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MESTRADO INTEGRADO EM MEDICINA

Risk factors for bleeding after gastric endoscopic submucosal dissection (ESD) and validation of the Bleeding after ESD Trend from Japan Score (BEST-J)

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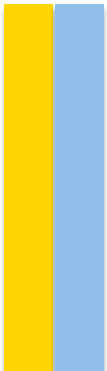

Risk factors for bleeding after endoscopic submucosal dissection (ESD) and validation of the Bleeding after ESD Trend from Japan Score (BEST-J)

ARTIGO ORIGINAL

Dissertação de Mestrado Integrado em Medicina

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Agradecimentos

Ao meu orientador, Professor Doutor Ricardo Küttner de Magalhães, e à minha coorientadora, Dra Sara Archer, por todo o apoio, orientação e motivação, ao longo da realização deste trabalho.
À Professora Doutora Carolina Lemos, pela sua generosa disponibilidade e ajuda, fundamentais na análise estatística.
À minha família, ao Gonçalo e aos meus amigos, por serem o meu maior suporte, fonte de motivação e de educação.
Ao meu colega Guilherme, por toda a colaboração e gargalhadas.

Resumo

Enquadramento: A dissecção endoscópica da submucosa (ESD) é um procedimento endoscópico amplamente aceite para o tratamento de cancro gástrico precoce. A sua principal complicação é a hemorragia pós-ESD. Foram identificados diversos fatores de risco para hemorragia pós-ESD, relacionados com as características clínicas do paciente, da lesão e os detalhes do procedimento. O *BEST-J score (Bleeding after ESD Trend from Japan)* é um modelo de previsão de hemorragia após ESD gástrica, criado no Japão. Este modelo envolve dez fatores de risco e tem-se mostrado uma boa ferramenta de apoio à decisão clínica, permitindo a estratificação do risco dos doentes submetidos a ESD gástrica.

Objetivos: O presente estudo tem como objetivo investigar e identificar fatores de risco para hemorragia após ESD de lesões gástricas, bem como validar o *BEST-J Score* para a população ocidental.

Metodologia: Todos os pacientes que foram submetidos a ESD para tratamento de lesões gástricas, entre as datas de 1 de janeiro de 2016 e 31 de dezembro de 2022, foram analisados retrospetivamente. Para avaliação do efeito das variáveis independentes na hemorragia pós-ESD, realizou-se uma análise multivariada, que incluiu variáveis estatisticamente significativas na análise univariada. A capacidade de previsão do modelo BEST-J foi avaliada através da análise da curva característica de operação do recetor (ROC), e das áreas sob a curva (AUC), bem como através de uma regressão logística binomial.

Resultados: Foram incluídas 317 lesões gástrica de 266 pacientes, tratadas por ESD. A incidência de hemorragia pós-ESD foi de 6,3%. Na análise multivariada dos fatores de risco relacionados com o paciente, a doença cerebrovascular (OR= 19,97, IC 95% 3,13-127,49, p= 0,002) e a utilização de DOAC (OR= 7,16, IC 95% 1,14-45,10, p=0,036) foram identificados como fatores preditores de hemorragia pós-ESD. Na análise multivariada dos fatores de risco relacionados com a lesão e com o procedimento, a realização de *ponte* com heparina após o procedimento (OR=8,48, IC 95% 2,74-26,28, p<0,001) foi identificada como um fator de risco para hemorragia pós-ESD. A AUC área sob a curva foi de 0,610 (IC 95% 0,47-0,75, p=0,098) para o *BEST-J score*. Na regressão logística binomial, o total de pontos no *BEST-J score* foi um fator preditivo estatisticamente significativo de hemorragia pós-ESD (OR=1,39, 95% CI 1,04-1,85, p=0,026).

Conclusões: Os fatores de risco mais importantes para hemorragia pós-ESD gástrica foram a doença cerebrovascular, a utilização de DOAC e a terapêutica de

ponte com heparina. O *BEST-J score* mostrou ser uma ferramenta útil no Ocidente, na categorização dos pacientes em diferentes grupos de risco para hemorragia pós-ESD gástrica.
Palavras-chave: resseção endoscópica; disseção endoscópica da submucosa; neoplasia gástrica; hemorragia pós-ESD; fatores de risco.

Abstract

Background: Endoscopic submucosal dissection (ESD) is a widely accepted endoscopic procedure to treat early gastric cancer. Its major complication is post-ESD bleeding. Many risk factors for post-ESD bleeding have been identified, related to patient clinical features, lesion characteristics and procedure details. BEST-J Score (Bleeding after ESD Trend from Japan) is a prediction model for bleeding after gastric ESD created in Japan. This model involves ten risk factors, and has been a good clinical decision-making support tool, enabling risk stratification of patients undergoing gastric ESD.

Objectives: The current study aims to investigate and identify risk factors for bleeding after ESD of gastric lesions, as well as to validate BEST-J Score for the western population.

Methods: All patients that underwent ESD for treatment of gastric lesions, between the dates of 1st of January 2016 and 31st of December 2022 were retrospectively analyzed. Multivariable logistic regression analysis was done to examine the effect of independent variables on post-ESD bleeding, including statistically significant variables in univariable analysis. The prediction accuracy of BEST-J model was evaluated by receiver-operating characteristic (ROC) curve analysis and the areas under the curve (AUC), and by binary logistic regression analysis.

Results: A total of 317 gastric lesions from 266 patients were treated by ESD. The incidence of post-ESD bleeding was 6.3%. On multivariable analysis of patient-related risk factors, cerebrovascular disease (OR= 19.97, 95% CI 3.13-127.49, p= 0.002), and use of DOAC (OR= 7.16, 95% CI 1.14-45.10, p=0.036) were identified as predictive factors for post-ESD bleeding. On multivariable analysis of lesion-related and procedure-related risk factors, bridging with heparin after the procedure (OR=8.48, 95% CI 2.74-26.28, p<0.001) was identified as a risk factor for post-ESD bleeding. The AUC was 0.610 (95% CI 0.47-0.75, p=0.098) for the BEST-J score. In binary logistic regression analysis, the total points in BEST-J score were a statistically significant predictive factor of bleeding after ESD (OR=1.39, 95% CI 1.04-1.85, p=0.026).

Conclusions: The strongest risk factors for gastric post-ESD bleeding were cerebrovascular disease, DOAC use, and heparin bridging therapy. BEST-J score demonstrated to be a valuable tool to categorize patients into different risk groups for gastric post-ESD bleeding in the West.

Keywords: endoscopic resection; endoscopic submucosal dissection; gastric neoplasms; post-ESD bleeding; risk factors.

List of Abbreviations

AUC – Area under the curve
BEST-J - Bleeding after ESD Trend from Japan
CI – Confidence Interval
DOAC - Direct oral anticoagulant
EMR – Endoscopic mucosal resection
ESD – Endoscopic submucosal dissection
IQR - Interquartile range
OR – Odds Ratio
R0 – Complete radical resection
ROC - Receiver-operating characteristic

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Introduction

Gastrointestinal cancers are among the most commonly diagnosed cancers worldwide: stomach cancer is the fifth most common. Regarding mortality, stomach cancer is the fourth leading cause of cancer death. [1] In Portugal, there is a high incidence and mortality rate of gastric cancer, compared to the European pattern, with significant regional differences, with the country's northern region being the most affected. [2]

The widespread use of endoscopy of the gastrointestinal tract has significantly contributed to the enhanced identification of early neoplastic lesions. The detection and treatment of gastric cancers at an early stage are of high importance and will result in a significantly better prognosis, with a 5-year survival rate that can be greater than 90%. [3-5]

Endoscopic resection was introduced in the 1970s as treatment for gastrointestinal neoplasia[3], marking the beginning of the development of numerous endoscopic techniques, such as endoscopic mucosal resection (EMR). However, with these techniques, *en bloc* resections were limited to lesions smaller than 20 mm in diameter, resulting in piecemeal resections for larger lesions. This may lead to incomplete removal, inadequate pathological staging, and an increased risk of local cancer recurrence. Therefore, the need to develop new methods to remove larger lesions *en bloc* emerged. [6]

Endoscopic submucosal dissection (ESD) is an endoscopic technique that was developed in the late 1990s in Japan, for the treatment of early gastric cancer. [5-7] It's a widely accepted and well-established procedure worldwide because of its minimally invasiveness, effectiveness, and favorable short-term and long-term clinical outcomes. ESD can be performed regardless of the lesion size, enables an accurate histopathological diagnosis, has high rates of *en bloc* and R0 resection, and low local recurrence. [8-12] An endoscopic knife is used, and a series of steps are involved in the technique, including assessment of the lesion and its margins, mucosal incision and submucosal dissection, ultimately leading to its resection .[13, 14]

Nowadays, in Europe, gastric ESD is recommended as the first-line endoscopic treatment for gastric superficial lesions with a null or very low risk of lymph node metastasis: dysplastic lesions of any size or differentiated intramucosal carcinomas (of any size if not ulcerated, and ≤ 30 mm if ulcerated). It can also be considered in gastric adenocarcinomas without ulceration that are

≤30mm, submucosal (sm1), well-differentiated, or ≤20 mm, intramucosal, and poorly differentiated. [5]

However, ESD has greater technical difficulty, longer procedure time, and increased risk of complications compared to EMR. ESD has a higher risk of bleeding because of the larger resection diameter and depth of submucosal incision. Thus, bleeding after the procedure is the major complication of gastric ESD. Other adverse events are perforation, aspiration pneumonia, stenosis, and venous thromboembolism. [6, 9, 10, 15, 16]

Post-procedure bleeding may need to be controlled by endoscopic hemostasis. In rare cases, blood transfusion might be necessary, due to the potential life-threatening nature of massive bleeding, which can result in cardiovascular complications and hemorrhagic shock.[9, 17, 18]

Many risk factors for post-procedure bleeding after gastric ESD have been studied and identified, including patient clinical features, medications, lesion characteristics and procedure details. The knowledge of this risk factors may allow better risk stratification and a clearer assessment of expected outcomes, namely guiding management after ESD. [7, 15] Patient clinical features such as male sex, cardiopathy, cirrhosis, and chronic kidney disease have been identified as significant risk factors. Among patients with chronic kidney disease, dialysis has been associated with an increased risk. [10, 15] Another significant risk factor for bleeding after gastric ESD is the use of antithrombotic agents. Antithrombotic agents include antiplatelet agents (aspirin, and P2Y12 receptor antagonists, such as clopidogrel and ticagrelor) and anticoagulant agents (vitamin K antagonists, such as warfarin and acenocoumarol, and DOAC). Because of their different mechanisms of action, these therapeutic agents may have a different weight as a risk factor for bleeding after ESD. Anticoagulant use, heparin bridging therapy, and dual antiplatelet therapy/multidrug combinations were identified as independent risk factors associated with bleeding. [7, 10, 15, 19-21]

Lesion characteristics and procedure factors, such as increased tumor and specimen size, localization in the lower third of the stomach, flat/depressed morphology, the severity of gastric atrophy, carcinoma histology, undifferentiated histopathological type, submucosal invasion ≥ 500 μm from the *muscularis mucosa*, ulceration of the lesion, presence of multiple tumors and prolonged procedure time were identified as important risk factors. [7, 10, 15, 20, 21]

Hatta *et al*. established a prediction model for bleeding after gastric ESD, in 2020: BEST-J score. Ten independent factors were identified as predictors of bleeding and were included in the score. [19] This model has been a good clinical decision-making support tool, enabling risk stratification of patients undergoing gastric ESD. However, further external validation is required in Western countries, namely in Portugal.

Objectives

The current study aims to investigate and identify risk factors for bleeding after ESD of gastric lesions, as well as to validate BEST-J Score for the Western population.

Methods

The present study was carried out in the Gastroenterology Department of *Centro Hospitalar Universitário de Santo António (CHUdSA).* All patients that underwent ESD for treatment of gastric lesions, between the dates of 1st of January 2016 and 31st of December 2022 were included, through a retrospective analysis, with a prospectively maintained database.

Demographic and clinical data, reports of complementary diagnostic exams, and therapeutics were collected through the analysis of the clinical records (SClínico®) of each patient.

This study was approved by *Conselho de Administração, Comissão de Ética para a Saúde, Gabinete Coordenador de Investigação* and *Direção de Departamento do Ensino, Formação e Investigação do CHUdSA* (N/ REF.a 2022.201(161-DEFI/162-CE). Written informed consent for gastric ESD was obtained from all patients before the procedure. Still, the need for informed consent to engage in this study was waived due to its retrospective nature and the anonymity of the database.

ESD was performed by endoscopy specialists and according to a standard procedure. In patients treated with antithrombotic agents, ESD and management of these agents were done based on the Guidelines for Endoscopy in patients on antiplatelet or anticoagulant therapy, published by the British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy. [22]

Bleeding after ESD was defined as clinical evidence of digestive bleeding (hematemesis/melena) or hemoglobin drop ≥2g/dL, as done in other studies.[9, 11, 15]

Interruption of antithrombotic agents was defined as stopping any or all antithrombotic agents, including temporary replacement by heparin or aspirin.

In order to identify risk factors for bleeding after gastric ESD, we compared patient-related factors, such as gender, age, comorbidities (hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, lung disease, chronic kidney disease and renal replacement therapy [hemodialysis or peritoneal dialysis]) and use of antithrombotic agents, including antiplatelet agents (aspirin, P2Y12 receptor antagonists or dual antiplatelet therapy), anticoagulant agents (warfarin, acenocoumarol, and DOAC) and antiplatelet in addition to anticoagulant agents. For the analysis of patient-related factors, if the same patient underwent multiple ESD on different days or had multiple tumors in one procedure, we selected the procedure complicated with bleeding, and, if this criterion was not present, we

selected the most recent one. For the analysis of lesion and procedure-related factors, each lesion was considered an independent procedure, and all gastric lesions were included.

To identify other risk factors for bleeding after gastric ESD, we analyzed the reports of upper gastrointestinal endoscopies and histopathological exams and compared lesion-related and procedure-related factors. Lesion-related factors include lesion size, vertical location, gastric mapping – revealing gastric atrophy or intestinal metaplasia, lesion morphology - categorized according to Paris classification, histopathology (including differentiation), ulceration, and multiple tumors. Procedure-related factors include the use of antithrombotic agents and their interruption, bridging with heparin or aspirin, and procedure time.

The gross morphology of the lesions was categorized according to Paris Classification in type 0-I (elevated or polypoid forms), type 0-II (Flat elevated, completely flat, and superficially depressed), type 0-III (depressed/excavated), and complex morphology when there was a combined form.

Other procedure features were also reported, such as resectability, including *en bloc* resection and complete radical resection (R0), and characteristics of bleeding after ESD (timing of bleeding, endoscopic hemostasis, the severity of the bleeding according to Forrest Classification, and the need of blood transfusion).

The BEST-J scoring system, shown in Table I, was applied to each lesion, and the following punctuation was given to each predictor: 4 points each for warfarin and DOAC use; 3 points for chronic kidney disease with hemodialysis; 2 points each for P2Y12 receptor antagonist (e.g., clopidogrel, ticagrelor) and aspirin; 1 point each for cilostazol, a tumor size >30mm, location in the lower-third of the stomach, and presence of multiple tumors, and −1 point for interruption of each kind of antithrombotic agents. Then, the total score was categorized as low-risk (0 to 1 point), intermediate-risk (2 points), high-risk (3 to 4 points), or very high-risk (≥5 points) for bleeding after ESD.[19]

Statistical analysis

All patients entered an anonymized database which included demographic, clinical, histopathological, and procedural characteristics. Posteriorly, the statistical analysis was performed using IBM® SPSS® Statistics version 27.0 (IBM Corp. Armonk, New York, USA).

Categorical variables were expressed as absolute frequencies and relative frequencies, *n (%),* and were compared using the Pearson Chi-square test or Fisher's

Exact test, as appropriate. Continuous variables were summarized as mean ± standard deviation or median and interquartile range (P25 to P75), when its distribution was normal and non-normal, respectively. They were recoded into categorical variables to be compared. Variables were considered statistically significant for a p-value < 0.05.

Binary logistic regression was used to identify independent predictors of bleeding after ESD. Univariable analysis was carried out by using bleeding after the procedure as the dependent variable. Variables with a p-value <0.05 on univariable analyses were included in the multivariable equations, and only non-related variables were included. Thereafter, odds ratio (OR) and Confidence intervals (CI) were estimated.

The post-ESD bleeding rates and respective 95% CI were obtained using the One-Sample Proportions test, and the difference in proportions and respective 95% CI were obtained using the Independent-Samples Proportions test.

The prediction accuracy of the BEST-J score was evaluated by receiver-operating characteristic (ROC) curve analysis and the areas under the curve (AUC). Binary logistic regression was also done to assess the correlation between bleeding after ESD and the total score.

Results

Baseline characteristics of patients and patient-related risk factors

A total of 317 lesions from 266 patients were treated with ESD during the 7-year duration of this study. Most of the patients were male (n= 157, 59.02%), and the mean age was 67.51 (± 9.98) years. Many patients had comorbidities, such as hypertension (n= 143, 53.76%), diabetes mellitus (n= 69, 25.94%), ischemic heart disease (n= 22, 8.27%), cerebrovascular disease (n= 9, 3.38%), lung disease (n= 18, 6.77%), chronic kidney disease (n=12, 4.51%) undergoing peritoneal dialysis (n=1, 0.38%) and liver cirrhosis (n=5, 1.88%).

Approximately one-fifth of the patients were under antithrombotic therapy (n=55, 20.68%). Among the antiplatelet agents, 6.77% of patients were taking aspirin (n=18), and 5.64% were taking P2Y12 receptor antagonists (n=15) – including clopidogrel and ticagrelor. Dual antiplatelet therapy was administered to 3 patients (1.13%). Regarding anticoagulant agents, 1.88% (n=5) of the patients were taking warfarin, 0.38% (n=1) acenocoumarol, and 7.52% (n=20) were taking DOAC. Only one patient was under antiplatelet and anticoagulant agents simultaneously (0.38%). Bleeding was reported in 7.52% (n=20) of the patients.

There was a statistically significant association between bleeding after ESD and cerebrovascular disease (p<0.001), use of antithrombotic therapy (p= 0.002), and, when separately evaluated, use of DOAC (p= 0.002).

In univariable logistic regression analysis, predictive patient-related factors for bleeding after gastric ESD were history of cerebrovascular disease (OR= 20.17, 95% CI 4.90-82.97, p= <0.001), antithrombotic therapy (OR= 4.47, 95% CI 1.76-11.37, p= 0.002), and DOAC use (OR= 7.10, 95% CI 2.37-21.29, p= <0.001). However, there was no significant difference between bleeding and gender, age, other comorbidities such as chronic kidney disease, therapy with aspirin, P2Y12 receptor antagonists, warfarin, and acenocoumarol.

Three variables were eligible for multivariable logistic regression analysis. Cerebrovascular disease (OR= 19.97, 95% CI 3.13-127.49, p= 0.002) and use of DOAC (OR= 7.16, 95% CI 1.14-45.10, p=0.036) were statistically significant. The association was not significant for antithrombotic therapy (OR=0.92, 95% CI 0.17-4.96, p=0.920).

The baseline characteristics of the patients are shown in Table I, and patient-related risk factors are shown in Table II.

Characteristics of gastric lesions and ESD, lesion-related and procedure-related risk factors

A total of 317 gastric lesions were submitted to gastric ESD. The median size of the lesions was 17.00 (IQR 12.00-25.00) mm. A total of 40.38% (n=128) of the lesions were located in the upper/middle third of the stomach, and 58.04 % (n=184) in the lower third. Gastric atrophy was present in 19.87% (n=63) of the cases, and intestinal metaplasia in 40.06% (n=127). No atrophy or intestinal metaplasia was detected in 28.71% (n=91). The morphology of the lesions was categorized according to Paris Classification: 0-I (n=28, 8.83%), 0-II (n=242, 76.34%), 0-III (n=3, 0.95%), and complex morphology (n=23, 7.26%). Regarding histopathology, 1.26% (n=4) were intestinal metaplasia, 44.16% (n=140) were low-grade dysplasia and 16.09 % (n=51) high-grade dysplasia. A total of 27.76% (n=88) were adenocarcinoma, of which 13.88% (n=44) were intramucosal carcinomas and 7.89% (n=25) were submucosal carcinomas. Other histopathological patterns were present in 7.89% (n=25) of the lesions. Of these lesions, 23.03% (n=73) were well/moderately differentiated, 2.52% (n=8) were poorly differentiated, and 1.26% (n=4) were diffuse or with a signet ring cell architecture. A total of 11.99% (n=38) of the lesions had ulceration.

Multiple tumors were observed in 25.87% (n=82) of the procedures, *en bloc* resection was possible in 99.37% (n=315) of ESD, and R0 resection was done in 92.43% (n=293). A total of 20.50% (n=65) of the procedures were done in patients taking antithrombotic therapy as a chronic medication, and in 17.98% (n=57), one agent was interrupted before the procedure. Bridging with heparin was done after 6.94% (n=22) of the procedures and with aspirin after 1.26% (n=4) of the procedures. The median procedure time was 54.00 (IQR 35.00-90.00) minutes.

Bleeding was reported in 6.31% (n=20) of ESD, 55.00% (n=11) of which occurred during hospitalization, and 45.00% (n=9) occurred after discharge. A substantial proportion (40.00%, n=8) of bleedings needed endoscopic treatment: 25.00% (n=5) were Forrest I and 15.00% (n=3) IIb. Blood transfusion was needed in 30.00% (n= 6) of the cases of bleeding.

There was a positive association between bleeding after gastric ESD and lesion location in lower third (p=0.040), complex morphology (p=0.047), use of antithrombotic agents as a chronic medication (p=0.002), interruption of this therapy (p<0.001), and heparin bridging therapy (p=<0.001). This relationship was verified in univariable logistic regression analysis, in which predictive lesion-related and procedure-related risk factors for bleeding after gastric ESD were location in

the lower third (OR=3.07, 95% CI 1.00-9.41, p=0.049), complex morphology (OR=3.66, 95% CI 1.11-12.03, p=0.033), use of antithrombotic agents (OR=4.40, 95% CI 1.75-11.09, p=0.002), interruption of one agent (OR=5.32 95% CI 2.10-13.49, p=<0.001), as well as heparin bridging therapy after the procedure (OR=10.12, 95% CI 3.52-29.09, p=<0.001).

There was a negative relationship between bleeding after gastric ESD and location on the upper/middle third (p=0.017), and Paris Classification 0-II (p=0.011). This relationship was verified in univariable logistic regression analysis, in which the location in the upper/middle third (OR=0.24, 95% CI 0.07-0.85, p=0.026), and Paris Classification 0-II (OR=0.28, 95% CI 0.11-0.70, p=0.007) were identified as protective factors.

Five variables were eligible for multivariable logistic regression analysis, and only heparin bridging therapy was statistically significant (OR=8.48, 95% CI 2.74-26.28, p<0.001). The association was not significant for location in the upper/middle third of the stomach (OR=0.09, 95% CI 0.01-1.28, p=0.076), lower third of the stomach (OR=0.37, 95% CI 0.03-4.19, p= 0.425), Paris Classification 0-II (OR=0.44, 95% CI 0.13-1.48, p=0.186) and complex morphology (OR= 1.77, 95% CI 0.38-8.32, p=0.472).

The characteristics of gastric lesions and gastric ESD are shown in Table III, and lesion-related and procedure-related risk factors are shown in Table IV. Characteristics of bleeding after gastric ESD are shown in Table V.

Validation of BEST-J Score

We carried out risk stratification for bleeding after ESD according to the BEST-J score. None of our patients had chronic kidney disease undergoing hemodialysis or was under treatment with cilostazol.

Most of our patients (n=198, 62.46%) had 0-1 points, therefore having lower risk for bleeding after ESD. There was only one patient who scored 7 points, and another patient who scored 8 points. None suffered from post-ESD bleeding.

The post-ESD bleeding rates for a total score of 0 to 5 were 3.22%, 6.62%, 1.47%, 8.70%, 25.00%, and 16.67%, respectively. The difference in proportions for a total score of 4 was statistically significant [-0.20, 95% CI -0.39-(-0.01), p-value=<0.001]. For other total scores the difference in proportions was not statistically significant.

When we categorized patients into low-risk, intermediate-risk, high-risk, and very high-risk groups for post-ESD bleeding, post-ESD bleeding rates for each

category were 5.56%, 1.47%, 16.28%, and 12.5%, respectively. The difference in proportions for high-risk group was statistically significant [-0.12, 95% CI -0.23-(-0.01), p-value= 0.004].

After ROC curve analysis, the AUC was 0.610 (95% CI 0.47-0.75, p=0.098) for the BEST-J score. In binary logistic regression analysis, the total points in BEST-J score were a statistically significant predictive factor of bleeding after ESD (OR=1.39, 95% CI 1.04-1.85, p=0.026).

The distribution of the total risk score and risk classification for bleeding after gastric ESD according to BEST-J Score is shown in Table VI, and ROC analysis with AUC is shown in Figure 1.

Discussion

Our study reveals that 6.31% of gastric ESDs were complicated with post-procedure bleeding, which is in line with multicentered studies that report bleeding after gastric ESD in 4.1-8.5% of the cases. [7, 10, 11, 17, 19, 23, 24]

Regarding patient-related risk factors for post-ESD bleeding, cerebrovascular disease, use of antithrombotic therapy in general, and, when separately evaluated, use of DOAC (when univariable analysis was done) were identified as risk factors. However, on multivariable analysis, only cerebrovascular disease, and use of DOAC demonstrated to be a significant predictive factor for bleeding. This analysis showed that patients with a history of cerebrovascular disease or under DOAC therapy, are approximately 20 times and 7 times more likely to have post-ESD bleeding, respectively. However, the first finding is relatively original in the literature. [15, 23, 25, 26]

As the population continues to age, the likelihood of performing ESD on patients with several medical conditions, such as cerebrovascular diseases, increases. Furthermore, many of these patients are under secondary prevention of cerebral infarction with long-term antithrombotic therapy, including antiplatelet or anticoagulant agents. [20, 27, 28] This may raise the possibility that the relationship between cerebrovascular disease and post-ESD bleeding is linked to antithrombotic therapy. In our study, patients who had cerebrovascular disease, were under different antiplatelet agents or anticoagulants and one without antithrombotic therapy. Indeed, antithrombotic therapy, including antiplatelet agents and anticoagulants, is considered a major risk factor for bleeding after gastric ESD. [7, 10, 15, 19-21] These agents individually have been eligible as significant risk factors, for example, P2Y12 receptor antagonist[29], aspirin[19], warfarin, and direct oral anticoagulant.[23] However, if the association between cerebrovascular disease and post-ESD was based on the role of antithrombotic therapy, we would expect ischemic heart disease to be also a risk factor for bleeding. Yet, this was not observed, highlighting the significant impact of cerebrovascular disease as an independent risk factor for bleeding. This innovative association rises the need to give special attention to these patients.

Other patient-related risk factors, such as male sex, older age, cardiopathy, cirrhosis, and chronic kidney disease undergoing hemodialysis [15, 18, 23] were not statistically significant predictive factors in our study. That may be due to our limited number of patients in comparison with multi-centered studies, the low

proportions of patients with these comorbidities, and also because patients' characteristics may be different.

When it concerns lesion and procedure-related risk factors for bleeding after ESD, on univariable analysis, location in the lower third of the stomach, complex morphology according to Paris classification, taking antithrombotic therapy, the interruption of this therapy and heparin bridging therapy were identified as risk factors. Location in the upper/middle third and Paris Classification 0-II were statistically significant protective factors. However, in multivariable analysis, bridging with heparin was the only statistically significant factor for bleeding after gastric ESD.

Location in the lower third of the stomach is recognized as a risk factor for bleeding in many studies.[17, 19, 23, 30] In line with those studies, our study showed location in the lower third as a risk factor and location in the upper/middle third as a protective factor.

The morphology was explored in several studies, with the majority finding no relationship between the macroscopic type of the lesions and bleeding after ESD.[31-34] On the opposite, the association between flat/depressed morphology and bleeding after ESD has been made in other studies, which is in contrast with our findings.[15, 35] To support our results, it is reasonable to assume that flat morphology (type 0-II lesions), which carry a decreased risk of fibrosis and less probability of large caliber vessels, is associated with a decreased risk of bleeding. On the other hand, complex morphology involves all types of morphology combined, including type 0-I lesions, that showed a positive relationship with bleeding, although not statistically significant.

Heparin bridging therapy is nowadays recommended for patients submitted to ESD, that are under therapy with warfarin for a high-risk condition for thromboembolism. It is started two days after stopping warfarin, omitted on the day of the procedure and continue until INR is adequate.[22] There is a lack of consensus in the available evidence regarding the impact of bridging therapy in post-procedure bleeding. In our study we found that bridging with heparin after the procedure is a risk factor for post-ESD bleeding, as reported in recent studies.[10, 22, 36, 37] Therefore, it may be necessary to reconsider whether bridging after the procedure is safe and balance the thromboembolic and bleeding risk.

Interruption of antithrombotic agents is intrinsically related with other variables, such as antithrombotic therapy and heparin bridging therapy. Therefore, it was not possible to evaluate this variable as an independent risk factor,

preventing us from obtaining statistical and clinical conclusions about its effect on bleeding after ESD.

Other lesion-related and patient-related risk factors that have been raised by many researchers were included in our study and were not revealed as statistically significant predictive factors, again maybe due to the small number of lesions included in this study.

Validation of BEST-J Score

Hatta *et al*. found ten statistically significant predictive factors for bleeding and created a predicting model for post-ESD bleeding including these variables. Their post-ESD bleeding rates for each category were 2.8% for low-risk, 6.1% for intermediate-risk, 11.4% for high-risk, and 29.7% for very high-risk. [19] When our patients were categorized according to the BEST-J score, the bleeding rates didn't gradually increase, but the high-risk (16.28%) and the very-high risk (12.5%) groups had greater bleeding rates than the intermediate and low-risk ones. In addition, the difference in proportions between the presence and absence of bleeding in patients categorized as BEST-J score 4, and in the high-risk group, was statistically significant. Therefore, when the score rises, bleeding becomes more probable. This association couldn't be made for scores higher than 5 and very-high risk groups, probably because the number of cases with scores higher than five is sparse.

The AUC was 0.610, which would show that the BEST-J score has moderately good discrimination. However, this association was not statistically significant (p=0.098). Yet, on binary logistic regression, the total points after applying the BEST-J score were a statistically significant predictive factor for bleeding after ESD.

However, when analyzing the ten variables of the BEST-J score, only DOAC use and location in the lower third were predictive risk factors in our study, while the other variables didn´t achieve a statistically significant correlation. Furthermore, for example, the use of cilostazol in clinical practice is not so common in Portugal, and in this study, none of the patients was using it. Also, some variables have the same risk score, such as warfarin and DOAC (4 points). In our study, we found that DOAC is associated with a significantly higher risk of bleeding, unlike warfarin, so it would be reasonable to have a higher risk score.

This study has key positive aspects since it identified risk factors for bleeding after gastric ESD and validated the BEST-J score for the Portuguese population. It enabled to assess the accuracy of the score in risk stratification and its future use in clinical practice, to guide the management of these patients and

to reduce the occurrence of this adverse effect. Also, the procedures were done by two experienced operators and during a long period of time (7 years). There was also a clear definition of post-ESD bleeding and of the management of antithrombotic therapy. Nevertheless, this study has limitations. First, its retrospective nature. Second, the data were collected from a single center, with a moderate sample size when compared to multicenter studies. Third, the timing of bleeding after ESD was not considered in the analysis of potential risk factors. Fourth, on the application of the BEST-J score, no patients had chronic kidney disease in hemodialysis and were under cilostazol, turning it difficult to analyze the power of these variables.

Conclusions

There are many known risk factors for bleeding after ESD, including patient-related, lesion-related, and procedure-related risk factors. In this study, we conclude that the strongest risk factors for bleeding in our center were a history of cerebrovascular disease, DOAC use, and heparin bridging therapy. Therefore, these patients should be closely monitored and a carefully observed after gastric ESD.

The total BEST-J score demonstrated to be a predictive factor for bleeding after ESD, with bleeding becoming more probable as the score rises. Therefore, it proved to be a valuable tool in categorizing patients into different risk groups for gastric post-ESD bleeding in the West. Nevertheless, it is necessary to consider other risk factors and a different prediction model that may have more impact in western populations.

Appendix

Table I – BEST-J Score (Bleeding after ESD Trend from Japan Score)[19]

Variables	Score
Warfarin	4
DOAC	4
CKD with hemodialysis	3
P2Y12RA	2
Aspirin	2
Cilostazol	1
Tumor size >30mm	1
Tumor location in lower third	1
Multiple tumors	1
Interruption of antithrombotic agents	-1

Table II – Baseline characteristics of patients

Variable	Total	Bleeding		p value
		Present	Absent	
Number of patients, n (%)	266	20 (7.52)	246 (92.48)	
Gender, n (%)				
Male	157 (59.02)	11 (7.01)	146 (92.99)	0.704
Female	109 (40.98)	9 (8.26)	100 (91.74)	
Age, years (mean ± SD)	67.51 ± 9.98			
<75 years, n (%)	198 (74.44)	15 (7.58)	183 (92.42)	0.952
≥75 years, n (%)	68 (25.56)	5 (7.35)	63 (92.65)	
Comorbidities, n (%)				
Hypertension	143 (53.76)	10 (6.99)	133 (93.01)	0.726
Diabetes mellitus	69 (25.94)	3 (4.3)	66 (95.7)	0.246
Ischemic heart disease	22 (8.27)	2 (9.09)	20 (90.91)	0.675
Cerebrovascular disease	9 (3.38)	5 (55.56)	4 (44.44)	**<0.001**
Lung disease	18 (6.77)	0 (0.00)	18 (100.00)	
Chronic kidney disease	12 (4.51)	1 (8.33)	11 (91.67)	1.000
Peritoneal dialysis	1 (0.38)	0 (0.00)	1 (100.00)	
Liver cirrhosis	5 (1.88)	1 (20.00)	4 (80.00)	0.326
Antithrombotic therapy, n (%)	55 (20.68)	10 (18.18)	45 (81.82)	**0.002**
Antiplatelet agents				
Aspirin	18 (6.77)	0 (0.00)	18 (100.00)	
Clopidogrel / Ticagrelor	15 (5.64)	2 (13.33)	13 (86.67)	0.313
Dual antiplatelet therapy	3 (1.13)	0 (0.00)	3 (100.00)	
Anticoagulant agents				
Warfarin	5 (1.88)	1 (20.00)	4 (80.00)	0.326
Acenocoumarol	1 (0.38)	1 (100.00)	0 (0.00)	0.075
DOAC	20 (7.52)	6 (30.00)	14 (70.00)	**0.002**
Antiplatelets + Anticoagulants	1 (0.38)	0 (0.00)	1 (100.00)	

Table III - Univariable and multivariable analysis investigating patient-related predictive factors for bleeding after ESD

Variables	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Gender (male vs. female)	0.84	0.34-2.09	0.704			
Age, years	0.99	0.94-1.03	0.620			
Comorbidities (yes vs. no)						
Hypertension	0.85	0.34-2.11	0.726			
Diabetes mellitus	0.48	0.14-1.70	0.255			
Ischemic heart disease	1.26	0.27-5.80	0.771			
Cerebrovascular disease	20.17	4.90-82.97	**<0.001**	19.97	3.13-127.49	**0.002**
Lung disease	-	-	-			
Chronic kidney disease	1.12	0.14-9.18	0.913			
Liver cirrhosis	3.18	0.34-29.93	0.311			
Antithrombotic therapy (yes vs. no)	4.47	1.76-11.37	**0.002**	0.92	0.17-4.96	0.920
Aspirin	-	-	-			
Clopidogrel / Ticagrelor	1.99	0.42-9.52	0.388			
Warfarin	3.18	0.34-29.93	0.311			
Acenocoumarol			1.000			
DOAC	7.10	2.37-21.29	**<0.001**	7.16	1.14-45.10	**0.036**

Table IV – Characteristics of gastric lesions and gastric ESD

Variable	Total, n (%)	Bleeding		p value
		Present, n (%)	Absent, n (%)	
Number of lesions	317	20 (6.31)	297 (93.69)	
Lesion size, mm (Median [P25–P75])	17.00 (12.00-25.00)			
< 30 mm	251 (79.18)	17 (6.77)	234 (93.23)	0.545
≥ 30 mm	59 (18.61)	2 (3.39)	57 (96.61)	
Vertical location				
Upper/middle third	128 (40.38)	3 (2.34)	125 (97.66)	**0.017**
Lower third	184 (58.04)	16 (8.70)	168 (91.30)	**0.040**
Gastric Mapping				
No atrophy	91 (28.71)	6 (6.59)	85 (93.41)	0.895
Gastric atrophy	63 (19.87)	7 (11.11)	56 (88.89)	0.088
Intestinal metaplasia	127 (40.06)	7 (5.51)	120 (94.49)	0.633
Paris Classification				
0-I	28 (8.83)	4 (14.29)	24 (85.71)	0.088
0-II	242 (76.34)	10 (4.13)	232 (95.87)	**0.011**
0-III	3 (0.95)	0 (0.00)	3 (100.00)	
Complex	23 (7.26)	4 (17.39)	19 (82.61)	**0.047**
Histopathology				
Intestinal metaplasia	4 (1.26)	0 (0.00)	4 (100.00)	
Low grade dysplasia	140 (44.16)	10 (7.14)	130 (92.86)	0.587
High grade dysplasia	51 (16.09)	2 (3.92)	49 (96.08)	0.752
Adenocarcinoma	88 (27.76)	5 (5.68)	83 (94.32)	0.776
Intramucosal carcinoma	44 (13.88)	2 (4.55)	42 (95.55)	1.000
Submucosal carcinoma	25 (7.89)	3 (12.00)	22 (88.00)	0.202
Other histopathology patterns	25 (7.89)	2 (8.00)	23 (92.00)	0.664
Differentiation				
Well/moderately differentiated	73 (23.03)	3 (4.11)	70 (95.89)	0.583
Poorly differentiated	8 (2.52)	1 (12.50)	7 (87.50)	0.410
Diffuse/ signet ring cell	4 (1.26)	0 (0.00)	4 (100.00)	
Ulceration				
Ulceration	38 (11.99)	3 (7.89)	35 (92.11)	0.719
No ulceration	264 (83.28)	17 (6.44)	247 (93.56)	1.000
Multiple tumors	82 (25.87)	2 (2.44)	80 (97.56)	0.094
Resectability				
En bloc resection	315 (99.37)	20 (6.35)	295 (93.65)	1.000
Complete resection	293 (92.43)	18 (6.14)	275 (93.86)	0.655
AT agents	65 (20.50)	10 (15.38)	55 (84.62)	**0.002**
Interruption of one agent	57 (17.98)	10 (17.54)	47 (82.46)	**<0.001**
Bridging				
Heparin	22 (6.94)	7 (31.82)	15 (68.18)	**<0.001**
Aspirin	4 (1.26)	1 (25.00)	3 (75.00)	0.230
Procedure time, min (Median [P25–P75])	54.00 (35.00-90.00)			
< 120 min	256 (80.76)	17 (6.64)	239 (93.36)	0.545
≥ 120 min	54 (17.03)	2 (3.70)	52 (96.30)	

Table V- Univariable and multivariable analysis investigating lesion-related and procedure-related predictive factors for bleeding after gastric ESD

Variables	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Lesion size, mm	1.01	0.98-1.05	0.579			
Vertical location (yes vs. no)						
Upper/middle third	0.24	0.07-0.85	**0.026**	0.09	0.01-1.28	0.076
Lower third	3.07	1.00-9.41	**0.049**	0.37	0.03-4.19	0.425
Gastric Mapping (yes vs. no)						
No atrophy	1.07	0.40-2.87	0.895			
Gastric atrophy	2.32	0.88-6.08	0.087			
Intestinal metaplasia	0.79	0.31-2.05	0.634			
Paris Classification						
0-I	2.84	0.88-9.18	0.081			
0-II	0.28	0.11-0.70	**0.007**	0.44	0.13-1.48	0.186
0-III	-	-	-			
Complex	3.66	1.11-12.03	**0.033**	1.77	0.38-8.32	0.472
Histopathology (yes vs. no)						
Low grade dysplasia	1.28	0.52-3.18	0.588			
High grade dysplasia	0.56	0.13-2.50	0.450			
Adenocarcinoma	0.86	0.30-2.44	0.776			
Intramucosal carcinoma	0.68	0.15-3.01	0.606			
Submucosal carcinoma	2.21	0.60-8.11	0.234			
Differentiation (yes vs. no)						
Well/moderately differentiated	0.57	0.16-2.01	0.384			
Poorly differentiated	2.18	0.26-18.65	0.477			
Ulceration (yes vs. no)						
Ulceration	1.32	0.37-4.74	0.669			
No ulceration	1.15	0.32-4.06	0.832			
Multiple tumors (yes vs. no)	0.30	0.07-1.33	0.113			
AT agents (yes vs. no)	4.40	1.75-11.09	**0.002**			
Interruption of 1 agent	5.32	2.10-13.49	**<0.001**			

Bridging (yes vs. no)						
Heparin	10.12	3.52-29.09	**<0.001**	8.48	2.74-26.28	**<0.001**
Aspirin	5.16	0.51-51.98	0.164			
Procedure time, min	1.00	0.99-1.01	0.425			

Table VI – Characteristics of bleeding after gastric ESD

Variables	N (%)
Timing of bleeding after ESD	
During hospitalization	11 (55.00)
After discharge	9 (45.00)
Endoscopic treatment	8 (40.00)
Forrest Classification	
I	5 (25.00)
IIa	0 (0.00)
IIb	3 (15.00)
IIc	0 (0.00)
Blood transfusion	6 (30.00)

Table VII – Distribution of the total risk score and risk classification for bleeding after gastric ESD - BEST-J Score

Variable	Total (n=317)	Bleeding (n=21)	Bleeding rate (95% CI) (%)	Difference in proportions (95% CI)	P value
Total points, n (%)					
0	62 (19.56)	2 (3.22)	3.22 (0.00-7.62)	0.04 (-0.02-0.09)	0.266
1	136 (42.90)	9 (6.62)	6.62 (2.07-11.16)	-0.01 (0.06-0.05)	0.845
2	68 (21.45)	1 (1.47)	1.47 (0.00-4.33)	0.06 (0.02-0.10)	0.064
3	23 (7.26)	2 (8.70)	8.70 (0.00-22.38)	-0.03 (-0.14-0.09)	0.625
4	20 (6.31)	5 (25.00)	25.00 (3.52-46.48)	-0.20 [-0.39- (-0.01)]	**< 0.001**
5	6 (1.89)	1 (16.67)	16.67 (0.00-54.82)	-0.11 (-0.40-0.19)	0.292
6	0 (0.00)	0 (0.00)	-	-	-
7	1 (0.32)	0 (0.00)	-	-	-
8	1 (0.32)	0 (0.00)	-	-	-
Risk categories					
Low risk	198 (62.46)	11 (5.56)	5.56 (2.36-8.75)	0.02 (-0.04-0.08)	0.477
Intermediate risk	68 (21.45)	1 (1.47)	1.47 (0.00-4.33)	0.06 (0.02-0.10)	0.064
High risk	43 (13.56)	7 (16.28)	16.28 (5.24-27.31)	-0.12 [(-0.23-(-0.01)]	**0.004**
Very high risk	8 (2.52)	1 (12.50)	12.50 (0.00-35.42)	-0.06 (-0.29-0.17)	0.466

Table VIII – Binary logistic regression for bleeding after ESD and BEST-J Score

Variables	Univariable		
	OR	95% CI	P value
BEST-J Score	1.38	1.04-1.85	**0.026**

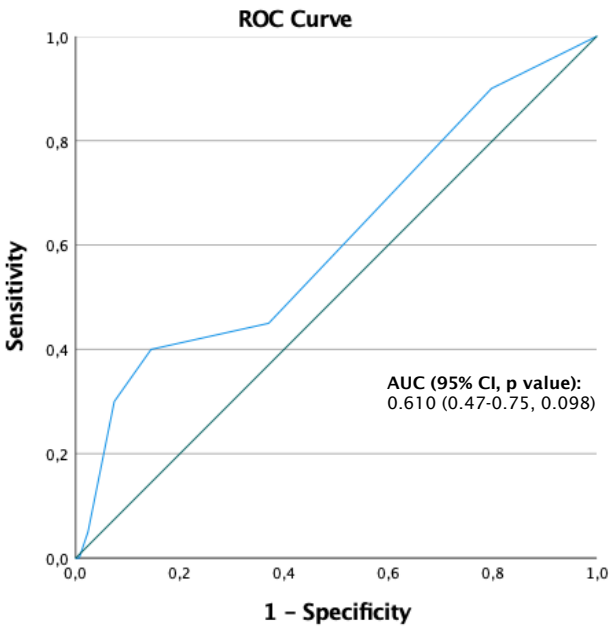

Fig. 1 - ROC curve and AUC of the BEST-J score

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