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Review Article

Clinical efficacy and safety of endoscopic metal titanium clip and local injection hemostasis for acute non-variceal upper gastrointestinal tract bleeding: a meta-analysis

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Abstract: This meta-analysis systematically evaluated the clinical efficacy and safety of endoscopic metal titanium clips versus local injection hemostasis for acute non-variceal upper gastrointestinal bleeding (ANVUGIB). A comprehensive search of PubMed, Cochrane Library, Embase, Web of Science, CNKI, and Wanfang data was conducted from inception to June 2025, identifying nine randomized controlled trials involving 871 patients. No significant differences were observed between the titanium clip and injection groups regarding initial hemostasis rate (RR = 1.02, 95% CI: 1.00-1.05, P = 0.08), hospitalization time (MD = -0.59 days, 95% CI: -1.75-0.57, P = 0.32), mortality (RR = 1.23, 95% CI: 0.62-2.43, P = 0.56), or blood transfusion volume (MD = -0.35 mL, 95% CI: -0.85-0.14, P = 0.16). However, the titanium clip group demonstrated significantly lower rebleeding rates (RR = 0.58, 95% CI: 0.36-0.92, P = 0.02) and reduced surgical requirements (RR = 0.32, 95% CI: 0.12-0.85, P = 0.02). Subgroup analysis showed that titanium clips were particularly advantageous in reducing rebleeding among peptic ulcer patients (RR = 0.25, P = 0.0008). Sensitivity analysis confirmed the robustness of these findings, and no significant publication bias was detected. In conclusion, while endoscopic metal titanium clips and local injection offer comparable initial hemostatic efficacy and safety for ANVUGIB, titanium clips are superior for reducing rebleeding and the need for surgical intervention, especially in patients with peptic ulcers or a high risk of rebleeding, and should therefore be prioritized as a hemostatic strategy.

Keywords: Titanium clip, injection hemostasis, acute non-variceal upper gastrointestinal tract, effect, meta-analysis

Introduction

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is a common acute and critical illness in clinical practice, accounting for 80% to 90% of all upper gastrointestinal bleeding cases. Its primary etiologies include peptic ulcers, acute gastric mucosal lesions, esophageal and gastric tumors (excluding varices), and vascular malformations [1, 2]. The disease has a rapid onset and progression, and can lead to hemorrhagic shock and multiple organ failure, with a mortality rate as high as 2% to 10% [3, 4]. Timely and effective hemostatic intervention is key to improving patient prognosis. At present, endoscopic hemostasis has become the first-line treatment for ANVUGIB, with the advantages of being minimally invasive, highly efficient, and directly targeted [5].

Endoscopic local injection hemostasis is a traditional and classic hemostatic method. Commonly used drugs include epinephrine, sclerosing agents, and tissue glue, which can achieve hemostasis by shrinking blood vessels, promoting thrombosis or inducing tissue necrosis. This procedure is simple, inexpensive, and widely used in primary healthcare institutions [6]. However, clinical practice has found that the rebleeding rate after local injection hemostasis is high. For patients with ruptured large-diameter vessels or active massive bleeding, the hemostatic effect is limited, and adverse reactions such as perforation and abdominal pain may occur [7, 8].

Endoscopic titanium clip hemostasis is a novel minimally invasive technique developed in recent years. It achieves physical closure by

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mechanically clipping the bleeding vessel and surrounding tissue, providing rapid and long-lasting hemostasis. It is now gradually being applied in the clinical treatment of ANVUGIB [9, 10]. Several randomized controlled trials have compared the clinical efficacy and safety of titanium clip hemostasis versus local injection hemostasis for this condition. However, some studies have small sample sizes and conflicting conclusions, lacking large-sample, high-quality systematic reviews and validation [11, 12]. Therefore, this study systematically searched relevant randomized controlled trials (RCTs) and used meta-analysis to comprehensively compare the key indicators such as immediate hemostasis success rate, rebleeding rate, length of hospital stay, and mortality rate between titanium clip hemostasis and local injection hemostasis in the treatment of ANVUGIB. The aim is to provide reliable evidence-based medical basis for clinicians to choose the optimal hemostasis scheme, and to provide a reference for future clinical research.

Materials and methods

This study strictly followed the Priority Reporting Guidelines for Systematic Reviews and Meta-analyses (PRISMA Guidelines). The research protocol has been registered in the PROSPERO database, registration number: CRD420261301168.

Literature search

Electronic searches were conducted in PubMed, Embase, Cochrane Library, Web of Science, CNKI, and Wanfang Database. The search period was from the database's inception to June 2025. Search methods combined specialized subject terms with unlimited free keywords.

To improve recall, English search terms included: acute nonvariceal upper gastrointestinal bleeding, ANVUGIB, gastrointestinal bleeding, gastroscopy, endoscopy, titanium clips, hemostatic clips, local injection, adrenaline, randomized controlled trial, and RCT. Taking PubMed database as an example, the literature search strategy is as follows: ("Gastrointestinal Hemorrhage"[Mesh] OR (Gastrointestinal Hemorrhage OR Hemorrhage, Gastrointestinal OR Gastrointestinal Hemorrhages OR Hematochezia OR Hematochezias OR nonvariceal upper gastrointestinal bleeding OR Peptic Ulcer Hemorrhage OR non-variceal upper GI bleeding OR ANVUGIB OR acute upper GI bleed OR peptic ulcer bleeding OR Upper Gastrointestinal Tract OR nonvariceal OR non variceal OR non-variceal OR upper gastrointestinal OR upper GI OR bleed OR hemorrhag) NOT (Esophageal AND Gastric Varices)) AND ("Hemostatic Techniques"[Mesh] OR (Hemostatic Techniques OR Hemostatic Technique OR Technique, Hemostatic OR Techniques, Hemostatic OR Hemostatic Technics OR Hemostatic Technic OR Technic, Hemostatic OR Technics, Hemostatic OR hemoclip OR clip OR endoscopic clip OR metal clip OR titanium clip OR through-the-scope clip)) AND ("Epinephrine"[Mesh] OR (Epinephrine OR Adrenaline OR 4-(1-Hydroxy-2-(methylamino)ethyl)-1,2-benzenediol OR Epitrate OR Medihaler-Epi OR Lyophrin OR Epifrin OR Epinephrine Bitartrate OR Epinephrine Hydrogen Tartrate OR Adrenaline Acid Tartrate OR Adrenaline Bitartrate OR Epinephrine Hydrochloride OR Adrenaline Hydrochloride OR Epinephrine Acetate OR Acetate, Epinephrine OR epinephrine injection OR adrenaline injection OR adrenaline)) AND ("Randomized Controlled Trial"[Mesh] OR (Randomized Controlled Trial OR RCT)). mp. [mp = title, abstract, full text, caption text].

The Chinese database search strategy (taking CNKI as an example) was as follows: (SU="acute non-variceal upper gastrointestinal bleeding" OR SU="ANVUGIB" OR SU="upper gastrointestinal bleeding" OR SU="peptic ulcer bleeding" OR SU="Dieulafoy lesion" OR SU="Mallory-Weiss syndrome")

AND (SU="metal titanium clip" OR SU="hemostatic clip" OR SU="titanium clip" OR SU="endoscopic clip")

AND (SU="local injection" OR SU="epinephrine" OR SU="adrenaline" OR SU="injection hemostasis")

AND (FT="randomized").

Inclusion and exclusion criteria

Inclusion criteria: ① Study subjects: Patients diagnosed with gastrointestinal bleeding, and whose bleeding site was confirmed by gastroscopy or other clinical instruments; ② Intervention and control measures: The experimental group received endoscopic titanium clip hemostasis (which may be combined with other drugs, with clear group definition), while the control group received adrenaline injection or other injection-based hemostasis regimens (which may be combined with other drugs, with clear group definition); ③ Outcome indicators: The literature must include at least one relevant indicator, such as immediate hemostasis rate, rebleeding rate, emergency surgery rate, mortality rate, etc.; ④ Study type: RCTs.

Exclusion criteria: ① Duplicate publications, conference papers, reviews, lectures, and studies where original data cannot be obtained; ② Literature without a control group, or where the control group did not use endoscopic treatment; ③ Experimental studies involving non-human subjects; ④ Literature with outcome indicators irrelevant to this study.

Data retrieval and screening

Evaluation phase: Two scholars independently conducted literature reviews based on established inclusion and exclusion criteria. If disagreements arose, disputes were resolved through discussion and negotiation, or by referring the findings to a third-party professional for objective judgment. For studies with incomplete data, researchers contacted the corresponding author to attempt to complete the dataset. Standardized definitions of outcome indicators: Initial hemostasis success rate was defined as the duration of cessation of active bleeding in the subject after endoscopic treatment at least 5 minutes; rebleeding rate was defined as a rebleeding event occurring within 72 hours to 30 days after initial hemostasis; hospital stay was uniformly extracted and analyzed in days. All data extraction was completed independently by two researchers and cross-checked.

Quality evaluation

To ensure the rigor of the study and the reliability of the data sources, this study adopted a dual-review mechanism. Two independent researchers collaborated to screen literature types, verify the accuracy of disease diagnoses, and conduct a risk of bias assessment. Referring to the Cochrane Manual of Systematic Reviews' risk of bias tool, a risk of bias assessment was conducted on each of the 6 specific items in the included studies. Specific items included: (1) random sequence generation; (2) allocation scheme concealment; (3) blinding implementation (including blinding by researchers, subjects, and outcome assessors); (4) outcome data integrity; (5) outcome reporting selectivity; and (6) other biases. Based on the information in the original research text, each item was divided into three levels: "low risk of bias", "high risk of bias", and "uncertain risk of bias". The evaluation results for each item in each study were recorded in detail. Two researchers independently completed the risk of bias assessment, and the chi-square test (Kappa test) was used to analyze the consistency of the assessment. A Kappa value of 0.85 indicated good consistency (Kappa > 0.75). If there were disagreements in the evaluation of an indicator, a unified conclusion was reached through consultation with a third researcher to ensure the objectivity and reliability of the evaluation results.

Statistical methods

This study used Review Manager 5.3 statistical software to perform data analysis. Meta-analysis was conducted based on the Cochrane scale to assess the risk of research bias. For continuous variables, the mean difference (MD) was used as the effect indicator, and the effect size was presented as a 95% confidence interval (CI). The I^2 statistic was used to assess heterogeneity among studies: when $I^2 \leq 50\%$, no significant heterogeneity was considered, and a fixed-effects model was used; otherwise, statistical heterogeneity was considered to exist, and a random-effects model was used. To verify the robustness of the meta-analysis results, sensitivity analysis was conducted by systematically excluding individual studies; simultaneously, a funnel plot was plotted to visually analyze included studies and determine whether publication bias existed. In this study, the significance level was set at $\alpha = 0.05$, and a P value < 0.05 was considered significant.

Results

Literature search results

This study retrieved 158 academic articles relevant to this research from PubMed, Cochrane Library, Web of Science, CNKI, and Wanfang

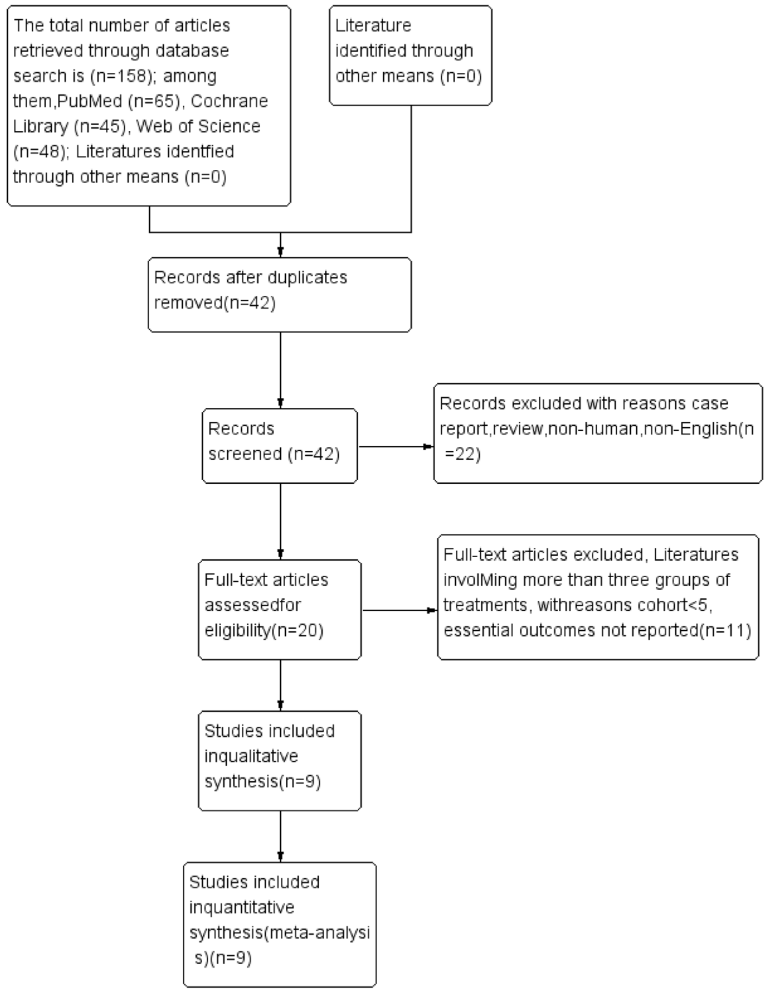

Figure 1. Flow chart for literature screening included in the study.

Database. After initial screening, which eliminated duplicate articles, non-original reviews, meta-analyses, research progress summaries, other types of meta-studies, animal experiments, and articles irrelevant to the research topic, a total of 147 articles were excluded. Subsequently, a full-text review was conducted on the remaining articles, strictly adhering to pre-set inclusion and exclusion criteria, ultimately selecting 9 RCTs as the basis for this study's analysis. The detailed literature screening flowchart is shown in **Figure 1**.

Basic information and quality assessment of included articles

This study ultimately included 9 articles that met the criteria, with a total patient sample size of 871. Detailed basic information on the included articles is shown in **Table 1**. All included studies exhibited implementation bias; the relevant quality assessment results are shown in **Figure 2**.

Immediate hemostasis rate

The eight studies included in this study [13-20] reported on the immediate hemostasis rate in patients, involving a total of 798 patients. Heterogeneity testing results ($P = 0.93$, $I^2 = 0\%$) indicated no significant heterogeneity among the groups; therefore, a fixed-effect model was adopted (**Figure 3**). Meta-analysis results showed no statistically significant difference in the immediate hemostasis rate between the titanium clip group and the injection group (RR = 1.02, 95% CI: 1.00-1.05, $Z = 1.73$, $P = 0.08 > 0.05$).

Rebleeding rate

The eight studies included in this study [13-15, 19, 20] reported on the occurrence of rebleeding in patients, involving a total of 824 patients. The heterogeneity test revealed moderate heterogeneity among the studies ($P = 0.006$, $I^2 = 67\%$). Therefore, a random effects model was used for the pooled analysis (**Figure 4**). The meta-analysis results indicated that the rebleeding rate in the titanium clip group was significantly lower than that of the injection group (RR = 0.58, 95% CI: 0.36-0.92, $P = 0.02$).

Length of hospital stay

The six studies included in this study [13-15, 17-19] reported data on the length of hospital stay, involving a total of 359 patients. Heterogeneity testing showed no significant heterogeneity among the studies ($P = 0.27$, $I^2 = 22\% < 50\%$), therefore a fixed-effect model was used for meta-analysis. The meta-analysis results showed no statistically significant difference in the length of hospital stay between the titanium clip group and the injection group (MD = -0.59 days, 95% CI: -1.75 to 0.57, $P = 0.32$, **Figure 5**).

Table 1. Basic characteristics of the included literature

Author (year)	Number of patients (titanium clip group/injection group)	Cause of the disease	Forrest Classification	Intervention measures		Age (years)		Sex (male/female)		Outcome indicators
				Titanium clip group	Injection group	Titanium clip group	Injection group	Titanium clip group	Injection group	
Park CH 2003 [13]	32 (16/16)	Dieulafoy Lesion	-	Hemostatic clip	Epinephrine injection	59.8±15.1	62.4±14.2	12/4	15/1	①②③④⑤⑥
Grgov S 2012 [14]	58 (28/30)	Peptic ulcer	Ia, Ib, IIa	Hemostatic clip	Hemostatic clip + Epinephrine injection	60.3±11.19	62.3±12.21	23/11	24/12	①②③④⑤⑥
Goto H 2002 [15]	22 (13/9)	UGIB	-	Hemostatic clip	Epinephrine injection	64±21	57±22	7/6	0/9	①②④⑥
Taghavi SA 2009 [16]	172 (83/89)	Peptic ulcer	Ia, Ib, IIa, IIb	Titanium clip + adrenaline	Argon ion coagulation + adrenaline	51.34±14.01	48.63±15.97	60/23	73/16	①②⑤⑥
Lo CC 2006 [17]	105 (52/53)	Peptic ulcer	Ia, Ib, IIa, IIb	Hemostatic clip + adrenaline	adrenaline	64±17	63±16	40/12	41/12	①②④⑤⑥
Huang SP 2002 [18]	35 (18/17)	Mallory-Weiss Syndrome	-	Titanium clip	Epinephrine injection	55.3±18.6	50.6±17.9	15/3	14/3	①②③④⑥
Saltzman JR 2004 [21]	47 (26/21)	Peptic ulcer	-	Hemostatic clip + adrenaline	Bipolar electrocoagulation + adrenaline	62±13	69±14	17/9	14/17	⑥
Świdnicka-Siergiejko A 2014 [19]	107 (55/52)	UGIB	Ia, Ib, IIa, IIb	Hemostatic clip + adrenaline	Epinephrine + bipolar coagulation	62.7±18.9	66.8±16.1	36/19	29/23	①②③④⑤⑥
Chua TS 2005 [20]	293 (91/202)	Peptic ulcer	-	Hemostatic clip + adrenaline	Epinephrine	61±17	66±16	59/32	152/50	②⑤⑥

Note: ① Initial hemostasis; ② Recurrent bleeding; ③ Blood transfusion demand; ④ Hospital stay; ⑤ Surgical intervention required; ⑥ Death; -, indicates that no report was made.

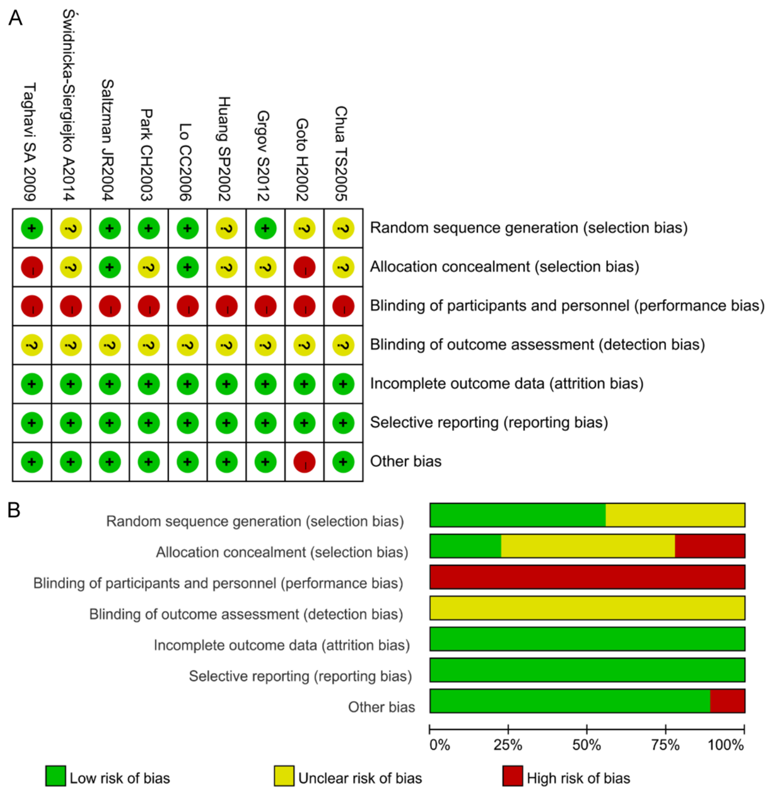

Figure 2. Risk of bias for the included literature. A: Summary chart of overall bias risk for the included studies; B: Overall bias risk chart for the included studies; "+" indicates "low bias". "?" For "unclear bias"; "-" indicates "high bias".

Mortality

This study included 9 studies [13-21] reporting mortality-related outcomes. Two studies [13, 15] were excluded from the quantitative meta-analysis because no deaths were observed in either group. Ultimately, 7 studies (a total of 871 patients) were included in the meta-analysis. Heterogeneity testing indicated good agreement among the studies (I^2 = 0%, P = 0.66), therefore a fixed-effect model was adopted. The pooled results showed no statistically significant difference in mortality between the titanium clip group and the injection group (RR = 1.23, 95% CI: 0.62-2.43, Z = 0.58, P = 0.56, **Figure 6**).

Blood transfusion requirements

Four studies [13, 14, 18, 19] reported transfusion volumes, involving a total of 232 patients. Heterogeneity testing indicated moderate heterogeneity among the studies (P = 0.07, I^2 = 58%), so a fixed-effect model was used for the meta-analysis. Meta-analysis results showed no significant difference in transfusion volume between the titanium clip group and the injection group (MD = -0.35 mL, 95% CI: -0.85 to 0.14, P = 0.16, **Figure 7**).

Surgical intervention

Six studies [13, 14, 16, 17, 19, 20] reported surgery-related outcomes, involving a total of 767 patients. Heterogeneity testing indicated good agreement among studies (I^2 = 0%, P = 0.75), and a fixed-effect model was adopted. The pooled results showed that the need for surgical intervention was significantly lower in the titanium clip group than in the injection group (RR = 0.32, 95% CI: 0.12-0.85, P = 0.02, **Figure 8**).

Subgroup analysis

According to the Cochrane Manual, subgroup analysis must meet two prerequisites: ① a total of ≥ 5 studies included; ② each subgroup must contain at least 2 studies. Even if these prerequisites are met, from a methodological perspective, subgroup analysis is still an exploratory analysis. This study conducted subgroup analyses based on the etiology of bleeding, focusing on the highly heterogeneous outcome measure (rebleeding rate).

Subgroup analysis results showed that the peptic ulcer-related subgroup included 4 studies [14, 16, 17, 20], with no significant difference in heterogeneity between studies (P = 0.49, I^2 = 0%). Meta-analysis using a fixed-effects model indicated that the rebleeding rate in the titanium clip group was significantly lower than that in the injection group (RR = 0.25, 95% CI: 0.12-0.56, P = 0.0008).

The upper gastrointestinal bleeding subgroup included 2 studies [15, 19], but heterogeneity testing was not possible (only one study provided data for meta-analysis. Results showed no statistically significant difference in rebleeding rate between the two groups (RR = 0.71,

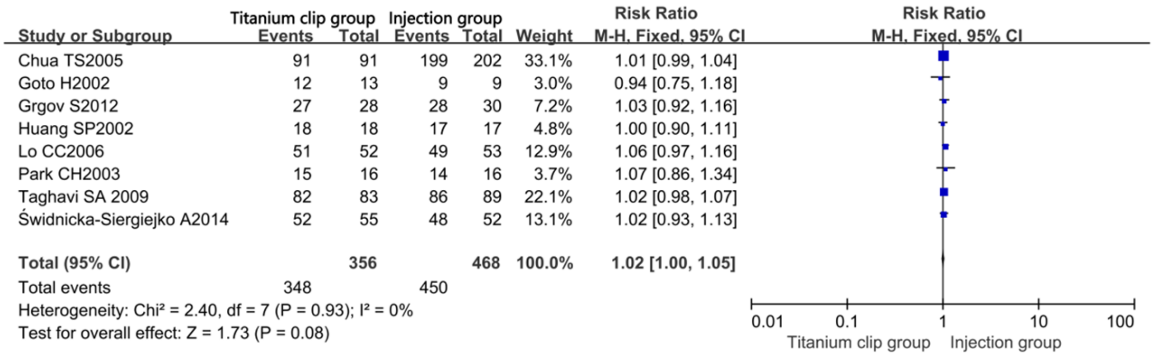

Figure 3. Forest plot of the initial hemostasis rates between the titanium clip group and the injection group.

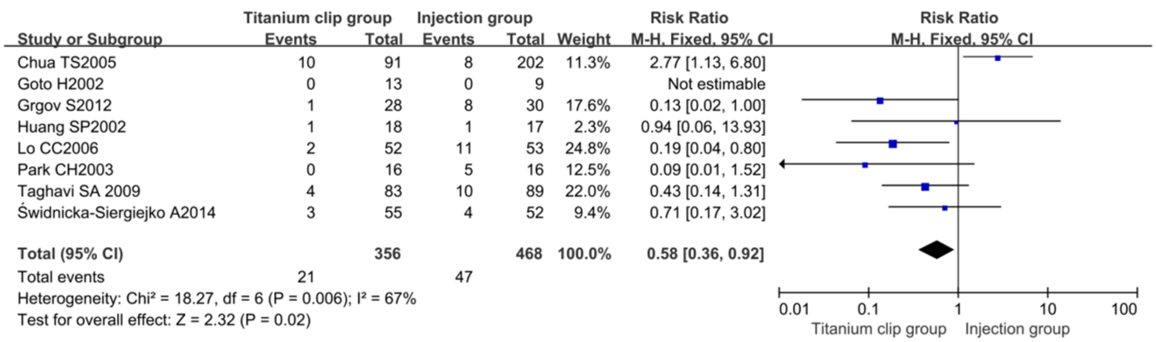

Figure 4. Forest plot of the recurrence of bleeding rates between the titanium clip group and the injection group.

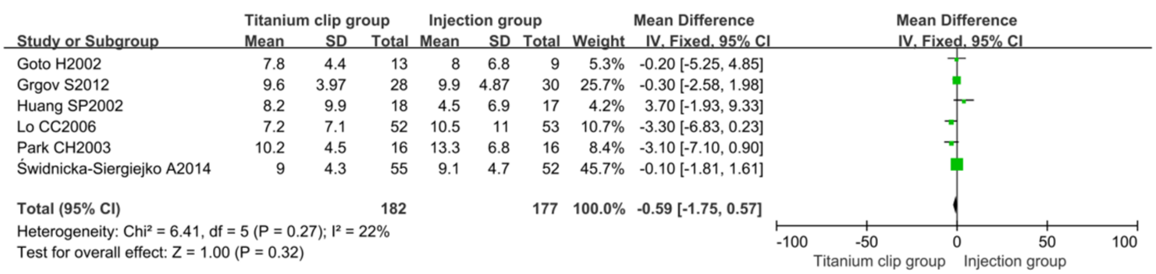

Figure 5. Forest plot of hospitalization time between the titanium clip group and the injection group.

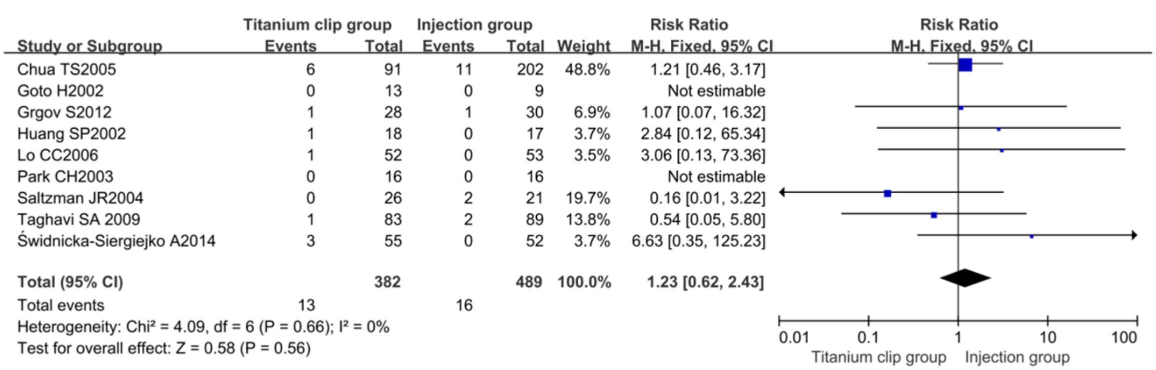

Figure 6. Forest plot of mortality rates for the titanium clip group and the injection group.

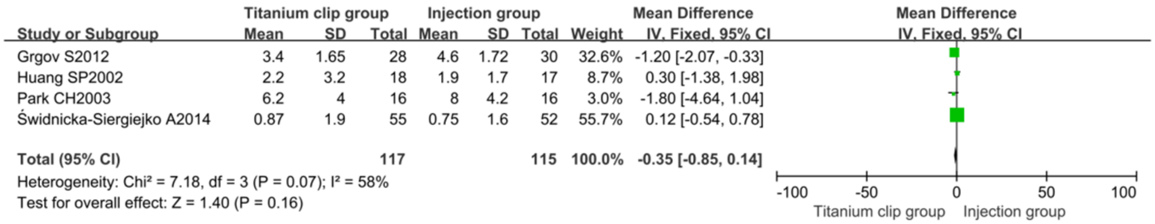

Figure 7. Forest plot of blood transfusion requirements for the titanium clip group and the injection group.

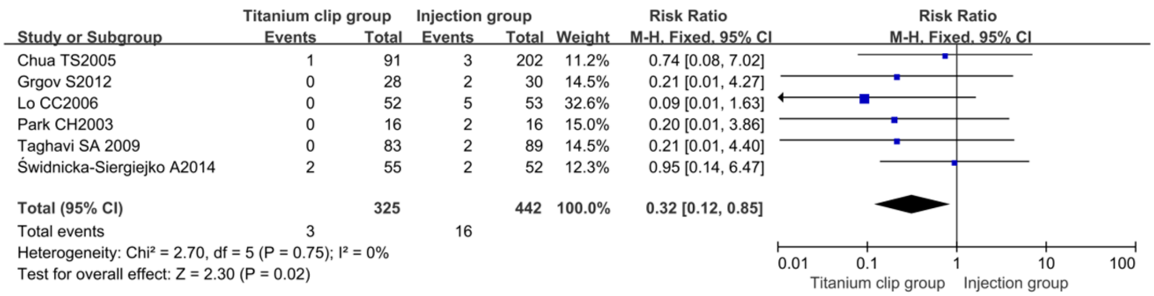

Figure 8. Forest plot of surgical interventions between the titanium clip group and the injection.

95% CI: 0.17-3.02, P = 0.64). Two studies [13, 18] were included in the other etiology subgroup, and there was no significant difference in heterogeneity between the studies (P = 0.22, I^2 = 33%). Results showed that the rebleeding rate in the titanium clip group was lower than that in the injection group, but the difference did not reach the statistical significance (RR = 0.23, 95% CI: 0.04-1.28, P = 0.09).

Subgroup difference tests indicated that there was no significant difference in effect size between the different etiology subgroups (P = 0.45, I^2 = 0%), suggesting that the etiology of bleeding was not the source of heterogeneity in the pooled rebleeding rate results of this study. Relevant results are shown in **Table 2**. Regarding the Forrest classification, since only four studies clearly reported this classification [14, 16, 17, 19], and all patients with clearly classified classifications had high-risk bleeding lesions, no relevant subgroup analysis was conducted.

Sensitivity analysis

To assess the robustness of the meta-analysis results, this study conducted sensitivity analysis after removing individual studies for each outcome measure.

(1) Immediate hemostasis rate: The original pooled results showed no significant difference in immediate hemostasis rate between the two groups (RR = 1.02, 95% CI: 1.00-1.05, P = 0.08). After removing individual studies, the pooled effect size RR fluctuated between 1.00 and 1.04, with all *P* values > 0.05, indicating that the conclusion of no difference between the two groups was robust.

(2) Rebleeding rate: The original pooled results showed that the rebleeding rate in the titanium clip group was significantly lower than that of the injection group (RR = 0.58, 95% CI: 0.36-0.92, P = 0.02). After excluding individual studies, the pooled effect size OR ranged from 0.25-0.34, with all *P* values < 0.05, indicating that the conclusion remained unchanged. This indicates that the positive result regarding rebleeding rate is not affected by individual studies and demonstrates good robustness.

(3) Hospital stay: The original pooled results showed no significant difference in hospital stay between the titanium clip group and the injection group (MD = -0.59 days, 95% CI: -1.75-0.57, P = 0.32). After excluding individual studies, the pooled effect size MD ranged from -0.27 - -1.00, with all *P* values > 0.05, suggesting that the conclusion of no difference

Table 2. Meta-analysis results of subgroups with different causes

Outcome indicator	Subgroup	Included in the study	Sample size	I^2 (%)	P	Effect size and its 95% confidence interval	Z	*P* value among subgroups
Rebleeding rate		8						
	Cause of the disease							
	Peptic ulcer	4	127	0	0.490	0.25 (0.11, 0.56)	0.360	< 0.001
	UGIB	2	7	-	-	0.71 (0.17, 3.02)	0.470	0.640
	Others	2	141	33.0	0.220	0.30 (0.16, 0.56)	1.680	< 0.001

between the two groups is robust. Mortality: The original pooled results showed no significant difference in mortality between the titanium clip group and the injection group (RR = 1.23, 95% CI: 0.62-2.43, Z = 0.58, P = 0.56). After eliminating each study, the range of the pooled effect size RR was 1.02-1.49, with all *P* values were > 0.05, indicating that the conclusion of no difference between the two groups was robust.

(4) Transfusion volume: There was no statistically significant difference in transfusion volume between the titanium clip group and the injection group (MD = -0.35 mL, 95% CI: -0.85-0.14, P = 0.16). After eliminating each study, the range of the pooled effect size MD was -0.95-0.06, with all *P*-values > 0.05, confirming no difference between the two groups.

(5) Surgical Requirement Rate: The pooled original results showed that the surgical requirement rate in the titanium clip group was significantly lower than that of the injection group (RR = 0.32, 95% CI: 0.12-0.85, Z = 2.30, P = 0.02). After removing each study individually, the pooled effect size ratio (OR) fluctuated between 0.23 and 0.43, with all *P* values < 0.05, indicating that the conclusion remained unchanged. This demonstrated that the positive result of the surgical requirement rate wasnot affected by individual studies and had good robustness.

Publication bias

The funnel plots were drawn for the immediate hemostasis rate (**Figure 9A**), rebleeding rate (**Figure 9B**), length of hospital stay (**Figure 9C**), mortality rate (**Figure 9D**), transfusion requirement (**Figure 9E**), and surgical intervention status (**Figure 9F**) in both the titanium clip and injection groups. The results showed that the funnel plots corresponding to immediate hemostasis rate, rebleeding rate, length of hospital stay, and mortality were symmetrically distributed, indicating that there was no significant publication bias in the literature included in this meta-analysis.

Discussion

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is a common gastrointestinal emergency. Rapid and effective hemostasis is key to reducing mortality, shortening hospital stay, and improving prognosis. At present, endoscopic treatment has become the preferred option, and titanium clip hemostasis and local injection hemostasis (mainly with adrenaline solution) are two widely used hemostasis techniques [22]. Although previous studies have suggested that the hemostatic effect of titanium clips may be more durable, the conclusions from different studies are still controversial, and there is a lack of comprehensive evidence from multiple centers and large samples [12]. This study included 9 RCTs with a total of 871 patients through meta-analysis, aiming to further clarify the differences in clinical efficacy and safety between the two hemostasis methods and provide a more reliable basis for clinical diagnosis and treatment decisions.

The results of this meta-analysis showed that there was no significant difference in the initial hemostasis success rate between the titanium clip group and the injection group, which is consistent with the conclusions of many previous studies. A prospective study conducted by Ljubicic et al. [23] also reported that for Forrest grade IIb hemorrhagic ulcers, the success rates of initial hemostasis with titanium clips and adrenaline injection were similar, indicating that both methods can achieve efficient immediate hemostasis, and clinicians can choose

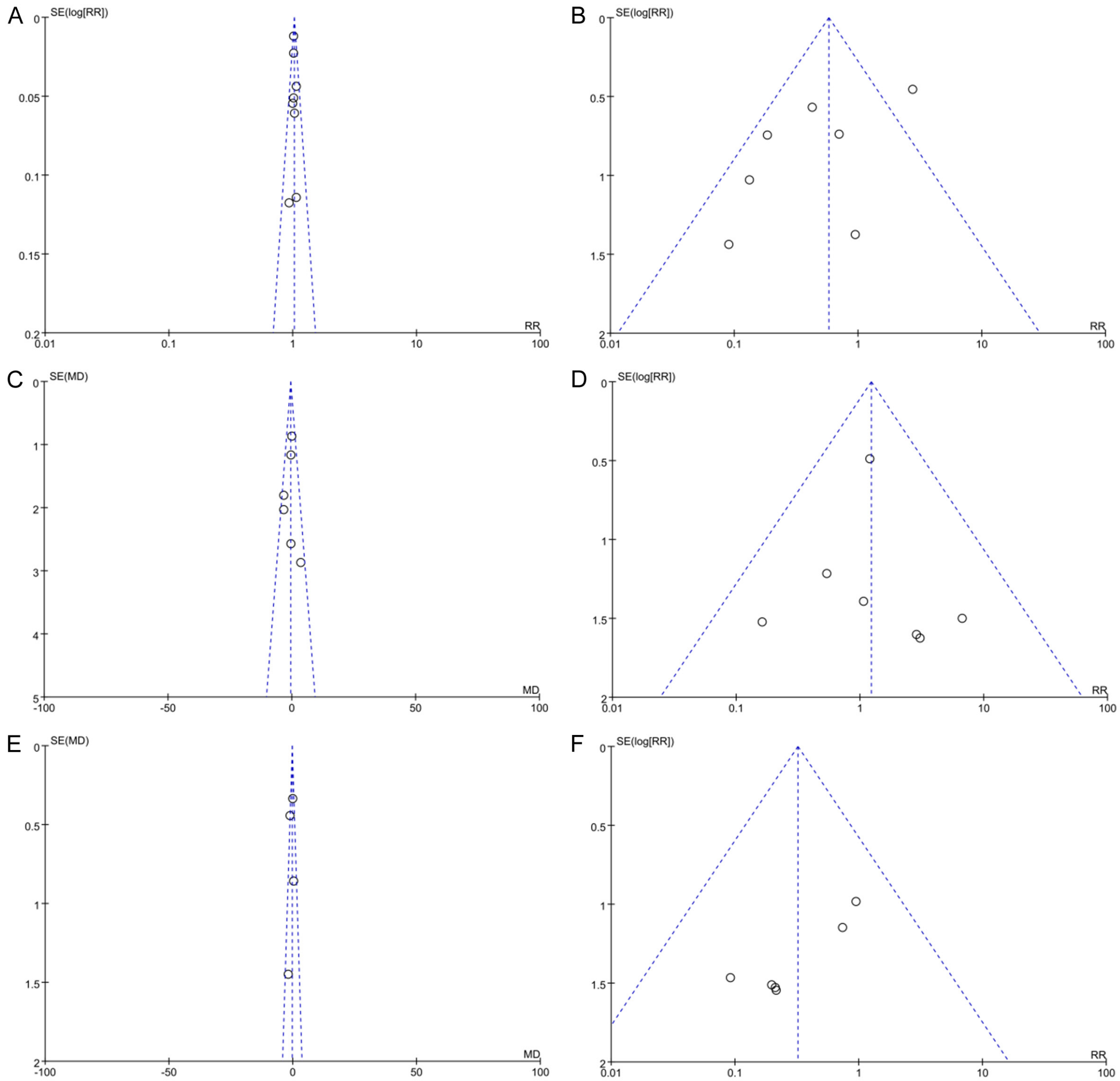

Figure 9. Funnel chart. A: Comparison of the initial hemostasis rate between the titanium clip group and the injection group; B: Comparison of the recurrent bleeding rate between the titanium clip group and the injection group; C: Comparison of the hospitalization time between the titanium clip group and the injection group; D: Comparison of the mortality rate between the titanium clip group and the injection group; E: Comparison of blood transfusion requirements between the titanium clip group and the injection group; F: Comparison of surgical intervention rates between the titanium clip group and the injection group.

flexibly according to their operating habits and the specific condition of patients. However, initial hemostasis is only the first step in treatment, and the persistence of hemostasis (i.e., prevention of rebleeding) is more critical for the final prognosis.

This study found that the rebleeding rate in the titanium clip group was significantly lower than that of the injection group, which is in part consistent with the conclusion of a large-scale multicenter RCTs conducted by Sung et al. [24]. Related studies have pointed out that for ulcers with visible vascular stumps, the effect of titanium clip treatment alone is better than that of injection treatment alone in reducing the rebleeding rate within 72 hours. From the perspective of mechanism of action, titanium clips achieve a more reliable hemostatic effect by mechanically closing the vascular stump, while adrenaline injection hemostasis mainly relies on vasoconstriction and local tissue swelling to play a role. Its hemostatic effect has a relatively short duration and is not suitable for arterial bleeding or spurting bleeding [25]. Most of the lesions included in this meta-analysis were high-risk ulcers with visible blood vessels or active bleeding. Titanium clips rely on mechanical force to directly close the bleeding vessel wall, and are less affected by the vessel diameter, ulcer depth and surrounding tissue edema, so the hemostatic effect is more stable; while injection hemostasis relies on local vasoconstriction and tissue compression to achieve hemostasis. When the bleeding vessel is thick and the ulcer base is deep, it is difficult to form continuous compression, and the hemostatic effect will decrease accordingly. Therefore, titanium clips function better for treatment of high-risk lesions [26]. Endoscopic proficiency and the timing of hemostasis also affect treatment outcomes. Titanium clip placement requires a high level of operator proficiency, especially in areas with high operational difficulty; insufficient proficiency can easily lead to clipping failure [27]. Endoscopic hemostasis completed within 24 hours of bleeding can significantly reduce the rebleeding rate [28]. Early intervention with skilled operators can maximize the advantages of mechanical hemostasis. According to the latest guidelines issued by the European Society of Gastrointestinal Endoscopy and the American Society of Gastrointestinal Endoscopy [29, 30], titanium clips have been recommended as the first-line treatment for high-risk ulcer bleeding, while injection therapy is mostly used as an adjunct therapy. The results of this study are highly consistent with the guidelines, further strengthening the relevant evidence.

The advantage of titanium clips in controlling rebleeding rates is the core conclusion of this study and supports prioritizing titanium clip hemostasis in clinical practice. More importantly, the surgical intervention rate in the titanium clip group was significantly lower than that of the injection group. Reducing the surgical intervention rate not only avoids the trauma and related risks of surgery, but also reduces the consumption of medical resources [31]. Titanium clips have significantly reduced the need for surgery due to rebleeding by controlling rebleeding more effectively. There was no statistical difference in the length of hospital stay between the two groups of patients. The analysis suggests that the length of hospital stay is affected by a variety of factors such as the patient's underlying disease, the management of complications, and the hospital's treatment process. A single hemostasis method cannot determine the length of hospital stay on its own. Barkun et al. [32] pointed out in the clinical guidelines that accurate initial hemostasis is one of the key factors for shortening the length of hospital stay, but it is not the only decisive factor.

In terms of safety, this analysis did not find significant differences in mortality and transfusion requirements between the two groups, further confirming the safety of titanium clip application [16]. Local injection of adrenaline theoretically carries the risk of inducing adverse cardiovascular events, with higher risks in elderly patients or those with underlying cardiovascular disease. However, no directly related serious adverse events were reported in the relevant studies included in this analysis [33]. This is likely related to the clinical use of dilution concentrations (standard ratio 1:10,000) and the method of local administration [34]. It is worth noting that titanium clip application requires a high level of skill from physicians. For ulcers in specific locations (such as the posterior wall of the gastric body or the posterior wall of the duodenal bulb), clip failure and clip dislodgement are common, which is an important factor to consider in clinical practice.

Subgroup analyses based on bleeding etiology showed that in the peptic ulcer subgroup, titanium clip hemostasis significantly reduced the rebleeding rate. In the nonvariceal upper gastrointestinal bleeding and other etiology subgroups, although the statistical difference did not reach the threshold, the overall efficacy showed a trend toward better results. Subgroup differences were not significant, indicating that the efficacy advantage of titanium clip hemostasis is not affected by the underlying bleeding etiology and is applicable to bleeding caused by various factors. From a mechanism of action perspective, titanium clips achieve hemostasis by mechanically clamping the vascular stump; the efficacy does not depend on vasoconstriction or the body's coagulation function, thus providing stable hemostasis for bleeding from different etiologies. Sensitivity analysis of this study confirmed the robustness of the core conclusions: after eliminating individual studies one by one, the pooled analysis of the remaining studies still showed that the rebleeding rate in the titanium clip group was significantly lower than that of the local injection group, confirming that the core conclusions did not depend on data from a single study. Publication bias testing showed that the funnel plots for all outcome indicators were generally symmetrical, suggesting a low likelihood of publication bias.

This study still has several limitations: ① Inconsistent quality of included studies: Some RCTs did not detail the randomization methods, blinding procedures, and dropout rates, possibly introducing bias; ② Incomplete control of heterogeneity sources: The rebleeding rate analysis showed moderate heterogeneity (I^2 = 67%), and although corrected using a random-effects model and subgroup analysis, unidentified confounding factors may still exist; ③ Large publication time span (2002-2014): Early studies used titanium clips and had different endoscopic clarity compared to current clinical consumables and equipment, leading to technical bias; ④ Differences in local injection regimens: Most studies used only epinephrine, while some combined it with bipolar electrocoagulation, affecting the consistency of results; ⑤ Lack of long-term follow-up data: This study only focuses on short-term treatment. The long-term hemostatic effect of titanium clips still needs further verification; ⑥ Some outcome indicators (such as transfusion requirements) were only included in a small number of studies, which will reduce the statistical power; ⑦ Due to the limitations of endoscopic operation, blinding of operators cannot be implemented, which poses a risk of implementation bias; ⑧ The analysis of Forrest grade subgroups is limited: only 4 studies clearly marked the Forrest grade of the lesions, and all of them were high-risk bleeding lesions (Forrest grade Ia~IIb). The remaining studies only defined active bleeding and exposed blood vessels as high-risk characteristics, which could not conduct subgroup comparisons of high- and low-risk bleeding lesions, which also reflects the current clinical situation-endoscopic hemostasis is mostly used for high-risk bleeding lesions; ⑨ Key covariate information is missing: most original studies did not clearly record the core indicators affecting efficacy, such as operator experience, blood vessel diameter, and ulcer depth, which could not be used for stratified analysis and meta-regression analysis. Future research should focus on conducting more rigorously designed, large-sample, and long-follow-up multicenter RCTs. These trials should standardize the reporting of key covariates such as surgeon experience, timing of hemostasis, and lesion characteristics (vessel diameter, ulcer depth). Factorial designs should also be employed to determine the optimal application of different hemostasis techniques in patients with varying risk stratifications.

Conclusion

Both endoscopic titanium clip hemostasis and local injection of hemostatic agents are effective in achieving initial hemostasis for treating ANVUGIB, with comparable safety profiles. Compared to injection hemostasis, titanium clip hemostasis offers significant advantages in reducing rebleeding rate and minimizing the risks of surgical intervention, making it particularly suitable for patients with peptic ulcer bleeding. It should be preferred, especially for those at high risk of rebleeding.

Disclosure of conflict of interest

None.

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