

# Prophylactic transcatheter angiographic embolization reduces Forrest IIa ulcer rebleeding

## A retrospective study

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### Abstract

The application of transcatheter angiographic embolization (TAE) is controversial in the treatment of ulcer bleeding. This study aims to determine rebleeding risk factors and evaluate the efficacy of prophylactic TAE (p-TAE) following endoscopic hemostasis in rebleeding prevention of Forrest IIa ulcers.

The medical records of Forrest IIa ulcer patients who underwent endoscopic hemostasis (E group) and endoscopic hemostasis plus p-TAE (E + p-TAE group) in West China Hospital from May 2009 to May 2018 were retrospectively reviewed. Baseline characteristics, clinical efficacy, and rebleeding risk factors were analyzed.

As a result, a total of 102 patients were included, with 75 and 27 patients in E and E + p-TAE group, respectively. Most of the baseline data in E and E + p-TAE group were similar except for the proportion of protruded non-bleeding visible vessel (NBVV) (E group vs E + p-TAE group, 50.7% vs 74.1%,  $P = .035$ ). The rebleeding rate of E + p-TAE group (3.7%) was significantly lower than E group (24.0%) ( $P = .02$ ). The protruded NBVV (OR: 6.896, 95% confidence interval [CI]: 1.532–30.642,  $P = .01$ ) and employment of p-TAE (OR: 0.038, 95% CI: 0.003–0.448,  $P = .009$ ) were identified as independent risk factors for Forrest IIa ulcer rebleeding. Additionally, log-rank test indicated the rebleeding occurrence was greatly reduced by p-TAE in patients with protruded NBVVs ( $P = .006$ ).

In conclusion, the protruded NBVV and employment of p-TAE were the independent risk factors tightly associated with rebleeding of Forrest IIa ulcer. P-TAE following endoscopic hemostasis could effectively prevent Forrest IIa ulcer from rebleeding.

**Abbreviations:** CI = confidence interval, GB score = Glasgow-Blatchford score, ICU = intensive care unit, INR = International normalized ratio, NBVV = non-bleeding visible vessel, OR = odds ratio, PPI = proton pump inhibitor, PT = prothrombin time, p-TAE = prophylactic transcatheter angiographic embolization, RBC = red blood cell, TAE = transcatheter angiographic embolization.

**Keywords:** Forrest IIa ulcer, prophylactic transcatheter angiographic embolization, rebleeding risk, non-bleeding visible vessel, endoscopic hemostasis

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## 1. Introduction

Gastrointestinal bleeding is the common complication of peptic ulcer disease with an estimated incidence of 19.4 to 57.0 per 100,000 ulcer patients.<sup>[1]</sup> Although the use of proton pump inhibitors (PPI) greatly improves the prognosis of ulcer bleeding, ulcers with major stigmata of recent hemorrhage, such as non-bleeding visible vessels (NBVVs), still require extra interventions, because they have high risk of rebleeding.<sup>[2–4]</sup> The Forrest classification of peptic ulcers has been widely accepted and used in clinical practice to predict risk for rebleeding. Forrest IIa ulcer, defined as ulcer with NBVVs, has an increased risk for rebleeding (odds ratio [OR]: 3.2, 95% confidence interval [CI]: 1.4–7.3).<sup>[5]</sup> Approximately 20% of patients may develop rebleeding after successful endoscopic hemostasis, which leads to a four- to five-fold increase in mortality.<sup>[6,7]</sup> Therefore, it is of great importance to identify high-risk patients in order to take further precautions for rebleeding after endoscopic hemostasis.

Endoscopy is highly effective in the diagnosis and treatment of upper gastrointestinal hemorrhage, and selective arterial embolization, that is, transcatheter angiographic embolization (TAE) is usually performed when endoscopy fails to control the bleeding.<sup>[8–10]</sup> However, the efficacy of prophylactic TAE (p-TAE) following endoscopic hemostasis in the treatment of ulcer bleeding is still in debate. Several studies found p-TAE following endoscopic hemostasis reduced rebleeding rate in

ulcers with high risks of rebleeding,<sup>[11–13]</sup> whereas Lau et al found p-TAE showed no significant effect in prevention of ulcer rebleeding.<sup>[14]</sup> The differences in conclusions of these studies could be due to the heterogeneity of included patients. Most of these studies included Forrest Ia, Ib, IIa and/or IIb ulcers without stratification, but the rebleeding rate after endoscopic hemostasis varies in ulcers of different kinds, which may influence the effect of p-TAE and bring bias to the conclusions.<sup>[15,16]</sup> Thus, it may be necessary to evaluate the efficacy of p-TAE separately in each kind of ulcers. Herein, we focused on Forrest IIa ulcer, which is highly risky to rebleed, and conducted this study to determine the rebleeding risk factors and the efficacy of p-TAE following endoscopic hemostasis in patients with Forrest IIa ulcer.

## 2. Materials and methods

### 2.1. Study design and patients selection

This retrospective study was approved by West China Hospital, Sichuan University, and was registered on Chinese Clinical Trial Registry (<http://www.chictr.org.cn/index.aspx>, registering No. ChiCTR1800020146). Written informed consent from patients was waived by Clinical Trial and Biomedical Ethics Committee of West China Hospital, Sichuan University due to the retrospective nature of this study. All procedures of this work were carried out in accordance with the guidelines and regulations of the institutional and national ethics committee. The data of patients with Forrest IIa ulcer<sup>[17]</sup> from May 2009 to May 2018 was searched from medical records system of West China Hospital. Patients were excluded if one or more following criteria were met:

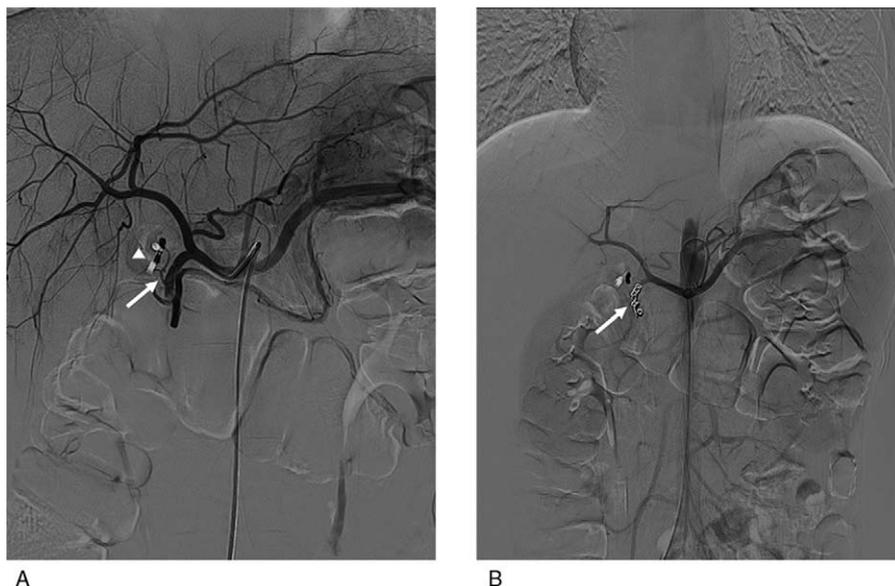
- 1) endoscopic hemostasis therapy was not performed;
- 2) suspected or confirmed to be malignant ulcer;
- 3) epinephrine injection used alone as endoscopic hemostasis therapy.

### 2.2. Endoscopic hemostasis and p-TAE procedure

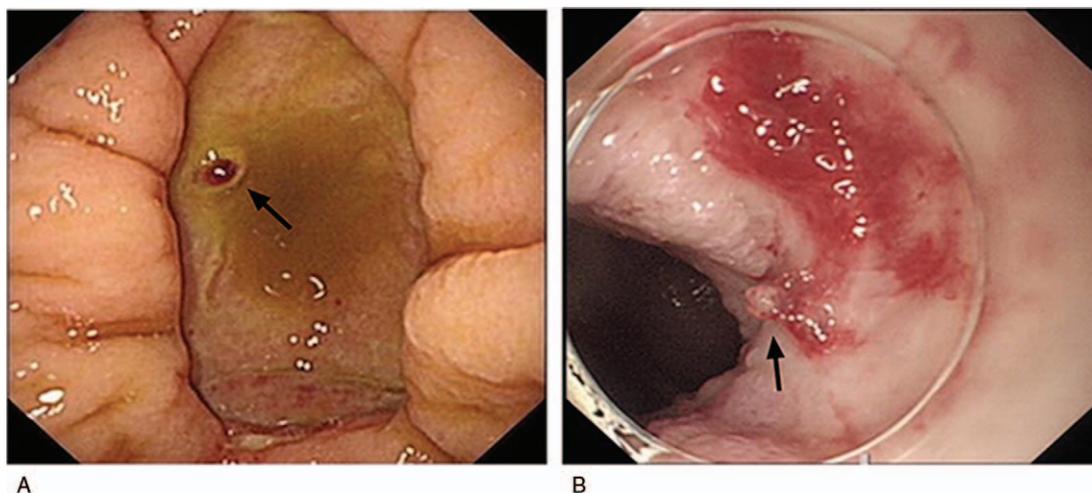
Patients in both groups received endoscopy as initial hemostasis therapy. Endoscopy was performed in Endoscopy Center with standard single channel endoscopes (GIF-260J, Olympus, Tokyo, Japan). When Forrest IIa ulcer was detected, hemoclips and heat coagulation were used alone or in combination as the hemostasis therapy. Epinephrine injection could be employed as an adjuvant modality amid the endoscopic hemostasis.

Patients in E+p-TAE group received p-TAE in angiographic suite within 24 hours after initial endoscopic hemostasis. A 5-Fr angiographic catheter (RH, Terumo, Japan) was inserted into femoral artery, and thereafter celiac and superior mesenteric angiograms were performed. Then, the microcatheter (Terumo, Tokyo, Japan) was cannulated into the culprit artery using super-selective technique. The ulcer sites in 70.4% patients were marked by hemoclips under endoscopy prior to p-TAE (Fig. 1). For these patients, the branches closest to the hemoclip were identified as the culprit vessel. Contrast agents were infused again to assure that the identified culprit artery provided blood to the same area where the hemoclip located. For 29.6% patients who underwent endoscopy without employing hemoclip, the culprit artery was navigated according to the ulcer sites which were indicated by endoscopy (usually the gastroduodenal artery for ulcers in duodenum, gastric antrum and pylorus, and the left gastric artery for ulcers in gastric corpus and fundus). Tortuous or enlarged arteries beneath ulcer sites were helpful to identify the culprit artery. After the culprit artery was determined, dual embolic agents of microcoils (Hilal, COOK, Bloomington, IN) and gelfoam were used to occlude the culprit artery until arterial flow was completely occluded.

All patients in both groups received intravenous PPI (esomeprazole or pantoprazole), followed by oral PPI after 72 hours without rebleeding.



**Figure 1.** Angiography of prophylactic embolization of the gastroduodenal artery in Forrest IIa ulcer. A) The ulcer marked with hemoclips (arrowhead) under endoscopy was supplied by the superior pancreaticoduodenal artery (arrow). B) Microcoils (arrow) were deployed in the gastroduodenal artery.



**Figure 2.** Endoscopic imaging of Forrest IIa ulcers with flat and protruded visible vessels. (A) Flat non-bleeding visible vessel (arrow). (B) Protruded non-bleeding visible vessel (arrow).

### 2.3. Data collections

Clinical data before endoscopic hemostasis, such as demographic information, laboratory tests, mean arterial pressure, heart rate, Glasgow-Blatchford score, infusion volume, red blood cell (RBC) transfusion, seniorities of endoscopists and interventional doctors, administration of PPI, vasopressor, anti-platelet and anti-coagulation medications were collected. The morphological features of ulcer (e.g., ulcer site, ulcer area, sites and protrusions of NBVVs) were also recorded.

Additionally, the modalities and sessions of endoscopic hemostasis, technical detail of p-TAE, rebleeding detail, intensive care unit (ICU) transfer and mortality were also recorded. Patients were followed up to 30 days after initial endoscopy.

### 2.4. Definitions

In this study, NBVVs were described as protruded (height >0.3 cm) and flat (height <0.3 cm), and the height of visible vessels was evaluated by comparing these vessels with the head of electro-surgical hemostatic forceps or hemoclips (lateral height  $\approx$  0.3 cm when the heads were closed) (Fig. 2). Rebleeding was defined by presence of fresh hematemesis, melena, drop of hemoglobin level >20 g/L per day, and/or signs of hypovolemic shock.<sup>[14]</sup> Rebleeding-free time was defined as the time duration between initial hemostasis and occurrence of rebleeding.

### 2.5. Statistical analyses

Quantitative data were expressed as mean  $\pm$  standard deviation, and categorical data were expressed as number and percentage. Student's and chi-square tests were used to analyze quantitative data and categorical data, separately. Kaplan-Meier curves were compared with the log-rank test.

The logistic regression model was used to evaluate the risk factors of rebleeding. Univariable analysis was firstly used to test each probable factor, and those with a  $P$  value < .10 by univariable analysis were further taken into multivariable analysis to identify if they were the independent risk factors of rebleeding. These data were expressed as OR and corresponding 95% CI.

A  $P$  value <.05 was considered significant. All data were analyzed by SPSS 19.0 software (SPSS, Chicago, IL).

## 3. Results

### 3.1. Patient enrollment and baseline characteristics

From May 2009 to May 2018, a total of 138 consecutive patients with acute upper gastrointestinal bleeding due to Forrest IIa ulcer were admitted to West China Hospital. Among them, 36 patients were excluded, and finally, 102 Forrest IIa ulcer patients who underwent endoscopic hemostasis alone (E group,  $n=75$ ) and endoscopic hemostasis plus p-TAE (E+p-TAE group,  $n=27$ ) were included into this study (Fig. 3).

Most of the baseline data in the two groups were similar except that larger percentage of patients in E+p-TAE group had protruded NBVV (E group vs E+p-TAE group, 50.7% vs 74.1%,  $P=.04$ ) (Table 1). The seniority of endoscopists in both groups were also similar (E group vs E+p-TAE group,  $20.3 \pm 10.4$  vs  $21.1 \pm 10.6$  years,  $P=.71$ ), and the seniority of interventional doctors in E+p-TAE group was  $8.9 \pm 1.9$  years. Both groups received similar intravenous dosage of PPIs (E group vs E+p-TAE group  $101.9 \pm 59.0$  vs  $123.0 \pm 67.4$  mg/d,  $P=.13$ ) before the first endoscopic hemostasis. Additionally, there was no significant difference between E and E+p-TAE groups in the modalities of endoscopic hemostasis (Table 2). The data shown above ensured the comparability of the two groups.

Regarding the embolization site of patients in E+p-TAE group, the left gastric artery was embolized in 16 (59.3%) patients, followed by the gastroduodenal artery in 9 patients (33.3%), the right gastric artery in 1 patient (3.7%) and the posterior gastric artery in 1 patient (3.7%).

### 3.2. Clinical efficacy

Eleven (14.7%) patients in E group and four (14.8%) patients in E+p-TAE group experienced intraprocedural bleeding during endoscopy, but all achieved stable hemostasis under endoscopy eventually. For p-TAE, the technical success rate was 100%. One (3.7%) patient experienced upper abdominal pain and nausea

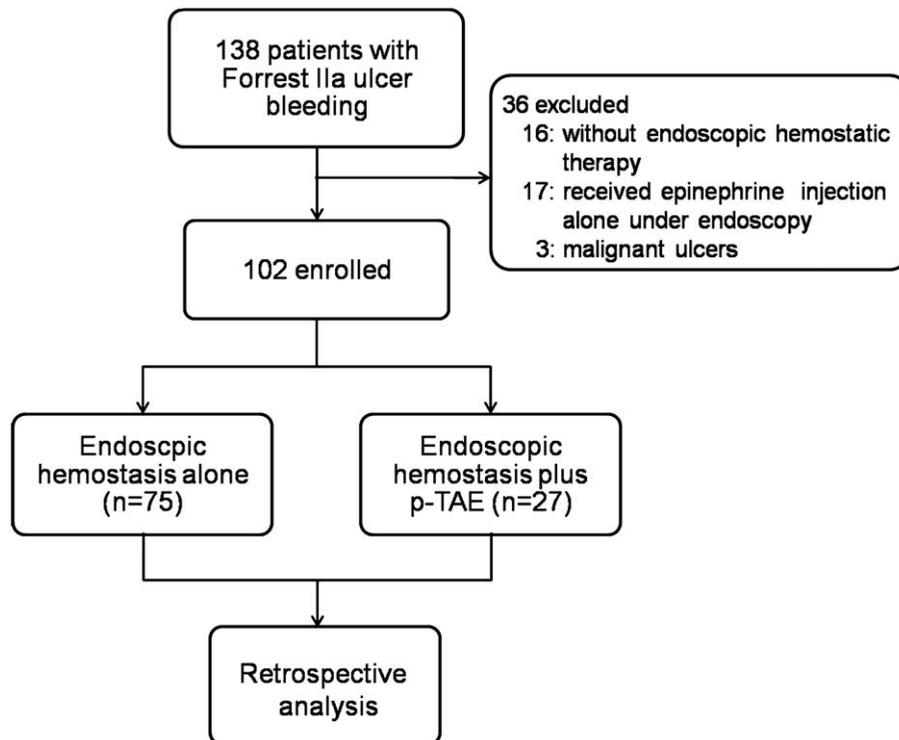


Figure 3. Flow diagram of patient enrollment and grouping. p-TAE: prophylactic transcatheter angiographic embolization.

after p-TAE but relieved on the next day. p-TAE did not incur severe adverse events.

Nineteen patients rebled after initial endoscopic hemostasis in total, and most of them fell into E group. The majority of

rebleeding (84.2%) occurred within the first week after the procedure (Table 3). Notably, rebleeding was significantly reduced in E+p-TAE group comparing with E group, especially in the first week after initial endoscopic hemostasis ( $P=.006$ , Table 3). Additionally, the log-rank test also suggested that E+p-TAE regimen reduced the rebleeding risk as it prolonged the rebleeding-free time (E group *vs* E+p-TAE group,  $23.8 \pm 11.7$  vs  $29.2 \pm 4.0$  days,  $P=.02$ , Fig. 4A).

With respect to the emergent treatment of rebleeding, Five patients in E group were transferred to surgery because of rebleeding (3 patients were transferred after the failure of second endoscopic hemostasis; 2 patients were transferred without a second endoscopic hemostasis). In contrast, no patients were transferred to surgery in E+p-TAE group. On the other hand, four patients and one patient underwent salvage TAE to tackle

Table 2  
Modalities of endoscopic hemostasis.

Modalities	E (n=75)	E+p-TAE (n=27)	P
With hemoclippling, n (%)	49 (65.3)	19 (70.4)	.40
Hemoclippling alone, n (%)	19 (25.3)	6 (22.2)	.75
Hemoclippling+epinephrine injection, n (%)	11 (14.7)	8 (29.6)	.09
Hemoclippling+heat coagulation, n (%)	6 (8.0)	4 (14.8)	.45
Hemoclippling+heat coagulation+epinephrine injection, n (%)	13 (17.3)	1 (3.7)	.11
Without hemoclippling, n (%)	26 (34.7)	8 (29.6)	.63
Heat coagulation+epinephrine injection, n (%)	13 (17.3)	1 (3.7)	.11
Heat coagulation alone, n (%)	13 (17.3)	7 (25.9)	.34
Endoscopy sessions	$1.13 \pm 0.34$	$1.04 \pm 0.19$	.96

E: endoscopic hemostasis; E+p-TAE: endoscopic hemostasis+prophylactic transcatheter angiographic embolization.

Table 1

Baseline characteristics before procedure.

Characteristics	E (n=75)	E+p-TAE (n=27)	P
Age, years	$57.8 \pm 19.1$	$53.0 \pm 17.6$	.25
Gender, male/female	64/11	22/5	.76
Intake of medications, n (%) <sup>†</sup>	20 (26.7)	5 (18.5)	.40
Hemoglobin, g/L	$64.2 \pm 21.6$	$63.1 \pm 12.0$	.81
Platelet, $\times 10^9/L$	$139.7 \pm 69.5$	$161.3 \pm 96.5$	.22
PT, seconds	$13.8 \pm 3.3$	$13.5 \pm 2.2$	.69
INR	$1.2 \pm 0.3$	$1.2 \pm 0.2$	.54
Heart rate	$89.0 \pm 19.5$	$91.6 \pm 18.6$	.54
Mean arterial pressure, mmHg	$81.6 \pm 15.2$	$80.0 \pm 13.2$	.63
GB Score	$10.9 \pm 2.3$	$10.6 \pm 2.6$	.55
Fluid infusion amount, L/day <sup>‡</sup>	$2.6 \pm 1.5$	$3.2 \pm 2.0$	.08
RBC transfusion amount, U <sup>‡</sup>	$4.9 \pm 6.1$	$7.2 \pm 8.4$	.12
Vasopressor drug administration, n (%)	14 (18.7)	9 (33.3)	.12
NBVs			
Protruded/Flat, n/n	38/37	20/7	.04
Central/Periphery, n/n	18/57	6/21	.85
Ulcer size, cm	$1.0 \pm 0.7$	$1.0 \pm 0.6$	.92
Ulcer site			
Stomach, n (%)	37 (49.3)	16 (59.3)	.68
Duodenum, n (%)	31 (41.3)	9 (33.3)	
Anastomosis, n (%)	7 (9.3)	2 (7.4)	

E: endoscopic hemostasis; E+p-TAE: endoscopic hemostasis+prophylactic transcatheter angiographic embolization; PT: prothrombin time; INR: international normalized ratio; GB score: Glasgow-Blatchford score; RBC: red blood cell. NBV: non-bleeding visible vessel.

<sup>†</sup> refers to anti-platelet and anti-coagulation medications.

<sup>‡</sup> refers to corresponding data within three days before endoscopy.

**Table 3**  
**Comparison of clinical efficacy of hemostasis therapy.**

Clinical efficacy	E (n=75)	E+p-TAE (n=27)	P
Overall Rebleeding, n (%) <sup>†</sup>	18 (24.0)	1 (3.7)	.02
Rebleeding within 1 week, n (%)	16 (21.3)	0 (0)	.006
Rebleeding from 1 week to 1 month, n (%)	2 (2.7)	1 (3.7)	>.99
Rebleeding with hemoclippping, n (%)	14 (18.7)	0 (0)	.05
Rebleeding without hemoclippping, n (%)	4 (5.3)	0 (0)	.57
Rebleeding with protruded NBVVs, n (%)	15 (20.0)	1 (3.7)	.005
Rebleeding with flat NBVVs, n (%)	3 (4.0)	0 (0)	>.99
Emergent treatment for rebleeding			
TAE, n (%)	4 (5.3)	1 (3.7)	>.99
Surgery, n (%) <sup>†</sup>	5 (6.7)	0 (0)	.32
Endoscopy, n (%)	10 (13.3)	1 (3.7)	.28
ICU transfer, n (%)	5 (6.7)	4 (14.8)	.24
Death, n (%)	2 (2.7)	0 (0)	>.99

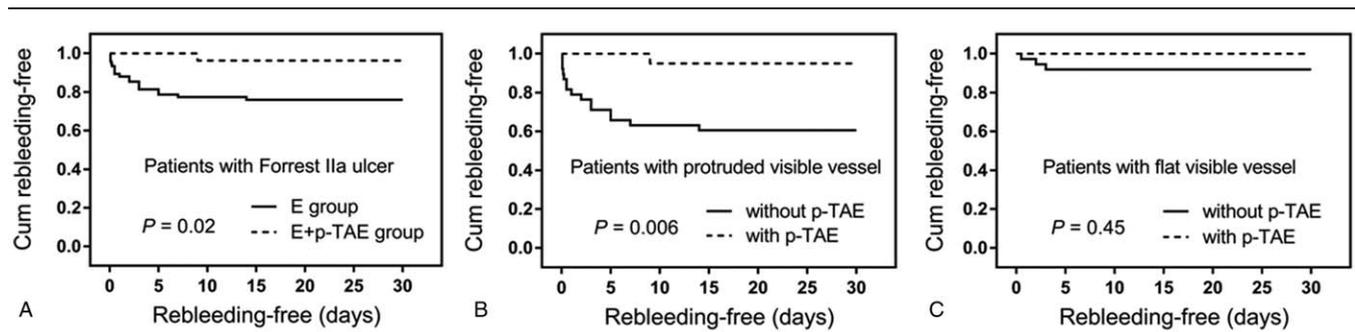
E: endoscopic hemostasis; E+p-TAE: endoscopic hemostasis+prophylactic transcatheter angiographic embolization; ICU: intensive care unit; NBVV: non-bleeding visible vessel; TAE: transcatheter angiographic embolization.

<sup>†</sup> two patients underwent subtotal gastrectomy, one and two patients underwent gastrotomy or duodenotomy with simple over-sewing of the bleeding ulcer and/or artery, respectively.

rebleeding in E and E+p-TAE groups, respectively, without significant differences between two groups ( $P > .99$ , Table 3). Moreover, nine (8.8%) patients were transferred to ICU due to either organ dysfunction or septic shock. Generally, E group had a higher absolute number of aggressive therapy demand after rebleeding, although statistical significance was not reached. Besides that, 2 (2.7%) patients died in E group (one died of hemorrhagic shock and the other one died of respiratory failure), whereas all patients in E+p-TAE survived.

Of Forrest IIa ulcer with protruded NBVVs, 15 (20%) rebled in E group, while only 1 (3.7%) rebled in E+p-TAE group, indicating that p-TAE following endoscopic hemostasis surpassed endoscopic hemostasis alone regarding rebleeding prevention in Forrest IIa ulcer with protruded NBVVs ( $P = .005$ , Table 3). Log-rank test also showed significant prolonged rebleeding-free time in patients with protruded NBVVs after receiving p-TAE (without p-TAE vs with p-TAE,  $19.9 \pm 13.6$  vs  $29.0 \pm 4.7$  days,  $P = .006$ , Fig. 4B). Protruded NBVVs might be view as an indication of p-TAE to improve clinical outcomes.

Differently, p-TAE did not show the advantage on rebleeding prevention in ulcers with flat NBVVs ( $P > .99$ , Table 3). Log-rank test also showed that p-TAE had no significant effect on



Days	0	5	10	15	20	25	30
<b>Figure 4A patients with Forrest IIa ulcer</b>							
E	75(0)	61(0)	58(0)	57(0)	57(0)	57(0)	57(57)
E+p-TAE	27(0)	27(0)	26(0)	25(0)	25(0)	25(0)	25(25)
<b>Figure 4B patients with protruded visible vessels in Forrest IIa ulcer</b>							
E	38(0)	27(0)	24(0)	23(0)	23(0)	23(0)	23(23)
E+p-TAE	20(0)	20(0)	19(0)	19(0)	19(0)	19(0)	19(19)
<b>Figure 4C patients with flat visible vessels in Forrest IIa ulcer</b>							
E	37(0)	34(0)	34(0)	34(0)	34(0)	34(0)	34(34)
E+p-TAE	7(0)	7(0)	7(0)	7(0)	7(0)	7(0)	7(7)

**Figure 4.** Kaplan-Meier curves of rebleeding-free. E: endoscopic hemostasis; E+p-TAE: endoscopic hemostasis+prophylactic transcatheter angiographic embolization.

**Table 4**  
Baseline characteristics of rebleeding and non-rebleeding patients.

Characteristics	Rebleeding (n=19)	Non-rebleeding (n=83)	P
Age, years	63.0±15.4	55.1±19.2	.10
Gender, male/female	18/1	68/15	.29
Intake of medications, n (%) <sup>†</sup>	4 (21.1)	21 (25.3)	>.99
Hemoglobin, g/L	57.6±15.8	65.4±20.0	.12
Platelet, ×10 <sup>9</sup> /L	134.5±79.3	148.0±77.5	.49
PT, seconds	15.1±3.4	13.4±2.8	.03
Heart rate	92.7±20.9	89.0±19.0	.46
Mean arterial pressure, mmHg	81.3±14.1	81.2±14.9	.99
GB Score	11.3±2.4	10.8±2.3	.35
Fluid infusion amount, L/day <sup>‡</sup>	3.3±2.0	2.6±1.5	.09
RBC transfusion amount, U <sup>‡</sup>	9.1±6.3	4.7±6.7	.01
Vasopressor drug administration, n (%)	6 (31.6)	17 (20.5)	.36
NBVs			
Protruded/Flat, n/n	16/3	42/41	.008
Central/Periphery, n/n	5/14	19/64	.77
Ulcer size, cm	1.1±0.7	0.9±0.6	.42
Ulcer site			.44
Stomach, n (%)	10 (52.6)	43 (51.8)	
Duodenum, n (%)	6(31.6)	34 (41.0)	
Anastomosis, n (%)	3 (15.8)	6 (7.2)	

PT: prothrombin time; GB Score: Glasgow-Blatchford score; RBC: red blood cell. NBV: non-bleeding visible vessel.

<sup>†</sup> refers to anti-platelet and anti-coagulation medications.

<sup>‡</sup> refers to corresponding data within three days before endoscopy.

rebleeding-free time in patients with flat NBVs, either (without p-TAE vs with p-TAE, 27.7±7.8 vs 30.0±0 days,  $P=.45$ , Fig. 4C). It seemed that p-TAE might not be recommended for Forrest ulcers with flat NBV.

**Table 5**  
Univariable and Multivariable analyses of rebleeding risk factors after endoscopy.

Factors	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.025 (0.995-1.056)	.099	1.038 (0.999-1.079)	.053
Gender	3.971 (0.491-32.097)	.20		
Intake of medications <sup>†</sup>	1.270 (0.379-4.255)	.70		
Platelet	0.998 (0.991-1.005)	.50		
PT	1.195 (1.011-1.413)	.037	1.053 (0.855-1.297)	.63
Hemoglobin	0.979 (0.952-1.006)	.12		
Heart rate	1.010 (0.985-1.035)	.45		
Mean arterial pressure	1.000 (0.967-1.035)	.99		
GB score	1.107 (0.894-1.370)	.35		
Fluid infusion amount	1.000 (1.000-1.001)	.099	1.000 (1.000-1.001)	.04
RBC transfusion amount	1.083 (1.010-1.161)	.025	1.087 (1.002-1.180)	.045
Vasopressor drug administration	0.558 (0.185-1.684)	.30		
NBV in ulcer crater				
Protrusion	5.206 (1.410-19.219)	.013	6.896 (1.532-30.642)	.01
Location	0.831 (0.265-2.605)	.75		
Ulcer size	1.341 (0.657-2.737)	.42		
Ulcer site				
Stomach	0.968 (0.357-2.625)	.97		
Duodenum	1.503 (0.520-4.347)	.45		
Anastomosis	0.416 (0.094-1.838)	.25		
Hemoclipping	0.425 (0.130-1.395)	.16		
Employment of p-TAE	0.122 (0.015-0.962)	.046	0.038 (0.003-0.448)	.009

OR: odds ratio; CI: confidence interval; PT: prothrombin time; GB score: Glasgow-Blatchford score; NBV: non-bleeding visible vessel; RBC: red blood cell; p-TAE: prophylactic transcatheter angiographic embolization.

<sup>†</sup> refers to anti-platelet and anti-coagulation medications.

### 3.3. Risk factors of rebleeding

Baseline characteristics between rebleeding (n=19) and non-rebleeding patients (n=83) with Forrest IIa ulcer were also compared. Prothrombin time (PT), RBC transfusion before endoscopic hemostasis, and proportion of protruded NBVs were found to present significant differences between 2 groups (Table 4).

Logistic regression was applied to determine rebleeding risk factors accurately. Univariable analysis firstly screened out 6 probable rebleeding risk factors with  $P$  value <.10, including age, PT, RBC transfusion, fluid infusion amount before procedure, protruded NBVs, and employment of p-TAE (Table 5). Thereafter, these six factors were taken into multivariable analysis, showing that RBC transfusion, fluid infusion amount before procedure, protruded NBVs and employment of p-TAE were the independent risk factors for the rebleeding of Forrest IIa ulcers, among which protruded NBVs and employment of p-TAE had more striking OR values (Table 5).

## 4. Discussion

Rebleeding is a common life-threatening event of bleeding ulcer. Forrest IIa ulcer has been considered as an equally treacherous lesion of rebleeding as Forrest Ia ulcer.<sup>[7]</sup> Several guidelines strongly recommend that Forrest IIa ulcer should receive endoscopic hemostasis because this lesion is at high risk for persistent bleeding or rebleeding due to profound arterial blood supply.<sup>[2,3,15]</sup> Highest frequency for Forrest IIa ulcer rebleeding was presented in the first week after endoscopic hemostasis as 84.2% of rebleeding occurred in this period. Although endoscopic hemostasis had a 78.7% success rate in preventing rebleeding within the first week, p-TAE following endoscopic

hemostasis further improved the prevention advantage as no rebleeding occurred within the first week in E+p-TAE group. The differences in prevention of rebleeding between the two groups under similar baseline characteristics and procedure details highlights the favorable outcomes of p-TAE following endoscopic hemostasis in preventing rebleeding of Forrest IIa ulcer.

Risk of post-endoscopic rebleeding differs between different Forrest classifications<sup>[7]</sup> and Forrest IIb ulcer, which was once considered to be of high rebleeding risk, has been recently proved to have a lower rebleeding risk.<sup>[16]</sup> In previous studies on p-TAE treating bleeding peptic ulcers, patients with different Forrest classifications including Forrest Ia, Ib, IIa and/or IIb were enrolled without stratification,<sup>[11-14]</sup> which might give rise to heterogeneous effects of p-TAE on ulcer rebleeding prevention. Moreover, in Lau's study, p-TAE was undertaken if the hemoglobin on admission was less than <90 g/L.<sup>[14]</sup> It is worth further discussion whether the patients who fulfilled the criteria should be recommended with p-TAE, as no significant differences of initial hemoglobin level lie between rebleeding and non-rebleeding peptic ulcers with Forrest classification higher than IIb.<sup>[18]</sup> The introduction of p-TAE into these patients might not produce extra benefits. Comparing with the aforementioned studies, our study was a real world study only focusing on Forrest IIa ulcer, therefore the heterogeneity of ulcer classification was better controlled. In addition, patients in our study did not follow Lau's criteria of p-TAE,<sup>[14]</sup> which eliminated the potential bias due to liberal introduction of p-TAE. Therefore, it seemed that the authentic effect of p-TAE of preventing rebleeding of Forrest IIa ulcer was properly showed in our study as p-TAE succeeded in decreasing rebleeding by 5.5-fold (from 24% to 3.7%). Also, no patients in E+p-TAE group died whereas two died in E group, further suggesting that p-TAE may be of great significance for the prognosis improvement.

Due to the development of endoscopic hemostasis modalities, the first choice of endoscopic hemostasis modalities for ulcer bleeding has changed. Several guidelines recommend that epinephrine injection should not be used as monotherapy in patients with Forrest IIa ulcer,<sup>[2,3,19]</sup> thus such patients were excluded from this study. In our study, the constituent ratio of different hemostasis modalities under endoscopy was similar between E and E+p-TAE group, which was insufficient to induce bias. Endoscopists' experience is an important independent prognostic factor for affecting rebleeding risk of ulcer.<sup>[20]</sup> As the experiences of endoscopists in both groups were similar in our study, the effective reduction of E+p-TAE on rebleeding reflected the necessity of p-TAE in real world state. Furthermore, the hemoclips placed by the endoscopists could navigate the interventional doctors to culprit artery,<sup>[21]</sup> and p-TAE might compensate for the insufficient endoscopic hemostasis.

Our study also determined four independent risk factors (employment of p-TAE, NBVV protrusion, amount of fulid infusion, and RBC transfusion) associated with Forrest IIa ulcer rebleeding. Of them, the employment of p-TAE and NBVV protrusion are the most striking two factors. As 90.7% of Forrest IIa ulcers have significant arterial flow into the ulcer,<sup>[16]</sup> the rupture of NBVV in ulcer results in extensive blood loss and increase of rebleeding risk. In our study, the employment of p-TAE, as aforementioned, was a protective factor of rebleeding with an OR value of 0.038. Therefore, p-TAE is a promising supplementary measure after endoscopic hemostasis to prevent rebleeding of Forrest IIa ulcer.

As for NBVV protrusion, a previous study emphasized its role and importance in ulcer rebleeding.<sup>[22]</sup> Our study also showed that protruded NBVVs indeed increase rebleeding risk of Forrest IIa ulcer by 6.896-fold. Intriguingly, the proportion of protruded NBVV in E+p-TAE group was significantly higher than E group, but its rebleeding occurrence was lower than E group, indicating the therapeutic efficacy of p-TAE on rebleeding prevention of Forrest IIa ulcer. Furthermore, the practical value of protrusion of NBVV is not limited to rebleeding risk prediction. In our study, The Kaplan-Meier curves and log-rank tests showed that rebleeding-free time was prolonged in Forrest ulcer with protruded NBVV comparing to those with flat NBVV, and Forrest IIa ulcer with protruded NBVV could benefit more from the employment of p-TAE. Hence, protrusion of NBVV could be used as the criteria to help to make the clinical decision whether it is necessary and beneficial to perform p-TAE in each individual with Forrest IIa ulcer.

Our study listed rebleeding risk factors of Forrest IIa ulcers, and highlighted that p-TAE is beneficial in certain Forrest IIa ulcer populations. Clinical decision making of p-TAE based on the patient stratification would obtain desirable outcomes. However, this retrospective study still has some limitations including single center, relatively small sample size, and the sample size in the two groups was unbalanced. These disadvantages are greatly attributed to the fact that p-TAE is not the prevailing treatment choice in Forrest IIa ulcer, and it is required to study this issue retrospectively before further prospective validations. In addition, several statistical methods, including log-rank test, logistic regression and subgroup analysis, were applied in this study to properly display the efficacy of p-TAE on rebleeding prevention under the balanced baseline characteristics and procedure details between two groups.

We therefore conclude that protruded visible vessels and employment of p-TAE are the independent risk factors tightly associated with rebleeding of Forrest IIa ulcers. p-TAE could compensate for the endoscopic hemostasis to effectively prevent rebleeding of Forrest IIa ulcers especially those with protruded visible vessels, which would be of great benefit to the prognosis of these patients. Further prospective studies are still needed to validate the conclusions drawn from this study.

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