



The recurrent bleeding risk of a Forrest IIc lesion at the second-look endoscopy can be indicated by high Rockall scores ≥ 6

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Abstract

Background The Forrest classification is widely applied to guide endoscopic hemostasis for peptic ulcer bleeding. Accordingly, practice guidelines suggest medical treatment only for ulcer with a Forrest IIc lesion because it has low rebleeding risk even without endoscopic therapy, ranging from 0 to 13%. However, the risk ranges widely and it is unclear who is at risk of rebleeding with such a lesion. This study assessed whether the Rockall score, which evaluates patients holistically, could indicate the risk of recurrent bleeding among patients with a Forrest IIc lesion at the second-look endoscopy.

Methods Patients who had peptic ulcer bleeding with Ia–IIb lesions received endoscopic hemostasis at the primary endoscopy, and they were enrolled if their Ia–IIb lesions had been fading to IIc at the second-look endoscopy after 48- to 72-h intravenous proton pump inhibitor (PPI) infusion. Primary outcomes were rebleeding during the 4th–14th day and 4th–28th day after the first bleeding episode.

Results The prospective cohort study enrolled 140 patients, who were divided into a Rockall scores ≥ 6 group or a Rockall scores < 6 group. The rebleeding rates in the Rockall scores ≥ 6 group and the Rockall scores < 6 group during the 4th–14th day and the 4th–28th day were 13/70 (18.6%) versus 2/70 (2.9%), $p=0.003$ and 17/70 (24.3%) versus 3/70 (4.3%), $p=0.001$, respectively, based on an intention-to-treat analysis and 5/62 (8.1%) versus 0/68 (0%), $p=0.023$ and 6/59 (10.2%) versus 0/67 (0%), $p=0.009$, respectively, based on a per-protocol analysis. The Kaplan–Meier curves showed that the Rockall scores ≥ 6 group had a significantly lower cumulative rebleeding-free proportion than the Rockall scores < 6 group ($p=0.01$).

Conclusions Combined Rockall scores ≥ 6 on arrival with a Forrest IIc lesion at the second-look endoscopy can identify patients at risk of recurrent peptic ulcer bleeding following initial endoscopic and intravenous PPI treatment.

Trial registration Trial registration identifier: NCT01591083

Keywords Peptic ulcer bleeding · Rockall score · Forrest classification · Second-look endoscopy · Recurrent bleeding

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Abbreviations

APTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
CI	Confidence interval
<i>H. pylori</i>	<i>Helicobacter pylori</i>
IQR	Interquartile range
ITT	Intention-to-treat
NSAID	Non-steroidal anti-inflammatory drug
PP	Per-protocol
PPI	Proton pump inhibitor
PT	Prothrombin time
SD	Standard deviation
SRH	Stigmata of recent hemorrhage
TAE	Transarterial embolization

Peptic ulcer bleeding is a common disease that has a risk of mortality, especially if recurrent bleeding occurs [1].

There are many factors correlated with the risk of recurrent bleeding in peptic ulcers, including endoscopic features and clinical parameters. The Forrest classification based on the endoscopic feature predicts recurrent bleeding (Table 1) [2]. In contrast to ulcers with the Forrest Ia, Ib, IIa, and IIb lesions, the risk of recurrent bleeding in ulcers with the IIc lesion without endoscopic therapy has been shown to be only 0–13% [3]. However, it is uncertain what kind of patient is at increased risk of recurrent bleeding if the features show the IIc lesion.

Previous studies showed that patients with comorbidities experience an increased risk of recurrent bleeding even when they receive endoscopic hemostasis and intravenous proton pump inhibitor (PPI) therapy [4–6]. The Rockall scoring system, which includes endoscopic features and clinical parameters, has been used to evaluate patients holistically and to predict recurrent bleeding and mortality from peptic ulcers (Table 1) [7].

Table 1 The criteria of the Forrest classification [2, 3] and the Rockall score [7]

Forrest classification						
Class	Ia	Ib	IIa	IIb	IIc	III
	Spurting artery	Oozing	Non-bleeding visible vessel	Adherent clot	Flat pigmented hematin	Clean base
Variables	Rockall scores					
	0	1	2	3		
Age (year)	< 60	60–79	≥ 80			–
Shock	Heart rate < 100 beats per minute and systolic blood pressure ≥ 100 mmHg	Heart rate ≥ 100 beats per minute	Systolic blood pressure < 100 mmHg			–
Comorbidities ^a	No	–	1. Coronary artery disease 2. Cardiac failure ^b 3. Any major comorbidity ^c	1. Liver failure ^d 2. Renal failure ^e 3. Malignant diseases, disseminated		
Diagnosis	Mallory–Weiss tear, no lesion	Others, including benign gastric or duodenal ulcers	Esophageal, gastric, or duodenal malignancy			–
Major stigmata of recent hemorrhage	Forrest IIc or III	–	Forrest Ia, Ib, IIa, or IIb or blood in upper gastrointestinal tract			–

^aWe modified the diagnostic criteria of comorbidities as follows to make this variable clearer to be scored than it was according to the old criteria

^bCardiac failure included congestive heart failure with New York Heart Association Function I to IV

^cAny major comorbidity included lung disease (chronic obstructive pulmonary disease, pulmonary tuberculosis, pneumonia, or empyema), chronic kidney disease stage III (estimated glomerular filtration rates between 30 and 60 mL/min/1.73 m²), rheumatoid arthritis, sepsis, new-onset cerebrovascular accident, intensive care unit stay, mechanical ventilator support for > 24 h, or any major surgery (on the central nervous system, thorax, abdomen, long bones or spinal bones) within 14 days prior to bleeding

^dLiver failure included liver cirrhosis, Child–Pugh A, B, or C

^eRenal failure included chronic kidney disease stage IV (estimated glomerular filtration rates between 15 and 30 mL/min/1.73 m²), stage V (estimated glomerular filtration rates < 15 mL/min/1.73 m²) with or without maintenance dialysis, or acute kidney injury with estimated glomerular filtration rates < 30 mL/min/1.73 m²

Previous studies have shown that comorbid patients have impaired tissue healing on peptic ulcers [8–10]. Studies have also shown that patients' Rockall scores are often ≥ 6 in those with comorbidities, who also exhibit an increased risk of recurrent peptic ulcer bleeding [11, 12]. Therefore, we propose that patients with Rockall scores ≥ 6 are still at risk of recurrent bleeding after initial treatment partially because of impaired tissue healing, which results in delayed fading out of the Forrest lesions.

Hence, in the present study, patients were enrolled who had significant peptic ulcer bleeding according to their ulcers at the primary endoscopy in an effort to investigate whether the Rockall score on arrival could predict recurrent peptic ulcer bleeding among patients whose major stigmata of recent hemorrhage (SRH) included the Forrest class Ia, Ib, IIa, and IIb lesions fading to the IIc lesion after initial endoscopic hemostasis and intravenous PPI infusion. Therefore, the present study is helpful not only with regard to identifying patients who are still at risk of recurrent bleeding but also with regard to identifying those who may require more aggressive acid control and/or endoscopic therapy to reduce the risk of recurrent peptic ulcer bleeding even though their SRH had been fading to minor after initial treatment.

Materials and methods

Study design

We conducted this prospective observational cohort study at a tertiary health care center. The study design was approved by the research and ethics committee with trial registration identifier NCT01591083, *ClinicalTrials.gov*. All participants were consecutively assessed for eligibility and enrolled from August of 2011 to July of 2016 after signing an informed consent. This study extended our original database to prove our hypothesis and was one of the studies analyzing the short-term and long-term outcomes in bleeding peptic ulcer populations based on our database [11–14].

Patients were eligible to be enrolled if they presented with upper gastrointestinal bleeding and had undergone primary endoscopy that showed bleeding peptic ulcers with major SRH, including Forrest Ia, Ib, IIa, and/or IIb types [2, 3]. The major SRH was treated using one or a combination of endoscopic therapies until active bleeding stopped or coagulation of vessels was achieved. The therapies included (1) local injection of normal saline or diluted epinephrine 1:10,000, (2) coagulation by heater probe (HPU-20, Olympus, Tokyo, Japan) with 20 J, bipolar electrocoagulation (ERBE ICC 200/APC 300, ERBE Elektromedizin GmbH, Tübingen) at 30 watts, or Forced Argon Plasma Coagulation (ERBE ICC 200/APC) at 60 W, and (3) mechanical therapy using band ligation or hemoclip therapy [15, 16].

After endoscopic hemostasis, a PPI therapy with an 80 mg loading dose followed by a 3-day intravenous continuous high-dose (8 mg/h) infusion of either esomeprazole (Nexium[®], AstraZeneca AB, Södertälje, Sweden) or pantoprazole (Pantoloc[®], Takeda, Singen, Germany) immediately after the primary endoscopy were prescribed. Afterward, all patients received oral esomeprazole or pantoprazole 40 mg once daily until the end of the 28-day study periods [17]. The second-look endoscopy was scheduled 2 or 3 days after the primary endoscopy (Fig. 1). Anti-platelet agents or warfarin were discontinued for 3 days after primary endoscopy and were resumed on the 4th day after the primary endoscopy. Enrolled participants were patients ≥ 20 years who had major SRH at the primary endoscopy and major SRH had resolved to be the IIc lesion, which was documented by the second-look endoscopy. Patients were excluded if they had expired or clinically relevant recurrent bleeding within 3 days after the primary endoscopy, had bleeding lesions other than peptic ulcer diseases, for example, gastric tumor/cancer, Dieulafoy lesions, or mechanical factor-induced bleeding (e.g., nasogastric tube or gastrostomy tube induction), were hypersensitive to esomeprazole or pantoprazole, or had previously been enrolled in the study. Accordingly, all enrolled patients had a score of 3 for the endoscopic Rockall variables.

The patients' baseline clinical data, comorbidities, drug history, laboratory, and endoscopic features were obtained on arrival. Comorbidities were evaluated according to the Rockall scoring system [7]. Additionally, patients with other major admission events including intensive care unit stay, mechanical ventilator support for > 24 h, or any major surgery within 14 days prior to bleeding were classified as having a score of 2 for comorbidities based on the Rockall scoring system (Table 1).

Outcome measures

All patients were monitored for 28 days after primary endoscopy, which was conducted within 24 h after the first bleeding episode. Clinically relevant recurrent bleeding from peptic ulcers during the study period was the primary endpoint. Clinically relevant recurrent bleeding was defined as the presence of gastrointestinal bleeding after the second-look endoscopy including melena, hematochezia, and/or recurrent bloody aspirates through a nasogastric tube, plus unstable hemodynamics including hypotension as systolic blood pressure < 90 mmHg, tachycardia > 120 beats/min, and/or a drop in hemoglobin concentration of > 2.0 g/dL again after the hemoglobin level was stable. The intention-to-treat (ITT) analysis of the primary endpoint included all of the enrolled patients, and the primary outcome was proposed as treatment failure if they dropped out of follow-up for any reason, including unwillingness to join the study, adverse effects, protocol violations, or others. The per-protocol (PP) analysis

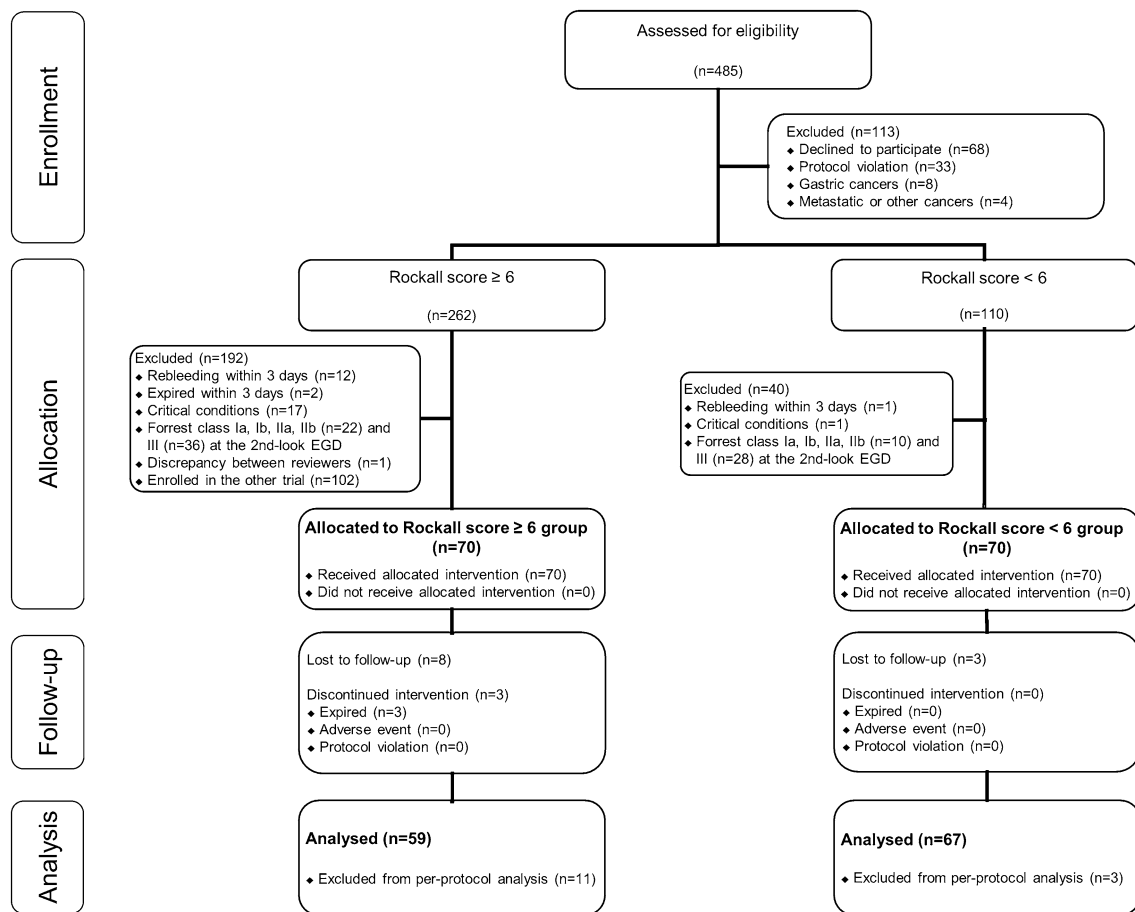


Fig. 1 The schematic flow chart for the study design

included patients not lost to follow-up and those who had not discontinued the intervention.

The secondary outcomes included (i) the number of units of blood transfused to maintain hemoglobin concentration ≥ 10 g/dL for patients with uremia or coronary artery disease or ≥ 7 g/dL for others during the 28-day period after either arrival to the emergency room or the first episode of peptic ulcer bleeding in patients with nosocomial bleeding [17], (ii) the length of hospital stay after the first episode of peptic ulcer bleeding, (iii) events in need of transarterial embolization or emergency surgery, which was indicated if there was continuous bleeding after endoscopic hemostasis, and (iv) mortality, which was defined as death due to any cause.

Review of endoscopic pictures

The primary or second-look endoscopy was conducted using either an Olympus GIF-XQ230 or a 240 fiberscope. The ulcer size was determined by using biopsy forceps, which when fully opened, the cups were 6 mm in diameter (FB-25K-1, Olympus). The gastroscopic pictures were photographed and then assessed by a three-member steering committee, who were all

blinded to the study. The grading of the Forrest classification met the criteria [2]. Equivocal or inconsistent results between the members were resolved by discussion and consensus. Patients were excluded if the result was discrepant.

Statistical analysis

According to the average recurrent bleeding rates of peptic ulcers, 17.3% had rebleeding with Rockall scores ≥ 6 [11], and 5% had rebleeding with the Forrest IIc lesion regardless of Rockall scores [3]. We estimated the recurrent bleeding rates of the Forrest IIc lesion among patients with Rockall scores ≥ 6 and < 6 to be 17.5% and 2.5%, respectively. A total of 124 patients was required to have a two-sided α value of 0.05 and a power of 80% ($\beta=0.20$). Assuming a rate of screening failure and a dropout rate of 10%, at least 136 patients had to be included. The Student's *t* test and a Pearson's χ^2 test with the Fisher's exact test were used to compare the continuous variables and nominal or dichotomous variables, respectively. Continuous variables were categorized to avoid multiplicative errors. All tests were two-tailed analyses, and *p* values of less than 0.05 indicated significant differences.

Results

Demographic features and patient follow-up

A total of 140 patients treated during the study period met the inclusion criteria requirements and were enrolled prospectively (Fig. 1). They were divided into the Rockall

scores ≥ 6 group ($n = 70$) and the Rockall scores < 6 group ($n = 70$) based on their Rockall scores on arrival. Baseline characteristics that were either directly or indirectly relevant to the Rockall score were significantly different between the two study groups, including age ≥ 70 year/o ($p < 0.001$), hemodynamic instability ($p = 0.047$), underlying comorbidities, or American Society of Anesthesiology (ASA) physical status classification ($p < 0.05$, Table 2).

Table 2 Comparison of baseline characteristics between the two study groups

Parameters <i>N</i> (%); mean \pm SD	Rockall scores ≥ 6 group ($n = 70$)	Rockall scores < 6 group ($n = 70$)	<i>p</i> value ^a
Female	20 (28.6)	18 (25.7)	0.70
Mean age (year)	70.6 \pm 11.9	58.1 \pm 14.0	<0.001
Age ≥ 70 year/o	45 (64.3)	13 (18.6)	<0.001
Hemodynamic instability ^b	17 (24.3)	8 (11.4)	0.047
Coronary artery disease and/or congestive heart disease	22 (31.4)	0 (0)	<0.001
Cirrhosis	8 (11.4)	0 (0)	0.01
End-stage renal disease with maintenance dialysis	7 (10.0)	0 (0)	0.01
Malignant diseases, disseminated	14 (20.0)	2 (2.9)	0.001
Lung diseases	8 (11.4)	1 (1.14)	0.03
Nosocomial bleeding ^c	12 (17.1)	1 (1.14)	0.001
ASA physical status classification (n)			
Class I:II:III:IV	0:18:46:6	27:42:1:0	<0.001
<i>H. pylori</i> infection ^d	27/64 (42.2)	43/70 (61.4)	0.03
NSAID use	26 (37.1)	25 (35.7)	0.86
Anti-platelet agent use	29 (41.4)	4 (5.7)	<0.001
Mean hemoglobin (g/dL)	8.5 \pm 2.3	11.0 \pm 2.5	<0.001
Hemoglobin levels < 10.0 g/dL	51 (72.9)	24 (34.3)	<0.001
Platelet count $< 80 \times 10^9/L$	3 (4.3)	1 (1.4)	0.62
PT prolong ≥ 4 s	6 (8.6)	1 (1.4)	0.12
APTT prolong ≥ 1.5 -fold	1 (1.4)	1 (1.4)	1.0
Serum albumin levels < 3.0 g/dL	24 (34.3)	3 (4.3)	<0.001
Rockall scoring system ^e			
Age 0:1:2	16 (22.9):41 (58.6):13 (18.6)	42 (60.0):23 (32.9):5 (7.1)	<0.001
Shock 0:1:2	24 (34.3):29 (41.4):17 (24.3)	33 (47.1):29 (41.4):8 (11.4)	0.10
Comorbidities 0:2:3	1 (1.4):41 (58.6):28 (40.0)	67 (95.7):3 (4.3):0 (0)	<0.001
Diagnosis at the primary endoscopy 0:1:2	0:70 (100):0	0:70 (100):0	–
Major SRH ^f at the primary endoscopy 0:1:2	0:0:70 (100)	0:0:70 (100)	–
The total Rockall scores 3:4:5:6:7:8:9:10	0:0:0:21 (30.0):21 (30.0):20 (28.6):7 (10.0):1 (1.4)	12 (17.1):32 (45.7):26 (37.1):0:0:0:0	<0.001

Activated partial thromboplastin time: normal range 26.0–38.0 s. Albumin: normal range 3.5–5.0 g/dL. Hemoglobin: normal range 11.6–14.8 g/dL. Platelet: normal range 151–366 $\times 10^9/L$. Prothrombin time: normal range 9.4–12.5 s

^aThe Student's *t* test, a Pearson's Chi-square test, and the Fisher's exact test with a 2-tailed analysis were used

^bSystolic blood pressure < 100 mmHg on arrival

^cNosocomial bleeding was peptic ulcer bleeding that developed more than 24 h after admission

^dThe number of patients who received *H. pylori* infection survey totaled 134

^eThe criteria of the Rockall scoring system was shown in Table 1

^fMajor SRH includes Forrest Ia, Ib, Ila, and IIb. The data are shown in Table 3 in detail

APTT activated partial thromboplastin time; ASA American Society of Anesthesiology; *H. pylori*, *Helicobacter pylori*; NSAID non-steroidal anti-inflammatory drugs; PT prothrombin time; SD standard deviation; SRH stigmata of recent hemorrhage

Based on the Rockall scoring system, more patients in the Rockall scores ≥ 6 group had scores of 1 and 2 for age and 2 and 3 for comorbidities, respectively, than those in the Rockall scores < 6 group ($p < 0.001$, Table 2). The rates of hemoglobin levels < 10.0 g/dL and serum albumin levels < 3.0 g/dL were higher in the Rockall scores ≥ 6 group than in the Rockall scores < 6 group ($p < 0.001$). These two factors were correlated with bleeding severity and/or comorbidities. There were no other between-group factors, including sex ($p = 0.70$), non-steroidal anti-inflammatory drugs use ($p = 0.86$), platelet counts $< 80 \times 10^9/L$ ($p = 0.62$), prothrombin time (PT) prolong ≥ 4 s ($p = 0.12$), and activated partial thromboplastin time (APTT) prolong ≥ 1.5 -fold ($p = 1.0$). Interestingly, the rates of *Helicobacter pylori* (*H. pylori*) infection were lower in the Rockall scores ≥ 6 group than in the Rockall scores < 6 group (42.2% versus 61.4%, $p = 0.03$, Table 1).

The endoscopic features at the primary endoscopy and the second-look endoscopy

The endoscopic features are listed in Table 3. Compared with the Rockall scores < 6 group, the Rockall scores ≥ 6 group had higher rates of gastric ulcer (58.6% versus 41.4%, $p = 0.04$) and lower rates of the Forrest class Ia and Ib lesions (11/70 [15.7%] versus 30/70 [42.9%], $p < 0.01$) at the primary endoscopy. Gastroscopic therapy was similar between the two study groups. In the Rockall scores ≥ 6 group and < 6 group, there were 10 (14.3%) and 5 (7.1%)

patients who received endoscopic epinephrine-injection monotherapy with an average dose of 10 mL, 6 (8.6%), and 5 (7.1%) patients who received other endoscopic monotherapy, and 54 (77.1%) and 60 (85.7%) patients who received endoscopic combination therapies, respectively ($p = 0.36$). The rates of ulcer location on the posterior duodenal wall or the proximal lesser curvature of the stomach, where it was difficult to perform endoscopic hemostasis, were similar between the two groups (10.0% versus 7.1%, $p = 0.55$). At the second-look endoscopy, all of the enrolled patients had ulcers with the Forrest class IIc lesion, and none of the patients received endoscopic hemostatic procedures at the second-look endoscopy.

The primary and secondary outcomes

Six patients had recurrent bleeding from the 4th to the 28th day, all of which were in the Rockall scores ≥ 6 group. Among these patients, five developed recurrent bleeding from the 4th to the 14th day. The recurrent bleeding rates from the 4th to the 14th day and from the 4th to the 28th day between the Rockall scores ≥ 6 group and the Rockall scores < 6 group were 13/70 (18.6%) versus 2/70 (2.9%), $p < 0.01$ and 17/70 (24.3%) versus 3/70 (4.3%), $p = 0.001$, respectively, based on the ITT analysis, and were 5/62 (8.1%) versus 0/68 (0%), $p = 0.02$ and 6/59 (10.2%) versus 0/67 (0%), $p = 0.01$, respectively, based on the PP analysis. The relative risks (95% confidence interval, CI) of recurrent bleeding were 6.50 (1.52–27.75) from the 4th to the 14th day and

Table 3 Comparison of endoscopic features between the two study groups

Parameters N (%); mean \pm SD	Rockall score ≥ 6 group (n = 70)	Rockall score < 6 group (n = 70)	p value ^a
The primary endoscopy			
Gastric ulcer	41 (58.6)	29 (41.4)	0.04
Size ≥ 2 cm	18 (25.7)	10 (14.3)	0.09
Forrest classification			
Ia: Ib: IIa: IIb	2 (2.9):9:(12.9):50 (71.4):9 (12.9)	1 (1.4):29:(41.4):32 (45.7):8 (11.4)	< 0.01
Gastroscopic therapy ^b			
Epinephrine: monotherapy: combination therapies	10 (14.3):6 (8.6):54 (77.1)	5 (7.1):5 (7.1):60 (85.7)	0.36
Ulcer location with difficult endoscopic hemostasis ^c	7 (10.0)	5 (7.1)	0.55

SD standard deviation

^aThe Student's *t* test, a Pearson's Chi-square test, and the Fisher's exact test with a 2-tailed analysis were used

^bGastroscopic monotherapy indicated one modality except epinephrine injection and combination therapies indicated at least two modalities for peptic ulcer hemostasis within one endoscopic session

^cUlcer location on the posterior duodenal wall or the proximal lesser curvature of the stomach

5.67 (1.74–18.48) from the 4th to the 28th day based on the ITT analysis (Table 4). The adjusted relative risks of recurrent bleeding for the gastric ulcer were 6.50 (1.52–27.75) from the 4th to the 14th day and 5.33 (1.63–17.49) from the 4th to the 28th day ($p < 0.01$ and 0.001 , respectively). For the Forrest classification, these rates were 11.0 (2.68–45.07) from the 4th to the 14th day and 12.5 (3.07–50.83) from the

4th to the 28th day ($p < 0.001$, Table 4). The Kaplan–Meier curves showed that the proportion of patients free from recurrent bleeding from the 4th to the 28th day was lower in the Rockall scores ≥ 6 group than in the Rockall scores < 6 group ($p = 0.01$, log-rank test, Fig. 2).

A sex-based analysis was also conducted. In the Rockall scores ≥ 6 group, the recurrent bleeding rates between

Table 4 Comparison of the primary and secondary outcomes between the two study groups

Recurrent bleeding rate of peptic ulcer N (%); median (IQR, 25th–75th percentile)	Rockall scores ≥ 6 group	Rockall scores < 6 group	Relative risk (95% CI)	p value ^a	Adjusted relative risk (95% CI)	p value ^a
Primary outcome						
ITT analysis						
From the 4th to the 14th day	13/70 (18.6)	2/70 (2.9)	6.50 (1.52–27.75)	< 0.01	6.50 (1.52–27.75) ^b 11.0 (2.68–45.07) ^c	< 0.01 ^b < 0.001 ^c
From the 4th to the 28th day	17/70 (24.3)	3/70 (4.3)	5.67 (1.74–18.48)	0.001	5.33 (1.63–17.49) ^b 12.5 (3.07–50.83) ^c	0.001 ^b < 0.001 ^c
PP analysis						
From the 4th to the 14th day	5/62 (8.1)	0/68 (0)	–	0.02	–	–
From the 4th to the 28th day	6/59 (10.2)	0/67 (0)	–	0.01	–	–
Secondary outcomes						
Blood transfusion (u)	4.5 (2.0–8.0)	0 (0–2.0)	–	< 0.001	–	–
Hospital stay (d)	5.0 (4.0–10.25)	4.0 (4.0–4.25)	–	< 0.001	–	–
TAE or surgery	2/70 (2.9)	0/70 (0)	–	0.50	–	–
Mortality	3/70 (4.3)	0/70 (0)	–	0.25	–	–

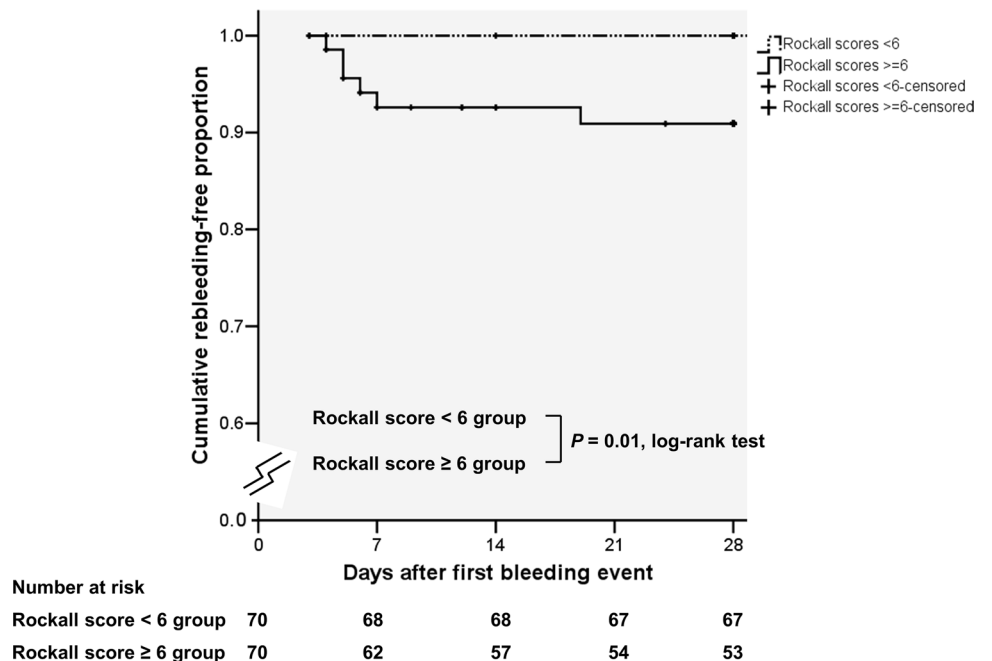
CI confidence interval, D day, IQR interquartile range, ITT intention-to-treat, PP per-protocol, TAE transarterial embolization, U unit

^aEither a Pearson’s Chi-square test with the Fisher’s exact test or the Mann–Whitney U test was used with a 2-tailed analysis

^bAdjusted for gastric ulcer

^cAdjusted for the Forrest classification at the primary endoscopy

Fig. 2 The cumulative rebleeding-free proportion from the 4th to the 28th day after the first bleeding event. The Rockall scores ≥ 6 group had a significantly lower cumulative rebleeding-free proportion as compared to the Rockall scores < 6 group ($p = 0.01$)



males and females from the 4th to the 14th day and from the 4th to the 28th day were 11/50 (22.0%) versus 2/20 (10.0%), $p=0.32$ and 13/50 (26.0%) versus 4/20 (20.0%), $p=0.76$, respectively, based on the ITT analysis, and 5/44 (11.4%) versus 0/18 (0%), $p=0.31$ and 5/42 (11.9%) versus 1/17 (5.9%), $p=0.66$, respectively, based on the PP analysis. There was no significant difference found between females and males.

The secondary outcomes were also compared. The Rockall scores ≥ 6 group had more units of blood transfusion and longer hospital stays than the Rockall scores < 6 group did (4.5 u versus 0 u and 5.0 days versus 4.0 days, respectively, $p < 0.001$, Table 4). The rates of transarterial embolization/surgery and mortality were similar between the two groups (2.9% versus 0%, $p=0.50$ and 4.3% versus 0%, $p=0.25$, respectively, Table 4). The causes of mortality included ischemic colitis in a heart failure patient, hip abscess with sepsis in a cirrhotic and uremic patient, and subdural hemorrhage in a cirrhotic, hepatoma, and uremic patient.

Discussion

This prospective study demonstrated that Rockall scores ≥ 6 on arrival can predict further clinically relevant recurrent bleeding from peptic ulcers among patients who present with the Forrest IIC lesion fading from a major SRH following initial endoscopic hemostasis and intravenous PPI treatment.

Recurrent peptic ulcer bleeding can be predicted by both the endoscopic features on peptic ulcer and the clinical features. There are endoscopic features proven to be correlated with an increased risk of recurrent bleeding, including gastric ulcer, ulcer size, the Forrest classification, gastroscopic therapy, and the ulcer location, where the efficacy of endoscopic hemostasis is limited [18]. In this study, the endoscopic features of the patients at the primary endoscopy were similar between the two groups, with the exception of gastric ulcers and the Forrest classification (Table 3). All enrolled patients received endoscopic hemostasis at the primary endoscopy to treat their major SRH according to clinical practice guidelines [15–19] and all of the major SRH had been fading to the Forrest IIC lesion after intravenous PPI infusion for 48–72 h. The recurrent bleeding rate of an ulcer with the Forrest IIC lesion is only 0–13% [3]; nevertheless, the particularly striking finding of this study was that the rates of recurrent peptic ulcer bleeding from the 4th to the 28th day were 24.3% (ITT) and 10.2% (PP) in the Rockall scores ≥ 6 group but only 4.3% (ITT) and 0% (PP) in the Rockall scores < 6 group even though ulcers presented with the IIC lesion ($p=0.001$ by ITT and 0.01 by PP, respectively, Table 4). Moreover, we adjusted for gastric ulcers and the Forrest classification to avoid confounding, and the adjusted

relative risks of recurrent bleeding were still increased in the Rockall scores ≥ 6 group (4th–28th day, 5.33 [1.63–17.49], $p=0.001$ and 12.5 [3.07–50.83], $p < 0.001$, respectively, Table 4).

The Rockall score ≥ 6 is strongly correlated with recurrent peptic ulcer bleeding [7, 11]. Our findings not only strengthened this supposition, but also illustrated that patients with Rockall scores ≥ 6 were still at risk of recurrent bleeding even though their SRH had been fading to minor. The Rockall scoring system includes endoscopic and clinical variables (Table 1). This study enrolled patients all of whom had score 3 for the endoscopic variables at the primary endoscopy (Table 2). Specifically, the clinical Rockall scores were ≥ 3 for patients who were at risk of recurrent bleeding. Our results suggested a rationale of doubling the oral PPI dose to 14 days or prolonging intravenous PPI infusion to 7 days in patients with Rockall scores ≥ 6 or clinical Rockall scores ≥ 3 [11, 20]. We conducted this study based on contemporary strategies; thus, the results could be generalizable to current clinical practice.

Additionally, current practice guidelines suggest medical treatment only for ulcers with minor SRH [15–19]; however, the level of evidence is only 2b [17] or in moderate quality [18]. Importantly, these suggestions are based on the risk of recurrent bleeding stratified by the Forrest classification, which evaluates endoscopic features only. Our results are highly original in terms of showing an increased risk of recurrent bleeding among patients with both Rockall scores ≥ 6 on arrival and a Forrest IIC lesion at the second-look endoscopy and suggest a potential indication to apply endoscopic therapy tailored to such a patient. A previous study showed that pre-emptive PPI before endoscopy accelerates the resolution of SRH but does not decrease the risk of recurrent bleeding; however, endoscopic therapy for ulcers with the Forrest IIC was not performed in that study [21]. Our findings provide new insights into who may be indicated for endoscopic therapy for ulcers with the Forrest IIC lesion after pre-emptive PPI.

The reasons why the Rockall score ≥ 6 is so predictive are uncertain. An imbalance between aggressive factors and the defensive mechanisms is responsible for peptic ulcers [22]. In this study, patients with Rockall scores ≥ 6 were older, had comorbidities, or had higher rates of hemodynamic instability on arrival ($p < 0.05$); however, they had lower rates of *H. pylori* infection than those with Rockall scores < 6 ($p=0.03$, Table 2). These findings suggest that the pathogenesis of peptic ulcers in patients with Rockall scores ≥ 6 may be due to an impaired defensive mechanism, i.e., the mucus–bicarbonate barrier, more than aggressive factors, i.e., *H. pylori* [22–24]. The secretion of mucus gel and bicarbonate is essential to maintain the mucus–bicarbonate barrier [25, 26], but it is impaired because the perfusion in the gastroduodenal mucosa is

compromised in patients with senility, comorbidity, or hemodynamic instability [8, 27]. Mucus and bicarbonate secretions are regulated by prostaglandins [28]; thus, a study of the role of prostaglandins in peptic ulcer disease in patients with Rockall scores ≥ 6 would be a promising direction for future studies. Although the reasons are uncertain, endoscopists could evaluate patients who are at risk of recurrent bleeding more holistically by using the Rockall score than by using the Forrest classification.

Both sexes were enrolled in this study to conduct sex-inclusive clinical research, which showed that the rates of recurrent bleeding were not significantly different between sexes in the Rockall scores ≥ 6 group. However, drawing this conclusion may be premature because of lacking an appropriate power; thus, further research is needed.

The study had some limitations. First, the results were based on the Forrest lesion at the second-look endoscopy. Second, this was an observational study only. Third, second-look endoscopy may increase the medical cost. Previous studies have shown that endoscopic hemostasis does not provide a significant advantage in ulcers with minor SRH [29–31]. Therefore, further studies are needed to validate the role of clinical Rockall scores ≥ 3 to predict the risk of recurrent bleeding and the benefit of endoscopic therapy to reduce risks of ulcers with the Forrest IIc lesion at the primary endoscopy. Moreover, it is also important to estimate the incremental cost-effectiveness ratio of second-look endoscopy in patients with high Rockall scores ≥ 6 .

In conclusion, the majority of patients who had recurrent bleeding from peptic ulcers with the Forrest IIc lesion at the second-look endoscopy were those whose Rockall scores were ≥ 6 or whose clinical Rockall scores were ≥ 3 on arrival. Accordingly, combined Rockall scores ≥ 6 or clinical Rockall scores ≥ 3 on arrival with a Forrest IIc lesion at the second-look endoscopy can identify patients who were still at risk of recurrent bleeding from peptic ulcers following initial endoscopic hemostasis and intravenous PPI therapy.

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Compliance with ethical standards

Disclosures Drs. Er-Hsiang Yang, Chung-Tai Wu, Hsin-Yu Kuo, Wei-Ying Chen, Bor-Shyang Sheu, and Hsiu-Chi Cheng have no conflict of interest or financial ties to disclose.

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