Clinical Characteristics, Treatment Outcomes and Risk Assessment of Patients with Acute Upper Gastrointestinal Bleeding in Rajavithi Hospital, Thailand

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Background: *Acute upper gastrointestinal bleeding (UGIB) is common and carries significant morbidity worldwide. Effective risk assessment for UGIB is required in order to deliver the optimal therapeutic plans.*
Objectives: *To describe clinical characteristics and treatment outcomes of acute UGIB in Thailand and to evaluate predictors for rebleeding and complications.*
Material and Method: *Consecutive patients with acute UGIB who underwent esophagogastroduodenoscopy at Rajavithi Hospital, Bangkok, between 2012 and 2015 were retrospectively analyzed. Important clinical data, endoscopic findings and hospital course were reviewed. Multivariate analysis was performed to identify the predictors of rebleeding and complications within 4 weeks.*
Results: *286 patients were included of whom 180 were non-variceal UGIB (NVUGIB) and 106 were variceal UGIB (VUGIB). Males accounted for 71.7% of participants and had amean age of 53.6 years. Of patients with NVUGIB, 43.4% were taking NSAIDs/ASA, and the most common causes of bleeding were peptic ulcers (62.8%) and gastritis (32.2%). All patients with VUGIB had cirrhosis, and 54.7% were Child-Pugh B/C. When compared to NVUGB, patients with VUGIB were more likely to have active bleeding on presentation, longer prothrombin time, and lower serum albumin and platelet counts. Endoscopic treatments were more commonly performed in VUGIB patients than in NVUGI Bones (62.3% vs. 20.6%, p<0.001). The overall rebleed in grate was 7.3% and mortality was 1%; with no significant difference between NVUGIB and VUGIB. Hospital complications (39.6% vs. 11.7%, p<0.001) and units of blood transfusion (1.85 vs. 1.46 units, p<0.001) were significantly higher in patients with VUGIB than in those with NVUGIB. In the NVUGIB cohort, lower serum sodium and bleeding from duodenal ulcers were independent predictors of rebleeding, where as female gender, hemodynamic instability, and rebleeding were independent predictors of complications. In the VUGIB cohort, lower platelet count was an independent predictor of rebleeding, and lower serum sodium was an independent predictor of complications. Based on the AIMS65 system, the overall rebleeding rates were 5.3% (8/151), 7.0% (6/86), 18.2% (6/33), 7.1% (1/14), 0% (0/1) and 0% (0/1), and complication rates were 9.3% (14/151), 23.2% (20/86), 48.5% (16/33), 78.6% (11/14), 100% (1/1) and 100% (1/1), corresponding to the AIMS65 score of 0, 1, 2, 3, 4 and 5 respectively.*
Conclusion: *The overall outcomes of UGIB were good, with better outcomes in NVUGIB than in VUGIB. AIMS65 score and serum sodium may be useful in predicting rebleeding and complications in UGIB.*

Keywords: *Upper gastrointestinal bleeding, UGIB, Gastrointestinal hemorrhage, Peptic ulcers, Esophageal varices, Predictors, AIMS65 score, Rebleeding, Complications*

J Med Assoc Thai 2017; 100 (Suppl. 1): S104-S115
Full text. e-Journal: *http://www.jmatonline.com*

Acute upper gastrointestinal bleeding (UGIB) is one of the most common, important and urgent worldwide problems treated by gastroenterologists[1,2]. In Thailand nationwide, the hospitalization incidence rate of UGIB has been put at 166.3 admissions per 100,000 population, and the hospitalization incidence rates of non-variceal UGIB (NVUGIB) and variceal UGIB (VUGIB) have been found to be 152.9 and 13.5 admissions per 100,000 population respectively[3]. Endoscopic therapies and proton pump inhibitors (PPIs) are currently cornerstones in the management of UGIB, and both of these treatments

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have been shown to reduce mortality and morbidity related to UGIB[1,2,4-6]. The role of emergency surgery has continued to diminish, while radiological intervention has increasingly been used in patients with severe and recurrent bleeding who do not respond to endoscopic treatment. Despite these advances, morbidity and mortality from UGIB have remained considerable (mortality around 10%)[1-6]; thus, the cost of UGIB treatment ishigh, placing a significant burden on large-scale healthcare resources[3].

Effective risk assessment for acute UGIB is important and plays a keyrole in preparingoptimal individualized therapeutic plans, taking into account such aspects as the degree of resuscitation/monitoring and the timing for esophagogastroduodenoscopy (EGD)[6]. Several clinical predictors and scoring systems have been proposed to predict the outcomes of UGIB in terms of rebleeding and complications. Age, comorbidity, hemodynamic instability, diagnosis, admission hemoglobin level, presentation, bleeding from esophageal varices, ulcer size, stigmata of recent hemorrhage, and blood transfusion requirements have all been described as significant risk factors for further bleeding and death[1,2,6-8]. Rockall score (introduced in 1996) and Glasgow-Blatchford score (first used in 2000) are accurate in predicting outcomes in patients with NVUGIB, but they are quite complex and difficult in bedside use[7,8]. A more recently proposed scoring system, AIMS65, has been found to be a simple, accurate risk score for predicting in-hospital mortality, length of hospital stay (LOS) and treatment cost in UGIB[9-11].

It is known that the clinical characteristics and outcomes of UGIB can vary according to geographical areas, local practice guidelines and medical facilities. For example, the causes of peptic ulcer disease in Thailand are mainly *Helicobacter pylori*, similarly to those of other countries in East Asia, whereas in Western countries, the prevalence of *H. pylori*-related peptic ulcersis relatively lower, with an increasing incidence of peptic ulcers resulting from the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin (ASA)[12,13]. In addition, a meta-analysis from Leontiadis et al reported that PPI therapy for peptic ulcer bleeding was more efficacious in Asia than elsewhere[5]. This may be because of an enhanced pharmacodynamic effect of PPI in Asian patients due to their more favorable CYP2C19 polymorphisms (less rapid metabolizers) and lower parietal cell mass compared to those of Caucasians[5,14].

Although several studies from Asian countries have reported the characteristics and outcomes of patients with UGIB, comprehensive data from Thailand is very limited[3,10,15]; thus, even among Asian countries, the characteristics and outcomes may be country-specific. Therefore, this study aimed to evaluate the clinical characteristics and outcomes of patients with UGIB (both NVUGIB and VUGIB) in Thailand, and potentially associated factors. The efficacy of AIMS65 score in predicting rebleeding and complications of UGIB was also evaluated.

Material and Method

Study population

This retrospective analytical study was conducted at the Department of Internal Medicine, Rajavithi Hospital, which is a tertiary care hospital in Bangkok and also the largest referral hospital of the Ministry of Public Health of Thailand, responsible mainly for the central regions of Thailand.The protocol of this research was reviewed and approved by the Ethics Committee of Rajavithi Hospital (No. 084/2559). All consecutive adult patients who presented with acute UGIB (e.g. hematemesis, coffee-ground vomiting, melena or hematochezia) and underwent EGD between January 2013 and January 2016 were included in thestudy. Exclusion criteria were acute life-threatening medical condition (e.g. acute myocardial infarction, acute renal or liver failure) atthe same time as UGIB, known advanced-stage malignancy, or inadequate available data for analysis.

General management of acute UGIB

Patients who presented with acute UGIB at Rajavithi Hospital were given initial resuscitation followed by diagnostic and therapeutic measures according to the International Consensus Guidelines[6,16]. Empiric therapy using an intravenous PPI was given before EGD for suspected peptic ulcer bleeding, whereas an intravenous vasoactive agent (e.g. somatostatin analogue, octreotide, or terlipressin) was given where there was suspicion of variceal bleeding. Intravenous prokinetic agents, such as metoclopramide and erythromycin prior to EGD were not given routinely in our center. EGD was performed on all patients hospitalized with acute UGIB by 5 experienced GI staff and GI fellows (under direct supervision of GI staff), except in cases where they were contraindicated. Early EGD in the first 24 hours after admission was performed on patients with signs of ongoing bleeding. For those with NVUGIB, endoscopic treatment was given in the form of injection

therapy with epinephrine, coaptive thermocoagulation, hemostatic clip, hemostatic spray or combination therapy in patients with active bleeding, non-bleeding visible vessels (NBVV) oradherent clots. High-dose PPI was administered by infusion for 72 hours after EGD in patients who received endoscopic intervention. Bleeding esophageal and gastric varices were typically treated with band ligation and cyanoacrylate injection respectively in addition to the use of vasoactive agents and intravenous antibiotics. The decision on whether to perform blood transfusion varied according to physicians' discretion. In general, a blood transfusion was given to patients with signs of ongoing bleeding, especially if they had instability of vital signs or anemic symptoms, or if hemoglobin was regularly raised to >7-8 mg/dL before EGD; however, transfusion strategies varied among individual caring physicians and GI staff. After the procedure, the patients were subsequently transferred toa medical ward for monitoring. Endoscopy was repeated in the event of rebleeding, and surgical or radio interventional consultation were performed often if bleeding persisted or if rebleeding occurred after two therapeutic endoscopies.

Clinical, endoscopic and laboratory data

Medical records and an endoscopy database of all patients were reviewed. Patient demographics, clinical presentations, initial vital signs, presence of comorbid conditions, medications taken at the time of admission and initial laboratory tests were obtained. We abstracted data describing endoscopic management, including endoscopic diagnosis and the presence of stigmata of recent bleeding, endoscopic hemostasis, and medication use following EGD. Outcome data were collected describing the overall course of treatment within 30 days after the initial EGD with specific attention to rebleeding, the need for surgery or radiological intervention, requirement for packed red blood cells (PRC) transfusion, LOS, in-hospital complications and mortality. The presence of hemodynamic instability was defined as systolic blood pressure (SBP) <100 mmHg, a heart rate (HR) >100 beats/min and/or orthostatic changes in SBP (a decrease of >10%) or HR (an increase of >10%) between a supine and seated position. Rebleeding was defined as the presence of hematemesis or melena with signs of hemodynamic instability or a decrease in hemoglobin level >2 g/dL in a previously stable patient. In-hospital complications were defined as the development of shock, organ(s) failure and/or sepsis during admission. The AIMS65 scoring system is composed of age (cut-off >65 years), serum albumin (cut-off <3.0 g/dL), SBP (cut-off <90 mmHg) and prothromb in time (cut-off INR >1.5), and a score of 2 has been indicated as a cut-off value for mortality risk[9]. Endoscopic grading of ulcer lesions was categorized according to Forrest's classification. Stigmata of recent bleeding included arterial spurting or pulsatile bleeding from the ulcer base, a non-bleeding visible vessel (NBVV), or an adherent clot covering the base of an ulcer. All endoscopic reports were reviewed by an experienced GI staff member (Bunchorntavakul C).

Statistical analysis

Data were summarized using descriptive statistics. Continuous variables were compared using the t-test or the Mann-Whitney U test. Categorical variables were compared using the χ^2 or Fisher exact test. The Kaplan-Meier method with the log-rank test was used to compare differences in the rates of rebleeding and complications in the 30 days after initial EGD. Binary logistic regression and Cox's regression analyses were used to detect possible prognostic variables on recurrent bleeding and complications, presented as Odds ratio (OR). Data analyses were performed using the SPSS version 21.0 (SPSS Inc. Chicago IL, USA) and STATA 11.0, with a conventional significance 2-tailed α level of 0.05.

Results

Patient characteristics

A total of 286 patients (205 men and 81 women) with acute UGIB were identified, of which 180 were non-variceal UGIB (NVUGIB) and 106 were variceal UGIB (VUGIB). The mean age was 53.59$\pm$15.17 years, and 68 patients (23.8%) were $\geq$65 years of age. All patients with VUGIB had underlying cirrhosis, and 45.3%, 29.2%, and 25.5% were Child-Pugh class A, B and C respectively. The most common etiologies of cirrhosis were alcohol (57.5%) and viral hepatitis (34%). Among patients with NVUGIB, 20.6%, 22.8%, and 2.2% were taking NSAIDs, ASA and anticoagulants respectively.

The demographic and clinical characteristics of the entire patient groupand each of the NVUGIB and VUGIB groups are summarized in Table 1. Patients with NVUGIB were more likely to be $\geq$65 years of age, female, and have medical comorbidities (e.g. diabetes, hypertension, dyslipidemia, cardiovascular and chronic kidney disease), compared to those with VUGIB. Patients with VUGIB were more likely to present with

Table 1. Demographic and clinical characteristics of patients with UGIB

Characteristics	Total (n = 286)	NVUGIB (n = 180)	VUGIB (n = 106)	*p*-value
Age, years	53.59±15.17	54.68±17.06	51.75±11.08	0.079
Age ≥65 years	68 (23.8%)	58 (32.2%)	10 (9.4%)	<0.001*
Male gender	205 (71.7%)	118 (65.6%)	87 (82.1%)	0.003*
Comorbidities DM	54 (18.9%)	43 (23.9%)	11 (10.4%)	0.005*
HT	128 (44.8%)	119 (66.1%)	9 (8.5%)	<0.001*
DLP	55 (19.2%)	54 (30%)	1 (0.9%)	<0.001*
CKD	28 (9.8%)	25 (13.9%)	3 (2.8%)	0.002*
CAD	16 (5.6%)	16 (8.9%)	0 (0%)	0.001*
HCC	16 (5.6%)	0 (0%)	16 (15.1%)	<0.001*
Presence of cirrhosis	10 (3.5%)	10 (5.6%)	106 (100%)	<0.001*
Etiology of cirrhosis:				
Alcohol/viral/NASH/others	NA	NA	61/36/6/3	NA
Child-Pugh classification:				
Class A/B/C	NA	NA	48/31/27	NA
Presence of ascites:				
None/mild-moderate/marked	NA	NA	32/51/23	NA
Medications:				
NSAIDs/ASA/anticoagulants	NA	37/41/4	NA	NA
Presenting symptoms				
Hematemesis	134 (46.9%)	72 (40%)	62 (58.5%)	0.003*
Melena	126 (44.1%)	102 (56.7%)	24 (22.6%)	<0.001*
Hematochezia	26 (9.1%)	6 (3.3%)	20 (18.9%)	<0.001*
Stool appearance				
Hematochezia	18 (6.3%)	2 (1.1%)	16 (15.1%)	<0.001*
Melena	254 (88.8%)	165 (91.7%)	89 (84%)	0.053
Yellowish/greenish	14 (4.9%)	13 (7.2%)	1 (0.9%)	0.021*
NG findings				
Fresh blood	73 (25.5%)	20 (11.1%)	53 (50%)	<0.001*
Coffee-ground content	199 (69.6%)	151 (83.9%)	48 (45.3%)	<0.001*
Clear	14 (4.9%)	9 (5%)	5 (4.7%)	>0.99
HD instability	32 (11.2%)	15 (8.3%)	17 (16%)	0.053

Values are represented as n (%), Mean ± SD, and Median (IQR). * = Significant at $p<0.05$. A *p*-value corresponds to Chi-square test (categorical data), t-test and Mann-Whitney U (continuous data).
DM = diabetes mellitus; HT = hypertension; DLP = dyslipidemia; CKD = chronic kidney disease; CAD = coronary artery disease; HCC = hepatocellular carcinoma; NASH = non-alcoholic steatohepatitis; NG = nasogastric lavage; NSAIDs = non-steroidal anti-inflammatory drugs; ASA = aspirin; HD = hemodynamics

hematemesis and hematochezia. On initial evaluations, patients with VUGIB were more likely to have fresh blood on NG lavage and hematochezia, with a trend towardshigher incidence of hemodynamics instability compared to those with NVUGIB.

Endoscopic and laboratory findings

Endoscopic and laboratory findings are summarized in Table 2. Initial hemoglobin levels did not differ between patients with NVUGIB and VUGIB, but those with VUGIB were more likely to have lower platelet counts, lower serum albumin and longer prothromb in time. Among patients with NVUGIB, 113/180 (62.8%) patients had peptic ulcer bleeding (88 gastric ulcer and 25 duodenal ulcer) and 29/113 patients (25.6%) had high-risk stigmata of rebleeding.

Treatment and outcomes

Treatment and outcomes of patients with UGIB are summarized in Table 3. Endoscopic treatments

Table 2. Laboratory and endoscopic findings of patients with UGIB

Variables	Total (n = 286)	NVUGIB (n = 180)	VUGIB (n = 106)	*p*-value
Hemoglobins, mg/dL	8.46±1.95	8.42±1.48	8.53±2.57	0.693
Platelets, cells/mm^3	223,227±109,624	276,911±89,211	132,066±75,640	<0.001*
Median (IQR)	217,500 (139,000 to 307,000)	280,000 (198,500 to 324,000)	111,500 (78,000 to 163,000)	<0.001*
Serum creatinine, mg/dL	1.09±0.51	1.11±0.42	1.04±0.63	0.266
Serum sodium, mEq/L	136.13±9.24	136.9±11.04	134.83±4.68	0.068
PT, seconds	14.19±5.5	12.43±3.74	17.2±6.61	<0.001*
Serum albumin, g/dL	3.38±1.46	3.55±0.59	3.09±2.25	0.041*
Median (IQR)	3.45 (2.9-3.9)	3.7 (3.3-3.9)	2.9 (2.4-3.3)	<0.001*
Endoscopic findings		GU: 88 (48.9%) DU: 25 (13.9%) Gastritis: 58(32.2%) MW tear: 7 (3.9%) Dieulafoy: 2 (1.1%)	EV: 97 (91.5%) GV: 9 (8.5%)	NA
Bleeding stigmata of PUD and EV/GV		Active: 2 (1.8%) NBVV: 23 (20.4%) Adherent clot: 4 (3.5%) Clean: 84 (74.3%)	Nipple: 32 (30.2%) Red wale: 55 (51.9%) No: 19 (17.9%)	NA

Values are presented as n (%), Mean ± SD, and Median (IQR). *p*-value corresponds to Chi-square test (categorical data), t-test and Mann-Whitney U(continuous data). * = Significant at $p<0.05$.
PT = prothrombin time; PUD = peptic ulcer disease; EV = esophageal varices; GV = gastric varices

were more commonly performed in patients with VUGIB when compared to NVUGIB (62.3% vs. 20.6% respectively, $p<0.001$). The overall rebleeding rate was 7.3%, with no significant difference between patients with NVUGIB and VUGIB (Fig. 2). The median time to rebleeding was 5 days after the initial EGD and all rebleeding episodes were successfully treated by repeat endoscopic therapy. During the 30-day period, one patient with NVUGIB died from acute myocardial infarction and two patients with VUGIB died from sepsis and acute renal failure. There was no need for surgery or radiological intervention during the study period. Patients with VUGIB were more likely to have more units of PRC transfusion, higher rates of in-hospital complications, and longer LOS compared to those with NVUGIB.

Rebleeding and complications according to AIMS65 scores

According to AIMS65 scores, the majority of patients were classified as low-to-moderate risk of mortality: 81.1% (232/286) had scores of 0-1 and 17.1% (49/286) had scores of 2-5. The mean AIMS65 score of the entire UGIB population was 0.71±0.92, and was significantly higher in patients with VUGIB than in those with NVGIB (1.17±1.11 vs. 0.44±0.65 respectively, $p<0.001$). Overall, the rebleeding rates of the entire population were 5.3% (8/151), 7.0% (6/86), 18.2% (6/33), 7.1% (1/14), 0% (0/1) and 0% (0/1), and the complication rates were 9.3% (14/151), 23.2% (20/86), 48.5% (16/33), 78.6% (11/14), 100% (1/1) and 100% (1/1), corresponding to the AIMS65 score of 0, 1, 2, 3, 4 and 5 respectively. Rebleeding and complications in patients with NVUGIB and VUGIB according to AIMS65 scores are shown in Fig. 2.

Prognostic factors for rebleeding and complications

Univariate analysis revealed that an increased risk of rebleeding in patients with NVUGIB was significantly associated with the presence of hematemesis ($p = 0.048$) and hemodynamic instability at presentation ($p<0.001$), presence of fresh blood on nasogastric lavage ($p = 0.005$), lower serum sodium ($p = 0.002$), albumin ($p = 0.003$), platelet count ($p = 0.049$), bleeding from duodenal ulcers ($p = 0.036$), presence of NBVV at the ulcer base ($p = 0.025$), requirement for endoscopic treatment ($p = 0.001$) and PRC transfusion ($p = 0.007$). Multivariate analysis, indicated that lower

Table 3. Treatment and outcomes of patients with UGIB

Variables	Total (n = 286)	NVUGIB (n = 180)	VUGIB (n = 106)	*p*-value
Endoscopic treatment	103 (36%)	37 (20.6%)	66 (62.3%)	<0.001*
Endoscopic treatment methods		Heat ± injections: 27 (15%) Clips: 20 (11.1%) APC: 19 (10.6%)	EVL: 45 (42.5%) EVS: 5 (4.7%) Glue: 18 (17%)	NA
Pharmacologic treatment				
PPIs	283 (99%)	180 (100%)	103 (97.2%)	0.050
Somatostatin analogs	97 (33.9%)	0	97 (91.5%)	NA
Terlipressin	3 (1%)	0	3 (2.8%)	NA
PRC transfusion	225 (78.7%)	139 (77.2%)	86 (81.1%)	0.459
Mean, units	1.85±1.56	1.46±1.13	2.5±1.93	<0.001*
Median (IQR), units	2 (1-3)	1 (1-2)	2 (1-4)	<0.001*
In-hospital complications	63 (22%)	21 (11.7%) Shock: 2 (1.1%) Resp failure: 4 (2.2%) ARF: 17 (9.4%)	42 (39.6%) Infections: 20 (18.9%) HE: 17 (16.0%) ARF: 14 (13.2%) SBP: 12 (11.3%) Resp failure: 10 (9.4%) Shock: 5 (4.7%)	<0.001*
Rebleeding	21 (7.3%)	13 (7.2%)	8 (7.5%)	>0.99
Days of rebleeding, days after an initial endoscopy				
Mean ± SD	6.66±5.52	6.24±5.06	7.36±6.17	0.099
Median (IQR)	5 (3 to 7)	4 (3 to 7)	5 (4 to 9)	0.037*
Length of stay, days				
Mean ± SD	7.63±7.75	7.36±7.09	8.08±8.78	<0.001*
Median (IQR)	5 (3 to 9)	5 (3 to 10)	5 (4 to 9)	0.320

Values presented as number (%), Mean ± SD, and Median (IQR). * = significant at $p<0.05$
A *p*-value corresponds to Chi-square test (categorical data), t-test and Mann-Whitney U (continuous data).
PPI = proton-pump inhibitors; PRC = packed red blood cells; APC = argon plasma coagulation; EVL = endoscopic variceal ligation; EVS = endoscopic variceal sclerotherapy; HE = hepatic encephalopathy; ARF = acute renal failure; SBP = spontaneous bacterial peritonitis

serum sodium ($p = 0.003$) and bleeding from duodenal ulcers ($p = 0.042$) remained significantly associated with rebleeding (Tables 4 and 6).

Univariate analysis revealed that an increased risk of complications in patients with NVUGIB was significantly associated with female gender ($p = 0.007$), the presence of hemodynamic instability at presentation ($p<0.001$), lower hemoglobin levels ($p = 0.002$), lower serum albumin ($p<0.001$), higher serum creatinine ($p = 0.004$), higher AMIS65 scores ($p = 0.009$), presence of NBVV ($p = 0.005$) and adherent clot at the ulcer base ($p = 0.040$), requirement for endoscopic treatment ($p<0.001$) and PRC transfusion ($p<0.001$), and the occurrence of rebleeding ($p<0.001$). Multivariate analysis found that female gender ($p = 0.023$), presence of hemodynamic instability at presentation ($p = 0.042$), and the occurrence of rebleeding ($p = 0.047$) remained significantly associated with in-hospital complications (Tables 4 and 6).

According to univariate analysis, an increased risk of rebleeding in patients with VUGIB was significantly associated with lower platelet count ($p<0.001$), bleeding from gastric varices ($p = 0.011$) and the use of terlipression ($p = 0.035$), while multivariate

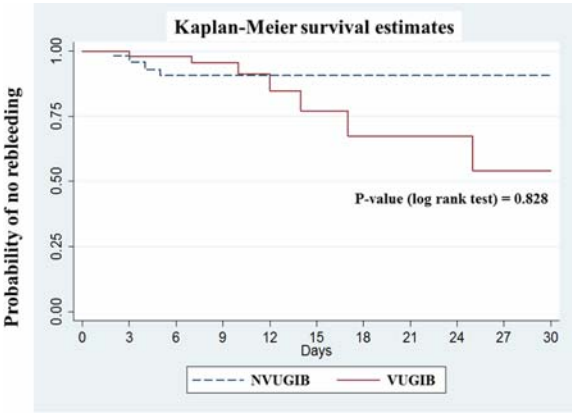

Fig. 1 Kaplan-Meier estimates of the likelihood that bleeding would not recur within 30 days in the NVUGIB and the VUGIB cohorts.

AIMS score	N	NVUGIB				N	VUGIB			
		Rebleeding		Complications			Rebleeding		Complications	
		n	YES %	n	YES %		n	YES %	n	YES %
0	115	7	6.1%	10	8.7%	36	1	2.8%	4	11.1%
1	53	3	5.7%	6	11.3%	33	3	9.1%	14	42.4%
2	10	3	30.0%	4	40.0%	23	3	13.0%	12	52.2%
3	2	0	0%	1	50.0%	12	1	8.3%	10	83.3%
4	0	0	0%	0	0%	1	0	0%	1	100.0%
5	0	0	0%	0	0%	1	0	0%	1	100.0%

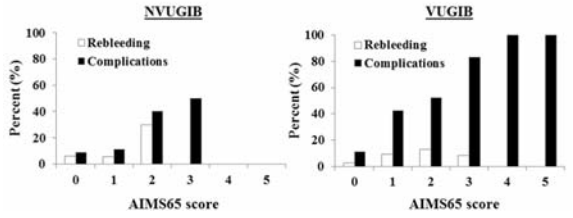

Fig. 2 Rebleeding and complications of patients with NVUGIB and VUGIB according to the AIMS65 scoring system.

Table 4. Univariate analysis: odds ratios (OR) for rebleeding and complications in patients with NVUGIB

Variables	Rebleeding		Complications	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age >60 years	0.34 (0.09 to 1.24)	0.102	0.78 (0.31 to 1.99)	0.607
Female gender	2.26 (0.76 to 6.73)	0.142	3.65 (1.42 to 9.37)	0.007*
ASA	0.55 (0.12 to 2.50)	0.443	1.84 (0.69 to 4.91)	0.225
Presenting with hematemesis	3.29 (1.01-10.68)	0.048*	2.20 (0.88 to 5.53)	0.094
Presenting with melena	0.23 (0.06 to 0.83)	0.025*	0.43 (0.17 to 1.09)	0.074
NG: fresh blood	4.92 (1.61 to 15.04)	0.005*	3.00 (0.96 to 9.35)	0.058
NG: coffee-ground	0.20 (0.07 to 0.60)	0.004*	0.32 (0.09 to 1.10)	0.071
HD unstable	10.65 (3.57 to 31.78)	<0.001*	19.13 (5.83 to 62.77)	<0.001*
Hemoglobin	0.67 (0.44 to 1.03)	0.067	0.55 (0.38 to 0.80)	0.002*
Platelets	1.00 (1.00 to 1.00)	0.049*	1.00 (1.00 to 1.00)	0.050
Serum creatinine	1.52 (0.67 to 3.42)	0.313	5.44 (1.70 to 17.39)	0.004*
Serum sodium	0.98 (0.96 to 0.99)	0.002*	1.01 (0.95 to 1.07)	0.802
PT	1.02 (0.94 to 1.11)	0.652	1.21 (0.97 to 1.50)	0.089
Serum albumin	0.43 (0.25 to 0.75)	0.003*	0.28 (0.14 to 0.53)	<0.001*
AIMS65	1.60 (0.81 to 3.16)	0.180	2.23 (1.23 to 4.05)	0.009*
DU	3.30 (1.08 to 10.11)	0.036*	0.82 (0.22 to 2.96)	0.756
Ulcer base: NBVV	3.60 (1.18 to 11.06)	0.025*	4.47 (1.57 to 12.70)	0.005*
Ulcer base: Adherent clot	3.47 (0.45 to 26.69)	0.232	8.26 (1.10 to 62.10)	0.040*
PRC	1.91 (1.20 to 3.04)	0.007*	2.14 (1.40 to 3.27)	<0.001*
Endoscopic treatment	5.39 (1.76 to 16.55)	0.001*	7.15 (2.73 to 18.74)	<0.001*
LOS	1.05 (1.02 to 1.08)	0.002*	1.08 (1.02 to 1.15)	0.008*
Rebleeding	NA	NA	18.95 (5.42 to 66.33)	<0.001*

* = significant at $p<0.05$

ASA = aspirin; NG = nasogastric lavage; HD = hemodynamics; PPI = proton-pump inhibitors; PT = prothrombin time; DU = duodenal ulcers; NBVV = non-bleeding visible vessels; PRC = packed red blood cells; LOS = length of hospital stay

analysis found that lower platelet count (p = 0.002) remained significantly associated with rebleeding (Table 5 and 6).

Univariate analysis found that an increased risk of complications in patients with VUGIB was significantly associated with the presence of marked

Table 5. Univariate analysis: odds ratios (OR) for rebleeding and complications in patients with VUGIB

Variables	Rebleeding		Complications	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age >60 years	1.69 (0.34 to 8.50)	0.526	1.23 (0.48 to 3.12)	0.669
Child-Pugh class C	1.00 (0.01 to 1.00)	0.946	2.41 (0.99 to 5.86)	0.053
Ascites: none	0.03 (0.00 to 1.00)	0.353	0.39 (0.16 to 0.99)	0.046*
Ascites: marked	0.98 (0.22 to 4.47)	0.980	5.01 (1.84 to 13.65)	0.002*
Presenting with hematemesis	1.61 (0.36 to 7.15)	0.531	0.29 (0.12 to 0.65)	0.003*
Presence of hematochezia	0.04 (0.00 to 1.00)	0.546	4.83 (1.68 to 13.91)	0.003*
HD unstable	1.99 (0.37 to 10.60)	0.422	10.17 (2.70 to 38.24)	0.001*
Hemoglobin	0.92 (0.69 to 1.23)	0.576	0.90 (0.77 to 1.06)	0.198
Platelets	1.00 (1.00 to 1.00)	<0.001*	1.00 (1.00 to 1.00)	0.745
Serum creatinine	0.70 (0.27 to 1.85)	0.472	4.52 (1.47 to 13.89)	0.009*
Serum sodium	0.95 (0.81 to 1.10)	0.522	0.82 (0.74 to 0.91)	<0.001*
PT	0.98 (0.84 to 1.14)	0.807	1.20 (1.07 to 1.34)	0.002*
Serum albumin	0.72 (0.20 to 2.62)	0.618	0.99 (0.83 to 1.18)	0.902
AIMS65	0.78 (0.40 to 1.50)	0.449	2.99 (1.85 to 4.82)	<0.001*
Bleeding from GV	0.05 (0.01 to 1.00)	0.011*	1.24 (0.31 to 4.92)	0.773
PRC	1.12 (0.79 to 1.58)	0.532	1.67 (1.30 to 2.15)	<0.001*
Terlipressin	13.54 (1.21 to 151.69)	0.035*	3.15 (0.28 to 35.89)	0.355
Endoscopic treatment	0.73 (0.18 to 2.95)	0.659	1.04 (0.47 to 2.32)	0.920
LOS	0.96 (0.90 to 1.02)	0.220	1.50 (1.24 to 1.81)	<0.001*
Rebleeding	NA	NA	2.75 (0.62 to 12.17)	0.183

HD = hemodynamics; PT = prothrombin time; GV = gastric varices; PRC = packed red blood cells; LOS = length of hospital stay

Table 6. Multivariate analysis: odds ratios (OR) for rebleeding and complications in patients with NVUIGB and VUGIB

NVUGIB			
Rebleeding		Complications	
Variables	OR (95% CI); *p*-value	Variables	OR (95% CI); *p*-value
Serum sodium	0.95 (0.91 to 0.98); $p = 0.003$	Female	6.16 (1.28 to 29.55); $p = 0.023$
DU	14.27 (1.11 to 183.95); $p = 0.042$	HD unstable	6.483 (1.07 to 39.12); $p = 0.042$
		Rebleeding	5.65 (1.03 to 31.13); $p = 0.047$
VUGIB			
Rebleeding		Complications	
Variables	OR (95% CI); *p*-value	Variables	OR (95%CI); *p*-value
Platelets	1.00 (1.00 to 1.00); $p = 0.002$	Serum sodium	0.86 (0.75 to 0.99); $p = 0.039$

DU = duodenal ulcers; HD = hemodynamics

ascites ($p = 0.002$), hematemesis ($p = 0.003$), hematochezia and hemodynamic instability at presentation ($p = 0.001$), lower serum sodium ($p<0.001$), higherserum creatinine ($p = 0.009$), higher prothrombin

time (p = 0.002), higher AMIS65 scores (p<0.001), and the requirement for PRC transfusion (p<0.001). According to multivariate analysis, lower serum sodium (p = 0.039) remained significantly associated with in-hospital complications (Table 5 and 6).

Discussion

The present study included almost 300 patients with acute UGIB from various etiologies, mainly peptic ulcer (n = 113) and esophageal variceal bleeding (n = 97). Based on the location of Rajavithi Hospital and the centralized referral system of the Ministry of Public Health of Thailand, the authors believe that the clinical characteristics of patients in the present study can be a good representation of acute UGIB patients presenting at secondary/tertiary medical centers in Thailand. The majority of the patients (about 80%) were considered low-risk according to the AIMS65 scoring system. Accordingly, it is not surprising that the overall outcome of UGIB in the present study was very good, with just 7.3% rebleeding, 22.0% in-hospital complications and only 1.0% mortality rates. Apart from the fact that we included a relatively low-risk population, this may be also due to the prompt resuscitation and the administration of appropriate medical treatment (100% of patients with NVUGIB received PPI and >94% of patients with VUGIB received vasoactive agent plus PPI), as well as the effective endoscopic interventions which were performed in 36% of cases.

The differentiation between patients with NVUGIB and VUGIB before EGD is important, as VUGIB was considered to carry a higher risk of developing complications. The use of vasoactive agents in addition to PPI before EGD for acute VUGIB has been recommended by the International Guidelines in order to stop/slow the bleeding which facilitates endoscopic diagnosis and treatment[16,17]. In the present study, the pre-endoscopic clinical findings that suggested VUIGB over NVUGIB were male gender, underlying cirrhosis, presenting symptoms of hematemesis and hematochezia, presence of fresh blood on NG lavage, longer prothrombin time, lower platelet count, and serum albumin levels. Notably, when the cut-off on-admission platelet count of 150,000 cell/mm^3 was applied, the accuracy in predicting VUGIB was 87.7% (AUROC 0.90), with sensitivity of 71.7%, specificity of 97.2%, positive predictive value of 93.8% and negative predictive value of 85.3%.

Similarly to data from previous research, patients with VUGIB were associated with poorer outcomes in terms of the need for endoscopic treatment, the number of units of PRC transfusion, in-hospital complications, and LOS compared to those with NVUGIB. Antibiotic prophylaxis is recommended in cirrhotic patients with UGIB in order to reduce the risks of rebleeding (from 39% to 14%), infections (from 45% to 14%) and death (from 24% to 15%)[16-19]. In the present study, prompt antibiotic prophylaxis and vasoactive agents were given in all cirrhotic patients with VUGIB; however, rebleeding, infections, and death still developed in 7.5%, 30.2%, and 1.9% of patients respectively. Interestingly, the rates of rebleeding and death of patients with VUGIB in the present study were lower than in randomized clinical trials in Western countries[18,19]. This may be partly due to the differences in the study populations and the more modern management of UGIB (most western studies in this regard were performed >15 years ago). Nevertheless, despite universal antibiotic prophylaxis, the infection rate of patients with VUGIB in the present study was about 2 times higher than in the Western countries[18,19]; this may be due to the high prevalence of resistant organisms in the community and may also reflect suboptimal infection control in the hospital.

The majority of the clinical outcome predictors identified by univariate and multivariate analyses in the present study have already been described previously in the literature. Despite endoscopic treatment for NVUGB, bleeding from duodenal ulcer was associated with a 3.3 times higher risk of rebleeding compared to other causes of bleeding (mainly gastric ulcers). Interestingly, low serum sodium, which has never been clearly described as an outcome predictor of UGIB, was found to be an independent predictor for rebleeding in patients with NVUGIB and for complications in patients with VUGIB. Many studies have shown that serum sodium concentration correlates with severity of cirrhosis, and the presence of hyponatremia is a strong predictor of mortality in patients with advanced cirrhosis[20-22]. Accordingly, it is likely that serum sodium can be another good predictor for complications in cirrhotic patients presenting with VUGIB. On the other hand, the rationale that serum sodium can predict rebleeding in patients with NVUGIB is unclear, and the role of serum sodium in the prediction of outcomes in UGIB needs further validation.

In the present study, the early application of the AIMS65 scoring system was shown to predict outcomes of patients with UGIB, both NVUGB and VUGIB, in terms of rebleeding and in-hospital

complications. The results support the usefulness of the AIMS65 scoring system in UGIB, and this is largely in keeping with previous reports from the USA, Korea and the Middle East[9-11]. In addition, the majority of patients included in the previous studies of the AIMS65 scoring system had NVUGIB, so that a considerable number of patients with VUGIB included in the present study may further confirm the effectiveness of the performance of the AIMS65 score in this population[9-11]. Nonetheless, it should be noted that the present study included only a small number of patients with AIMS65 score 3-5, so it is not clear whether the results can be applied in this higher-risk population.

The present study had several limitations including its retrospective nature, limited number of participants and heterogeneity of the study population. It should also be noted that many patients with UGIB who were contraindicated for EGD but underwent EGD at the ICU or at the Department of Surgery were not included in the analysis. These omissions could compromise its statistical power for identifying clinical predictors, and there was a possibility of selection bias. Therefore, the results of the present study were mainly representative of low-to-moderate risk patients with UGIB, and may not be able to be used with high-risk patients.

In conclusion, the overall outcomes of UGIB in Thailand were good, with better outcomes in NVUGIB compared to VUGB. The already-described clinical predictors of morbidity/mortality were helpful. AIMS65 scores and serum sodium may be useful in predicting rebleeding and complications in UGIB.

What is already known on this topic?

Despite the advancement in medical and endoscopic therapies, morbidity and mortality from UGIB have remained considerable.

Several clinical predictors and scoring systems, such as AIMS65, have been shown to predict the outcomes of UGIB.

What this study adds?

The overall treatment outcomes of UGIB in Rajavithi Hospital were similar to, or maybe even better than, those reported from the Western countries in general.

This study confirms the effectiveness of the performance of AIMS65 scores in predicting outcomes in both NVUGIB and VUGIB in Thailand

Platelet count may be a good indicator to distinguish between NVUGIB (>150,000/mm^3) and VUGIB (<150,000/mm^3)

Serum sodium may be a potential predictor of outcomes in UGIB.

Acknowledgements

The authors are thankful to all GI staff (Dr. Piyathida Hansomburana, Dr. Siam Sirinthornpunya, Dr. Kitti Chuengyong and Dr. Apichet Sirinawasatien), GI fellows, and endoscopic nurses in the Endoscopic Unit, Division of Gastroenterology, Department of Medicine, Rajavithi Hospital, for their contributions to the care of patients with UGIB included in this study.

Potential conflicts of interest

None.

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ลักษณะทางคลินิกผลลัพธ์จากการรักษาและการประเมินความเสี่ยงในผู้ป่วยเลือดออกจากทางเดินอาหารส่วนต้นในโรงพยาบาลราชวิถี

เฉลิมรัฐ บัญชรเทวกุล, ยุรนันท์ ยอดเกตุ, นัฐติยาพร สิงหเสนา

ภูมิหลัง: *ภาวะเลือดออกจากทางเดินอาหารส่วนต้นพบได้บ่อยและทำให้เกิดอัตราป่วยอย่างมีนัยสำคัญ ทั่วโลกการประเมินความเสี่ยงในผู้ป่วยเลือดออกจากทางเดินอาหารส่วนต้นอย่างมีประสิทธิภาพมีความสำคัญในการวางแผนการรักษาผู้ป่วยอย่างเหมาะสม*

วัตถุประสงค์: *เพื่อบรรยายลักษณะทางคลินิกและผลลัพธ์ของการรักษาผู้ป่วยเลือดออกจากทางเดินอาหารส่วนต้น รวมทั้งเพื่อหาปัจจัยเสี่ยงต่อการเกิดเลือดออกซ้ำและภาวะแทรกซ้อน*

วัสดุและวิธีการ: *ข้อมูลพื้นฐาน ผลส่องกล้องและข้อมูลสำคัญระหว่างเข้ารับการรักษาตัวในโรงพยาบาลของผู้ป่วยเลือดออกจากทางเดินอาหารส่วนต้นที่ได้รับการส่องกล้องในโรงพยาบาลราชวิถี (กรุงเทพมหานคร) ระหว่างปี พ.ศ. 2555 ถึง พ.ศ. 2558 ได้ถูกนำมาวิเคราะห์แบบย้อนหลัง การวิเคราะห์พหุตัวแปรถูกนำมาใช้เพื่อหาปัจจัยเสี่ยงต่อการเกิดเลือดออกซ้ำและภาวะแทรกซ้อนใน 4 สัปดาห์*

ผลการศึกษา: *ผู้ป่วย 286 รายถูกรวบรวมโดย 180 รายเป็นเลือดออกจากทางเดินอาหารส่วนต้นจากสาเหตุที่ไม่ใช่เส้นเลือดขอด (NVUGIB) และ 106 เป็นเลือดออกจากทางเดินอาหารส่วนต้นจากเส้นเลือดขอด (VUGIB) ผู้ป่วยร้อยละ 71.1 เป็นผู้ชาย และมีอายุเฉลี่ย 53.6 ปี ผู้ป่วย NVUGIB ร้อยละ 43.4 ทานยา NSAIDs และ/หรือแอสไพริน และส่วนมากมีสาเหตุเลือดออกจากแผลในทางเดินอาหารส่วนต้น (ร้อยละ 62.8) และกระเพาะอาหารอักเสบ (ร้อยละ 32.2) ผู้ป่วย VUGIB ทุกรายมีภาวะตับแข็ง (ร้อยละ 54.7 เป็น Child-Pugh B/C) ผู้ป่วย VUGIB มักมีเลือดออกชัดเจนเมื่อมาถึงโรงพยาบาลมีการแข็งตัวของเลือดยาวนานกว่า มีระดับอัลบูมินและเกร็ดเลือดต่ำกว่าอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับผู้ป่วย NVUGIB ผู้ป่วย VUGIB ได้รับการรักษาโดยการส่องกล้องมากกว่าผู้ป่วย NVUGIB อย่างมีนัยสำคัญ (ร้อยละ 62.3 vs. 20.6, p<0.001) พบอัตราเลือดออกซ้ำร้อยละ 7.3 และอัตราตายร้อยละ 1 โดยไม่มีความแตกต่างระหว่างผู้ป่วย NVUGIB และ VUGIB ผู้ป่วย VUGIB เกิดภาวะแทรกซ้อนในโรงพยาบาล (ร้อยละ 39.6 vs. 11.7, p<0.001) และต้องรับเลือดจำนวนมากกว่า (1.85 vs. 1.46 ถุง, p<0.001) ผู้ป่วย NVUGIB อย่างมีนัยสำคัญ การวิเคราะห์พหุตัวแปรในผู้ป่วย NVUGIB พบว่า ระดับโซเดียมต่ำ และภาวะเลือดออกจากแผลในลำไส้เล็กส่วนต้น เป็นตัวทำนายการเกิดเลือดออกซ้ำและพบว่า เพศหญิง สัญญาณชีพไม่คงที่ และการเกิดเลือดออกซ้ำเป็นตัวทำนายการเกิดภาวะแทรกซ้อน การวิเคราะห์พหุตัวแปรในผู้ป่วย VUGIB พบว่าภาวะเกร็ดเลือดต่ำเป็นตัวทำนายการเกิดเลือดออกซ้ำ และพบว่าระดับโซเดียมต่ำเป็นตัวทำนายการเกิดภาวะแทรกซ้อน เมื่อประเมินด้วยระบบ AIMS65 พบอัตราเลือดออกซ้ำร้อยละ 5.3 (8/151), 7.0 (6/86), 18.2 (6/33), 7.1 (1/14), 0 (0/1) และ 0 (0/1) อัตราเกิดภาวะแทรกซ้อนร้อยละ 9.3 (14/151), 23.2 (20/86), 48.5 (16/33), 78.6 (11/14), 100 (1/1) และ 100 (1/1) ในผู้ป่วยที่มี AIMS65 คะแนน 0, 1, 2, 3, 4 และ 5 ตามลำดับ*

สรุป: *ผู้ป่วยเลือดออกจากทางเดินอาหารส่วนต้นมีผลลัพธ์โดยรวมดี โดยพบว่าผู้ป่วย NVUGIB มีผลลัพธ์ดีกว่า VUGIB ระบบ AIMS65 และระดับโซเดียมมีประโยชน์ในการทำนายการเกิดเลือดออกซ้ำและภาวะแทรกซ้อนในผู้ป่วยเลือดออกจากทางเดินอาหารส่วนต้น*