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Endoscopic Clips Marking for Transcatheter Arterial Embolization in Refractory Peptic Ulcer Bleeding Patients: A Cohort Study

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ABSTRACT

Background & Aims: Transcatheter arterial embolization (TAE) is recommended for refractory peptic ulcer bleeding. There are 46% of patients showed no detectable contrast extravasation during TAE. Endoscopic clip in bleeding lesion is visible and could be used as a marker in TAE. We aimed to learn whether endoscopic clips marking would ameliorate the prognosis.

Methods: We retrospectively collected data of patents who received TAE because of refractory peptic ulcer bleeding, between 1 January 2016 to 31 December 2022. 188 patients were included and divided into two groups according to clips visibility in angiography. Baseline data about age, gender, bleeding severity, comorbidities, history of antiplatelet or anticoagulation drugs and endoscopic findings were balanced with the inverse probability of treatment weighting method.

Results: There were 59 patients without clips received TAE, and 129 with clips. The in-hospital rebleeding rate after TAE was much higher in patients without clip than with clips (45.8% vs 33.3%). Cox regression analysis indicated that endoscopic clips marking decreased the rebleeding (aHR=0.492, 95%CI: 0.242-1.001, p=0.050). Also, in patient with clips, the empirical TAE rate was higher (64.3% vs 11.9%, p<0.001). No difference in in-hospital all-cause mortality was found (without clips vs with clips 11.9% vs 12.4%). The hospital stay length and embolized vessels types showed no differences between the two groups.

Conclusions: In refractory peptic ulcer bleeding patients, endoscopic clips marking decreased the in-hospital rebleeding rate after TAE, but did not affect the mortality.

Key words: refractory peptic ulcer bleeding – transcatheter arterial embolization – peptic ulcer – nonvariceal upper gastrointestinal bleeding – endoscopic clips marking.

Abbreviations: aCCI: age-adjusted Charlson Comorbidity index; GBS: Glasgow-Blatchford score; HB: hemoglobin; IPTW: inverse probability of treatment weighting; OGD: oesophago-gastro-duodenoscopy; SI: shock index; SMD: standardized mean difference; TA: transcatheter angiography; TAE: transcatheter arterial embolization.

INTRODUCTION

Peptic ulcer is the most common non-variceal upper gastrointestinal bleeding diseases. Standard first-line treatments include proton pump inhibitors and therapeutic endoscopy. However, rebleeding occurs in 5-27% of patients following endoscopy hemostasis, with mortality rates reaching as high as 8% [1-3]. For patients with refractory bleeding, transcatheter arterial embolization (TAE) is recommended [4]. However, rebleeding occurs in approximately 49% of cases post-TAE, increasing mortality rates to 51% [5, 6].

One reason for rebleeding following TAE might be inaccurate embolization. It is reported that in 46% of cases, angiography fails to reveal contrast extravasation, complicating the precise localization of the exact embolization site [7]. Song et al. [8] indicated that endoscopic clips marking could facilitate accurate identification of the bleeding vessel. Similarly, Wang et al. [9] retrospectively found that clips marking improved the success rate of TAE and reduced operation time. However, these studies had limited sample sizes and did not comprehensively assess critical outcomes, such as rebleeding rates and mortality.

In this study, we retrospectively analyzed data from patients who underwent TAE due to recurrent bleeding or persistent bleeding following therapeutic endoscopy. Using a propensity

score approach, we evaluated whether endoscopic clips marking improves TAE outcomes in patients with refractory peptic ulcer bleeding.

METHODS

Study Design

We screened data from patients who underwent emergency transcatheter angiography (TA) for gastrointestinal bleeding from 1 January 2016 to 31 December 2022. In total of 465 patients, 364 received treatment during TA, including 45 underwent transjugular intrahepatic portosystemic shunt for gastroesophageal variceal bleeding, 6 received partial splenic artery embolization for left-sided portal hypertension related variceal bleeding, 3 underwent hepatic artery embolization for hepatic arterio-venous fistula associated variceal bleeding. A total of 310 patients received TAE for non-variceal gastrointestinal bleeding, of whom 188 had refractory peptic ulcer bleeding and were included in this study. This study was approved by the Medical Ethics Committee, and informed consent was remitted.

All the patients received TAE due to recurrent or ongoing bleeding after therapeutic endoscopy. According to the visibility of metal clips in angiography images, patients were categorized into two groups: (1) without clips; and (2) with clips. The study flowchart is presented in Fig. 1.

Data Collection

Patients' data were collected from the Hospital Information System. Bleeding severity was assessed using the Glasgow-Blatchford score (GBS) and Shock index (SI). The age-adjusted Charlson Comorbidity Index (aCCI) was used to evaluate patients' comorbidities. Additional analyzed parameters included lesion location, Forrest classification, embolized vessel, history of antiplatelet or anticoagulation use, and hospital stay length calculated from the date of TAE.

The primary outcomes are the post-TAE in-hospital rebleeding rate and in-hospital all-cause mortality. Rebleeding was confirmed through endoscopic examination or persistent hematemesis or melena necessitating blood transfusion. Secondary outcomes included: (1) rates of targeted TAE and empirical TAE, (2) hospital stay length, and (3) embolized vessels. Targeted TAE was defined as embolization of offending vessels, including vessels with active contrast agent extravasation and arterial aneurysm formation. Empirical TAE was defined as embolization of vessels without active contrast extravasation or arterial aneurysm formation.

Statistical Analysis

Baseline characteristics were balanced using the inverse probability of treatment weighting (IPTW) method, with a standardized mean difference (SMD) ≤ 0.1 indicating a satisfactory covariate balance. Balanced characteristics included gender, age, GBS, SI, hemoglobin (HB) concentration, aCCI, lesion location, Forrest classification, and history of antiplatelet or anticoagulation use. The chi-square test was used to analyze proportion difference. Student's t test and Mann–Whitney U test was used for parametric and nonparametric data, respectively. Cox proportional hazards regression was used to analyze in-hospital rebleeding and mortality, with proportional hazards assumption verified via the Schoenfeld residual test. For assumptions violations, a time-dependent variable was incorporated. Variables were selected for multivariate analysis with a p value cut-off ≤ 0.1, and if fewer than three variables met this threshold, a p value cut-off ≤ 0.5 was applied. Both of rebleeding and mortality were also analyzed with the Kaplan–Meier method. All statistical

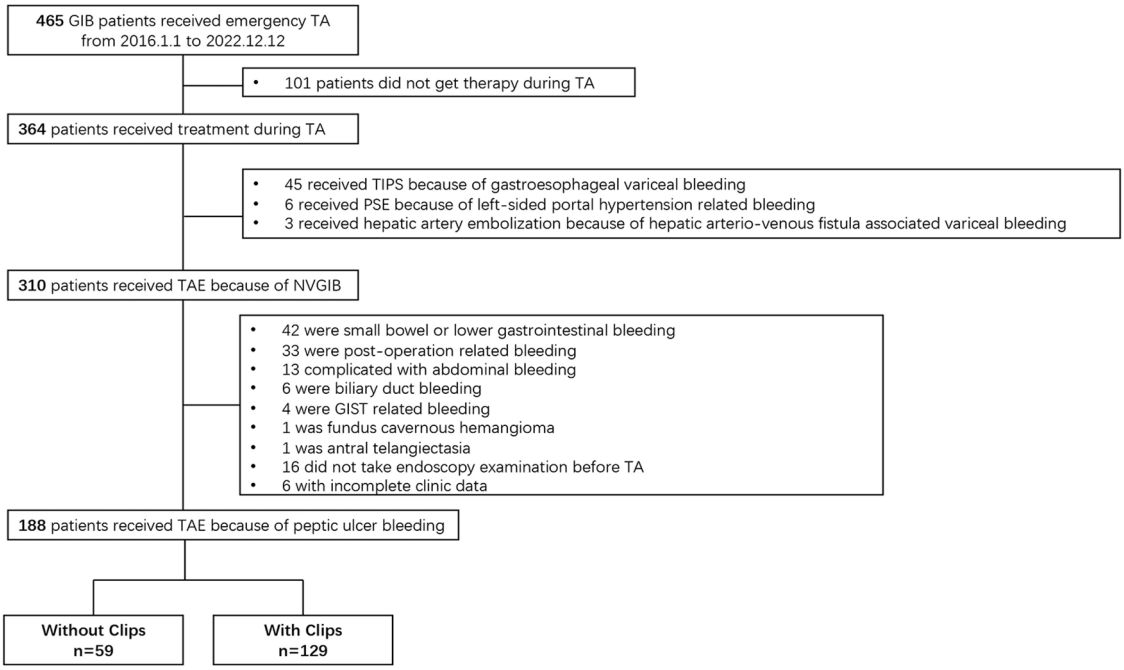

Fig. 1. Study flowchart. GIB: gastrointestinal bleeding; TA: transcatheter angiography; TIPS: transjugular intrahepatic portosystemic shunt; PSE: partial splenic artery embolization; TAE: transcatheter angiography embolization; NVGIB: non-variceal gastrointestinal bleeding; GIST: gastrointestinal stromal tumor.

data were analyzed using SPSS version 23.0 and R Project for Statistical Computing software, V.4.2.3.

RESULTS

From 1 January 2016 to 31 December 2022, a total of 188 patients with refractory peptic ulcer bleeding underwent emergency TAE. All patients received prior oesophago-gastro-duodenoscopy (OGD) and proton pump inhibitor treatment. Among these patients, 60 received once endoscopic hemostasis (45 with hemostatic clips, 1 with injection therapy, 1 with thermal coagulation, 1 with over-the-scope clips, 6 with hemostatic clips and injection, 4 with hemostatic clips and thermal coagulation, 1 with injection and thermal coagulation, 1 with hemostatic clips, injection and thermal coagulation). Additionally, two patients underwent endoscopic hemostasis twice (1 with repeated hemostatic clips and the other with thermal coagulation followed by hemostatic clips). The majority of patients were male, with a mean age of 60.03±15.22 years. The mean interval between endoscopic procedure and TAE was 42.40±66.97 hours.

Of the 188 patients, 129 had visible clips on angiography, used to treat or mark ulcers during prior OGD, while 59 did not. Baseline characteristics are showed in Table I. No significant difference in aCCI was observed between the two groups. Bleeding severity, indicated by GBS, was similar (14.22±3.78 vs 14.17±3.25), though patients without clips exhibited a significant higher SI compared to those with clips (1.17±0.40 vs 1.06±0.27, p=0.034). both groups presented severe anemia (5.66±1.93 g/dL vs 5.76±1.53 g/dL) due to refractory bleeding. The history of antiplatelet or anticoagulation drugs use in the two groups were similar (10.2% vs 14.7%, p=0.533).

Duodenal ulcers were the most common lesions, observed in 54.2% (32/59) of patients without clips, and 60.5% (78/129) of patients with clips. Gastric ulcers accounted for 32.3% (19/59) and 34.9% (45/129) in each group, respectively. Anastomotic ulcers were the least frequent. Forrest classification differed significantly between groups (p<0.001): 54.2% (32/59) of patients without clips were classified as Forrest IIb-III, whereas Forest Ib (32.6%, 42/129) and IIa (39.5%, 51/129) predominated among patients with clips. To adjust for these baseline differences, IPTW was used, balancing variables such as age, gender, aCCI, GBS, SI, HB concentration, lesion location, Forrest classification and history of antiplatelet/anticoagulation use (Table I).

A significant difference in the choice of blood occluding agents for TAE was observed between groups (p<0.001): in the patients without clips, 49.2% (29/59) of patients received glue and micro-coil, 25.4% (15/59) received glue alone, and 25.4% (15/59) received micro-coil alone. In the patients with clips, 28.6% (37/129) patients received glue and micro-coil, 17.8% (23/129) received glue alone, and 53.5% (69/129) received micro-coil alone.

The In-hospital Rebleeding Rate and All-cause Mortality

The in-hospital rebleeding rate was lower among patients with clips (33.3%, 42/129) compared to those without clips (45.8%, 27/59), although this difference was not statistically significant (Table III). After balancing the baseline, Cox regression analysis showed that endoscopic clips marking significantly reduced the in-hospital rebleeding rate after TAE (aHR=0.492, 95%CI: 0.242-1.001, p=0.05) (Table II and Fig. 2), and no other factors showed significant effect on this outcome. Rebleeding events predominantly occurred within the first 7 days post-TAE, and rates of 81.5% (22/27) in group without clips, and 81.4% (35/43) in group with clips.

Table I. Baseline characteristics of patients

	Unmatch				IPTW			
	Without Clips n = 59	With Clips n = 129	p	SMD	Without Clips n = 185	With Clips n= 189	p	SMD
Male (%)	49 (83.1)	110 (85.3)	0.862	0.061	149.2 (80.7)	156.7 (82.9)	0.778	0.058
Age (mean (SD))	57.86 (15.44)	61.02 (15.08)	0.188	0.207	60.89 (14.69)	60.51(15.39)	0.886	0.025
aCCI (mean (SD))	5.73 (2.85)	5.64 (2.86)	0.849	0.030	5.59 (2.60)	5.77 (2.93)	0.706	0.062
GBS (mean (SD))	14.22 (3.78)	14.17 (3.25)	0.926	0.014	14.06 (3.49)	14.07 (3.16)	0.979	0.004
SI (mean (SD))	1.17 (0.40)	1.06 (0.27)	0.034	0.310	1.08 (0.39)	1.09 (0.26)	0.909	0.022
HB concentration (mean (SD))	56.63 (19.31)	57.57 (15.31)	0.718	0.054	56.36 (19.04)	57.01 (15.10)	0.841	0.038
Lesion location	-	-	-	-	-	-	-	-
Gastric ulcer (%) ulcer	19 (32.2)	45 (34.9)	0.846	0.057	67.3 (36.4)	63.6 (33.7)	0.765	0.057
Duodenal ulcer (%) ulcer	32 (54.2)	78 (60.5)	0.519	0.126	103.9 (56.1)	111.9 (59.2)	0.743	0.062
Anastomotic ulcer (%) ulcer	8 (13.6)	6 (4.7)	0.063	0.313	13.9 (7.5)	13.5 (7.2)	0.935	0.013
Forrest Classification (%)			<0.001	0.948			0.989	0.065
Ia	3 (5.1)	18 (14.0)	-	-	23.3 (12.6)	21.1 (11.2)		
Ib	11 (18.6)	42 (32.6)	-	-	46.2 (25.0)	51.9 (27.5)		
IIa	13 (22.0)	51 (39.5)	-	-	63.9 (34.5)	64.3 (34.0)		
IIb-III	32 (54.2)	18 (14.0)	-	-	51.7 (27.9)	51.7 (27.4)		
History of antiplatelet/anticoagulation (%)	6 (10.2)	19 (14.7)	0.533	0.138	13.2 (7.1)	22.8 (12.1)	0.274	0.169

aCCI: age-adjusted Charlson comorbidity index; GBS: Glasgow-Blatchford score; SI: shock index; HB: hemoglobin; SMD: standardized mean difference; IPTW: inverse probability of treatment weighting.

Table II. Outcome of Cox regression model

			Univariate		Multivariate	
	No. of patients	No. of events	HR (95% CI)	p	aHR (95% CI)	p
In-hospital rebleeding rate						
Without Clips	59	27	1	reference	1	reference
With Clips	129	43	0.486 (0.235, 1.007)	0.052	0.492 (0.242, 1.001)	0.050
In-hospital mortality						
Without Clips	59	7	1	reference	1	reference
With Clips	129	16	0.543 (0.096, 3.087)	0.491	0.470 (0.072, 3.048)	0.429

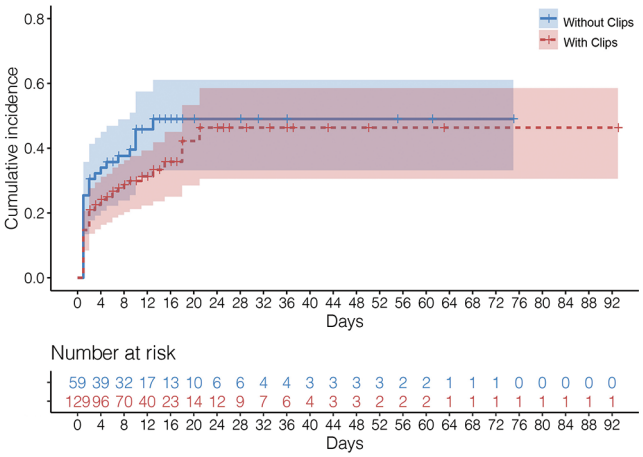

Fig. 2. Kaplan-Meier curve of in-hospital rebleeding without IPTW balance.

The in-hospital all-cause mortality was 11.9% (7/59) in patients without clips, and 12.4% (16/129) in those with clips (Table III). Cox regression analysis revealed no significant difference between the two groups (aHR=0.470, 95%CI: 0.072-3.048, p=0.429) (Table II and Fig. 3). However, GBS and aCCI were identified as independent risk factors of in-hospital all-cause mortality (GBS: aHR=1.228, 95%CI: 1.073-1.705, p=0.003) (aCCI: aHR=1.197, 95%CI: 1.013-1.414, p=0.035) (Fig. 4).

Other Clinical Outcomes after TAE

The proportion of targeted TAE was higher in patients without clips, while empirical TAE was more common among in patients with clips (p<0.001) (Table III). The number of targeted TAEs was similar between the groups (52 vs 46), with the increased case count in group with clips contributed primarily to empirical TAEs. Metal clips on angiography likely facilitated lesion targeting, thereby increasing empirical TAE frequency. The gastroduodenal artery was the most commonly embolized vessel in both groups, with no significant differences in vessel type (Table III). 28.9% (13/45) of gastric ulcers, 38.5% (30/78) of duodenal ulcers, and 25% (1/6) of anastomotic ulcers occurred rebleeding in patients with clips after TAE, with no significant difference found (p=0.548). Among the

Table III. Clinical outcomes

	Without Clips n = 59	With Clips n = 129	p	p'
In-hospital mortality (%)	7 (11.9)	16 (12.4)	1.000	0.714
In-hospital rebleeding rate (%)	27 (45.8)	43 (33.3)	0.141	0.174
Targeted TAE (%)	52 (88.1)	46 (35.7)	<0.001	<0.001
Empirical TAE (%)	7 (11.9)	83 (64.3)	-	-
Hospital stay length (mean (SD))	20.02 (21.32)	15.09 (14.06)	0.062	0.090
Embolized vessel type (n)			0.812	0.892
Gastroduodenal artery	28	55	-	-
Pancreaticoduodenal artery	12	26	-	-
Left gastric artery	10	26	-	-
Right gastric artery	2	9	-	-
Short gastric artery	0	1	-	-
Posterior gastric artery	1	0	-	-
Branch of hepatic artery	3	1	-	-
Branch of gastroepiploic artery	1	4	-	-
Branch of superior mesenteric artery	1	2	-	-
Branch of cystic artery	1	0	-	-
Unknown	0	5	-	-

p': data was analyzed after IPTW.

patients with clips, 55.8% (72/129) had clips on the lesion edge for marking due to the failed endoscopy hemostasis, and 44.2% (57/129) received clips initially for hemostatic purposes, there was no difference in in-hospital rebleeding found in subgroup analysis (p=0.790). There was no prophylactic TAE patients included in our study, therefore for patients with clips initially used for hemostatic purpose, the clips failed to prevent rebleeding and were used as markers in the following TAE.

The mean hospital stay length after TAE was 20.02±21.32 days in patients without clips, and 15.09±14.06 days in those with clips, with no significant difference observed.

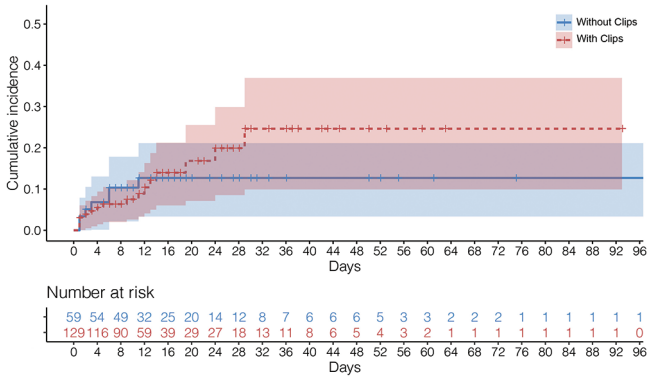

Fig. 3. Kaplan–Meier curve of in-hospital all-cause mortality without IPTW balance.

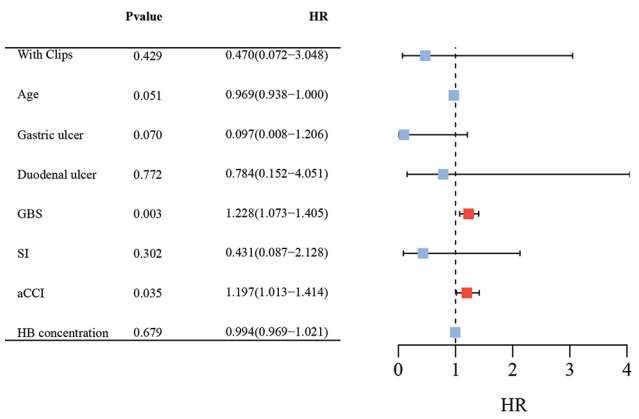

Fig. 4. Multivariate analysis results of in-hospital all-cause mortality after IPTW balance.

DISCUSSION

In the present study, our findings indicate that in patients with refractory peptic ulcer bleeding undergoing TAE, endoscopic clips marking before TAE would help to decrease the in-hospital rebleeding, but does not ameliorate the in-hospital mortality.

Transarterial embolization is considered a salvage therapy for patients with refractory non-variceal upper gastrointestinal bleeding [10, 11]. However, due to the extensive vascular network supplying the stomach and duodenum, achieving effective hemostasis via embolization can be challenging. In this study, 22.1% of patients with gastrointestinal bleeding did not undergo embolization during angiography, primarily because abnormal or bleeding vessels could not be identified. Previous studies reported that 39-46% non variceal upper gastrointestinal bleeding cases show no contrast extravasation or arterial aneurysm on angiography, likely due to intermittent bleeding or pharmacologic intervention [7, 12]. This phenomenon may explain the smaller patient number in group of without clips, as radiologists may avoid performing embolization without angiographic confirmation. Clips marking aids in localizing the possible offending vessel supplying the ulcer area, thereby increasing the likelihood of TAE. Empirical embolization is considered as safe and effective as targeted embolization [13-15].

Endoscopic clips marking of the bleeding ulcer shortens procedure time by guiding angiographers to the correct artery [7, 9]. Besides, it enables super-selection of the culprit vessel, potentially reducing post-TAE complications [13]. Eriksson et al. [16] reported a case series in which clips marking facilitated identification of the culprit vessel, distinct from the gastroduodenal artery, even in the absence of contrast extravasation. In our study, provocative angiography was more frequently utilized in patients with clips marking, involving contrast injection near the clips to provoke contrast extravasation. Importantly, no severe ischemia events were reported following TAE in our cohort.

Interestingly, the combination use of glue and micro-coil was more common among patients without clips, while the use of micro-coil alone was more frequent in patients with clips. This may reflect a lack of confidence in radiologists in cases without clips marking, leading to a preference for "double insurance" to ensure successful hemostasis. However, despite using a single occlusion method, the in-hospital rebleeding rate remained lower in patients with clips, suggesting that clips not only simplify the procedure but may also improve outcomes and economic efficiency.

Our study found no significant reduction in in-hospital all-cause mortality with clips marking. Some patients discharged against medical advice due to personal preference despite poor health and recurred bleeding, possibly confounding the observed in-hospital all-cause mortality rate and masking any potential benefit of clips marking. Notably, the mortality rate in our study was lower than the previously reported range of 19-51% [6, 17], likely because patients who were ineligible for TAE and who may have had a higher mortality were excluded.

Our study has several limitations. First, there were no data about prophylactic embolization, the generalizability of this study in these patients is limited. Second, ulcer size was not included in our analysis due to incomplete documentation in endoscopic reports. Lastly, this is a retrospective study, outcomes were restricted to in-hospital rebleeding and mortality, more robust endpoints such as 30-days rebleeding rate and mortality rates were unavailable. Variation in observation periods could also reduce the statistical power, as most rebleeding events and deaths occurred shortly after TAE, potentially underestimating the advantages of clips in TAE. A well-designed prospective study is warranted.

CONCLUSIONS

Endoscopic clips marking of the bleeding area significantly reduces in-hospital rebleeding in patients with refractory peptic ulcer bleeding undergoing TAE.

Conflicts of interest: None to declare.

Authors' contributions: X. Xiao designed the study and finished the manuscript; X. Xing and Y.L. performed the data acquisition and the statistical analysis. X.W. and X.L. provided the transcatheter angiography information. J.Y. critically revised the manuscript. All the authors read and approved the final version.

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