SYSTEMATIC REVIEW AND META-ANALYSIS

Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis

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Background and Aims: Postprocedural bleeding (PPB) is the most common adverse event associated with endoscopic resection. Several studies have tried to identify risk factors for PPB after gastric EMR and endoscopic submucosal dissection (ESD), with controversial results. This systematic review and meta-analysis aimed to identify significant risk factors for PPB after gastric EMR and ESD.

Methods: Three online databases were searched. Pooled odds ratio (OR) was computed for each risk factor using a random-effects model, and heterogeneity was assessed by Cochran's Q test and I^2.

Results: Seventy-four articles were included. Pooled PPB rate was 5.1% (95% confidence interval, 4.5%-5.7%), which did not vary according to different study designs. Male sex (OR, 1.25), cardiopathy (OR, 1.54), antithrombotic drugs (OR, 1.63), cirrhosis (OR, 1.76), chronic kidney disease (OR, 3.38), tumor size > 20 mm (OR, 2.70), resected specimen size > 30 mm (OR, 2.85), localization in the lesser curvature (OR, 1.74), flat/depressed morphology (OR, 1.43), carcinoma histology (OR, 1.46), and ulceration (OR, 1.64) were identified as significant risk factors for PPB, whereas age, hypertension, submucosal invasion, fibrosis, and localization (upper, middle, or lower third) were not. Procedure duration > 60 minutes (OR, 2.05) and the use of histamine-2 receptor antagonists instead of proton pump inhibitors (OR, 2.13) were the procedural factors associated with PPB, whereas endoscopist experience and preprocedural proton pump inhibitors were not. Second-look endoscopy was not associated with decreased PPB (OR, 1.34; 95% confidence interval, .85-2.12).

Conclusions: Risk factors for PPB were identified that can help to guide management after gastric ESD, namely adjusting further management. Second-look endoscopy is not associated with decreased PPB. (Gastrointest Endosc 2016;84:572-86.)

Endoscopic submucosal dissection (ESD) and EMR are well-established treatments for early gastric neoplasms.[1] Bleeding is the most frequent adverse event associated with ESD and EMR, occurring in 7.1% to 9.4% and 7.1% to 8.6% of the procedures, respectively.[2-4] Specifically, postprocedural bleeding (PPB) is reported to occur in 4.53% after ESD and 3.97% after EMR.[2]

Both patient and lesion characteristics, as well as medications and procedural technical features, may influence the risk of bleeding. Several studies have addressed this issue over time, aiming at identifying risk factors for PPB. However, some controversy exists, and the significant risk factors for post-EMR/ESD bleeding are yet to be identified. The identification of these risk factors is of paramount importance to estimate bleeding risk and to stratify patients, namely to guide management after ESD/EMR. Therefore, we aimed at identifying the risk factors for PPB after EMR and ESD for early gastric neoplasms.

Abbreviations: AT, antithrombotic therapy; CI, confidence interval; ESD, endoscopic submucosal dissection; H_2RA, histamine-2 receptor antagonist; OR, odds ratio; PPB, postprocedural bleeding; PPI, proton pump inhibitor; RCT, randomized controlled trial; SLE, second-look endoscopy.

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METHODS

Study search and selection

Studies were identified through scanning of 3 electronic databases (MEDLINE through PubMed, Scopus, and ISI Web of Knowledge), with the last search performed on July 15, 2015. The search query for PubMed was ([gastric OR stomach] AND ["endoscopic submucosal dissection" OR "endoscopic mucosal resection"]) AND (bleeding OR

hemorrhage). Queries for other databases were adapted from this query. Additional studies were identified by checking the list of references of all included studies and reviews on the topic.

Two independent investigators (D.L., M.N.C.) screened titles and abstracts to exclude irrelevant studies. The full text of relevant studies was then analyzed by these same authors according to the criteria below. Disagreements were solved by consensus with the intervention of a third reviewer (P.P.N.) when required. This phase was performed with Covidence online platform (www.covidence.org).

Abstracts and fully published studies were considered for inclusion with no date or language restrictions. Inclusion criteria were (1) retrospective or prospective, case-control or cohort studies and clinical trials (including randomized controlled trials [RCTs]); (2) studies evaluating patients submitted to EMR or ESD to treat gastric superficial neoplasms (dysplastic lesions or early gastric cancers); (3) studies with PPB rates reported separately from intraprocedural bleeding; and (4) studies where risk factors for PPB were analyzed. Articles were excluded if (1) PPB rates were not clearly reported; (2) fewer than 20 patients were included; (3) they were feasibility studies of innovative techniques/devices without control group; (4) they were comments, reviews, letters, or surveys; (5) they were case reports; or (6) they were animal studies.

Quality evaluation and data extraction

Data extraction and quality assessment were performed by D.L. using prespecified forms that were refined after piloting in 10 studies. Another reviewer (M.N.C.) independently checked the extracted data, and disagreements were solved by consensus. Data extraction forms included (1) author, (2) publication year, (3) setting, (4) study period, (5) study design, (6) randomization methods if applicable, (7) allocation concealment, (8) blinding, (9) type of endoscopic resection (EMR/ESD), (10) number of participants, (11) definition of PPB, (12) frequency of PPB (total and for each risk factor), (13) antacids (route, dosage, duration of therapy), (14) antithrombotic management, (15) operator (single/multiple, experienced/nonexperienced), and (16) second-look endoscopy (SLE). In the data extraction form, crude data and results of statistical analysis were recorded for each risk factor. Quality evaluation was performed using the Cochrane risk of bias tool for RCTs[5] and the Newcastle-Ottawa scale for observational studies.[6] Also, the quality of reporting of acid inhibition strategy and antithrombotic management was assessed.

Data synthesis and statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for each categoric risk factor and the mean or median for continuous data was registered (or calculated whenever possible). Studies providing data allowing the calculation of ORs were then included in a meta-analysis, performed by computing pooled ORs (for categoric variables) and mean differences (for continuous variables) using a random-effects model. Pooled PPB prevalence was calculated with a random-effects model with OpenMetaAnalyst.[7] Meta-analysis was performed using RevMan 5.3.[8] Heterogeneity was evaluated with the Cochran Q test and I^2. Significant heterogeneity was defined as $I^2 > 40\%$ and $P < .05$. For continuous outcomes, median and interquartile range/range were transformed into mean and standard deviation through the methods proposed by the Cochrane collaboration and Hozo et al.[9] Sensitivity analysis was planned, excluding these studies and whenever significant heterogeneity was found. Subgroup analysis was planned according to study design, time of bleeding (early or delayed), and antithrombotic management. This study was conducted in accordance with the PRISMA recommendations for reporting systematic reviews and meta-analysis.[10]

RESULTS

Characteristics of included studies and quality evaluation

In total, 1043 studies were identified (1038 through database search and 5 through manual searching), and 74 references (71 studies) were finally included in this systematic review (Fig. 1). A summary of the included studies and quality evaluation (15 RCTs, 3 prospective trials, 5 prospective cohort studies, and 48 retrospective cohort and case-control studies) is shown in Table 1. Seventy-three percent of RCTs were judged to have low risk of bias, whereas observational studies had a median and mean Newcastle-Ottawa score of 7 and 7.5, respectively. Almost all studies reported that proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H_2RAs) were administered in the periprocedural period, although route, dosage, frequency of administration, and duration of treatment were not accurately reported in 42% of the studies. Moreover, the management of antithrombotics was not clearly reported in 24 studies (32%).

PPB definition and rate

The most common definition of PPB was clinical evidence of bleeding (hematemesis/melena) or hemoglobin drop $\geq$ 2 g/dL requiring endoscopic hemostasis. Definitions of early and delayed bleeding were heterogeneous among studies, with some studies defining early bleeding as those occurring in the first 24 hours, whereas others considered early bleeding those that occurred in the first 48 hours or in the first 5 days after ESD.

PPB rates ranged from .6%[11] to 26.9%,[12] and the pooled PPB rate was 5.1% (95% CI, 4.5%-5.7%), with significant heterogeneity across studies ($I^2 = 84.46$, $P < .001$). However, PPB rates were not significantly different according to study design (5.9% in RCTs, 6.1% in prospective studies, and 4.9% in retrospective studies; $I^2 > 80\%$).

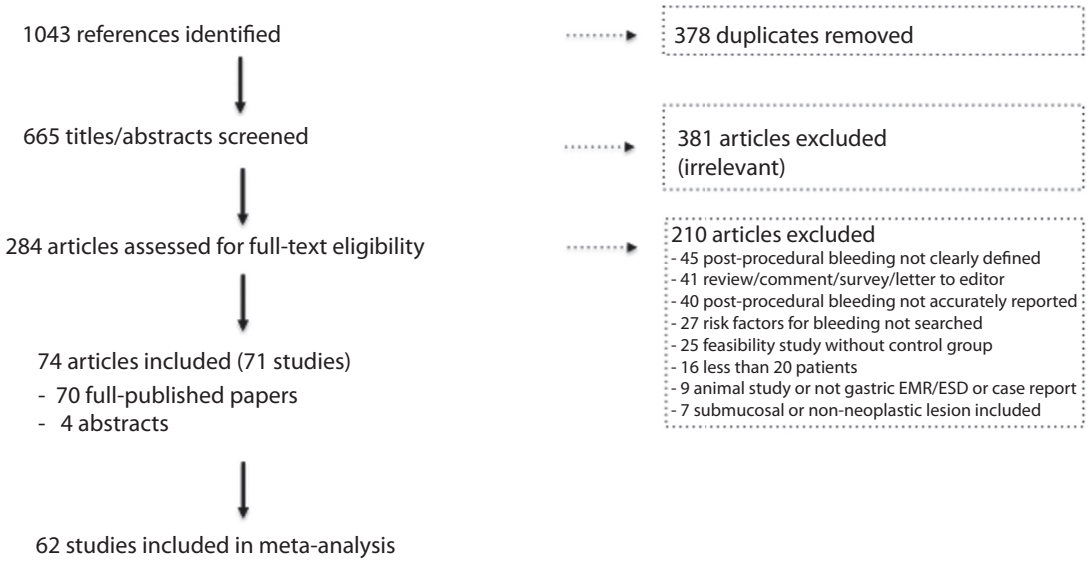

Figure 1. Flowchart of included studies.

The time of bleeding was determined in 28 studies. Definitions of early and delayed bleeding were also heterogeneous across studies. Most bleeding episodes (213/374; 56.9%) occurred more than 24 hours after ESD. Among the 4 studies classifying early PPB as bleeding < 48 hours after ESD, 92 of 135 PPB events (68.2%) occurred in this time period. As stated below, among those studies reporting delayed bleeding (>48 hours after ESD) only, upper localization was associated with a higher bleeding risk.

Risk factors for PPB

All included studies explored risk factors for PPB after ESD, whereas risk factors for PPB after EMR were evaluated in 3 studies. Most studies (54%) evaluated multiple risk factors (case-control design), whereas 46% focused on single risk factors (eg, age, size, premedication with PPIs). Significant risk factors found in the meta-analysis are summarized in Figure 2, and the effect estimates for each risk factor are shown in Tables 2, 3, and 4.

Patient factors. Age was not identified as a risk factor in most studies,[13-33] with only 1 study reporting that younger patients may be at higher risk for PPB.[34] Furthermore, 10 studies found no significant differences in elderly patients,[19,25,30,35-41] although 1 study identified age > 80 years as an independent risk factor for PPB.[42] PPB rates were similar between genders in most studies,[13-18,20-23,25-34,36,39,42-44] with only 1 study reporting an association male sex associated with PPB.[24]

Arterial hypertension was not identified as a risk factor in most studies,[13-15,17,18,20-24,28-31,33,42,43,45] although 2 studies reported significantly higher PPB rates in hypertensive patients.[16,36] However, the adjusted OR was .67 in the latter study.[36] Similarly, diabetes mellitus was not identified as a significant risk factor in any study.[13-18,20-24,28-31,33,34,36,42,44,45]

Cardiopathy (ischemic heart disease in most studies),[10,13,17,20,23,28,29,31,34,36,42,44,45] cerebrovascular disease,[15,21-23,28,36,42,45] and cirrhosis[14,17,18,22,24,26,28,29,34,36,43,45] were not identified as risk factors for PPB in most studies. Chronic kidney disease was not identified as a risk factor in some studies despite a trend to higher bleeding.[14,17,22,28,30,34,42] However, 3 studies found significantly increased PPB rates in patients with chronic kidney disease[45] and undergoing dialysis.[18,46]

Comorbidities[28,45] and American Society of Anesthesiologists Physical Status Classification System status[47] were not identified to be associated with PPB, although 1 study found increased PPB risk in patients with significant comorbidities.[25] Other clinical factors were analyzed in a few studies. *Helicobacter pylori* infection,[13,14,22] body mass index,[22,29,36] hyperlipidemia,[24,29,31,34,42] hyperuricemia,[36] pulmonary disease,[34] history of peptic ulcer,[31] hemoglobin level,[22] prothrombin, and activated partial thromboplastin time[22,25] were not found to be associated with PPB. Thrombocytopenia was associated with PPB in 1 study,[43] although 2 studies did not find differences in PPB rates.[16,22]

Finally, previous gastric surgery (ESD in gastric remnant or gastric tube) was not associated with increased PPB.[22,48,49] However, 1 study found a higher PPB rate when the anastomotic site was involved.[48]

After meta-analysis, male sex, cardiopathy, cirrhosis, and chronic kidney disease were significantly associated with PPB. Among patients with chronic kidney disease, dialysis was associated with an increased PPB risk (Table 2). Again, age, hypertension, diabetes mellitus, and cerebrovascular disease were not found to influence PPB.

TABLE 1. General characteristics of included studies

	Country	Period	Resection method, n	Overall PPB (%)	Risk factors evaluated	Quality*	Included in meta-analysis†
RCTs							
Ono S, 2009[11]	Japan	04-07	ESD, 155	.6	Single (pre-PPI)	Low risk	Yes
Lee BI, 2011[69]	Korea	08-09	ESD, 52	1.9	Single (closure)	Unclear risk	No
Watanabe Y, 2006[79]	Japan	02-03	ESD, 98	3.1	Single (pre-PPI)	High risk	Yes
Imaeda H, 2011[80]	Japan	08-10	ESD, 123	4.1	Single (PPI vs H_2RA)	Low risk	Yes
Kim S, 2014[74]	Korea	11-12	ESD, 120	4.2	Single (early diet)	Low risk	No
Mochizuki S, 2015[84]	Japan	12-13	ESD, 262	4.6	Multiple	Low risk	Yes
Kim JS, 2014[22]	Korea	12-13	ESD, 446	5.2	Multiple	Low risk	Yes
Tomita T, 2012[32]	Japan	08-10	ESD, 156	5.7	Multiple	Low risk	Yes
Baeg MK, 2014[77]	Korea	NR	ESD, 98	6.1	Single (pre-PPI)	Unclear risk	Yes
Uedo N, 2006[81],‡	Japan	05	ESD, 105	6.7	Single (PPI vs H_2RA)	Unclear risk	Yes
Ahn JY, 2015[62]	Korea	08-09	ESD, 79	7.6	Single (ecabet sodium)	Low risk	Yes
Jeong HK, 2007[60]	Korea	05-06	ESD, 164	7.9	Multiple	Low risk	Yes
Choi CW, 2015[14]	Korea	12-13	ESD, 273	8.4	Multiple	Low risk	Yes
Uedo N, 2007[59]	Japan	05-06	ESD, 143	10.5	Multiple	Low risk	Yes
Ryu HY, 2013[61]	Korea	11-12	ESD, 155	13.5	Multiple	Low risk	Yes
Prospective studies							
Hikichi T, 2014[78]	Japan	07-08	ESD, 55	1.8	Single (pre-PPI)	8	Yes
Lim SM, 2013[83]	Korea	08-11	ESD, 1461	4.4	Single (fatigue)	9	No
Park CH, 2015[30]	Korea	11-12	ESD, 459	5.4	Multiple	9	Yes
Kikuchi D, 2013[73]	Japan	08-10	ESD, 89	5.6	Single (EUS findings)	7	No
Na S, 2015[28]	Korea	11-12	ESD, 706	5.8	Multiple	7	Yes
Nishide N, 2012[48]	Japan	02-09	ESD, 1541	10.6	Single (remnant)	7	Yes
Tsuji Y, 2015[72]	Japan	13-14	ESD, 86	13.9	Single (PGA sheets)	9	No
Ono S, 2015[12]	Japan	12-14	ESD, 26	26.9	Multiple	8	Yes
Retrospective studies							
Ahn SY, 2014[75]	Korea	07-08	ESD, 105	.9	Single (early discharge)	7	No
Ahn JY, 2011[64]	Korea	94-09	ESD, 833; EMR, 537	1.3/1.5	Single (indication)	7	Yes
Oda I, 2012[82]	Japan	99-08	ESD, 464	1.5	Single (experience)	6	Yes
Shimura T, 2007[55]	Japan	99-05	ESD, 59; EMR, 48	1.7/4.2	Multiple	7	Yes
Lee JY, 2010[49]	Korea	04-08	ESD, 43	2.3	Single (remnant)	7	Yes
Isomoto H, 2010[19]	Japan	01-07	ESD, 713	2.5	Single (age)	7	Yes
Yamaguchi N, 2009[63]	Japan	01-07	ESD, 713	2.5	Single (indication)	7	Yes
Kim ER, 2015[20]	Korea	09-10	ESD, 550	2.5	Multiple	8	Yes
Higashiyama M, 2011[18]	Japan	05-09	ESD, 924	3.0	Multiple	9	Yes
Akasaka T, 2011[76]	Japan	03-08	ESD, 1188	3.1	Multiple	4	No
Mukai S, 2013[70]	Japan	07-12	ESD, 234	3.4	Single (clipping)	7	No
Sugimoto T, 2012[39]	Japan	02-08	ESD, 485	3.7	Multiple	9	Yes
Asakuma Y, 2011[57],‡	Japan	02-07	ESD, 386	3.9	Multiple	6	No
Goto O, 2009[68]	Japan	04-07	ESD, 119	4.0	Snaring	8	No
Kim SE, 2013[23]	Korea	06-11	ESD, 396	4.0	Multiple	7	Yes
Cho SJ, 2012[15]	Korea	99-03	ESD, 514	4.1	Multiple	9	Yes
Kawai N, 2007[52],‡ and 2012[53]	Japan	03-05	ESD, 552	4.2	Single (antithrombotics)	6	Yes
Okada K, 2011[29]	Japan	05-08	ESD, 582	4.3	Multiple	9	Yes

(*continued on the next page*)

TABLE 1. Continued

	Country	Period	Resection method, n	Overall PPB (%)	Risk factors evaluated	Quality*	Included in meta-analysis†
Kim HH, 2012[21]	Korea	08-10	ESD, 442	4.3	Multiple	7	Yes
Takeuchi T, 2013[54]	Japan	02-12	ESD, 833	4.3	Multiple	7	Yes
Sanomura Y, 2014[50]	Japan	05-12	ESD, 94	4.3	Single (antithrombotics)	7	Yes
Ebi M, 2014[16]	Japan	05-12	ESD, 186	4.3	Multiple	9	Yes
Kosaka T, 2014[65]	Japan	02-07	ESD, 438	4.3	Single (indication)	7	Yes
Man-i M, 2013[47]	Japan	07-10	ESD, 527	4.4	Single (ASA)	7	Yes
Hirasaki S, 2007[56]	Japan	02-06	ESD, 112	4.5	Single (size)	7	Yes
Kim BJ, 2010[45]	Korea	03-06	ESD, 337	4.7	Single (comorbidity)	7	Yes
Matsumura T, 2014[26]	Japan	05-14	ESD, 425	4.7	Multiple	7	Yes
Toyokawa T, 2012[42]	Japan	03-10	ESD, 1123	5.0	Multiple	7	Yes
Takahashi F, 2014[34]	Japan	04-13	ESD, 459	5.0	Multiple	7	Yes
Suzuki H, 2015[71]	Japan	95-06	ESD, 1713	5.1	Single (experience)	7	Yes
Chinda D, 2015[35]	Japan	04-09	ESD, 307	5.2	Single (age)	7	Yes
Yoshio T, 2013[40]	Japan	03-11	ESD, 1250	5.3	Single (antithrombotics)	6	No
Koh R, 2013[24]	Japan	00-10	ESD, 1166	5.3	Multiple	9	Yes
Jeong JY, 2012[67]	Korea	06-11	ESD, 167	5.4	Single (fibrosis)	7	Yes
Choi CW, 2014[13]	Korea	08-12	ESD, 616	5.6	Multiple	9	Yes
Onochi K, 2010[51],‡	Japan	03-09	ESD, 468	5.6	Single (antithrombotics)	6	Yes
Goto O, 2010[17]	Japan	03-08	ESD, 454	5.7	Multiple	7	Yes
Takizawa T, 2008[31]	Japan	00-04	ESD, 1083	5.8	Multiple	8	Yes
Tusji Y, 2010[33]	Japan	07-09	ESD, 398	5.8	Multiple	9	Yes
Lim JH, 2012[25]	Korea	05-10	ESD, 1591	5.9	Multiple	9	Yes
Zhang Y, 2014[41]	China	10-13	ESD, 187	5.9	Single (age)	7	Yes
Nakamura M, 2012[43]	Japan	06-11	ESD, 544	6.9	Multiple	9	Yes
Miyahara K, 2012[36] Mannen K, 2010[44]	Japan	01-10	ESD, 1082	6.9	Multiple	9	Yes
Onozato Y, 2006[37] and 2008[38]	Japan	02-06	ESD, 226	7.5	Multiple	7	Yes
Oka S, 2006[66]	Japan	90-04	ESD, 195; EMR, 825	11.3/7.0	Single (ulceration)	6	No
Mukai S, 2012[27]	Japan	07-10	ESD, 161	13	Multiple	9	Yes
Numata N, 2013[46]	Japan	04-12	ESD, 79	13.9	Single (dialysis)	7	Yes
Chung I-K, 2009[58]	Korea	06-07	ESD, 1000	15.6	Multiple	9	Yes

NR, Not reported; *PGA,* polyglycolic acid sheets; *ASA,* American Society of Anesthesiologists Physical Status Classification System; *RCT*, randomized controlled trial; *PPB*, postprocedural bleeding; *ESD*, endoscopic submucosal dissection.

*Quality evaluation using Cochrane risk of bias table for randomized controlled trials and Newcastle-Ottawa scale for observational studies.

†Risk factors evaluated in only 1 study were not included in meta-analysis as well as studies not providing data, allowing calculation of odds ratio.

‡Abstract.

Medications. Seventeen studies[32,39,48,49,55,57,58,63-68,70,71,76,82] did not report whether patients with antithrombotic therapy (AT) were included, and 9 studies[11,59,60,62,73,74,77,79,81] excluded patients on AT (pooled PPB rates, 5.0% and 5.4%). Seven studies[16,27,35,52,53,56,75] did not clearly report AT management (pooled PPB, 3.6%), whereas this was adequately reported in the remaining studies.

AT was not identified as a risk factor in 17 studies.[13,14,16-18,20-23,27-31,36,42,43] However, meta-analysis showed that PPB was significantly associated with AT use (Fig. 3). In subgroup analysis PPB risk was not significantly increased if AT were withheld 1 week before and after ESD, whereas AT resumption immediately after ESD was significantly associated with PPB.

Regarding low-dose aspirin, a study found that PPB was more frequent in continuous aspirin users than in those who never used or discontinued aspirin therapy, with a trend to later bleeding.[15] On the other hand, 2 studies found no significant increase in PPB rates in patients submitted to ESD under low-dose aspirin despite a tendency to higher bleeding.[25,26,50] Other studies found that PPB was associated with the use of anticoagulants[51] and double AT[52,53] but not with antiplatelet monotherapy. On

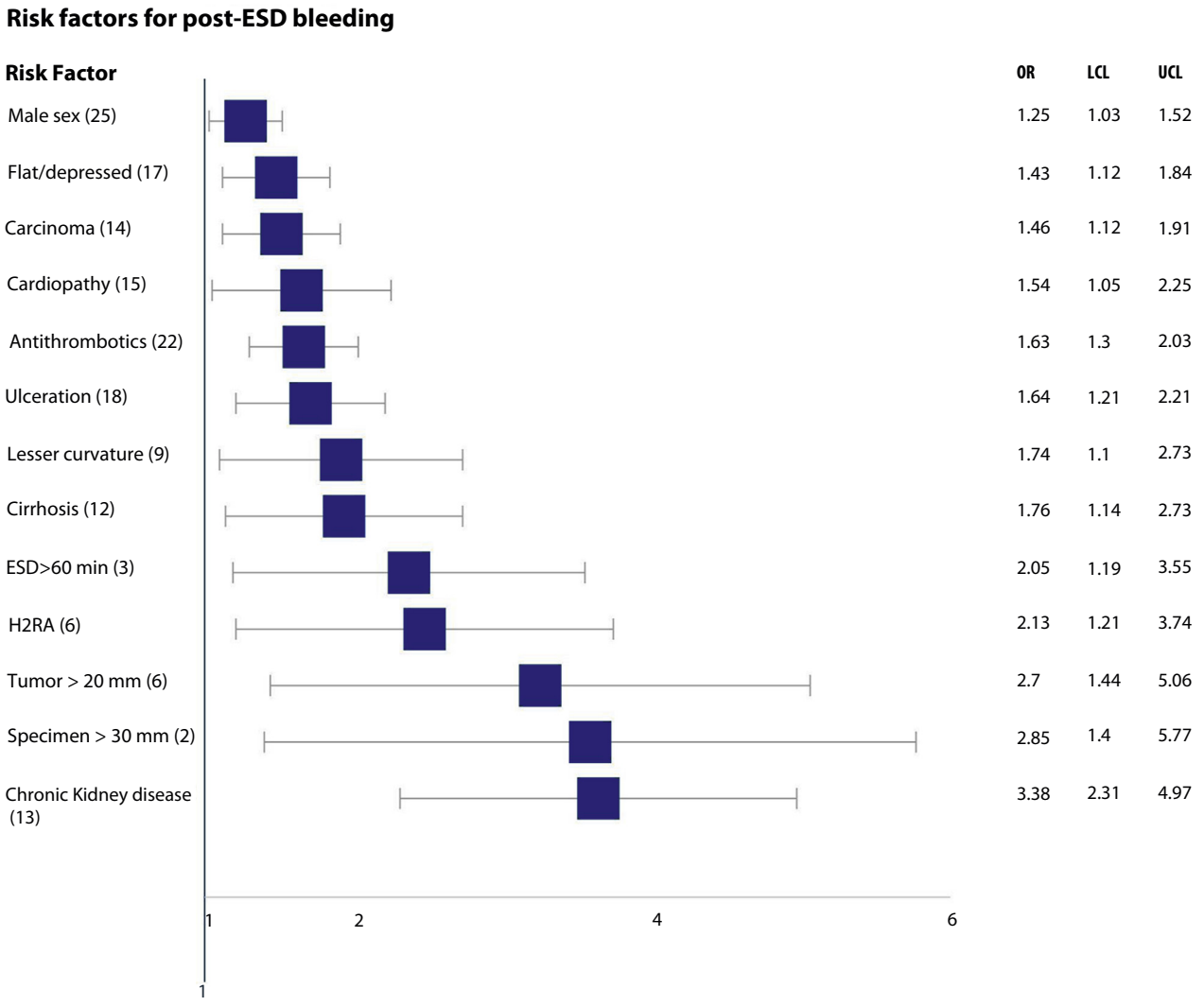

Figure 2. Significant risk factors for post-procedural bleeding after gastric ESD. In the first column, the numbers between parentheses refer to the number of studies used in the calculation of odds ratio. *LCL*, lower confidence limit (95%); *UCL*, upper confidence limit (95%).

the other hand, thienopyridines were associated with higher PPB risk even with discontinuation for 5 to 8 days before and resumption at a median of 3 days after ESD.[12]

Heparin replacement was not identified as a significant risk factor in 1 study,[43] although an opposite result was found in another study.[40] Gastroprotective agents were associated with lower PPB in patients undergoing AT in 1 study.[54] Corticosteroid use was not identified as a risk factor for PPB.[16,24,43]

Lesion characteristics. Tumor size and resected specimen size were evaluated as risk factors in several studies. Lesion sizes > 10 mm[55] and >20 mm[43,56] were not found to increase PPB in some studies, whereas lesion sizes > 20 mm,[20,22,39,57-59] >30 mm,[39] and >40 mm[58] were found to be associated with higher PPB risk in others. Regarding specimen size, the larger the ulcer, the higher the risk, with an artificial ulcer > 30 mm,[36] ≥34 mm,[60] >40 mm,[23-26,30,61] and >50 mm[36,43] identified as risk factors for PPB in diverse studies. When the studies evaluated the mean sizes of tumors and resected specimens between those with PPB and those without, the results were conflicting, with some reporting significant differences between tumor[22,26,34,42] and specimen[21,23,24,29,34,42] sizes and others not finding significant differences between the 2 groups.[13,14,16-18,20,27,28,31-33,51]

In addition, results concerning whether tumor location impacts PPB were controversial. Four studies reported that tumors located in the lower third[33,34,36,57] and in the middle/lower third[27,31,37,38] of the stomach had significantly higher bleeding rates, whereas the upper location of the stomach was found to be a significant risk factor in other studies.[30,58] However, several studies reported no significant differences in PPB according to tumor location.[14-18,20-29,32,39,42,43,51,55,61] Horizontal localization (anterior or posterior wall; lesser or greater curvature) was not found to influence PPB in individual studies.[15-17,20-24,27,29] Regarding the relationship between

TABLE 2. Demographic and clinical risk factors

Risk factor (number of studies)	PPB/total (%)	OR_{PPB}*	I^2
Age (20)		–.46 y (–.49, 1.42)	16%
>75 y	22/525 (4.2%) 40/908 (4.4%)	.99 (.58-1.69)	0%
Male (25)	583/11,103 (5.2%) 155/3865 (4.0%)	**1.25 (1.03-1.52)**	4%
Hypertension (20)	193/4108 (4.7%) 315/7253 (4.3%)	1.06 (.86-1.30)	13%
Diabetes mellitus (20)	78/1644 (4.7%) 473/10,263 (4.6%)	1.06 (.83-1.36)	0%
Cardiopathy (15)	63/951 (6.6%) 399/8771 (4.5%)	**1.54 (1.05-2.25)**	33%
Cerebrovascular disease (8)	7/221 (3.2%) 223/4798 (4.6%)	1.67 (.42-6.61)	69%
Cirrhosis (12)	23/287 (8.0%) 362/6895 (5.2%)	**1.76 (1.14-2.73)**	0%
Chronic kidney disease (13)	38/275 (13.8%) 359/7439 (4.8%)	**3.38 (2.31-4.97)**	0%
Chronic kidney disease (7)	20/171 vs 177/3553	**2.97 (1.76-5.01)**	0%
Hemodialysis (6)	18/104 vs 182/3886	3.94 (2.24-6.94)	0%
Significant comorbidities (4)	58/899 (6.4%) 103/2151 (4.8%)	1.49 (.81-2.75)	60%
Helicobacter pylori (4)	35/1022 (3.4%) 29/676 (4.3%)	.87 (.50-1.50)	0%
Hyperlipidemia (5)	26/489 (5.3%) 206/3809 (5.4%)	1.07 (.70-1.63)	0%
Previous gastric surgery (4)	6/92 (6.5%) 232/3056 (7.6%)	.91 (.41-2.01)	0%

Values in bold indicate significant risk factors.
PPB, Post-procedural bleeding; *OR*, odds ratio.
*Mean $difference_{PPB - no\ PPB}$ (95% CI).

time of bleeding and tumor location, lower sites were associated with earlier bleeding in 4 studies.[29,33,34,62]

Macroscopic type was also explored in several studies, with most finding no relation between morphology and PPB.[13,18,20-24,28,29,32,34,39,42,43,61] However, flat,[58] depressed,[16] and flat/depressed[14,17] lesions were associated with increased PPB in some studies.

Most studies did not find significant differences in PPB according to histology (dysplasia or carcinoma)[15,18,20,22,27,28,30,34,39,42] or invasion depth (mucosal vs submucosal),[18,22-24,26-34,42,43] with few studies reporting a significantly increased risk of PPB in lesions harboring carcinoma[17,25] and submucosal invasion.[14,36] Tumor differentiation[14,21,24,29,43] and lymphovascular invasion[43] were not found to influence PPB. Expanded indication lesions were associated with higher PPB in 1 study,[63] whereas PPB was not significantly different between standard and expanded indications in 3 studies despite a tendency for higher bleeding in the latter group.[48,64,65]

Ulceration was not associated with PPB,[14,17,18,22,24,26,28-31,33,34,37-39,43,58,65,66] except in 1 study.[27] Submucosal fibrosis has also been analyzed and was not identified as an independent risk factor.[13,14,61,67] The presence of scarring was not identified as an influence on PPB in 3 studies,[32,51,58] although it was associated with higher PPB in 2 studies.[36,59]

After meta-analysis, increased tumor and specimen size, flat/depressed morphology (Fig. 4), localization in the lesser curvature, ulceration, carcinoma histology, and expanded indication were identified as significant risk factors for PPB (Table 3). On the other hand, vertical localization was not found to influence overall PPB, although localization in the upper third was significantly associated with PPB in the group of studies that only reported the frequency of delayed bleeding (Fig. 5). Submucosal invasion and fibrosis/scarring were not found to influence PPB despite a tendency for higher bleeding in the latter situation. Concerning EMR, 3 studies did not identify size and location,[55] indication,[64] or ulceration[66] as risk factors for PPB and were not included in the meta-analysis.

Procedural details. Poor control of bleeding[18] and snaring as the final step of ESD[68] were associated with

TABLE 3. Lesion-related factors

Risk factor (number of studies)	PPB/total (%)	OR_{PPB}*	I^2
Tumor size (11)		**3.04 mm (.80-5.27)**	46%
>20 mm (6)		2.70 (1.44-5.06)	69%
>30 mm (1)		3.61 (1.23-10.58)	N/A
>40 mm (2)		3.70 (1.10-12.45)	63%
Resection size (14)		**5.29 mm (3.40-7.17)**	33%
>30 mm (2)		2.85 (1.40-5.77)	43%
>40 mm (4)		2.51 (1.78-3.55)	0%
>50 mm (2)		2.99 (1.56-5.74)	59%
Vertical localization (28)			
Upper (25)	101/1938 (5.2%)		
Middle (25)	277/4960 (5.6%)		
Lower (25)	442/7962 (5.5%)		
Upper vs middle/lower (26)		.99 (.72-1.37)	43%
Upper/middle vs lower (28)		.99 (.80-1.21)	41%
Horizontal localization (9)			
Anterior wall	38/905 (4.2%)	.98 (.63-1.52)	0%
Posterior wall	49/1087 (4.5%)		
Lesser curvature	91/1683 (5.4%)	**1.74 (1.10-2.73)**	0%
Greater curvature	30/1087 (2.8%)		
Lesion morphology			
Elevated (17)	212/4717 (4.5%)		
Flat (9)	97/781 (12.4%)		
Depressed (10)	103/1773 (5.8%)		
Flat vs elevated		**1.75 (1.25-2.45)**	0%
Depressed vs elevated		1.24 (.84-1.82)	34%
Flat vs depressed		1.22 (.84-1.76)	0%
Flat/depressed vs elevated		**1.43 (1.12-1.84)**	32%
Histopathology (14)			
Carcinoma	283/5513 (5.1%)	**1.46 (1.12-1.91)**	13%
Dysplasia	108/3052 (3.5%)		
Submucosal cancer (18)	83/1619 (5.1%)	1.18 (.91-1.53)	0%
Intramucosal cancer	443/8444 (5.2%)		
Ulceration (18)	73/1056 (6.9%) 390/8288 (4.7%)	**1.64 (1.21-2.21)**	12%
Fibrosis/scarring (6)	29/276 (10.5%) 126/2281 (5.5%)	1.87 (.96-3.62)	42%
Expanded criteria (4)	119/1419 (8.4%) 82/1931 (4.2%)	**2.03 (1.24-3.33)**	27%

Values in bold indicate significant risk factors.
PPB, Post-procedural bleeding; *OR*, odds ratio.
*Mean $difference_{PPB - no\ PPB}$ (95% CI).

increased PPB. Piecemeal resection, although not associated with higher PPB in most studies,[13,14,17,20,22,34,42,61] was associated with an increased but not statistically significant risk of bleeding (Table 4).

Additional preventive measures to reduce PPB with mucosal closure with snare and clips[69] or selective artery clipping[70] did not decrease PPB, but coagulation of visible vessels[31,71] and use of polyglycolic acid sheets and fibrin glue[72] were associated with lower PPB rates (only in high-risk patients in the latter study). Vascularization of lesions evaluated by EUS,[73] early diet resumption,[74] and outpatient management

TABLE 4. Procedure-related factors

Risk factor (number of studies)	PPB/total (%)	OR_{PPB}*	I^2
Piecemeal resection (9)	14/226 (6.2%) 188/4234 (4.4%)	1.78 (.89-3.55)	25%
Procedure duration (10)		**6.73 min (2.89-10.56)**	4%
>60 min (3)	41/605 (6.8%) 50/1447 (3.4%)	**2.05 (1.19-3.55)**	25%
Preprocedural PPI (4)			
Preprocedural PPI	2/208 (.96%) 4/198 (2.02%)	.70 (.14-3.53)	4%
H_2RA vs PPI (6)			
H_2RA	44/757 (5.8%) 17/481 (3.5%)	**2.13 (1.21-3.74)**	0%
Experience (5)			
<50 (4)	100/1786 (5.6%) 127/2534 (5.0%)	.99 (.75-1.33)	0%
<100 (3)	118/1909 (6.2%) 44/858 (5.1%)	1.12 (.77-1.63)	0%
SLE (7)			
SLE	59/1349 (4.4%)	1.34 (.85-2.12)	0%
No SLE	41/1369 (2.9%)		
RCT (3)		1.22 (.58-2.57)	11%
Retrospective (4)		1.45 (.79-2.65)	0%

Values in bold indicate significant risk factors.
PPB, Post-procedural bleeding; *OR*, odds ratio; *PPI*, proton pump inhibitor; *H_2RA*, histamine-2 receptor antagonist; *SLE*, second-look endoscopy; *RCT*, randomized controlled trial.
*Mean $difference_{PPB - no\ PPB}$ (95% CI).

in low-risk patients[75] were also not found to influence PPB.

Most studies found no significant differences in procedure duration between those with and without PPB.[16,20,21,23,24,27-31,33] However, procedure length greater than 75 minutes,[18] 90 minutes,[26] 4 hours,[36] and 5 hours[76] was associated with increased PPB in some studies. In our meta-analysis (Table 4), procedure duration was significantly higher in patients with PPB and duration > 60 minutes was significantly associated with PPB.

Medications (PPIs, H_2RAs, and mucoprotectives). Pretreatment with PPIs before ESD was not associated with PPB reduction[11,77-79] as well as ecabet sodium added to PPIs.[62] Bolus PPI injection for 3 days yielded similar PPB rates when compared with 72 hours' perfusion in an RCT.[14]

With regard to the direct comparison between PPIs and H_2RAs, no significant differences in PPB were reported in 3 RCTs[32,59,80] and in a retrospective study,[20] whereas PPB was significantly lower in the PPI group in 2 studies.[60,81] In our meta-analysis, H_2RAs were associated with a significantly increased PPB risk.

Operator experience and fatigue. Seven studies found no differences in PPB according to operator experience,[17,18,31,36,42,61,82] with only 1 study reporting significant differences in PPB between beginner (<50 ESD) and experienced (>200 ESD) operators.[33] Meta-analysis found that experience is not significantly associated with PPB (Table 4). Regarding fatigue, ESD workload > 2 hours (but not prior other activities) was identified as a significant risk factor for early bleeding in a single study.[83]

Second-look endoscopy. SLE was not performed or not reported in 30 studies, whereas SLE was routinely performed after ESD in 34 studies (mostly on the first or second day). Seven studies directly compared PPB rates in patients with and without SLE (3 RCTs and 4 retrospective studies).[20,22,26,30,34,61,84] The PPB rate in studies that performed SLE was not significantly different from studies that did not perform or did not report the use of SLE.

The clinical usefulness of SLE was evaluated in 7 studies (Table 4).[20,22,26,30,34,61,84] PPB occurred in 59 of 1349 patients who underwent SLE (4.37%) and in 41 of 1369 patients who did not have SLE (2.99%), with no significant differences in the meta-analysis. Fourteen studies[13,14,17,18,20,21,23,26,28,30,34,46,61,84] reported the time of bleeding in relation with SLE, and in these studies 53.3% of the bleeding episodes occurred before SLE. Prophylactic hemostasis on SLE was associated with a significantly increased risk of PPB (compared with no prophylactic hemostasis on SLE).

DISCUSSION

This systematic review and meta-analysis evaluated risk factors for PPB after endoscopic resection (EMR or ESD) for gastric superficial neoplasms. This is a noteworthy issue because the literature is controversial, and many studies are underpowered to detect small but clinically significant differences.

Previous meta-analysis reported procedure-related bleeding to occur in 4% to 9% of ESDs.[2-4] In our review, bleeding after ESD occurred in 5.1% of all procedures. We believe this is the best estimate for PPB because all studies included were selected only if a clear definition of PPB was provided and reported separately from intraprocedural bleeding.

We found that male gender, cardiopathy (and AT), cirrhosis, and chronic kidney disease were significant clinical risk factors for PPB. However, although cardiopathy was significantly associated with PPB, this increased risk is most probably associated with the use of antithrombotics. In fact, AT was associated with an increased risk of PPB (OR, 1.76). However, the difference in PPB rates was not significant in the studies that discontinued antithrombotics 1 week before and 1 week after ESD, suggesting that this may be the optimal time of AT suspension whenever possible. Additionally, we found that continuous low-dose aspirin was not associated with a significant increase in PPB in most studies.

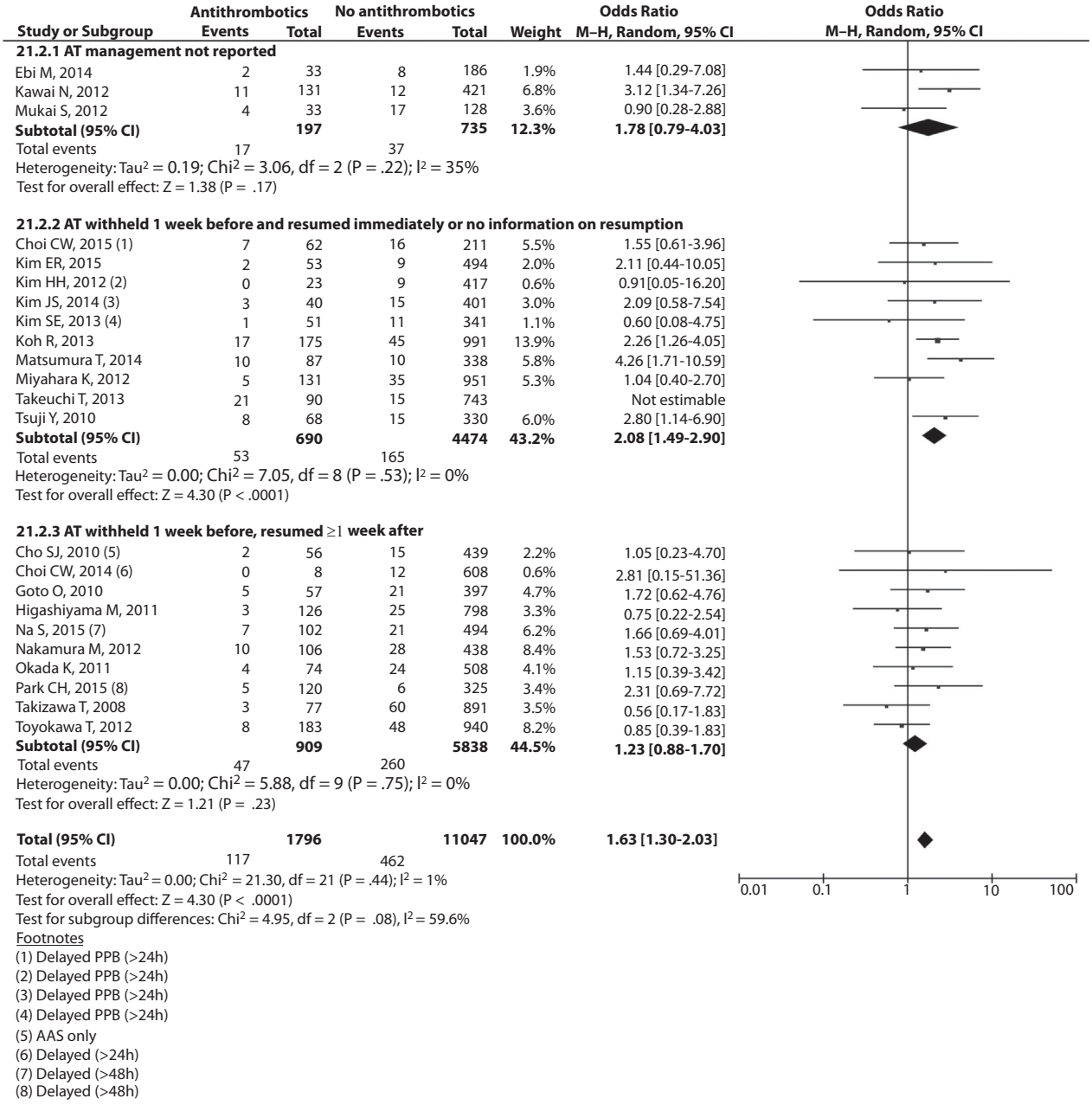

Figure 3. Forrest plot of PPB rate according to antithrombotic medication. Antithrombotic medication was associated with a significantly increased risk of PPB (pooled OR, 1.63; 95% CI, 1.30-2.03; I^2 = 1%). On subgroup analysis, antithrombotic medication was not significantly associated with PPB in studies that withheld antithrombotics for 1 week before and after ESD (OR, 1.23; 95% CI, .88-1.70; I^2 = 0%). *PPB*, post-procedural bleeding.

Regarding tumor-related characteristics, tumor size > 20 mm, resected specimen size > 30 mm, localization in the lesser curvature, flat or depressed morphology, carcinoma histology, ulceration, and expanded criteria were associated with increased PPB. On the other hand, vertical localization was not found to affect overall PPB, but upper lesions were in fact associated with delayed bleeding.

Procedural factors also may be associated with increased risk of PPB, namely procedure duration > 60 minutes and the use of H_2RA as antacid medication. Operator's experience was not found to influence PPB, although high-risk lesions are typically resected by the most experienced operators. Single studies found preventive coagulation of visible vessels as a beneficial measure in reducing PPB, and 2 recent studies suggested that polyglycolic acid sheets with fibrin glue may reduce PPB after gastric and colonic ESD.[72,85] However, interventions like preprocedural PPIs, mucoprotectives, and routine closure with clips or artery clipping were not found to be of benefit. Endoscopic suturing of large mucosal defects after gastric

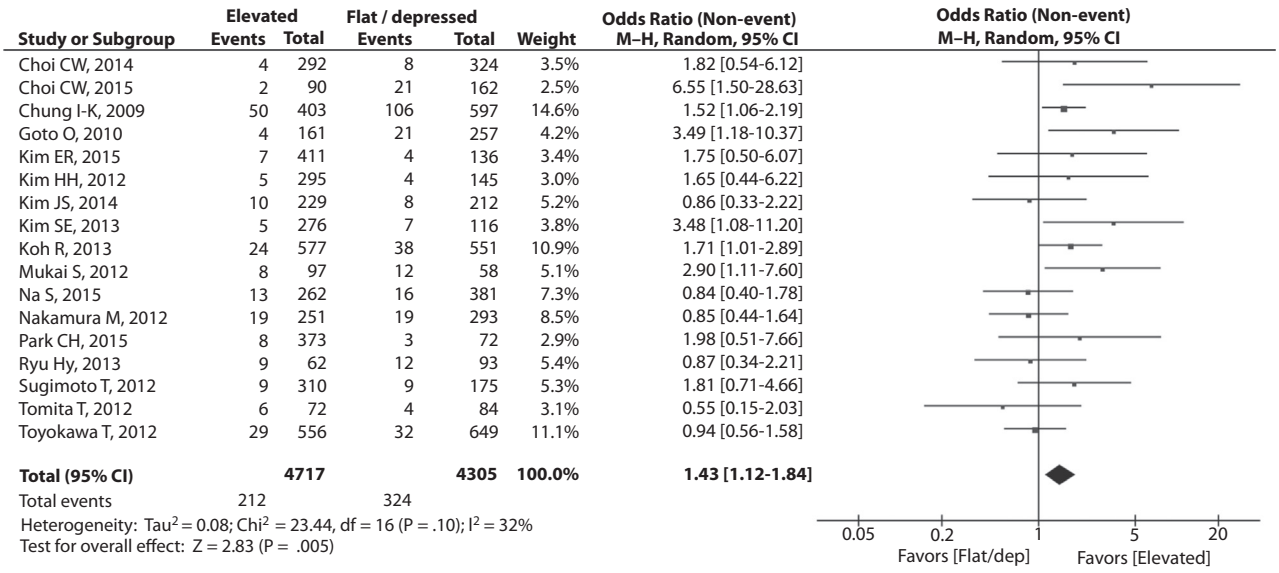

Figure 4. Forrest plot of PPB rate according to lesion morphology (flat/depressed vs elevated). Flat/depressed morphology was significantly associated with PPB in the meta-analysis (OR, 1.43; 95% CI, 1.12-1.84; $I^2 = 32\%$). *PPB*, post-procedural bleeding.

and colonic ESD were also reported in a single-arm study and no adverse events were seen.[86] This systematic review may help in the selection of patients who are more likely to benefit from these developing techniques.

On the other hand, studies evaluating the benefit of preprocedural PPI and mucoprotectives had a low event rate and may be underpowered. Indeed, although mucoprotectives were associated with faster healing of the artificial ulcer in 2 recent reviews,[87,88] its impact on PPB was not evaluated, and so it remains unclear if these faster healing decreases PPB.

SLE is routinely performed after ESD in several centers to perform hemostasis in cases of active bleeding or high-risk stigmata. Our findings clearly suggest that SLE is not associated with decreased PPB. Furthermore, more than one half of bleeding episodes occur before SLE, and even prophylactic hemostasis on SLE is not capable of reducing PPB. This suggests that even when SLE is performed, special attention should be given to patients in which prophylactic hemostasis is performed. Our findings are consistent with a recent meta-analysis limited to RCTs assessing SLE usefulness.[89] Nevertheless, it remains unclear whether a subset of patients can benefit. The results were similar in retrospective studies and RCTs, although retrospective studies could have been prone to selection bias (eg, in 1 study the decision to perform SLE was made at the discretion of the endoscopist,[30] and in another study the reasons to decide whether to perform SLE were not reported[34]).

This systematic review and meta-analysis has some limitations. First, one cannot identify interactions and confounding between risk factors, although we believe that the high number of included patients and the low heterogeneity in most evaluated risk factors allow us to draw some important conclusions. Second, the different temporal definitions of early and delayed bleeding made difficult a separate analysis of risk factors for early and delayed PPB. Third, most evidence is derived from observational studies, although subgroup analysis did not find differences according to study design and most studies were judged to have low risk of bias. Fourth, some risk factors were not strictly defined in some studies and were not stratified according to disease stage (eg, Child-Pugh classification in cirrhosis) and so subgroup analyses were not possible.

To our knowledge, this is the first systematic review about risk factors for PPB after endoscopic resection of early gastric neoplasms and identified the most consistently reported risk factors. As recommendations, we suggest that (1) the definition of early and delayed bleeding should be standardized (eg, considering early bleeding < 24 hours after ESD) and (2) AT management should also be reported in detail. Based on the significant risk factors presented on Figure 2, we also suggest that early discharge can be considered in patients with 0 to 1 risk factors. For others, hospital stay may be prolonged and the role of SLE adequately assessed. Randomized trials should be performed incorporating these risk factors in randomization and addressing the role for specific interventions such as the use, duration, and dosage of PPIs; SLE, and follow-up aiming at reducing the odds for bleeding.

In conclusion, we have identified risk factors associated with PPB after ESD that can help gastroenterologists to identify patients at increased risk. It is our hope that this can guide management, namely in terms of the adequate period of surveillance after endoscopic resection.

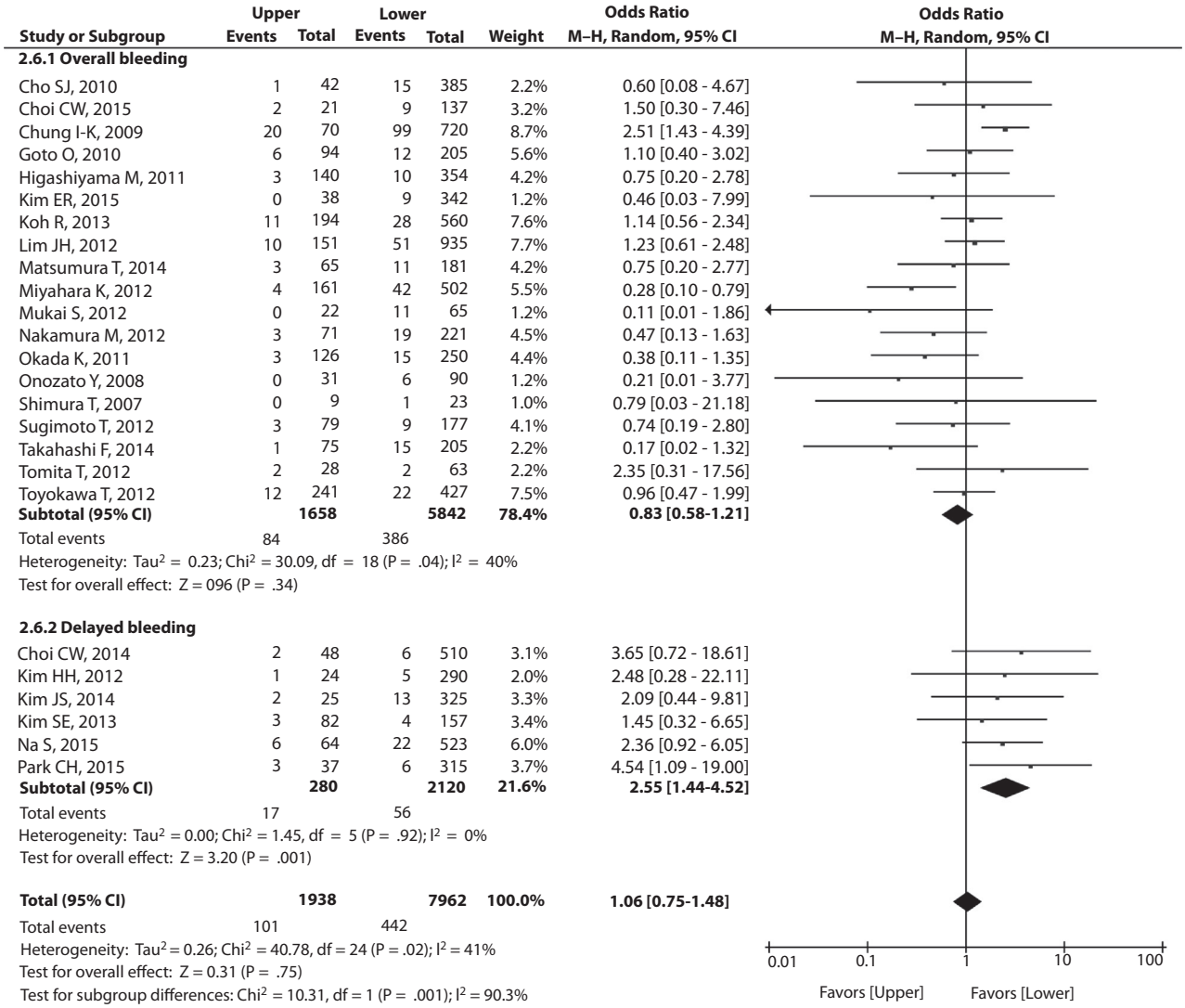

Figure 5. Forrest plot of PPB rate according to localization (upper vs lower). Localization of the lesion in upper or lower thirds of the stomach was not found to influence PPB ($OR_{upper\ localization}$ = 1.06; 95% CI, .75-1.48; I^2 = 41%). However, in subgroup analysis upper localization was significantly associated with PPB when only studies reporting delayed bleeding were considered (OR, 2.55; 95% CI, 1.44-4.52; I^2 = 0%). *PPB*, post-procedural bleeding.

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