

ORIGINAL RESEARCH

# Evaluating the Significance of Titanium Clip Marking Under Endoscopy in Upper Gastrointestinal Bleeding Patients with Failed Endoscopic Hemostasis

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## ABSTRACT

**Objective** • This study investigated the role of titanium clip marking during endoscopy in managing patients with upper gastrointestinal bleeding (UGIB) for whom endoscopic hemostasis has proven ineffective.

**Methods** • A total of 63 UGIB patients admitted to the Affiliated Hospital of Zunyi Medical University between January 2018 and November 2020 were selected as the study cohort. Patients were randomly assigned to one of two groups: the control group (n=23) and the combined group (n=40). The control group underwent transcatheter arterial embolization (TAE), while the combined group received endoscopic metallic titanium clip-assisted TAE. This study compared the rates of successful embolization, clinical success, recurrence, operation time, radiation exposure time, radiation dosage, levels of hs-CRP, Cor, NE, TNF- $\alpha$ , IL-6, and ADH before and after treatment, as well as postoperative complications between the two groups.

**Results** • The combined group of patients exhibited significantly higher rates of successful embolization and

clinical success compared to the control group ( $P < .05$ ). Additionally, the recurrence rate and levels of hs-CRP, Cor, NE, TNF- $\alpha$ , IL-6, and ADH were significantly lower in the combined group compared to the control group ( $P < .05$ ). Furthermore, patients in the combined group had shorter operation times, reduced radiation exposure times, and lower radiation dosages compared to the control group ( $P < .05$ ). There was no statistically significant difference in the occurrence of postoperative complications between the two groups ( $P > .05$ ).

**Conclusions** • Using titanium clip marking during endoscopy provides valuable guidance in managing patients with upper gastrointestinal bleeding who have not responded to endoscopic hemostasis. This finding is especially relevant in digital subtraction angiography (DSA) and transcatheter arterial embolization (TAE) treatments. It enhances the clinical efficacy and safety of the procedure. (*Altern Ther Health Med*. [E-pub ahead of print.]

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## INTRODUCTION

Upper Gastrointestinal Bleeding (UGIB) refers to hemorrhagic disorders in the gastrointestinal tract, primarily affecting the ligament of Treitz and higher regions, including the esophagus, stomach, duodenum, pancreas, bile ducts, and colonic anastomosis.<sup>1</sup> Epidemiological data indicate an annual incidence of 80 to 150 cases per 100 000 individuals, with a mortality rate ranging from 2% to 15%.<sup>2</sup> Common UGIB symptoms include hematemesis, melena, or

hematochezia, often accompanied by secondary signs such as syncope, fatigue, and weakness.<sup>1-2</sup>

The treatment of UGIB includes various approaches, including pharmacotherapy and advanced endoscopic hemostasis. Conventional pharmacotherapy has been the standard approach for UGIB, which offers the advantage of immediate intervention and broad accessibility but is limited by potential side effects and the risk of recurrence. Advances in digestive endoscopy technology have given rise to endoscopic hemostasis as an effective treatment for UGIB.<sup>3</sup> While highly effective, it faces challenges related to comorbidities, anemia severity, bleeding intensity, and lesion characteristics.<sup>4</sup>

The evolving landscape of interventional techniques, innovative embolization materials, and proficient interventional radiologists has heightened the utilization of angiography and embolization in the management of UGIB.<sup>5</sup> Transcatheter arterial embolization (TAE), assisted by digital subtraction angiography (DSA), has emerged as a primary treatment approach owing to its impressive clinical success rates and minimal complications.<sup>6</sup>

DSA, a critical tool in diagnosing and intervening in various clinical conditions, plays a vital role in locating the responsible vessels for gastrointestinal bleeding.<sup>7</sup> While positive DSA results are crucial for the success of TAE, adverse outcomes can be influenced by factors such as bleeding volume, location, intermittent bleeding during angiography, patient compliance, and medications.<sup>8</sup> In cases of negative DSA results, experimental embolization is often considered in clinical practice.<sup>9</sup> However, the effectiveness and safety of this approach remain uncertain.

This study aimed to examine the effectiveness and safety of employing titanium clip marking under endoscopy for localization, followed by TAE treatment, in UGIB patients who have not responded to initial endoscopic hemostasis. This study also aimed to determine whether this innovative approach enhances TAE treatment's success rate and safety in patients with UGIB.

## MATERIALS AND METHODS

### Study Design

This study enrolled 63 patients with UGIB admitted to the Affiliated Hospital of Zunyi Medical University between January 2018 and November 2020. The cohort comprised 43 males and 20 females, aged 25 to 85 years (mean age:  $58.38 \pm 8.98$  years). Utilizing a random number table method, patients were randomly allocated to either the control group ( $n=23$ ) or the combination group ( $n=40$ ). Notably, there were no statistically significant differences in gender and age between the two groups ( $P > .05$ ), ensuring comparability. This study was conducted following the principles of the Helsinki Declaration.

### Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) patients presenting with upper gastrointestinal bleeding, manifesting as hematemesis, melena, or hematochezia; (2) patients who had not responded to conservative or endoscopic treatment; (3) patients with unexplained gastrointestinal bleeding. Exclusion criteria were as follows: (1) patients with variceal bleeding resulting from liver cirrhosis; (2) patients with coagulation disorders; (3) patients with recent myocardial infarction, severe coronary heart disease, or acute heart failure.

### Patient Preparation

Before treatment, patient preparation involves a structured process. Patients were initially advised to undergo fasting, ensuring an empty stomach for the procedure. This step was followed by replenishment of blood volume, correction of shock, and removal of gastric clots and secretions. This comprehensive preparation laid the foundation for the subsequent medical intervention, promoting its safety and effectiveness.

### Transcatheter Arterial Embolization (TAE) Treatment Procedure

In the control group, patients underwent TAE treatment. The procedure involved the following steps: (1) arterial

access: the procedure began with a successful femoral artery puncture performed under local anesthesia using 2% lidocaine. It ensured patient comfort during the intervention; (2) catheter insertion: a sheath was inserted, providing access to the arterial system. A 5F RH catheter or Yashiro catheter was selectively advanced into specific arteries, including the celiac trunk, superior mesenteric artery, inferior mesenteric artery, gastroduodenal artery, and left gastric artery. This precise catheter placement allowed for DSA angiography.

(3) Angiography: DSA angiography was conducted to identify and visualize the responsible vessels for gastrointestinal bleeding; (4) Embolization treatment: in cases where positive DSA findings were observed, embolization treatment was initiated. It involved the use of spring coil embolization or the slow injection of gelatin sponge particles and/or gelatin sponge strips to effectively embolize the bleeding artery, stopping further hemorrhage; (5) catheter withdrawal: after successful embolization, the catheter was carefully withdrawn to the main artery; (6) confirmation of hemostasis: verification of no further opacification at the embolized site was performed to confirm the effective hemostasis.

(7) Closure and monitoring: pressure was applied to the puncture site to ensure hemostasis. A compression dressing was applied, and the punctured limb was immobilized for 8 hours. Patients remained in a supine position for 24 hours to minimize the risk of complications. Continuous monitoring included assessing for bleeding or oozing at the puncture site and vigilance in monitoring dorsalis pedis artery pulsation on both sides, along with regular vital signs checks.

### Two-Step Procedure in the Combination Group

In the combination group, patients underwent a two-step procedure involving endoscopic placement of a metal titanium clip followed by TAE treatment.

**Endoscopic Titanium Clip Placement.** An Olympus GIF-H260/240 electronic gastroscope was employed for this stage. A sheath was properly connected to the gastroscope, facilitating the placement of the titanium clip. After identifying the lesion using endoscopy, a pusher was inserted through the endoscope channel to the distal end of the endoscope. The titanium clip was rotated into the optimal position, allowing it to grasp the lesion and surrounding tissue. Once proper localization was achieved, the clip release device was withdrawn along the original path.

**TAE Treatment.** After the successful localization, TAE treatment was carried out in a manner consistent with the steps undertaken in the control group. This two-step procedure in the combination group ensured precise localization of the bleeding site under endoscopy before proceeding with TAE treatment, thereby contributing to the overall effectiveness of the intervention.

### Observation Indicators

**Successful Embolization.** Successful embolization was defined as the absence of contrast agent extravasation at the

lesion site or no further opacification of the aneurysmal cavity or arteriovenous malformation.

**Clinical Success.** Clinical success was determined by the absence of post-embolization bleeding or hemodynamic instability within 30 days after the procedure. The clinical success rate was calculated as the ratio of cases with complete hemostasis to the total embolization cases. Clinical success rate = Complete hemostasis cases/total embolization cases. A decrease in hemoglobin of more than 1g/dL indicated rebleeding.

**Procedural Metrics.** Parameters recorded for both groups included operation time, radiation time, radiation dose, and postoperative complications.

**Biomarker Analysis.** The study involved the measurement of high-sensitivity c-reactive protein (hs-CRP), cortisol (Cor), Neutrophils (NE), tumor necrosis factor-alpha (TNF- $\alpha$ ), Interleukin-6 (IL-6), and antidiuretic hormone (ADH) levels before and after treatment in both groups. In the context of UGIB, these biomarkers played a critical role as indicators: (1) elevated hs-CRP indicated gastrointestinal inflammation, which is common in conditions such as ulcers or gastritis; (2) increased cortisol levels signified a stress response, particularly in cases of severe bleeding; (3) elevated neutrophil levels indicated an inflammatory reaction to internal damage; (4) high levels of TNF- $\alpha$  and IL-6 reflected persistent inflammation associated with ulcerative diseases or inflammatory disorders that cause UGIB; (5) ADH release, triggered by reduced blood volume, assisted in water retention during severe UGIB. These changes in biomarkers played a significant role in diagnosing UGIB and assessing disease severity, guiding clinical interventions.

### Statistical Analysis

The statistical analysis was conducted utilizing IBM's statistical package for social science (SPSS) software, version 20.0 (Armonk, NY, USA). Normally distributed count data were presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) and assessed using *t* tests. For comparing count data, Fisher's exact test was applied. A significance level of  $P < .05$  was used to determine the statistical significance of differences.

## RESULTS

### Comparison of Treatment Outcomes

The control group, consisting of 23 patients, exhibited a contrast success rate of 82.6% and a treatment success rate of 60.87%. In contrast, the combination group, comprising 40 patients, indicated an impressive 100% contrast success rate and a notably higher treatment success rate of 92.5%. Table 1 provides a full comparison of treatment outcomes in two patient groups. The statistical analysis, utilizing F statistics and *P* values, revealed significant differences between the two groups, highlighting the superior effectiveness of the combination treatment approach in comparison to the control group.

### Recurrence Rates Comparison

A comparison of recurrence rates between the two patient groups revealed distinct outcomes. In the control

**Table 1.** Comparison of Treatment Effect Between Two Groups of Patients [n (%)]

| Group             | n  | Contrast Success Rate | Treatment Success Rate |
|-------------------|----|-----------------------|------------------------|
| Control Group     | 23 | 19(82.6)              | 14(60.87)              |
| Combination Group | 40 | 40(100)               | 37(92.5)               |
| F                 |    | 7.428                 | 3.891                  |
| P value           |    | .006                  | .049                   |

Note: The table displays the comparison of treatment outcomes between two groups, showing the number of patients (n), the contrast success rate, and the treatment success rate, represented as percentages in parentheses.

**Table 2.** Comparison of Recurrence Rate Between Two Groups of Patients [n (%)]

| Group             | n  | Recurrence Rate |
|-------------------|----|-----------------|
| Control Group     | 14 | 3(21.4)         |
| Combination Group | 37 | 2(5.4)          |
| F                 |    | 4.496           |
| P value           |    | .034            |

Note: This table presents a comparison of the recurrence rates between the two groups of patients. It provides the number of patients (n) in each group and the corresponding recurrence rates in percentages.

**Table 3.** Comparison of Operation Time and Radiation Time Between Two Groups ( $\bar{x} \pm s$ )

| Group             | n  | Operation Time (min) | Radiation Time (min) |
|-------------------|----|----------------------|----------------------|
| Control Group     | 19 | 130.30 $\pm$ 22.26   | 48.12 $\pm$ 10.22    |
| Combination Group | 40 | 69.50 $\pm$ 15.68    | 17.46 $\pm$ 6.39     |
| t                 |    | 12.090               | 14.098               |
| P value           |    | .000                 | .000                 |

Note: This table illustrates a comparison of operation time and radiation time between the two groups of patients. It provides the number of patients (n), mean operation time, and mean radiation time, along with standard deviations ( $\bar{x} \pm s$ ).

group, three patients experienced recurrent bleeding, with two of them demonstrating improvement after undergoing surgical intervention. Unfortunately, one patient in this group failed to attain successful hemostasis and, tragically, did not survive. In contrast, within the combined group, only two patients encountered recurrence. However, both patients achieved successful hemostasis after undergoing surgical intervention. The recurrence rate within the combined group was notably lower than that observed in the control group, as indicated by a significant difference ( $P < .05$ ), refer to Table 2.

### Surgical and Radiation Exposure Times Comparison

When comparing surgical time and radiation exposure time between the two patient groups, notable differences emerged. The combined group displayed significantly shorter durations in both surgical procedures and radiation exposure in comparison to the control group ( $P < .05$ ), refer to Table 3.

### Comparison of Radiation Doses

In a comparison of radiation doses between the two patient groups, a significant difference was observed. The combined group received markedly lower radiation doses in comparison to the control group ( $P < .05$ ), refer to Table 4.

**Table 4.** Comparison of Radiation Dose Between Two Groups of Patients ( $\bar{x} \pm s$ )

| Group             | n  | Radiation Dose (mGy) |
|-------------------|----|----------------------|
| Control Group     | 19 | 1868.20±332.63       |
| Combination Group | 40 | 661.91±121.65        |
| <i>t</i>          |    | 20.394               |
| <i>P</i> value    |    | .000                 |

Note: This table presents a comparison of radiation doses in milligrays (mGy) between the two groups of patients. It includes the number of patients (n) in each group and the mean radiation dose with standard deviations ( $\bar{x} \pm s$ ).

**Table 5.** Comparison of the Levels of hs-CRP, Cor, and NE Before And After Treatment Between Two Groups of Patients ( $\bar{x} \pm s$ )

| Group             | n  | hs-CRP(mg/L) |            | Cor(nmol/L)  |              | NE(µg/L)   |            |
|-------------------|----|--------------|------------|--------------|--------------|------------|------------|
|                   |    | Before       | After      | Before       | After        | Before     | After      |
| Control Group     | 14 | 18.16±8.52   | 12.82±7.42 | 379.37±17.01 | 328.51±19.42 | 73.52±5.62 | 41.57±4.85 |
| Combination Group | 37 | 18.74±3.52   | 5.47±2.58  | 382.63±17.57 | 288.53±18.65 | 74.25±7.58 | 29.25±2.58 |
| <i>t</i>          |    | 0.247        | 3.62       | 0.604        | 6.76         | 0.375      | 9.03       |
| <i>P</i> value    |    | 1.186        | .020       | 1.45         | .002         | 1.29       | .002       |

Note: This table presents a comparison of different biomarker levels: hs-CRP: high-sensitivity C-reactive protein; Cor: cortisol; and NE: neutrophils before and after treatment in two groups of patients. The table provides the mean values ( $\bar{x}$ ) with standard deviations (s) for each parameter, both before and after treatment. Additionally, it includes the *t* values and corresponding *P* values, indicating the statistical significance of differences between the two groups for each parameter.

**Table 6.** Comparison of the Levels of TNF-α, IL-6 and ADH Before And After Treatment Between Two Groups of Patients ( $\bar{x} \pm s$ )

| Group          | n  | TNF-α(µg/L) |            | IL-6(ng/L)  |            | ADH(mU/L)  |           |
|----------------|----|-------------|------------|-------------|------------|------------|-----------|
|                |    | Before      | After      | Before      | After      | Before     | After     |
| Control        | 14 | 19.87±3.25  | 10.25±2.95 | 90.25±9.52  | 52.25±1.21 | 10.98±1.09 | 7.35±0.94 |
| Combination    | 37 | 20.25±2.52  | 6.57±1.22  | 91.25±10.25 | 38.25±3.52 | 11.25±1.02 | 3.56±1.03 |
| <i>t</i>       |    | 0.395       | 4.53       | 0.328       | 21.11      | 0.804      | 3.79      |
| <i>P</i> value |    | .698        | .002       | 1.254       | .000       | 1.16       | .014      |

Note: This table provides a comparison of the levels of TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; and ADH: antidiuretic hormone before and after treatment in two groups of patients. The table includes mean values ( $\bar{x}$ ) with standard deviations (s) for each parameter, both before and after treatment. Additionally, it presents the *t* values and corresponding *P* values, indicating the statistical significance of differences between the two groups for each parameter.

**Table 7.** Comparison of Postoperative Complications Between Two Groups of Patients [n(%)]

| Group             | n  | Low Fever | Stomach Ache | Complication |
|-------------------|----|-----------|--------------|--------------|
| Control Group     | 14 | 2(14.3)   | 2(14.3)      | 4(28.6)      |
| Combination Group | 37 | 3(8.1)    | 3(8.1)       | 6(16.2)      |

Note: This table compares postoperative complications between two groups of patients, presented as frequencies and percentages [n(%)]. The percentages indicate the proportion of patients in each group who experienced these complications.

**Comparison of Biomarker Levels Before and After Treatment**

A comparison of hs-CRP, Cor, NE, TNF-α, IL-6, and ADH levels before and after treatment between the two patient groups revealed significant differences. The combined group exhibited markedly lower levels of hs-CRP, Cor, NE, TNF-α, IL-6, and ADH after treatment in comparison to the control group (*P* < .05), refer to Table 5 and Table 6.

**Postoperative Complications Comparison**

A comparison of postoperative complications between the two patient groups is presented in Table 7. In the control group (n=14), 14.3% of patients experienced low fever, and 14.3% had stomachache, resulting in an overall complication rate of 28.6%. In comparison, the combination group (n=37) exhibited a lower incidence of complications, with 8.1% experiencing low fever, 8.1% reporting stomach aches, and an overall complication rate of 16.2%. These findings suggest a potential advantage in postoperative outcomes for the combination group.

**DISCUSSION**

UGIB is characterized by bleeding originating from the proximal end of the Treitz ligament. This condition is typically categorized into two primary groups: variceal and non-variceal bleeding.<sup>5</sup> Non-variceal upper gastrointestinal bleeding, which arises from conditions such as peptic ulcers, acute gastric mucosal lesions, and upper gastrointestinal malignancies, represents a frequent and life-threatening emergency within the field of emergency medicine.<sup>6-8</sup> It is notably distinguished by substantial blood loss and a high rate of bleeding, factors that significantly intensify the challenges associated with its treatment.<sup>9</sup>

Failure to administer timely and effective treatment can result in severe consequences, including shock and, in extreme cases, fatality. Hence, it is imperative to promptly implement effective therapeutic measures, aiming not only to enhance the prognosis of the disease but also to elevate the quality of life for individuals affected. As reported by clinical practitioners,<sup>10</sup> patients who exhibit hemodynamic instability and signs of upper gastrointestinal bleeding should undergo an urgent endoscopic examination within 24 hours.

Endoscopic hemostasis represents a minimally invasive, easily performed, and secure treatment modality for upper gastrointestinal bleeding. It has demonstrated substantial efficacy in controlling bleeding, reducing inflammation, and lowering the risk of rebleeding. This approach primarily controls the disease's progression, effectively shortens the time required for hemostasis, reduces hospital stay, and diminishes the need for blood transfusions. Consequently, it holds considerable clinical value and has gained widespread clinical application.<sup>11</sup>

However, the utilization of endoscopic treatment in cases of acute upper gastrointestinal bleeding is constrained by several factors, including anatomical considerations, a history of previous bleeding episodes, the presence of concomitant severe illnesses, the diverse range of underlying causes, and the heightened risk of treatment failure, especially when dealing with substantial bleeding volumes.<sup>12</sup>

For patients who do not respond to endoscopic hemostasis, a common strategy involves attempting transcatheter arterial embolization.<sup>13</sup> If hemostasis is not successfully achieved through this method, surgical intervention becomes a viable consideration. It is vital to recognize that upper gastrointestinal bleeding is a complex condition with multifaceted underlying causes.

Accurate assessment of the bleeding site and etiology plays a crucial role in diagnosis and treatment. DSA serves as a valuable tool, offering clear visualization of vascular structures and real-time monitoring of contrast agent flow within the vessels. This capability enables precise identification of the bleeding site and qualitative determination of the underlying cause. However, it's important to note that DSA is an invasive procedure that may not be well tolerated by severely ill patients and is not readily repeatable.

Interventional physicians maintain the perspective that DSA should precede interventional surgery. However, the process of vascular imaging can present challenges, including factors such as suboptimal patient cooperation, vasospasm induced by shock or catheter insertion, interference from clotting medications, artifacts that can affect image quality, suboptimal positioning of the catheter tip, and the skill of the operator. These factors can collectively lead to subpar image quality and, in some cases, result in false-negative angiography outcomes.

In a retrospective analysis conducted by Noh et al.,<sup>14</sup> clinical data from 321 patients with gastrointestinal bleeding was reviewed. The findings indicated a positive detection rate of 50.8% for DSA. Moreover, if suspicious bleeding sources had already been identified through other examinations, the positive rate of arterial angiography was notably higher. It is worth noting that the clinical success rate was observed to be lower in the prophylactic embolization group when compared to the targeted embolization group.

In a study conducted by Zhao et al.,<sup>15</sup> the use of titanium clips for guidance in transcatheter embolization treatment of patients with failed endoscopic therapy for bleeding gastric ulcers was investigated. Compared to patients without titanium clip guidance, embolization treatment guided by titanium clips demonstrated better success rates and survival rates. Furthermore, no complications related to embolization treatment were observed, indicating a higher level of safety.

In this study, endoscopic localization of suspected bleeding or the bleeding site using titanium clips was performed to guide DSA and TAE. This approach aimed to improve the success rate of embolization and clinical outcomes while reducing the rate of recurrent bleeding after intervention. The core principle of embolization treatment is to act quickly and precisely while also ensuring that unintended embolization of other arteries, which can lead to complications, is to be avoided. In principle, the shorter the bleeding duration and the lesser the blood loss, the more favorable the patient's prognosis.

In a study by Wang et al.,<sup>16</sup> 1-2 titanium clips were positioned at the bleeding lesion's edge during endoscopic examination. This procedure facilitated the surgical team in swiftly and accurately pinpointing the diseased blood vessels, thus reducing the duration of TAE and enhancing its success rate. Additionally, these clips can act as guides for surgeons to perform super-selective embolization of the affected blood vessels, ultimately minimizing the risk of trauma.

In this study, a clamp with an auxiliary rotation device was employed during the endoscopic examination to accurately mark and locate the lesion, thereby streamlining

the subsequent TAE treatment. This method significantly reduced the duration of TAE treatment, lowered patient radiation exposure, and, consequently, reduced radiation dosage. This approach not only enhances the effectiveness of patient treatment and prognosis but also enhances the safety of the procedure. The utilization of titanium clips and rotation devices during endoscopic examination demonstrated a significant reduction in TAE treatment duration, resulting in decreased radiation exposure and improved safety. This approach holds promise for enhancing patient treatment effectiveness and prognosis.

### Study Limitations

This study has a few limitations that warrant consideration. First, the relatively small sample size and the single-center design may restrict the broader applicability of the findings to a more diverse patient population. Second, the study predominantly focused on short-term outcomes, overlooking long-term follow-up data that could offer a more comprehensive understanding of the technique's durability and sustained benefits. Furthermore, the study did not investigate the potential variations in the effectiveness of the titanium clip marking technique based on the location or underlying cause of upper gastrointestinal bleeding, which could provide valuable insights into its versatility. These limitations emphasize the need for larger, multicenter investigations with extended follow-up periods to confirm the findings and explore the technique's adaptability across diverse clinical scenarios.

### CONCLUSION

In conclusion, this study highlights the significant potential of employing titanium clip marking during endoscopic examination for patients with upper gastrointestinal bleeding. The method not only aids in precisely locating the bleeding site but also provides invaluable guidance for subsequent interventional treatments, notably DSA. This approach offers distinct advantages by addressing the challenges and avoiding risks often associated with surgical procedures, resulting in expedited surgeries, reduced radiation exposure, and enhanced procedural success rates, ultimately enhancing clinical safety. Furthermore, the simplicity and cost-effectiveness of the titanium clip marking procedure make it a practical addition to endoscopic examinations. The study's findings support its clinical viability and also emphasize its potential for broader adoption in the management of upper gastrointestinal bleeding cases. However, further research, including larger-scale, multicenter studies with extended follow-up, is warranted to confirm and expand upon these promising results.

### CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

### AUTHORS' CONTRIBUTIONS

JZ and KY designed the study and performed the experiments; RS collected the data, BL analyzed the data, and JZ and KY prepared the manuscript. All authors read and approved the final manuscript.

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## ETHICAL COMPLIANCE

The ethics committee of the Affiliated Hospital of Zunyi Medical College approved this study. Signed written informed consent was obtained from the patients and/or guardians.

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