Risk factors determining the need for second-look endoscopy for peptic ulcer bleeding after endoscopic hemostasis and proton pump inhibitor infusion

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Background and study aims: The need for routine second-look endoscopy in cases of peptic ulcer bleeding remains uncertain. We investigated risk factors related to the need for second-look endoscopy after endoscopic hemostasis and proton pump inhibitor (PPI) infusion.
Patients and methods: We prospectively enrolled 316 patients with peptic ulcer bleeding after endoscopic hemostasis. Second-look endoscopy was scheduled after 72-hour PPI infusion (Day-3 subgroup) or one day early (Day-2 subgroup). If early rebleeding developed within 3 days, emergent second-look endoscopy was conducted. Risk factors for early rebleeding (use of E2nd score to predict the need for early second-look endoscopy) and persistent major stigmata in the Day-3 subgroup (use of R2nd score to predict the need for routine second-look endoscopy) were analyzed using univariable and multivariable regression.

Results: Excluding 10 of 316 patients with early rebleeding, the rate of persistent major stigmata was lower in the Day-3 subgroup than in the Day-2 subgroup (4.8% *vs.* 15.4%, $P = 0.002$). Endoscopic epinephrine-injection monotherapy and hypoalbuminemia < 3.0 g/dL were two independent risk factors for early rebleeding ($P \leq 0.05$). The Forrest Ia-Ib type and hypoalbuminemia < 3.5 g/dL were two independent risk factors for persistent major stigmata on the day-3 second-look endoscopy ($P < 0.05$). The E2nd score was highly accurate for prediction of early rebleeding (AUROC 0.86; 95% CI, 0.73~0.99), and the R2nd score could predict persistent major stigmata at second-look endoscopy (AUROC 0.84; 95% CI, 0.69~0.99).
Conclusions: For patients with peptic ulcer bleeding, E2nd and R2nd scores can indicate the need for early and routine second-look endoscopy, respectively

(Trial registration identifier: NCT02197039).

Introduction

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Peptic ulcer bleeding is a common, yet lethal disease [1]. The appearance of stigmata of recent hemorrhage (SRH) in cases of peptic ulcer indicates a higher rate of peptic ulcer rebleeding [2]. Based on endoscopic management to treat SRH, peptic ulcer rebleeding can be reduced [3,4]. To further improve control of rebleeding, the concept of a second-look endoscopy has been proposed [5–7]. Between the two endoscopic sessions, acid suppression is generally recommended to elevate the intragastric pH value and thus prevent peptic ulcer rebleeding [8,9]. Given the limited scale of the studies and inadequacy of acid suppression because only a histamine-2 receptor antagonist was applied in these trials [5–7], the exact impact of second-look endoscopy on peptic ulcer rebleeding control remains uncertain [9–11]. With the availability of more potent gastric acid sup-pression by proton pump inhibitor (PPI) infusion after endoscopic therapy, a recent consensus suggests that second-look endoscopy should be reserved for certain high-risk patients [12].
After endoscopic treatment for SRH of peptic ulcer, a 72-hour intravenous (IV) PPI infusion followed by oral PPI already has been adopted as the standard approach to prevent peptic ulcer rebleeding [9]. Nevertheless, it has limited effectiveness in certain high-risk patients, such as those with comorbidities [13,14]. It is possible that due to poor SRH fading after 72-hour PPI infusion in certain patients, second-look endoscopy may be helpful to retreat SRH. Accordingly, there is a pressing need to elucidate which patient risk factors result in a need for second-look endoscopy in a period when PPI infusion is readily available [15].
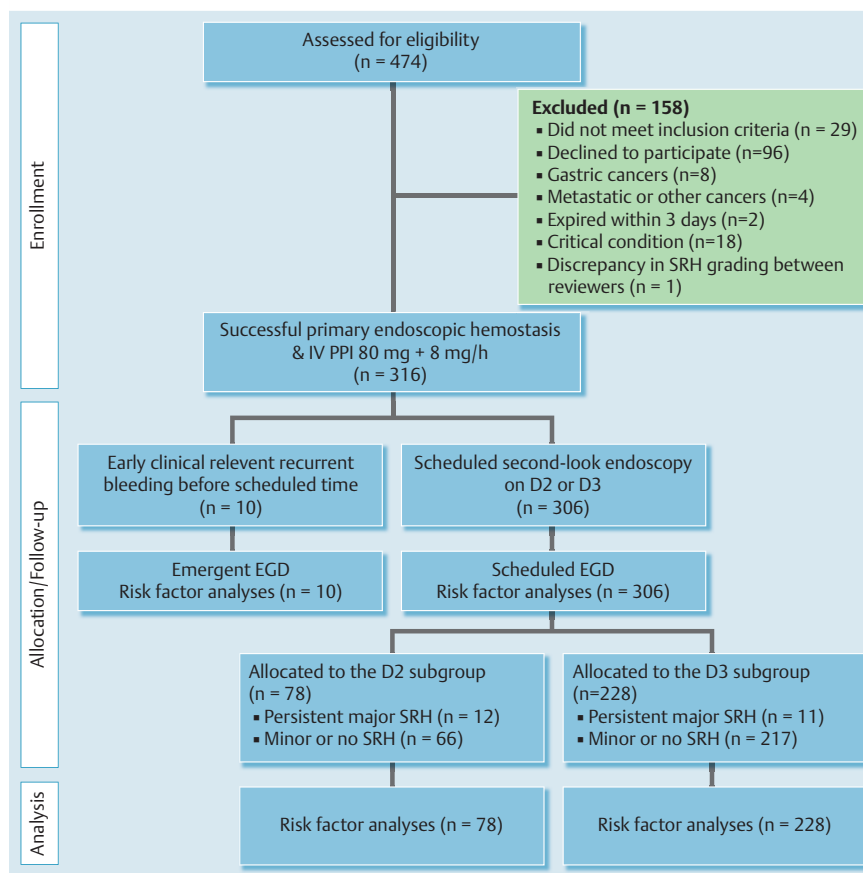The aim of the present study, therefore, was to investigate risk profiles that help identify early re-

Fig. 1 The schematic flow chart for the study design.

Patients and methods

Study design

This study was conducted at the inpatient wards of National Cheng Kung University Hospital, a tertiary health care center in Tainan, Taiwan. The research and ethics committee of the hospital approved the study design (trial registration identifier: NCT02197039, ClincalTrials.gov), and all participants gave written informed consent before enrollment. A schematic flow chart of the study protocol is shown in ● **Fig. 1**.

Eligible participants included patients aged ≥20 years who had undergone gastroscopy for melena, hematochezia, or hematemesis due to bleeding peptic ulcers with major SRH. The major SRH were classified as Forrest Ia, Ib, IIa, and IIb types [16]. At the primary endoscopy, which was done within 24 hours of suspicious gastrointestinal bleeding on day 0, the adherent clot was vigorously washed away, and all SRH patients were given one or a combination of endoscopic therapies including local injection of diluted epinephrine 1:10000, heater probe (HPU-20, Olympus, Tokyo, Japan) at 20 J, bipolar electrocoagulation (ERBE ICC 200/APC 300, ERBE Elektromedizin GmbH, Tübingen) at 30 watts, Forced Argon Plasma Coagulation (ERBE ICC 200/APC) at 60 watts

bleeding or poor fading of major SRH in a large cohort of patients with peptic ulcer bleeding after PPI infusion. The study illustrated the independent risk factors related to peptic ulcer rebleeding in order to obtain two scores. These data can help readily identify patients who require either early second-look endoscopy or routine second-look endoscopy to improve control of peptic ulcer rebleeding even after PPI infusion.

per goal consecutively, band ligation, or hemoclip therapy until cessation of active bleeding or achievement of co-aptive coagulation [3,4]. Treatment procedures were performed by experienced endoscopists.

Patients were enrolled after successful endoscopic hemostasis. Each enrolled patient received an 80-mg loading dose of IV esomeprazole (Nexium®, AstraZeneca AB, Södertälje, Sweden) immediately after hemostasis was achieved by gastroscopy. The patients then received 3 days of continuous high-dose (8 mg/h) IV esomeprazole as therapy [8]. Patients who took clopidogrel received the same doses and duration of IV pantoprazole (Pantoloc®, Takeda, Singen, Germany) therapy. Patients taking warfarin or undergoing antiplatelet therapy discontinued such medications and therapies for 3 days after primary endoscopy.

The second-look endoscopy was scheduled on day 3, after postendoscopic hemostasis high-dose IV PPI therapy up to nearly 72 hours. If day 3 was Sunday or a holiday, the second-look endoscopy was conducted ahead of schedule on day 2 (● **Fig. 1**). Otherwise, the second-look endoscopy was conducted immediately before the schedule if the patient had early clinically relevant rebleeding. Clinically relevant rebleeding was defined as: 1) continuous melena, hematochezia, or the presence of recurrent bloody aspirates through a nasogastric tube; and 2) relapse of hemodynamic instability, including systolic blood pressure <90 mmHg, heart rate >120 beats/min, or a drop in hemoglobin concentration of >2.0 g/dL. Patients were excluded if they had tumors, Dieulafoy, or mechanical factor-related bleeding (e. g., gastrostomy tube induction), PPI use for more than 1 day within a week before enrollment, hypersensitivity to esomeprazole or pantoprazole, had previously participated in the study, or had expired before the second-look endoscopy.

Predictive measures

Patients were prospectively followed until the second-look endoscopy. The primary analytical goals were to characterize all patients and to identify predictors of early clinically relevant rebleeding or persistent major SRH at the second-look endoscopy through univariable and multivariable regression modeling. The patients' baseline clinical, laboratory, and endoscopic characteristics were obtained at the time of admission. The range of comorbidities was evaluated using the Rockall score [17]. Recent history of any major surgery within 14 days prior to bleeding, intensive care unit stay, mechanical ventilator support for >24 hours, exposure to nonsteroidal anti-inflammatory, sympathomimetic pressors, or inotropic drugs during the first 3 days after primary endoscopy was also evaluated. Nosocomial bleeding was defined as peptic ulcer bleeding that developed more than 24 hours after admission.

Independent review of endoscopic pictures

The endoscope employed was either an Olympus GIF-XQ230 or a 240 fibrescope. Ulcer size was estimated with biopsy forceps, with fully opened cups being 6 mm in diameter (FB-25K-1, Olympus). The endoscopists and staff who checked the gastroscopy were all blinded to the study. The investigator who enrolled the participants was not the same investigator who evaluated the Forrest type ulcers. A three-member steering committee provided quality assurance. All ulcer lesions and stigmata were photographed and then assessed by the committee. Independent review verified the endoscopic pictures to identify potential stigmata meeting the Forrest classification criteria [16]. Any stigmata considered equivocal by one of the reviewers was reviewed in full. An external observer audited whether the results were inconsistent between the investigators. Any disagreements were resolved by discussion and consensus. If the grading was still discrepant, patients were excluded.

Statistical analysis

We estimated the rate of persistent major SRH at second-look endoscopy to be 18% according to the average rebleeding rate (7.5%) after the fourth day with current treatment protocols based on our previous trial [18], and the average rebleeding risk was estimated to be 40% with all major SRH cases [2]. In a prospective cohort study, assuming the proposed proportion exposed in the control group was 0.1 and that the proposed control-to-case ratio was 4.5 (0.82/0.18), the statistical power for detecting an odds ratio (OR) of three would be 80% on the basis of 299 patients using a two-sided test at the α value of 0.05. The estimated incidence of rebleeding during the first 72 hours before the schedule was proposed to be 5% [8,18], so at least 315 patients had to be included.

The patient characteristics were compared and tested using either the Pearson's χ^2 test, Fisher's exact test, or the Student's t test. Continuous variables were categorized to avoid multiplicative errors. Receiver operating characteristic (ROC) curves for determining cut-off values that best discriminated between groups were derived for each parameter, e.g. serum albumin levels. A multiple logistic regression analysis using selection of variables significant at the 0.20 level was applied to assess independent risk factors related to outcomes. The odds ratio obtained by the multiple logistic regression was transformed into the relative risk (RR) and its confidence interval (CI) was estimated directly with a statistical model to assess the predicted individual probabilities. We converted the RR transformed from the multiple lo-

gistic regressions to indicate the weight for each significant prediction variable and produce a scoring system that required the addition of integer values. The scoring systems were trained and validated in a 10-fold cross-validation strategy with 10 rounds of 10 repetitions [19]. All tests were two-tailed, and P values less than 0.05 indicated significant differences.

Results
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Demographic features and patient follow-up

From August 2011 to July 2014, 474 patients with peptic ulcer bleeding were consecutively assessed for eligibility for this study (○ Fig. 1). One hundred and fifty-eight patients were excluded: 29 did not meet the inclusion criteria; 96 declined to participate; 12 had bleeding from gastric cancer, metastatic or other cancers; two died within 3 days; 18 had critical conditions; and one had discrepant SRH grading between reviewers.

Among the 316 patients that were included (96 females, 220 males), the mean age was 67.1 years, and 167 (52.8%) had bleeding from gastric ulcers, 143 (45.3%) from duodenal ulcers, and 6 (1.9%) from anastomotic ulcers. There were 9 (2.8%) Forrest type Ia, 97 (30.7%) type Ib, 169 (53.5%) type IIa, and 41 (13.0%) type IIb ulcers. Forty-three patients (13.6%) received endoscopic epinephrine-injection monotherapy with an average dose of 10 mL (range 8 to 15 mL) of diluted epinephrine 1:10,000, 22 (7.0%) received other endoscopic monotherapy, and 251 (79.4%) received endoscopic combination therapies. Three hundred and five patients received esomeprazole, and 11 received pantoprazole.

Ten patients had early clinically relevant rebleeding and were designated as the "emergent group" for the second-look endoscopy. At the emergent second-look endoscopy, hemostatis was achieved in seven patients but two of them had rebleeding within 1 week. The remaining three patients received either emergent transarterial embolization or surgery.

Excluding 10 patients with early rebleeding, 306 patients were designated as the "scheduled group" and were further divided into either the Day-2 subgroup (n=78) or the Day-3 subgroup (n=228). Of all of the patients, one died suddenly during at the second-look endoscopy, and two patients had morbidity but did not die within 3 days of the second-look endoscopy, including one with sudden cardiac collapse and the other with duodenal perforation.

Predictors of early clinical relevant rebleeding before second-look endoscopy

○ Table 1 demonstrates that early clinical relevant rebleeding was more common in patients with than without end-stage renal disease with maintenance dialysis, endoscopic epinephrine-injection monotherapy, or serum albumin levels <3.0 g/dL ($P \le$ 0.05). Multiple logistic regression confirmed that endoscopic epinephrine-injection monotherapy and serum albumin levels <3.0 g/dL were two independent risk factors (P=0.002 and 0.05, respectively, ○ Table 1).

Based on these two independent risk factors for early peptic ulcer rebleeding, in this study, the E2nd (early second-look) score was created, which is the sum of the score from the initial endosopic therapies (score 2: epinephrine-injection monotherapy; score 0: others) plus the score of patient's serum albumin levels (score 1: <3.0 g/dL; score 0: ≥3.0 g/dL). The prediction rates from the E2nd score were increased in stepwise fashion in a trend from a score of 0 to 3 (0.5% [1/201], 2.8% [2/72], 9.7% [3/31], and 33.3% [4/12],

Table 1 Univariable analysis and multivariable logistic regression to determine factors associated with early clinical relevant rebleeding before the schedule

Variables, n (%)	Risks of early clinical relevant rebleeding before the schedule		Univariable analysis		Multivariable analysis	
	With the variable	Without the variable	Relative risk (95 % CI)	P value[1]	Relative risk[2] (95 % CI)	P value
Female	2/96 (2.1)	8/220 (3.6)	0.57 (0.12 – 2.65)	0.73	–	–
Age ≥ 70 y/o	5/150 (3.3)	5/166 (3.0)	1.11 (0.33 – 3.75)	1.0	–	–
Hemodynamic instability[3]	2/60 (3.3)	8/256 (3.1)	1.07 (0.23 – 4.90)	1.0	–	–
Cirrhosis	0/30 (0)	10/286 (3.5)	0 (NA)	0.61	–	–
End–stage renal disease with maintenance dialysis	3/28 (10.7)	7/288 (2.4)	4.41 (1.21 – 16.11)	0.05	1.69 (0.46 – 6.19)	0.63
Malignant diseases	1/43 (2.3)	9/273 (3.3)	0.71 (0.09 – 5.43)	1.0	–	–
Lung diseases	2/42 (4.8)	8/274 (2.9)	1.63 (0.36 – 7.42)	0.63	–	–
Nosocomial bleeding	4/54 (7.4)	6/262 (2.3)	3.23 (0.94 – 11.08)	0.07	0.38 (0.11 – 1.31)	0.42
Rockall scores ≥ 6	9/228 (3.9)	1/88 (1.1)	3.47 (0.45 – 27.02)	0.29	–	–
H. pylori infection[4]	1/133 (0.8)	6/158 (3.8)	0.20 (0.02 – 1.62)	0.13	0.14 (0.02 – 1.13)	0.14
NSAID use	4/134 (3.0)	6/182 (3.3)	0.91 (0.26 – 3.15)	1.0	–	–
Aspirin use	0/78 (0)	10/238 (4.2)	0 (NA)	0.13	0 (NA)	1.0
Ulcer ≥ 2 cm	4/61 (6.6)	6/255 (2.4)	2.79 (0.81 – 9.57)	0.11	1.63 (0.48 – 5.60)	0.61
Forrest Ia or Ib type	4/106 (3.8)	6/210 (2.9)	1.32 (0.38 – 4.58)	0.74	–	–
Gastric high lesser curve ulcers	1/9 (11.1)	9/307 (2.9)	3.79 (0.54 – 26.82)	0.25	–	–
Posterior duodenal ulcers	1/22 (4.5)	9/294 (3.1)	1.49 (0.20 – 11.19)	0.52	–	–
Endoscopic epinephrine-injection monotherapy	7/43 (16.3)	3/273 (1.1)	14.81 (3.98 – 55.11)	<0.001	18.33 (4.93 – 68.19)	0.002
Hb levels < 10.0 g/dL	9/190 (4.7)	1/126 (0.8)	5.97 (0.77 – 46.53)	0.06	1.64 (0.21 – 12.78)	0.72
Platelet count < 80 × 10⁹/L	1/17 (5.9)	9/299 (3.0)	1.95 (0.26 – 14.55)	0.43	–	–
PT prolong ≥ 4 seconds	3/34 (8.8)	7/282 (2.5)	3.55 (0.96 – 13.11)	0.08	0.98 (0.27 – 3.62)	0.97
aPTT prolong ≥ 1.5-fold	1/4 (25.0)	9/312 (2.9)	8.67 (1.41 – 53.24)	0.12	0.47 (0.08 – 2.90)	1.0
Serum albumin levels < 3.0 g/dL	6/84 (7.1)	4/232 (1.7)	4.14 (1.20 – 14.32)	0.03	10.39 (3.01 – 35.91)	0.05

aPTT, activated partial thromboplastin time; CI, confidence interval; Hb, hemoglobin; H. pylori, Helicobacter pylori; NA, not available; NSAID, nonsteroidal anti-inflammatory drugs; PT, prothrombin time.

[1] The Pearson's chi-square test and the Fisher's exact test with 2-tailed analysis were used as appropriate.

[2] The odds ratio obtained by multiple logistic regression was transformed into the relative risk and its confidence interval was estimated directly by a statistical model.

[3] Systolic blood pressure < 100 mmHg on arrival.

[4] The number of patients who received H. pylori infection survey was 291. Activated partial thromboplastin time: normal range 26.0 – 38.0 seconds. Hemoglobin: normal range 11.6 – 14.8 g/dL. Platelet: normal range 151 – 366 × 10⁹/L. Prothrombin time: normal range 9.40 – 12.5 seconds. Serum albumin: normal range 3.5 – 5.0 g/dL.

$P < 0.001$), respectively. The area under the receiver operating characteristic curve (AUROC) of the E2nd score was 0.86 (95 % CI, 0.73 – 0.99) (○ **Fig. 2**). The ROC curve of the E2nd score showed the optimal value to be 2. E2nd scores ≥ 2 have a 70.0 % sensitivity and 88.2 % specificity for prediction of early rebleeding. The likelihood ratios for a positive test and negative test were found to be 5.95 and 0.34, respectively.

Predictors of persistent major stigmata of recent hemorrhage at the second-look endoscopy

For patients in the scheduled group, there were no significant differences in clinical, endoscopic, and laboratory characteristics between the Day-2 subgroup and the Day-3 subgroup (○ **Table 2**), except for a higher rate of comorbid malignancy (16.7 % vs. 5.1 %, P = 0.01) and a lower rate of persistent major SRH (4.8 % vs. 15.4 %, P = 0.002) in the Day-3 subgroup as compared to the Day-2 subgroup.

Because the 24-hour shorter PPI infusion in the Day-2 subgroup with earlier second-look endoscopy may have served as a confounder limiting major SRH resolution, we simply enrolled the Day-3 subgroup with a nearly 72-hour standard duration of PPI infusion for the risk factor analysis related to persistent major SRH. As shown in ○ **Table 3**, patients with Forrest Ia-Ib type ulcers or serum albumin levels < 3.5 g/dL appeared to have evidence

of more persistent major SRH than those who did not ($P < 0.05$). Multiple logistic regression confirmed that Forrest Ia-Ib type (P = 0.001) and serum albumin levels < 3.5 g/dL (P = 0.047) were two independent risk factors for persistent major SRH (○ **Table 3**). We thus derived a predictive model, the R2nd (routine second-look) score to predict persistent major SRH after a 72-hour PPI infusion. The R2nd score was created as follows: the R2nd score = Forrest types (score 1: Ia – Ib; score 0: IIa – IIb) + serum albumin levels (score 1: < 3.5 g/dL; score 0: ≥ 3.5 g/dL). The prediction rates of the R2nd score in a range from 0 to 2 were increased stepwise (1.4 % [1/71], 0.8 % [1/123], and 26.5 % [9/34], P < 0.001). The AUROC of the R2nd score was 0.84 (95 % CI, 0.69 – 0.99) (○ **Fig. 3**). The ROC curve showed that an optimal R2nd score of 2 had a sensitivity of 81.8 % and a specificity of 88.5 % for prediction of persistent major SRH after a 72-hour PPI infusion. The likelihood ratios for a positive test and negative test were 7.10 and 0.21, respectively.

Number needing endoscopy based on E2nd and R2nd scores used to identify high-risk patients

The accuracy, sensitivity, specificity, and AUROC based on 10-fold cross-validation procedures were 87.7 %, 70.0 %, 88.2 %, and 0.852 for the E2nd score and 88.2 %, 81.8 %, 88.5 %, and 0.829 for the R2nd score, respectively. The Nagelkerke R-square scores were 0.285 and 0.294, respectively.
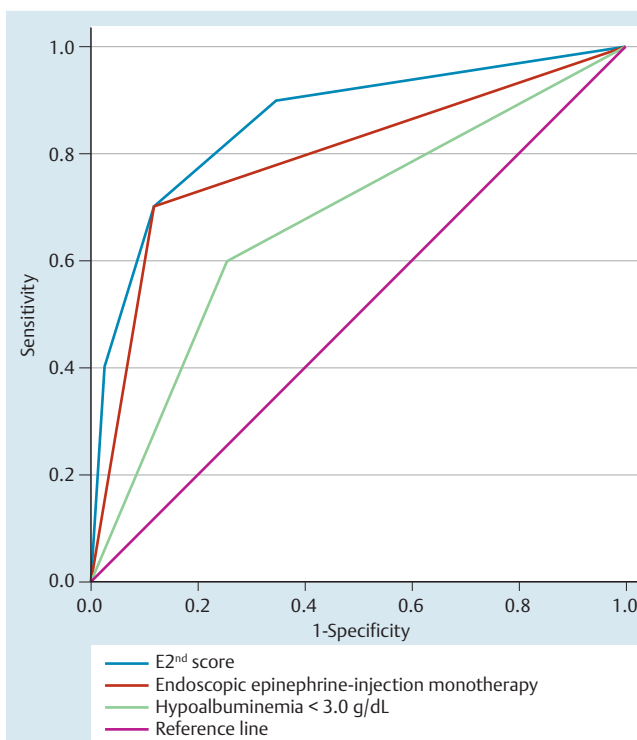
Fig. 2 Receiver operator characteristic curves for E2nd score, endoscopic epinephrine-injection monotherapy, and hypoalbuminemia < 3.0 g/dL to predict early clinically relevant recurrent bleeding. The data point was the measured index value.
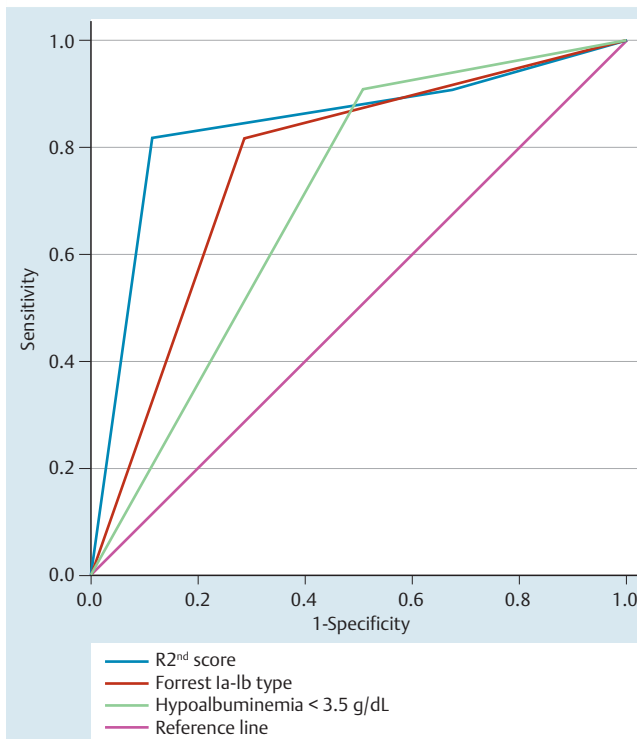

Fig. 3 Receiver operator characteristic curve for R2nd score, Forrest Ia-Ib type and hypoalbuminemia < 3.5 g/dL to predict persistent major SRH at the second-look endoscopy. The data point was the measured index value.

Table 2 Comparison of baseline characteristics of the Day-2 and Day-3 subgroups

Variables, N (%), mean (SD)	The scheduled group		
	The Day-2 subgroup (n = 78)	The Day-3 subgroup (n = 228)	P value[1]
Female	20 (25.6)	74 (32.5)	0.26
Age (years)	66.7 (15.4)	67.3 (13.6)	0.72
Hemodynamic instability[2]	12 (15.4)	46 (20.2)	0.35
Cirrhosis	4 (5.1)	26 (11.4)	0.11
End-stage renal disease with maintenance dialysis	8 (10.3)	17 (7.5)	0.44
Malignant diseases	4 (5.1)	38 (16.7)	0.01
Lung diseases	7 (9.0)	33 (14.5)	0.21
Heart diseases	16 (20.5)	49 (21.5)	0.86
Nosocomial bleeding	9 (11.5)	41 (18.0)	0.18
ASA physical status class ≥ III	37 (47.4)	117 (51.3)	0.55
Rockall scores ≥ 6	52 (66.7)	166 (72.8)	0.30
H. pylori infection[3]	38 (52.1)	94 (44.5)	0.27
NSAID use	30 (38.5)	100 (43.9)	0.41
Aspirin use	18 (23.1)	60 (26.3)	0.57
Any antiplatelet agent or warfarin use	28 (35.9)	83 (36.4)	0.94
Ulcer ≥ 2 cm	16 (20.5)	41 (18.0)	0.62
Forrest Ia or Ib type	31 (39.7)	71 (31.1)	0.16
Gastric high lesser curve ulcers	4 (5.1)	4 (1.8)	0.12
Posterior duodenal ulcers	7 (9.0)	14 (6.1)	0.39
Endoscopic epinephrine-injection monotherapy	12 (15.4)	24 (10.5)	0.25
Hb levels < 10.0 g/dL	43 (55.1)	138 (60.5)	0.40
Platelet count < 80 × 10⁹/L	5 (6.4)	11 (4.8)	0.56
PT prolong ≥ 4 seconds	5 (6.4)	26 (11.4)	0.21
aPTT prolong ≥ 1.5-fold	1 (1.3)	2 (0.9)	1.0
Serum albumin levels < 3.5 g/dL	36 (46.2)	120 (52.6)	0.32

aPTT, activated partial thromboplastin; ASA, American Society of Anesthesiology; CI, confidence interval; Hb, hemoglobin; *H. pylori*, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drugs; PT, prothrombin time; SD, standard deviation.
[1] The Pearson's chi-square test and the Fisher's exact test or the Student's *t* test with 2-tailed analysis was used as appropriate.
[2] Systolic blood pressure < 100 mmHg on arrival.
[3] The number of patients who received *H. pylori* infection survey was 73 in the D2 subgroup and 211 in the D3 subgroup, respectively. Activated partial thromboplastin time: normal range 26.0 – 38.0 seconds. Hemoglobin: normal range 11.6 – 14.8 g/dL. Platelet: normal range 151 – 366 × 10⁹/L. Prothrombin time: normal range 9.40 – 12.5 seconds. Serum albumin: normal range 3.5 – 5.0 g/dL.

We proposed a scenario to calculate the effectiveness of the E2nd and R2nd scores. First, according to the E2nd scores that were ≥ 2, 13.6 % of the sample was selected to conduct early second-look endoscopy within 24 hours and might prevent 2.2 % of patients from experiencing early rebleeding. Among patients with E2nd scores < 2, 1.0 % had early rebleeding. Second, in the remaining 85.4 %, given R2nd scores of 2, 12.7 % of the sample was selected to conduct the second-look endoscopy, and 3.4 % were identified with persistent major SRH. Of the patients with R2nd scores < 2, 0.7 % had persistent major SRH. Finally, 26.3 % of patients received second-look endoscopy, 5.6 % of whom were found to have high-risk lesions. Thus, the positive rate for second-look endoscope would have been 21.3 %, which is higher than the 7.3 % positive rate that would have been seen, had routine second-look endoscopy been conducted on all the patients. The absolute risk reduction for negative second-look endoscopy was 14.0 %, and the number needing endoscopy was 7.1.

Table 3 Univariable analysis and multivariable logistic regression to determine factors associated with persistent major stigmata of recent hemorrhage at second-look endoscopy on day 3

Variables, N (%)	Risks of persistent major SRH at the second-look endoscopy on day 3		Univariable analysis		Multivariable analysis	
	With the variable	Without the variable	Relative risk (95 % CI)	P value[1]	Relative risk[2] (95 % CI)	P value
Female	5/74 (6.8)	6/154 (3.9)	1.73 (0.55 – 5.50)	0.34	–	–
Age ≥ 70 y/o	5/105 (4.8)	6/123 (4.9)	0.98 (0.31 – 3.11)	0.97	–	–
Hemodynamic instability[3]	4/46 (8.7)	7/182 (3.8)	2.26 (0.69 – 7.40)	0.24	–	–
Cirrhosis	2/26 (7.7)	9/202 (4.5)	1.73 (0.39 – 7.56)	0.36	–	–
End-stage renal disease with maintenance dialysis	1/17 (5.9)	10/211 (4.7)	1.24 (0.17 – 9.13)	0.58	–	–
Malignant diseases	1/38 (2.6)	10/190 (5.3)	0.5 (0.07 – 3.79)	0.70	–	–
Lung diseases	2/33 (6.1)	9/195 (4.6)	1.31 (0.30 – 5.81)	0.66	–	–
Nosocomial bleeding	3/41 (7.3)	8/187 (4.3)	1.71 (0.47 – 6.17)	0.42	–	–
Rockall scores ≥ 6	8/166 (4.8)	3/62 (4.8)	1.0 (0.27 – 3.63)	1.0	–	–
H. pylori infection[4]	5/94 (5.3)	4/117 (3.4)	1.56 (0.43 – 5.63)	0.52	–	–
NSAID use	5/100 (5.0)	6/128 (4.7)	1.07 (0.34 – 3.40)	1.0	–	–
Aspirin use	5/60 (8.3)	6/168 (3.6)	2.33 (0.74 – 7.37)	0.16	2.39 (0.76 – 7.56)	0.20
Ulcer ≥ 2 cm	4/41 (9.8)	7/187 (3.7)	2.61 (0.80 – 8.49)	0.11	2.56 (0.79 – 8.33)	0.19
Forrest Ia or Ib type	9/71 (12.7)	2/157 (1.3)	9.95 (2.21 – 44.88)	0.001	13.10 (2.91 – 59.10)	0.001
Gastric high lesser curve ulcers	1/4 (25.0)	10/224 (4.5)	5.6 (0.92 – 33.96)	0.18	10.37 (1.71 – 62.90)	0.09
Posterior duodenal ulcers	1/14 (7.1)	10/214 (4.7)	1.53 (0.21 – 11.11)	0.51	–	–
Endoscopic epinephrine-injection monotherapy	0/24 (0)	11/204 (5.4)	0 (NA)	0.61	–	–
Hb levels < 10.0 g/dL	8/138 (5.8)	3/90 (3.3)	1.74 (0.47 – 6.38)	0.53	–	–
Platelet count < 80 × 10⁹/L	1/11 (9.1)	10/217 (4.6)	1.97 (0.28 – 14.07)	0.43	–	–
PT prolong ≥ 4 seconds	1/26 (3.8)	10/202 (5.0)	0.78 (0.10 – 5.83)	1.0	–	–
aPTT prolong ≥ 1.5-fold	0/2 (0)	11/226 (4.9)	0 (NA)	1.0	–	–
Serum albumin levels < 3.5 g/dL	10/120 (8.3)	1/108 (0.9)	9.0 (1.17 – 69.16)	0.01	7.99 (1.04 – 61.41)	0.049

aPTT, activated partial thromboplastin time; CI, confidence interval; Hb, hemoglobin; *H. pylori*, *Helicobacter pylori*; NA, not available; NSAID, non-steroidal anti-inflammatory drugs; PT, prothrombin time; SRH, stigmata of recent hemorrhage.

[1] The Pearson's chi-square test and the Fisher's exact test with 2-tailed analysis were used as appropriate.

[2] The odds ratio obtained by multiple logistic regression was transformed into the relative risk and its confidence interval was estimated directly by a statistical model.

[3] Systolic blood pressure < 100 mmHg on arrival.

[4] The number of patients who received *H. pylori* infection survey was 211. Activated partial thromboplastin time: normal range 26.0~38.0 seconds. Hemoglobin: normal range 11.6~14.8 g/dL. Platelet: normal range 151~366×10⁹/L. Prothrombin time: normal range 9.40~12.5 seconds. Serum albumin: normal range 3.5~5.0 g/dL.

Discussion
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This prospective study demonstrated that the E2nd score can predict early clinically relevant rebleeding. Patients who received IV PPI infusion for a longer duration achieved more major SRH resolution. The R2nd score had good negative predictive value for persistent major SRH after adequate PPI infusion.

Endoscopic epinephrine-injection monotherapy has been reported to be strongly predictive of endoscopic treatment failure [3, 4, 12, 20]. Our findings not only strengthen this supposition, but also illustrate that hypoalbuminemia < 3.0 g/dL is another significant independent risk factor for early peptic ulcer rebleeding (○ **Table 1**). Based on the combination of these two risk factors, our E2nd score can accurately predict early peptic ulcer rebleeding (○ **Fig. 2**). Because most rebleeding develops within 24 hours [21], adding an early second endoscopic treatment within 24 hours should be considered to reduce rebleeding risk [3, 22]. It would be highly original to offer a simple score to indicate the need for an early second-look endoscopy.

Most trials conducted to evaluate the impact of second-look endoscopy for peptic ulcer bleeding were based on non-PPI or non-high-dose PPI therapy [5 – 7]. Because preemptive high-dose IV PPI therapy accelerates SRH resolution [23, 24], it is necessary to validate whether additional high-dose IV PPI therapy after endoscopic hemostasis could improve the fading of SRH

and thus decrease the need for second-look endoscopy. Our study design was highly original in that it offered a time-course comparison of SRH fading according to the high-dose PPI infusion typically used in peptic ulcer bleeding. Our data showed that there were higher rates of persistent major SRH in the Day-2 subgroup than in the Day-3 subgroup (15.4 % *vs.* 4.8 %, *P* = 0.002). These data imply that once high-dose PPI infusion is initiated, it is rational to administer it for at least 3 days to achieve better SRH fading of peptic ulcer bleeding. Nevertheless, nearly 4.8 % of patients under consideration still needed a second-look endoscopy to improve the control of rebleeding risk.

The particularly striking finding from this study was that our R2nd score combined with the Forrest Ia-Ib type and serum albumin levels < 3.5 g/dL could predict persistent major SRH on day 3 (○ **Table 3**). A recent Cochrane review showed that for Forrest Ia-Ib type ulcers, endoscopic combined therapies reduce rebleeding risks [25]. Nevertheless, our study showed that 9 of 11 patients who still had persistent major SRH on day 3 had Forrest Ia-Ib type ulcers at primary endoscopy, all of whom received endoscopic combined therapies. Interestingly, the serum albumin levels in these patients all were < 3.5 g/dL. Therefore, this study not only reinforced the important role of endoscopic features [2], but also raised the potential role of hypoalbuminemia in outcomes related to peptic ulcer bleeding.

The reasons why hypoalbuminemia was such a strong predictor are uncertain. The serum albumin level is disease-specific, and it indirectly reflects the nutritional status of both acute and chronically ill patients [26, 27]. AIMS65 scores and other trials also have revealed that hypoalbuminemia is an outcome predictor in upper gastrointestinal bleeding [14, 28–30]. Furthermore, our study showed that combined with serum albumin levels, E2nd and R2nd scores were better able to predict outcomes than do endoscopic features alone (○ Fig. 2 and ○ Fig. 3). Neither hypoalbuminemia nor albumin administration resulted in significant changes in the free plasma concentration or in the pharmacologic effect of omeprazole [31]. Therefore, we propose that hypoalbuminemia can serve as a simple biomarker of comorbidity.

Second-look endoscopy is a very high-cost and invasive intervention. Previous education practices have suggested that "where high-dose IV PPI therapy was commenced, routine second-look endoscopy was not necessary" [32]. In this study, we used contemporary strategies and found that most patients really did not need routine second-look endoscopy, but it was still indicated for a high-risk group, such as can be selected using E2nd scores ≥ 2 or R2nd scores = 2 for which the estimated number suggesting the need to scope was 7.1. Because selective second-look endoscopy may be cost-effective if the number is ≤ 10 [33], our data suggest that it could be generalizable to current clinical practice to help reduce the risk of rebleeding in high-risk patients.

Our study had some limitations. First, the primary outcomes were early rebleeding and persistent major SRH, rather than long-term rebleeding or mortality. However, the clinical benefit of therapeutic endoscopy for high-risk stigmata has been proven [3, 4, 19, 34]. Second, the patients were divided into the Day-2 or Day-3 subgroups in a non-randomized manner. However, we enrolled almost all patients with peptic ulcer bleeding in our hospital consecutively to reduce potential enrollment bias. Moreover, there were no significant differences between the two subgroups in baseline characteristics. Third, we might have missed other risk factors that have been reported to correlate with endoscopic hemostasis failure [35], e.g., ulcer size ≥ 2 cm because of relative risks < 3. Of note, these risk factors were not significant because the effects were accounted for by more significant factors.

In conclusion, E2nd and R2nd scores, including both endoscopic features and serum albumin levels, could predict the need for early and routine second-look endoscopy, respectively. Only two parameters are needed for each score, thus the calculation can be made easily and its use is intuitive. Even when high-dose PPI infusion is administered, routine second-look endoscopy should be considered based on R2nd score, as a cost-effective treatment of high-risk patients.

Competing interests: None

Acknowledgements
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