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Transcatheter arterial embolization of nonvariceal gastrointestinal bleeding with *n*-butyl cyanoacrylate or coils: a systematic review and meta-analysis

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This report is of a systematic review and meta-analysis evaluating the efficacy and safety of transcatheter arterial embolization (TAE) for nonvariceal gastrointestinal bleeding (GIB) with *n*-butyl cyanoacrylate (NBCA) or coils as the primary embolic agent. The primary outcome was the clinical success rate. The secondary outcomes were technical success rates, 30-day rebleeding rates, major complication rates, and 30-day overall mortality rates. A systematic search was performed in PubMed, Embase, and Cochrane Library. Articles included had been published in English from January 2000 to August 2023 and assessed patients with nonvariceal upper and lower GIB (UGIB and LGIB) who received TAE with NBCA or coils. Single-arm meta-analyses were performed for these outcomes. Subgroup analyses comparing NBCA and coils were conducted if there were more than 10 articles selected for each outcome. Thirty-seven articles were selected for analysis. The pooled rates of TAE for UGIB and LGIB were clinical success 73.0% and 76.5%, technical success 94.9% and 91.4%, 30-day rebleeding 25.0% and 17.1%, major complications 3.5% and 10.0%, and 30-day overall mortality 20.7% and 11.4%, respectively. The subgroup analysis showed a significant difference only for the technical success rates of LGIB between NBCA and the coils ($p < 0.001$). The systematic review and meta-analysis indicate that TAE with NBCA or coils as the primary embolic agent is safe and effective for both UGIB and LGIB.

Keywords Embolization, Therapeutic, Gastrointestinal Hemorrhage, Radiology, Interventional, Systematic Review, Meta-Analysis

Gastrointestinal bleeding (GIB) is a common medical emergency associated with significant morbidity and mortality[1]. Transcatheter arterial embolization (TAE) is a minimally invasive therapy that is widely used to control both nonvariceal upper (UGIB) and lower GIB (LGIB), especially when prior therapeutic endoscopy cannot achieve hemostasis[2,3]. TAE for GIB is often performed with *n*-butyl cyanoacrylate (NBCA) or coils as the primary embolic agent[4,5].

Coils are highly thrombogenic and result in the complete occlusion of the target vessel after appropriate packing[4]. However, there is a size limitation to their use as they cannot always reach very small vessels, particularly if complex anastomoses have formed[4,6]. Moreover, coils are not always effective in patients affected by coagulopathy as their mechanism of action depends on the status of hemostasis[4]. In contrast, NBCA is not limited by those factors as it can be injected via very-small-caliber micro catheters and reach very small vessels to block the vessels independently of the status of hemostasis[7]. However, there is concern about the

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risk of reflux during the injection and of nontarget embolization with potential splanchnic or visceral ischemic complications[8,9].

Thus, the choice of the optimal embolic agent for TAE for GIB is still debatable[10]in the absence of published guidelines[11]. Furthermore, randomized controlled trials (RCTs) comparing embolic agents would be difficult in patients with GIB because such patients require emergency treatment[12]. Therefore, a systematic review and meta-analysis integrating NBCA and coil data on TAE for GIB would not only provide an overview of TAE for GIB, but also allow subgroup analyses of NBCA and coils to assess each embolic agent.

Although there have been two systematic reviews and meta-analyses on TAE with only NBCA for GIB[7,10], no systematic review and meta-analysis integrating TAE with NBCA and coils as the primary embolic agent for GIB has been published. Thus, our objective was to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of TAE with NBCA or coils as the primary embolic agent for GIB as the primary embolic agent.

Materials and methods

We used guidelines from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) to compile this report. The protocol was registered in PROSPERO (CRD42023458652).

Search strategy

With the assistance of librarians, PubMed, the Cochrane Library, and Embase data resource were systematically searched for articles published from January 2000 to August 2023 using relevant Medical Subject Heading (MeSH) terms and keywords (Supplement Table S1).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) articles written in English; (2) availability of full-text articles; (3) RCTs and observational studies; and (4) articles reporting data and results of the use of TAE with either NBCA or coils as the primary embolic agent for acute nonvariceal GIB. The exclusion criteria were as follows: (1) case reports; (2) review articles; (3) letters and editorials; (4) preclinical studies; (5) articles with a sample size of <5 cases; (6) articles with no extractable data; (7) articles reporting mixed results from different techniques or results from other techniques; and (8) articles with data included in subsequent articles or duplicate reports.

Outcomes and data extraction

The primary outcome was the clinical success rate. The following secondary outcomes were also investigated: technical success rate, 30-day rebleeding rate, major complication rate, and 30-day mortality rate.

For each study, two reviewers (T. M. and J. S.) independently retrieved information on the outcomes and study characteristics, including the first author, publication year, study country, study design, patient characteristics, and bleeding location (UGIB or LGIB). For all articles, the following data were extracted separately for both UGIB and LGIB: NBCA-lipiodol ratio; number of coils; type of coils (pushable or detachable coils); technical success, which was defined as the complete cessation of contrast extravasation or blood flow from the bleeding artery; clinical success, which was defined as no rebleeding, surgical resection as a result of major complication or GIB-related mortality within 30 days of TAE (if patients died of any cause unrelated to GIB within 30 days, they were excluded from the analysis of the clinical success.); 30-day rebleeding; major complications; and 30-day mortality. The third reviewer (R. Y.) was consulted if any discrepancies arose in the two reviewers' findings. The complications were classified in accordance with the classification system of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), i.e., from grade 1 (no complication) to grade 6 (death)[13]. Grades 3–6 were defined as major complications.

Risk of bias assessment in the included studies

The quality of the included studies was assessed using version 2 of the Cochrane Collaboration tool for RCTs (RoB2)[14]and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS)[15].

Analysis of subgroups

Subgroup analyses were conducted to compare NBCA and coils if there were >10 articles selected for each outcome.

Statistical analysis

The statistical technique chosen for this study was a single-arm meta-analysis, incorporating subgroup analysis to compare embolic agents. Where comparative studies were available, single-arm data were extracted from those studies and included in the meta-analysis. As considerable between-study heterogeneity was anticipated in the primary outcome, a random-effects model was used to pool the effect sizes. The restricted maximum likelihood estimator was used to calculate the heterogeneity variance τ^2. The Knapp-Hartung adjustment was used to calculate the confidence interval around the pooled effect. With a forest plot to display the outcome data from the respective studies, the following heterogeneity measures were assessed: τ^2, I^2, and Q-statistics. For the I^2 statistic, values of $<25\%$ were defined as low heterogeneity, 25–50% as moderate, and $>50\%$ as high heterogeneity. A meta-regression analysis was conducted to identify the source of inter-study heterogeneity when I^2 was greater than 50%. For the meta-regression analysis, a value of $p<0.05$ was used to identify the source of heterogeneity. Funnel plots and Egger's test were used to analyze publication bias; values of $p<0.05$ were considered statistically significant in Egger's test. Egger's test and meta-regression analysis were performed if at least four articles were selected for each meta-analysis. Sensitivity analyses were conducted by excluding articles with <10 cases. The same method was also used for the analysis of the secondary outcomes. Descriptive

and basic statistics were analyzed using Microsoft Excel (version16.66.1). The meta package of R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) was used for the meta-analyses. Quality assessment plots were produced using risk-of-bias visualization 'robvis'[16]. For the summary of RoBANS, studies were considered to have an overall low risk of bias if they were classified as low risk in all six domains. Studies were considered to have an unclear risk of bias if at least one domain was rated as unclear risk (but no domains were rated as high risk) and as high risk if at least one domain was rated as high risk.

Results

Search results

At first, literature searches identified a total of 1635 records. However, 1459 studies were left to be screened after eliminating duplicates. Following the evaluation of titles and abstracts, 1371 studies were eliminated, leaving 88 of these records to undergo a full-text review. Finally, 51 articles were excluded by applying the eligibility criteria, leaving 37 articles for systematic review and meta-analysis of the efficacy and safety of TAE for GIB with NBCA or coils[4–6,8,11,12,17–47] (Fig. 1).

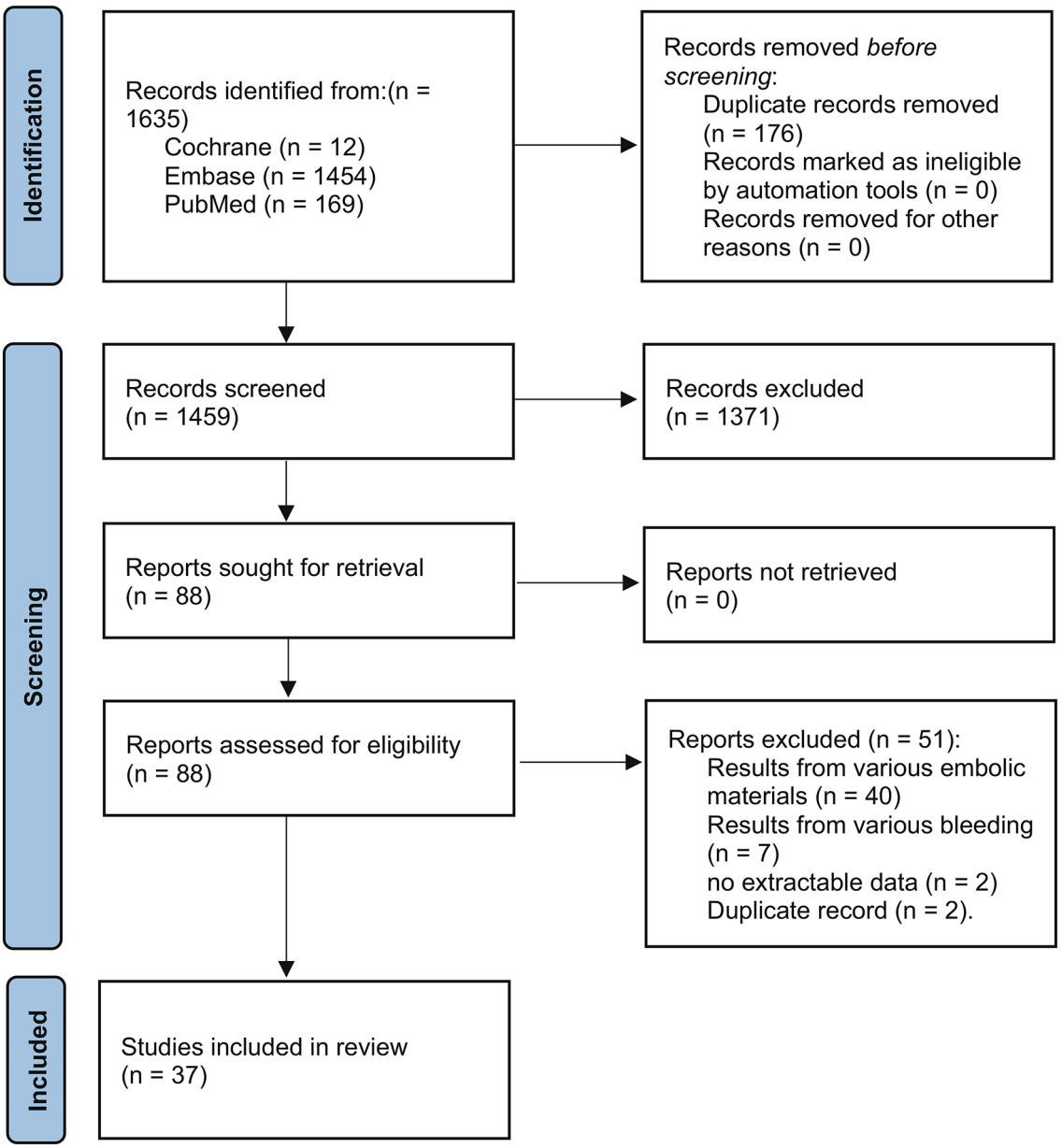


Fig. 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of the article selection process.

Risk-of-bias assessment

As none of the included articles had reported RCTs, none were evaluated in RoB2. Thirty two of the included articles were on single-arm retrospective studies, four articles were on retrospective case–control studies, and one article was on a single-arm prospective study. The selected articles were assessed as high ($n=34$), unclear ($n=2$), and low ($n=1$) by RoBANS (Fig. 2).

Characteristics of the included studies

The 37 selected articles involved a total of 989 cases (Tables 1 and 2). The average-weighted mean age of the subjects was 67 years. There were 67% males and 33% females in the 33 articles. Nineteen articles dealt with UGIB[4,6,8,11,22,24,27,28,30–34,37,40,43,44,46,47], 16 articles with LGIB[5,17–21,23,25,26,29,35,38,39,41,42,45], and two articles[12,36]with both. Of the 21 articles that addressed UGIB, 13 articles[6,8,11,12,24,27,33,34,36,37,40,43,46]reported the use of NBCA and 8 articles[4,22,28,30–32,44,47]of coils as the primary embolic agent. Of the 13 articles on the use of NBCA for UGIB, the NBCA-lipiodol ratio ranged from 20 to 50% in 12 articles[6,8,11,12,24,27,33,36,37,40,43,46], while the most diluted NBCA-lipiodol ratio was 17% in the remaining article[34]. Of the eight articles on the use of coils for nonvariceal UGIB, three articles involved pushable coils[22,31,47], three articles pushable or detachable coils[4,32,44], while the remaining two articles did not clarify the nature of the coils[28,30]. The number of coils used was not stated in any of the eight articles. Of the 13 articles reporting the use of NBCA, eight articles described coagulopathy[6,11,34,36,37,40,43,46]. Of the 8 articles reporting the use of coils, one article described coagulopathy[4]. Of the 18 articles that addressed LGIB, five articles reported the use of NBCA[12,25,29,36,42], 12 articles of coil[5,17–21,23,26,35,38,39,41], and one article of coil or NBCA[45]as the primary embolic agent. The NBCA-lipiodol ratio ranged from 20 to 50% in three articles on the use of NBCA for nonvariceal LGIB[12,42,45]. However, the most diluted NBCA-lipiodol ratio was 10% and 17%, respectively, in the other two papers on NBCA[29,36]; the NBCA-lipiodol ratio was unknown in the remaining article[25]. Of 13 articles reporting the use of coils for UGIB, nine articles were on pushable coils[17–21,23,26,35,45], one article on pushable or detachable coils[38], and the remaining three articles on detachable coils[5,39,41]. The average-weighted mean number of coils used was 3.5 in the 5 articles in which the average number of coils could be verified[19,21,23,39,41]. Of 13 articles on coils, two articles described coagulopathy[5,41], while three of six articles on NBCA described coagulopathy[25,36,42]. One article was unclear as to the number of patients in the NBCA and coil groups who had developed coagulopathy[45].

Analysis of primary and secondary outcomes

The pooled clinical success rates of TAE for UGIB and LGIB, which were the primary outcomes, were 73.0% (95% CI, 65.3–79.6%, $I^2=21.5\%$) (Fig. 3a) and 76.5% (95% CI, 70.5–81.5%, $I^2=0\%$) (Fig. 3b), respectively. There was significant publication bias for the clinical success rates of TAE for UGIB ($p=0.043$) and LGIB ($p=0.006$) in Egger's test and the funnel plots (Supplement Fig. S1).

The rates for the secondary outcomes of TAE for UGIB and LGIB were as follows: pooled technical success 94.9% (95% CI, 91.6–97.0%, $I^2=23.1\%$) (Fig. 4a) and 91.4% (95% CI, 87.7–94.0%, $I^2=0\%$) (Fig. 4b); 30-day rebleeding 25.0% (95% CI, 19.5–31.3%, $I^2=24.4\%$) (Fig. 4c) and 17.1% (95% CI, 13.4–21.6%, $I^2=0\%$) (Fig. 4d); major complications 3.5% (95% CI, 1.7–7.1%, $I^2=52.8\%$) (Fig. 4e) and 10.0% (95% CI, 7.2–13.7%, $I^2=0\%$) (Fig. 4f); and 30-day overall mortality 20.7% (95% CI, 13.2–31.1%, $I^2=46.7\%$) (Fig. 4g) and 11.5% (95% CI, 6.1–20.5%, $I^2=48.2\%$) (Fig. 4h), respectively. There was no significant publication bias for only 30-day overall mortality for UGIB assessed by Egger's test ($p=0.199$) and the funnel plots (Supplement Fig. S2g). There was significant publication bias for technical success rates for UGIB ($p=0.006$) and LGIB ($p<0.001$), 30-day rebleeding for UGIB ($p=0.022$) and LGIB ($p=0.008$), major complications for UGIB ($p=0.023$) and LGIB ($p=0.010$), and 30-day overall mortality for LGIB ($p<0.001$) as assessed by Egger's test and the funnel plots (Supplement Fig. S2a-f, h).

As I^2 was $>50\%$ for the major complications of TAE for UGIB, meta-regression analysis was conducted. There was no evidence that the publication year or the study region (Asia or the other region) influenced the values of the major complication rates of TAE for UGIB (Table 3). The major complication rates of TAE for UGIB were only influenced by the sample size ($p=0.028$) (Table 3).

Subgroup analysis

Subgroup analysis could be performed for all outcomes except for the clinical success rates for UGIB (Table 4, Supplement Fig. S3). The subgroup analysis showed a significant difference only for the technical success rates of LGIB between NBCA and coils ($p<0.001$) (Table 5, Supplement Fig. S4).

Sensitivity analysis

The data of the sensitivity analyses largely overlap with those of the primary analyses, and subgroup analyses showed similar results, indicating the robustness of the findings (Supplement Table S2–5).

Discussion

This systematic review and meta-analysis investigated the efficacy and safety of TAE with NBCA or coils as the primary embolic agent for GIB and explored the differences between NBCA and coils in subgroup analyses. Our present findings may promote the understanding of TAE for GIB and act as a decision-making reference in clinical practice.

Regarding literature collection, previous systematic reviews of TAE for GIB with NBCA had collected articles since 1980 [10] or 1990 [7]. Given the changes in technology, including improvements in digital subtraction angiography, catheter systems, and microcatheters, this systematic review and meta-analysis focused on articles published since 2000. Moreover, article collection was done to be as up-to-date as possible, that is, through

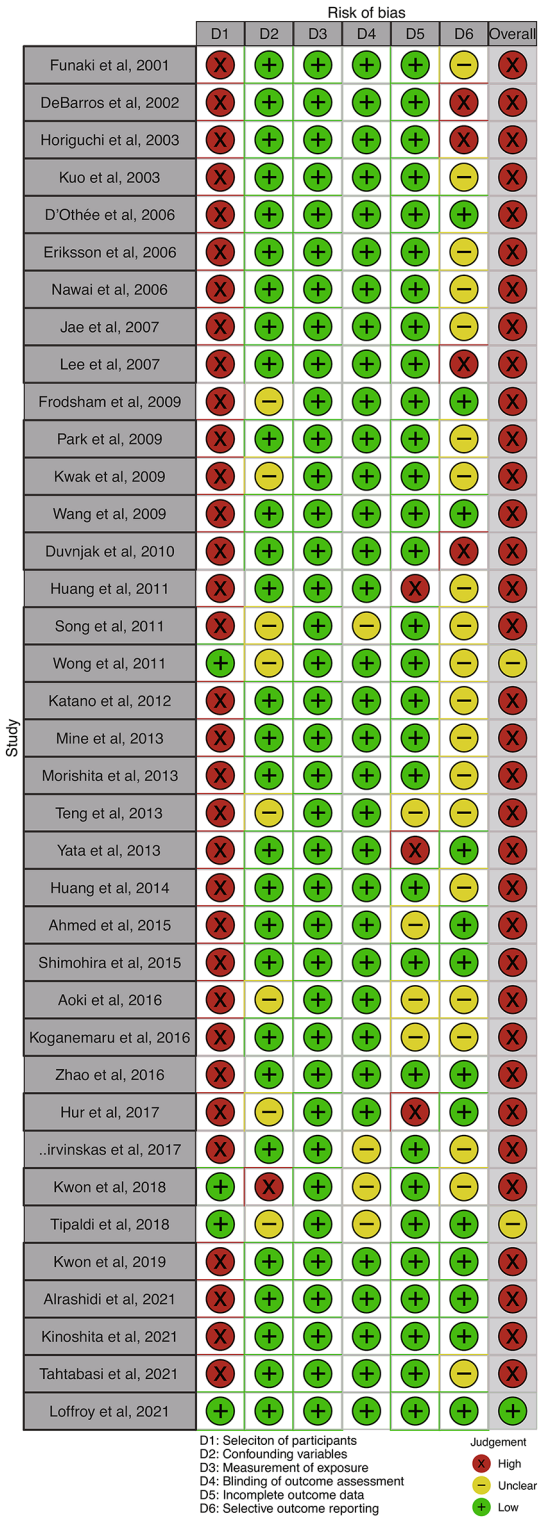


Fig. 2. Risk-of-bias assessment. Risk-of-bias assessments were performed using the Risk-of-Bias Assessment Tool for Nonrandomized Studies (RoBANS). Green (+) indicates low risk of bias; yellow (-) indicates unclear risk of bias; and red (×) indicates high risk of bias. For the summary of risk of bias, studies were considered to have an overall low risk of bias (green +) if they were classified as low risk in all six domains. Studies were considered to have an unclear risk of bias (yellow -) if at least one domain was rated as unclear risk (but no domains were rated as high risk) and as high risk (red ×) if at least one domain was rated as high risk.

Author	Study type	Study period	Country	No. of patients	Sex (M/F)	Mean age	Primary embolic agent	NBCA-lipiodol ratio (%)	No. of coils	Type of coils	Coagulopathy
Eriksson et al., 2006[22]	R	2003–2005	Sweden	10 of 13	5/5	75	Coil	NA	NR	Pushable	NR
Jae et al., 2007[8]	P	1999–2002	Korea	32 of 32	28/4	59	NBCA	25 to 50	NA	NA	NR
Lee et al., 2007[24]	R	2004–2005	Taiwan	16 of 16	11/5	68	NBCA	20 to 30	NA	NA	NR
Park et al., 2009[27]	R	2000–2008	Korea	5 of 5	4/1	57	NBCA	20 to 50	NA	NA	NR
Wang et al., 2009[6]	R	2004–2009	China	20 of 20	13/7	63	NBCA	25 to 50	NR	NA	8 of 17
Duvnjak et al., 2010[28]	R	2007–2009	Denmark	40 of 40	26/14	67	Coil	NA	NR	NR	NR
Song et al., 2011[30]	R	2006–2007	Korea	12 of 16	7/5	58	Coil	NA	NR	NR	NR
Wong et al., 2011[31]	RC	2000–2009	China	32 of 88	21/11	73	Coil	NA	NR	Pushable	NR
Katano et al., 2012[32]	R	2004–2010	Japan	15 of 15	12/3	62	Coil	NA	NR	Detachable or pushable	NR
Mine et al., 2013[33]	R	2006–2012	Japan	21 of 21	17/4	66	NBCA	20 to 50	NA	NA	NR
Morishita et al., 2013[34]	R	2006–2011	Japan	15 of 15	12/3	68	NBCA	17 to 40	NA	NA	3 of 15
Yata et al., 2013[36]	R	2005–2012	Japan	16 of 37	8/8	69	NBCA	25 to 50	NA	NA	1 of 16
Huang et al., 2014[37]	R	2008–2012	Taiwan	49 of 49	31/18	67	NBCA	20 to 50	NA	NA	16 of 49
Aoki et al., 2016[40]	R	2008–2014	Japan	5 of 5	5/0	71	NBCA	25 to 40	NA	NA	4 of 5
Hur et al., 2017[43]	R	2006–2015	Korea	152 of 152	109/43	66	NBCA	25 to 33	NA	NA	53 of 152
Širvinskas et al., 2017[44]	R	2013–2015	Lithuania	36 of 36	27/9	66	Coil	NA	NR	Detachable or pushable	NR
Kwon et al., 2018[12]	R	2007–2016	Korea	15 of 46	NR	NR	NBCA	20 to 50	NA	NA	NR
Tipaldi et al., 2018[4]	R	2011–2017	Italy	41 of 71	NR	60	Coil	NA	NR	Detachable or pushable	9 of 41
Alrashidi et al., 2021[46]	RC	2004–2020	Saudi Arabia	5 of 9	5/0	64	NBCA	25	NA	NA	1 of 5
Tahtabasi et al., 2021[47]	R	2018–2019	Turkey	6 of 18	6/0	53	Coil	NA	NR	Pushable	NR
Loffroy et al., 2021[11]	R	2008–2019	France	78 of 148	52/26	72	NBCA	25 to 50	NA	NA	24 of 78

Table 1. Characteristics of the included studies on transcatheter arterial embolization for upper gastrointestinal bleeding. NA, not applicable; NBCA, *n*-butyl cyanoacrylate; No., number; NR, not reported; R, retrospective; RC, retrospective comparative.

Author	Study type	Study period	Country	No. of patients	Sex (M/F)	Mean age	Primary embolic agent	NBCA-lipiodol ratio (%)	No. of coils (Mean)	Type of coils	Coagulopathy
Funaki et al., 2001[17]	R	1995–2000	US	27 of 27	16/11	72	Coil	NA	NR	Pushable	NR
DeBarros et al., 2002[18]	R	1993–1999	US	16 of 27	10/6	69	Coil	NA	NR	Pushable	NR
Horiguchi et al., 2003[19]	R	NR	Japan	6 of 14	4/2	65	Coil	NA	4–5 (4.2)	Pushable	NR
Kuo et al., 2003[20]	R	1992–2002	US	22 of 22	11/11	62	Coil	NA	NR	Pushable	NR
D'Othée et al., 2006[21]	R	1997–2004	US	19 of 19	13/6	70	Coil	NA	2–6 (3)	Pushable	NR
Nawai et al., 2006[23]	R	2002–2003	Malaysia	6 of 6	2/4	74	Coil	NA	2–12 (7.2)	Pushable	NR
Frodsham et al., 2009[25]	R	2005–2009	US	14 of 14	9/5	77	NBCA	NR	NA	NA	5 of 14
Kwak et al., 2009[26]	R	2003–2007	Korea	17 of 36	13/4	65	Coil	NA	NR	Pushable	NR
Huang et al., 2011[29]	R	2006–2008	Taiwan	27 of 27	22/5	63	NBCA	10 to 40	NA	NA	NR
Teng et al., 2013[35]	R	1997–2009	Korea	26 of 26	19/7	69	Coil	NA	NR	Pushable	NR
Yata et al., 2013[36]	R	2005–2012	Japan	21 of 37	16/5	67	NBCA	17 to 50	NA	NA	10 of 21
Ahmed et al., 2015[38]	R	2002–2012	US	38 of 39	NR	60	Coil	NA	NR	Detachable or pushable	NR
Shimohira et al., 2015[39]	R	NR	Japan	5 of 5	2/3	76	Coil	NA	1–4 (2.4)	Detachable	NR
Koganemaru et al., 2016[41]	R	2010–2014	Japan	5 of 5	4/1	59	Coil	NA	1–2 (1.6)	Detachable	2 of 5
Zhao et al., 2016[42]	R	2013–2015	China	7 of 7	2/5	70	NBCA	25 to 33	NA	NA	0 of 7
Kwon et al., 2018[12]	R	2007–2016	Korea	6 of 46	NR	NR	NBCA	20 to 50	NA	NA	NR
Kwon et al., 2019[45]	RC	2005–2017	Korea	81 of 127	NR	NR	NBCA	25 to 50	NA	NA	NR
Kwon et al., 2019[45]	RC	2005–2017	Korea	8 of 127	NR	NR	Coil	NA	NR	Pushable	NR
Kinoshita et al., 2021[5]	R	2013–2019	Japan	17 of 17	15/2	69	Coil	NA	2–8	Detachable	1 of 17

Table 2. Characteristics of the included studies on transcatheter arterial embolization for lower gastrointestinal bleeding. NA, not applicable; NBCA, *n*-butyl cyanoacrylate; No., number; NR, not reported; R, retrospective; RC, retrospective comparative.

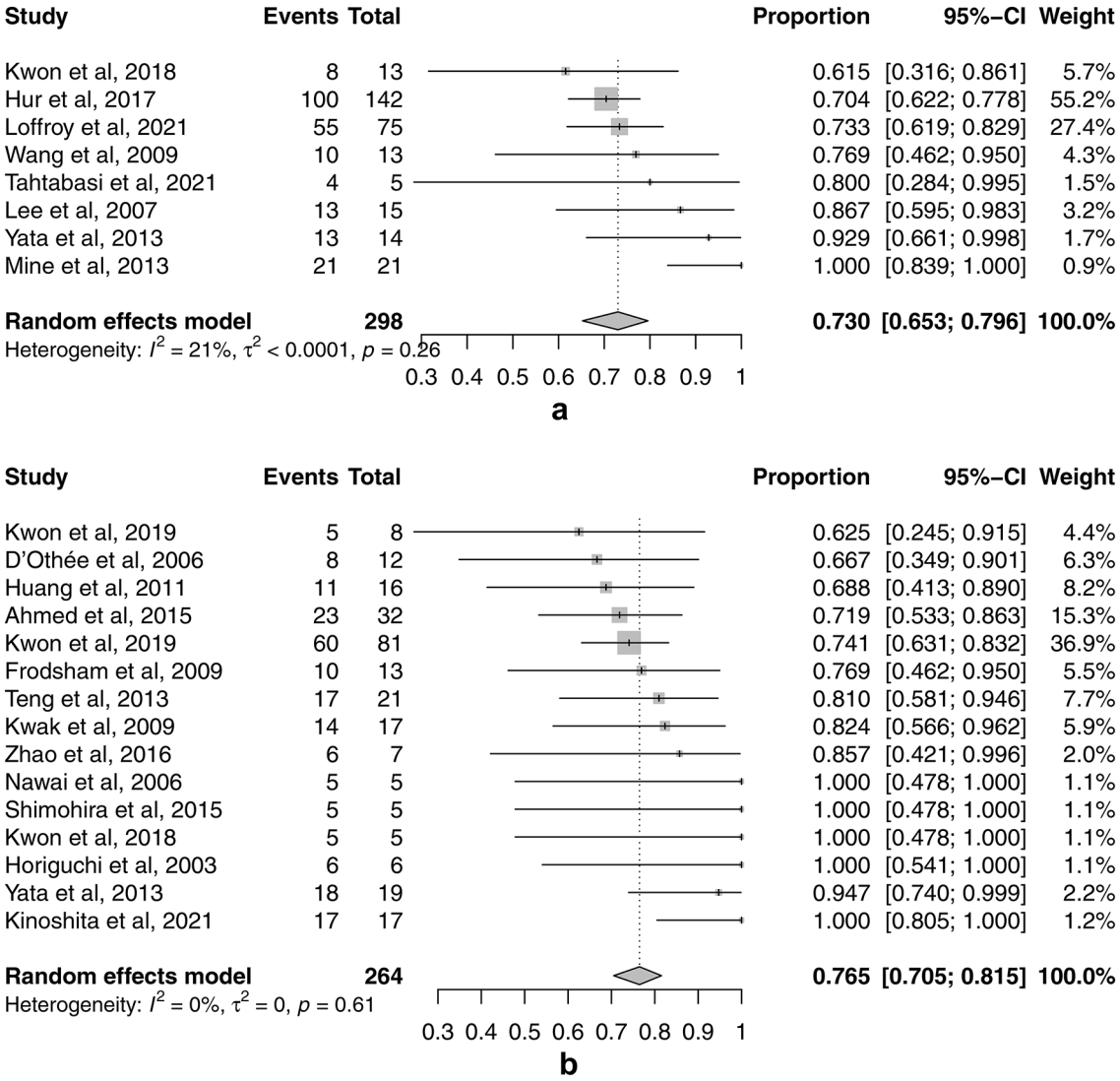


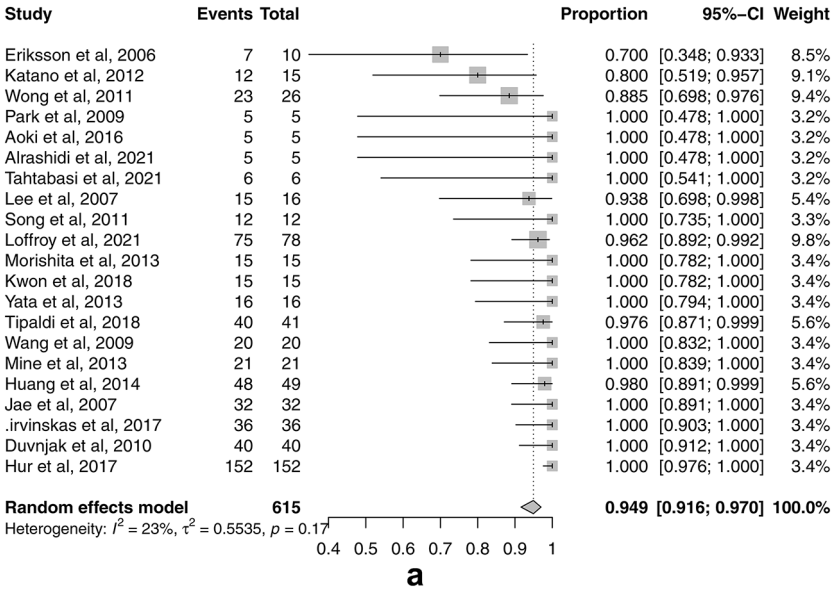
Fig. 3. Forest plots of the pooled clinical success rates of transcatheter arterial embolization (TAE) for nonvariceal upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB). (**a**) The forest plot of the pooled clinical success rate of TAE for UGIB. (**b**) The forest plot of the pooled clinical success rate of TAE for LGIB.

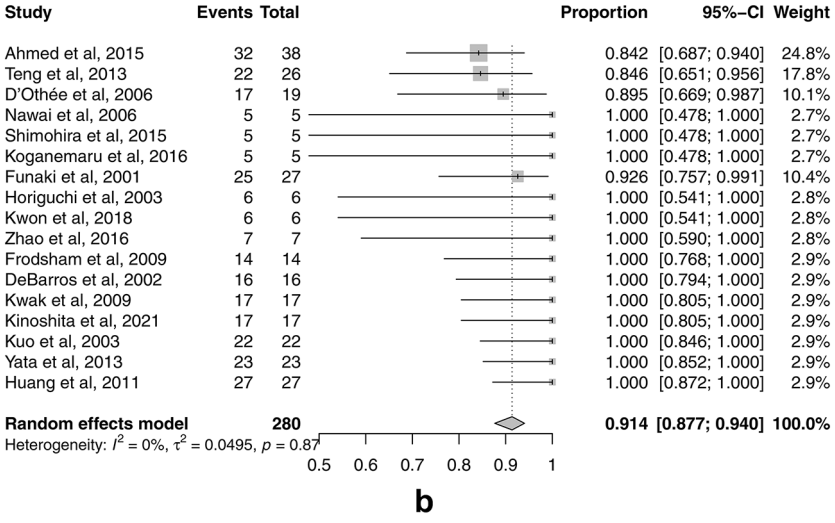
August 2023 because there have been several new articles on TAE for GIB[5,11,46,47]after the publication of previous systematic reviews[7,10].

There was significant publication bias in all outcomes except for 30-day overall mortality for UGIB in this study. This could be attributed to the tendency for "positive" results to be published, whereas "negative" results are often rejected or not even submitted.

Owing to the presence of rich anastomoses between adjacent arteries in the upper gastrointestinal tract, TAE of both feeding arteries and potential collateral channels is required for effective hemostasis[8]. TAE with NBCA or coils as the primary embolic agent for UGIB was found to be safe and effective in this systematic review and meta-analysis. Because there were only eight articles on the clinical success rate for UGIB in this meta-analysis, subgroup analysis comparing NBCA and coils was not conducted. Seven of the eight articles on the clinical success rates of TAE for UGIB reported the use of NBCA as the primary embolic agent. These results suggest that NBCA is the preferred primary embolic agent for TAE for UGIB in current clinical practice. A recent retrospective study with a relatively large sample size reported that NBCA as the primary agent allowed for faster and better clinical success than other embolic agents when used for TAE to safely stop refractory peptic ulcer bleeding[11]. However, the subgroup analyses showed no significant differences between NBCA and coils for all secondary outcomes of TAE for UGIB in this study. Caution should be exercised in interpreting these results as these subgroup analyses may lack the statistical power necessary to detect subgroup differences.

Because some of the articles were unclear on the mean age and sex ratio, meta-regression analyses could not be conducted for these factors on major complications of TAE for UGIB. The finding that the major complication rates of TAE for UGIB was influenced only by sample size ($p = 0.028$) may refer to the observed correlation





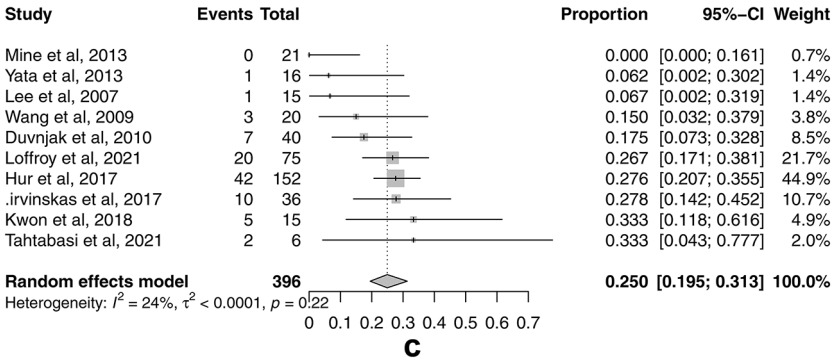
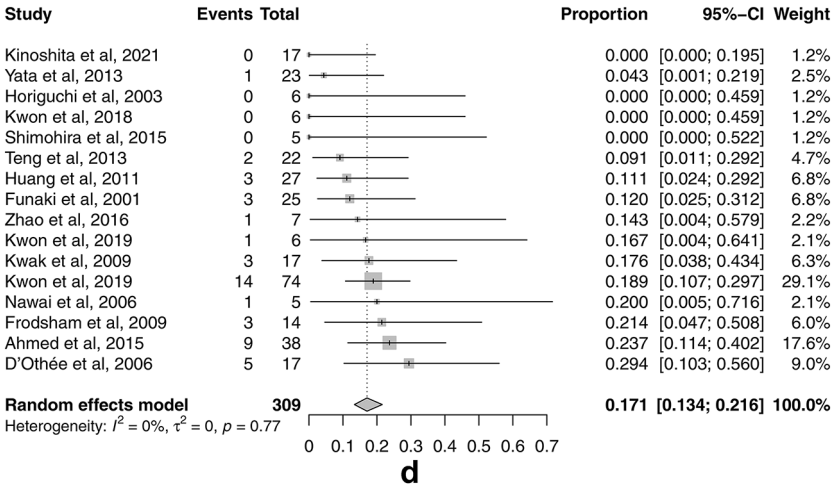
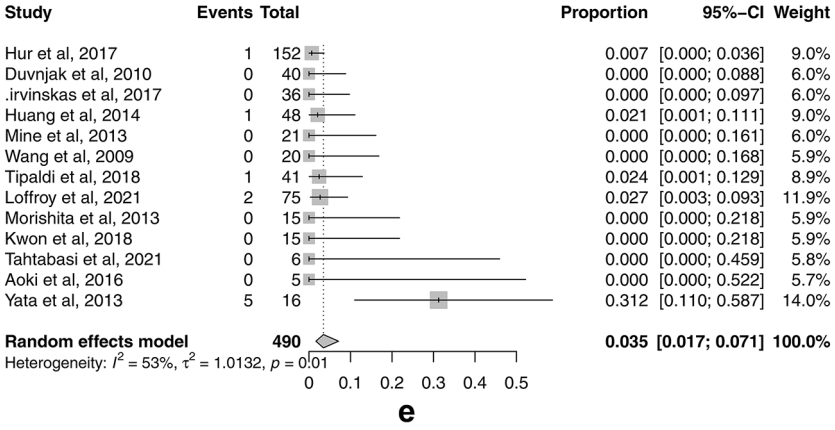


Fig. 4. Forest plots of the pooled secondary outcomes of transcatheter arterial embolization (TAE) for nonvariceal upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB). (**a**) The forest plot of the pooled technical success rate of TAE for UGIB. (**b**) The forest plot of the pooled technical success rate of TAE for LGIB. (**c**) The forest plot of the pooled 30-day rebleeding rate of TAE for UGIB. (**d**) The forest plot of the pooled 30-day rebleeding rate of TAE for LGIB. (**e**) The forest plot of the pooled major complication rate of TAE for UGIB. (**f**) The forest plot of the pooled major complication rate of TAE for LGIB. (**g**) The forest plot of the pooled 30-day overall mortality rate of TAE for UGIB. (**h**) The forest plot of the pooled 30-day overall mortality rate of TAE for LGIB.





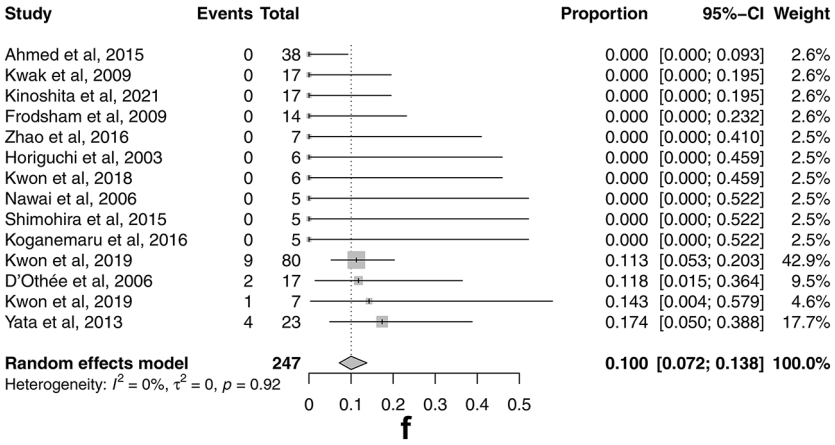
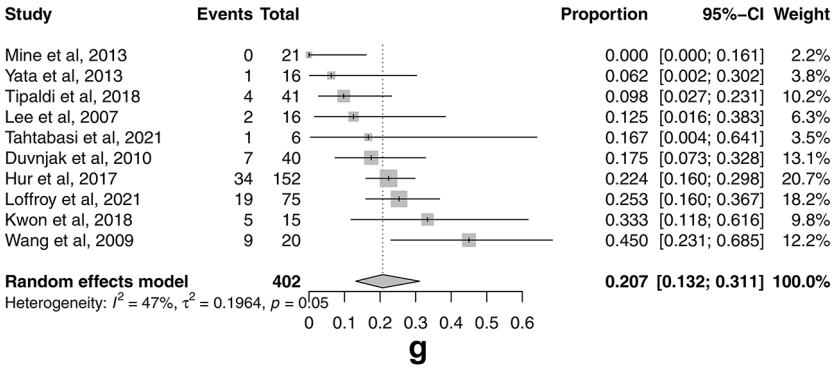


Figure 4. (continued)

between the volume of cases treated in TAE for UGIB and the outcomes for the patients, which indicates a volume–outcome relationship.

The vascular network in the lower gastrointestinal tract is smaller than that in the upper gastrointestinal tract[45]. Therefore, one of the major complications of TAE for LGIB is bowel infarction. Although the major complication rates of LGIB (10.0% (95% CI, 7.2–13.7%)) were higher than those of UGIB (3.5% (95% CI, 1.7–7.1%,)), TAE with NBCA or coils as the primary embolic agent for LGIB was found to be safe and effective in this systematic review and meta-analysis. There were no significant differences in the clinical success rates, 30-day rebleeding rates, major complication rates, and 30-day overall mortality rates between TAE with coils and NBCA for LGIB in the subgroup analyses. Animal studies have shown that bowel ischemia or infarction can be prevented by limiting NBCA embolization to three or fewer vasa recta[48]. However, caution is necessary to avoid inadvertent embolization of non-target vessels and extensive embolization, which may occur when an excessively



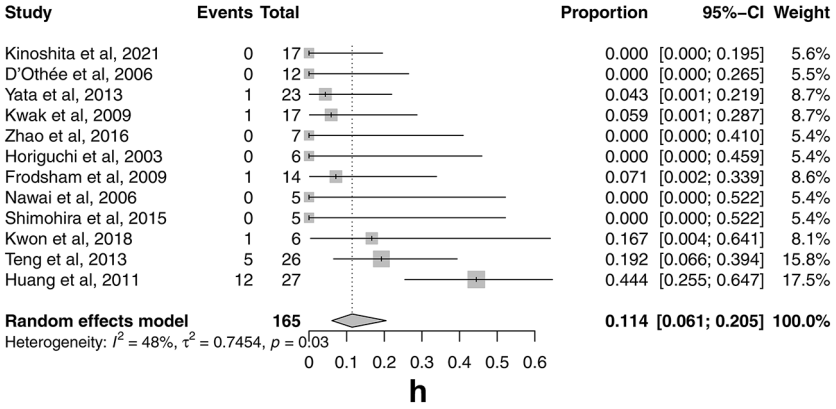


Figure 4. (continued)

	R^2	95% CI	*p*-value
Publication year	0%	-0.261 to 0.178	0.682
Sample size	36.4%	-0.035 to -0.002	0.028
Country (Asia or the other)	0%	-2.225 to 1.167	0.507

Table 3. Meta regression analysis of major complication rates of TAE for nonvariceal UGIB. CI, Confidence interval; TAE, transcatheter arterial embolization; UGIB, upper gastrointestinal bleeding.

	Proportion	95%CI	I^2	$p_{subgroup}$
Technical success rate (k = 21)				0.060
Coils (k = 8)	0.918	0.789–0.971	44.7%	
NBCA (k = 13)	0.967	0.949–0.979	0%	
30-day rebleeding rate (k = 10)				0.759
Coils (k = 3)	0.237	0.105–0.451	0%	
NBCA (k = 7)	0.253	0.179–0.345	42.0%	
Major complication rate (k = 13)				0.358
Coils (k = 4)	0.023	0.007–0.072	0%	
NBCA (k = 9)	0.039	0.014–0.103	64.2%	
30-day overall mortality rate (k = 10)				0.054
Coils (k = 3)	0.143	0.059–0.305	0%	
NBCA (k = 7)	0.244	0.146–0.378	50.7%	

Table 4. Subgroup analyses of TAE for nonvariceal UGIB. CI, confidence interval; NBCA, *n*-butyl cyanoacrylate; TAE, transcatheter arterial embolization; UGIB, upper gastrointestinal bleeding.

	Proportion	95%CI	I^2	$p_{subgroup}$
Clinical success rate (k = 15)				0.851
Coils (k = 9)	0.770	0.667–0.849	0%	
NBCA (k = 6)	0.760	0.657–0.840	0%	
Technical success rate (k = 17)				< 0.001
Coils (k = 12)	0.896	0.850–0.930	0%	
NBCA (k = 5)	0.965	0.925–0.984	0%	
30-day rebleeding rate (k = 16)				0.619
Coils (k = 10)	0.180	0.124–0.254	0%	
NBCA (k = 6)	0.161	0.104–0.241	0%	
Major complication rate (k = 14)				0.113
Coils (k = 9)	0.072	0.039–0.127	0%	
NBCA (k = 5)	0.117	0.071–0.185	0%	
30-day overall mortality rate (k = 12)				0.499
Coils (k = 7)	0.098	0.049–0.188	0%	
NBCA (k = 5)	0.145	0.033–0.455	67.0%	

Table 5. Subgroup analyses of TAE for nonvariceal LGIB. CI, confidence interval; LGIB, lower gastrointestinal bleeding; NBCA, *n*-butyl cyanoacrylate; TAE, transcatheter arterial embolization.

large volume of NBCA is used, or when the mixture is injected at an inappropriate rate[9,25]. In contrast, the subgroup analysis showed a significant difference in the technical success rates of LGIB between NBCA and coils ($p = 0.0009$). However, recently, the development of smaller microcatheters with various detachable coils has made superselective embolization possible, improving the technical success rate of TAE with coils for LGIB[5,39,41]. Therefore, whether coils or NBCA should be the first choice in TAE for LGIB may require further study.

Out of 14 articles describing coagulopathy, coils and NBCA were used as the primary embolic agents in three and 11 articles, respectively. These results suggest that coil embolization does not always stop bleeding in patients with coagulopathy. However, the shorter procedural time associated with the use of NBCA than with microcoil embolization is particularly valuable in patients with life-threatening bleeding[49,50]. This is important in cases of massive bleeding that require urgent hemostasis. Therefore, if coagulopathy has been apparent in advance, or if hemostasis is determined to be necessary in a short procedural time, the use of NBCA should be considered for TAE for UGIB and LGIB. Naturally, to achieve hemostasis with TAE using NBCA as the primary embolic agent for UGIB or LGIB, sufficient training is required and a learning curve should be considered to minimize possible ischemic complications[8,9,25,51].

Several limitations should be mentioned when interpreting the results. First, most of the included articles had a retrospective design and a high overall risk of bias. Second, unfortunately, only four comparative studies were identified, which precluded comparative meta-analyses. Thus, the focus of the study was on obtaining single-arm pooled estimates and performing subgroup analyses. Third, the study period is broad, and there may be considerable differences in clinical and technical practices. Despite these limitations, we believe that this systematic review and meta-analysis provides useful information for the current clinical utility of TAE for GIB.

In conclusion, the systematic review and meta-analysis presented here indicate that TAE with NBCA or coils as the primary embolic agent is safe and effective for both nonvariceal UGIB and LGIB.

Data availability

All generated or analyzed data during this study have been included in this published article.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by T. M., M. O., J. S. and R. Y. Data analyses and preparing figures were performed by T. M. and T. H. The first draft of the manuscript was written by T. M. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Not applicable. This study did not involve human participants.

Consent for publication

Not applicable.

Additional information

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