Prophylactic transcatheter arterial embolization for high-risk ulcers following endoscopic hemostasis: A meta-analysis

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Research article

Keywords: embolization, gastrointestinal bleeding, interventional radiology, ulcer

Posted Date: November 19th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-111096/v1

Abstract

Background: To conduct a meta-analysis to assess the safety and efficacy of prophylactic transcatheter arterial embolization (PTAE) for the treatment of high-risk bleeding peptic ulcers after achieving endoscopic hemostasis.

Methods: PubMed and Cochrane Library were queried for full-text articles published up to December 2019. The following keywords were used: “prophylactic embolization”, “supplement embolization”, “gastrointestinal bleeding”, and “ulcer bleeding”. High-risk ulcers were defined based on endoscopic findings (i.e. large ulcers, Forrest class I-IIb) and/or clinical presentation (i.e. hypotension, decreased hemoglobin during endoscopy). Only comparative studies investigating PTAE versus conservative treatment after achieving endoscopic hemostasis were included. Baseline study characteristics, re-bleeding rate, need for surgery, mortality, and PTAE-related complication rates were investigated. Quantitative analyses were performed with STATA 15.1.

Results: Among the five original studies included, a total of 265 patients received PTAE and 617 were managed conservatively after endoscopy. The rebleeding rate (6.8% vs 14.3%, p=0.003) and mortality (4.5% vs 8.8%, p=0.032) of patients from the PTAE group were lower than the control group. PTAE also reduced the cumulative need of future surgical intervention (3.0% vs 14.4%, p=0.005). The PTAE-related major and minor events were 0.75% and 14.4%, respectively.

Conclusion: PTAE had therapeutic potentials in reducing rebleeding risk, need of surgical intervention, and morality in high-risk peptic ulcers after achieving endoscopic hemostasis. The embolization-associated adverse events were minimal. Future studies should aim to increase the sample size and resources for performing endovascular interventions.

Introduction

In the United States, acute nonvariceal upper gastrointestinal bleeding (UGIB) occurs with an incidence of 160 per 100,000 and represents an estimated 7 billion dollars on the annual economic healthcare burden[1,2]. Furthermore, mortality for UGIB remains as high as 14% despite aggressive medical interventions[3]. Currently, endoscopic interventions such as clipping, thermal coagulation, and epinephrine injection remain the first-line standard[4–6]. Despite successful endoscopic hemostatic control and adjunctive anti-acid treatment, some ulcers (i.e. hemodynamically unstable patients, larger ulcers, etc.) remain at high-risk for rebleeding[7–9], leading to increased mortality compared to initial events[10]. Prior retrospective studies have explored the use of prophylactic transcatheter arterial embolization (PTAE) in this patient population to decrease the rebleeding risks, demonstrating promising results[11–13].

In a recently published randomized controlled trial (RCT), Lau et al evaluated the efficacy of prophylactic transcatheter arterial embolization (PTAE) after successful endoscopic control of UGIB[8]. No statistically significant difference was observed between the outcomes of patients who received PTAE and no further intervention (endoscopy only, EO), as measured by 30-day rebleeding, mortality, and re-intervention rates were observed. However, as noted by Loffroy et al. in a response letter to the editor, a large majority of rebleeding and deaths were patients allocated to the PTAE group who failed to receive the intervention[14]. As also cited, statistical significance may also have been seen due to underpowering of the prior studies. In order to overcome this limitation, the purpose of this study was to conduct a meta-analysis of previously published literature to evaluate the safety and efficacy of PTAE in preventing rebleeding after successful endoscopic control of high risk arterial UGIB.

Materials & Methods

Literature search

This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement[15]. PubMed and Cochrane Library were queried to identify peer-reviewed articles concerning prophylactic embolization of high-risk peptic ulcers versus no intervention after endoscopic hemostasis control. High-risk ulcers were defined based on endoscopic findings (i.e. Forrest class I-IIb) and/or clinical presentations (i.e. hypotension, low hemoglobin during endoscopy). All databases were queried from their establishment to December 2019. The following keywords were used: “Prophylactic Embolization”, “Supplement Embolization”, “Gastrointestinal Bleeding”, and “Ulcer Bleeding”.

Inclusion criteria and exclusion criteria

The following inclusion criteria were adopted: a) population: patients with arterial UGIB; b) diagnosis: endoscopy visualization; c) treatment: PTAE for endoscopically treated bleeding; d) outcomes: mortality, rebleeding, need for subsequent surgical intervention, PTAE-related complications; e) study design: comparative studies of PTAE versus no further intervention (endoscopy only, EO) after endoscopic management. A study was excluded if any of the following criteria were met: a) non-human studies; b) sample size less than 5; c) Letter, editorial, commentary, review, or case-reports; d) duplicated or patient samples used by more than one study; e) non-comparative studies.

Endnote X8 (Clarivate Analytics, Philadelphia, Pennsylvanian) was used to identify and delete duplicates. Titles, abstracts, and key words were screened, followed by the review of full texts of the remaining studies. A detailed screening process is depicted in Fig. 1.

Data Collection and Statistical Analysis

Baseline characteristics were extracted from each study including author, year of publication, country, study design, sample size, Forrest classification, indication of PTAE, rebleeding, mortality, need for surgery, and PTAE-related complications. Quality Assessment was performed using the Cochrane Collaboration’s tool for randomized controlled trials and Newcastle Ottawa Scale for cohort studies[16,17]. Two researchers screened and extracted the data from the original studies. Any disagreement was discussed and arbitrated by a third author if not resolved.

Quantitative analysis was performed with Stata 15.1 (STATA Corp., College Station, TX, USA). Meta-analysis was conducted with the -*metan* function. A fixed-effect model was implemented if heterogeneity $I^2 < 50$. A random-effect model was used if $I^2 > 50$. Outcomes were pooled if reported by original articles. Overall rebleeding, mortality, and need-of-surgery rates were calculated by dividing the cumulative number of events by the total number of patients from each study. Publication bias was evaluated with funnel plot and Egger's test. Sensitivity analysis was performed with the one-study remove approach (metaninf analysis).

Results

Baseline Characteristics of the Included Studies

After duplicated studies were removed, a total of 76 studies underwent the screening process. Excluded studies included 4 case reports, 11 review papers, 5 conference abstracts, 6 commentaries or editorials, and 43 irrelevant studies. Next, two irrelevant articles were removed upon full-text assessment. Finally, five unique studies were included in the meta-analysis.

A total of 882 patients were included[8, 11–13,18]: 265 and 617 patients received PTAE and endoscopy only, respectively (Table 1). Two studies were randomized controlled trials (RCT). Among 167 patients who were randomized into the PTAE arm, 40 patients did not receive PTAE (23.9%)[8,18]. Seven out of 14 (50.0%) rebleeding and 4 out of 5 (80.0%) deaths were from this subgroup[8,18]. The lack of radiological resources was the most common cause (34.3%) followed by the inability to catheterize the targeted vessel (28.6%, Fig. 2). Because of this subgroup's potential impact on the intention-to-treat analysis as suggested by Loffroy et al[14], only patients from per-protocol-analyses of these two studies were considered in the following meta-analysis.

Table 1

Baseline characteristics and outcomes of the included studies. ITT: intention-to-treat; EO: Endoscopy-only group; PPA: per-protocol-analysis; PTAE: prophylactic embolization group; RC: retrospective cohort study; RCT: randomized-controlled trial. NS: not specified.

Study	Country	Design	Sample Size	Follow-up Period	Forrest Class	PTAE Indication
Lau 2019	China	RCT	EO:123 PTAE: 96 (PPA), 118 (ITT)	30 days	Ia: 38 (17.4%) Ib: 82 (37.4%) IIa: 99 (45.2%)	Spurting hemorrhage during endoscopy; ulcers ≥ 20 mm; hemoglobin < 9 g/dL on admission; systolic pressure < 90 mmHg and pulse > 110 beats per minute
Laursen 2014	Denmark	RCT	EO: 56 PTAE: 31 (PPA), 49 (ITT)	30 days	Ia: 11 (10%) Ib: 34 (32%) IIa 53 (50%) IIb: 7 (7%)	Forrest Class I-IIb
Mille 2015	Germany	RC	EO: 47 PTAE: 55	30 days	Ia: 19 (16%) Ib: 39 (33%) IIa: 14 (12%) IIb: 10 (9%) IIc: 8 (7%) III: 27 (23%)	Ulcer located in the posterior duodenal bulb; Forrest I-IIc with a Rockall Score ≥ 6; active bleeding or ulcer ≥ 1 cm on endoscopy; systolic pressure < 100 mm Hg, age > 80 years, ≥ 2 anticoagulants, >=2 comorbidities
Kamiski 2017	Latvia	RC	EO: 50 PTAE: 25	NS	Ia: 16 (21.3%) Ib:11 (14.7%) IIa: 33 (44.0%) IIb:15 (20.0%)	Forrest I-IIb and Rockall Score ≥ 5

Study	Country	Design	Sample Size	Follow-up Period	Forrest Class	PTAE Indication
Kamiski 2019	Latvia	RC	EO: 341 PTAE: 58	NS	Ia: 46 (11.5%) Ib: 61 (15.3%) IIa:104 (26.1%) IIb: 188 (47.1%)	Forrest I-IIb and Rockall Score ≥ 5
Total			EO: 617 PTAE: 265			

Rebleeding

All five studies reported the risk of rebleeding: 18/265 (6.8%) patients in the PTAE group and 88/617 (14.3%) patients in the EO group rebled (S. Table 1). The OR of rebleeding was significantly higher in patients without additional PTAE: 2.34 [95%CI: 1.33–4.13], p = 0.003 (Fig. 3). Subgroup analysis according to study type was consistent with the overall findings: 2.304 [95%CI: 1.10–4.81] in retrospective cohort studies (RC, p = 0.026) and 2.41 [95%CI: 0.99–5.85] (p = 0.053) in RCT. The borderline lack of significance among RCTs was largely due to the lack of statistical power.

Need of Surgery

In total, eighty-nine patients from the EO group eventually required surgical intervention to control rebleeding (14.4%), compared to eight patients from the PTAE group (3.0%, S.Table 2). Overall, EO had a significantly higher need of surgery than PTAE (OR: 2.898 95%CI [1.374–6.112], p = 0.005). Three of the five studies reported no need for surgical intervention among PTAE patients, including both RCTs and 1 RC (S. Table 2).

Table 2
Complications from prophylactic transcatheter embolization.

Study	Embolization-related Complication
Lau 2019	None
Laursen 2014	1 coil migration, asymptomatic
Mille 2015	8 minor complications; 2 major complications.
Kamiski 2017	None
Kamiski 2019	None
Total	Minor: 9/265 (3.4%) Major: 2/265 (0.75%)

Mortality

Among five studies, 12/262 (4.5%) and 54/617 (8.8%) patients from the PTAE and EO groups died during follow-up assessments (S. Table 3, Fig. 5). Overall, EO had a significantly higher mortality than PTAE (OR: 2.11, 95%CI [1.07–4.15], p = 0.032), which also held true for the RCT subgroup (OR: 6.294, 95%CI [1.14–34.82], p = 0.035).

Complication Rate

According to the Quality Improvement Guidelines for percutaneous transcatheter embolization per the Society of Interventional Radiology[19], nine patients encountered minor complications that did not require further intervention (3.4%), 8 of which were asymptomatic (Table 2). Only two major complications occurred: 1 pancreatitis and 1 hepatic failure (0.75%). All complications were due to coil migration.

Publication Bias and sensitivity analysis

Funnel plots (Fig. 6) and Egger's tests were implemented to evaluate publication bias. In terms of rebleeding rates and need of surgery, no publication bias was appreciated according to funnel plot (Fig. 6) and Egger's test (p = 0.336 and 0.739). In terms of mortality rates, funnel plot suggested possible asymmetry (Fig. 6); Egger's test was significant for publication bias (p = 0.028). Results of the metaninf analysis indicated that the elimination of studies might affect the final results (Supplement Fig. 1.1, 1.2, Table 5.1, 5.2).

Subgroup Analysis of Clinically Relevant Variables

Subgroup analysis was performed based on the follow-up duration, hemoglobin level at presentation, and non-aspirin NSAID use (Supplement Fig. 4). PTAE has a significantly lower odds of rebleeding and mortality in patient cohorts with greater than 20% NSAID and hemoglobin greater than 8.0 g/dl. At 30-day follow-up, neither mortality nor rebleeding rate was statistically significant in terms of PTAE's efficacy over conservative management after endoscopy. Due to significant baseline differences between PTAE and endoscopy-only groups, subgroup analysis of the following variables was not possible: Forrest Classification[13], Rockall score[13], ASA Physical Classification[12], and anticoagulation use (warfarin, heparin)[13].

Discussion

Transcatheter arterial embolization (TAE) is widely acknowledged for its effectiveness in treating brisk arterial bleeding[20]. It has largely replaced surgery as a first-line therapy for UGIB refractory to endoscopic treatment due to its high efficacy and favorable safety profile[21]. However, a subgroup of ulcers remains at high-risk of future rebleeding despite achieving hemostasis via endoscopy. In 2012, based on the available data at that time, the American College of Gastroenterology Guidelines only recommended medical treatment of the underlying etiology, for example, withholding aspirin, treating *H.pylori*, etc. Afterwards, studies of using PTAE to decrease this risk and mortality in selected patients have been published in the last five years[8,22]. These high-risk lesions are typically large in size (i.e. greater than 10 mm), belong to Forrest class I-IIb and/or were treated in hemodynamically unstable patients[8,13,23]. Whereas residual blood flow underneath a treated lesion may serve as a source of rebleeding, the intermittent nature of UGIB bleeding is dependent on a patient's hemodynamic status. For example, a hypotensive patient may present with a lesion that appeared hemostatic at endoscopy however following blood transfusion the normalized blood pressure could initiate rebleeding[24–26]. As such, most authors considered PTAE as an option if the ulcer is considered to be high-risk based on based on endoscopic findings (i.e. large ulcers, Forrest class I-IIb) and/or clinical presentation (i.e. hypotension, decreased hemoglobin during endoscopy) [8, 11–13,18].

According to the present meta-analysis, PTAE was highly effective in reducing the risk of rebleeding compared to EO (2.34 [95%CI: 1.33–4.13], p = 0.003). Compared to patients who did not receive additional embolization after endoscopy, the PTAE group has a statistically significantly lower rebleeding rate of 6.8%. This value is also lower than the reported rates of emergent embolization for nonvariceal UGIB that range from 9 to 47%[27–31]. For nonvariceal UGIB recalcitrant to TAE, surgery is considered to be the final, definitive treatment option but confers a mortality risk as high as 43%[34,35]. Three out of the five included study cohorts required surgical intervention, with a higher cumulative rate in patients that did not receive PTAE after endoscopy (14.4% vs 3.0%; OR: 2.898 95%CI [1.374–6.112], p = 0.005). Further, the PTAE group also has a statistically significantly lower mortality rate than its EO counterpart (4.5% vs 8.8%, OR: 2.11, 95%CI [1.07–4.15], p = 0.032), though publication bias exists (Fig. 6C). A total of twelve PTAE patients from four studies died. According to Laursen et al, the majority of deaths were non-UGIB related (5/7) such as sepsis and malignancy[18]. In one case, an endovascular coil migrated to the hepatic artery, leading to acute hepatic failure and death. Of note, this patient had poor baseline liver function at admission due to advanced cirrhosis as isolated coil migration to the hepatic artery is not expected to routinely cause fulminant hepatic failure due to the dual blood supply of the liver. Coil migration also occurred in nine other patients, which were all asymptomatic without elevation of liver enzymes. Eight of these nine patients were from the same study, so this type of complication may have been operator dependent. Nevertheless, only two studies observed complications from PTAE with a major and minor complication rate of 0.75% and 3.4%, respectively[13,18]. In comparison to the differences of mortality and rebleed rates between PTAE and EO groups, the risk of PTAE-related major complication was considered rather minimal. Based on subgroup analysis (supplement table 4), patients with NSAID usage is more likely to benefit from PTAE, because of the higher rebleeding rates in this population[32]. Compared to patients with hemoglobin greater than 8.0 g/dl, patients with lower hemoglobin level are less likely to benefit from PTAE, which is consistent with the finding of previously published literature on TAE[33]. However, these results were based on study-level evidence. Stratified analysis using patient-level data are warranted in future studies.

There are several limitations of this study. First, only five studies were included, and three of them were retrospective cohorts, which are inferior to RCT and prospective studies. Due to limited evidence available, study removal during sensitivity analysis could render the overall results loss of statistical significance (supplement Fig. 1.1, 1.2). Second, the length of follow-up time varied among studies. Subgroup analysis on 30-day follow-up did not suggest statistically significant advantage of PTAE in terms of rebleeding and mortality reduction, despite the cumulative overall results did suggest its efficacy (supplement table 4). The rebleeding and mortality rates are expected to likely increase cumulatively over time. Only Lau et al implemented a Kaplan-Meier curve to characterize these evolutions[8]. Finally, limited evidence was available regarding the risk factors of rebleeding and deaths after PTAE. None of the authors provided the baseline characteristics separately between successful and failed PTAE subgroups.

Given these limitations, several important aspects should be addressed during future study design. In addition to increasing sample size, future RCTs with intention-to-treat protocols should aim to reduce the number of patients allocated to PTAE that fail to receive the procedure. For example, increased access to centers with expert resources in interventional radiology or modification of protocols to conduct angiography immediately following endoscopy should be considered. Further, standardization of technique is also important with respect to embolic(s) used and method of embolization. As suggested by Loffroy et al, variations may contribute to varied rebleeding risk, and few authors from prior literature have specified procedure details[14,27]. Finally, stratification based on lesion type and size should also be performed, as the post-hoc analysis by Lau et al suggested that PTAE reduced rebleeding risk in ulcers greater than 15mm[8]. Additional clinical trials with long-term clinical outcomes are needed to confirm these observations.

Conclusion

PTAE compared to observation alone appears to safely reduce the risk of rebleeding, need for surgical intervention, and morality in high-risk peptic ulcers after successful endoscopic hemostasis. Future studies should aim to increase the sample size and resources for performing endovascular interventions.

Abbreviations

Endoscopy-only (EO); Prophylactic transarterial embolization (PTAE); retrospective cohort (RC); randomized-controlled trial (RCT); transcatheter arterial embolization (TAE); Upper gastrointestinal bleed (UGIB)

Declarations

Ethics approval and consent to participate: Not applicable, as this is a systematic review and meta-analysis.

Consent for publication: Not applicable, as this is a systematic review and meta-analysis.

Availability of data and materials: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request

Competing interests: None.

Funding: None

Authors' contributions:

QY: manuscript writing, data collection, statistical analysis

CL: manuscript writing, data collection, statistical analysis

MP: data collection, manuscript reviewing

OA: manuscript writing, reviewing, supervision

Acknowledgements: None

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Figures

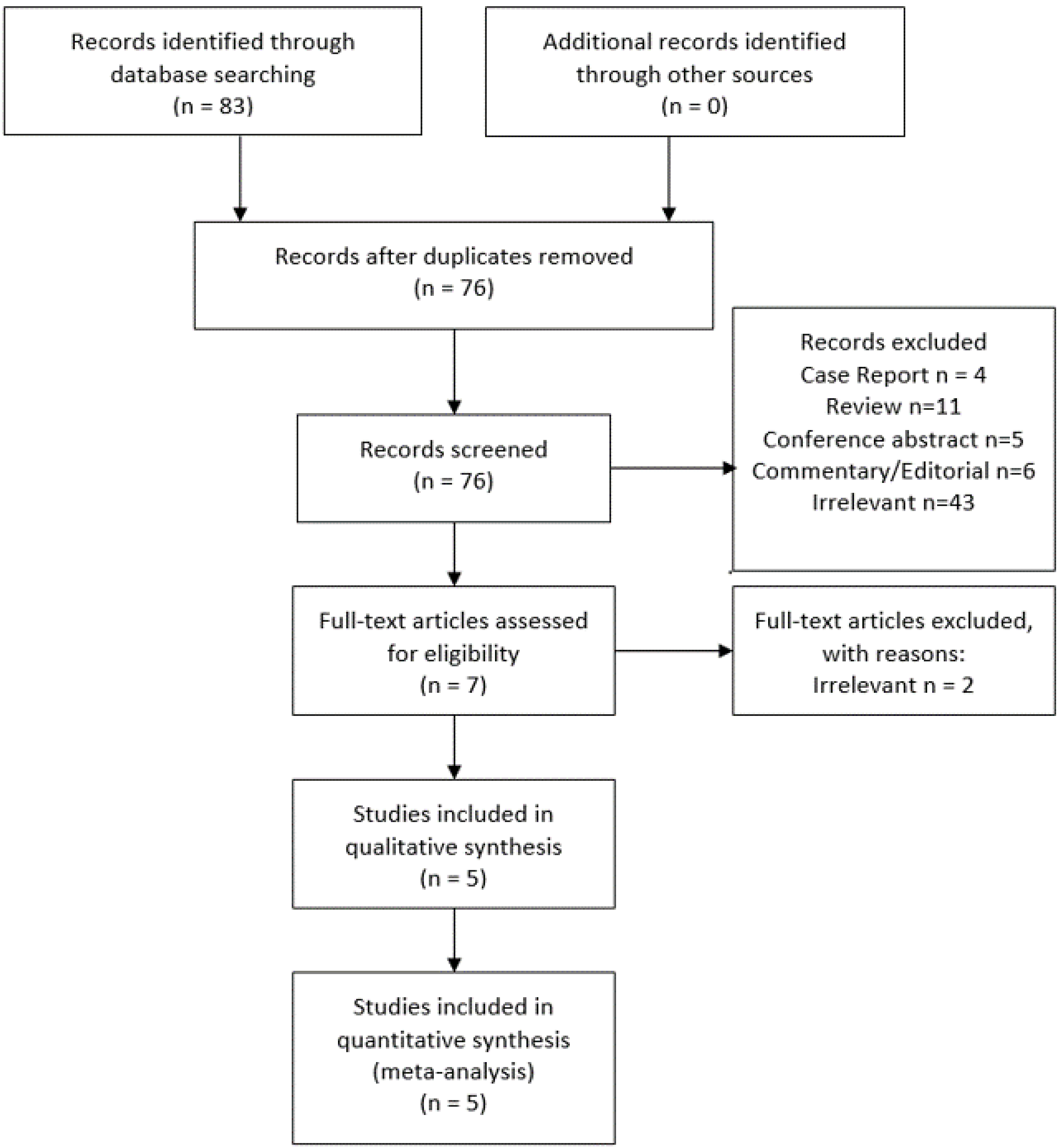
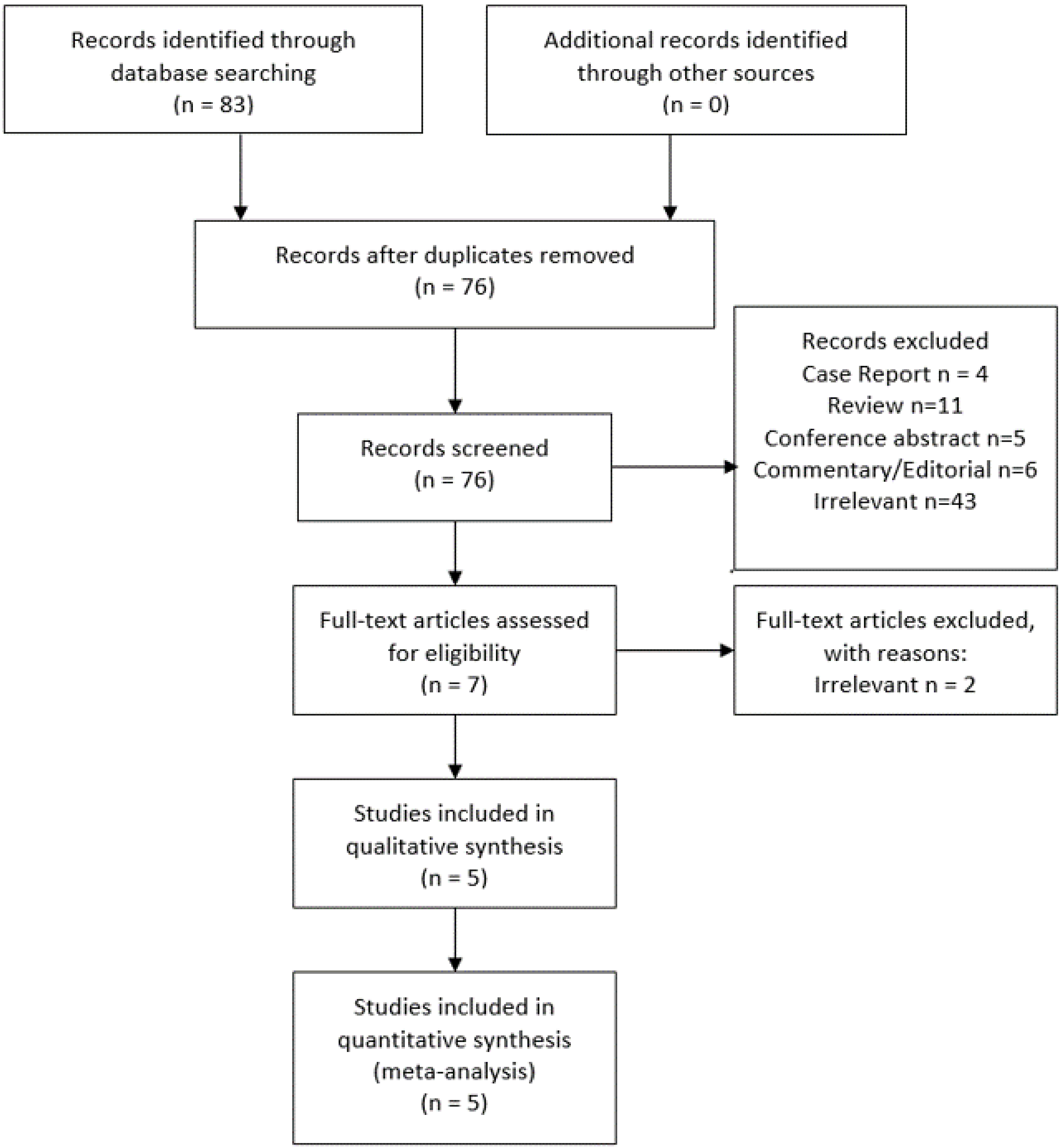


Figure 1

Flow-Diagram of the screening process



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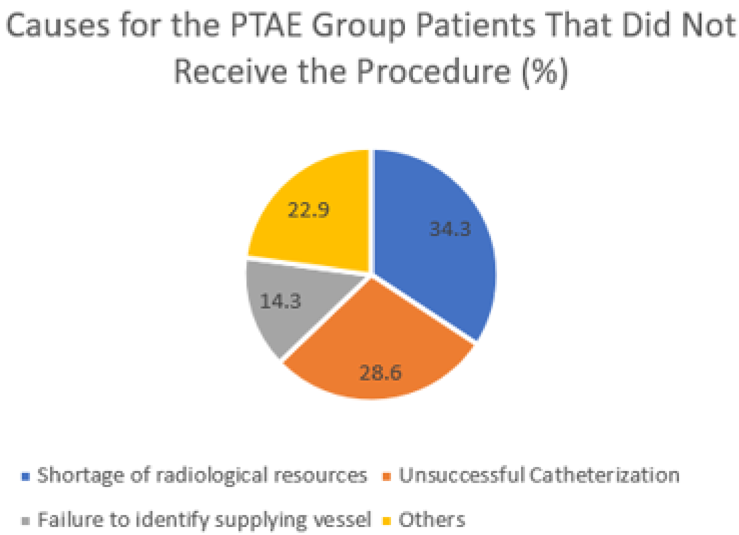


Figure 2

Reasons for failure to receive embolization among patients allocated to PTAE.

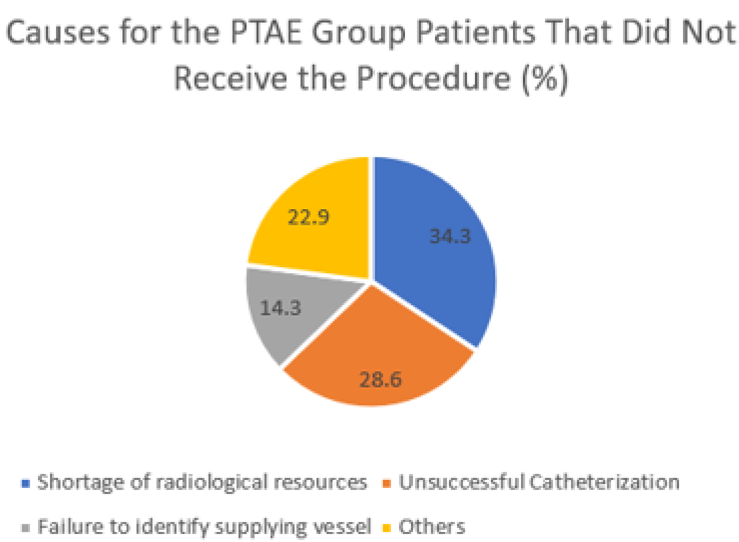

Causes for the PTAE Group Patients That Did Not Receive the Procedure (%)
22.9
34.3
14.3
28.6
Shortage of radiological resources
Unsuccessful Catheterization
Failure to identify supplying vessel
Others

Figure 2

Reasons for failure to receive embolization among patients allocated to PTAE.

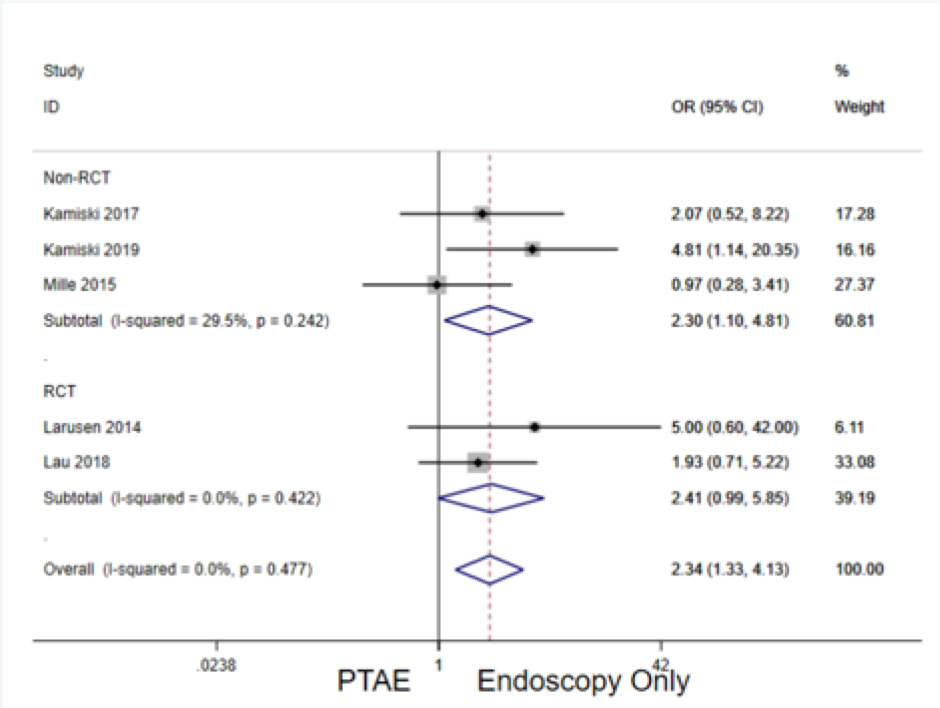
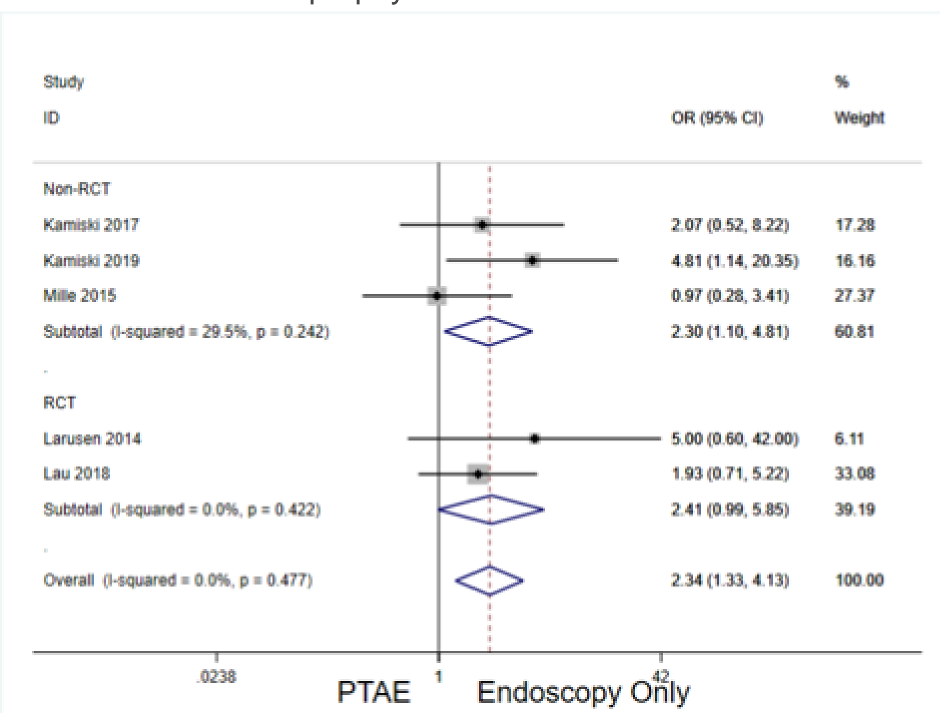


Figure 3

Forest plot for OR comparing rebleeding between PTAE and EO groups (overall: 2.34 [95%CI: 1.33-4.13], p=0.003. A fixed-effect model was implemented (I2=0.0%). CI: confidence interval. EO: endoscopy only. OR: odds ratio. PTAE: prophylactic transcatheter embolization.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Forest plot for OR comparing rebleeding between PTAE and EO groups (overall: 2.34 [95%CI: 1.33-4.13], p=0.003. A fixed-effect model was implemented (I2=0.0%). CI: confidence interval. EO: endoscopy only.

OR: odds ratio. PTAE: prophylactic transcatheter embolization.

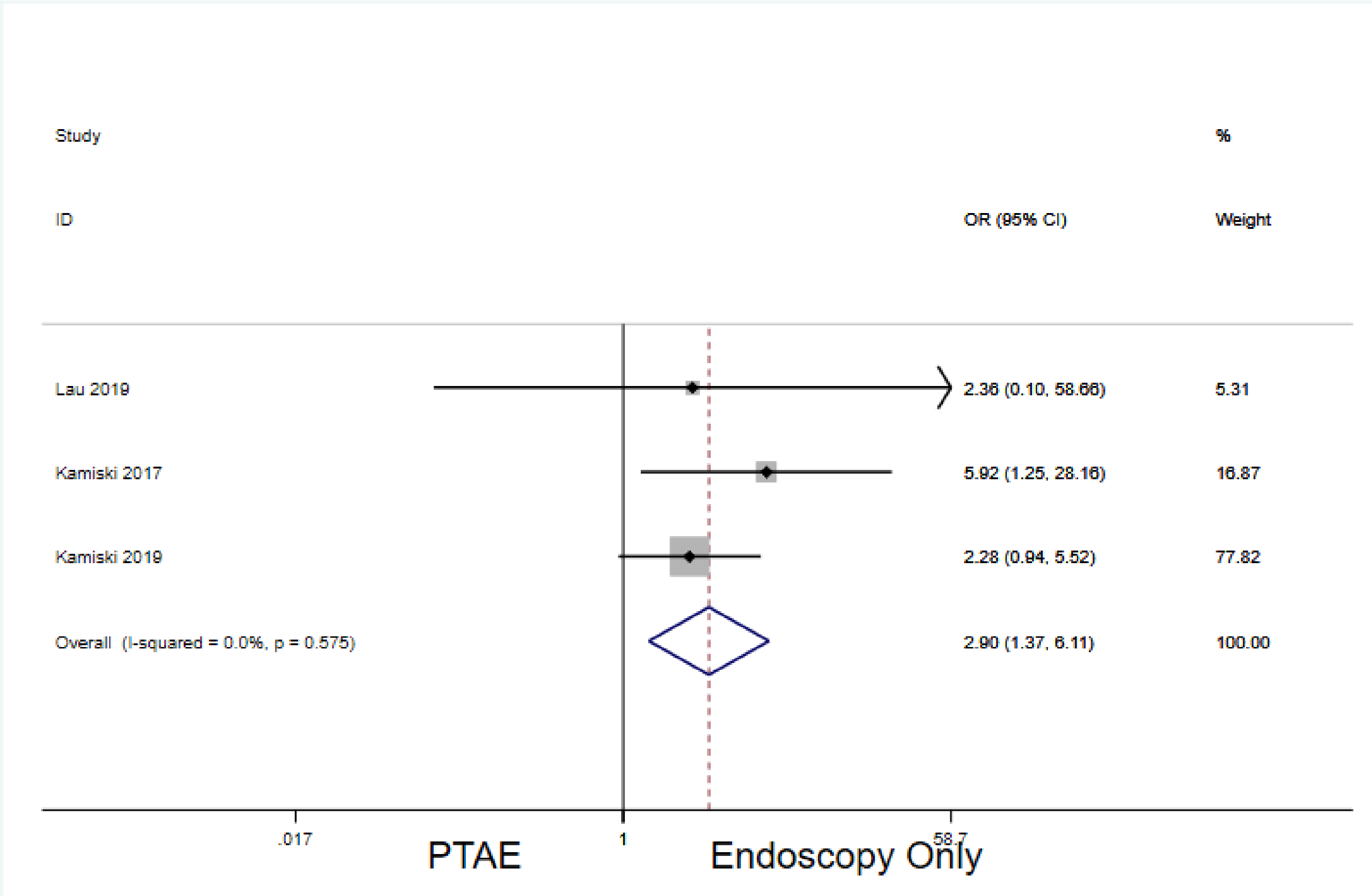


Figure 4

Forest plot for OR comparing the need of surgery between PTAE and EO groups (OR: 2.898 95%CI [1.374-6.112], p=0.005). A fixed-effect model was implemented I2=0.0%. CI: confidence interval. EO: endoscopy only. OR: odds ratio. PTAE: prophylactic transcatheter embolization.

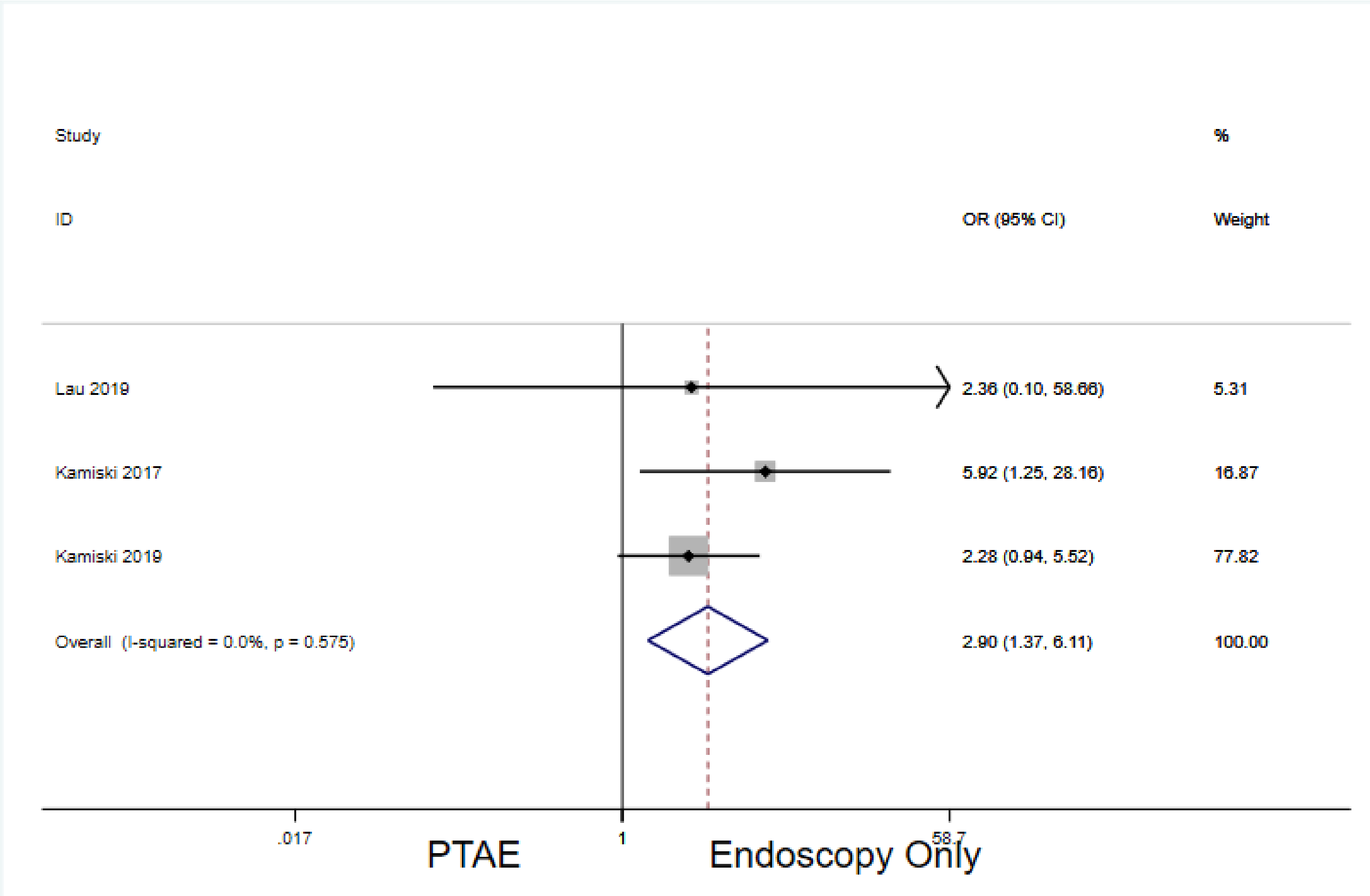


Figure 4

Forest plot for OR comparing the need of surgery between PTAE and EO groups (OR: 2.898 95%CI [1.374-6.112], p=0.005). A fixed-effect model was implemented I2=0.0%. CI: confidence interval. EO: endoscopy only. OR: odds ratio. PTAE: prophylactic transcatheter embolization.

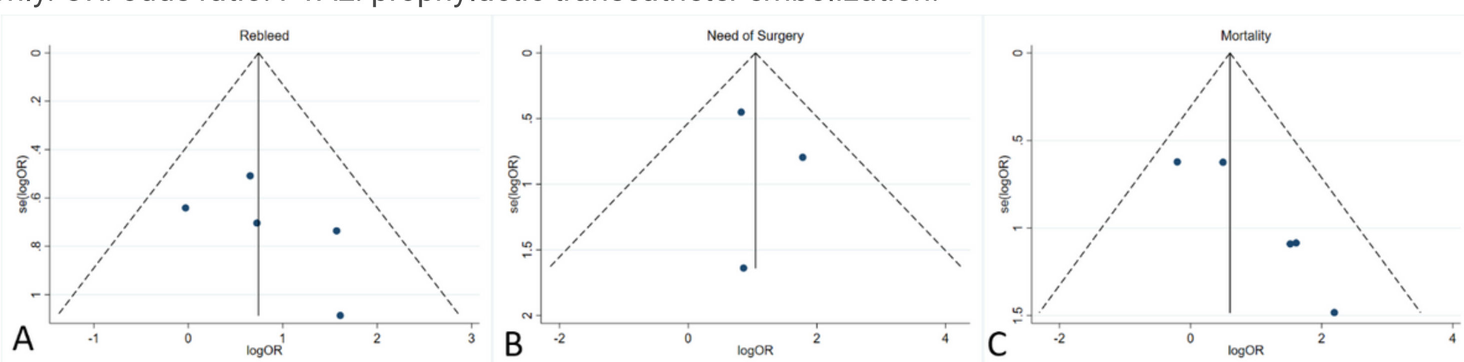
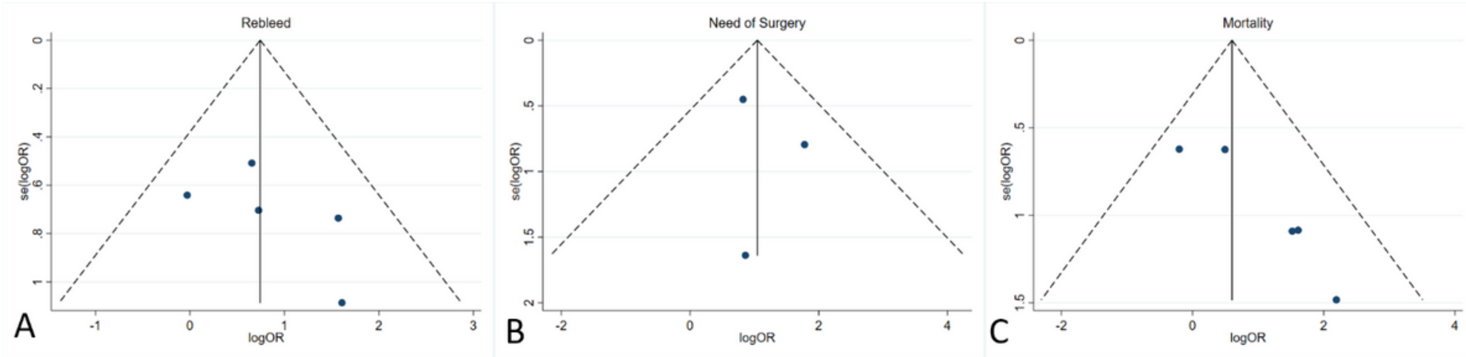


Figure 5

Funnel plots were implemented to evaluate publication bias. A: Odds ratio (OR) of rebleeding after prophylactic transcatheter embolization (PTAE) and endoscopy-only (EO). B: OR of surgical requirement after PTAE and EO. C: OR of mortality after PTAE and EO.



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Supplementary Files

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- SupplmentClark.docx
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