ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2020 October 28; 8(5): 348-434

Published by Baishideng Publishing Group Inc

World Journal of Meta-Analysis

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ABOUT COVER

Editorial board member of *World Journal of Meta-Analysis*, Dr. Huang is Distinguished Professor at the First Affiliated Hospital, Zhejiang Chinese Medical University in Zhejiang, China. Having received his Bachelor's degree from Zhejiang University in 1999, Dr. Huang undertook postgraduate training first at Zhejiang University, receiving his Master's degree in 2005, and then at Zhejiang Chinese Medical University, receiving his PhD in 2012. He rose to Chief Physician in the Gastroenterology Division of the First Affiliated Hospital, Zhejiang Chinese Medical University in 2016 and has held the position since. His ongoing research interests involve the application of evidence-based medicine in digestive diseases. Currently, he serves as Commissioner of the Spleen and Stomach Disease Branch of the China Association of Chinese Medicine. (L-Editor: Filipodia)

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WJMA mainly publishes articles reporting research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Saurabh Chandan

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2308-3840/editorialboard.htm

PUBLICATION DATE
October 28, 2020

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World Journal of Meta-Analysis

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World J Meta-Anal 2020 October 28; 8(5): 411-434

DOI: 10.13105/wjma.v8.i5.411

ISSN 2308-3840 (online)

META-ANALYSIS

Effects of antithrombotic agents on post-operative bleeding after endoscopic resection of gastrointestinal neoplasms and polyps: A systematic review and meta-analysis

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Supported by Liaoning Science and Technology Foundation, No. 20170541052.

Conflict-of-interest statement: No conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

There are some studies investigating the relationship between antithrombotic medication and postoperative bleeding after endoscopic resection (ER) with controversial results.

AIM

To perform a meta-analysis evaluating the effects of antithrombotic therapy on postoperative bleeding after ER.

METHODS

A systematic search was conducted on PubMed, Web of Science, Cochrane Library. The Newcastle-Ottawa scale was used to evaluate the quality of studies. Stata 12.0 was used for statistical analysis. The odds ratio (OR) and 95%CI were calculated and heterogeneity was quantified using Cochran's *Q* test and I^2.

RESULTS

Total 66 studies were included in the meta-analysis. Pooled data suggested that antithrombotic therapy was significantly associated with postoperative bleeding (OR = 2.302, 95%CI: 2.057-2.577, *P* = 0.000) after ER. The risk of postoperative bleeding after endoscopic submucosal dissection, endoscopic mucosal resection and polypectomy in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.439, 95%CI: 1.916-3.105; OR = 2.688, 95%CI: 1.098-6.582; OR = 2.112, 95%CI: 1.434-3.112).

CONCLUSION

The risk of postoperative bleeding after ER correlated with the types and management of antithrombotic agents by our meta-analysis.

Key Words: Endoscopic resection; Antithrombotic; Anticoagulants; Postoperative

Manuscript source: Invited manuscript

Received: September 17, 2020
Peer-review started: September 18, 2020
First decision: September 29, 2020
Revised: October 7, 2020
Accepted: October 27, 2020
Article in press: October 27, 2020
Published online: October 28, 2020

P-Reviewer: Hosoe N, Komeda Y, Rege S
S-Editor: Wang JL
L-Editor: A
P-Editor: Ma YJ

bleeding; Endoscopic mucosal resection; Endoscopic submucosal dissection

Core Tip: In recent years, more and more people suffering from cardiovascular disease and/or cerebrovascular disease receive antithrombotic therapy which change patients' coagulation status and may lead to high risk of postoperative bleeding after endoscopic resection (ER). The relationship between the postoperative bleeding after ER and antithrombotic agents is still uncertain. With this reason, a systematic review and meta-analysis was carried out to identify whether the use of antithrombotic drugs increases the risk of the postoperative bleeding after ER.

Citation: Xiang BJ, Huang YH, Jiang M, Dai C. Effects of antithrombotic agents on post-operative bleeding after endoscopic resection of gastrointestinal neoplasms and polyps: A systematic review and meta-analysis. *World J Meta-Anal* 2020; 8(5): 411-434
URL: https://www.wjgnet.com/2308-3840/full/v8/i5/411.htm
DOI: https://dx.doi.org/10.13105/wjma.v8.i5.411

INTRODUCTION

Endoscopic resection (ER) is deemed as an effective method for gastrointestinal neoplasia and polyp. ER is an acceptable technique to enable *en bloc* resection of gastric adenomas, early oesophageal, gastric and colorectal cancer and incidence and its related mortality of colorectal cancer[1-3]. This includes polypectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). For example, patients with oesophageal neoplasia receiving ER can maintain the integrity of oesophageal structure and function, whereas the quality of life can be affected by oesophagectomy[4].

Although the therapeutic effect of ER has been greatly affirmed, Postoperative bleeding as a major complication is still a problem to be solved. Postoperative bleeding after ER is defined as bleeding within 30 d from a mucosal defect shown by massive melena, a decrease in blood hemoglobin level of more than 2 g/dL, or requirement of endoscopic hemostasis or transfusion[1,5,6]. A study has shown that the incidence rate of postoperative bleeding after esophageal or colorectal ESD ranged from 0.0% to 4.6%[7]. And the incidence rate of postoperative bleeding after ESD due to gastric neoplasm ranged from 1.8% to 15.6%[7]. A study that included 3788 cases of polypectomy by Choung found that postoperative bleeding occurred in 42 cases (1.1%)[8]. Another study with 30881 cases of polypectomy by Rutter also reported that the postoperative bleeding developed in 291 cases (0.94%)[9]. Preventive strategies such as acid secretion inhibitors and prophylactic clipping have been developed to reduce the postoperative bleeding risk after ER, but postoperative bleeding cannot be completely avoided. Some factors such as the size of polyp and a patient's coagulation status have been reported to be associated with the risk of postoperative bleeding after ER.

In recent years, more and more people suffering from cardiovascular disease and/or cerebrovascular disease receive antithrombotic therapy which change patients' coagulation status and may lead to high risk of postoperative bleeding after ER. The relationship between the postoperative bleeding after ER and antithrombotic agents is still uncertain. With this reason, a systematic review and meta-analysis was carried out to identify whether the use of antithrombotic drugs increases the risk of the postoperative bleeding after ER.

MATERIALS AND METHODS

We carried out a systematic review and meta-analysis of the hemorrhagic data of different antithrombotic users after ER from published studies. The review and analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[10].

Search method

We used PubMed, Web of Science and Cochrane Library to search for articles published in English from inception to February 2019. The search queries were: (1) (((antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (endoscopic submucosal dissection OR ESD)) AND (bleeding OR hemorrhage); (2) (((antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (EMR OR endoscopic mucosal resection)) AND (bleeding OR hemorrhage); (3) (((antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (endoscopic polypectomy)) AND (bleeding OR hemorrhage); and (4) (((antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (APC OR argon plasma coagulation)) AND (bleeding OR hemorrhage).

Study selection

The studies that met the following inclusion criteria were included: (1) Polypectomy, EMR, ESD, polypectomy incorporated argon plasma coagulation and the hot and cold snare; (2) Randomized controlled trials, retrospective studies or cohort studies were performed to investigate the risk of postoperative bleeding after ER in patients with gastrointestinal neoplasm receiving antithrombotic medication; (3) The incidence rate of postoperative bleeding can be extracted in the antithrombotic medication group and the non-antithrombotic medication group; and (4) Anticoagulants and antiplatelet drugs were incorporated in antithrombotic agents.

The studies were excluded if: (1) The postoperative bleeding rate or antithrombotic therapy information could not be extracted; (2) Antithrombotic drugs and NSAIDS were recorded together; (3) Endoscopic treatment such as biopsy, sphincterotomy or ampullectomy was carried out; (4) Reviews, case reports, guidelines, or animal studies were screened out; (5) The articles were not written in English; and (6) The full text could not be obtained.

Methodological quality assessment

The Newcastle-Ottawa scale was used to evaluate the quality of the included studies. And the Newcastle-Ottawa scale includes three aspects: Selection, comparability, exposure (retrospective studies) or outcome (cohort studies)[11].

Data extraction

Two authors worked together to extract the basic information about the first author, publication year, country, research method (retrospective/cohort), ER method (ESD/EMR/polypectomy), number, age and gender. Moreover, the odds ratio (OR) and 95%CI of the postoperative bleeding rate were calculated in the antithrombotic group (continued/discontinued) and the non-antithrombotic group.

Statistical analysis

Statistical analysis was performed by Stata 12.0. The Cochran's Q test and I^2 (P < 0.10 was considered significant) were used to identify heterogeneity. The value I^2 of 0-25% indicated insignificant heterogeneity; 26%-50%, low heterogeneity; 51%-75%, moderate heterogeneity; and greater than 75%, high heterogeneity[12]. If there was no significant heterogeneity, the OR and 95%CI were calculated in a fixed-effect model. Otherwise, a random-effect model was used. The funnel plot was used to assess publication bias.

RESULTS

Assessment of the studies

The initial literature yielded 1258 articles (454 articles from PubMed, 679 articles from Web of Science, 125 articles from Cochrane Library). After the exclusion of 929 articles due to duplicates and lack of relevance, 329 articles were retrieved for full text evaluation. 263 articles were excluded after reviewing the full text (Figure 1). Ultimately, 66 studies were included in the meta-analysis (Fifty-nine retrospective studies, seven prospective observational studies). The characteristics of included studies were described in the Table 1. The included studies were carried out from different countries (Fifty from Japan, six from Korean, five from USA, two from Italy, one from UK, one from Australia, one from Holland). The mean age was older than 60 years old in most studies.

Table 1 Characteristics of included studies and participants

Ref.	Country	Research method	Location	Age (yr)	Gender male, %
So *et al*[49], 2019	South Korea	Retrospective study	Gastric lesion	68.8/68.5	954, 79.7%
Kishida *et al*[45], 2019	Japan	Retrospective study	Colorectal lesion	64/68	55, 41.66%
Inoue *et al*[65], 2019	Japan	Prospective observational study	Gastrointestinal lesion	67.4 ± 8.3	201, 58.6%
Harada *et al*[56], 2019	Japan	Retrospective study	Gastric lesion	72.3 ± 8.82	414, 69.3%
Arimoto *et al*[54], 2018	Japan	Retrospective study	Colorectal lesion	68.5	492, 58.3%
Azumi *et al*[39], 2018	Japan	Retrospective study	Gastric lesion	73 (41-94)	284, 64.8%
Fujita *et al*[67], 2018	Japan	Retrospective study	Colorectal lesion	72.2 ± 7.4/72.9 ± 8.3	63, 73.8%
Horikawa *et al*[58], 2018	Japan	Retrospective study	Gastric lesion	78 (56-89)	77, 77%
Izumikawa *et al*[40], 2018	Japan	Retrospective study	Gastric lesion	-	255, 75.25%
Kono *et al*[41], 2018	Japan	Retrospective study	Gastric lesion	72 (66-78)	652, 74.77%
Oh *et al*[60], 2018	South Korea	Retrospective study	Gastric lesion	70 (49-85)	173, 80.47%
Park *et al*[63], 2018	South Korea	Prospective observationalstudy	Colorectal lesion	55.8 ± 11.9/52.4 ± 12.3	2661, 68.46%
Sanomura *et al*[59], 2018	Japan	Retrospective study	Gastric lesion	69.8 ± 9.2	719, 70%
Seo *et al*[55], 2018	South Korea	Retrospective study	Colorectal lesion	63 (55-69.5)	723, 60.8%
Sakai *et al*[64], 2018	Japan	Retrospective study	Colorectal lesion n	72.6 ± 7.2/69.1 ± 10.9	669, 66.63%
Yamashita *et al*[36], 2018	Japan	Retrospective study	Colorectal lesion	66.6 ± 10.6	373, 57.4%
Yanagisawa *et al*[35], 2018	Japan	Retrospective study	Gastrointestinal lesion	-	314, 72.02%
Matsumoto *et al*[46], 2018	Japan	Retrospective study	Colorectal lesion	70/65	551, 65.44%
Harada *et al*[61], 2017	Japan	Prospective observational study	Gastric lesion	76.8 ± 6.0/72.7 ± 7.9	40, 88.88%
Yano *et al*[33], 2017	Japan	Retrospective study	Gastric lesion	72 (33-94)	1319, 74.65%
Ueki *et al*[14], 2017	Japan	Retrospective cohort study	Gastric lesion	71.2 ± 8.4	264, 72.5%
Yoshio *et al*[78], 2017	Japan	Retrospective study	Gastric lesion	75/76	90, 90.91%
Gotoda *et al*[15], 2017	Japan	Retrospective study	Gastric lesion	75, 68.8-81.0	410, 77.5%
Furuhata *et al*[17], 2017	Japan	Retrospective study	Gastric lesion	69	1377, 77.3%
Shibuya *et al*[1], 2017	Japan	Retrospective study	Colonic lesion	-	Unclear
Bronsgeest *et al*[42], 2017	Holland	Retrospective study	Colorectal lesion	67.4 ± 8.3	201, 58.6%
Ishigami *et al*[34], 2017	Japan	Retrospective study	Lower gastrointestinal lesion	64.9 ± 11.1	526, 68%
Pigò *et al*[3], 2017	Italy	Retrospective study	Colorectal lesion	65.4	385, 63.2%
Kono *et al*[76], 2017	Japan	Prospective observationalstudy	Upper gastrointestinal lesion	74 ± 8.3	44, 89.8%
Lin *et al*[75], 2017	United States	Retrospective study	Colorectal lesion	-	Unclear
Sato *et al*[38], 2017	Japan	Retrospective study	Gastric lesion	71.1	1786, 75.1%
Igarashi *et al*[27], 2017	Japan	Retrospective study	Gastric lesion	72.4	758, 77.7%
Amato *et al*[31], 2016	Italy	Prospective observational study	Gastrointestinal lesion	59 ± 12.1	54.3%
Kubo *et al*[32], 2016	Japan	Retrospective study	Gastrointestinal lesion	63.9	467,59.3%
Shindo *et al*[25], 2016	Japan	Retrospective study	Gastric lesion	71 ± 8, 32-87	190, 72.5%
Yoshida *et al*[52], 2016	Japan	Retrospective study	Colorectal lesion	68.2 ± 10.3	Unclear
Ninomiya *et al*[53], 2015	Japan	Retrospective study	Colorectal lesion	67 ± 11.1	410, 70.4%
Al-Mammari *et al*[4], 2015	United Kingdom	Prospective observational study	Oesophageal lesion	71, 65-78	85, 72.6%
Odagiri *et al*[16], 2015	Japan	Retrospective cohort study	Colorectal lesion	-	4495, 59.4%
Namasivayam *et al*[5], 2014	United States	Retrospective study	Gastrointestinal lesion	69	Unclear
Terasaki *et al*[21], 2014	Japan	Retrospective study	Colorectal lesion	66.9 ± 11.2	233, 64.2%

Tounou *et al*[50], 2014	Japan	Retrospective study	Gastric lesion	71.8, 36-92	257, 73.4%
Suzuki *et al*[18], 2014	Japan	Retrospective study	Colorectal lesion	65.5, 29-86	183, 57.7%
Matsumura *et al*[23], 2014	Japan	Retrospective study	Gastric lesion	72.1 ± 8.6	302, 71.1%
Beppu *et al*[74], 2014	Japan	Retrospective study	Colorectal lesion	59.5 ± 11.6	176, 84.6%
Inoue *et al*[77], 2014	Japan	Retrospective study	Colorectal lesion	69.2	95, 81.2%
Sanomura *et al*[66], 2014	Japan	Retrospective study	Gastric lesion	73.7 ± 8.9	64, 82.1%
Yoshio *et al*[47], 2013	Japan	Retrospective study	Gastric lesion	70	951, 76.1%
Takeuchi *et al*[29], 2013	Japan	Retrospective study	Gastric lesion	5.2	477, 57.2%
Koh *et al*[37], 2013	Japan	Retrospective study	Gastric lesion	70.3 ± 8.6	817, 74%
Mukai *et al*[6], 2012	Japan	Retrospective study	Gastric lesion	72.4 ± 8.8	116, 72%
Lim *et al*[51], 2012	South Korea	Retrospective study	Gastric lesion	62.6	1143, 71.8%
Miyahara *et al*[48], 2012	Japan	Retrospective study	Gastric lesion	71.7 ± 8.9, 36-92	763, 70.5%
Cho *et al*[57], 2012	South Korea	Retrospective study	Colorectal lesion	62.2	385, 74.9%
Toyokawa T *et al*[24], 2011	Japan	Retrospective study	Gastric lesion	26-95	811, 72.2%
Higashiyama *et al*[19], 2011	Japan	Retrospective study	Gastric lesion	69, 29-91	702, 76%
Metz *et al*[2], 2011	Australia	Prospective observational study	Colonic lesion	68, 26-93	Unclear
Tokioka *et al*[30], 2011	Japan	Retrospective study	Gastric lesion	69.4	378, 73.4%
Okada K *et al*[22], 2011	Japan	Retrospective study	Gastric lesion	68.4, 33-94	425, 73%
Mannen *et al*[20], 2010	Japan	Retrospective study	Gastric lesion	71.6 ± 8.6, 36-91	323, 74.1%
Goto *et al*[13], 2010	Japan	Retrospective study	Gastric lesion	68.3	347, 76.4%
Witt *et al*[44], 2009	United States	Retrospective cohort study	Colorectal lesion	69.6	691, 56.4%
Ono *et al*[28], 2019	Japan	Retrospective study	Gastric lesion	67	Unclear
Takizawa *et al*[26], 2008	Japan	Retrospective study	Gastric lesion	66 ± 10, 29-93	779, 80.5%
Sawhney *et al*[62], 2007	United States	Retrospective study	Colorectal lesion	65.1	169, 97.7%
Yousfi *et al*[43], 2004	United States	Retrospective study	Gastrointestinal lesion	70.5, 45-91	100, 61.7%

Effect analysis

A total of 48691 cases after ER were enrolled, of which 8918 cases were receiving antithrombotic medication and 39773 cases were not taking any antithrombotic drugs[1,2,4,6,13-33]. The average postoperative bleeding rate in the antithrombotic group was 8.44%, while it was 5.28% in the non-antithrombotic group. With the random-effects model, the risk of postoperative bleeding in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.421, 95%CI: 1.831-3.200, P = 0.000, I^2 = 82.5%). In addition, a more homogeneous analysis (I^2 = 36.0%) was carried out after six articles[3,5,29,34-36] were screened out in the sensitivity analysis and the results remained unchanged (OR = 2.302, 95%CI: 2.057-2.577, P = 0.000) (Figure 2). Besides this, the results were not changed when data from retrospective and prospective studies were separately analyzed.

A total of 27014 cases after ESD were enrolled in this meta-analysis (3624 cases were receiving antithrombotic medication and 23390 cases were not taking antithrombotic drugs[1,6,13-30,33,37-41]). The average postoperative bleeding rate after ESD in the antithrombotic group was 13.91%, while it was 7.77% in the non-antithrombotic group. With the random-effects model, the risk of postoperative bleeding after ESD in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.439, 95%CI: 1.916-3.105, P = 0.000, I^2 = 63.5%). Moreover, a more homogeneous analysis (I^2 = 0.0%) was carried out after six articles[6,20,24,26,29,36] were screened out in the sensitivity analysis and the results remained unchanged (OR = 2.507, 95%CI: 2.185-2.875, P = 0.000, Figure 3). The risk of postoperative bleeding after gastric ESD in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.295, 95%CI: 1.757-2.998, P = 0.000, I^2 = 64.1%)[6,13-15,17,19,20,22-29,33]. Meanwhile, the risk of postoperative bleeding after colorectal ESD in the antithrombotic group was higher than the non-antithrombotic group (OR = 3.305, 95%CI: 1.561-6.998, P = 0.002, I^2 =

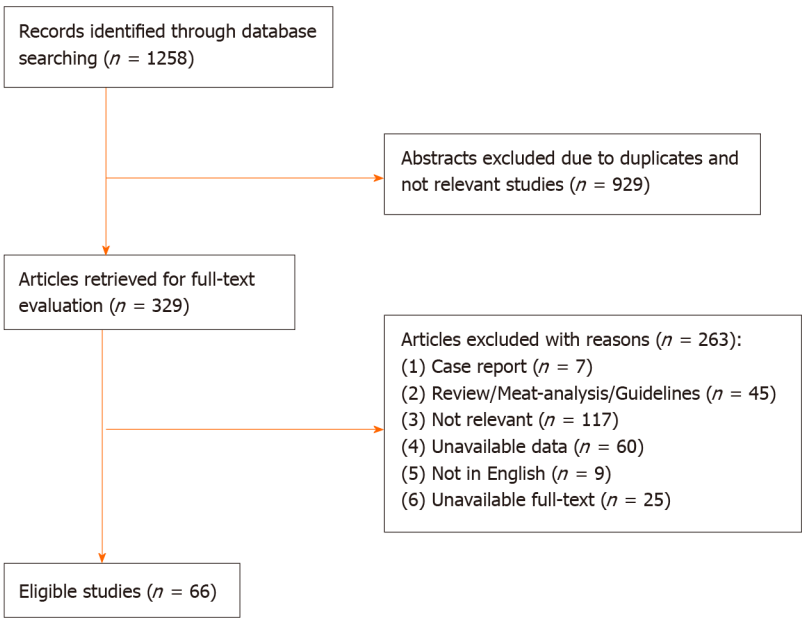

Figure 1 A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis.

65.0%)[1,15,18,21,36].

A total of 5514 cases after EMR were enrolled in this meta-analysis (1475 cases were receiving antithrombotic medication and 4039 cases were not taking any antithrombotic drugs[1,2,4,5,42]). The average postoperative bleeding rate after EMR in the antithrombotic group was 2.85%, while it was 1.29% in the non-antithrombotic group. With the random-effects model, the risk of postoperative bleeding after EMR in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.688, 95%CI: 1.098-6.582, P = 0.030. I^2 = 72.7%). Furthermore, a more homogeneous analysis (I^2 = 5.3%) was carried out after one article[5] was screened out in the sensitivity analysis and the results remained unchanged (OR = 3.765, 95%CI: 2.380-5.954, P = 0.000, Figure 4). The risk of postoperative bleeding after colorectal EMR in the antithrombotic group was higher than the non-antithrombotic group (OR = 3.711, 95%CI: 2.332-5.904, P = 0.005, I^2 = 32.9%). But the analysis on the risk of postoperative bleeding after gastric EMR could not be carried out due to insufficient data.

A total of 10709 cases of polypectomy were enrolled in this meta-analysis (2554 cases were receiving antithrombotic medication and 8155 cases were not taking any antithrombotic drugs[1,3,35,43-46]). The average postoperative bleeding rate in the antithrombotic group was 4.89%, while it was 1.69% in the non-antithrombotic group. With the random-effects model, there was no significant difference (OR = 2.338, 95%CI: 0.610-8.954, P = 0.215, I^2 = 93.6%) in the postoperative bleeding rate between the two groups. Another more homogeneous analysis (I^2 = 44.4%) was carried out after two articles[3,35] were screened out in the sensitivity analysis and the results were found to have changed (OR = 2.112, 95%CI: 1.434-3.112, P = 0.006, Figure 5). The risk of postoperative bleeding after colorectal polypectomy in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.921, 95%CI: 1.821-4.687, P = 0.000, I^2 = 31.9%). Table 2 shows the number of cases with or without antithrombotic agents and hemorrhagic outcome.

Quality assessment and publication bias

The Newcastle-Ottawa scale was used to assess the quality of the included studies in this meta-analysis. Thirteen articles had 6 stars, twenty-three articles had 7 stars, twenty-eight articles had 8 stars, and the others had 9 stars (Table 3). At the same time, the funnel plot did not show any features associated with publication bias (Figure 6).

Subgroup analyses

Among the ESD group, we performed several subgroup analyses to independently evaluate the effects of different types of antithrombotic agents in postoperative bleeding: (1) In gastric ESD retrospective comparison studies of single

Table 2 Number of cases with or without antithrombotic agents and hemorrhagic outcome

Ref.	Resection method	Total	Drug	Post-bleeding	No bleeding
So *et al*[48], 2019	ER	1197	Antithrombotic agent (+/-)	40/50	359/748
			Continued antithrombotic agent (+/-)	11/7	69/138
			Discontinued antithrombotic agent (+/-)	29/43	330/657
			HR (+)	5	9
Kishida *et al*[45],2019	Polypectomy	6382	Antithrombotic agent (+/-)	15/40	986/5341
			Single APT (+)	4	683
			Single anticoagulants (+)	2	85
			Multiple APT (+)	3	163
			Multiple antithrombotic agents (+)	2	39
			Single antithrombotic agent (+)	13	947
			HR (+)	4	16
Inoue *et al*[65], 2019	EMR	102	VKA (+)	12	73
			Discontinued VKA (+)	0	4
			Continued VKA (+)	0	2
			HR (+)	15	98
			DOAC (+)	3	14
			Discontinued DOAC (+)	0	3
Inoue *et al*[65], 2019	ESD	54	VKA (+)	14	31
			Discontinued VKA (+)	1	2
			Continued VKA (+)	0	1
			HR (+)	13	31
			DOAC (+)	2	7
			Discontinued DOAC (+)	2	4
Harada *et al*[56], 2019	ESD	597	Antithrombotic agent (-)	21	422
			Single-LDA (+)	10	85
			DAPT (+)	10	49
			Continued LDA (+)	15	80
			Discontinued APT (+)	5	54
Arimoto *et al*[54], 2018	ESD	919	Antithrombotic agent (-)	26	757
			APT (+)	5	131
			Discontinued APT (+)	5	105
			Continued APT (+)	0	26
Azumi *et al*[39], 2018	ESD	438	Antithrombotic agent (+/-)	6/15	72/345
Fujita *et al*[67], 2018	EMR	84	Discontinued anticoagulants (+)	1	42
			HR (+)	4	37
Horikawa *et al*[58], 2018	ESD	100	Antithrombotic agent (-)	1	49
			Continued LDA	1	49
Izumikawa *et al*[40], 2018	ESD	273	Antithrombotic agent (+/-)	15/11	66/207
Kono	ESD	872	Antithrombotic agent (+/-)	23/38	159/652

et al[41], 2018			Single antithrombotic agent	12	130
			Multiple antithrombotic agents (+)	11	29
			Discontinued antithrombotic agent (+)	8	120
			Discontinued		
			Single APT (+)	3	88
			Multiple APT (+)	3	16
			Single anticoagulants (+)	1	13
			Continued		
			Single APT (+)	1	16
			Multiple APT (+)	4	2
			Single anticoagulants (+)	7	13
			HR (+)	10	21
Oh *et al*[60], 2018	ESD	215	Single APT (+)	14	147
			Multiple APT (+)	15	39
			LDA (+)	12	82
			Thienopyridine (+)	2	54
			Continued APT (+)	23	130
			Discontinued APT (+)	6	56
Park *et al*[63], 2018	Polypectomy	3887	APT (+)	12	339
			Anticoagulants (+)	0	15
Sanomura *et al*[58], 2018	ESD	1243	Antithrombotic agent (-)	40	1127
			Anticoagulants (+)	11	65
			Warfarin (+)	5	32
			DOAC (+)	4	14
Seo *et al*[55], 2018	ESD	1189	Antithrombotic agent (-)	26	945
			APT (+)	7	175
			Aspirin (+)	2	139
			Warfarin (+)	0	10
			DOAC (+)	1	2
			Single antithrombotic agent (+)	10	326
			Multiple antithrombotic agents (+)	0	23
			Discontinued antithrombotic agent (+)	7	206
			Continued antithrombotic agent (+)	0	5
Sakai *et al*[64], 2018	Polypectomy	1004	Discontinued anticoagulants (+)	12	0
			HR (+)	8	70
			Warfarin (+)	7	55
			DOAC (+)	1	15
Yamashita *et al*[36], 2018	ESD	650	Antithrombotic agent (+/-)	7/18	21/652
			Warfarin (+)	5	14
			DOAC	2	7
Yanagisawa *et al*[35], 2018	Polypectomy	436	Antithrombotic agent (+/-)	30/2	188/216
			Discontinued anticoagulants (+)	0	23

			Continued anticoagulants (+)	10	83
			HR (+)	20	82
			Continued warfarin (+)	2	41
			Continued DOAC (+)	8	42
			Warfarin (+)	20	125
			DOAC (+)	10	63
Matsumoto *et al*[46], 2018	Polypectomy	1003	Antithrombotic agent (+/-)	2/2	184/815
Harada *et al*[61], 2017	ESD	45	Continued warfarin (+)	2	20
			HR	5	18
Yano *et al*[33], 2017	ESD	144	Antithrombotic agent (+/-)	47/103	287/1330
Ueki *et al*[14], 2017	ESD	364	Antithrombotic agent (+/-)	7/17	67/273
			Discontinued antithrombotic agent (-)	7	67
			Discontinued single APT (+)	4	57
			Discontinued single anticoagulants (+/-)	2	4
			Aspirin (+)	4	43
			Thienopyrindine (+)	0	7
Yoshio *et al*[78], 2017	ESD	97	Warfarin (+)	18	55
			DOAC	5	19
Gotoda *et al*[15], 2017	ESD	529	Antithrombotic agent (+/-)	12/14	96/407
			APT (+)	8	80
			Single antithrombotic agent (+)	6	80
			Multiple antithrombotic agents (+)	7	17
			Single APT (+)	3	69
			Multiple APT (+)	5	11
			Warfarin (+)	3	11
			Aspirin (+)	2	33
			Thienopyridine (+)	0	10
Furuhata *et al*[17], 2017	ESD	1781	Antithrombotic agent (+/-)	33/68	220/1460
			Single antithrombotic agent (+)	11	139
			Multiple antithrombotic agents (+)	6	30
			Continued single APT (+)	1	14
			HR (+)	15	37
Shibuya *et al*[1], 2017	ESD	259	Antithrombotic agent (+/-)	4/6	32/217
Shibuya *et al*[1], 2017	EMR	3018	Antithrombotic agent (+/-)	16/15	510/2477
Shibuya *et al*[1], 2017	Polypectomy	892	Antithrombotic agent (+/-)	3/5	163/721
Bronsgeest *et al*[42], 2017	EMR		Antithrombotic agent (+/-)	13/15	107/277
			APT (+)	4	53
			Anticoagulants (+)	4	43
Ishigami *et al*[34], 2017	ER	773	Antithrombotic agent (+/-)	10/14	35/714
			HR (+)	10	35
Pigò *et al*[3], 2017	Polypectomy	609	Antithrombotic agent (+/-)	38/32	72/467
			Single APT	14	57

			Multiple APT	3	8
			HR (+)	21	7
			Aspirin (+)	10	32
			Thienopyridine	4	25
Kono *et al*[76], 2017	ESD/EMR	49	Single antithrombotic agent (+)	4	24
			Multiple antithrombotic agents (+)	7	14
			Discontinued antithrombotic agent (+)	5	20
			Continued antithrombotic agent (+)	6	18
			HR (+)	4	12
Lin *et al*[75], 2017	Polypectomy	4923	Aspirin (+)	36	3897
			Thienopyridine (+)	5	590
Sato *et al*[38], 2017	ESD	2378	Antithrombotic agent (+/-)	46/76	401/1855
			APT (+)	35	270
			Anticoagulants (+)	2	33
			HR (+)	6	33
			Aspirin (+)	12	199
			Thienopyridine (+)	0	19
			Warfarin (+)	1	16
			DOAC (+)	1	17
Igarashi *et al*[27], 2017	ESD	976	Antithrombotic agent (+/-)	35/30	332/692
			Discontinued antithrombotic agent (+)	26	250
			Continued antithrombotic agent (+)	5	49
			HR	4	33
			Multiple antithrombotic agents (+)	9	70
			Single antithrombotic agent (+)	26	262
			Continued aspirin (+)	4	29
			Discontinue aspirin (+)	19	152
			Continued thienopyridine (+)	1	17
			Discontinued thienopyridine (+)	9	63
			Continued anticoagulants (+)	1	11
			Discontinued anticoagulants (+)	3	27
Amato *et al*[31], 2016	ER	2692	Antithrombotic agent (+/-)	16/16	595/2069
			APT (+)	11	461
			Anticoagulants (+)	5	134
Kubo *et al*[32], 2016	ER	788	Antithrombotic agent (+/-)	16/13	194/565
			APT (+)	8	146
			Anticoagulants (+)	11	72
			HR (+)	10	63
Shindo *et al*[25], 2016	ESD	262	Antithrombotic agent (+/-)	10/13	38/201
			Discontinued antithrombotic agent (+)	0	25
			Continued APT (+)	2	8

			HR (+)	8	5
Yoshida *et al*[52], 2016	ESD	678	Antithrombotic agent (-)	10	585
			APT (+)	3	60
			Anticoagulants (+)	3	17
Ninomiya *et al*[53], 2015	ESD	609	Antithrombotic agent (-)	28	537
			Discontinued APT (+)	2	11
			Continued APT (+)	5	26
Al-Mammari *et al*[4], 2015	EMR	117	Antithrombotic agent (+/-)	1/1	14/101
Odagiri *et al*[16], 2015	ESD	7567	Antithrombotic agent (+/-)	49/282	440/6796
Namasivayam *et al*[5],2014	EMR	1712	Antithrombotic agent (+/-)	4/10	772/912
			APT (+)	3	521
			Anticoagulants (+)	0	89
			Single antithrombotic agent (+)	1	617
			Multiple antithrombotic agents (+)	3	111
			Thienopyridine (+/-)	0/10	17/912
Terasaki *et al*[21], 2014	ESD	363	Antithrombotic agent (+/-)	4/20	36/303
Tounou *et al*[50], 2014	ESD	350	Antithrombotic agent (-)	16	245
			Discontinued single APT (+)	7	37
			Continued single APT (+)	2	12
			Dual APT (+)	11	20
			Aspirin (+)	9	44
			Thienopyridine (+)	0	5
Suzuki *et al*[18], 2014	ESD	317	Antithrombotic agent (+/-)	1/13	27/276
			HR	0	6
Matsumura *et al*[23], 2014	ESD	425	Antithrombotic agent (+/-)	10/10	77/328
			Discontinued antithrombotic agent (+)	2	39
			Continued antithrombotic agent (+), HR (-)	3	22
			HR (+)	5	16
Beppu *et al*[74], 2014	ER	208	APT (+)	9	18
			Anticoagulants (+)	12	9
			Aspirin (+)	6	11
			Thienopyridine (+)	3	7
Inoue *et al*[77], 2014	Polypectomy	117	Discontinued antithrombotic agent (+)	1	71
			HR (+)	9	36
Sanomura *et al*[66], 2014	ESD	78	Continued LDA (+)	1	27
			Discontinued LDA (+)	3	63
Yoshio *et al*[47], 2013	ESD	1250	Antithrombotic agent (-)	45	972
			Discontinued antithrombotic agent (-)	12	197
			HR (+)	9	15
Takeuchi *et al*[29], 2013	ESD	833	Antithrombotic agent (+/-)	21/15	69/728
Koh *et al*[37], 2013	ESD	1166	Antithrombotic agent (+/-)	17/45	158/946

Mukai *et al*[6], 2012	ESD	161	Antithrombotic agent (+/-)	4/17	29/111
Lim *et al*[51], 2012	ESD	1591	Antithrombotic agent (-)	68	1249
			Discontinued APT (+)	6	96
			Continued APT (+)	20	152
Miyahara *et al*[48], 2012	ESD	1082	Antithrombotic agent (-)	68	883
			Discontinued antithrombotic agent (+)	7	124
Cho *et al*[57], 2012	ESD	514	Antithrombotic agent (-)	15	424
			Discontinued APT (+)	2	54
			Continued APT (+)	4	15
Toyokawa *et al*[24], 2011	ESD	1123	Antithrombotic agent (+/-)	8/48	175/892
Higashiyama *et al*[19], 2011	ESD	924	Antithrombotic agent (+/-)	123/773	3/25
Metz *et al*[2], 2011	EMR	269	Antithrombotic agent (+/-)	8/11	30/220
			APT (+)	6	18
			Anticoagulants (+)	1	10
			HR (+)	1	2
			Aspirin (+)	5	12
			Thienopyridine (+)	1	6
Tokioka *et al*[30], 2011	ESD	515	Antithrombotic agent (+/-)	3/23	37/452
Okada *et al*[22], 2011	ESD	582	Antithrombotic agent (+/-)	4/24	70/484
Mannen *et al*[20], 2010	ESD	436	Antithrombotic agent (+/-)	1/38	32/365
Goto *et al*[13],2010	ESD	454	Antithrombotic agent (+/-)	5/21	52/376
Witt *et al*[44], 2009	Polypectomy	1225	Antithrombotic agent (+/-)	11/2	414/798
Ono *et al*[28], 2019	ESD	444	Antithrombotic agent (+/-)	6/20	50/368
Takizawa *et al*[26], 2008	ESD	968	Antithrombotic agent (+/-)	3/60	74/831
Sawhney *et al*[62], 2007	Polypectomy	173	APT (+)	17	51
			Anticoagulants (+)	14	12
Yousfi *et al*[43], 2004	Polypectomy	162	Antithrombotic agent (+/-)	32/49	27/54
			APT (+)	32	27

ER: Endoscopic resection; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; APT: Antiplatelet; LDA: Low dose of aspirin; HR: Heparin replacement; DOAC: Direct oral anticoagulant; Thienopyridine: Thienopyridine derivatives.

antithrombotic user (No. bleeding/total = 43/524) *vs* non-antithrombotic agent user (No. bleeding/total = 112/2671)[15,17,27]: The risk of postoperative bleeding in single antithrombotic agent group was significantly higher than the non-antithrombotic agent group [OR = 2.061, 95%CI: 1.405-3.024, P = 0.000 (I^2 = 0.0%)]; (2) In gastric ESD retrospective comparison studies of multiple antithrombotic user (No. bleeding/total = 33/179) *vs* non-antithrombotic agent user (No. bleeding/total = 150/3361)[15,17,27,41]: The risk of postoperative bleeding in multiple antithrombotic agents group was significantly higher than the non-antithrombotic agent group [OR = 4.985, 95%CI: 3.251-7.561, P = 0.000 (I^2 = 40.6%)]; (3) In gastric ESD retrospective comparison studies of multiple antithrombotic (No. bleeding/total = 33/179) user *vs* single antithrombotic user (No. bleeding/total = 55/666)[15,17,27,41]: The risk of postoperative bleeding in multiple antithrombotic agents group was higher than the single antithrombotic agent group [OR = 2.492, 95%CI: 1.563-3.974, P = 0.000 (I^2 = 43.9%)]; (4) In gastric ESD retrospective comparison studies of discontinued antithrombotic user *vs* (No. bleeding/total = 81/1074) non-antithrombotic agent user (No. bleeding/total = 216/3894)[14,25,27,47-49]: The risk of postoperative bleeding in discontinued antithrombotic agent group was slightly higher than the non-antithrombotic agent group [OR = 1.405, 95%CI: 1.069-1.848, P = 0.015 (I^2 = 34.4%)]; (5)

Table 3 The quality assessment of included studies

Ref.	Selection				Comparability	Outcome/exposure			Stars
	1	2	3	4		1	2	3	
So *et al*[49], 2019	*	*	*	*	**	*	*	*	9
Kishida *et al*[45], 2019	*	*			*	*	*	*	6
Inoue *et al*[65], 2019	*	*	*		**	*	*	*	8
Harada *et al*[56], 2019	*	*		*	**	*	*	*	8
Arimoto *et al*[54], 2018	*	*	*	*	*	*	*	*	8
Azumi *et al*[39], 2018	*	*		*	**	*	*	*	8
Fujita *et al*[67], 2018	*	*		*	**	*	*	*	8
Horikawa *et al*[58], 2018	*	*		*	**	*	*	*	8
Izumikawa *et al*[40], 2018	*	*			*	*	*	*	6
Kono *et al*[41], 2018	*	*		*	*	*	*	*	7
Oh *et al*[60], 2018	*	*		*		*	*	*	6
Park *et al*[63], 2018	*	*	*		**	*	*	*	8
Sanomura *et al*[59], 2018	*	*		*	*	*	*	*	7
Seo *et al*[55], 2018	*	*	*	*	*	*	*	*	8
Sakai *et al*[64], 2018	*	*		*	*	*	*	*	7
Yamashita *et al*[36], 2018	*	*		*	*	*	*	*	7
Yanagisawa *et al*[35], 2018	*	*		*	**	*	*	*	8
Matsumoto *et al*[46], 2018	*	*		*		*	*	*	6
Harada *et al*[61], 2017	*	*		*	*	*	*	*	7
Yano *et al*[33], 2017	*	*		*	*	*	*	*	7
Ueki *et al*[14], 2017	*	*		*	*	*	*	*	7
Yoshio *et al*[78], 2017	*	*	*	*	*	*	*	*	8
Gotoda *et al*[15], 2017	*	*		*	*	*	*		6
Furuhata *et al*[17], 2017	*	*		*	**	*	*	*	8
Shibuya *et al*[1], 2017	*	*		*	**	*	*	*	8
Bronsgeest *et al*[42], 2017	*	*	*	*	*	*	*	*	8
Ishigami *et al*[34], 2017	*	*		*	*	*	*	*	7
Pigò *et al*[3], 2017	*	*		*	*	*	*	*	7
Kono *et al*[76], 2017	*	*	*	*	*	*	*	*	8
Lin *et al*[75], 2017	*	*		*	*	*	*	*	7
Sato *et al*[38], 2017	*	*		*	**	*	*	*	8
Igarashi *et al*[27], 2017	*	*		*	**	*	*		7
Amato *et al*[31], 2016	*	*	*		*	*	*	*	7
Kubo *et al*[32], 2016	*	*	*	*	*	*	*		7
Shindo *et al*[25], 2016	*	*		*	*	*	*		6
Yoshida *et al*[52], 2016	*	*		*	*	*	*		6
Ninomiya *et al*[53], 2015	*	*		*	*	*	*		6
Al-Mammari *et al*[4], 2015	*	*	*		*	*	*	*	7
Odagiri *et al*[16], 2015	*	*	*	*	*	*	*		7
Namasivayam *et al*[5], 2014	*	*		*	*	*	*		6

Terasaki *et al*[21], 2014	*	*		*	**	*	*		7
Tounou *et al*[50], 2014	*	*		*	*	*	*	*	7
Suzuki *et al*[18], 2014	*	*		*	*	*	*	*	7
Matsumura *et al*[23], 2014	*	*			**	*	*		6
Beppu *et al*[74], 2014	*	*		*	**	*	*	*	8
Inoue *et al*[77], 2014	*	*		*	**	*	*	*	8
Sanomura *et al*[66], 2014	*	*		*	**	*	*	*	8
Yoshio *et al*[47], 2013	*	*	*	*	*	*	*		7
Takeuchi *et al*[29], 2013	*	*		*	**	*	*	*	8
Koh *et al*[37], 2013	*	*		*	**	*	*	*	8
Mukai *et al*[6], 2012	*	*		*	*	*	*		6
Lim *et al*[51], 2012	*	*		*	**	*	*	*	8
Miyahara *et al*[48], 2012	*	*	*	*	**	*	*		8
Cho *et al*[57], 2012	*	*		*	**	*	*	*	8
Toyokawa T *et al*[24], 2011	*	*	*	*	*	*	*		7
Higashiyama *et al*[19], 2011	*	*		*	*	*	*	*	7
Metz *et al*[2], 2011	*	*	*		**	*	*	*	8
Tokioka *et al*[30], 2011	*	*		*	**	*	*	*	8
Okada K *et al*[22], 2011	*	*		*	*	*	*		6
Mannen *et al*[20], 2010	*	*		*	*	*	*		6
Goto *et al*[13], 2010	*	*		*	**	*	*	*	8
Witt *et al*[44], 2009	*	*		*	*	*	*	*	7
Ono *et al*[28], 2019	*	*		*	**	*	*		7
Takizawa *et al*[26], 2008	*	*		*	**	*	*	*	8
Sawhney *et al*[62], 2007	*	*		*	**	*	*	*	8
Yousfi *et al*[43], 2004	*	*	*	*	**	*	*	*	9

In gastric ESD retrospective comparison studies of continuous antithrombotic user (No. bleeding/total = 18/144) *vs* non-antithrombotic user (No. bleeding/total = 50/1081)[25,27,49]: The risk of postoperative bleeding in continuous antithrombotic agent group was higher than the non-antithrombotic agent group [OR = 2.886, 95%CI: 1.513-5.504, P = 0.001 (I^2 = 0.0%)]; (6) In gastric ESD retrospective comparison studies of continuous antithrombotic user (No. bleeding/total = 18/144) *vs* dis-continued antithrombotic user (No. bleeding/total = 55/660)[25,27,49]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.615, 95%CI: 0.919-2.837, P = 0.096 (I^2 = 32.9%)]; (7) In gastric ESD retrospective comparison studies of antiplatelet (APT) (No. bleeding/total = 100/891) user *vs* non-antithrombotic user (No. bleeding/total = 212/4620)[15,38,41,50,51]: The risk of postoperative bleeding in the APT agent group was higher than the non-antithrombotic agent group [OR = 2.545, 95%CI: 1.979-3.273, P = 0.000 (I^2 = 38.8%)]. In colorectal ESD retrospective comparison studies of APT user (No. bleeding/total = 22/425) *vs* non-antithrombotic user (No. bleeding/total = 90/2914)[52-55]: The risk of postoperative bleeding in the APT agent group was higher than the non-antithrombotic agent group [OR = 1.821, 95%CI: 1.127-2.944, P = 0.014 (I^2 = 25.8%)]; (8) In gastric ESD retrospective comparison studies of discontinued APT user (No. bleeding/total = 17/271) *vs* non-antithrombotic user (No. bleeding/total = 127/2450)[41,51,56]: There was no significant difference in the risk of postoperative bleeding risk between the two groups [OR = 1.218, 95%CI: 0.721-2.060, P = 0.461 (I^2 = 0.0%)]. In colorectal ESD retrospective comparison studies of discontinued APT user (No. bleeding/total = 9/179) *vs* non-antithrombotic user (No. bleeding/total = 69/1787)[53,54,57]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.494, 95%CI: 0.725-3.081, P = 0.277 (I^2 = 0.0%)]; (9) In gastric ESD retrospective comparison

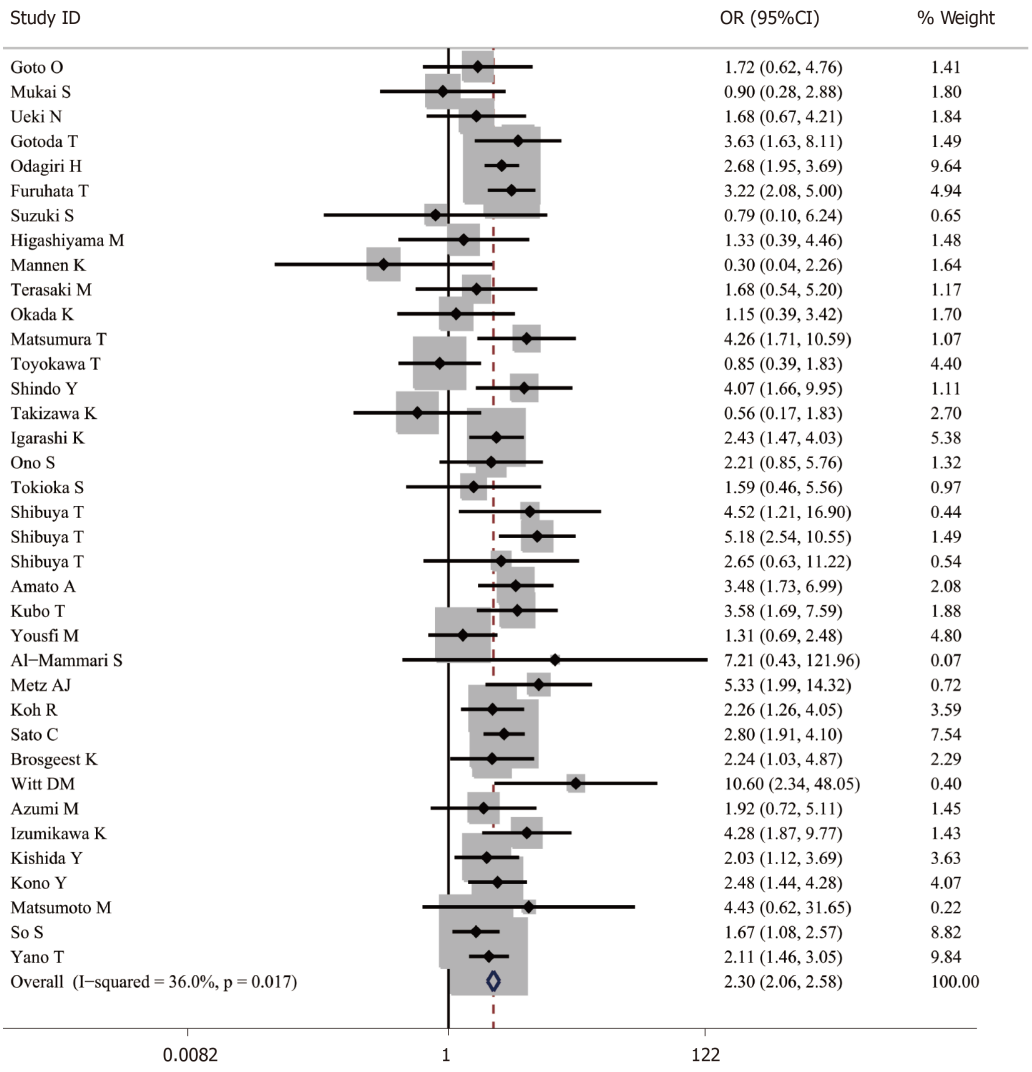

Figure 2 Forest plot of antithrombotic group *vs* non-antithrombotic group in endoscopic resection.

studies of continuous APT user (No. bleeding/total = 43/350) *vs* non-antithrombotic user (No. bleeding/total = 141/2710)[25,41,51,56,58]: The risk of postoperative bleeding in continuous APT agent group was higher than the non-antithrombotic agent group [OR = 2.955, 95%CI: 2.026-4.310, P = 0.000 (I^2 = 0.0%)]. In colorectal ESD retrospective comparison studies of continuous APT user (No. bleeding/total = 9/75) *vs* non-antithrombotic user (No. bleeding/total = 69/1787)[53,54,57]: The risk of postoperative bleeding risk in continuous APT agent group was higher than the non-antithrombotic agent group [OR = 3.409, 95%CI: 1.652-7.036, P = 0.001 (I^2 = 43.9%)]; (10) In gastric ESD retrospective comparison studies of continuous APT user (No. bleeding/total = 44/299) *vs* discontinued APT user (No. bleeding/total = 20/297)[41,56,59,60]: The risk of postoperative bleeding in continuous APT agent group was higher than the discontinued APT agent group [OR = 2.004, 95%CI: 1.095-3.668, P = 0.024 (I^2 = 0.0%)]. In colorectal ESD retrospective comparison studies of continuous APT user (No. bleeding/total = 9/75) *vs* discontinued APT user (No. bleeding/total = 9/179)[53,54,57]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.740, 95%CI: 0.616-4.910, P = 0.296 (I^2 = 50.6%)]; (11) In gastric ESD retrospective comparison studies of multiple APT user (No. bleeding/total = 33/131) *vs* non-antithrombotic user (No. bleeding/total = 89/1815)[15,41,50,56]: The risk of postoperative bleeding in multiple APT agent group was higher than the non-antithrombotic agent group [OR = 6.437, 95%CI: 4.048-10.237, P = 0.000 (I^2 = 7.3%)]; (12) In gastric ESD retrospective comparison studies of multiple APT user (No. bleeding/total = 48/185) *vs* single APT user (No. bleeding/total = 40/494)[15,41,50,56,60]: The risk of postoperative bleeding in multiple APT agent group was higher than the single APT agent group [OR = 3.606, 95%CI: 2.270-5.726, P = 0.000 (I^2 = 39.4%)]; (13) In gastric ESD retrospective comparison studies of continuous single APT

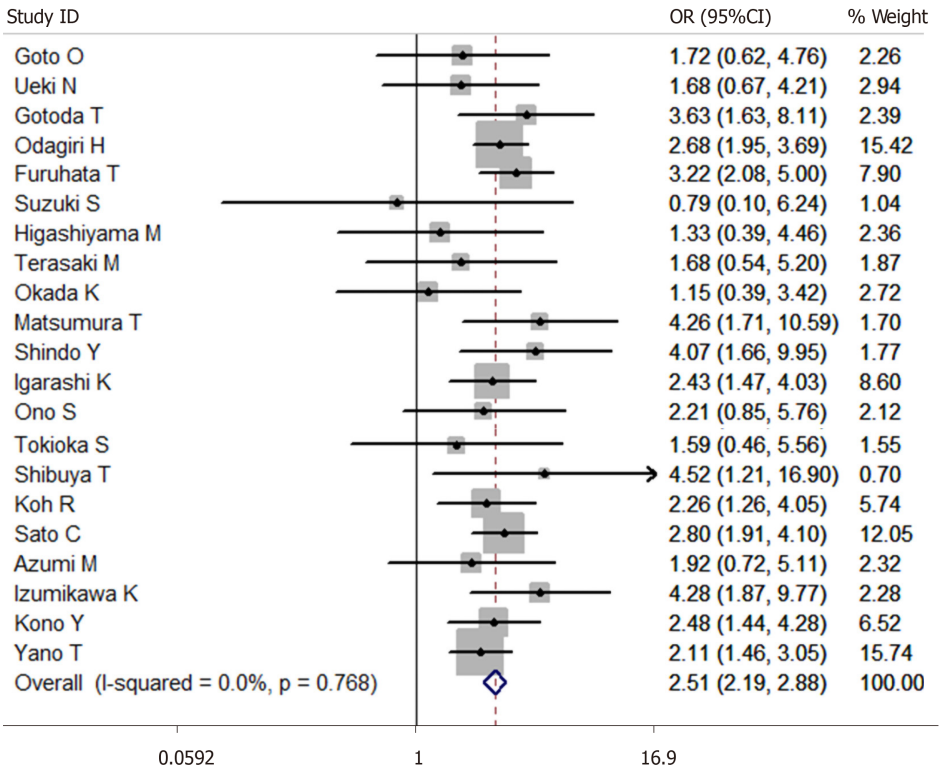

Figure 3 Forest plot of antithrombotic group *vs* non-antithrombotic group in endoscopic submucosal dissection.

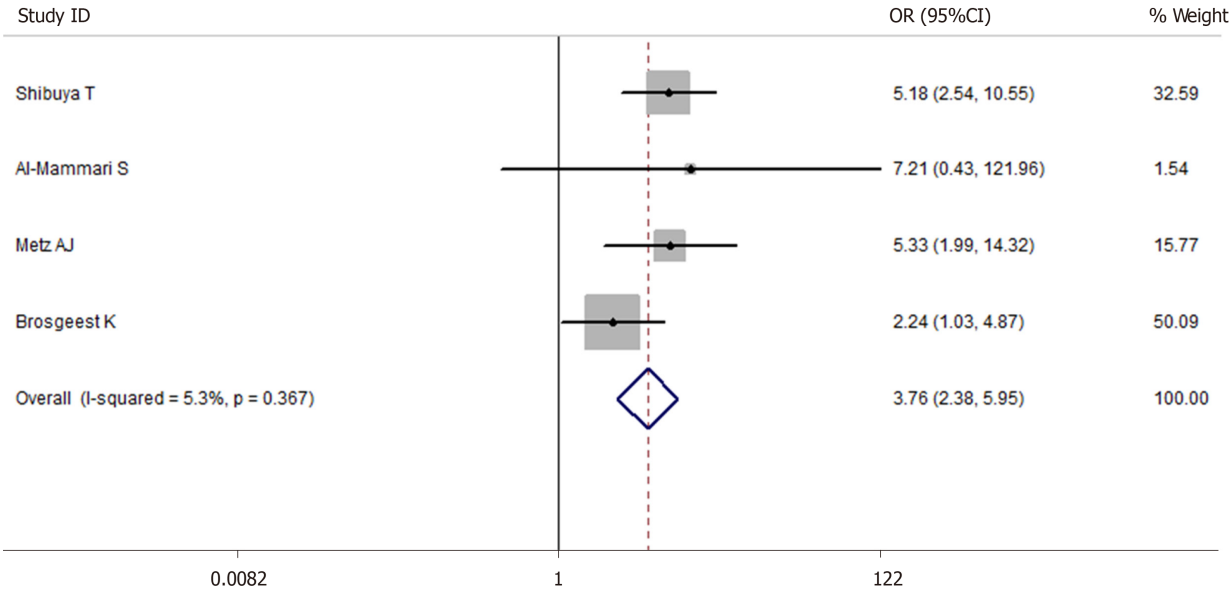

Figure 4 Forest plot of antithrombotic group *vs* non-antithrombotic group in endoscopic mucosal resection.

user (No. bleeding/total = 5/96) *vs* non-antithrombotic user (No. bleeding/total = 71/1262)[17,41,50,58]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.427, 95%CI: 0.524-3.886, P = 0.486 (I^2 = 0.0%)]; (14) In gastric ESD retrospective comparison studies of aspirin user (No. bleeding/total = 38/491) *vs* non-antithrombotic user (No. bleeding/total = 145/3396): The risk of postoperative bleeding in aspirin agent group was higher than the non-antithrombotic agent group [OR = 1.889, 95%CI: 1.293-2.759, P = 0.000 (I^2 = 47.0%)]; (15) In gastric ESD retrospective comparison studies of continuous aspirin user (No. bleeding/total = 36/320) *vs* discontinued aspirin user (No. bleeding/total = 34/391): There was no significant difference in the postoperative bleeding risk between the two groups [OR = 1.430, 95%CI: 0.786-2.603, P = 0.241 (I^2 = 0.0%)]; (16) In gastric ESD

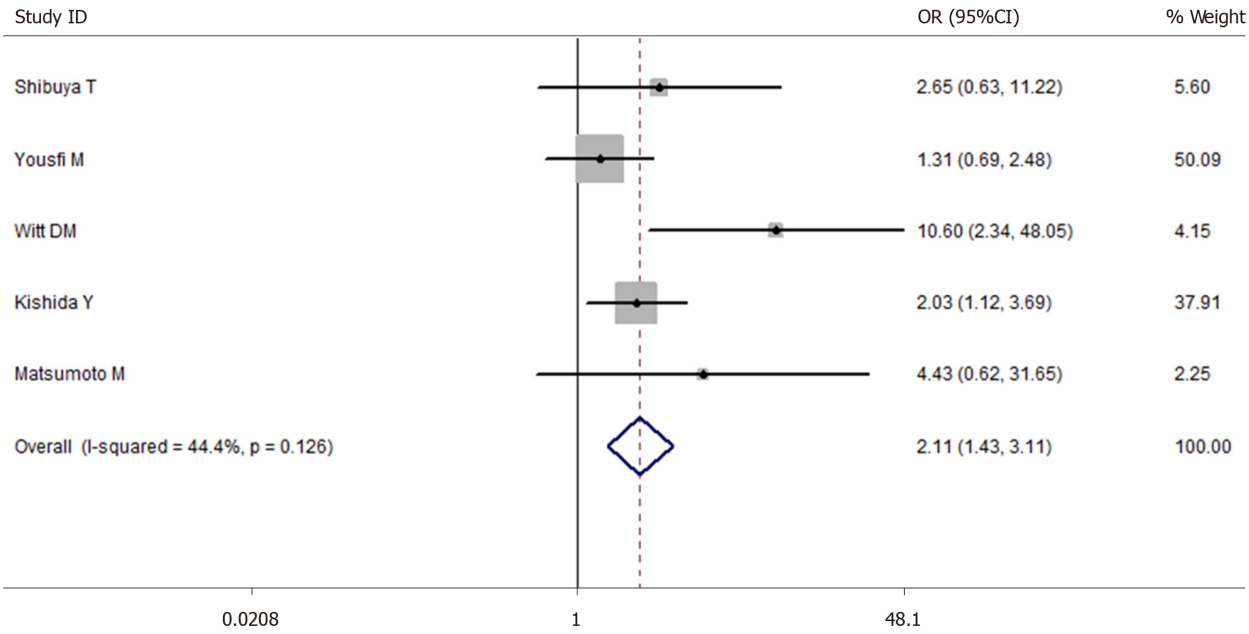

Figure 5 Forest plot of antithrombotic group *vs* non-antithrombotic group in polypectomy.

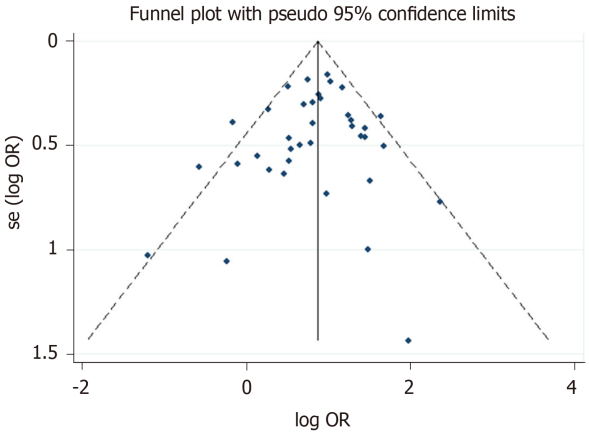

Figure 6 Funnel plot of antithrombotic group *vs* non-antithrombotic group in endoscopic resection.

retrospective comparison studies of discontinued aspirin user (No. bleeding/total = 31/325) *vs* non-antithrombotic user (No. bleeding/total = 147/3047)[27,51,53,56]: The risk of postoperative bleeding in discontinued aspirin agent group was higher than the non-antithrombotic agent group [OR = 2.093, 95%CI: 1.349-3.246, P = 0.001 (I^2 = 33.1%)]; (17) In gastric ESD retrospective compatison studies of thienopyridine derivatives user (No. bleeding/total = 0/41) *vs* non-antithrombotic user (No. bleeding/total = 123/2903)[14,15,38,50]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 0.983, 95%CI: 0.234-4.132, P = 0.981 (I^2 = 0.0%)]; (18) In gastric ESD retrospective comparison studies of aspirin user (No. bleeding/total = 39/440) *vs* thienopyridine derivatives user (No. bleeding/total = 78/2009)[14,15,38,50,60]: The risk of postoperative bleeding in the aspirin agent group was higher than the thienopyridine derivatives agent group [OR = 1.806, 95%CI: 1.062-3.037, P = 0.029 (I^2 = 47.0%)]; (19) In gastric ESD comparison studies (two retrospective studies and one prospective study) of anticoagulant user (No. bleeding/total = 21/145) *vs* non-antithrombotic user (No. bleeding/total = 154/3788)[38,41,59]: The risk of postoperative bleeding [OR = 4.029, 95%CI: 2.442-6.646, P = 0.000 (I^2 = 18.1%)] in the anticoagulant agent group was significantly higher than the non-antithrombotic agent group; (20) In gastric ESD comparison studies (three retrospective studies and one prospective study) of warfarin user (No. bleeding/total = 24/127) *vs* direct oral anticoagulants (DOAC) user (No. bleeding/total = 10/60)[38,47,59]: There was no significant difference

in the risk of postoperative bleeding between the two groups [OR = 0.940, 95%CI: 0.407-2.171, P = 0.885 (I^2 = 0.0%)]; (21) In gastrointestinal ESD retrospective comparison studies of anticoagulant user (No. bleeding/total = 13/89) *vs* APT user (No. bleeding/total = 49/501)[38,41,52]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.677, 95%CI: 0.852-3.302, P = 0.135 (I^2 = 64.1%)]; (22) In gastric ESD retrospective comparison studies of heparin replacement (HR) (No. bleeding/total = 25/128) user *vs* non-antithrombotic user (No. bleeding/total = 154/3681)[23,27,38,41]: The risk of postoperative bleeding [OR = 5.547, 95%CI: 3.457-8.900, P = 0.000 (I^2 = 16.9%)] in HR agent group was significantly higher than the non-antithrombotic agent group; (23) In gastric ESD retrospective comparison studies of HR user (No. bleeding/total = 32/125) *vs* continuous antithrombotic user (No. bleeding/total = 10/101)[17,25,27,61]: The risk of postoperative bleeding in the HR agent group was significantly higher than the continuous antithrombotic agent group [OR = 2.859, 95%CI: 1.257-6.503, P = 0.012 (I^2 = 0.0%)]; and (24) In gastric ESD retrospective comparison studies of HR user (No. bleeding/total = 29/120) *vs* continuous single APT user (No. bleeding/total = 7/83)[17,27,41]: The risk of postoperative bleeding in HR agent group was significantly higher than the continuous single APT agent group (OR = 2.988, 95%CI: 1.173-7.761, P = 0.000 (I^2 = 3.1%)].

Among the EMR group, we performed several subgroup analyses to evaluate the effects of different types of antithrombotic agents on postoperative bleeding: (1) APT (No. bleeding/total = 13/605) user *vs* non-antithrombotic user (No. bleeding/total = 36/1445)[2,5,42]: OR = 1.744, 95%CI: 0.398-7.643, P = 0.461 (I^2 = 78.8%). There were two retrospective studies and one prospective study in the subgroup analysis. There were two studies about colorectal EMR and one study about gastric EMR in the subgroup analysis; (2) Anticoagulant user (No. bleeding/total = 44/567) *vs* non-antithrombotic user (No. bleeding/total = 218/8131)[2,5,42]: There was no significant difference in the risk of postoperative bleeding risk between the two groups [OR = 1.409, 95%CI: 0.552-3.597, P = 0.474 (I^2 = 0.0%)]. There were two retrospective studies and one prospective study in the subgroup analysis. There were two studies about colorectal EMR and one study about gastric EMR in the subgroup analysis; and (3) Anticoagulant user (No. bleeding/total = 5/147) *vs* APT user (No. bleeding/total = 13/605)[2,5,42]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 0.768, 95%CI: 0.261-2.261, P = 0.631 (I^2 = 0.0%)]. There were two retrospective studies and one prospective study in the subgroup analysis. There were two studies about colorectal EMR and one study about gastric EMR in the subgroup analysis.

Among the polypectomy group, we also performed several subgroup analyses to evaluate the effects of different types of antithrombotic agents on postoperative bleeding: (1) APT (No. bleeding/total = 56/994) user *vs* non-antithrombotic user (No. bleeding/total = 121/5983)[3,43,45]: OR = 1.766, 95%CI: 1.192-2.616, P = 0.005 (I^2 = 73.9%) (retrospective studies). There were two studies about colorectal polypectomy and one study about gastric polypectomy in the subgroup analysis; (2) Anticoagulant user (No. bleeding/total = 16/128) *vs* APT user (No. bleeding/total = 33/1106)[45,62,63]: The risk of postoperative bleeding after colorectal polypectomy in the anticoagulant agent group was significantly higher than the APT agent group [OR = 3.132, 95%CI: 1.442-6.803, P = 0.004 (I^2 = 9.0%)] (retrospective studies); and (3) Warfarin user (No. bleeding/total = 32/226) *vs* DOAC (No. bleeding/total = 13/98)[35,36,64]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.126, 95%CI: 0.557-2.275, P = 0.741 (I^2 = 0.0%)] (retrospective studies). There were two studies about colorectal polypectomy and one study about gastric polypectomy in the subgroup analysis.

A subgroup analysis was planned to assess the risk of postoperative bleeding according to the difference in the size of the lesion, dosage and cessation period of antithrombotic agent, but we failed to perform the analysis because of insufficient data.

Thromboembolic event

Thromboembolic event is defined as arterial thromboembolism. This includes stroke, transient ischemic attack and infarction perioperative period. These thromboembolic events in included studies were available in nineteen articles (one event in the heparin therapy group[17], five events in the antithrombotic group[5,27], three events in the HR group[35,47,64], one event in the discontinued anticoagulant therapy group[30], one event in the discontinued antithrombotic therapy group[32], two events in the withdrawal period of antiplatelet therapy group[2,51], one event in the anticoagulant therapy group[44], one event in the withdrawal period of anti-vitamin K antagonisis therapy

group[65], four events in the low dose aspirin interrupted group[66]). No thromboembolic events occurred in seven studies[36,41,49,58,59,67].

DISCUSSION

Despite several practice guidelines about the cessation or continuation of antithrombotic drugs before ER made by the British Society of Gastroenterology[68], the European Society of Gastrointestinal Endoscopy[68], the American Society for Gastrointestinal Endoscopy[69] and the Japan Gastroenterological Endoscopy Society[70], the effect of antithrombotic drugs on the risk of postoperative bleeding was still controversial in some studies[4,6,13,14,16,19-22,24,26,27,31,37,48,57]. Our study found that antithrombotic agents confer a higher risk for postoperative bleeding after ESD and EMR. But the risk of postoperative bleeding after polypectomy was not significantly elevated in the patients with antithrombotic drugs from our study, which was in consistent with the results of a study by Matsumoto *et al*[46]. Nevertheless, there was significant heterogeneity in the analysis of antithrombotic group *vs* non-antithrombotic group. To explain the heterogeneity (I^2 = 82.5%) of our meta-analysis, we got the following findings: (1) Different methods were used to prevent postoperative bleeding; (2) Different definitions on postoperative bleeding[2,19]; (3) Different types and doses of antithrombotic agents; and (4) Different follow-up time, ranging 24 h to 3 mo. In order to reduce the heterogeneity, we have done the subgroup analyses to assess the effect of different types of antithrombotic agents in the risk of postoperative bleeding.

Some studies found that APT did not correlate with the risk of postoperative bleeding[32,52]. At the same time, the risk of delayed postoperative bleeding after ESD was not increased in a single APT agent (continued or discontinued)[17]. In contrast, it has been demonstrated that APT (especially dual APT) increases the risk of postoperative bleeding[50]. A retrospective study by Singh *et al*[71] showed that clopidogrel alone was not an independent risk factor for postoperative bleeding, but a randomized trial by Chan *et al*[72] showed that continued clopidogrel use results in a higher risk of postoperative bleeding compared to the discontinued clopidigrel use group. Our study found that continued single APT agent use did not increase the risk of postoperative bleeding, but multiple APT agents increased the risk of postoperative bleeding after ER.

Some studies found that low dose aspirin and continued use of aspirin didn't induce a higher risk of postoperative bleeding after polypectomy and gastric ESD[23,43,50]. However, Ninomiya *et al*[53] found that continued use of aspirin increased the risk of postoperative bleeding after colorectal ESD. A study by Metz *et al*[2] demonstrated that the use of aspirin within 7 d of the operation was an independent risk factor for postoperative bleeding after colonic EMR. In a meta-analysis by Shalman *et al*[73], the risk of immediate bleeding in patients with aspirin was not increased, but the risk of delayed bleeding in patients with aspirin or thienopyridine derivatives was increased. Our study found that the use of aspirin significantly increased the risk of postoperative bleeding, but thienopyridine derivatives did not increase the risk of postoperative bleeding after ER. Nevertheless, the guidelines recommend continuing aspirin and withdrawing thienopyridine derivatives in the endoscopic resection[68-70]. Therefore, more prospective or randomized controlled trials are needed to determine the effects of aspirin and thienopyridine on the risk of postoperative bleeding after ER.

Several guidelines about gastroenterological endoscopy recommend that anticoagulant agent should be discontinued with HR[68-70]. APT plus HR (meaning that anticoagulants were substituted by heparin before polypectomy) were not correlated with postoperative bleeding, but anticoagulant or anticoagulant plus HR were risk factors for postoperative bleeding[32]. Besides, HR alone was related to postoperative bleeding in univariate analysis but was not in multivariate analysis[32]. And our study has reached the same conclusion. Cessation of antithrombotic therapy could result in thromboembolic events such as cerebral infarction and hemorrhagic shock. But the risk of the thromboembolic events in the included studies is relatively low.

There were several drawbacks in this meta-analysis. First of all, the results of our meta-analysis were derived from retrospective studies. Retrospective studies may underestimate the risk of postoperative bleeding. Further prospective studies are needed to confirm our results. Secondly, the surveillance periods of included studies were not exactly the same. Finally, different types and doses of antithrombotic agents were used in the included studies, which may lead to bias.

CONCLUSION

In conclusion, the risk of postoperative bleeding after ER (polypectomy, EMR and ESD) correlated with the types and management of the antithrombotic agents according to our meta-analysis. Interrupting or switching antithrombotic therapy might result in the increased risk of serious thromboembolic events. Therefore, it is important to comprehensively assess the risk of postoperative bleeding and thromboembolic events in the patients with antithrombotic drugs after ER.

ARTICLE HIGHLIGHTS

Research background

Endoscopic resection (ER) is deemed as an effective method for gastrointestinal neoplasia, polyp, gastric adenomas, early oesophageal, gastric and colorectal cancer. More and more people suffering from cardiovascular disease and/or cerebrovascular disease receive antithrombotic therapy which change patients' coagulation status and may lead to high risk of postoperative bleeding after ER. The relationship between the postoperative bleeding after ER and antithrombotic agents is still uncertain.

Research motivation

This study explored the relationship between the postoperative bleeding after ER and antithrombotic agents.

Research objectives

The aim of this study is to identify whether the use of antithrombotic drugs increases the risk of the postoperative bleeding after ER by a systematic review and meta-analysis.

Research methods

A systematic search was conducted on PubMed, Web of Science, Cochrane library. The Newcastle-Ottawa scale was used to evaluate the quality of studies. Stata 12.0 was used for statistical analysis. The odds ratio and 95%CI were calculated and heterogeneity was quantified using Cochran's Q test and I^2.

Research results

Total 66 studies were included in the meta-analysis. Pooled data suggested that antithrombotic therapy was significantly associated with postoperative bleeding after ER. The risk of postoperative bleeding after endoscopic submucosal dissection, endoscopic mucosal resection and polypectomy in the antithrombotic group was higher than the non-antithrombotic group.

Research conclusions

The risk of postoperative bleeding after ER correlated with the types and management of antithrombotic agents by our meta-analysis.

Research perspectives

Our results can guide the use of antithrombotic drugs before ER and evaluate the risk of postoperative bleeding.

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