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To cite this version:

Olivier Chevallier, Pierre-Olivier Comby, Kevin Guillen, Julie Pellegrinelli, Thomas Mouillot, et al.. Efficacy, safety and outcomes of transcatheter arterial embolization with N-butyl cyanoacrylate glue for non-variceal gastrointestinal bleeding: A systematic review and meta-analysis. Diagnostic and Interventional Imaging, 2021, 102 (7-8), pp.479-487. 10.1016/j.diii.2021.03.004 . hal-03613338

HAL Id: hal-03613338

https://hal.science/hal-03613338v1

Submitted on 2 Aug 2023

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Version of Record: https://www.sciencedirect.com/science/article/pii/S2211568421000814
Manuscript_2031961ec537f00182c8079021372384

Efficacy, safety and outcomes of transcatheter arterial embolization with N-butyl cyanoacrylate glue for non-variceal gastrointestinal bleeding: a systematic review and meta-analysis

Short title:

Transcatheter arterial embolization with N-butyl cyanoacrylate glue for non-variceal gastrointestinal bleeding

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Abstract

Purpose: To perform a systematic review and meta-analysis to determine the safety, efficacy, and outcomes of transcatheter arterial embolization (TAE) with N-butyl cyanoacrylate (NBCA) as the single embolic agent for the management of non-variceal upper and lower gastrointestinal bleeding (GIB).

Materials and methods: A literature search using MEDLINE/PubMed, EMBASE, and SCOPUS databases was performed for studies published from January 1980 to December 2019. Data from eligible studies were extracted and evaluated by two independent reviewers. Exclusion criteria were sample size <5, article reporting the use of NBCA with other embolic agents, no extractable data, and duplicate reports. Technical success, clinical success, 30-day rebleeding, 30-day overall and major complications, and 30-day mortality were evaluated. The estimated overall rates were calculated with their 95% confidence intervals, based on each study rate, weighted by the number of patients involved in each study. Heterogeneity across studies was assessed using the Q test and I^2 statistic.

Results: Fifteen studies with 574 patients were included. For upper GIB (331 patients), the technical and clinical success rates, and 30-day rebleeding and mortality rates, were 98.8% (328 of 331 patients) and 88.0% (237 of 300 patients), and 12.5% (69 of 314 patients) and 15.9% (68 of 331 patients), respectively. Thirty-day overall and major complications occurred in 14.3 % (28 of 331 patients) and 2.7% (7 of 331 patients) of patients, respectively. For lower GIB (243 patients), the technical and clinical success rates, and 30-day rebleeding and mortality rates, were 98.8% (78 of 78 patients) and 78.0% (145 of 189 patients), and 15.7% (33 of 218 patients) and 12.7% (14 of 78 patients), respectively. Thirty-day overall and major complications occurred in 13.0% (25 of 228 patients) and 8.6% (19 of 228 patients) of patients, respectively.

Conclusion: TAE with NBCA is safe and effective for treating non-variceal GIB, with high clinical success and very low major complication rates.

Keywords

1. Gastrointestinal hemorrhage;

2. Embolization, Therapeutic;

3. Cyanoacrylates;

4. Meta-analysis

Abbreviations

CI: Confidence interval; EC: European Community; GIB: Gastrointestinal bleeding; LCL: Lower confidence limit; LGIB: Lower gastrointestinal bleeding; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; NBCA: N-butyl cyanoacrylate;

TAE: Transcatheter arterial embolization;UF: Ultra fluid;UCL: Upper confidence limit;UGIB: Upper gastrointestinal bleeding

1. Introduction

Although acute non-variceal gastrointestinal bleeding (GIB) usually resolves spontaneously or responds to conservative medical management, some patients require endoscopic treatment, transcatheter arterial embolization (TAE) or, in some instances, surgical hemostasis [1–4]. TAE has been proven effective in controlling bleeding and decreasing mortality when endoscopy cannot achieve hemostasis in patients with refractory upper GIB (UGIB) or lower GIB (LGIB) [5–7]. Several hemostatic or embolic agents may be used, such as vascular coils, gelatine sponge, and particles [7–9]. However, the choice of the best embolic agent is still debated. Liquid adhesive agents, especially N-butyl cyanoacrylate (NBCA), have produced very good results in both UGIB and LGIB [10–12]. NBCA is a liquid embolic agent that polymerises in contact with ion-rich fluids such as blood. It has several advantages over other embolic agents. Its quick administration and rapid polymerisation allow fast hemostasis, which is highly useful in patients with hemodynamic instability or massive focal bleeding [13, 14]. Due to its liquid nature, NBCA allows distal embolization through a flow-directed strategy, particularly of small or tortuous arteries that are difficult to catheterise [15]. Furthermore, it remains effective despite coagulopathy, which is common in GIB [4, 10–12]. Before administration, NBCA need to be mixed with iodized oil (Lipiodol® Ultra Fluid (UF);

Guerbet, Roissy-Charles de Gaulle, France) to make it radiopaque and to delay its polymerisation rate [16, 17]. Although the outcomes of TAE with NBCA for the treatment of non-variceal bleeding have been reported [10–13], most of the data has come from small studies, and NBCA remains underutilised both overall and for TAE in GIB, due to concern about the risk of reflux during the injection and of nontarget embolization with potential ischemic bowel complications [18]. A meta-analysis therefore appeared mandatory to clarify the role of NBCA for TAE in GIB.

The goal of this study was to perform a systematic review and a meta-analysis of published studies to assess the safety, efficacy, and outcomes of TAE with NBCA as the only embolic agent for the management of non-variceal UGIB and LGIB.

2. Materials and methods

Institutional review board approval was not required for this retrospective assessment of published data, in accordance with our country legislation. The analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

2. 1. Search strategy

A literature search using the MEDLINE/PubMed, EMBASE, and SCOPUS databases was performed in March 2020 to identify relevant studies published from January 1980 to December 2019. The search terms were: "(lipiodol OR oil OR ethiod OR poppyseed oil) AND (glue OR cyanoacrylate OR histoacryl OR nbca OR enbucrilate OR enbucrylate OR glubran) AND (bleeding OR hemorrhage) AND (gastrointestinal OR gi OR intestinal OR gastric) AND (embolization OR embolisation OR sclerotherapy OR embolization, therapeutic [MeSH Terms]) AND (human OR patient)". A few additional studies were found through a manual search of reference lists of other studies and of articles from previous searches. Duplicate publications were identified by juxtaposing author names, study dates, treatment comparisons, sample sizes, or outcomes, and were then excluded.

2. 2. Inclusion and exclusion criteria

Two interventional radiologists reviewers with 15 (RL) and 5 (OC) years of experience, respectively, working independently of each other performed the literature search and selected the eligible articles. Disagreements were resolved by consensus.

The selected studies were required to meet the following inclusion criteria: 1) original research article written in English; 2) the study participants were human; 3) prospective and retrospective studies; 4) patients underwent TAE with NBCA-Lipiodol® UF mixture alone for GIB; 5) article presented outcomes of TAE with NBCA-Lipiodol® UF mixture for at least 5 patients; 6) data and results concerning both UGIB and LGIB were clearly identified and distinguishable.

Studies meeting the following criteria were excluded: 1) review articles, letters to the editor, editorials, abstracts, chapters contained within a book, case reports; and preclinical studies; 2) publications that reported data on fewer than 5 patients; 3) articles reporting mixed results from different techniques or results from only combined embolic agents or other techniques; 4) articles presenting no clear results for TAE with NBCA-Lipiodol® UF mixture in at least 5 patients or showing duplicate results; 5) articles presenting data and results from UGIB and LGIB that were not clearly identified and distinguishable.

First, the article titles and abstracts were reviewed. Second, full-text articles were assessed for eligibility. Finally, articles related to variceal GIB were excluded to be analysed in a separate meta-analysis to come.

2. 3. Data extraction and definition

The following data were recorded from the included full-text articles: first author, publication year, study country, study design (prospective versus retrospective, comparative or not, randomised or not), and bleeding location (UGIB or LGIB). For all studies and each arm of comparative studies, the following data were extracted separately for both UGIB and LGIB: number of analysed patients, percentage of male patients, mean patient age, type of NBCA glue, NBCA-Lipiodol® UF ratio, technical success, clinical success, 30-day rebleeding, 30-day overall and major complications, and 30-day mortality.

The clinical endpoints were as follows: technical success (defined as total occlusion of the target vessel), clinical success (defined as no rebleeding within 30 days of TAE), 30-day rebleeding, 30-day overall and major (defined according to the Society of Interventional

Radiology guidelines) complications [20], and 30-day mortality. Minor complications result in no consequence and no therapy or nominal therapy and include overnight admission for observation only. Major complications were defined as complications resulting in minor hospitalization (<48 hours) and therapy, or requiring major therapy and an unplanned increase in the level of care and prolonged hospitalization, or resulting in permanent adverse sequelae or death [20].

2. 4. Statistical analyses

The different rates of interest (technical success, clinical success, 30-day rebleeding, 30-day overall complications, 30-day major complications, and 30-day mortality) were reported for each study with their 95% confidence interval (95%CI) calculated using the Clopper exact method. The estimated overall rates were calculated with their 95%CI, based on each study rate weighted by the number of patients involved in each study, with random effect modelling. A forest plot was drawn for each rate of each study and for each overall estimated rate, with their corresponding 95%CIs. Heterogeneity across studies was assessed using the Q test and I^2 statistic. A significant Q test demonstrated heterogeneity across studies. I^2 statistic values were interpreted as follows: 0% to 40%, heterogeneity might not be important; 30% to 60%, possible moderate heterogeneity; 50% to 90%, possible substantial heterogeneity; and 75% to 100%, considerable heterogeneity [21].

Statistical analyses were performed by an expert statistician with 30 years of experience (SAG) using MedCalc for Windows, version 19.2.6 (MedCalc Software, Ostend, Belgium).

3. Results

3. 1. Article selection and patient characteristics

Figure 1 shows the PRISMA flow diagram for the inclusion/exclusion of studies. Fifteen studies were ultimately included in the meta-analysis [10, 12, 13, 22–33]. Among these studies, 14 were conducted in Asia (Japan, South Korea and Taiwan) and 1 in the USA. There were 2 prospective cohort studies and 13 retrospective studies including 2 comparative studies and 11 single-arm cohort studies. There was no randomised controlled trial. The study periods ranged from 1999-2002 to 2005-2017 [25, 27]. Among the total of 644 patients included in these studies, 70 patients who were treated with other embolic agents than NBCA-Lipiodol® UF mixture were excluded, leaving 574 patients for the analysis. Mean age was 64.1 years

and there were 413 (72%) men and 161 (28%) women. Table 1 reports the main characteristics of the studies and patients. Nine studies dealt with UGIB, 5 studies with LGIB, and one study with both. Three hundred thirty-one patients presented UGIB (mean age, 65.5 years; 71.9% of men) and 243 patients presented LGIB (mean age, 62.3 years; 72.2% of men).

3. 2. Types of NBCA glue and NBCA-Lipiodol® UF ratio used

The types of NBCA glue and the NBCA-Lipiodol® UF mixture ratio used in the included studies were as follows. Histoacryl® (B. Braun, Melsungen, Germany) was the most used NBCA glue (11 studies; 439 patients) [10, 13, 23, 25, 27, 28–33]. The type of NBCA glue used was not specified in 4 studies (135 patients) [12, 22, 24, 26]. The most used NBCA-Lipiodol® UF mixture ratio range was 1:1 to 1:4, in 14 studies involving 526 patients [10, 13, 25, 27–33]. Other ratio ranges were 1:1 to 1:5 in 1 study (21 patients) [33] and 1:1.5 to 1:9 in 1 study (27 patients) [23].

3. 3. Technical and clinical outcomes

For UGIB, data on technical and clinical outcomes were available for 10 studies [10, 13, 22, 27–33] and 8 studies [13, 22, 27, 29–33], respectively. Technical success was achieved in 328 (98.8%) of 331 patients (95% CI: 97.1%–99.7%) (Fig. 2a) with no significant heterogeneity (P = 0.38; I^2=6.8%). Clinical success was achieved in 237 (88.0%) of 300 patients (95% CI: 77.5%–95.5%), with possible substantial heterogeneity to considerable heterogeneity (P < 0.0001; I^2 = 79.3%) (Fig. 2.b).

For LGIB, data on technical and clinical outcomes were available for 4 studies [12, 23, 26, 33] and 4 studies [24–26, 33], respectively. Technical success was achieved in 78 (98.8%) of 78 patients (95%CI, 95.3%-99.9%; Fig. 3a) with no significant heterogeneity (P = 1.00; I^2 = 0.0%). Clinical success was achieved in 145 (78.0%) of 189 patients (95% CI: 68.3%–86.3%), with possible moderate heterogeneity to substantial heterogeneity (P = 0.11; I^2 = 50.3%) (Fig. 3b). Table 2 reports the pooled technical and clinical success rates for each study.

3. 4. 30-day rebleeding and mortality rates

For UGIB, data on the 30-day rebleeding rate were available in 9 of the 10 studies. Thirty-day rebleeding occurred in 69 (12.5%) of 314 patients (95% CI: 4.8%–23.2%) [10, 13, 22, 27, 29–33], with possible substantial heterogeneity to considerable heterogeneity across studies (P < 0.0001; I^2 = 80.9%) (Fig. 2c). Data on the 30-day mortality rate were available in 10 of the 10 studies (331 patients) [10, 13, 22, 27–33]. The 30-day mortality rate was 15.9% (95% CI: 8.3%–25.3%), with possible substantial heterogeneity (P = 0.0002; I^2 = 72.3%) (Fig. 4a).

For LGIB, data on the 30-day rebleeding rate were available in 6 of the 6 studies. Thirty-day rebleeding occurred in 33 (15.7%) of 218 patients (95%CI: 11.2%–20.8%) [12, 23–26, 33], with possible substantial heterogeneity to considerable heterogeneity across studies (P < 0.0001; I^2 = 80.9%) (Fig. 3c). Data on the 30-day mortality rate were available in 4 of the 6 studies (78 patients) [12, 23, 26, 33]. The 30-day mortality rate was 12.7% (95% CI, 0.7%–36.1%), with possible substantial to considerable heterogeneity (P = 0.0002; I^2 = 84.8%) (Fig. 5a). Table 2 reports the pooled 30-day rebleeding and mortality rates by study.

3. 5. Overall and major complication rates

For UGIB, data on 30-day complications were available for 10 studies including 331 patients [10, 13, 22, 27–33]. Thirty-day overall complications occurred in 28 (14.3%) of 331 patients (95% CI: 2.8%-32.6%), with considerable heterogeneity (P < 0.0001; I^2 = 92.6%) (Fig. 4b). Thirty-day major complications occurred in 7 (2.7%) of 331 patients (95%CI: 0.6%–6.1%), with possible moderate heterogeneity (P = 0.05; I^2 = 46.1%) (Fig. 4c).

For LGIB, data on 30-day complications were available for 5 studies including 228 patients [12, 23–25, 33]. Thirty-day overall complications occurred in 25 (13.0%) of 228 patients (95% CI: 3.8%–26.7%), with possible substantial heterogeneity to considerable heterogeneity (P < 0.0001; I^2 = 84.2%) (Fig. 5b). Thirty-day major complications occurred in 19 (8.6%) of 228 patients (95% CI: 3.4%–15.8%), with possible substantial heterogeneity (P = 0.04; I^2 = 60.3%) (Fig. 5c). Table 3 shows the pooled 30-day overall complication and major complication rates by study.

Seven studies reported gastrointestinal (GI) ischemic complications resulting from the use of NBCA glue [10, 12, 22, 24, 25, 32, 33]. Digestive ischemic complications were reported in 9 and 26 patients for UGIB and LGIB, respectively. Table 4 shows all the reported complications. In addition, 2 patients developed ischemic ulcers that were discovered after

hemicolectomy for repeat lower GIB after TAE [24]. Follow-up endoscopy after TAE was performed only in some patients in some studies [10, 23, 25–27, 29, 31–33] and routinely in others [12, 22, 30]. Furthermore, some authors specified only that no serious ischemic complications occurred [27], no symptoms or signs of GI ischemia or clinically significant GI stenosis or obstruction occurred [10], or no symptomatic GI ischemia, stenosis or obstruction occurred [32].

4. Discussion

Our meta-analysis of 15 studies involving 574 patients demonstrates that the use of NBCA-Lipiodol® UF mixture for TAE of non-variceal UGIB and LGIB patients is safe and efficient, with respectively a very high technical success rate of 98.8% (95% CI: 97.1%–99.7%) and 98.8% (95% CI: 95.3%–99.9%), a high clinical success rate of 88.0% (95%CI: 77.5%–95.5%) and 78.0% (95% CI: 68.3%–86.3%), a low 30-day rebleeding rate of 12.5% (95% CI, 4.8%–23.2%) and 15.7% (95% CI: 11.2%–20.8%), and a low risk of 30-day major complications of 2.7% (95% CI: 0.6%–6.1%) and 8.6% (95% CI: 3.4%–15.8%), respectively.

Only few studies reporting the safety and efficacy of NBCA-Lipiodol® UF mixture for TAE of non-variceal GIB were found, and most of these studies were conducted in Asia. The only other systematic review and meta-analysis of the safety and efficacy of NBCA-TAE for GIB included 15 studies [34]; 4 of these studies were not included in our meta-analysis because they reported outcomes of fewer than 5 patients or pooled different techniques or embolization agents [35–38]. Our results are consistent with those of this previous meta-analysis. Our study demonstrated slightly higher clinical success and lower major complications rates for UGIB, slightly lower clinical success and higher major complications rates for LGIB. NBCA-Lipiodol® UF mixture for TAE of non-variceal GIB produced similar clinical success rates to those reported with other embolic agents [8, 9, 39–47]. In one study, for all embolic agents combined, the TAE clinical success rate was 67% for UGIB and 76% for LGIB, with rebleeding rates of 33% and 24%, respectively [48]. With NBCA, a noticeably lower rebleeding rate of 12.5% and 15.7% for respectively UGIB and LGIB was found in our study. Unfortunately, 2 others studies were not included in our meta-analysis since results from UGIB and LGIB were not distinguishable [11, 50].

The rate of major complications in our study was also consistent with previous reports, with a higher rate in LGIB group [8, 39, 40, 43, 49, 51–54]. The risk of GI ischemic complications after NBCA glue embolization has always been a major concern. Seven studies that reported

GI ischemic complications resulting from the use of NBCA in 35 patients were found in our study [10, 12, 22, 24, 25, 32, 33]. However, many of these ischemic complications were discovered during follow-up endoscopy and most of them resolved spontaneously. Only 3 to 9 patients required surgery, all of them in LGIB group, 3 because of extensive vascular occlusion, including 2 preventive appendectomies, one because of bowel perforation, and 0 to 6 because of transmural bowel infarction (resulting in surgery or death within 30 days) [12, 24, 25]. However, ischemic damage may have been underestimated since endoscopy was not performed routinely in all studies. Bowel ulcerations resulting from NBCA-induced ischemia can be managed conservatively in most patients and therefore do not constitute true major complications. Our data suggest that NBCA-Lipiodol® UF mixture may not cause a higher number of relevant ischemic complications compared to other commonly used embolic agents. Histoacryl® was the most widely used NBCA glue, although it has not received the European Community (EC) mark and is not approved by the Food and Drug Administration [10, 13, 23, 25, 27, 28–33]. The type of NBCA glue was not specified in the other four studies [12, 22, 24, 26]. Glubran®2 (GEM Srl, Viareggio, Italy), the only EC-marked glue for endovascular administration, was used in another study [50]. With Glubran®2, the comonomer methacryloxysulfolane is added to produce a more pliable and stable polymer with a lower polymerisation temperature and less cytotoxicity than Histoacryl® [4, 50]. Thus, Glubran®2 may result in a less potent inflammatory reaction and therefore carry a lower risk of pain.

One of the main findings of this meta-analysis was the low reported rate of bowel ischemic complications requiring surgery. Indeed, whereas most of interventional radiologists are afraid of using glue for GIB, embolization with NBCA may be associated with lower rates of major complications. It can be explained by the fact that it is usually technically easier to perform superselective arterial embolization with liquids such as NBCA than with other embolic agents, avoiding extensive and non-target embolization [15].

NBCA embolization continues to be viewed with some circumspection due to reported risks of glue migration into nontarget arteries and of microcatheter blockage by NBCA. But bowel infarction is only a theoretical concern. Indeed, NBCA has been reported as an effective embolic material with favorable outcome for UGIB and LGIB in the present meta-analysis. This can be explained by the characteristics of NBCA. The glue/Lipiodol® ratio affects the viscosity of the liquid and the glue polymerization time. It is recommended to adjust the ratio to the length of the segment to be occluded. Thus, the mixture has sufficient low viscosity to

allow distal embolization of the feeding artery but at the same time it is viscous enough to prevent the embolic agent from propagating too far into the capillary bed, preserving circulation in the distal post-embolic tissue via collateral channels in the intramural microcirculation [15, 27]. Glue/ Lipiodol® has several other advantages. Lipiodol® makes the NBCA/lipiodol mixture radio-opaque, allowing for easier control under fluoroscopy, compared with other embolic materials which are not directly visualized such as particles [15]. In addition, NBCA is a liquid and can therefore be used to occlude vessels in which the microcatheter cannot be advanced. This situation is particularly frequent in LGIB. The shorter procedural time with NBCA compared to microcoil embolization is also particularly valuable in patients with life-threatening bleeding. Last, NBCA can be more efficient than other embolic agents in patients with coagulopathy, polymerization of glue in contact with blood being not dependent of coagulation status of the patient [15]. Of course, it is important to take a number of precautions designed to minimize the complication rate. Flushing the microcatheter before the injection with dextrose to remove all ionic solutions and promptly pulling the catheter back after the injection to avoid adhesion to the vessel and trapping of glue are important [10]. Wedging the catheter and injecting contrast alone before the glue to calculate the volume needed have been also recommended [14,18].

The strengths of this meta-analysis include the comprehensive literature search strategy and robust methodology, as well as the reporting of results in accordance with PRISMA guidelines. However, our analysis had several limitations. First, among the 15 included studies, 13 were retrospective case series. However, the 2 prospective studies included in the analysis demonstrated similar results with very high technical and clinical success rates and low complication rates [26, 27]. Second, a considerable variability across studies in the definitions of the main variables and outcomes was found. The definitions of technical success differed only slightly, but the definitions of clinical success varied considerably. To minimise the impact of this variability, similar definitions for the main outcomes of interest were applied. Third, heterogeneity in the embolization occurred across studies. Thus, variations occurred in the type of NCBA glue and in the NBCA-Lipiodol® UF ratio. Fourth, significant heterogeneity in the results occurred across studies for all outcomes except technical success. However, a random effect model was used to minimise this source of bias. Fifth, publication bias may have occurred, since negative results are often not published. Sixth, the quality of the included studies was not assessed. Finally, early ischemic GI complications and late complications such as intestinal stenosis may have been missed or

underestimated, as most patients did not undergo routine endoscopy after TAE or had only short follow-ups.

In conclusion, the present meta-analysis of 15 studies involving 574 patients demonstrated that the use of NBCA for TAE of non-variceal UGIB and LGIB was safe and effective, with a very high technical success rate, high clinical success rate, and low risk of major complications. Randomised trials are warranted to compare NBCA glue with other embolic agents, and to compare different types of NBCA glue.

Informed consent and patient details

Institutional ethic committee approval is not required for systematic review and meta-analysis

Disclosure of interest

The authors declare that they have no competing interest.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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Table & Figure legends

Table 1. Characteristics of the studies included in the meta-analysis.

Table 2. Technical success, clinical success, 30-day rebleeding and mortality rates by study in patients treated with NBCA-Lipiodol® Ultra Fluid mixture for non-variceal gastrointestinal bleeding.

Table 3. Thirty-day overall complication and major complication rates by study in patients treated with NBCA-Lipiodol® Ultra Fluid mixture for non-variceal gastrointestinal bleeding.

Table 4. Types of reported complications in patients treated with NBCA-Lipiodol® Ultra Fluid mixture for non-variceal gastrointestinal bleeding

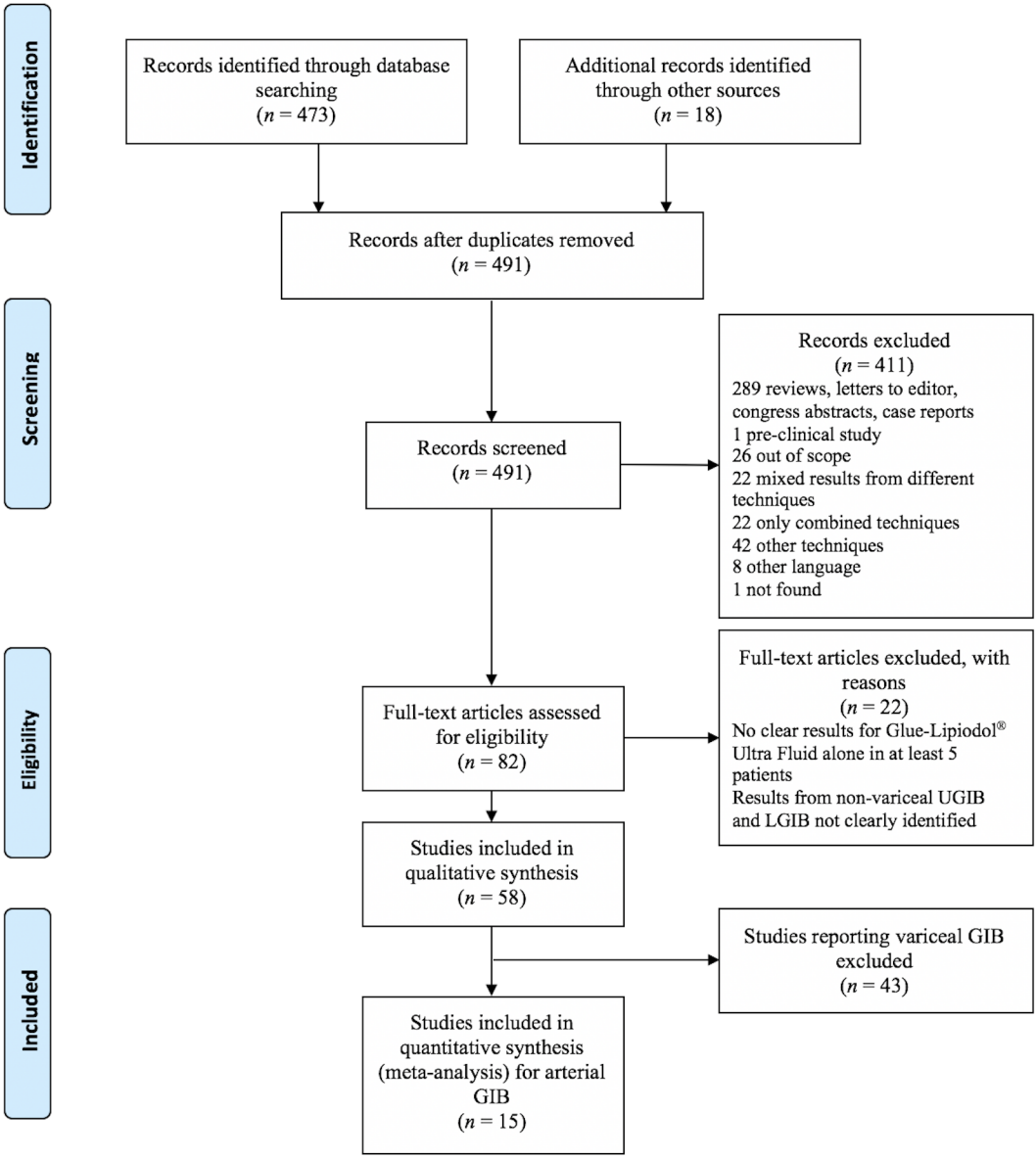
Figure 1. PRISMA flow diagram of the article selection process. GIB, gastrointestinal bleeding

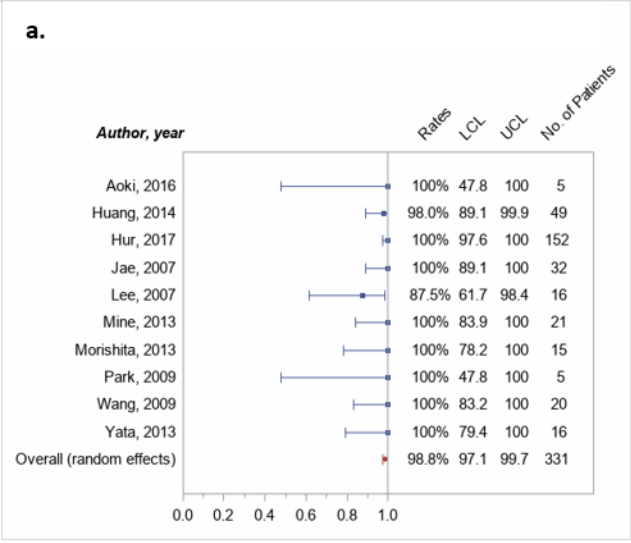
Figure 2. Forest plots of technical success (a), clinical success (b) and 30-day rebleeding (c) rates by study for UGIB. UCL, upper confidence limit; LCL, lower confidence limit

Figure 3. Forest plots of technical success (a), clinical success (b) and 30-day rebleeding (c) rates by study for LGIB. UCL, upper confidence limit; LCL, lower confidence limit

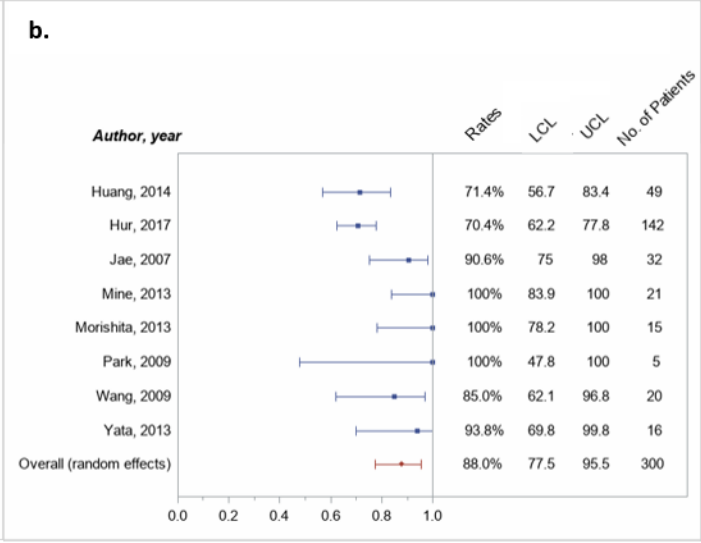
Figure 4. Forest plots of 30-day mortality (a), 30-day complications (b) and 30-day major complications (c) rates by study for UGIB. UCL, upper confidence limit; LCL, lower confidence limit

Figure 5. Forest plots of 30-day mortality (a), 30-day complications (b) and 30-day major complications (c) rates by study for LGIB. UCL, upper confidence limit; LCL, lower confidence limit.

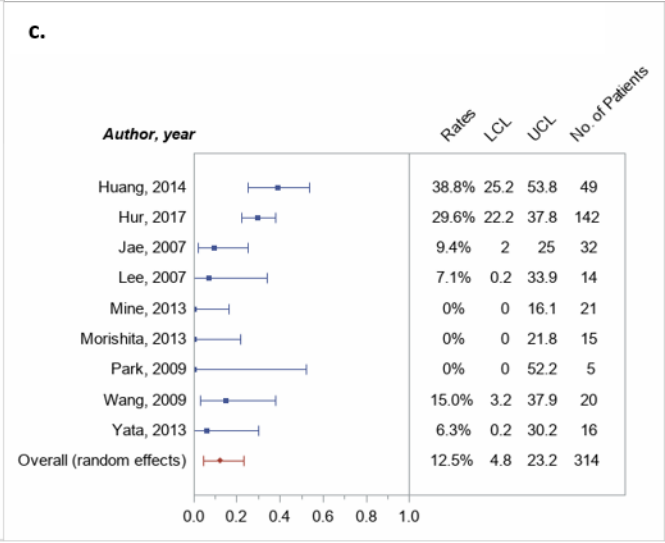

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 473)
Additional records identified through other sources (n = 18)
Records after duplicates removed (n = 491)
Records screened (n = 491)
Records excluded (n = 411)
289 reviews, letters to editor, congress abstracts, case reports
1 pre-clinical study
26 out of scope
22 mixed results from different techniques
22 only combined techniques
42 other techniques
8 other language
1 not found
Full-text articles assessed for eligibility (n = 82)
Full-text articles excluded, with reasons (n = 22)
No clear results for Glue-Lipiodol® Ultra Fluid alone in at least 5 patients
Results from non-variceal UGIB and LGIB not clearly identified
Studies included in qualitative synthesis (n = 58)
Studies reporting variceal GIB excluded (n = 43)
Studies included in quantitative synthesis (meta-analysis) for arterial GIB (n = 15)



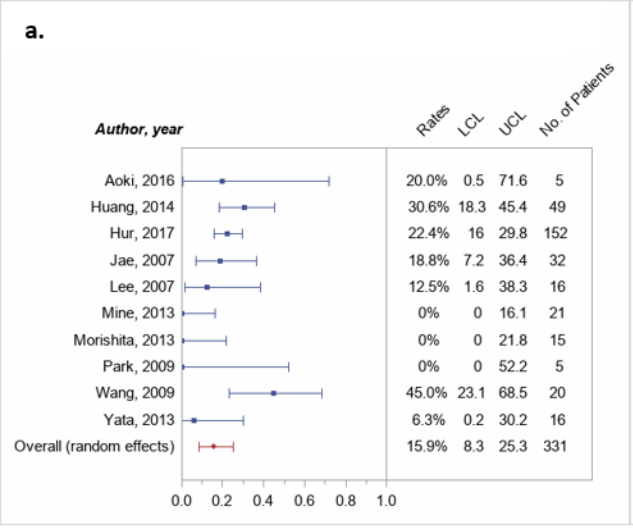
Technical success
Overall rate (random effects model): 98.8% (95% CI: 97.1%-99.7%)
Heterogeneity: Q=9.66, p=0.3791, I^2=6.79%



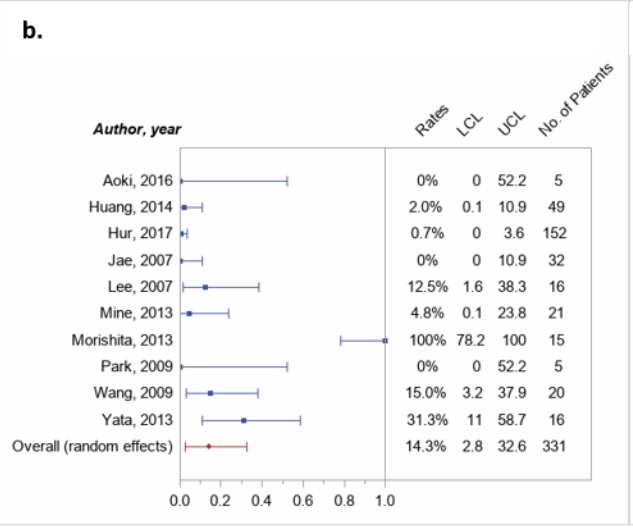
Clinical success
Overall rate (random effects model): 88.0% (95% CI: 77.5%-95.5%)
Heterogeneity: Q=33.82, p<0.0001, I^2=79.30%



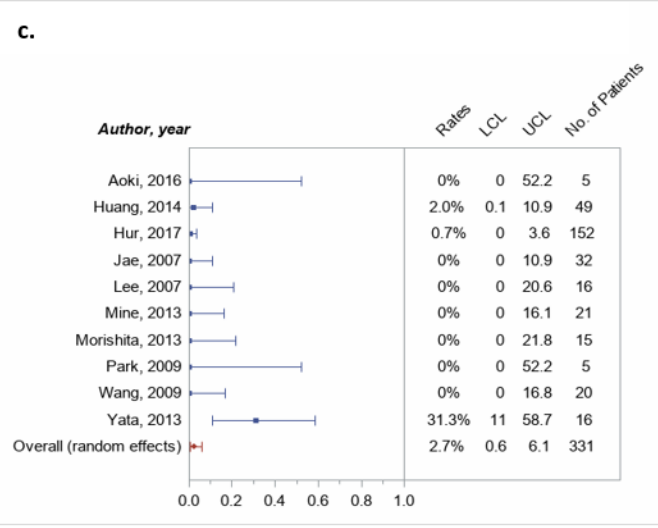
30-day rebleeding
Overall rate (random effects model): 12.5% (95% CI: 4.8%-23.2%)
Heterogeneity: Q=41.79, p<0.0001, I^2=80.86%



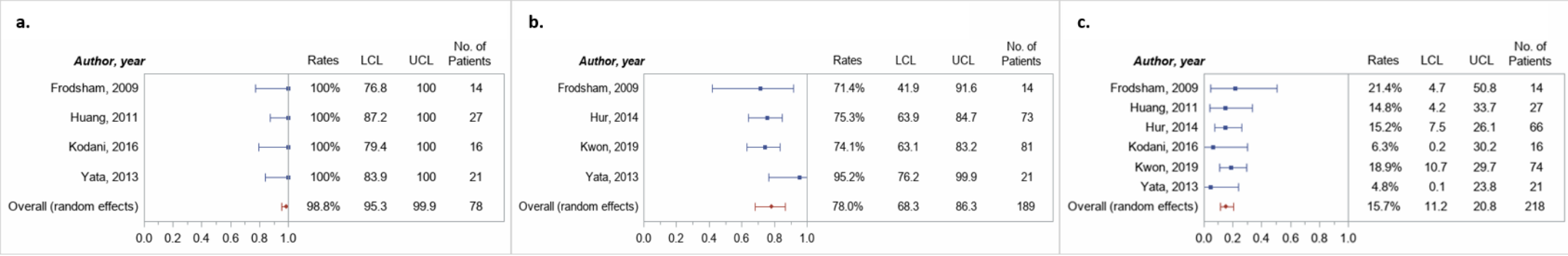
30-day mortality
Overall rate (random effects model): 15.9% (95% CI: 8.3%-25.3%)
Heterogeneity: Q=32.44, p=0.0002, I^2=72.26%



30-day complications
Overall rate (random effects model): 14.3% (95% CI: 2.8%-32.6%)
Heterogeneity: Q=122.14, p<0.0001, I^2=92.63%



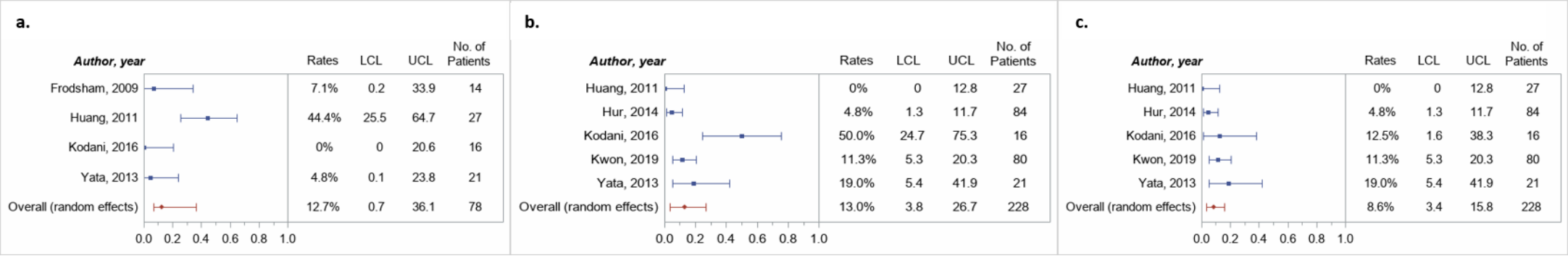
30-day major complications
Overall rate (random effects model): 2.7% (95% CI: 0.6%-6.1%)
Heterogeneity: Q=16.69, p=0.0538, I^2=46.07%



Technical success
Overall rate (random effects model): 98.8% (95% CI: 95.3%-99.9%)
Heterogeneity: Q=0.06, p=0.9960, I^2=0.00%

Clinical success
Overall rate (random effects model): 78.0% (95% CI: 68.3%-86.3%)
Heterogeneity: Q=6.04, p=0.1099, I^2=50.29%

30-day rebleeding
Overall rate (random effects model): 15.7% (95% CI: 11.2%-20.8%)
Heterogeneity: Q=3.96, p=0.5558, I^2=0.00%



30-day mortality
Overall rate (random effects model): 12.7% (95% CI: 0.7%-36.1%)
Heterogeneity: Q=19.68, p=0.0002, I^2=84.75%

30-day complications
Overall rate (random effects model): 13.0% (95% CI: 3.8%-26.7%)
Heterogeneity: Q=25.27, p<0.0001, I^2=84.17%

30-day major complications
Overall rate (random effects model): 8.6% (95% CI: 3.4%-15.8%)
Heterogeneity: Q=10.07, p=0.0393, I^2=60.27%

Author, year	Study type	Study period	Country	No. of patients*	Gender (male, %)	Mean age* (years)	Type of glue	NBCA-Lipiodol® UF ratio
Upper GI tract bleeding								
Aoki M et al. [2016] [28]	R	2008-2014	Japan	5	100	71	Histoacryl®	1:1.5 to 1:3
Huang YS et al. [2014] [13]	R	2008-2012	Taiwan	49	63.3	67	Histoacryl®	1:1 to 1:4
Hur S et al. [2017] [29]	R	2006-2015	Korea	152	71.7	65.5	Histoacryl®	1:2 to 1:3
Jae HJ et al. [2007] [27]	P	1999-2002	Korea	32	87.5	59.1	Histoacryl®	1:1 to 1:3
Lee CW et al. [2007] [10]	R	2004-2005	Taiwan	16	68.8	67.7	Histoacryl®	1:1.5 to 1:4
Mine T et al. [2013] [22]	R	2006-2012	Japan	21	81.0	66	NS	1:1 to 1:4
Morishita H et al. [2013] [30]	R	2006-2011	Japan	15	80.0	71.3	Histoacryl®	1:1.5 to 1:4
Park JH et al. [2009] [31]	R	2000-2008	Korea	5	80.0	59	Histoacryl®	1:1 to 1:4
Wang YJ et al. [2009] [32]	R	2004-2009	Taiwan	20	65.0	62.8	Histoacryl®	1:1 to 1:3
Yata S et al. [2013] [33]	R	2005-2012	Japan	16	50.0	68.5	Histoacryl®	1:1 to 1:3
Lower GI tract bleeding								
Frodsham A et al. [2009] [26]	P	2005-2009	USA	14	64.3	77	NS	1:2
Huang CC et al. [2011] [23]	R	2006-2008	Taiwan	27	81.5	63	Histoacryl®	1:1.5 to 1:9
Hur S et al. [2014] [24]	RC	2006-2013	Korea	84	-	61.2	NS	1:1 to 1:3
Kodani M et al. [2016] [12]	R	2007-2013	Japan	16	87.5	63.7	NS	1:1 to 1:4
Kwon JH et al. [2019] [25]	RC	2005-2017	Korea	81	66.4	59.1	Histoacryl®	1:1 to 1:3
Yata S et al. [2013] [33]	R	2005-2012	Japan	21	76.2	67.2	Histoacryl®	1:1 to 1:5

No., number; GI, gastrointestinal; NBCA, N-butyl cyanoacrylate; R, retrospective; P, prospective; RC, retrospective comparative; NS, not specified; UF, Ultra Fluid; *patients treated with NBCA-Lipiodol® UF mixture.

Author, year	Technical success			Clinical success			30-day rebleeding			30-day mortality		
	No. of patients evaluated	*No. of patients with technical success*	*Technical success rate (%)*	*No. of patients evaluated*	*No. of patients with clinical success*	*Clinical success rate (%)*	*No. of patients evaluated*	*No. of patients with 30-day rebleeding*	*30-day rebleeding rate (%)*	*No. of patients evaluated*	*No. of deaths within 30-day*	*30-day mortality rate (%)*
Upper GI tract bleeding												
Aoki M et al. [2016] [28]	5	5	100.0	-	-	-	-	-	-	5	1	20.0
Huang YS et al. [2014] [13]	49	48	98.0	49	35	71.4	49	19	38.8	49	15	30.6
Hur S et al. [2017] [29]	152	152	100.0	142	100	70.4	142	42	29.6	152	34	22.4
Jae HJ et al. [2007] [27]	32	32	100.0	32	29	90.6	32	3	9.4	32	6	18.8
Lee CW et al. [2007] [10]	16	14	87.5	-	-	-	14	1	7.1	16	2	12.5
Mine T et al. [2013] [22]	21	21	100.0	21	21	100.0	21	0	0.0	21	0	0.0
Morishita H et al. [2013] [30]	15	15	100.0	15	15	100.0	15	0	0.0	15	0	0.0
Park JH et al. [2009] [31]	5	5	100.0	5	5	100.0	5	0	0.0	5	0	0.0
Wang YJ et al. [2009] [32]	20	20	100.0	20	17	85.0	20	3	15.0	20	9	45.0
Yata S et al. [2013] [33]	16	16	100.0	16	15	93.8	16	1	6.3	16	1	6.3
Lower GI tract bleeding												
Frodsham A et al. [2009] [26]	14	14	100.0	14	10	71.4	14	3	21.4	14	1	7.1
Huang CC et al. [2011] [23]	27	27	100.0	-	-	-	27	4	14.8	27	12	44.4
Hur S et al. [2014] [24]	-	-	-	73	55	75.3	66	10	15.2	-	-	-
Kodani M et al. [2016] [12]	16	16	100.0	-	-	-	16	1	6.3	16	0	0.0
Kwon JH et al. [2019] [25]	-	-	-	81	60	74.1	74	14	18.9	-	-	-
Yata S et al. [2013] [33]	21	21	100.0	21	20	95.2	21	1	4.8	21	1	4.8

No., number; GI, gastrointestinal.

Author, year	No. of patients evaluated	30-day overall complications		30-day major complications	
		No. of patients	*Rate (%)*	*No. of patients*	*Rate (%)*
Upper GI tract bleeding					
Aoki M et al. [2016] [28]	5	0	0.0	0	0.0
Huang YS et al. [2014] [13]	49	1	2.0	1	2.0
Hur S et al. [2017] [29]	152	1	0.7	1	0.7
Jae HJ et al. [2007] [27]	32	0	0.0	0	0.0
Lee CW et al. [2007] [10]	16	2	12.5	0	0.0
Mine T et al. [2013] [22]	21	1	4.8	0	0.0
Morishita H et al. [2013] [30]	15	15	100.0	0	0.0
Park JH et al. [2009] [31]	5	0	0.0	0	0.0
Wang YJ et al. [2009] [32]	20	3	15.0	0	0.0
Yata S et al. [2013] [33]	16	5	31.3	5	31.3
Lower GI tract bleeding					
Huang CC et al. [2011] [23]	27	0	0.0	0	0.0
Hur S et al. [2014] [24]	84	4	4.8	4	4.8
Kodani M et al. [2016] [12]	16	8	50.0	2	12.5
Kwon JH et al. [2019] [25]	80	9	11.3	9	11.3
Yata S et al. [2013] [33]	21	4	19.0	4	19.0

No., number; GI, gastrointestinal.

	No. of patients
Upper GIB	
No. of patients evaluated	328
Overall complications	28
30-day minor complications	21
- *Epigastric pain, nausea, occasionally vomiting [30]*	15
- *Gastric ulcers [10, 32]*	5
- *Mild pyloric stenosis [22]*	1
30-day major complications	7
- *TAE-induced ulcers [33]*	3
- *Hepatic infarction [13]*	1
- *Pancreatic head infarction [29]*	1
- *Hepatic abscess [33]*	2
Complications requiring surgery	0
Lower GIB	
No. of patients evaluated	228
Overall complications	25
30-day minor complications	8
- *Mucosal ischemia (mucosal swelling, ulcer, ulcer scar) [12]*	8
30-day major complications	19
- *TAE-induced ulcer [33]*	3
- *Ischemia resulting from extensive vascular occlusion in the small bowel or colon (all appendix) bleeding [24]*	4
- *Transient bowel ischemia [25]*	3
- *Transmural bowel infarction [25]*	6
- *Bowel perforation (intestinal tuberculosis) [12]*	1
- *Stricture in the sigmoid colon [12]*	1
- *Acute ischemia of the lower limb [33]*	1
Complications requiring surgery	4–10
- *Elective laparotomy for a gastrojejunostomy site infarction [24]*	1
- *Preventive appendectomies (high risk of appendiceal infarction) [24]*	2
- *Patients with transmural bowel infarction underwent surgery or died within 30 days [25]*	0–6
- *Femoro-femoral bypass surgery [33]*	1

No., number; GIB, gastrointestinal bleeding