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A multicenter prospective study of the treatment and outcome of patients with gastroduodenal peptic ulcer bleeding in Japan

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Abstract

Gastroduodenal peptic ulcers are the main cause of nonvariceal upper gastrointestinal bleeding (UGIB). We believe that recent advances in endoscopic techniques and devices for diagnosing upper gastrointestinal tract tumors have advanced hemostasis for UGIB. However, few prospective multicenter studies have examined how these changes affect the prognosis. This prospective study included 246 patients with gastroduodenal peptic ulcers treated at 14 participating facilities. The primary endpoint was in-hospital mortality within 4 weeks, and the secondary endpoints required intervention and refractory bleeding. Subsequently, risk factors affecting these outcomes were examined using various clinical items. Furthermore, the usefulness of the risk stratification using the Glasgow-Blatchford score, rockall score and AIMS65 based on data from the day of the first urgent endoscopy were examined in 205 cases in which all items were complete there are two periods. Thirteen (5%) patients died within 4 weeks; and only 2 died from bleeding. Significant risk factors for poor outcomes were older age and severe comorbidities. Hemostasis was required in 177 (72%) cases, with 20 cases of refractory bleeding (2 due to unsuccessful endoscopic treatment and 18 due to rebleeding). Soft coagulation was the first choice for endoscopic hemostasis in 57% of the cases and was selected in more than 70% of the cases where combined use was required. Rockall score and AIMS65 predicted mortality equally, and Glasgow-Blatchford score was the most useful in predicting the requirement for intervention. All scores predicted refractory bleeding similarly. Although endoscopic hemostasis for UGIB due to peptic ulcer had a favorable outcome, old age and severe comorbidities were risk factors for poor prognosis. We recommend that patients with UGIB should undergo early risk stratification using a risk scoring system.

Abbreviations: AUC = area under the receiver-operating characteristic curve, CT = computed tomography scan, ESD = Endoscopic submucosal dissection, GBS = Glasgow-Blatchford score, GDPU = gastroduodenal peptic ulcers, *H. pylori* = *Helicobacter pylori*, ICU = intensive care unit, LDA = low-dose aspirin, NSAIDs = non-steroidal anti-inflammatory drugs, RS = rockall score, UGIB = upper gastrointestinal bleeding.

Keywords: antithrombotic agents, comorbidities, older age, risk scoring system, upper gastrointestinal bleeding, urgent endoscopy

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study was conducted according to the guidelines of the Declaration of Helsinki. This study was approved by Tottori University (approval code: 1505A002) and the review board of each institution prior to patient registration.

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1. Introduction

Upper gastrointestinal bleeding (UGIB) is a common medical emergency and an important cause of mortality. Gastroduodenal peptic ulcers (GDPUs) are the main cause of non-variceal UGIB.[1,2] Non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin (LDA) and *Helicobacter pylori* (*H pylori*) infection, are the main risk factors for GDPU.[3] Although the global incidence and mortality are decreasing, GDPU remains a common condition.[4,5] The prevalence of *H pylori* has declined mainly in the young population; however, the incidence of drug-induced ulcers due to NSAIDs and antithrombotic drugs increases with age.[6–8]

The results of endoscopic hemostasis of hemorrhagic GDPUs have improved over the years.[1] Various hemostatic methods exist, and recommended and non-recommended treatments are mentioned in Japanese and international guidelines.[9–15] However, soft coagulation hemostasis using hemostatic forceps has recently become widely used in Japan as a simple and effective hemostatic method. The widespread use of this hemostatic technique has paralleled the widespread performance of endoscopic submucosal dissection (ESD) for early gastric cancer. During ESD, hemostasis of active bleeding and prophylactic coagulation of the visible vessels were performed using soft coagulation with hemostatic forceps. The drawback of ESD is post-procedural bleeding, a risk factor reportedly involving patient comorbidities (especially dialysis) and antithrombotic drug use. The usefulness of soft coagulation with hemostatic forceps as a hemostatic method for UGIB due to GDPUs has been reported.[16–19]

In addition, guidelines from various countries also address what should be done before urgent endoscopy (e.g., using a risk scoring system to predict prognosis or using computed tomography [CT] to identify the source of bleeding), management after hemostatic procedures (e.g., whether to take a second look, guidelines for blood transfusion, etc), and prevention of ulcer recurrence. Although these innovations have improved UGIB outcomes, patients with serious comorbidities, particularly older patients, have poor prognoses.[2,7,8]

Therefore, several national and international guidelines recommend that patients with UGIB undergo early risk stratification to predict outcomes using risk scoring systems.[9–15] Commonly known risk scoring systems, the Glasgow-Blatchford score (GBS) and Rockall score (RS), were devised to identify patients with acute non-variceal UGIB at high risk of poor outcomes.[20,21] The items of the GBS (Table 1), which are used to predict the need for urgent endoscopy and hemostasis, consist of clinical variables without endoscopic data.[20] Many subsequent reassessments have reported that the GBS is superior to other scoring systems in predicting the need for hemostasis intervention. On the other hand, the calculation items of the RS (Table 2), which are used to predict outcomes such as rebleeding and prognosis, are based on clinical variables and endoscopic findings.[21] The original article defines patients with scores of 0 to 2 as a low-risk mortality group. Despite recommendations to evaluate risk stratification scores in UGIB, these scoring systems are not used regularly in clinical practice because of their complexity. However, the AIMS65 score evaluates only 5 risk factors, (scoring 1 point each): albumin less than 3.0 g/dL; an international normalized ratio more than 1.5; altered mental status; systolic blood pressure of 90 mm Hg or lower; and age over 65 years (Table 3).[22] The original article defined a score of 0 to 1 as low risk. AIMS65 was able to predict in-hospital mortality, length of stay, and cost of admission. This is a simple risk scoring system for predicting outcomes in patients with acute UGIB. In fact, several studies, including ours, have reported the

Table 1

Glasgow-Blatchford bleeding score (GBS).

Systric BP (mm Hg)	**Score**	**BUN (mg/dL)**	**Score**
≥110	0	<18.1	0
100–109	1	18.2–22.3	2
90–99	2	22.4–27.9	3
<90	3	28.0–69.9	4
		≥70	6
Hb for male (g/dL)	**Score**	**Hb for female (g/dL)**	**Score**
≥13.0	0	≥12.0	0
12.0–12.9	1	10.0–11.9	1
10.0–11.9	3	<10.0	6
<10.0	6		
Other comorbidities, symptom, condition		**score**	**Score range**
melena, pulse (bpm) ≥ 100		1	0–23
syncope, cardiac failure, liver disease		2	

GBS = Glasgow-Blatchford score.

Table 2

Rockall risk score.

Score	**0**	**1**	**2**	**3**
Age (yr)	<60	60–79	≥80	
Hemodynamics				
Systric BP (mm Hg)	≥100	≥100	<100	
Pulse (bpm)	<100	≥100		
Comorbidities	None		IHD, cardiac failure Other major comorbidities	renal/liver failure disseminated malignancy
Endoscopic diagnosis	None MWS	Ulcer Erosion	Malignant lesions of UGIT	
Stigmata of hemorrhage	No stigmata or dark spot on ulcer		Blood adherent clot, Spurting or visible vessel	
Score range 0–11				

RS = rockall score.

Table 3

AIMS65 Scoring system.

Risk factor	Score
Albumin < 3.0g/dL	1
International normalized ratio > 1.5	1
altered Mental status	1
Systolic blood pressure ≤ 90 mm Hg	1
age > 65 yrs	1
Score range	**0–5**

usefulness of AIMS65 for risk stratification, especially in predicting mortality.[2,23,24]

Moreover, although clinical studies on UGIB due to GDPUs are available with the formulation of evidence-based guidelines, most of them are retrospective, with only a few prospective multicenter studies. Therefore, we conducted a multicenter observational study with prospective registration in 14 centers (with various characteristics) to clarify the risk factors of mortality, requiring hemostasis, and refractory bleeding for bleeding GDPUs in clinical practice.

2. Methods

2.1. Patient registration

All patients who underwent urgent endoscopy due to definite hematemesis or melena and had recognized stigmata of bleeding from a gastroduodenal ulcer within 1 year between 2015 and 2016 at Tottori University, Shimane University, and 12 other related facilities were enrolled in the present study. Patients with iatrogenic bleeding or malignancy were excluded from this study. A total of 246 patients with GDPU were enrolled in this study (Fig. 1). Written informed consent was obtained from all patients before urgent endoscopic examination. This study was conducted in accordance with the principles of the Declaration of Helsinki. Each institution's review board approved the study prior to patient registration. We recorded the patient information, medical history, laboratory data, clinical information at the first visit, and treatment status, as listed below.

2.2. Data collection

Data on each patient's age, sex, and outpatient or inpatient status were also collected. Details regarding medical history, including comorbidities, peptic ulcer treatment, and *H pylori* eradication status, were also obtained. Data regarding concomitant medications such as NSAIDs, antithrombotic agents such as LDA and warfarin, direct oral anticoagulants, steroids, and acid secretion inhibitors such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists were also recorded. Clinical data at the first visit (including symptoms, vital signs, physical findings, and mental status), laboratory data at the first visit, date and time of the first visit, elapsed time until urgent endoscopy, cause of bleeding (gastric, duodenal, or gastroduodenal ulcer), *H pylori* status, and inspection method of *H pylori* infection were collected. Endoscopic findings, such as Forrest classification, number and location of ulcers, requirement for intervention, and hemostasis method (endoscopic, interventional radiology, or surgery), were collected. The clinical course, including blood transfusion, fasting period, length of hospitalization, intensive care unit (ICU) admission, rebleeding, re-intervention timing, salvage treatment method, and prognosis (recovering, death, cause of death), was recorded.

2.3. Clinical endpoints

The clinical outcomes of patients who underwent urgent endoscopy for UGIB ulcers were investigated prospectively. The primary endpoint was in-hospital death within 4 weeks. The secondary end points were the requirement for hemostasis and refractory bleeding (unsuccessful endoscopic hemostasis and rebleeding). Rebleeding was defined as bleeding or visible vessels (Forrest classification Ia, Ib, and IIa) requiring hemostasis again after a successful procedure.

2.4. Risk stratification

The patients with incomplete data whose risk stratification scores needed to be calculated were excluded. Consequently, the risk stratification study cohort included 205 patients (Fig. 1). These patients were stratified using the GBS, RS, and AIMS65 based on data collected on the day of the first urgent endoscopy.

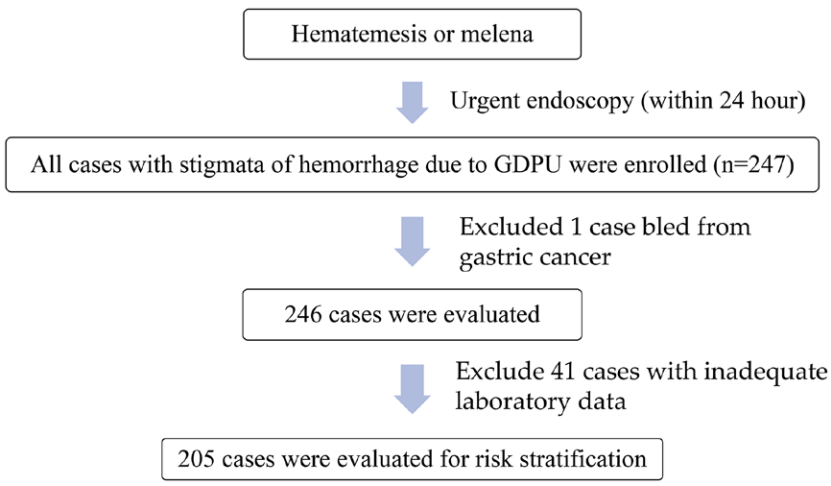

Figure 1. Flowchart of patient enrollment. GDPU: A mucosal defect of ≥ 5 mm, but smaller defects can be included if there are visible blood vessels (e.g., Dieulafoy ulcer). GDPU = gastroduodenal peptic ulcers.

2.5. Statistical analysis

Categorical variables were expressed as counts and percentages and were compared using the chi-square or Fisher's exact test. Continuous variables were expressed as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test. All *p*-values were 2-sided, with < 0.05 considered statistically significant. Logistic regression analysis was performed to determine the risk factors for requirement of hemostasis, rebleeding, and in-hospital mortality. Parameters showing $P < .1$ in the univariate analysis were included in the multivariate analysis.

In the risk stratification study, the area under the receiver-operating characteristic curve (AUC) was calculated to determine the ability of the scoring systems to predict the primary and secondary outcomes and compare them using EZR version 1.54 (https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html). We calculated a cutoff point for each scoring system that maximized the sum of the sensitivity and specificity in predicting the primary and secondary endpoints. The patients were stratified into low-risk or high-risk groups using these cutoff thresholds and compared them using Fisher's exact test.

3. Results

3.1. Patient background and characteristics

The most frequent cause of GDPU in the study cohort was gastric ulcer (169 cases; 69%), followed by duodenal ulcers in 68 (27%) cases and gastroduodenal ulcers in 9 (4%). The median age was 68 years (IQR, 57–81 years), and 164 (67%) patients were men. Eighty-eight (36%) patients were prescribed medications known to increase the risk of UGIB, including antithrombotic drugs (n = 46), NSAIDs (n = 44), and steroids (n = 10). Antithrombotic agents prescribed included LDA (n = 17), warfarin potassium (n = 15), direct oral anticoagulants (n = 10), thienopyridine derivative agents (n = 10; clopidogrel for 9 of them), and cilostazol (n = 3). Only 31 patients (13%) received prophylactic PPIs. Among the cohort, 134 patients were *H pylori*-positive, 60 were *H pylori*-negative, and 52 were not examined. Most cases were evaluated using blood anti-*H pylori* antibodies. Patient characteristics are shown in Table 4.

3.2. Clinical management of UGIB

UGIB occurred in 39 (16%) in-hospital and 207 (84%) outpatient. In addition, 130 (53%) patients visited the hospital on weekdays during daytime hours and 116 (47%) visited during holidays and at night. The median time from arrival at the hospital to the first endoscopy was 98 minutes; 210 (85%) endoscopies were performed within 6 hours of arrival, which is considered urgent. CT was performed before endoscopy in 178 (77%) patients [plain CT, 123 (50%); contrast-enhanced CT, 55 (23%)]. The median time to emergency endoscopy for patients who did not undergo CT was 70 minutes, 105 minutes for those who underwent plain CT, and 120 minutes for those who underwent contrast-enhanced CT. Blood transfusions were performed in 112 (46%) patients and 19 (8%) patients were managed in the ICU. Hemostatic intervention and outcomes (clinical endpoints) are summarized in Table 5 and are detailed below.

3.3. Primary endpoint: mortality

The in-hospital 4-week mortality rate was 5% (n = 13). Of these, 2 deaths were considered bleeding-related, while the remaining 11 patients died from worsening comorbidities (Table 6). The patients who died had a significantly higher median age (83 vs 68 years, $P < .001$), prevalence of comorbidities (100% vs 64%, $P = .005$), antithrombotic agent use (46% vs 17%, $P = .004$), and in-hospital onset (54% vs 14%, $P = .001$) than those who recovered. PPI users had a significantly higher mortality rate than non-users (16% vs 4%, $P = .014$). The mortality rate was significantly higher in patients with duodenal ulcer complications than in those with gastric ulcers alone (62% vs 30%, $P = .027$). Although the number of in-hospital deaths was small and should probably not be evaluated in a multivariate analysis, a logistic regression analysis was performed on the 6 items that showed significant differences. Other items with significant differences were older age and in-hospital onset. Patient characteristics and risk factors in the death and recovery groups are shown in Table 7.

3.4. Secondary endpoint: require intervention and refractory bleeding

Of the 246 patients, 177 (72%) required clinical interventions. Twenty cases of refractory bleeding required hemostasis interventions (2 because of unsuccessful initial endoscopic hemostasis and 18 because of rebleeding after endoscopic treatment) (Table 5). Soft coagulation using hemostatic forceps was selected as the first choice for endoscopic hemostasis in 57% (101/177) of cases, while hemostasis clips were chosen in 26% (45/177). Salvage treatment was performed in 2 patients in whom initial endoscopic treatment was unsuccessful: 1 was treated with interventional radiology and the other with surgery. Of the 18 patients with rebleeding, 14 underwent successful endoscopic re-intervention, and 3 achieved hemostasis with interventional radiology. One patient in whom re-intervention was unsuccessful and another who was treated by interventional radiology died of bleeding.

Table 4

Patient characteristics in 246 cases.

		n (%)
Sex	Men	164 (67%)
Age, yr	Median (IQR)	69 (57–81)
Symptom	Hematemesis	81 (33%)
	Melena	128 (52%)
	Both	37 (15%)
Endoscopic diagnosis	Gastric ulcer	169 (69%)
	Duodenal ulcer	68 (27%)
	Gastroduodenal ulcer	9 (4%)
PPI use		31 (13%)
Current *Helicobacter pylori* status	Positive	134 (55%)
	Negative	60 (24%)
	Unknown	52 (21%)
Comorbidities*	All	157 (64%)
	Cardiac disease	40 (16%)
	Orthopedic disorder	34 (14%)
	Cerebral disease	20 (8%)
	Malignancy	9 (4%)
Concomitants*	Antithrombotic agent	46 (19%)
	LDA	17 (7%)
	Warfarin	15 (6%)
	DOAC	10 (4%)
	Clopidogrel	9 (3%)
	NSAID	44 (18%)
	Steroid	10 (4%)
Onset place	Outpatient	207 (84%)
	In-hospital	39 (16%)
Visit timing	Weekday, Daytime	130 (53%)
	Holiday, night time	116 (47%)

* There were some overlapping cases.

DOAC = direct oral anticoagulant, IQR = interquartile range, LDA = low-dose aspirin, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor.

Compared with those who did not require treatment, patients who required hemostasis were significantly younger (median age:66 vs 75 years, $P = .007$) and had lower incidence rates of duodenal ulcers (25% vs 46%, $P = .002$) and lower rates of concomitant PPIs (9% vs 22%, $P = .013$). The prevalence of comorbidities tended to be lower in the hemostasis group (60% vs 74%, $P = .054$, OR 0.53:0.27–1.01). Conversely, there was no significant difference in the use of antithrombotic drugs (19% vs 19%, $P = 1.000$) and NSAIDs (16% vs 27%, $P = .242$) between the groups that required hemostasis and those that did not. Multivariate analysis (logistic regression analysis) was performed on the 5 items with $P < .2$ on univariate analysis. Multivariate analysis showed significantly lower rate of hemostatic intervention for duodenal ulcers. The characteristics and risk factors of patients who required hemostasis are shown in Table 8.

Among the patients requiring treatment, those with refractory bleeding tended to have a higher rate of PPI use (20% vs 8%, $P = .0882$) and a higher prevalence of duodenal ulcers (40% vs 24%, $P = .169$) than those with non-refractory bleeding. Furthermore, there were no differences in the use of antithrombotic drugs and NSAIDs or in the prevalence of comorbidities. Multivariate analysis (logistic regression analysis) of the 2 items that had $P < .2$ on univariate analysis showed no significantly different risk factors (Table 9). Patients with refractory bleeding had significantly higher rates of ICU admission (25% vs 8%, $P = .0280$) and transfusion (90% vs 43%, $P = .0000601$) than those without refractory bleeding.

4. Relationship between the risk scoring systems and outcomes (Clinical endpoints)

4.1. Clinical endpoints in the risk stratification study cohort

Of the 205 patients who underwent a risk stratification study, 160 (78%) required clinical interventions. Eighteen cases of refractory bleeding (2 because of unsuccessful initial endoscopic hemostasis and 16 because of rebleeding after endoscopic treatment) required hemostasis interventions. The in-hospital 4-week mortality rate was 5% (10 patients). Of these, 2 deaths were considered bleeding-related, and the remaining 8 were attributed to worsening comorbidities (Table 10).

Table 5

Result summary of primary and secondary endpoint.

Outcome	Details		Total
Hemostasis	Used	177 (72%)	246
	Not used	69 (28%)	(100%)
Refractory bleeding	Re-bleeding	18 (7%)	20
	Unsuccessful endoscopic treatment	2 (1%)	(8%)
Poor prognosis	Death from comorbidity	11 (4%)	13
	Death from bleeding	2 (1%)	(5%)

4.2. Risk stratification for mortality

The AUCs for predicting mortality using the AIMS65 score, GBS, and RS were 0.816 (95% confidence interval [CI], 0.688–0.944), 0.757 (95% CI, 0.583–0.930), and 0.828 (95% CI, 0.730–0.926), respectively; there was no statistical difference between the AIMS65 score and those of other 3 scoring systems (AIMS65 vs GBS, $P = .27$; AIMS65 vs RS, $P = .82$). The cutoff values for the low-risk versus high-risk mortality groups were 2 for the AIMS65 score (sensitivity, 0.80; specificity, 0.68), 13 for the GBS (sensitivity, 0.70; specificity, 0.70), and 7 for the RS (sensitivity, 0.70; specificity, 0.82) (Table 11).

4.3. Risk stratification for requirement of hemostasis and refractory bleeding

The AUCs for predicting the requirement of hemostasis before the initial urgent endoscopy based on the AIMS65 score and GBS were 0.557 (95% CI, 0.474–0.638) and 0.648 (0.552–0.745), respectively; there was no significant difference between the AIMS65 score and GBS ($P = .06$) (Fig. 2). The cutoff values for the low-risk and high-risk groups for the requirement of hemostasis were 2 for the AIMS65 score and 9 for the GBS (Table 12). Since estimating the need for hemostasis is the same as predicting the need for urgent endoscopy, the RS, in which endoscopic findings are one of the score items, was excluded from the comparison study.

AUCs for predicting refractory bleeding using the AIMS65 score, GBS, and RS were 0.675 (95% CI, 0.537–0.813), 0.668 (95% CI, 0.506–0.829), and 0.641 (95% CI, 0.480–0.802), respectively, with the AUC of the AIMS65 score being similar to that of the others (AIMS65 vs GBS, $P = .90$; AIMS65 vs RS, $P = .58$). The cutoff values for the low-risk versus high-risk groups for refractory bleeding were 3 for the AIMS65 score, 15 for the GBS, and 7 for the RS (Table 12).

5. Discussion

In this prospective multicenter study, we examined the clinical situation of patients with UGIB due to GDPU occurring within a year. Before the study commenced, soft coagulation with hemostatic forceps was the most common choice for endoscopic hemostasis, as expected; including the second choice of

Table 6

Details of Patients with poor prognosis.

	Death from bleeding: 2 cases
Case 1.	46 yrs old women, Duodenal ulcer, SLE (poor control, high dose steroid and LDA use, no PPI use), severe CRF, cytomegalovirus infection, underwent interventional radioligy (TEA) and surgery
Case 2.	82 yrs old man, Gastric ulcer with large vessel (artery), warfarin use due to Atrial fibrillation (INR 8.1), no PPI use, successful in hemostasis temporarily but circulatory dynamics not recovering
Death from comorbidity: 11 cases	
	Heart failure and/or ischemic heart disease: 5
	Respiratory failure and/or pneumonia: 3
	Malignancy: 1, Hepatic failure: 1, Unknown death: 1

SLE = systemic lupus erythematosus, CRF = chronic renal failure, LDA = low-dose aspirin, TAE = transcutaneous arterial embolism, INR = international normalized ratio.

combination therapy, more than 70% of patients underwent endoscopic hemostasis using this method. Soft coagulation with hemostatic forceps has been widely performed with ESD for gastric cancer, and the simplicity of the procedure likely contributed to its selection for hemostasis in these cases. The success rate of endoscopic hemostasis was 97%, including the treatment of rebleeding. Several recently updated guidelines also introduce the efficacy of soft coagulation with monopolar forceps, although the evidence level is not high.[9,11,14,15]

The time from arrival to emergency endoscopy was short (median, 98 minutes; 85% performed within 6 hours of arrival). Recently, Lau et al reported that urgent endoscopy (within 6 hours after gastroenterological consultation) was not associated with higher mortality than early endoscopy (6–24 hours after gastroenterological consultation) in patients with UGIB at high risk for further bleeding or death (GBS ≥ 12).[25] Almost all guidelines do not recommend emergency endoscopy earlier than 24 hours. However, it is better for the patient and emergency room physician to perform the examination and procedure immediately. In this study, the time from visit to examination was not different on weekends or after hours than on weekdays or business hours, with no difference in treatment outcomes. Although some studies have shown a poor prognosis in weekend UGIB,[26] this is unlikely in Japan. However, these data were obtained before the COVID-19 pandemic and the situation may change in the future. From the time of the visit to examination, 73% of all registered patients underwent CT within a short period. Although guidelines do not explicitly recommend it, pre-endoscopic CT is becoming a routine practice.

Furthermore, although this study found that 13 (5%) in-hospital deaths occurred within 4 weeks, only 2 (1%) were bleeding-related deaths. The other 11 patients were older adults (2 in their 70 seconds, 5 in their 80 seconds, and 5 in their 90 seconds) with severe comorbidities who died from exacerbation of these diseases. Patients with poor prognosis had significantly higher rates of antithrombotic drug use, prevalence of duodenal ulcer bleeding and in-hospital onset, and lower rates of PPI use than those who survived. These risk factors have been reported in previous studies to be associated with poor prognosis and refractory bleeding. We assume that the relationship between comorbidities and antithrombotic drugs has confounding factors. Therefore, we also performed multivariate analysis and found that advanced age and in-hospital onset remained significant risk factors. However, this multivariate analysis may have been statistically inaccurate because of the 6 independent variables for the 13 death events. In particular, statistically significant differences in comorbidities, which are considered important risk factors, disappeared in the multivariate analyses. One reason for this is that patients with NSAID-induced orthopedic diseases, which do not directly cause death but cause GDPU, are also considered to have comorbidities. Of the 13 deaths, 11 were due to worsening comorbidities, leaving no doubt as to the importance of the presence of comorbidities in mortality risk.

Similar to our results in the present study, previous reports have shown that in-hospital cases have poorer prognoses.[27] It is not difficult to imagine that the risk for mortality is also increased by bleeding events in the presence of comorbidities and the need for inpatient management. Recently, a registry-based study in cardiology reported that recurrent myocardial infarction and major bleeding (mostly gastrointestinal) were almost equally associated with the risk of death in patients after coronary stent insertion for acute coronary disease.[28] Hence, gastrointestinal bleeding during hospitalization for other diseases is a major risk factor for mortality. Thus, as indicated guidelines, prophylactic

Table 7

Characteristics and risk factors for patients with poor prognosis.

				Multivariate analysis		
Prognosis	**Recovering n = 233**	**Dead n = 13**	***p*-value**	**OR**	**[95% CI]**	***P*-value**
Age (yrs, median)	68	83	<.001*	1.06	1.00–1.12	*.043*
Male	155 (67%)	9 (69%)	1.000†			
Comorbidities	144 (62%)	13 (100%)	.005†	1.68	0.00–Inf	.992
NSAID use	42 (18%)	2 (15%)	1.000†			
Antithrombotic use	39 (17%)	7 (54%)	.004†	2.99	0.82–10.9	.097
PPI use	26 (11%)	5 (39%)	.014†	1.47	0.378–5.76	.576
Duodenal ulcer	69 (30%)	8 (62%)	.027†	2.79	0.771–10.1	.118
In-hospital onset	32 (14%)	7 (54%)	.001†	3.71	1.04–13.2	*.044*

NSAIDs = non-steroidal anti-inflammatory drugs.

* Mann–Whitney *U* test.

† Fisher's exact test.

Table 8

Characteristics and risk factors for patients with required hemostasis.

				Multivariate analysis		
Hemostasis	**Necessary n = 177**	**Unnecessary n = 69**	***P*-value**	**OR**	**[95% CI]**	***P*-value**
Age (yr, median)	66	75	.007*	0.99	0.97–1.01	.273
Male	124 (70%)	40 (58%)	.098†	1.62	0.86–3.05	.132
Comorbidities	106 (60%)	51 (74%)	.054†	0.71	0.36–1.40	.322
NSAIDs use	28 (16%)	16 (27%)	.242†			
Antithrombotic use	33 (19%)	13 (19%)	1.000†			
PPI	16 (9%)	15 (22%)	.013†	0.51	0.22–1.18	.113
Duodenal ulcer	45 (25%)	32 (46%)	.002†	0.42	0.23–0.77	*.005*

NSAIDs = non-steroidal anti-inflammatory drugs.

* Mann–Whitney *U* test.

† Chi-square exact test.

Table 9

Characteristics and risk factors for patients with refractory bleeding.

	Refractory bleeding			Multivariate analysis		
Required intervention n = 177	Yes n = 20	No n = 157	*P* value	OR	[95% CI]	*P*-value
Age (yr, median)	67	66	.516*			
Male	13 (65%)	111 (71%)	.791†			
Comorbidities	14 (70%)	92 (59%)	.461†			
PPI	4 (20%)	12 (8%)	.088‡	1.68	0.51–5.57	.394
NSAIDs use	5 (25%)	25 (16%)	.342‡			
Antithrombotic use	3 (15%)	30 (20%)	1.000‡			
Duodenal ulcer	8 (40%)	37 (24%)	.169†	1.40	0.53–3.66	.495

NSAIDs = non-steroidal anti-inflammatory drugs.

* Mann–Whitney *U* test.

† Chi-square exact test.

‡ Fisher's exact test.

Table 10

Result summary of primary and secondary endpoint in the risk stratification study.

Outcome	Details	Total
Hemostasis	Used	160 (78%)	205
	Not used	45 (22%)	(100%)
Refractory bleeding	Rebleeding	16 (8%)	18
	Unsuccessful endoscopic treatment	2 (1%)	(9%)
Poor prognosis	Death from comorbidity	8 (4%)	10
	Death from bleeding	2 (1%)	(5%)

Table 11

Comparison of risk scoring systems for predicting the primary endpoint.

Outcome		AIMS65	GBS	RS
Mortality	AUC	0.816	0.757	0.828
	95% CI	0.688–0.944	0.583–0.930	0.730–0.926
	Cutoff	2	13	7
	Sensitivity	0.80	0.70	0.70
	Specificity	0.68	0.70	0.82

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CRS = clinical rockall score, GBS = Glasgow-Blatchford score, RS = rockall score.

PPI administration is necessary for antithrombotic drug and NSAID users. In our study cohort, only 11% of the patients were using PPIs. In a previous study, a cohort of patients with UGIB had low PPI utilization and poor adherence to guidelines, and the adherence to PPIs for ulcer prevention in NSAIDs users was inversely associated with upper gastrointestinal ulcers and bleeding events[29]. Prevention of UGIB and related deaths with PPI administration is most important in patients with severe comorbidities, especially older patients, who are using antithrombotic agents or other drugs that cause GDPUs.

It has become common knowledge that bleeding events in patients taking antithrombotic agents predisposec them to not only bleeding-related death, but also death from thrombotic events due to the discontinuation of antithrombotic drugs.[30] There is increasing evidence that older age (>75 years) is the most significant risk factor for UGIB and bleeding-related mortality in patients on long-term antiplatelet medications.[31] More attention must be paid to managing patients with UGIB on antithrombotic agents, particularly older patients. In contrast, there are reports that patients with UGIB taking antiplatelet medications have a lower risk of hemostatic procedures.[32] However, as mentioned above, it is important to remember that patients taking antiplatelet agents have severe comorbidities such as cardiovascular and cerebrovascular diseases and that bleeding events and subsequent withdrawal of antiplatelet agents ultimately lead to mortality risk. In recent years, the use of antithrombotic drugs has been identified as an important risk factor for postoperative bleeding after ESD for gastric cancer.[33] Post-procedural bleeding that occurs despite adequate hemostasis and vascularization during the endoscopic procedure is similar to rebleeding after hemostasis of UGIB; therefore, caution is warranted in antithrombotic drug users.

With regard to the need for endoscopic procedures, the hemostatic procedural rate was significantly lower for duodenal ulcers in the multivariate analysis. Conversely, duodenal ulcer was a risk factor for death, albeit only in univariate analysis. In individual cases, all patients with duodenal ulcers who died were treated with hemostasis. We found no significant risk factors, including age, comorbidities, or concomitant administration of antithrombotic agents, in patients with refractory bleeding. The results of endoscopic hemostasis have improved considerably in recent years, and the results of our study, as described above, are very satisfactory.

In the risk stratification study, both AIMS65 and RS had an AUC of 0.8 or higher, which is considered useful for mortality risk assessment, and there was no difference in the prediction of mortality (primary endpoint). To stratify the mortality risk, AIMS65, which consists of 5 simple items that can be calculated without information on comorbidities, is the simplest system, and its use has been recommended by previous studies.[2,23,24] During this study, the cutoff value was calculated as 2 points. Patients with a score of 3 or more points were considered to be at higher risk for mortality. Although many guidelines recommend risk stratification by GBS and RS, the calculations were complex and difficult to use in emergency situations. In fact, a survey in the United States found that 53% of physicians had heard of UGIB risk scoring systems, but only 30% had used them.[34] However, we believe that AIMS65, which can be easily calculated with only 5 clinical data, is very suitable for assessing the risk of early mortality in UGIB, and is recommended in updated guidelines.[9,11,15]

The GBS was significantly better able to predict the need for treatment intervention, despite the higher proportion of hemostatic treatment required because of our study design. The GBS was originally developed as a risk stratification score to predict the need for emergency endoscopy and treatment, and its usefulness was confirmed during this study. Similar results have been reported by several large prospective studies.[35] *Almost all guidelines state that a GBS score of 0 to 1 does not require emergency endoscopy and can be managed on an outpatient basis.* However, patients with a GBS score of 0-1 represent a small proportion of UGIB patients, and the sensitivity is high but the specificity is low. Although the cutoff value in our study cohort was 9 points, as indicated in the aforementioned paper,[26] we

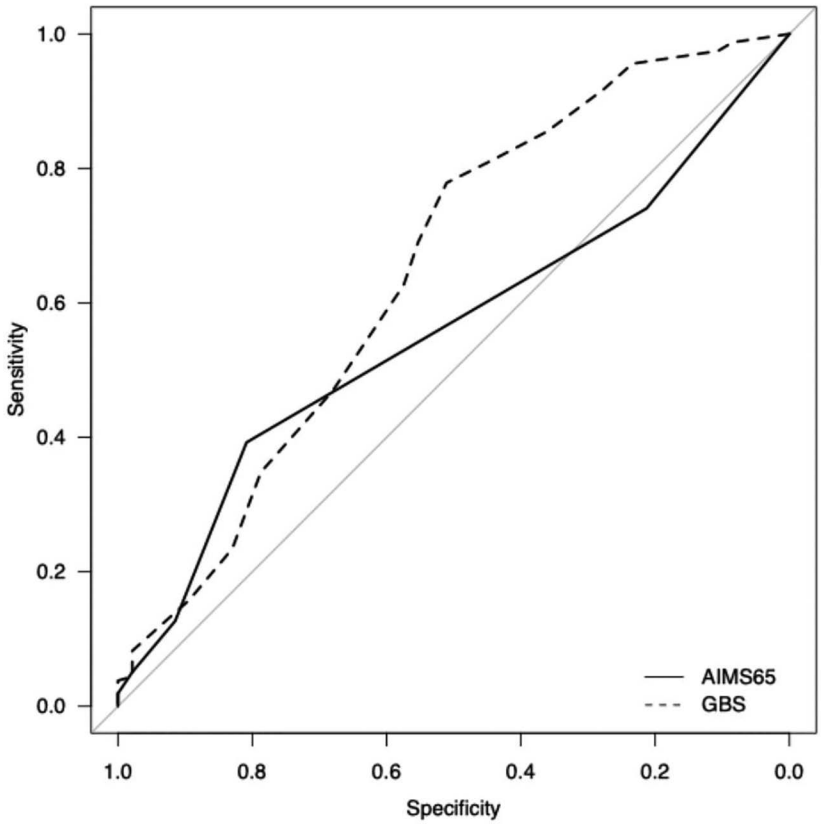

Figure 2. Comparison of the AUC between AIMS65 and GBS for predicting the requirement for hemostasis. GBS = Glasgow-Blatchford score.

Table 12

Comparison of risk scoring systems in predicting the secondary endpoints.

Outcome		AIMS65	GBS	RS
Require hemostasis	AUC	0.557	0.648	N/A
	95% CI	0.474–0.638	0.552–0.745	
	Cutoff	2	9	
	Sensitivity	0.39	0.78	
	Specificity	0.81	0.51	
Refractory bleeding	AUC	0.675	0.668	0.641
	95% CI	0.537–0.813	0.506–0.829	0.480–0.802
	Cutoff	3	15	7
	Sensitivity	0.38	0.44	0.50
	Specificity	0.91	0.88	0.83

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CRS = clinical rockall score, GBS = Glasgow-Blatchford score, RS = rockall score.

believe that it is difficult to determine from GBS alone whether to immediately perform an emergency endoscopy.

Although the strength of this study is its multicenter, prospective design with various features, it has some limitations. First, the number of patients was small. We included patients with UGIB with evident hematemesis or melena. Furthermore, the target disease was gastrointestinal ulcers and not all non-variceal UGIB. As mentioned previously, bleeding from gastroduodenal ulcers has decreased in clinical practice. The mortality rate was 5%, which is less than that in previous reports; the number of deaths was only 13, which may not have been sufficient for statistical analysis. Second, even though *H pylori* infection status is an important and rudimentary item, it was only examined in approximately 80% of the patients in this study. However, the incidence of peptic ulcers is decreasing owing to a reduction in the global rate of *H pylori* infection. In Japan, the number of patients with *H pylori* eradication has increased following insurance coverage. We expect that UGIB secondary to GDPU will decrease, and that idiopathic ulcers without *H pylori* infection or concomitant drug use will increase. The population in our study area was small, and further studies covering a wider area (including facilities in urban areas) with a longer observation period are required.

In conclusion, the prognosis of UGIB is poor in older patients with severe comorbidities, especially in-hospital onset. We recommend that patients with UGIB should undergo early risk stratification using a risk scoring system. In these high-risk patients and those on antithrombotic therapy, PPIs should be administered as prophylaxis to prevent GDPU-induced bleeding events.

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