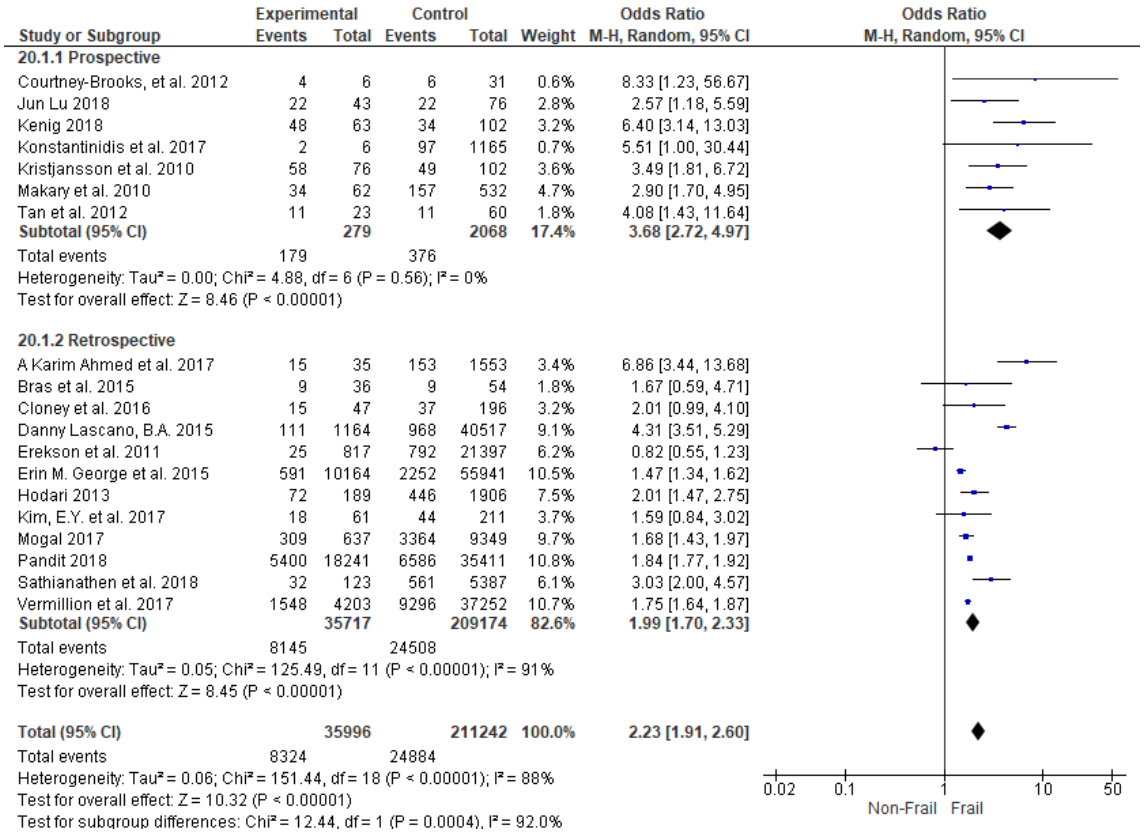

Figure 7: Forest plot for postoperative complications in frail patients as stratified by prospective and retrospective studies.

Sub-analysis by location of studies

The association of frailty and occurrence of any postoperative complications was reported in 3 studies from Europe (65, 67, 72), 13 from the USA (11, 23, 64, 66, 69, 71, 73-76, 78-80) and 3 from Asia (68, 70, 77). The cumulative analysis shows a significant association of frailty with postoperative complications in studies from Europe (OR=3.61; 95% CI: 1.83-7.15; I^2=56%; p=0.002), from the USA (OR=2.10; 95% CI: 1.78-2.47; I^2=91%; p<0.00001) and from Asia (OR=2.27; 95% CI: 1.37-3.78; I^2=91%; p<0.00001) (**Figure 8**).

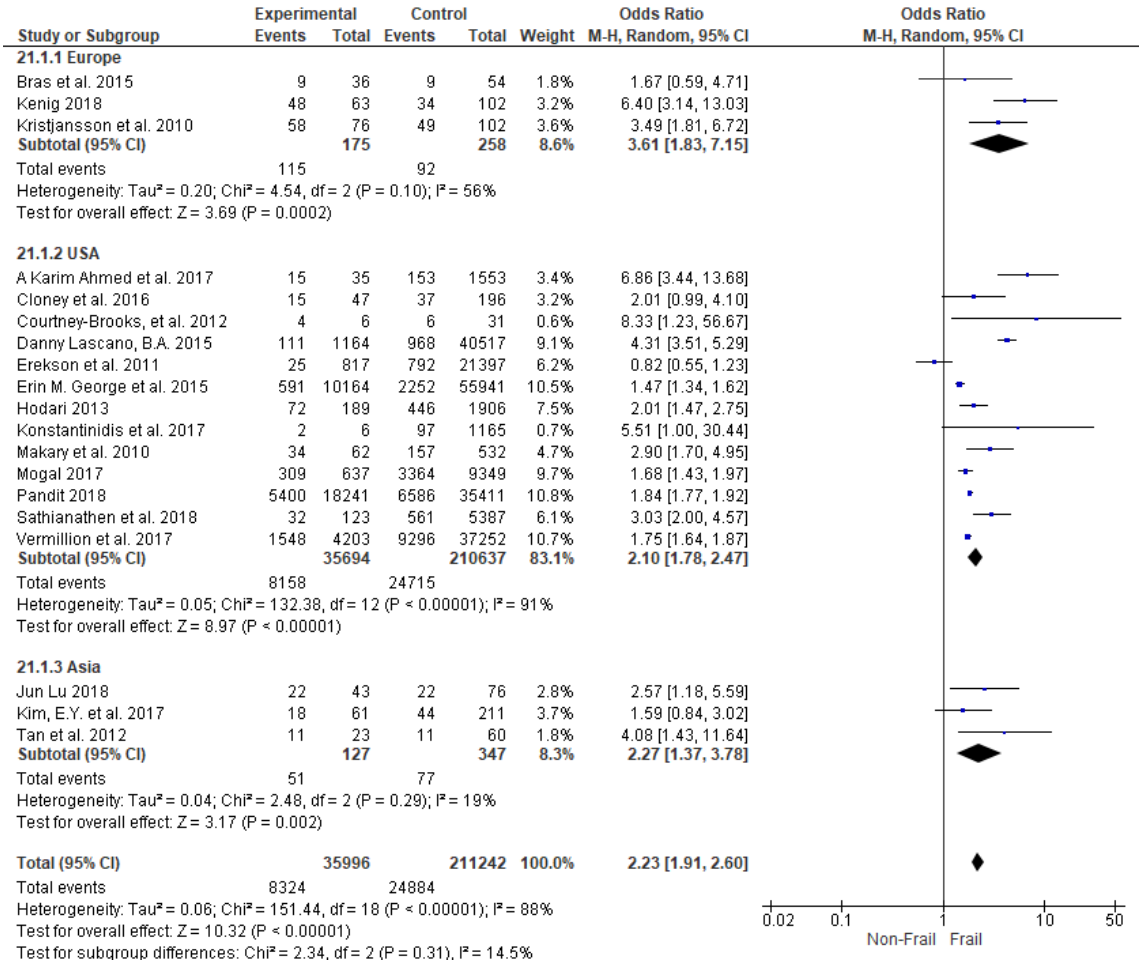

Figure 8: Forest plot for postoperative complications in frail patients as stratified by place of the study.

Sub-analysis by sample size

Ten studies (11, 23, 66, 71, 74-76, 78-80) had reported the association of frailty and the occurrence of postoperative complications with a sample of less than one thousand patients and nine studies (64, 65, 67-70, 72, 73, 77) had reported the association with more than one thousand patients. The cumulative analysis of the data showed a significant association of frailty with postoperative complications of both lower (OR= 2.04; 95% CI: 1.72-2.42; p<0.00001; I^2=93%; p<0.00001) and higher sample sized studies (OR= 2.87; 95% CI: 1.91-2.60; p<0.00001;I^2=34%; p<0.00001).

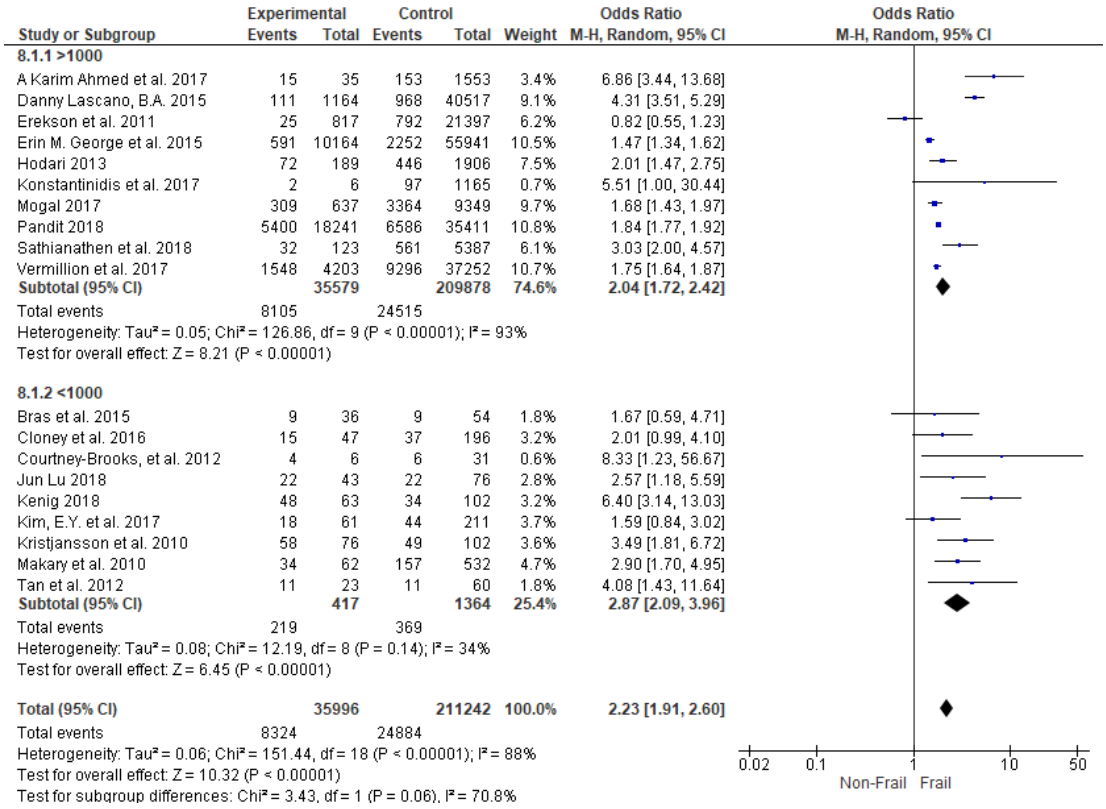

Figure 7: Forest plot for postoperative complications in frail patients as stratified by sample size.

Sub-analysis by age

The association of frailty and postoperative complications in patients with 65 or more years old was determined in 11 studies (11, 64-70, 72, 73, 76), thus excluding other studies that included younger patients. Three articles (73) (66) (72) did not show significant association between frailty and postoperative complications. Pooled analysis showed an OR of 2.63 (95% CI: 2.02-3.44; I^2=60%; p=0.0001) of postoperative complications for frail patients older than 65 (**Figure 8**).

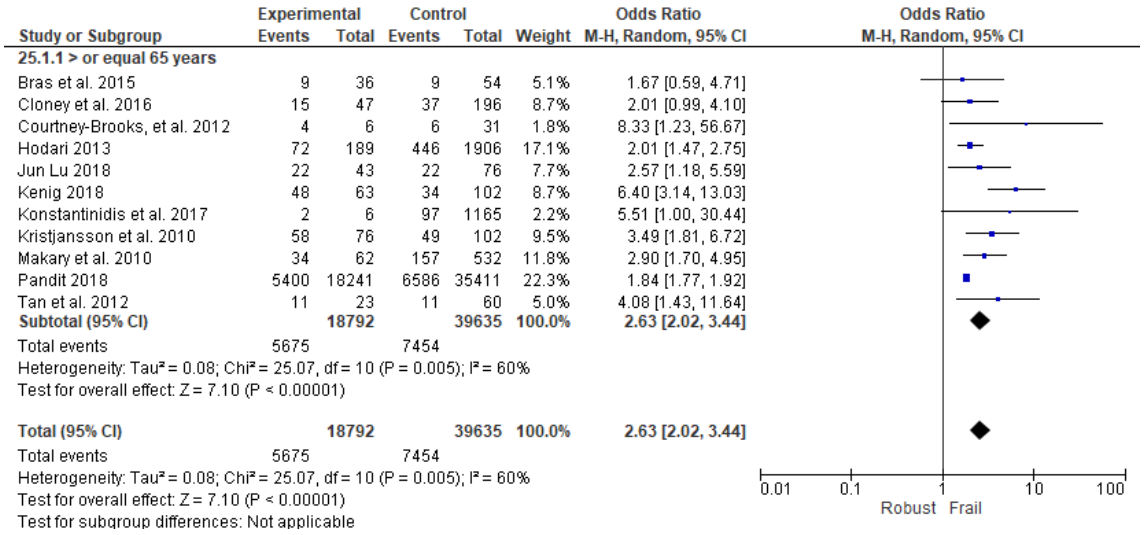

Figure 9: Forest plot for postoperative complications in frail patients older than 65 years.

Sub-analysis by follow-up period

The association of frailty and postoperative complications was determined in 13 articles (23, 64-67, 69, 70, 72, 74-76, 79, 80) with the follow-up 30 days after surgery, 2 articles (68, 77) with a follow-up of more than one year after surgery and 4 articles (11, 71, 73, 78) did not reported the timing of follow-up. Three articles did not observe a significant risk of complications at 30 days after surgery (74) (66) (72) and one article at a follow-up above 1 year (77). The cumulative analysis showed a significant association of frailty with postoperative complications at 30 days (OR= 2.01, 95% CI: 1.68-2.40; I^2=80%; p<0.00001) and above 1 year after surgery (OR= 1.93, 95% CI: 1.18-3.17; I^2=0%; p<0.009) (**Figure 10**).

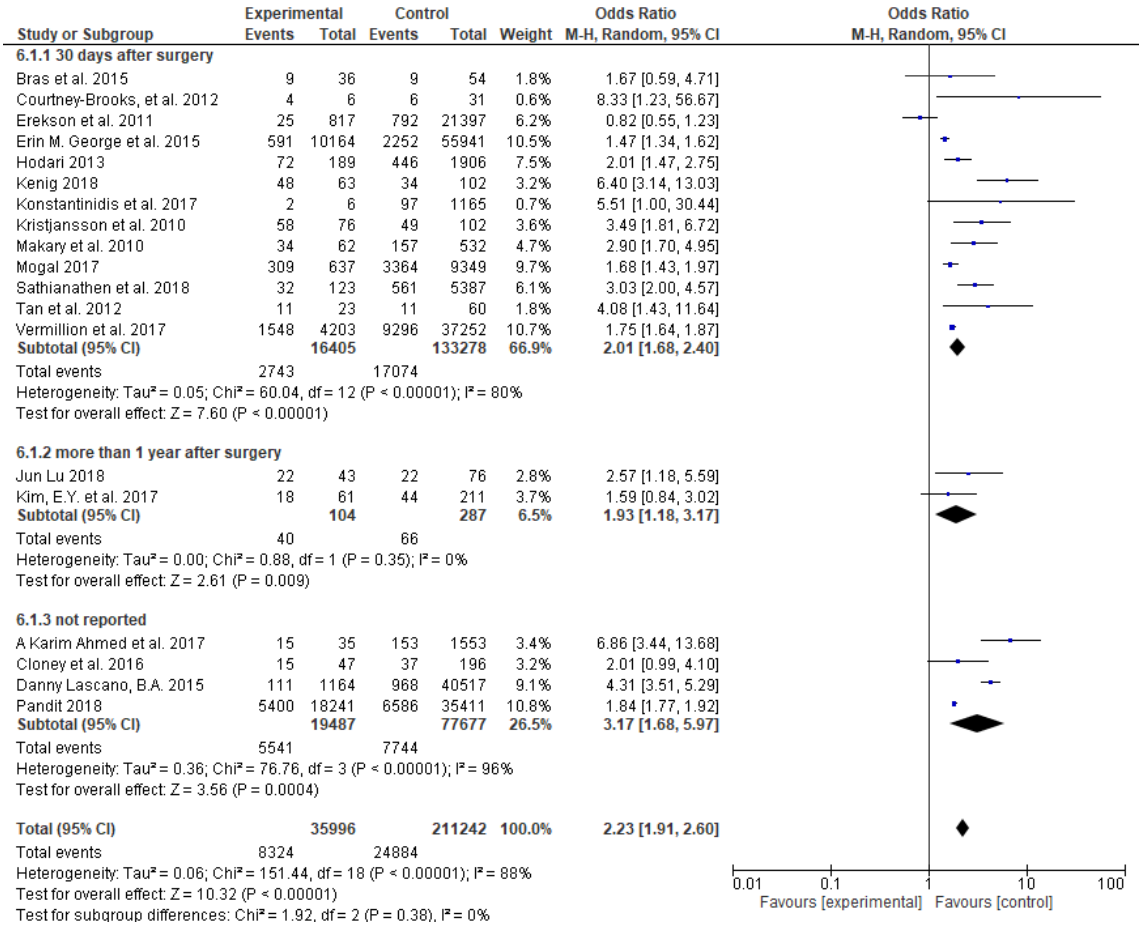

Figure 10: Forest plot for postoperative complications in frail patients older than 65 years by time of follow-up.

Sensitivity analysis

We performed sensitivity analysis by re-calculating the OR after omitting every single study and, as shown in **Table 4**, frailty continued to be associated with increased risk of postoperative complications.

Table 4: Sensitivity analysis of the meta-analysis and systematic review.

		OR		Heterogeneity	
Study that was removed	**Total**	**IC**	**P value**	**I^2**	**P value**
A Karim Ahmed et al. 2017 (71)	2.13	(1.84-2.48)	P<0.00001	88%	P<0.00001
Bras et al. 2015 (72)	2.24	(1.92-2.62)	P<0.00001	89%	P<0.00001
Cloney et al. 2016 (73)	2.24	(1.92-2.62)	P<0.00001	89%	P<0.00001
Courtney-Brooks, et al. 2012 (64)	2.21	(1.90-2.57)	P<0.00001	89%	P<0.00001
Danny Lascano, B.A. 2015 (78)	1.98	(1.74-2.26)	P<0.00001	79%	P<0.00001
Erekson et al. 2011 (74)	2.36	(2.03-2.75)	P<0.00001	88%	P<0.00001
Erin M. George et al. 2015 (75)	2.35	(1.99-2.78)	P<0.00001	87%	P<0.00001
Hodari 2013 (76)	2.25	(1.92-2.64)	P<0.00001	89%	P<0.00001
Jun Lu 2018 (68)	2.22	(1.90-2.59)	P<0.00001	89%	P<0.00001
Kenig 2018 (65)	2.14	(1.84-2.49)	P<0.00001	88%	P<0.00001
Kim, E.Y. et al. 2017 (58)	2.26	(1.93-2.64)	P<0.00001	89%	P<0.00001
Konstantinidis et al. 2017 (66)	2.21	(1.90-2.58)	P<0.00001	89%	P<0.00001
Kristjansson et al. 2010 (67)	2.19	(1.88-2.56)	P<0.00001	88%	P<0.00001
Makary et al. 2010 (69)	2.20	(1.88-2.57)	P<0.00001	89%	P<0.00001
Mogal 2017 (23)	2.31	(1.96-2.73)	P<0.00001	89%	P<0.00001
Pandit 2018 (11)	2.39	(1.94-2.95)	P<0.00001	89%	P<0.00001
Sathianathen et al. 2018 (79)	2.18	(1.87-2.55)	P<0.00001	88%	P<0.00001
Tan et al. 2012 (70)	2.20	(1.89-2.57)	P<0.00001	89%	P<0.00001
Vermillion et al. 2017 (80)	2.37	(1.95-2.88)	P<0.00001	89%	P<0.00001

Publication bias

Publication bias was assessed visually using a funnel plot and there was no significant evidence of publication bias (**Figure 11**).

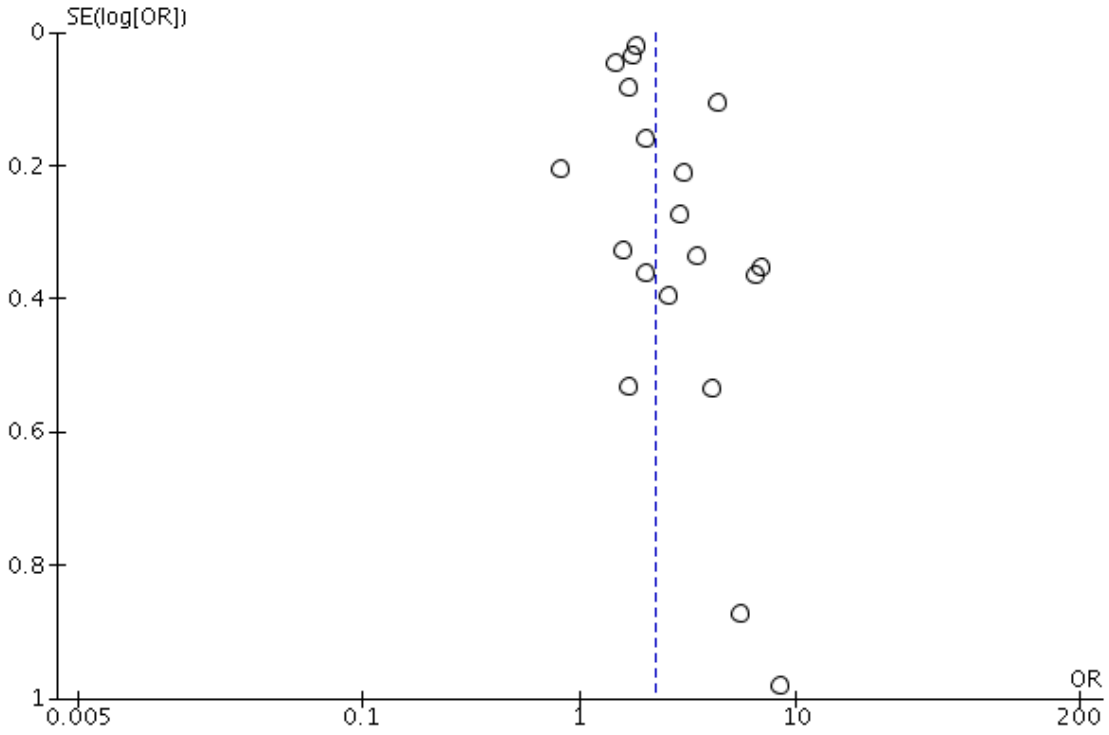

Figure 11: Funnel plot of frailty and postoperative complications.

DISCUSSION

The purpose of this systematic review and meta-analysis was to evaluate the association between frailty status and postoperative complications. By including 19 articles and a total of 243 328 patients, we found that frailty was associated with increased risk of postoperative complications in cancer patients. The risk was present in both frail and pre-frail patients, was consistent across different frailty instruments and was present in patients with different types of cancer.

Frailty has been conceptualized in the literature as a loss of physiologic reserve leading to increased vulnerability to stressors. It is associated with characteristics such as impaired mobility, weakness, malnutrition, comorbidity, polypharmacy, cognitive impairment, depression and social isolation (81-83). So, a frail patient responds to a surgery or a chemotherapy with a more severe homeostasis disorder, putting more functional pressure on their organs and physiological system.

Not being able to deal with the functional pressure, the stress imposed by surgery or chemotherapy can result in dysfunction or failure of organs and physiological system, which may lead to premature death of the patient or the development of complications (81-83). Postoperative complications are of major concern as they have both clinical effects during the immediate postoperative period and long-term effects on quality of life impairment and increased mortality (84). Moreover, they are one of the main reasons for delay in time to initiation of adjuvant chemotherapy, which will reduce the chances of survival (84).

Early identification of patients at higher risk should be a priority. Our findings support the utility of preoperative assessment of frailty status, as frail was associated with higher risk of postoperative complications, even after sensitivity analysis. Previous meta-analysis has provided similar conclusions in specific surgical subspecialties such as vascular (19), cardiac (20), orthopedic surgery (21) and also in cancer (22).

One of the novelties of our review is that it suggests that the risk of postoperative complications is already present in pre-frail patients, suggesting a “dose-response” relationship between the severity of frailty and the risk of complications, highlighting the need to consider tools that allow grading frailty

severity. However, care should be made as the heterogeneity remained high. One possible cause could be due to the diversity of instruments that were used by the different studies.

Frailty, as defined by FP, mFI or CGA, was associated with a higher risk of post-operative complications but only FP and CGA presented low heterogeneity. Thus, studies using the mFI are one possible source of heterogeneity as they were the most numerous in our analysis. In addition, while frailty defined by FP and CGA seem to be effective to be used in the preoperative assessment of cancer patients (high OR and lower heterogeneity), this interpretation should not be done. Indeed, it has been shown that different instruments provide different results (limited agreement) even if applied in the same population (85). It would be interesting to perform observational studies comparing, in the same population, the diagnostic accuracy for prediction adverse events after surgery with FP, mFI, CGA and others.

In addition, we also found that retrospective studies were an important source of heterogeneity and all these studies used mFI except two articles (66, 68). In fact, studies using mFI usually obtain their data through historical records and relevant information might be missing (leading to poor classification) or was introduced by different persons (leading to more subjectivity). This can also explain why we found high heterogeneity in higher sample sized. Indeed, 7 out of 10 studies with sample size above 1000 used mFI to assess frailty. Another potential source of heterogeneity was the time of follow-up.

Furthermore, our study shows that frailty was associated with a higher risk of complications after surgery in patients with different cancer types, including gastrointestinal, urologic, head and neck and abdominal (low-to-moderate heterogeneity), but not for gynecological.

Future studies should address if these differences are due to cancer-specific issues as, for instance, cachexia is highly prevalent among the first 3 (86). Frailty and cachexia are two different syndromes, but they can be present concurrently in the same patient, which might have additional implications (87). Finally, follow-up time was also an important source of heterogeneity, particularly for 30 days-postoperative complications.

Overall, our work suggests that screening for frailty could be an additional value in preoperative risk assessment in oncologic patients to: 1) determine surgical risk and assist in treatment decisions; 2) refer frail patients to optimization/capacitation programs to prepare them for the surgery or chemotherapy, such as a pre-habilitation program. The goal would be to increase the tolerance of their organs and physiological systems to aggression.

LIMITATIONS

There are some limitations in our systematic review that should be taken into count. A considerable heterogeneity across the studies was observed and our analysis was not adjusted for possible cofounding factors (e.g. age, gender, severity of disease). In some articles, insufficient information was available for calculating OR. Despite the corresponding authors were contacted, we did not obtain the information, which invalidated their inclusion in the systematic review.

CONCLUSIONS

This systematic review and meta-analysis suggest that frailty is associated with a higher risk of postoperative complications in oncologic patients. Thus, given the growing number of patients presenting for surgical procedures, frailty may be a valuable tool in perioperative assessment of older cancer patients by helping clinicians to tailor treatment options, facilitating shared decisions making, improving patient selection and helping to optimize patients preoperatively so as to reduce surgical complications.

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ETHICS APPROVAL.

Not applicable.

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4. Conclusão

Depois de realizar este estudo podemos concluir que este é um pequeno contributo em direção à prevenção de complicações pós-operatórias de doentes oncológicos através da avaliação da fragilidade. A identificação precoce das complicações pós-operatórias deve ser prioritária e o nosso trabalho suporta a utilidade da avaliação da fragilidade em período pré-operatório.

O nosso estudo permite concluir que:

- O risco de desenvolver complicações pós-operatórias se encontra presente não só nos doentes frágeis como também nos pré-frágeis. Isto destaca a necessidade de se considerar ferramentas que avaliem o grau de severidade da fragilidade;

- O risco permaneceu elevado mesmo após terem sido realizadas outras subanálises, como para o tipo de instrumento de avaliação, severidade das complicações, localização dos estudos, tamanho da amostra, tempo após cirurgia;

- O tipo de cancro parece influenciar as complicações pós-operatórias, não tendo sido observado risco significativo no caso do cancro ginecológico;

- A heterogeneidade mostrou-se alta e uma das razões pode dever-se à grande diversidade de ferramentas utilizadas para a avaliação da fragilidade. Das ferramentas associadas a um maior risco de complicações o Índice de Fragilidade Modificado apresentou elevada heterogeneidade.

- O facto de grande parte dos estudos serem retrospetivos, mostrou também ser uma importante fonte de heterogeneidade. Esta pode ocorrer devido á utilização dos dados obtidos retrospetivamente nos registos clínicos, onde pode faltar informação ou, pelo facto de ter sido introduzido por outras pessoas.

Em suma, os resultados da nossa revisão sistemática e meta-análise sugerem que a avaliação da fragilidade é útil na determinação do risco cirúrgico, tendo potencial para auxiliar nas decisões de tratamento e encaminhar os doentes frágeis e pré-frágeis para programas de otimização com o objetivo de capacitar o doente para o tratamento, aumentando a tolerância do sistema fisiológico à agressão.

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