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【 ORIGINAL ARTICLE 】

Novel and Simple Criteria for Predicting Mortality of Peptic Ulcer Disease

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Abstract:

Objective Conventional risk scores of peptic ulcer disease (PUD) are based on many parameters, and their application in clinical practice is therefore limited. The aim of this study was to establish simple and reliable criteria for predicting PUD-associated mortality.

Methods A total of 499 patients with PUD were divided into 2 groups: the training cohort (n=333) and the validation cohort (n=166). To minimize selection bias due to missing values, we used imputed datasets generated by the multiple imputation method (training-cohort dataset, n=33,300; validation-cohort dataset, n=16,600).

Results In the training-cohort dataset, the heart rate-to-systolic blood pressure ratio (HR/SBP) and serum albumin (s-Alb) level were significant independent predictive factors for mortality according to the multivariate analysis [HR/SBP, odds ratio (OR): 1.72; 95% confidence interval (CI), 1.06-2.80, p=0.028; s-Alb, OR: 0.23, 95% CI, 0.11-0.51, p<0.001]. The model comprising HR/SBP and s-Alb was able to detect mortality due to PUD with an area under the curve (AUC) of 0.855. In the validation-cohort dataset, this model also showed good efficacy with an AUC of 0.835. The novel criteria combining HR/SBP and s-Alb developed by a decision tree analysis showed 73.3% sensitivity and 87.6% specificity for predicting mortality in the total-cohort dataset. Our criteria were superior to the Glasgow Blatchford and Rockall scores and similar to the AIMS65 and Progetto Nazionale Emorragia Digestiva scores for predicting mortality.

Conclusion The combination of the HR/SBP ratio and s-Alb level is a good predictor of mortality in patients with PUD.

Key words: peptic ulcer, mortality, serum albumin, heart rate, systolic pressure

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Introduction

Peptic ulcer disease (PUD), including gastric ulcer (GU) and duodenal ulcer (DU), is a common condition worldwide, with an incidence of 0.10-0.19% (1, 2) and an overall mortality of 3.7-6.2% (1, 3-6). Since the incidence of and risk of bleeding from PUD increase with age (2, 7), PUD will remain an important cause of mortality and healthcare spending in the aging international community.

The severity of PUD varies widely from patient to patient, and pre-treatment risk classification is critical for detecting high-risk patients in need of intensive treatment. PUD is the main cause of upper gastrointestinal bleeding (UGIB), and the UGIB international guidelines also recommend risk stratification to identify high-risk patients for optimal triaging (8). For this purpose, various scoring systems, such as the Glasgow-Blatchford score (GBS) (9), Rockall score (RS) (10), AIMS65 (11), and Progetto Nazionale Emorragia Digestiva score (PNED) (12), have been developed. A retro-

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spective study comprising a large number of participants found that AIMS65 and PNED were useful for predicting mortality caused by UGIB (13), whereas other studies observed an insufficient power of the GBS, RS, and AIMS65 with regard to predicting mortality (14-16). In addition, these risk scores are based on many clinical and laboratory parameters, making them too complicated to apply in emergency situations. These scores are therefore not widely used in clinical practice.

We previously identified criteria based on the findings of nasogastric tube (NGT) lavage and the heart rate (HR): systolic blood pressure (SBP) ratio (HR/SBP) for identifying patients with active UGIB in need of urgent endoscopy (17). The detection of active bleeding and subsequent intervention might reduce the mortality of UGIB; however, it has been suggested that NGT placement may not reduce mortality rates in UGIB patients (18, 19). Simple and reliable markers for predicting the mortality of UGIB, including PUD, are thus warranted to optimize management strategies.

We conducted the present study to identify a simple set of predictive markers for predicting PUD-associated mortality.

Materials and Methods

Patients and study design

We retrospectively collected data from 284 patients with PUD at Nagoya City University Hospital from January 2017 to February 2019 and from 215 patients with PUD at Japanese Red Cross Nagoya Daini Hospital from May 2010 to March 2012 who had been diagnosed using esophagogastroduodenoscopy (EGD). Written informed consent was obtained from all participating patients.

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by institutional review boards at Japanese Red Cross Nagoya Daini Hospital and Nagoya City University Hospital (No. 60-18-0081).

Treatment for peptic ulcer

All patients with PUD were given proton pump inhibitors or potassium-competitive acid blockers orally or intravenously. Patients with severe symptoms were hospitalized, fasting, and received intravenous infusion for several days. If severe anemia and/or hemodynamic instability existed, the patients received blood transfusion. When bleeding or visible vessels were found on EGD, endoscopic hemostasis (i.e., endoscopic clips, epinephrine injection, and coagulation using hemostatic forceps) was performed. If endoscopic hemostasis was not successful, interventional radiology (IVR) and/or surgery were performed.

Definition

Endoscopic findings were collected according to the Forrest classification (20). Mortality was defined as death occurring within 30 days following endoscopy or hospital admission. Active bleeding ulcer was defined as an ulcer with active bleeding or fresh blood/dark red clots in the stomach. Rebleeding was defined as 1) bleeding at the second endoscopy or 2) hematemesis and/or melena or shock (SBP <90 mmHg and/or HR >100 bpm) after the first endoscopy or longer than 24 hours of hospitalization. Prothrombin time values were provided as international normalized ratios (INR). Clinical and laboratory data collected just before endoscopy or hospital admission were used in this study, and the GBS, RS, AIMS65, and PNED scores were calculated for each patient based on these data (9-12). The parameters of each risk score are shown in Supplementary material 1.

Study design

A flowchart of the study is displayed in Fig. 1. We randomly divided the 499 total patients into a training cohort (n =333) and a validation cohort (n=166). The collected data had some missing values, especially for AIMS65 (22.4%) and INR (17.4%) (Supplementary material 2). Since the missing values were considered missing in a non-random way, a complete-case analysis (CCA) excluding cases with any missing values was not recommended due to potential selection bias and a decrease in power (21). To minimize selection bias, we used an imputed dataset generated by multiple imputation by the chained equation (MICE) method in all analyses (m=100) (22). First, we generated 100 imputed datasets from each cohort by MICE. Next, we identified the predictive factors of mortality based on an analysis of the 100 training-cohort datasets. After that, we verified the established predictive model using the 100 validation-cohort datasets. Finally, we established the novel criteria for predicting mortality of PUD using the imputed training-cohort dataset (n=33,300), and the criteria were subsequently verified in the imputed validation-cohort dataset (n=16,600).

Statistical analyses

Univariate analyses were performed by the Mann-Whitney *U* test or chi-squared test, as appropriate. For the multivariate analysis, we used a logistic regression model with the forward selection method by the likelihood ratio. We calculated odds ratios (OR) and 95% confidence intervals (CI) of the predictive factors with logistic regression. Instead of the actual measured values, the adjusted values of the Z score were used to calculate OR. The efficacy of the predictive model and other risk score systems was evaluated using a receiver operating characteristic (ROC) curve analysis based on the area under the curve (AUC) with the 95% CI. A decision tree analysis was used to identify the predictive criteria for PUD-associated mortality. A two-tailed probability (p) value <0.05 was considered statistically significant.

Results

Patients

The patient characteristics are shown in Table 1. Of the

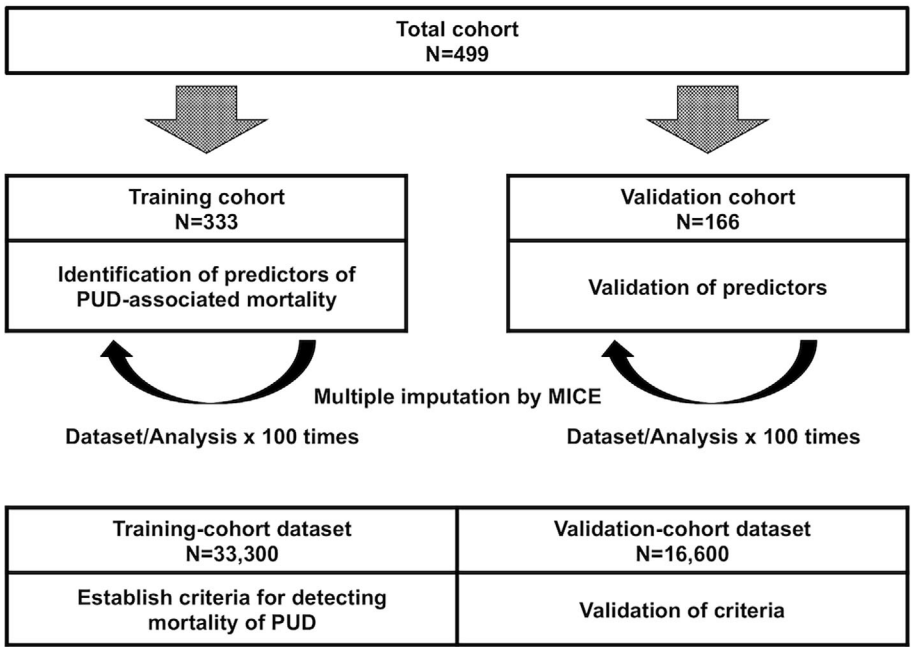


Figure 1. **Study flowchart. PUD: peptic ulcer disease, MICE: multiple imputation by chained equation**

499 patients, 362 (72.5%) had a GU, 147 (29.5%) had a DU, 141 (28.3%) had an active bleeding ulcer, and 418 (83.8%) required hospitalization. In total, 186 (37.3%) patients underwent endoscopic hemostasis, 4 (0.8%) received IVR, and 1 (0.2%) underwent surgery. Rebleeding occurred in 42 (8.4%) patients. Mortality was observed for 10 (3.0%) patients in the training cohort and 5 (3.0%) patients in the validation cohort. While seven patients died of uncontrollable bleeding despite any hemostasis, eight died from other comorbidities (Supplementary material 3).

Predictive factors of mortality

In order to identify potential predictive factors of mortality, we divided the training cohort into the mortality group (n=10) and the survival group (n=323) and then conducted univariate and multivariate analyses for each risk factor. The univariate analysis revealed that the HR/SBP and INR were significantly higher while blood hemoglobin (Hb) and serum albumin (s-Alb) levels were significantly lower in the mortality group than in the survival group (HR/SBP, p=0.036; Hb, p=0.003; INR, p=0.018; s-Alb, p<0.001). In the multivariate analysis, the HR/SBP ratio [OR, 1.72 (95% CI, 1.06-2.80), p=0.028] and s-Alb level [OR, 0.23 (95% CI, 0.11-0.51), p<0.001] were significant independent risk factors for mortality in the training-cohort dataset (Table 2).

Next, we conducted an ROC analysis to evaluate the efficacy of combining the HR/SBP ratio and s-Alb. The combined markers showed good efficacy with an AUC=0.855 (95% CI, 0.730-0.979), which was comparable to AIMS65 (AUC=0.838) and PNED (AUC=0.869) and appeared superior to GBS (AUC=0.756) and RS (AUC=0.708) (Fig. 2A).

Validation of predictive factors

Next, we verified the validity of the HR/SBP ratio and s-Alb level using the independent validation-cohort dataset. Again, significant differences were noted in the HR/SBP ratio and s-Alb level between the two groups (HR/SBP, p=0.043; s-Alb, p=0.011) (Table 3). The HR/SBP and s-Alb in combination predicted PUD-associated mortality with an excellent AUC of 0.835 (95% CI, 0.606-1.000) in the validation cohort (Fig. 2B). In addition, the HR/SBP and s-Alb were independent predictive factors of mortality in the total-cohort dataset [HR/SBP, OR: 1.93 (95% CI, 1.33-2.81), p<0.001; s-Alb, OR: 0.28 (95% CI, 0.15-0.53), p<0.001] (Supplementary material 4). In the total-cohort dataset, the HR/SBP and s-Alb in combination showed excellent performance with an AUC of 0.852, which was superior to GBS and RS (Supplementary material 5A). These results derived from the MICE method were similar to those of the CCA (Supplementary material 5B, 6).

Urgent endoscopy should be performed for patients with active bleeding ulcers to improve their prognosis. Therefore, we examined whether or not the model consisting of HR/SBP and s-Alb was also useful for identifying active bleeding ulcers. Multivariate analyses revealed that the HR/SBP ratio [OR, 1.77 (95% CI, 1.43-2.20), p<0.001] and s-Alb level [OR, 0.76 (95% CI, 0.61-0.94), p=0.012] were independent predictors of active bleeding (Supplementary material 7). Their combination showed an AUC of 0.693 for the prediction of active bleeding, which was comparable to that of the GBS (AUC=0.691) and seemed to outperform clinical RS (AUC=0.559) and AIMS65 (AUC=0.584) (Supplementary material 8).

Table 1. Characteristics of Patients.

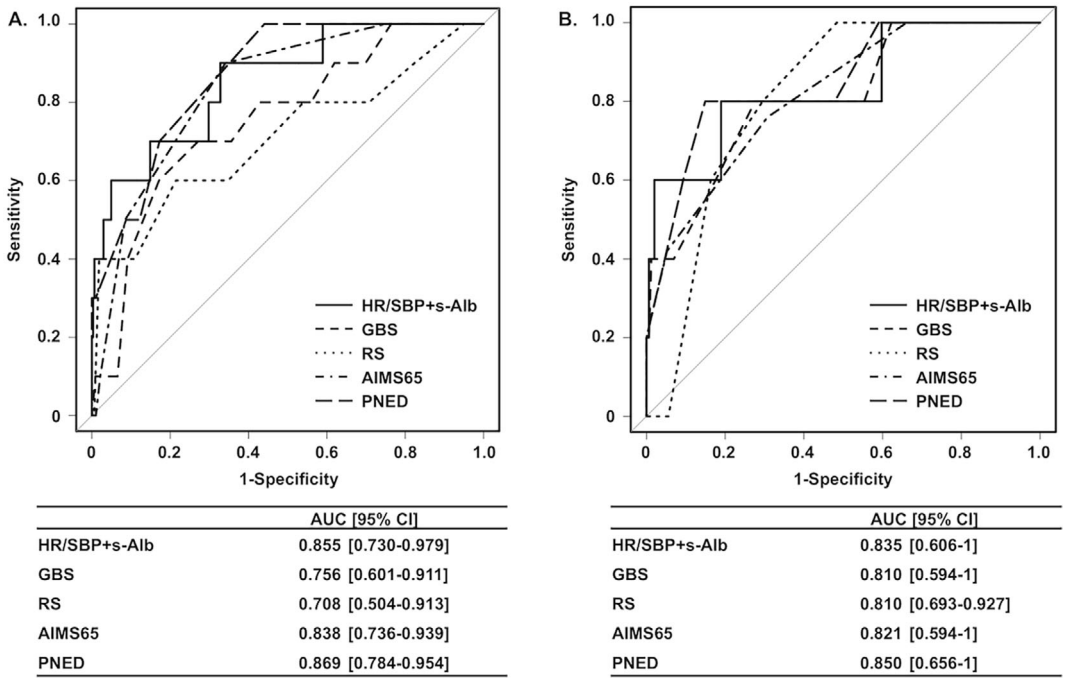
Patient characteristics		Training cohort n=333	Validation cohort n=166	Total cohort n=499
Gender	Male / Female	213/120	108/58	321/178
Age	Median, IQR	73 (63-80)	71 (61-81)	73 (62-80)
Clinical diagnosis	Gastric ulcer	240 (72.1%)	122 (73.5%)	362 (72.5%)
	Duodenal ulcer	102 (30.6%)	45 (27.1%)	147 (29.5%)
Forrest classification	Ia	30 (9.0%)	14 (8.4%)	44 (8.8%)
	Ib	20 (6.0%)	20 (12.0%)	40 (8.0%)
	IIa	79 (23.7%)	31 (18.7%)	110 (22.0%)
	IIb	11 (3.3%)	3 (1.8%)	14 (2.8%)
	IIc	6 (1.8%)	12 (7.2%)	18 (3.6%)
	III	187 (56.2%)	86 (51.8%)	273 (54.7%)
Active bleeding ulcer		92 (27.6%)	49 (29.5%)	141 (28.3%)
Drugs	NSAIDs	100 (30.0%)	48 (28.9%)	148 (29.7%)
	Antiplatelet	71 (21.3%)	29 (17.5%)	100 (20.0%)
	Anticoagulant	36 (10.8%)	12 (7.2%)	48 (9.6%)
	Steroids	14 (4.2%)	8 (4.8%)	22 (4.4%)
	PPI / P-CAB / H2RA	54 (16.2%)	29 (17.5%)	83 (16.6%)
Hospitalization		274 (82.3%)	144 (86.7%)	418 (83.8%)
Intervention	Blood transfusion	154 (46.2%)	83 (50.0%)	237 (47.5%)
	Endoscopic hemostasis	122 (36.6%)	64 (38.6%)	186 (37.3%)
	IVR	4 (1.2%)	0 (0.0%)	4 (0.8%)
	Surgery	1 (0.3%)	0 (0.0%)	1 (0.2%)
Rebleeding		25 (7.5%)	17 (10.2%)	42 (8.4%)
Mortality		10 (3.0%)	5 (3.0%)	15 (3.0%)

IQR: interquartile range, NSAIDs: non-steroid anti-inflammatory drugs, PPI: proton pump inhibitor, P-CAB: potassium-competitive acid blocker, H2RA: histamine H2-receptor antagonist, IVR: interventional radiology

Table 2. Univariate and Multivariate Analyses in the Training-cohort Dataset.

	Mortality n=10	Survival n=323	Univariate	Multivariate	
			p value	Odds ratio [95% CI]	p value
Age (years)	79 (75-87)	73 (63-80)	0.052		
HR/SBP	1.05±0.47	0.73±0.26	0.036	1.72 [1.06-2.80]	0.028
NSAIDs	4 (40.0%)	97 (30.0%)	0.499		
Antiplatelet/Anticoagulant	3 (30.0%)	95 (29.4%)	0.968		
Cardiac failure/ Ischemic Heart disease	2 (20.0%)	79 (24.5%)	0.746		
Hepatic failure	1 (10.0%)	13 (4.0%)	0.354		
Renal failure	3 (30.0%)	44 (13.6%)	0.143		
Malignant tumor	2 (20.0%)	52 (16.1%)	0.742		
Other major comorbidity	5 (50.0%)	105 (32.5%)	0.247		
Blood hemoglobin (g/dL)	6.8±1.2	9.5±3.1	0.003		
INR	1.32±0.35	1.20±0.51	0.018		
s-Alb (g/dL)	2.3±0.6	3.3±0.6	<0.001	0.23 [0.11-0.51]	<0.001
BUN (mg/dL)	52.7±37.4	38.9±28.1	0.164		
Active bleeding ulcer	5 (50.0%)	87 (26.9%)	0.108		

95% CI: 95% confidence interval, HR/SBP: heart rate-to-systolic blood pressure ratio, NSAIDs: non-steroid anti-inflammatory drugs, INR: international normalized ratio of prothrombin time, s-Alb: serum albumin, BUN: blood urea nitrogen



A.	AUC [95% CI]
HR/SBP+s-Alb	0.855 [0.730-0.979]
GBS	0.756 [0.601-0.911]
RS	0.708 [0.504-0.913]
AIMS65	0.838 [0.736-0.939]
PNED	0.869 [0.784-0.954]

B.	AUC [95% CI]
HR/SBP+s-Alb	0.835 [0.606-1]
GBS	0.810 [0.594-1]
RS	0.810 [0.693-0.927]
AIMS65	0.821 [0.594-1]
PNED	0.850 [0.656-1]

Figure 2. **Receiver operator characteristics curve. A: Training-cohort dataset. B: Validation-cohort dataset. HR/SBP: heart rate-to-systolic blood pressure ratio, s-Alb: serum albumin, AUC: area under the curve, 95% CI: 95% confidence interval**

Table 3. **Univariate and Multivariate Analyses in the Validation-cohort Dataset.**

	Mortality n=5	Survival n=161	Univariate	Multivariate	
			p value	Odds ratio [95% CI]	p value
HR/SBP	1.19±0.50	0.73±0.23	0.043	2.54 [1.26-5.09]	0.010
s-Alb (g/dL)	2.6±0.4	3.3±0.7	0.011	0.41 [0.15-1.15]	0.093

95% CI: 95% confidence interval, HR/SBP: heart rate-to-systolic blood pressure ratio, s-Alb: serum albumin

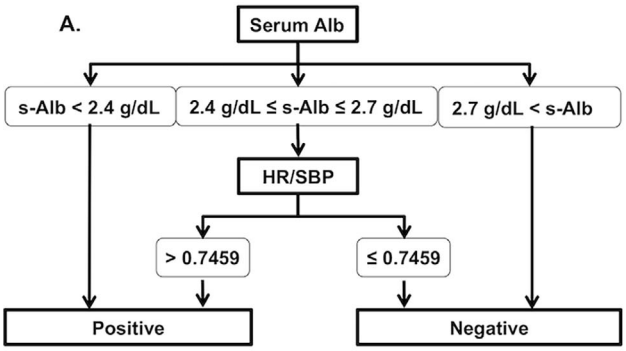
Development of the criteria

From a clinical perspective, the criteria for predicting PUD-associated mortality should be clear-cut and simple for a quick evaluation in emergency situations. We thus performed a decision tree analysis to develop criteria including the HR/SBP and s-Alb level in a dataset in which the missing values were imputed 100 times by MICE (n=49,900). From the results of the decision tree analysis in the training-cohort dataset (n=33,300), 's-Alb <2.4 g/dL' or 's-Alb 2.4-2.7 g/dL and HR/SBP >0.7459' were considered optimal criteria for predicting mortality and were named the Iwasaki-Shimura (IS) criteria (Fig. 3A). The IS criteria showed a sensitivity of 70.0% and a specificity of 87.8%. Furthermore, the IS criteria also showed good performance (sensitivity and specificity of 80.0% and 86.9%, respectively) in the independent validation-cohort dataset (n=16,600; Fig. 3B). The efficacies of each of the other risk scores at the proposed cut-off values in the imputed total-cohort dataset are displayed in Fig. 3C. The IS criteria were superior to GBS and RS, while their efficacy for predicting PUD-associated mortality was similar to that of AIMS65 and PNED (10, 12, 13, 23).

Discussion

In the present study, we established simple and novel predictive criteria for PUD mortality consisting of only two parameters: HR/SBP and s-Alb. Since intensive care and early intervention for patients with high-risk PUD might reduce the mortality, risk classification before treatment is important for PUD. For this purpose, several risk scoring systems for classification of severity in patients with UGIB have been developed, including GBS, RS, AIMS65, and PNED (9-12). However, the clinical use of these risk scores is currently limited, possibly due to the fact that they are relatively com-

A.



B.

	Sensitivity	Specificity	Accuracy
Traning set (N=33,300)	70.0%	87.8%	87.3%
Testing set (N=16,600)	80.0%	86.9%	86.7%

C.

Cut-off		Total imputed dataset (N=49,900) Sensitivity (%)	Specificity (%)	Accuracy (%)
GBS [13]	5	100	21.3	23.6
RS [10]	5	86.7	47.2	48.4
AIMS65 [23]	3	47.9	92.6	91.3
PNED [12]	4	73.3	82.3	82.1
IS criteria		73.3	87.6	85.2

Figure 3. **Novel criteria for predicting peptic ulcer disease-associated mortality. A: IS criteria. 's-Alb <2.4 g/dL' or 's-Alb 2.4-2.7 g/dL and HR/SBP >0.7459' predicts future mortality. B: Efficacy of the IS criteria. C: Comparison of the IS criteria with other scores. HR/SBP: heart rate-to-systolic blood pressure ratio, IS criteria: Iwasaki-Shimura criteria**

plicated to calculate, as they involve many parameters. Notably, despite their simplicity, our novel criteria showed equivalent predictability to other useful but more complex scores, including AIMS65 and PNED. The AUCs of GBS, RS, AIMS65, and PNED for detecting UGIB-associated mortality have been reported to be 0.64-0.87, 0.72-0.81, 0.75-0.91, and 0.77-0.81, respectively (12-16, 23-25). PNED reportedly outperforms RS in predicting the risk of death from UGIB (12). Of these four risk scoring systems, only AIMS65 contains s-Alb as a parameter and showed the highest accuracy of 91.3% in the present dataset; however, its sensitivity of 47.9% is too low for clinical use. Although PNED showed a sensitivity and accuracy comparable to that of our newly developed criteria, the simplicity of our criteria might make them more useful than PNED. Importantly, PNED is not suitable for pre-treatment risk classification because it includes the presence or absence of rebleeding as a parameter, which cannot be known before treatment.

The functions of s-Alb are mainly to maintain osmotic pressure in the normal blood circulation and to bind various substances in the body for transportation without degradation (26). Many studies have shown that s-Alb is inversely correlated with all-disease mortality, particularly in elderly patients (27-31). Debilitating diseases with malignancy and chronic inflammatory diseases cause a change in the transcapillary escape rate of albumin and enhance its transition from the blood to tissue spaces (32). Therefore, patients with severe comorbidities might exhibit a low level of s-Alb. One study found that GBS combined with s-Alb could identify inpatient mortality in UGIB patients better than GBS and RS alone (33). Another study showed that patients who died from gastrointestinal bleeding had significantly lower s-Alb levels than those who survived (34). Low levels of s-Alb can reflect not only serum protein loss caused by severe PUD but also a poor physical condition due to debilitating illness. s-Alb might thus be a representative parameter that reflects the basic physical function under comorbidity and aging as well as severity of PUD.

The HR/SBP ratio, also known as the Shock Index, reflects the circulation dynamics and is associated with patient mortality in the emergency department (35). We previously reported that the HR/SBP ratio is related to active bleeding in patients with UGIB (17). Several other reports also indicated that the HR/SBP ratio is a good predictor for the detection of high-risk UGIB patients or patients who need endoscopic intervention (36, 37). Since a large UGIB-related blood loss could trigger tachycardia, i.e., HR elevation, and a drop in SBP, the HR/SBP ratio may reflect an acute critical condition of severely affected UGIB patients. We feel that these are explanations as to why our criteria consisting of the HR/SBP ratio and s-Alb level can efficiently identify PUD patients with a poor prognosis.

When a dataset with missing values is analyzed, the National Research Council does not recommend using the CCA method, as it builds on the improbable assumption that the data are missing completely at random (38). As such, we applied the MICE method for replacing missing values and developed a large dataset in the present study. Nevertheless, the IS criteria demonstrated consistent efficacies in both the training and validation datasets. Based on these results, the

IS criteria can be applied in emergency situations involving PUD because of its major benefits of simplicity and high accuracy.

Two limitations associated with the present study warrant mention. First, this was a retrospective study carried out at only two institutions; a prospective, multicenter trial would be required in the future validation. However, the diagnostic power of the conventional four scoring systems was more or less within the previously reported ranges, suggesting the validity of the present datasets. In addition, the efficacy of the IS criteria was proven in two independent large datasets. We therefore believe that the current data might provide a solid basis for using the IS criteria for the prediction of PUD-associated mortality. We are currently planning a multicenter prospective observational study to verify the IS criteria. Second, we included all cases by replacing any missing values using MICE and did not omit such cases, as would have been the case when performing a CCA. Consequently, the results of MICE were consistent with those of the CCA in the present study. This bias is thus negligible for the present study.

In conclusion, the simple and novel criteria comprising the HR/SBP ratio and s-Alb level help identify patients with high-risk PUD.

The authors state that they have no Conflict of Interest (COI).

References

1. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther **29**: 938-946, 2009.
2. Lin KJ, Garcia Rodriguez LA, Hernandez-Diaz S. Systematic review of peptic ulcer disease incidence rates: do studies without validation provide reliable estimates? Pharmacoepidemiol Drug Saf **20**: 718-728, 2011.
3. Kang JY, Elders A, Majeed A, Maxwell JD, Bardhan KD. Recent trends in hospital admissions and mortality rates for peptic ulcer in Scotland 1982-2002. Aliment Pharmacol Ther **24**: 65-79, 2006.
4. Sung JJ, Tsoi KK, Ma TK, Yung MY, Lau JY, Chiu PW. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. Am J Gastroenterol **105**: 84-89, 2010.
5. Ahsberg K, Ye W, Lu Y, Zheng Z, Stael von Holstein C. Hospitalisation of and mortality from bleeding peptic ulcer in Sweden: a nationwide time-trend analysis. Aliment Pharmacol Ther **33**: 578-584, 2011.
6. Malmi H, Kautiainen H, Virta LJ, Farkkila MA. Increased short- and long-term mortality in 8146 hospitalised peptic ulcer patients. Aliment Pharmacol Ther **44**: 234-245, 2016.
7. Sonnenberg A. Temporal trends and geographical variations of peptic ulcer disease. Aliment Pharmacol Ther **9** (Suppl): 3-12, 1995.
8. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med **152**: 101-113, 2010.
9. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet **356**: 1318-1321, 2000.
10. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut **38**: 316-321, 1996.
11. Saltzman JR, Tabak YP, Hyett BH, Sun X, Travis AC, Johannes RS. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. Gastrointest Endosc **74**: 1215-1224, 2011.
12. Marmo R, Koch M, Cipolletta L, et al. Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED Score and Prospective Comparison with the Rockall Score. Am J Gastroenterol **105**: 1284-1291, 2010.
13. Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ **356**: i6432, 2017.
14. Oakland K, Kahan BC, Guizzetti L, et al. Development, validation, and comparative assessment of an international scoring system to determine risk of upper gastrointestinal bleeding. Clin Gastroenterol Hepatol **17**: 1121-1129. e2, 2019.
15. Kim MS, Choi J, Shin WC. AIMS65 scoring system is comparable to Glasgow-Blatchford score or Rockall score for prediction of clinical outcomes for non-variceal upper gastrointestinal bleeding. BMC Gastroenterol **19**: 136, 2019.
16. Redondo-Cerezo E, Vadillo-Calles F, Stanley AJ, et al. MAP (ASH): a new scoring system for the prediction of intervention and mortality in upper gastrointestinal bleeding. J Gastroenterol Hepatol **35**: 82-89, 2020.
17. Iwasaki H, Shimura T, Yamada T, et al. Novel nasogastric tube-related criteria for urgent endoscopy in nonvariceal upper gastrointestinal bleeding. Dig Dis Sci **58**: 2564-2571, 2013.
18. Huang ES, Karsan S, Kanwal F, Singh I, Makhani M, Spiegel BM. Impact of nasogastric lavage on outcomes in acute GI bleeding. Gastrointest Endosc **74**: 971-980, 2011.
19. Rockey DC, Ahn C, de Melo SW Jr. Randomized pragmatic trial of nasogastric tube placement in patients with upper gastrointestinal tract bleeding. J Investig Med **65**: 759-764, 2017.
20. Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. Lancet **2**: 394-397, 1974.
21. Little RJ, Cohen ML, Dickersin K, et al. The design and conduct of clinical trials to limit missing data. Stat Med **31**: 3433-3443, 2012.
22. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Stat Med **29**: 2920-2931, 2010.
23. Tang Y, Shen J, Zhang F, Zhou X, Tang Z, You T. Scoring systems used to predict mortality in patients with acute upper gastrointestinal bleeding in the ED. Am J Emerg Med **36**: 27-32, 2018.
24. Shung DL, Au B, Taylor RA, et al. Validation of a machine learning model that outperforms clinical risk scoring systems for upper gastrointestinal bleeding. Gastroenterology **158**: 160-167, 2020.
25. Gu L, Xu F, Yuan J. Comparison of AIMS65, Glasgow-Blatchford and Rockall scoring approaches in predicting the risk of in-hospital death among emergency hospitalized patients with upper gastrointestinal bleeding: a retrospective observational study in Nanjing, China. BMC Gastroenterol **18**: 98, 2018.
26. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. Mol Aspects Med **33**: 209-290, 2012.
27. Phillips A, Shaper AG, Whincup PH. Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. Lancet **2**: 1434-1436, 1989.
28. Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum albumin level and physical disability as predictors of mortality in older persons. JAMA **272**: 1036-1042, 1994.
29. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. N Engl J Med **329**:

1001-1006, 1993.

30. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol **50**: 693-703, 1997.

31. Corti MC, Salive ME, Guralnik JM. Serum albumin and physical function as predictors of coronary heart disease mortality and incidence in older persons. J Clin Epidemiol **49**: 519-526, 1996.

32. Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet **1**: 781-784, 1985.

33. Shafaghi A, Gharibpoor F, Mahdipour Z, Samadani AA. Comparison of three risk scores to predict outcomes in upper gastrointestinal bleeding; modifying Glasgow-Blatchford with albumin. Rom J Intern Med **57**: 322-333, 2019.

34. Koseoglu Z, Ozkan OV, Semerci E, et al. The relationship between mortality and inflammation in patients with gastrointestinal bleeding. J Int Med Res **37**: 1508-1514, 2009.

35. Kristensen AK, Holler JG, Hallas J, Lassen A, Shapiro NI. Is shock index a valid predictor of mortality in emergency department patients with hypertension, diabetes, high age, or receipt of beta- or calcium channel blockers? Ann Emerg Med **67**: 106-113 e 106, 2016.

36. Horibe M, Kaneko T, Yokogawa N, et al. A simple scoring system to assess the need for an endoscopic intervention in suspected upper gastrointestinal bleeding: a prospective cohort study. Dig Liver Dis **48**: 1180-1186, 2016.

37. Rassameehiran S, Teerakanok J, Suchartlikitwong S, Nugent K. Utility of the shock index for risk stratification in patients with acute upper gastrointestinal bleeding. South Med J **110**: 738-743, 2017.

38. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med **367**: 1355-1360, 2012.