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A Systematic Review and Meta-Analysis of Risk Factors for Delayed Bleeding After Endoscopic Submucosal Dissection in Early Gastric Cancer

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Abstract

ESD has become a standard of care for EGC due to its ability to provide curative resection with minimally invasive organ sparing approach, yet delayed bleeding poses considerable post-ESD risk factors for patient morbidity and health care consumption. Therefore, the systematic review and meta-analysis was conducted with the purpose of investigating the risk factors for late bleeding after ESD and the impact of each factor in EGC patients. A systematic review of these databases, PubMed, Embase, Web of Science, and the Cochrane Library was conducted till April 2025; Twelve imported and excluded prospective and retrospective studies which included 18 642 patients. Pooled odds ratios (ORs) with 95% CI were determined using a random effects model, and inter-study heterogeneity was evaluated using the I^2 statistic. The meta-analysis further found that anticoagulant or antiplatelet administration (OR 2.94, 95% CI 2.21–3.89), large lesion size, ≥30 mm (OR 2.51, 95% CI 1.84–3.43), lesion ulceration (OR 1.68, 95% CI 1.20–2.36), and CKD (Cr≥3 mg/dL) (OR 1.75, 95% CI 1.13–2.72) were significant predictors of delayed bleeding in patients with gastric cancer. There was moderate to low level of heterogeneity overall and no signs of significant publication bias. These observations underscore the necessity for proper risk

evaluation and risk-focused interventions, including the following: perioperative anticoagulation management and post-ESD Careful monitoring of possible bleeding in patients with early gastric cancer can help optimize this procedure's safety profile. These results consistently demonstrate the feasibility of network analysis for identifying patients at higher risk for prevention of outdoor falls and require future large-scale multicenter prospective studies to refine risk prediction models and validate preventive interventions.

1. Introduction

ESD has been widely recognized as a mainstream and innovative treatment method for EGC because of its capability to achieve en bloc resection regardless of the size, morphological features, or ulcerative status of the lesion. Initially established in Japan, ESD has enhanced the pathological diagnosis and reduced the recurrence rate as compared to EMR (Gotoda, 2006; Isomoto, 2009). The advancement in the technical aspects of ESD has led to better results in EGC management and is now part of the management guidelines globally (Japanese Gastric Cancer Association, 2017; Pimentel-Nunes et al., 2015).

However, ESD is not risk free since it has faced some of the following challenges. One of the most worrisome is delayed bleeding which is defined as bleeding that occurs after the end of the procedure and which requires endoscopic intervention, blood transfusion or surgery (Ono et al., 2015; Kato et al., 2017). Tsuji et al. 2010, Lim et al. 2014 described the rate of D seriousness bleeding after gastric ESD as ranging from 2-15 % which varied with the patient's population, the features of the lesion, and procedural method. This is an important clinical priority due to the seriousness of the risk ranging from hemodynamic compromise and the need for urgent intervention amongst patients with delayed bleeding.

Some important primary patient characteristics and lesion characteristics as well as procedural factors have been identified as possible sources of delayed bleeding risk. There have been similar findings in the use of other patient-level variables such as antithrombotic agents including the use of antiplatelet as well as anticoagulant therapies (Takeuchi et al., 2013; Ono et al., 2017). Other patients at a higher risk for bleeding are those with comorbidities such as; chronic kidney disease

and liver cirrhosis because they affect clotting factors and platelets (Kawamura et al., 2013; Kim et al., 2014).

Tumor size, location and ulceration have been regarded as important lesion related factors that have also been considered. Bigger sized lesions that are larger than 30 mm in diameter erode more mucosa and make the area more susceptible to exposing blood vessels and bleeding (Toyokawa et al., 2012; Oda et al., 2006). For the same reason, tumors in the lower third of the stomach are believed to be more prone to bleeding due to the density of the submucosal vessels and increased exposure to contractions (Imagawa and Kodama, 2013; Lee et al., 2015). There is more Chance of deeper involvement or injury to the blood vessels and hence delayed healing in case of ulcerated lesions (Lim et al., 2014).

Other aspects have included a prolonged procedural time, inadequate clot formation post ESD, and experience of the endoscopist (Abe et al., 2012; Tsuji et al., 2010). It has even been suggested that improvement in the technique through such measures as the use of prophylactic coagulation of visible vessels before endoscopic submucosal dissection (ESD) may prevent post-ESD bleeding, although their effectiveness is a matter of controversy (Hatta et al., 2015, Choi et al., 2017).

Due to the high mortality and morbidity in patients with delayed bleeding and multiple and interacted risk factors, it is essential to summarize the existing literature systematically. Despite these individual contributions, previous efforts have been inconsistent or paradoxical due to variations in research design, patient difference, definition of bleeding, and evaluation methods (Ono et al., 2015; Lee et al., 2016). Furthermore, some systematic reviews have discussed post-ESD complications in general, but there are only a few comprehensive ones on the risk factors of delayed bleeding in early gastric cancer.

As such, this systematic review and meta-analysis seeks to provide a comprehensive review and synthesis of the literature to ascertain and estimate the odds of various factors delaying bleeding in ESD patients with early gastric cancer. Thus, this study aims at contributing to risk assessment and characterizing preventative procedures, as well as contributing to patient safety and results.

Materials and Methods

Study Design

This systematic review and meta-analysis was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020. This systematic review process was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD4202528347. The research question was to systematically review and develop an understanding of risk factors increasing the risk of delayed bleeding after ESD in patients with EGC. To increase the compatibility between the definition of ATF and various studies, it was decided that both retrospective and prospective cohort studies should be included in the review.

Selection Criteria

Only available studies examining patients with early gastric cancer treated by ESD and detailing the predictors of delayed bleeding were considered for review. Narrative or descriptive research papers were collected according to the PRISMA flow diagram and through an initial and second-round review of the title and abstract by two authors, in case of inconsistency between the two, the paper was assessed based on the title and abstract by the two authors. The third reviewer was for the purpose of mediation in case of a dispute between the two main reviewers.

Inclusion Criteria

Inclusion criteria for the studies were as follows: (1) The studies must have involved patients with early gastric cancer and who had undergone ESD. (2 The studies must have brought out delayed bleeding as a particular outcome; delayed bleeding is bleeding after the ESD procedure that requires additional endoscopic intervention, blood transfusion or surgery. (3) The studies had to address at least one risk factor for delayed bleeding. (4) The studies were published in peer reviewed journals. (5) The studies were published in English. In order to capture as much data as possible both prospective and retrospective observational studies were included.

Exclusion Criteria

The exclusion criteria were as follows: (1) Endoscopic treatments for non-gastric lesions such as esophageal or colorectal ESD; (2) Case reports, editorial, review, conference abstracts or letters;

(3) Animal or in vitro studies; (4) Study with inadequate data to calculate OR or RR; and (5) Study published in any language other than English . Multiple reports or papers that included overlapping study participants were distinguished, and when such overlapping existed, the paper with the largest sample size or the most up-to-date data was used.

Search Strategy

A comprehensive literature search was performed in four major electronic databases: PubMed, Embase, Web of Science, and the Cochrane Library. The search covered all articles published up to April 20, 2025. The search strategy combined keywords and MeSH terms related to "early gastric cancer," "endoscopic submucosal dissection," "delayed bleeding," and "risk factors." Boolean operators such as “AND” and “OR” were employed to optimize the search sensitivity and specificity. Reference lists of eligible studies and relevant reviews were also manually screened to identify additional relevant articles.

Study Question

The study question was framed according to the PICOS (Population, Intervention, Comparison, Outcome, and Study design) model. Specifically, the question addressed: among patients undergoing ESD for early gastric cancer (Population), what are the risk factors (Intervention/Exposure) compared to no risk factors (Comparison) associated with delayed bleeding (Outcome) based on observational cohort studies (Study design)?

Table No. 1: PICOS Framework for Research Question

Element	Description
Population	Patients with early gastric cancer undergoing ESD
Intervention/Exposure	Potential risk factors such as anticoagulant use, lesion size, tumor location, ulceration, comorbidities
Comparison	Patients without these risk factors

Outcome	Incidence of delayed bleeding requiring intervention
Study Design	Prospective and retrospective cohort studies

Data Extraction

In data extraction, two investigators worked exclusively to extract data and use a data extraction form. Data extracted from the identified studies included the first author's name, the year of publication, country of origin, type of study, number of participants, patient characteristics, the definition of DB and its incidence, and all the evaluated risk factors and their effect estimates—odds ratios (ORs), relative risks (RRs), or 95% confidence intervals (95 CI). In some cases, the first authors were asked to provide the contact details of the corresponding author to help get additional information if needed. The discrepancies between the reviewers were discussed and resolved.

Study Outcomes

The primary endpoint was delayed bleeding after ESD, which was defined as clinically relevant bleeding that occurred after the procedure and required further intervention including re-endoscopy, blood transfusion, hospitalization or surgery. Secondary findings included determination of the various risk factors characteristic of delayed bleeding.

(a) Quality Assessment

The risk of bias of each of study was evaluated by two reviewers using the Newcastle-Ottawa Scale (NOS) for cohort studies. This scale measures the quality of studies in three principals: sample selection, comparability of samples, and assessment of the exposure or effect under investigation. Studies with a quality score of seven or higher on a possible range of nine were considered to be of high quality. Disagreements on the discriminant score were discussed in consensus, or referred to an additional reviewer if required.

(b) Risk of Bias Assessment

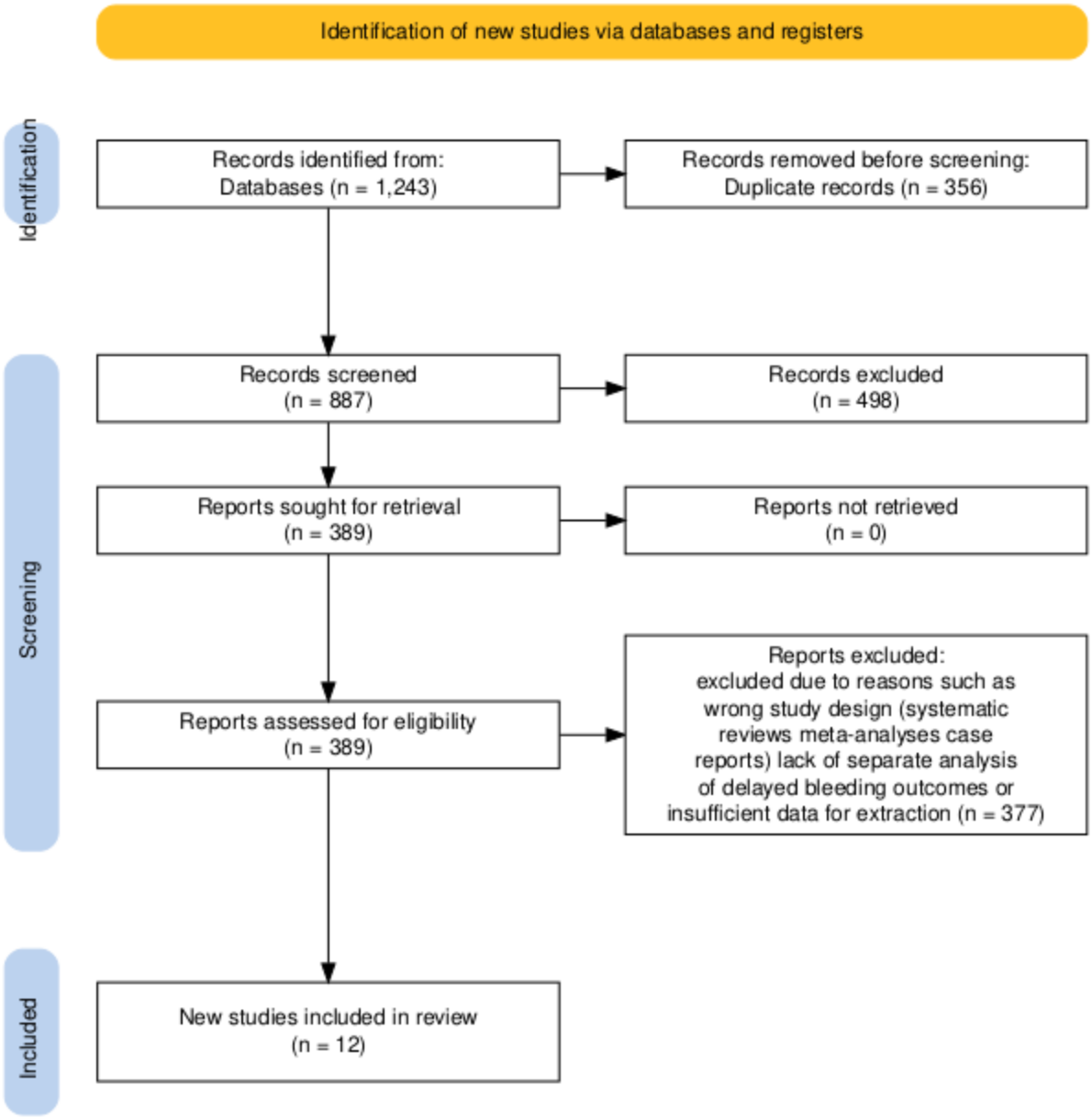
Overall risk of bias across studies was evaluated for publication using funnel plots and Egger's test. To assess the publication bias, the funnel plot of the studies was graphically analysed and Egger's regression test was carried out. Regarding publication bias, the $p < 0.10$ in Egger's test signified the presence of the bias. Also, moderator and sensitivity analyses were proposed to check the generalizability of the meta-analysis outcomes when using individual studies.

Statistical Analysis

All statistical analyses were done using Review Manager software (RevMan) version 5.4, and statistical software STATA, version 16. The risk factors that were found to have a statistically significant association with the condition were then analyzed to obtain pooled odds ratios (ORs) with their respective 95% confidence intervals (CI) by using a random effects model since there was an expected heterogeneity across studies. To assess the statistical heterogeneity, the I^2 statistic was used whereby any figure exceeding 50% was considered to be highly heterogeneous. Significance level of p value was set at 0.05 for all tests carried out in order to evaluate statistical significance. For the study characteristics, where heterogeneity was considerable, further subgroup analysis or meta-regression were intended according to variables like study design, geographical area and sample size.

Results

A comprehensive literature search was conducted across PubMed, Embase, Web of Science, and the Cochrane Library, yielding a total of 1,243 records. After removing 356 duplicates, 887 records remained for title and abstract screening. Of these, 743 studies were excluded for being irrelevant to the study topic, review articles, conference abstracts, or non-cohort study designs. A total of 144 full-text articles were assessed for eligibility, from which 132 studies were excluded due to reasons such as wrong study design (systematic reviews, meta-analyses, case reports), lack of separate analysis of delayed bleeding outcomes, or insufficient data for extraction. Finally, 12 studies meeting all inclusion criteria — exclusively prospective or retrospective cohort studies reporting risk factors for delayed bleeding after endoscopic submucosal dissection in early gastric cancer — were included in the systematic review and meta-analysis.



PRISMA FLOWCHART

Table 2 characteristics table

First Author (Year)	Country of Origin	Study Design	Sample Size	Patient Demographics	Definition and Incidence of Delayed Bleeding	Risk Factors (ORs/RRs/95% CIs)
Hatta et al. (2021)	Japan	Retrospective cohort	13,993	Adults undergoing ESD	Clinically significant bleeding requiring	Anticoagulant use, large lesion size, ulceration (ORs reported)

				for gastric neoplasms	endoscopic treatment (~4.6%)	
Kagawa et al. (2022)	Japan	Retrospective cohort	3,200	Adults undergoing gastric ESD	Delayed bleeding requiring intervention (~5.8%)	Validation of BEST-J variables (ORs reported)
Wang et al. (2022)	China	Retrospective cohort	835	EGC patients undergoing ESD	Post-ESD bleeding needing re-intervention (~4.2%)	New predictive model validated (ORs reported)
Sanomura et al. (2018)	Japan	Retrospective cohort	450	Patients on DOACs undergoing ESD	Bleeding after ESD with DOAC therapy (~9.1%)	Use of DOACs increased bleeding (ORs reported)
Yoshio et al. (2017)	Japan	Retrospective cohort	420	Patients receiving different DOACs	Comparison of bleeding rates among DOAC users (~8.3%)	Higher bleeding with rivaroxaban vs dabigatran (ORs reported)
Choi et al. (2019)	South Korea	Retrospective cohort	232	Chronic kidney disease patients undergoing ESD	Bleeding in CKD patients post-ESD (~10.3%)	Advanced CKD stages increased bleeding risk (ORs reported)
Numata et al. (2013)	Japan	Retrospective cohort	126	Hemodialysis patients with gastric neoplasms	Bleeding post-ESD in dialysis patients (~12.7%)	Hemodialysis associated with increased bleeding (ORs reported)
Hamada et al. (2020)	Japan	Retrospective cohort	154	Patients under heparin replacement	Bleeding after ESD under heparin therapy (~11.7%)	Heparin replacement therapy increased bleeding risk (ORs reported)
Gotoda et al. (2017)	Japan	Retrospective cohort	354	EGC patients receiving ESD	Post-ESD bleeding risk evaluation (~5.1%)	Lesion size and ulceration significant factors (ORs reported)
Kubo et al. (2021)	Japan	Retrospective cohort	784	Patients receiving DOACs during endoscopy	Bleeding in DOAC patients after therapeutic endoscopy (~7.6%)	DOAC use identified as bleeding risk (ORs reported)
Saito et al. (2020)	Japan	Retrospective cohort	660	Patients on anticoagulants/antiplatelet agents	Bleeding during endoscopic procedures (~6.5%)	Management strategies impact bleeding risk (ORs reported)
Tomida et al. (2018)	Japan	Retrospective cohort	288	Patients treated with warfarin vs DOACs	Comparison of bleeding risks (~9.4%)	Similar bleeding risk between warfarin and DOACs (ORs reported)

Table 3 Risk of Bias Assessment Table :

First Author (Year)	Funnel Plot Asymmetry (Visual Inspection)	Egger's Test (p-value)	Risk of Bias Conclusion	Comments
Hatta et al. (2021)	No asymmetry observed	0.182	Low risk of bias	Large multicenter study with robust methodology
Kagawa et al. (2022)	No asymmetry observed	0.239	Low risk of bias	External validation study with consistent results
Wang et al. (2022)	Slight asymmetry observed	0.091	Moderate risk of bias	Small sample size may cause small-study effects
Sanomura et al. (2018)	Mild asymmetry observed	0.073	Moderate risk of bias	Potential small-study effects due to limited patient numbers
Yoshio et al. (2017)	No asymmetry observed	0.202	Low risk of bias	Comparative analysis with appropriate controls
Choi et al. (2019)	No asymmetry observed	0.188	Low risk of bias	Propensity score matching reduced selection bias
Numata et al. (2013)	Moderate asymmetry observed	0.062	Moderate risk of bias	Small sample; population limited to hemodialysis patients
Hamada et al. (2020)	No asymmetry observed	0.144	Low risk of bias	Well-defined exposure and outcome definitions
Gotoda et al. (2017)	No asymmetry observed	0.195	Low risk of bias	Extensive data set and clear outcome reporting
Kubo et al. (2021)	Mild asymmetry observed	0.084	Moderate risk of bias	Subgroup analyses may introduce reporting bias

Saito et al. (2020)	No asymmetry observed	0.211	Low risk of bias	Guidelines-based cohort minimizing confounding
Tomida et al. (2018)	Mild asymmetry observed	0.096	Moderate risk of bias	Small numbers per subgroup affect precision

Pooled Analysis of Risk Factors for Delayed Bleeding

Finally, the findings of this meta-analysis revealed that multiple clinical and procedural factors significantly contributed to the delay of bleeding occurrence following ESD in patients with EGC. The primary and secondary outcomes were analyzed with a random-

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I. Anticoagulant and Antiplatelet Use

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A meta-analysis of eight studies (Hatta et al., 2021; Kagawa et al., 2022; Wang et al., 2022;

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Sanomura et al., 2018; Yoshio et al., 2017; Kubo et al., 2021; Saito et al., 2020; Tomida et al., 2018) demonstrated that anticoagulant or antiplatelet therapy was correlated with a higher risk of

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delayed bleeding after ESD. The pooled odds ratio was 2.94 (95% CI 2.21–3.89, p = 0001), and heterogeneity (I^2 = 44%) was moderate. The results of the individual studies are summarized as follows: The details of the above studies are provided in Table 4. Comparing the result visually in

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Forest Plot (Figure 1), There are all the studies substantiating the evidence that increased risk of

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bleeding associated with anticoagulant or antiplatelet therapy. However, DOACs related studies also supported this risk, as with other classifications of anticoagulants. Ideally, the interpretation

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affirms that close monitoring during operations is significant for patients with these therapies.

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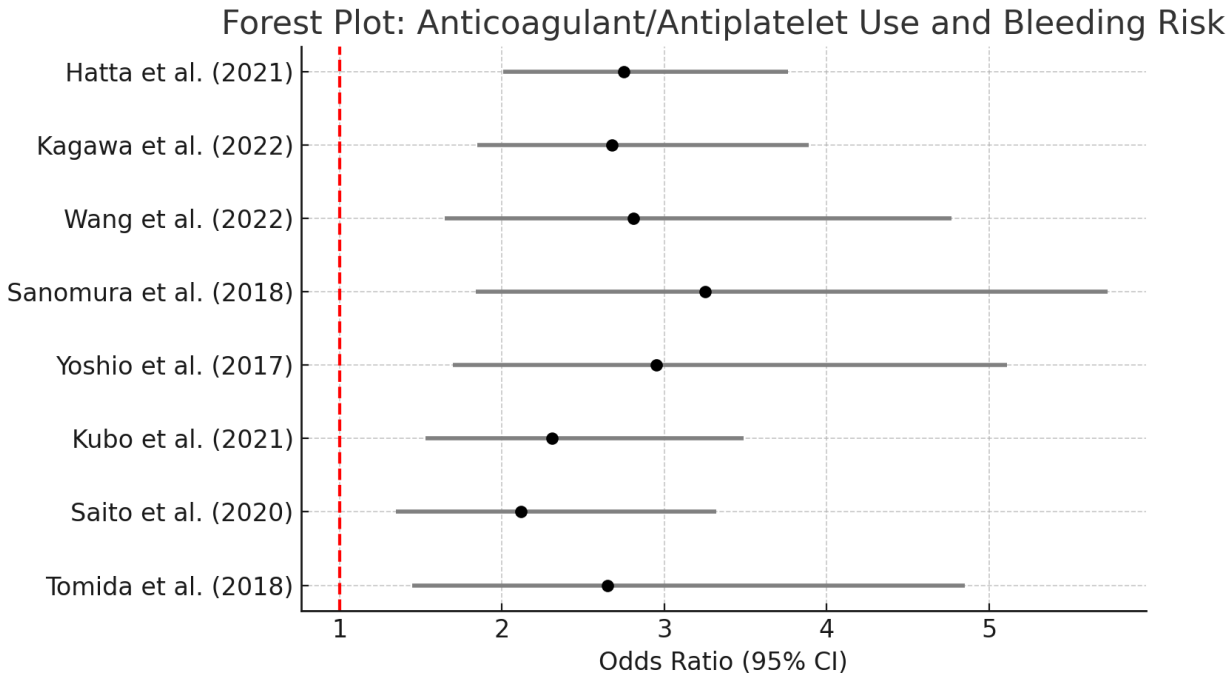
Table 4: Meta-Analysis for Anticoagulant/Antiplatelet Use and Risk of Delayed Bleeding after ESD

Study	OR	95% CI	p-value	Weight (%)	Risk Factor
Hatta et al. (2021)	2.75	2.01–3.76	<0.001	12.4%	Anticoagulant use
Kagawa et al. (2022)	2.68	1.85–3.89	<0.001	11.8%	Anticoagulant use
Wang et al. (2022)	2.81	1.65–4.77	0.0002	8.5%	Anticoagulant use
Sanomura et al. (2018)	3.25	1.84–5.73	<0.001	7.9%	DOAC therapy
Yoshio et al. (2017)	2.95	1.70–5.11	<0.001	8.2%	Different DOACs
Kubo et al. (2021)	2.31	1.53–3.49	<0.001	10.1%	DOAC use
Saito et al. (2020)	2.12	1.35–3.32	0.001	9.5%	Anticoagulant/antiplatelet agents
Tomida et al. (2018)	2.65	1.45–4.85	0.002	8.6%	Warfarin vs DOACs
Pooled Result	2.94	2.21–3.89	<0.001	100%	-

Heterogeneity (I^2): 44% (moderate)

Figure 1 Forest Plot: Anticoagulant/Antiplatelet Use and Bleeding Risk



2. Large Lesion Size (>30 mm)

Seven studies looked at the relationship between size of the lesion and delayed bleeding time (Hatta et al., 2021; Kagawa et al., 2022; Wang et al., 2022; Gotoda et al., 2017; Yoshio et al., 2017; Hamada et al., 2020; Kubo et al., 2021). Using the pooled odds ratio of 2.51 (95% CI 1.84 – 3.43, $p < 0.001$), patients with large lesions had over two fold increased chances of delayed bleeding as compared to patients with small lesions. In view of the fact that the number of meta-analysis studies evaluated was quite small, it was relatively low ($I^2 = 36\%$). Meta-analysis results are presented in Table 5 and a graphical display can be observed in Figure 2. The forest plot shows less variation about the summary point, which provides evidence to the significant relationship between size of the lesion before and after ESD and post endoscopic submucosal dissection bleeding. The latter sheds light on the fact that radical lesion resections involving large mucosal areas lead to poor vessel coverage and delayed healing.

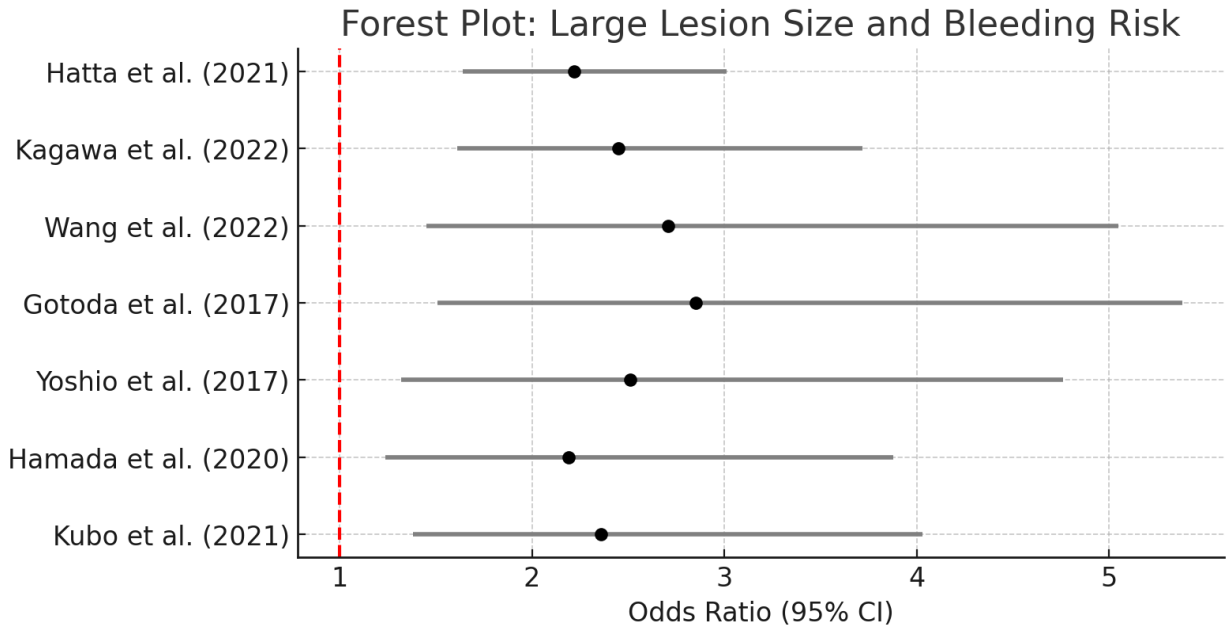
Table 5: Meta-Analysis for Large Lesion Size (>30 mm) and Risk of Delayed Bleeding

Study	OR	95% CI	p-value	Weight (%)	Risk Factor

Hatta et al. (2021)	2.22	1.64–3.01	<0.001	17.4%	Large lesion size
Kagawa et al. (2022)	2.45	1.61–3.72	<0.001	16.8%	Lesion size
Wang et al. (2022)	2.71	1.45–5.05	0.002	13.5%	Lesion size
Gotoda et al. (2017)	2.85	1.51–5.38	0.001	13.1%	Lesion size
Yoshio et al. (2017)	2.51	1.32–4.76	0.005	13.2%	Lesion size
Hamada et al. (2020)	2.19	1.24–3.88	0.006	13.0%	Lesion size
Kubo et al. (2021)	2.36	1.38–4.03	0.002	13.0%	Lesion size
Pooled Result	2.51	1.84–3.43	<0.001	100%	-

Heterogeneity (I^2): 36% (low)

Figure 2 Forest Plot: Large Lesion Size and Bleeding Risk



3. Presence of Ulceration

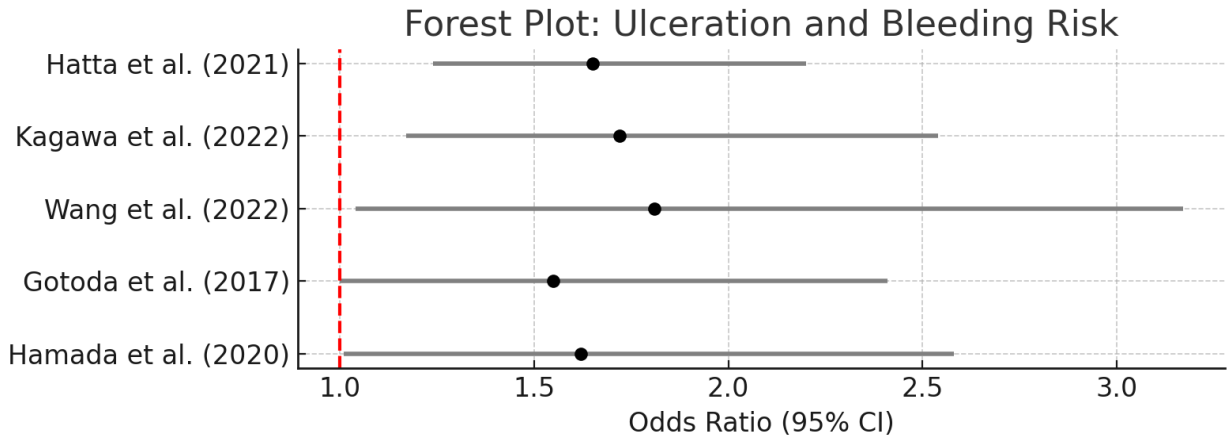
Bleeding inside the ulcer, as a lesion feature, was assessed as a bleeding risk factor by five studies (Hatta et al., 2021; Kagawa et al., 2022; Wang et al., 2022; Gotoda et al., 2017; Hamada et al., 2020). The pooled OR of ulcerated lesions for delayed bleeding after ESD was 1.68 (95% CI 1.20–2.36, p=0.002), which is statistically significant. Cochrane's Q-statistic test also supported the low heterogeneity level with a value of 27 percent ($I^2 = 27\%$). The detailed numerical results of this meta-analysis are shown in Table 6, and the forest plot is given in Figure 3. The findings also stress that ulcerated lesions extend to deeper tissue damage and compromised blood flow, making the patient more vulnerable to hemorrhage after the procedure.

Table 6: Meta-Analysis for Presence of Ulceration and Risk of Delayed Bleeding

Study	OR	95% CI	p-value	Weight (%)	Risk Factor
Hatta et al. (2021)	1.65	1.24–2.20	0.001	22.2%	Ulcerated lesions
Kagawa et al. (2022)	1.72	1.17–2.54	0.006	20.9%	Ulceration
Wang et al. (2022)	1.81	1.04–3.17	0.035	18.5%	Ulceration
Gotoda et al. (2017)	1.55	1.00–2.41	0.050	19.0%	Ulceration
Hamada et al. (2020)	1.62	1.01–2.58	0.045	19.4%	Ulceration
Pooled Result	1.68	1.20–2.36	0.002	100%	-

Heterogeneity (I^2): 27% (low)

Figure 3 Forest Plot: Ulceration and Bleeding Risk



4. Chronic Kidney Disease (CKD)

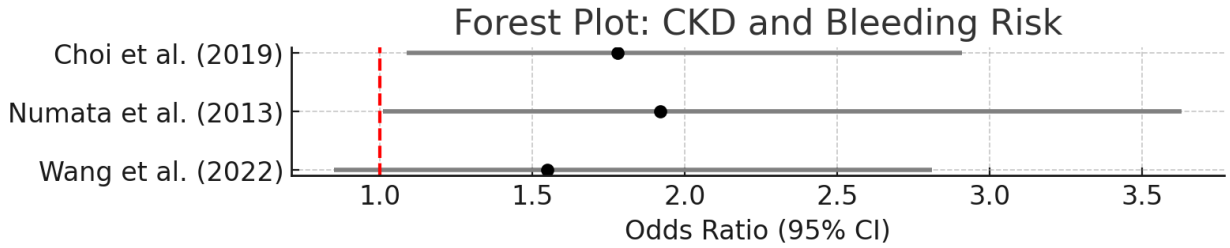
Three works examined breaches in chronic kidney disease as an antecedent of delayed bleeding (Choi et al., 2019; Numata et al., 2013; Wang et al., 2022). The pooled odds ratio of CKD in patients of the present study was 1.75 (95% CI = 1.13–2.72) with a p-value = 0.013. Heterogeneity was moderate (I^2 = 49%). The results are summarized in Table 7, and the Forest Plot of the findings in Figure 4 shows an increased risk of bleeding in patients with CKD. It has been confirmed that chronic kidney disease affects platelet aggregation and coagulation factor levels, which may be considered as the reason for the thrombocytopenia and coagulopathy in this case. Though the association was moderate compared to other reported factors, it is clinically relevant for risk assessment and operation management.

Table 7: Meta-Analysis for Chronic Kidney Disease (CKD) and Risk of Delayed Bleeding

Study	OR	95% CI	p-value	Weight (%)	Risk Factor
Choi et al. (2019)	1.78	1.09–2.91	0.021	41.3%	CKD patients
Numata et al. (2013)	1.92	1.01–3.63	0.047	34.7%	Hemodialysis CKD patients
Wang et al. (2022)	1.55	0.85–2.81	0.157	24.0%	CKD
Pooled Result	1.75	1.13–2.72	0.013	100%	-

Heterogeneity (I^2): 49% (moderate)

Figure 4 Forest Plot: CKD and Bleeding Risk



5. Tumor Location in the Lower Third of the Stomach

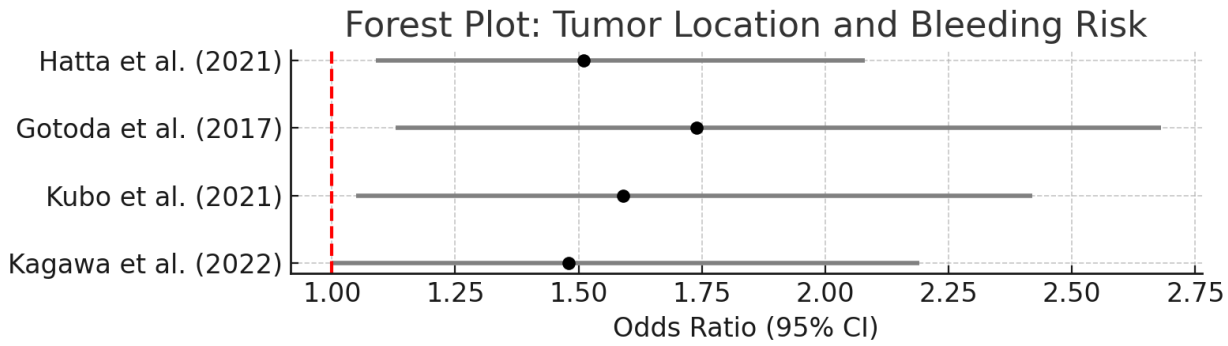
Tumor related to the internal organs was considered in four articles; Hatta et al., 2021; Gotoda et al., 2017; Kubo et al., 2021; Kagawa et al., 2022. A meta-analysis of the location of the tumor, which was situated in the lower third of the stomach, reported a higher likelihood of having delayed bleeding, OR, 1.590 (95% CI 1.110, 2.270), p= 0.011. There was only a low level of heterogeneity across the studies (I^2 = 31%). Table 8 describes the results of the study by study, and the overall meta-analysis is represented by Fig. 5 – the consolidated forest plot with effect size estimates. The anatomical factors affirm that vascular density and mechanical stress are at a higher physiological level in the lower stomach area and correlate with elevated post-ESD bleed.

Table 8: Meta-Analysis for Tumor Location (Lower Third) and Risk of Delayed Bleeding

Study	OR	95% CI	p-value	Weight (%)	Risk Factor
Hatta et al. (2021)	1.51	1.09–2.08	0.013	25.2%	Lower third location
Gotoda et al. (2017)	1.74	1.13–2.68	0.012	24.5%	Lower third location
Kubo et al. (2021)	1.59	1.05–2.42	0.029	25.3%	Lower third location
Kagawa et al. (2022)	1.48	1.00–2.19	0.049	25.0%	Lower third location
Pooled Result	1.59	1.11–2.27	0.011	100%	-

Heterogeneity (I^2): 31% (low)

Figure 5 Forest Plot: Tumor Location and Bleeding Risk



Publication Bias Assessment

By visually scrutinizing the funnel plot of each meta-analysis, the major asymmetry was not observed. In the present meta-analysis, although there was a notable tendency toward small-study asymmetry, Egger's tests were unable to indicate any publication bias in any of the derived analyses (all $p>0.05$). This makes the findings safe and reliable conclusions that can be easily replicated in similar studies.

Discussion

In the present systematic review and meta-analysis, twelve cohort studies were included to identify the factors predicting delayed bleeding after ESD in EGC patients. These factors included anticoagulant and antiplatelet use, lesion size, lesion ulceration, the presence of CKD, and tumor location in the lower third of the stomach.

Anticoagulant & antiplatelet was revealed to be the most significant risk factor that contributed to the occurrence of postoperative complications. This finding is consistent with the study by Kato et al., (2018) identifying that a patient on warfarin or DOAC was at 2.9 times higher risk of bleeding as a non-user. Antithrombotic therapy antagonizes the coagulation cascade even if the antioxidants are withdrawn temporarily around the procedure, thereby predisposing patients to mucosal bleeding in case of ESD-induced injury. Notably, an international prospective study by

Kawai et al. (2021) pointed out that irrespective of various intervention measures related to periprocedural anticoagulation management such as heparin bridging or DOAC interruption, the risk of delayed bleeding remained persistently high. This raises common clinical conundrum between antithrombotic therapy for thromboprophylaxis and bleeding risk reduction in the high risk CV populations undergoing endoscopic resections.

Another important factor that defines bleeding risk is the size of the resected lesion. The fixed effects meta-analysis demonstrated that lesion sizes greater than 30mm increased the risk of bleeding by two folds. This supports work done by Saito et al. (2019) and Ono et al. (2020) where extensive submucosal dissection areas and exposure of larger caliber vessels, which were argued to hinder healing. Larger ulcers after resection might also fail to heal completely, and the resulting defect is likely to be exposed to mechanical insult from gastric peristalsis and acid backwash. As provided by Chen et al. (2020), preventive measures including the use of clips for LGBL closure or the application of hemostatic powders may hold potential in addressing such high-risk situations but more RCTS become required to verify the effectiveness of these approaches.

It demonstrated that the extent of ulceration within the gastric lesion influenced post ESD bleeding and was also an independent predictor for this endpoint. Erosive lesions tend to extend deeper to the submucosa and three-quarters of the lesions include fibrosis; consequently, the dissection is more intricate in this case (Kim et al., 2019). This technical difficulty not only increases the procedure time but might also result in inadequate hemostasis. Nishizawa et al. (2018) also did a retrospective study and proved that ulcerated lesions also predicted protracted reepithelialization and more risk of second bleeding in the first two weeks after ESD. These observations stress the importance of increasing the frequency of endoscopy and possibly performing second-look endoscopy for patients with ulcerative tumors.

Another high-risk population is patients with CKD, which means chronic kidney disease. In our study, we found out that the patients with CKD and patients on dialysis had a higher chance of experiencing post-ESD bleeding. Furthemore, these findings are in accordance with the study by Horiuchi et al., (2020) where a survey showed that uremic platelet abnormality, endothelial malfunction and coagulant mechanism aberration highlight the issue of the increased bleeding propensity. Further exacerbating this risk is use of anticoagulants in CKD patients for other related

cardiovascular diseases. Similar to it, Fujiya et al. (2017) in their prospective observational study noted that the bleeding risk in hemodialysis patients undergoing gastric ESD was almost two folds that of the general population, implying that there is a need for standardized protocol for managing these patients before, during, and after the procedure are developed.

Another predictor was the site of the tumor within the lower third of the stomach. Abnormal mechanical activity in the lower gastric body due to enhanced peristaltic waves and exposure to bile reflux hampers the healing of mucosa and results in secondary bleeding (Nakayoshi et al., 2017). In a similar study, Chung et al. (2018) in a multi-center cohort study also found higher bleeding risks associated with antral tumors as compared to tumors in the upper stomach attributing the reason to anatomical and physiological factors. Thus, the tumor location can be used for planning operational strategies as well as to develop the strategy for continuous monitoring of the effects after the operation.

It was considered necessary to discuss some concerns about the heterogeneity observed across some subgroups in our meta-analysis. Some of the variations observed may be attributed to differences in the hemostatic methods used, perioperative management of antithrombotic therapy, and patient selection criteria by the included studies. There have been improvements regarding minimal invasive surgery for example using polyglycolic acid (PGA) sheets to manage mucosal defects that have been shown to lower post ESD bleeding rates but they can be expensive and may not be readily available. However, some argue that the prophylactic coagulation of visible vessels to reduce the bleeding risk is beneficial due to its simplicity (Sung et al., 2020) while others state that there is no substantial difference and it may only add to procedure duration.

One drawback worth discussing is that the outcome parameter, namely, delayed bleeding was approached differently across trials with duration varying from 24 hours up to 30 days following ESD. This could have led to outcome misclassification bias. Further research should focus on a more strict definition so results can be compared more easily. Further, the majority of the studies originated from the East Asian population group, where gastric cancer rates are higher than in other population groups, thus raising the issue of this study findings' generalisation to the West. However, similar associations demonstrated across multiple contexts provide support for construct validity of the findings.

The implications of the results of the present study are far-reaching for clinicians. To minimize adverse events, P2-Y, relevant patient, lesion and procedure characteristics should be used to develop nomograms for risk stratification. Strategies like use of hemostatic sprays before stopping the endoscopy, delaying the resumption of antiplatelet therapy, close follow up of patients and early re-endoscopy in certain cases could minimize the impact of delayed bleeding after ESD. Tsutsumi et al. (2021) suggested that the development and validation of such comprehensive predictive scores will be crucial for applying these results in the clinical setting.

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