Chronic Kidney Disease, Hemodynamic Instability, and Endoscopic High-Risk Appearance Are Associated with 30-Day Rebleeding in Patients with Non-Variceal Upper Gastrointestinal Bleeding

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The results of studies that evaluated predictive factors for rebleeding in non-variceal upper gastrointestinal bleeding are inconsistent. The aim of this study was to investigate predictive factors for 30-day rebleeding in these patients. A consecutive 312 patients presenting symptoms and signs of gastrointestinal bleeding were enrolled in this prospective, observational study. Clinical and demographic characteristics and endoscopic findings were evaluated for potential factors associated with 30-day rebleeding using logistic regression analysis. Overall, 176 patients were included (male, 80.1%; mean age, 59.7 ± 16.0 yr). Rebleeding within 7 and 30 days occurred in 21 (11.9%) and 27 (15.3%) patients, respectively. We found that chronic kidney disease (CKD) (OR, 10.29; 95% CI, 2.84-37.33; $P < 0.001$), tachycardia (pulse > 100 beats/min) during the admission (OR, 3.79; 95% CI, 1.25-11.49; $P = 0.019$), and Forrest classes I, IIa, and IIb (OR, 6.14; 95% CI, 1.36-27.66; $P = 0.018$) were significant independent predictive factors for 30-day rebleeding. However, neither Rockall nor Blatchford scores showed statistically significant relationships with 30-day rebleeding in a multivariate analysis. CKD, hemodynamic instability during hospitalization, and an endoscopic high-risk appearance are significantly independent predictors of 30-day rebleeding in patients with non-variceal upper gastrointestinal bleeding. These factors may be useful for clinical management of such patients.

Key Words: Nonvariceal Upper Gastrointestinal Bleeding; Rebleeding; Kidney Failure, Chronic; Predictive Factors

INTRODUCTION

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a common gastrointestinal cause of hospital admission and generates significant morbidity and mortality despite advancements in endoscopic and acid-suppressive therapy (1). Recent studies have identified rebleeding as a significant predictor of mortality (2-6). Thus, prediction of rebleeding within 30 days helps to differentiate high- from low-risk patients. A recently reported international consensus on NVUGIB recommended that patients who are at low risk for rebleeding, on the basis of clinical and endoscopic criteria, may be discharged promptly after endoscopy (7). Therefore, clinical parameters that predict rebleeding should be identified; these must be easily accessible, accurate, and equally effective in various ethnic groups. Some studies have reported risk factors for rebleeding, and several risk scoring models to improve medical decision-making have been developed. However, the risk factors vary widely among reports due to significant heterogeneity in study design. Most scoring systems were designed to predict mortality or a combination of mortality and rebleeding rather than only rebleeding (5). To deal with the disparity in the quality of studies of NVUGIB, methodology recommendations have been proposed by an International Consensus Conference (8). We attempted to follow these recommendations by applying the suggested clinical and endoscopic criteria, and by including key baseline characteristics.

The aims of this study were 1) to describe clinical characteristics, endoscopic findings, and clinical outcomes and 2) to identify predictive factors for 30-day rebleeding in patients admitted to the emergency unit for NVUGIB.

MATERIALS AND METHODS

All adult patients (older than 18 yr) presenting with symptoms or signs of gastrointestinal bleeding at Keimyung University Dongsan Hospital in Daegu, Korea, between April 2010 and January 2012 were enrolled prospectively in a previously designed database. Patients with bleeding from esophageal or gastric

varices or lower gastrointestinal causes and those who did not complete an at least 30-day follow-up period were excluded from the analysis. Patients with hemodynamic instability received crystalloid solutions and blood transfusions. All patients used intravenous proton pump inhibitors (PPI). All endoscopic procedures were performed within 24 hr after arrival at the hospital by experts who had experience with more than 1000 endoscopy cases.

Variables included demographic data, clinical manifestations of bleeding (hematemesis, melena, hematochezia, and anemia of acute onset), tobacco use, alcohol consumption (heavy consumption was defined as > 40 g per day and > 60 g per day for women and men, respectively, for > 5 yr) (9), and the use of non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelet agents (aspirin, clopidogrel, and cilostazol), steroids, and proton pump inhibitors (PPI). Comorbidities, such as diabetes mellitus, hypertension, heart failure, cirrhosis, chronic kidney disease (CKD) (CKD was defined as patients with an estimated glomerular filtration rate < 60 mL/min for ≥ 3 months calculated using the four-variable Modification of Diet in Renal Disease Study equation) (10), cerebrovascular disease, peripheral vascular disease, and metastatic malignancy, were registered. Past history of gastrointestinal bleeding or peptic ulcer disease and hemodynamic instability (pulse > 100 beats/min, hypotension with a systolic pressure < 90 mmHg at admission and during the hospital stay) were recorded. Laboratory data including hemoglobin, platelets, prothrombin time, and blood urea nitrogen were collected. Results of nasogastric (NG) tube aspiration and rectal examination were also recorded. Blatchford and Rockall scores were calculated. In order to avoid the risk of potential multi-collinearity between variables, we used Blatchford score ≥ 12 and Rockall score ≥ 5 as variables for the logistic regression analysis of rebleeding (11, 12). Urgent endoscopy meant performance of endoscopy within 12 h of admission (7). The presence of blood in the stomach when no specific lesion was visualized was classified as bleeding of unidentified cause (13, 14). In all patients, stigmata of recent hemorrhage at the mucosal lesion were classified according to the Forrest classification (15). Active bleeding (Forrest I), exposed vessel (Forrest IIa), and adherent clot (Forrest IIb) were regarded as high-risk endoscopic stigmata. All endoscopic appearances were reviewed and corrected by two expert endoscopists to improve interobserver agreement. All active bleeding was controlled by endoscopic treatments, including hemoclipping, epinephrine injection, electrocoagulation, or argon plasma coagulation (APC). Although the lesions with high-risk stigmata were instructed to be endoscopically treated by a strict hospital protocol, the decision to perform therapeutic endoscopy was at the discretion of the individual endoscopist. Survey of gastric biopsies for *Helicobacter pylori* was not performed routinely, but frequencies of practice and detection were recorded. Initial endoscopy findings of bleeding evidence and lesion locations were described.

A 30-day rebleeding was defined as new onset of hematemesis, coffee-ground vomitus, or hematochezia with hypovolemic shock or a decrease in blood hemoglobin of more than 2 g/dL after a 24-hr period of stable vital signs following successful endoscopic treatment (13, 16) within 30 days of the index bleeding episode. Rebleeding was in all cases confirmed by endoscopy.

Statistical analyses

Statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA). Student's t-test was used for comparisons of continuous variables. Data were expressed as means ± SD. Categorical variables were compared using Pearson's chisquare test or the Fisher's exact test. Logistic regression was used for the analysis of predictors of rebleeding. A two-tailed *P* value of less than 0.05 was considered to indicate statistical significance.

Ethics statement

This study protocol was reviewed and approved by the institutional review board of Keimyung University Dongsan Hospital (No 11-294). Informed consent was obtained from patients.

RESULTS

During the study period, 312 patients with gastrointestinal bleeding were admitted. Bleeding was due to esophageal or gastric varices in 71 patients, and lower gastrointestinal bleeding in 56 patients. These were excluded from the study. Nine patients were lost to follow-up. Therefore, 176 (56.4%) patients with NVUGIB were included in the study (Fig. 1). The baseline characteristics of these 176 patients at admission are shown in Table 1. The mean age of the patients was 59.7 yr with a male predominance
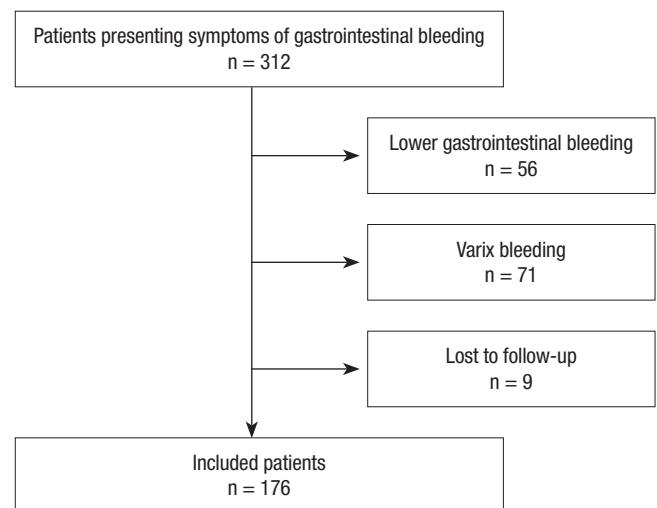

Fig. 1. Flow diagram illustrating participants in the study.

Table 1. Clinical and demographic characteristics of patients with non-variceal upper gastrointestinal bleeding (n=176)

Factors	Findings
Male, No (%)	141 (80.1)
Age (yr)	59.72 ± 15.99
Initial vital sign	
SBP (mmHg)	117.06 ± 23.28
Pulse rate (beat/min)	89.05 ± 17.88
Initial laboratory data	
Hemoglobin (g/L)	8.8 ± 2.9
Platelets (× 10⁹/L)	254 ± 119
BUN (mg/dL)	42.04 ± 28.24
PT (sec)	13.34 ± 8.75
Bleeding related symptoms, No (%)	
Hematemesis	89 (50.6)
Melena	72 (40.9)
Hematochezia	12 (6.8)
Acute onset anemia	3 (1.7)
Positive nasogastric tube aspiration, n = 169, No (%)	117 (69.2)
Rectal examination positive, n = 171, No (%)	117 (68.4)
Heavy alcoholics, No (%)	67 (38.1)
Current smoker, No (%)	66 (37.5)
Past history of gastrointestinal bleeding, No (%)	49 (27.8)
Past history of peptic ulcer disease, No (%)	57 (32.4)
Comorbidities, No (%)	
Hypertension	77 (43.8)
Diabetes mellitus	42 (23.8)
Cardiovascular disease	20 (11.4)
Liver cirrhosis	29 (16.5)
Chronic renal disease	27 (15.3)
Cerebrovascular disease	26 (14.8)
Heart failure	25 (14.2)
Metastatic malignancy	8 (4.5)
Peripheral vascular disease	2 (1.1)
Use of medication, No (%)	
Antiplatelet agents	50 (28.4)
Vitamin K antagonists	8 (4.5)
NSAID	35 (19.9)
PPI co-medication	7 (4.0)
Tachycardia (pulse ≥ 100 beats/min) during the hospital stay, No (%)	59 (33.5)
Hypotension (SBP < 90 mmHg) during the hospital stay, No (%)	39 (22.2)
Urgent endoscopy, No (%)	114 (64.8)
Endoscopy finding, No (%)	
Gastric ulcer	96 (54.5)
Duodenal ulcer	26 (14.8)
Mallory-Weiss syndrome	22 (12.5)
Gastric & duodenal ulcer	10 (5.7)
Dieulafoy lesion	5 (2.8)
Angiodysplasia	2 (1.1)
Stomach cancer	2 (1.1)
Hemorrhagic gastritis	1 (0.6)
No evidence of upper gastrointestinal bleeding	12 (6.8)
Endoscopy lesion location, No (%)	
Cardia, angle, antrum	81 (46.0)
Body	49 (27.8)
Duodenum	34 (19.3)
No specific lesion	12 (6.8)
Forrest classification, No (%)	
I	40 (22.7)
IIa	33 (18.8)
IIb	20 (11.4)
IIc	45 (25.6)
III	26 (14.8)
No evidence of bleeding	12 (6.8)
Helicobacter pylori infection, n = 98, No (%)	41 (41.8)
Blatchford score	11.55 ± 3.34
Rockall score	4.67 ± 2.00

SBP, systolic blood pressure; BUN, blood urea nitrogen; PT, prothrombin time; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Table 2. Rebleeding outcomes of patients with non variceal upper gastrointestinal bleeding (n=176)

Timing	Rebleeding, No (%)
Within 1 week	21 (11.9)
Within 30 days	27 (15.3)
During follow-up period*	38 (21.0)

*Median follow-up period of 192 days (interquartile range 65-380).

(80.1%). The proportions of positive NG aspiration and digital rectal examination results were 69.2% (117/169) and 68.4% (117/171), respectively. A past history of gastrointestinal bleeding was found in 49 (27.8%), and of peptic ulcer disease in 57 (32.4%). The most frequent comorbidity was hypertension (43.8%), followed by diabetes mellitus (23.8%). CKD was present in 27 (15.3%) patients. The percentages of current smokers and heavy drinkers of alcohol were 37.5% and 38.1%, respectively. Thirty-five patients (19.9%) were taking NSAIDs. Over half of the patients (101, 57.4%) had a severe-bleeding-related symptom (hematemesis or hematochezia) as the presenting symptom. Mean serum hemoglobin level on admission was 8.8 ± 2.9 g/dL. Tachycardia (pulse > 100 beats/min) and hypotension (systolic blood pressure < 90 mmHg) during the hospital stay were found in 33.5% and 22.2% of patients, respectively.

Urgent endoscopy was performed in 114 (64.8%) patients. One-hundred and thirty-seven patients (77.8%) had peptic ulcer disease, which was the most frequent source of bleeding. The causes of bleeding in the other 39 patients were as follows: Mallory-Weiss syndrome (12.5%), stomach cancer (1.1%), angiodysplasia (1.1%), and hemorrhagic gastritis (0.6%). The cause of bleeding in 12 (6.8%) patients was not identified. Lesions were found at body in 49 patients (27.8%). High-risk endoscopic stigmata, such as Forrest classifications I, IIa, and IIb, were documented in 93 (52.9%) patients. Mean Rockall and Blatchford scores were 4.67 ± 2.00 and 11.55 ± 3.34, respectively.

Overall, rebleeding occurred in 37 (21.0%) patients during the median follow-up period of 192 days (interquartile range 65-380); rebleeding within 1 week and 30 days of admission occurred in 21 (11.9%) and 27 (15.3%) patients, respectively (Table 2).

Factors predictive of 30-day rebleeding after non-variceal upper gastrointestinal bleeding

Table 3 shows the results of univariate analysis of rebleeding. Male gender (P = 0.019), a positive NG tube aspiration result (P = 0.001), past history of peptic ulcer disease (P = 0.019), CKD (P < 0.001), Blatchford score ≥ 12 (P = 0.037), lesion location in the body (P < 0.001), high-risk endoscopic stigmata (P < 0.001), and tachycardia (pulse > 100 beats/min) during admission (P < 0.001) were significant risk factors for 30-day rebleeding. However, only the following parameters were independent predictors of 30-day rebleeding in the multivariate analysis: CKD (OR, 10.29; 95% CI, 2.84-37.33; P < 0.001), tachycardia (pulse > 100

Table 3. Univariate analyses of predictive factor for 30-day rebleeding (n=176)

Factors	30-day rebleeding (+), n = 27	30-day rebleeding (-), n = 149	P value
Male, No (%)	26 (96.3)	115 (77.2)	0.019
Age (yr)	60.15 ± 16.70	59.64 ± 15.92	0.884
Initial vital sign			
SBP < 90 mmHg	7 (25.9)	20 (13.4)	0.142
Pulse rate > 100 beat/min	11 (40.7)	36 (24.2)	0.097
Initial laboratory data			
Hemoglobin (g/dL)	8.02 ± 2.31	9.01 ± 3.07	0.060
Platelets (× 10^9/L)	290 ± 120	248 ± 120	0.096
BUN (mg/dL)	47.8 ± 31.8	40.9 ± 27.5	0.304
PT (sec)	14.29 ± 8.64	13.17 ± 8.79	0.543
Severe bleeding related symptoms, (hematemesis, hematochezia), No (%)	20 (74.1)	81 (54.4)	0.061
Positive nasogastric tube aspiration, No (%), n = 169	25 (92.6)	92 (61.7)	0.001
Positive rectal examination, No (%), n = 171	21 (77.8)	96 (64.4)	0.176
Heavy alcoholics, No (%)	10 (37.0)	57 (38.3)	0.905
Current smoker, No (%)	13 (48.1)	53 (35.6)	0.214
Past history of peptic ulcer disease, No (%)	14 (51.9)	43 (28.9)	0.019
Past history of gastrointestinal bleeding, No (%)	9 (33.3)	40 (26.8)	0.489
Comorbidities, No (%)			
Hypertension	11 (40.7)	66 (44.3)	0.743
Diabetes mellitus	6 (22.2)	36 (24.2)	0.828
Cardiovascular disease	2 (7.4)	18 (12.1)	0.523
Liver cirrhosis	3 (11.1)	26 (17.4)	0.576
Chronic kidney disease	14 (51.9)	13 (8.7)	< 0.001
Cerebrovascular disease	7 (11.1)	19 (12.8)	0.076
Heart failure	4 (14.8)	21 (14.1)	1.000
Metastatic malignancy	3 (11.1)	5 (3.4)	0.106
Peripheral vascular diasese	1 (3.7)	1 (0.7)	0.284
Medication			
Antiplatelet agents	9 (33.3)	41 (27.5)	0.537
Vitamin K antagonists	0	8 (5.4)	0.610
NSAID	6 (22.2)	29 (19.5)	0.741
PPI co-medication	0	7 (4.7)	0.597
Urgent endoscopy*	18 (66.7)	96 (64.4)	0.823
Blatchford score ≥ 12	21 (77.8)	84 (56.4)	0.037
Rockall score ≥ 5	18 (66.7)	75 (50.3)	0.118
Endoscopy finding, No (%)			
Peptic ulcer disease	24 (88.9))	113 (75.8)	0.133
Non peptic ulcer disease	3 (11.1)	36 (24.2)	
Endoscopy lesion location, No (%)			
Body	15 (55.6)	34 (22.8)	< 0.001
Other than body	12 (44.4)	115 (77.2)	
High risk endoscopic stigmata, Forrest classification I, IIa, and IIb, No (%)	24 (88.9)	69 (46.3)	< 0.001
Tachycardia (pulse > 100 beats/min) during the admission, No (%)	19 (70.4)	40 (26.8)	< 0.001
Hypotension (SBP < 90 mmHg) during the admission, No (%)	9 (33.3)	30 (20.1)	0.129
Positive helicobacter pylori infection, No (%), n = 98	9 (33.3)	32 (21.5)	0.180

*Endoscopy which was performed within 12 hr of admission. NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SBP, systolic blood pressure.

beats/min) during the hospital stay (OR, 3.79; 95% CI, 1.25-11.49; P = 0.019), and high-risk endoscopic stigmata (OR, 6.14; 95% CI, 1.36-27.66; P = 0.018) (Table 4).

DISCUSSION

In this study, we identified factors that were independently associated with the risk of 30-day rebleeding in a cohort of 176 patients presenting with NVUGIB. We found that CKD; tachycardia (pulse > 100 beats/min) during the hospital stay; and high-risk endoscopic stigmata of Forrest classifications I, IIa,

and IIb were independently associated with rebleeding within 30 days. These risk factors are easy to identify following the initial bleeding event, are valuable for predicting clinical outcomes, and may be useful for guiding clinical management of patients with NVUGIB. Identifying patients at high risk for rebleeding is important for cost-effective management of NVUGIB. Many risk stratification schemes use both clinical and endoscopic criteria (2, 4, 17, 18). The Rockall score is the best known of all risk-stratification tools for upper gastrointestinal bleeding. It includes three non-endoscopic (age, shock, and comorbidity), and two endoscopic (endoscopic diagnosis and presence or absence of

Table 4. Multivariate analysis of predictive factor for 30-day rebleeding (n=176)

Factors	Odds ratio	95% confidence interval	P value
Male	13.74	0.98-191.60	0.051
Positive nasogastric tube aspiration	2.90	0.45-18.62	0.261
Past history of peptic ulcer disease	1.38	0.44-4.34	0.578
Chronic kidney disease	10.29	2.84-37.33	< 0.001
Tachycardia (pulse ≥ 100 beats/min) during the admission	3.79	1.25-11.49	0.019
Lesion location of body	3.35	0.99-11.31	0.051
Forrest classification I, IIa, and IIb	6.14	1.36-27.66	0.018
Blatchford score ≥ 12	1.47	0.42-5.06	0.540

endoscopic stigmata of recent hemorrhage) variables (2). The Blatchford score, another risk stratification system, does not include an endoscopic parameter, but uses only clinical (systolic blood pressure, heart rate, melena and/or syncope, hepatic disease and/or cardiac failure) and laboratory (blood urea nitrogen and hemoglobin) variables to predict the need for treatment (3). Recently reported international consensus recommendations have emphasized the importance of early risk stratification using prognostic scales, such as the Rockall or Blatchford score (7). We calculated Rockall and Blatchford scores according to index clinical and endoscopic variables. Although univariate analysis showed that only Blatchford scores was significantly correlated with 30-day rebleeding in patients with NVUGIB, it failed to show statistical significance after adjustment for other variables in a multivariate analysis. This result corresponds with other studies, that the Rockall score is unsatisfactory for the prediction of rebleeding (19, 20). Also, there are discrepancies in the accuracy of the Blatchford score system (21). Some studies were unable to demonstrate a high specificity for the Blatchford score in discriminating high- and low-risk patients with upper gastrointestinal bleeding (21, 22). Furthermore, this score was originally designed not to assess risk of rebleeding but to determine whether patients with upper gastrointestinal bleeding require treatment to manage their bleeding (23). Therefore, it remains to be seen that the Rockall and the Blatchford score are effective tools for prediction of rebleeding in NVUGIB.

In this study, NVUGIB patients with CKD had a high risk of rebleeding, which is similar to other reports (6, 24, 25). The pathogenesis and risk factors for gastrointestinal bleeding in patients with CKD are unclear. It seems that an acquired defect of primary hemostasis caused by platelet dysfunction and an altered platelet-vessel wall interaction is responsible for hemorrhagic tendencies (26, 27). In Cheung's study, end stage renal disease (ESRD) requiring dialysis was an independent predictor of peptic ulcer rebleeding, and there was no difference in rebleeding between patients with non-dialysis-dependent CKD and a normal control group (25). It is possible that some of these patients used anticoagulants routinely (e.g., heparin) during hemodialysis, exhibited accumulation of medications due to poor clearance, and had impaired healing of ulcers caused by

sporadic circulation variability in the gastrointestinal tract during hemodialysis (28). In the present study, of 27 patients who had CKD, only nine had ESRD (hemodialysis or peritoneal dialysis for > 6 months). In the context of these results, patients with CKD, not only ESRD but also CKD not requiring dialysis, seemed to have higher rebleeding rates. A recent study also reported that non-dialysis-dependent CKD patients rebled more frequently than the control group, indicating a significant rebleeding risk in patients with CKD after initial NVUGIB (24). Therefore, patients with both ESRD and CKD who do not require dialysis might need intensive endoscopic hemostasis combined with PPIs and a longer hospital stay under close monitoring, than those without.

Hemodynamic instability has been reported to be a significant risk factor for rebleeding and mortality. A systolic blood pressure < 90 mmHg, tachycardia > 100 beats/min, and peripheral signs of shock indicate hemodynamic instability and were evaluated at admission in most studies (5). We also evaluated systolic blood pressure, diastolic blood pressure, and pulse rate at admission. However, none of these factors was significantly associated with increased 30-day rebleeding in the present study. This discrepancy between studies might be attributed to differences in the populations and methods used. We found that patients who had tachycardia during the hospital stay had a high risk of 30-day rebleeding (OR, 3.79; 95% CI, 1.25-11.49; $P = 0.019$). Although hemodynamic instability after diagnostic endoscopy might limit its applicability as a prognostic variable for deciding early additional measures, it emphasizes the importance of close monitoring for patients with NVUGIB.

It is well known that the outcome of bleeding from peptic ulcer is dependent partly on the endoscopic stigmata of bleeding as described by Forrest (15), and endoscopic hemostatic therapy is indicated for patients with high-risk stigmata (active bleeding or a visible vessel in an ulcer bed) (29). The role of endoscopic therapy for ulcers with an adherent clot (Forrest classification IIb) is controversial (7). The risk of rebleeding with adherent clots after washing without endoscopic therapy can be low or high, depending on the presence of concurrent illnesses (30-32). In the present study, we did not try to shave adherent clots with the snare technique, and usually used water irrigation. There-

fore, lesions with clots resistant to vigorous irrigation could not be distinguished from ulcers with exposed vessels. Therefore, we included Forrest IIb among the high-risk bleeding stigmata. In our study, patients with Forrest classifications I, IIa, and IIb had a significantly higher risk of rebleeding (OR, 6.14; 95% CI, 1.36-27.66; P = 0.018). This suggests that particularly in patients with high risk endoscopic stigmata (including Forrest classification IIb), careful management with close monitoring for the recurrent bleeding according to the guidelines is essential.

The strengths of this study were as follows: it was of a prospective observational design, and we evaluated many variables that have been recommended as key baseline characteristics for comparisons across studies (8). In addition, risk scoring systems, including Rockall and Blatchford scores, were calculated. In all cases, endoscopy to evaluate the cause of bleeding was performed within 24 h. Limitations of the study include its small size and performance in a single center. Hence, the findings should be considered within the context of these limitations.

In conclusion, in patients with NVUGIB, the risk of rebleeding is significantly increased with CKD; Forrest classification I, IIa, or IIb; and the occurrence of tachycardia (> 100 beats/min) during the hospital stay. However, Rockall and Blatchford scores are not relevant to the prognosis. In these high-risk patients, emergency endoscopic hemostasis, intensive pharmacological therapy, and a longer hospital stay under close monitoring should be considered. Further studies with a larger number of subjects are required to support this result.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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