Renal Dysfunction is an Independent Risk Factor for Rebleeding After Endoscopic Hemostasis in Patients with Peptic Ulcer Bleeding

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ABSTRACT

Background: *Despite the progress in endoscopic hemostasis and pharmacological treatment, the mortality rate of peptic ulcer bleeding remains at 5–10%. Rebleeding after peptic ulcer bleeding is believed to be a risk factor for mortality. This study aimed to evaluate whether renal dysfunction is a predictor of rebleeding after endoscopic hemostasis in patients with peptic ulcer bleeding.*

Methods: *In this retrospective study, consecutive patients with peptic ulcer bleeding who underwent endoscopic hemostasis at our Hospital from January 2010 to December 2018 were enrolled. The relationship between rebleeding within 30 days after endoscopic hemostasis and the patients' admission and endoscopic characteristics were analyzed using univariate and multivariate regression models.*

Results: *Out of 274 patients with peptic ulcer bleeding, 17 (6.2%) patients experienced rebleeding. In the analysis of the patients' admission characteristics, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 was an independent risk factor for rebleeding (odds ratio 4.77, 95% confidence interval 1.168-18.211, p = 0.03). Patients with eGFR < 15 mL/min/1.73 m^2 with or without hemodialysis had the highest rebleeding rate at 36.8%. With respect to endoscopic characteristics, the rate of rebleeding was associated with combination therapy (p < 0.0001) and active bleeding (p = 0.03).*

Conclusion: *Renal dysfunction might be an independent risk factor for rebleeding after endoscopic hemostasis in patients with peptic ulcer bleeding.*

Keywords: *Renal dysfunction, endoscopic hemostasis, peptic ulcer, peptic ulcer hemorrhage*

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is the most common cause of hospitalization in patients with gastrointestinal disease. UGIB is important as its mortality rate remains at 2.5–10%, and its economic burden is increasing.[1,2] UGIB is caused by a wide variety of diseases; peptic ulcer bleeding (PUB) is the most common cause of UGIB[3] despite the decreasing trend in the incidence of PUB.[4]

Despite the progress in endoscopic hemostasis and pharmacological treatment with potent acid suppressants, such as proton pump inhibitors (PPIs), the mortality rate of PUB remains at 5–10%.[5] Rebleeding after PUB is believed to be a risk factor for mortality, and the rate of rebleeding after endoscopic hemostasis for PUB ranges from 6.3% to 25.2%.[6] Previous studies reported that the clinical risk factors of rebleeding are hemodynamic instability, hemoglobin level, transfusion,[6] comorbidity,[7] chronic kidney disease (CKD),[8,9] antiplatelet drugs,[10] and in-hospital bleeding.[11] Further, the reported risk factors related to rebleeding after endoscopic hemostasis were active bleeding, large ulcer size, ulcer location,[6] and exposed blood vessels > 2 mm in diameter.[12]

Although several risk factors for rebleeding after endoscopic hemostasis have been reported, few reports have examined comorbidities as risk factors for rebleeding of PUB.

This study mainly aimed to evaluate whether renal dysfunction is a predictor for rebleeding after endoscopic hemostasis in patients with PUB. Other risk factors for rebleeding were also evaluated.

MATERIALS AND METHODS

Patients

In this retrospective study, consecutive patients with PUB who underwent endoscopic hemostasis at our Hospital

This study was presented at Digestive Disease Week 2019, 18 - 20 May 2019, San Diego, United States of America.
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from January 2010 to December 2018 were enrolled. Patients with failed endoscopic hemostasis and other causes of bleeding except PUB (varices, Mallory-Weiss tears, reflux esophagitis, hemorrhagic gastritis, angioectasia, malignancies, or bleeding after endoscopic resection) were excluded. Moreover, patients without 30 days of follow-up were excluded. Patients who transferred to our hospital after endoscopic hemostasis were also excluded.

Data Collection

We collected data on the following variables: patients' admission characteristics (age, sex, blood pressure, pulse rate, hematemesis, melena, syncope, comorbidities, medications [antithrombotic drugs and nonsteroidal anti-inflammatory drugs]), and laboratory data (hemoglobin, blood urea nitrogen [BUN], albumin, and estimated glomerular filtration rate [eGFR]). eGFR was calculated using the serum creatinine level, age, and sex according to the following Japanese formula: eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$ ($\times$ 0.739 if female).[13] eGFR more accurately represents renal function than that by serum creatinine level alone.[14] According to the Japanese practice guidelines for the treatment of CKD, patients with renal dysfunction were divided into five groups: stage 1, eGFR $\geq$ 90 mL/min/1.73 m^2; stage 2, eGFR 60–89 mL/min/1.73 m^2; stage 3, eGFR 30–59 mL/min/1.73 m^2; stage 4, eGFR 15–29 mL/min/1.73 m^2; and stage 5, eGFR <15 mL/min/1.73 m^2 or hemodialysis (HD) requirement.[15] CKD stage 5 is usually synonymous with end-stage renal disease (ESRD).

Helicobacter pylori (*H. pylori*) status was determined using serology, rapid urease test, urea breath test, or stool antigen test. The *H. pylori* status was judged as positive if any of the four tests was positive. Whether *H. pylori* was eradicated or not was confirmed using referral letters or patient interviews.

MAIN POINTS

- *The rebleeding risk of peptic ulcer bleeding (PUB) after endoscopic hemostasis has not been evaluated according to the patients' renal function category.*
- *The rebleeding rate of PUB after endoscopic hemostasis increased as the renal function category worsened.*
- *Patients with eGFR < 15 mL/min/1.73 m^2 not undergoing HD, as well as those undergoing HD, had a high risk for rebleeding.*
- *Renal dysfunction may be an independent factor for rebleeding after endoscopic hemostasis in patients with PUB.*

Glasgow Blatchford[16] and clinical Rockall[17,18] scores were calculated. When we calculated the clinical Rockall scores, we defined renal failure as eGFR < 30 mL/min/1.73 m^2.

Medications and Endoscopic Procedures

All patients were initially administered intravenous PPI (lansoprazole 60 mg/day [Takeda Pharma, Osaka, Japan] or omeprazole 40 mg/day [AstraZeneca, Osaka, Japan]) and then switched to oral PPI, where possible. For peptic ulcer disease, only these regular doses and dose regimens of intravenous PPI are covered by the national insurance system in Japan. Previous studies have reported that regular-dose PPI is not inferior to high-dose PPI at the rebleeding rate after endoscopic hemostasis.[19,20]

Endoscopic procedures were performed by expert endoscopists or by trainees under the supervision of expert endoscopists. If a trainee started the endoscopic procedures and failed to achieve endoscopic hemostasis, the expert continued the endoscopy. The bleeding status was described using the Forrest classification: active spurting bleeding (Ia), active oozing bleeding (Ib), nonbleeding visible vessel (IIa), and adherent clot (IIb).[21]

Thermal coagulation, hemostatic clipping, and injection therapy were selected for endoscopic hemostasis. These methods were used alone or in combination. For thermal coagulation, monopolar hemostatic forceps with soft coagulation were mainly used. In a few cases, argon plasma coagulation was used. For injection therapy, hypertonic saline epinephrine solution containing epinephrine (1:10,000 dilution) was used. The method of endoscopic hemostasis was selected by each endoscopist. Almost all patients underwent second-look endoscopy.

Rebleeding was defined as the presence of clinical signs of bleeding, such as fresh hematemesis, melena, anemia, vital sign instability, or the requirement for repeated endoscopic hemostasis for active bleeding within 30 days of initial endoscopic hemostasis.

We analyzed the association between rebleeding after endoscopic hemostasis and the patients' admission characteristics and endoscopic characteristics using univariate and multivariate regression models.

Statistical Analysis

Continuous and categorical variables are shown as means $\pm$ standard deviation, median (range), and proportions. Data were compared using the chi-square test, Fisher's

exact test, or Student's t-test, as appropriate. Receiver Operating Characteristic (ROC) curve analysis was used to determine the cutoff value of eGFR for predicting rebleeding. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using JMP software (ver. 12.2.0; SAS Institute Inc., Cary, NC, USA).

RESULTS

From January 2010 to December 2018, 277 patients with PUB underwent endoscopic hemostasis at our hospital. Patients with failed endoscopic hemostasis (n = 1), those without 30 days of follow-up (n = 1), and those who were transferred to our hospital after endoscopic hemostasis (n = 1) were excluded according to the exclusion criteria (Figure 1).

Table 1 shows the clinical characteristics of all patients. A total of 195 ulcers occurred in the stomach and 79 in the duodenum. Rebleeding occurred in 17 patients (6.2%). Univariate analysis demonstrated that the BUN level and clinical Rockall score were significantly higher ($p < 0.0001$, $p = 0.005$, respectively), and the eGFR level and proportion of patients with *H. pylori*-positive status were significantly lower ($p < 0.0001$, $p = 0.01$, respectively) in the rebleeding group than that in the no rebleeding group (Table 2). The proportion of patients who had severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2) in the rebleeding group was higher than that in the no rebleeding group (6 / 257 vs. 11 / 17, $p<0.0001$). The number of patients receiving hemodialysis in the rebleeding group was higher than that in the no rebleeding group (7 / 257 vs. 2 / 17, p=0.10), although no statistically significant difference was observed. The ROC analysis of the cutoff value of eGFR for predicting rebleeding was performed, and the area under the ROC curve (AUC) was 0.77 (95% confidence interval, 0.64–0.91) (Figure 2). Sensitivity and specificity were the highest when eGFR cutoff value of 34.8 mL/min/1.73 m^2 was used, at 64.7% and 85.2 %, respectively. Therefore, eGFR <30 ml/min/1.73 m^2 was used instead of the eGFR level for multivariate analysis. The clinical Rockall score and *H. pylori* status in multivariate analysis were not included since the clinical Rockall score includes several parameters such as renal failure and *H. pylori* status was not fully examined. Multivariate analysis revealed that eGFR < 30 mL/min/1.73 m^2 was an independent risk factor for rebleeding after endoscopic hemostasis (odds ratio 4.77, 95% confidence interval [CI] 1.168–18.211, p = 0.03) (Table 3).

Table 4 shows the clinical characteristics of each group according to the severity of renal dysfunction (eGFR < 30 mL/min/1.73 m^2 [severe] and ≥ 30 mL/min/1.73 m^2

Table 1. Clinical Characteristics of all Patients

Age (years, mean ± SD)	69.6 ± 14.9
Sex (male/female)	193/81
Drug used	
Antithrombotic drug	69
(antiplatelet/anticoagulants)	54/20
NSAIDs	68
Location (stomach/duodenum)	195/79
Hemoglobin (g/dL, mean ± SD)	8.82 ± 2.67
BUN (mg/dL, mean ± SD)	46.0 ± 30.3
Albumin (g/dL, mean ± SD)	3.03 ± 0.59
eGFR (mL/min/1.73 m^2, mean ± SD)	63.3 ± 28.0
Liver cirrhosis	7
Chronic heart failure	24
Coronary heart disease	15
Hemodialysis	9
Diabetes	44
Cerebral infarction	30
Metastatic neoplasm	9
Glasgow blatchford score (mean ± SD)	10.4 ± 3.6
Clinical rockall score (mean ± SD)	2.7 ± 2.03
H. pylori (positive/eradicated/negative)	142/7/98

SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

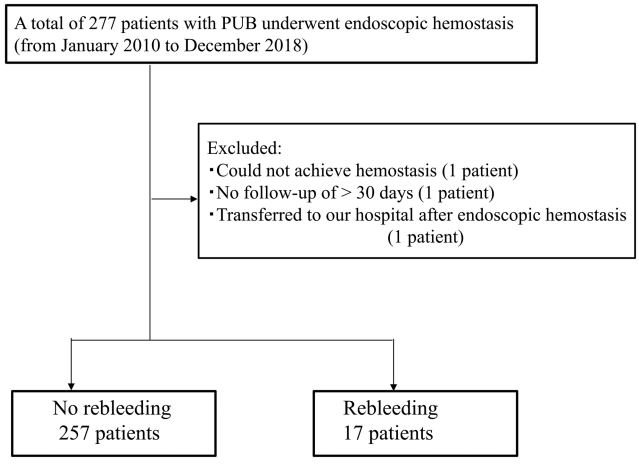

Figure 1. Flowchart of Patient Inclusion in This Study. PUB, Peptic Ulcer Bleeding.

Table 2. Univariate Analysis for the Incidence of Rebleeding After Initial Hemostasis

	No Rebleeding (n = 257)	Rebleeding (n = 17)	*P*-Value
Age (years, mean ± SD)	69.4 ± 14.8	73.1 ± 16.7	0.31
Sex (male/female)	182/75	11/6	0.59
Drug used			
Antithrombotic drug (antiplatelet/anticoagulants)	50/18	4/2	0.75/0.35
NSAIDs	61	7	0.14
Location (stomach/duodenum)	185/72	10/7	0.27
Hemoglobin (g/dL, mean ± SD)	8.86 ± 2.68	8.31 ± 2.54	0.41
BUN (mg/dL, mean ± SD)	44.0 ± 27.9	76.8 ± 46.7	< 0.0001
Albumin (g/dL, mean ± SD)	3.04\ ± 0.59	2.90 ± 0.61	0.35
eGFR (mL/min/1.73 m^2, mean ± SD)	65.1 ± 26.9	35.8 ± 30.5	< 0.0001
eGFR < 30 mL/min/1.73 m^2	11	6	<0.0001
Hemodialysis	7	2	0.10
Liver cirrhosis	6	1	0.36
Chronic heart failure	22	2	0.65
Coronary heart disease	13	2	0.24
Diabetes	40	4	0.49
Cerebral infarction	28	2	1.0
Metastatic neoplasm	9	0	1.0
Glasgow blatchford score (mean ±SD)	10.36 ± 3.69	11.29 ± 3.00	0.31
Clinical rockall score (mean ±SD)	2.59 ± 2.02	4.00 ± 1.87	0.005
H. pylori (positive/ negative (eradicated))	139/94 (7)	3/11 (0)	0.01
Time to rebleeding, median (range), day	-	2 (1-21)	-

SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

[not severe]). Univariate analysis demonstrated that the proportion of patients who took anticoagulants (p = 0.006), had chronic heart failure (p = 0.003) and had diabetes (p = 0.03) and the BUN level (p < 0.0001) was significantly higher in patients with eGFR < 30 mL/min/1.73 m^2 than that in other patients. It also demonstrated that hemoglobin level (p = 0.0001), albumin level (p < 0.0001), and proportion of patients with *H. pylori*-positive status (p = 0.0002) were lower in patients with eGFR < 30 mL/min/1.73 m^2 than that in other patients.

The analysis of endoscopic characteristics showed that rebleeding was associated with active bleeding (Forrest Ia and Ib) (p = 0.01) and combination therapy (p < 0.0001) (Table 5). The Forrest classification at the time of rebleeding showed 14 for Forrest I, which was initially from 6 Forrest I and 8 Forrest II and 3 for Forrest II, which was initially 2 Forrest I and 1 Forrest II.

In addition, Figure 3 shows that patients with eGFR < 15 mL/min/1.73 m^2 had a higher rebleeding rate than other patients. Among patients with eGFR < 15 mL/min/1.73 m^2, the rates of rebleeding in those without and with HD were 45.5% and 25%, respectively (Table 6).

DISCUSSION

The mortality rate of PUB is still as high as 5–10%.[5] It is therefore important to investigate the cause of rebleeding after endoscopic hemostasis. However, at present, it remains unclear whether there is an association between rebleeding risk and renal function. It has been reported that the prevalence of CKD is around 13% worldwide.[22] Older people have a high prevalence of CKD, and due to the growing aging population, the number of patients with CKD is increasing.

The present study shows that renal dysfunction may be an independent factor for rebleeding after endoscopic

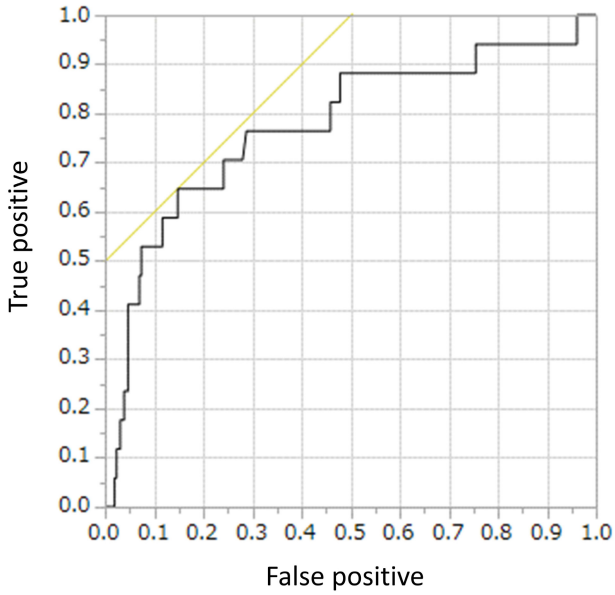

Figure 2. Receiver Operating Characteristic (ROC) Curve of the eGFR Level for Detection of Rebleeding After Endoscopic Hemostasis.

Table 3. Multivariate Analysis for the Incidence of Rebleeding After Initial Hemostasis

	Odds Ratio	95% CI	*P*-Value
BUN	1.01	0.995–1.026	0.17
eGFR < 30 mL/min/1.73 m^2	4.77	1.168-18.211	0.03

CI, confidence interval; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

hemostasis in patients with PUB. Moreover, this study revealed that patients with an eGFR less than around 30 have a high rebleeding risk among patients with various degrees of renal dysfunction. Moreover, patients with eGFR < 15 mL/min/1.73 m^2 not undergoing HD, as well as those undergoing HD, have a high risk for rebleeding.

In this study, the eGFR was based on the blood test at the initial bleeding time. In about one-third of patients (39/112) with eGFR <60 mL/min/1.73 m^2, the eGFR categories at the initial bleeding time were worsened from those before the bleeding episode or after the bleeding had subsided. Only four patients had two or more worsened GFR categories. Severe bleeding might make eGFR lower; however, the effect is considered to be limited. PUB is an acute disease, and the underlying renal dysfunction was unknown in most patients. Therefore, it is appropriate to use renal function at the initial bleeding time for evaluating the rebleeding risk.

Previous reports showed that patients undergoing HD had a higher prevalence of peptic ulcer disease.[23] A nationwide 7-year population study in Taiwan showed that both patients undergoing HD and patients with CKD had a significantly higher incidence of ulcer bleeding than controls.[24]

Kim et al. reported that CKD defined as glomerular filtration rate < 60 mL/min/1.73 m^2 was an independent risk factor for rebleeding after endoscopic hemostasis in patients with PUB.[9] Cheung et al. reported that among patients with PUB, only those with ESRD undergoing HD were at a higher risk of rebleeding than patients with normal kidney function, whereas patients with CKD and ESRD not undergoing HD were not.[8] Previous reports demonstrated that a cause of the higher rebleeding rate in patients with CKD and ESRD might be impaired hemostasis caused by uremic platelet dysfunction, platelet-vessel wall interaction, and anemia.[24,25]

Beyene et al. reported that renal dysfunction caused impaired wound healing in mice models.[26] Renal dysfunction worsens wound healing through tissue edema, diminished angiogenesis, and impaired cell proliferation, such as fibroblasts.[26,27] In PUB, these factors also play an important role in ulcer healing, and disorders of these factors may impair ulcer healing–this may increase the risk of rebleeding. Some patients with eGFR < 30 mL/min/1.73 m^2 showed late rebleeding; this may be due to a disorder of ulcer healing.

Data on the long-term risk of rebleeding in patients with PUB were also reported. Moreover, with respect to the 10-year risk of peptic ulcer rebleeding, patients with ESRD undergoing HD have a higher risk of rebleeding than matched controls.[28] Thus, in patients undergoing HD, the risk of rebleeding of PUB is higher than in patients with normal kidney function in the short and long term. However, in patients with CKD not undergoing HD, the rebleeding risk is controversial.[8,9] In a report by Cheung et al., CKD patients not undergoing HD were not at a higher risk of rebleeding, and the authors presumed that this might have been because many of their patients had CKD stage 3, which means less severe kidney disease.[8] Research is yet to compare rebleeding risks between CKD patients with or without HD, and rebleeding risks have not been evaluated according to the patients' kidney function category (CKD stage). This study has

Table 4. Clinical Characteristics and Rebleeding Rate of Groups by eGFR

	eGFR ≥ 30 mL/min/1.73 m^2 (n = 235)	eGFR < 30 mL/min/1.73 m^2 (n = 39)	*P*-Value
Age (years, mean ±SD)	69.0 ± 1.0	73.7 ± 2.4	0.07
Sex (male/female)	170/65	23/16	0.10
Drug used			
Antithrombotic drug	53	16	0.02
(antiplatelet/anticoagulants)	44/13	10/7	0.38/0.006
NSAIDs	57	11	0.69
Location (stomach/duodenum)	170/65	25/14	0.34
Hemoglobin (g/dL, mean ± SD)	9.07 ± 2.68	7.32 ± 2.05	0.0001
BUN (mg/dL, mean ± SD)	38.5 ± 18.8	91.2 ± 44.6	< 0.0001
Albumin (g/dL, mean ± SD)	3.11 ± 0.57	2.56 ± 0.49	< 0.0001
eGFR (mL/min/1.73 m^2, mean ± SD)	71.1 ± 21.6	16.2 ± 8.9	-
Hemodialysis	0	9	-
Liver cirrhosis	5	2	0.26
Chronic heart failure	15	9	0.003
Coronary heart disease	14	1	0.70
Diabetes	33	11	0.03
Cerebral infarction	24	6	0.40
Metastatic neoplasm	8	1	1.0
H. pylori (positive /negative(eradicated))	134/82 (7)	8/23 (0)	0.0002
Rebleeding (%)	8 (3.4%)	9 (23.1)	<0.0001
Time to rebleeding, median (range), day	2 (1-21)	1.5 (1-8)	0.43

SD, standard deviation; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; BUN, blood urea nitrogen.

Table 5. Endoscopic Characteristics of Patients

	No Rebleeding (n = 257)	Rebleeding (n = 17)	*P*-Value
Forrest classification (Ia/Ib/IIa/IIb)	26/29/191/11	2/6/9/0	0.01*
Forrest classification at rebleeding time		8/6/3/0	
Ulcer size (mm, mean ± SD)	15.0 ± 10.8	15.9 ± 12.7	0.74
Endoscopic hemostasis			
Monotherapy			0.79
Coagulation (MHFSC/APC)	175/5	5/0	
Hemostatic clip	22	1	
Epinephrine injection (HSE)	9	0	
Combination therapy	46	11	< 0.0001**

*Forrest I vs. Forrest II by chi-square test.
**Monotherapy vs. combination therapy by chi-square test.
SD, standard deviation; MHFSC, monopolar hemostatic forceps with soft coagulation; APC, argon plasma coagulation; HSE, hypertonic saline epinephrine solution.

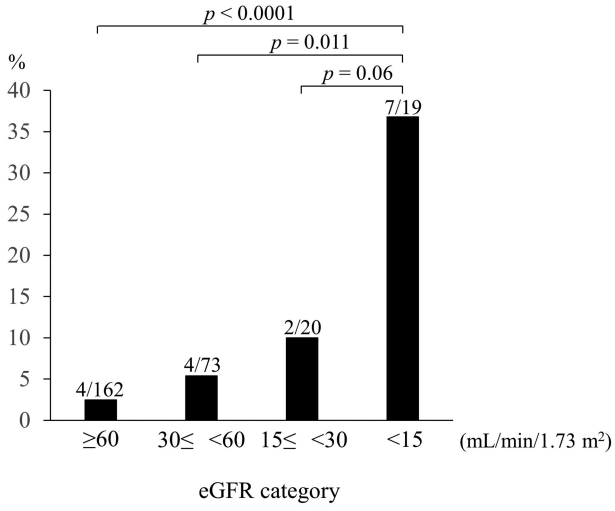

Figure 3. Rebleeding Rate by eGFR Category. Rebleeding Rate in eGFR < 15 mL/min/1.73 m^2 was Higher Than That in Other Categories(≥60, 30 30≤ <60, 15≤ <30, <15). (p < 0.0001, p = 0.011, p = 0.06, respectively). eGFR, Estimated Glomerular Filtration Rate.

Table 6. Rebleeding Rate by Hemodialysis Requirement Among Patients with Chronic Kidney Disease Stage 5

	No Hemodialysis	With Hemodialysis	*P*-Value
Rebleeding rate (%)	5/11 (45.5%)	2/8 (25%)	0.63

Stage according to Kidney Disease Improving Global Outcomes guidelines: stage 5, estimated glomerular filtration rate < 15 mL/min/1.73 m^2. p-Value by Fisher's exact test.

shown that the rebleeding rate increases as the eGFR category gets worse.

In patients undergoing gastric endoscopic submucosal dissection (ESD), which can cause artificial gastric ulcers, several studies have reported that the presence of CKD confers a high risk of delayed bleeding. Libanio et al. reported that patients with CKD had the highest risk of delayed bleeding after gastric ESD in a meta-analysis.[29] Among patients with CKD, delayed bleeding occurred more frequently only in those with CKD stage 4/5.[30] These studies showed that severe CKD itself, not dialysis, contributed to the increased risk. In the report by Yoshioka et al., patients with CKD stage 4 had a higher risk ratio of bleeding than those with CKD stage 5, which included patients undergoing HD.[30] Our results are consistent with these data. In our study, the rebleeding rate in patients with eGFR < 15 mL/min/1.73 m^2 not undergoing HD was higher than that in patients undergoing HD (not statistically significant). This may be related to the fact that HD improves uremia and platelet function, as demonstrated in a previous report.[31]

In our study, patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2) more frequently had chronic heart failure and diabetes and took more anticoagulants. Thus, the high rebleeding rate in patients with renal dysfunction may be attributed to the many comorbidities of these patients.

The presence of *H. pylori* infection was tested in 248 (90.2%) patients. Of the patients tested for *H. pylori*, 202 (73.5%) were tested only using serology; thus, we could not collect complete data on *H. pylori*. From the limited data, there were more *H. pylori*-negative patients among those with rebleeding. The relationship between H. pylori and rebleeding in the short term was not reported. Idiopathic peptic ulcers (IPU), which exclude *H. pylori,* NSAIDs, and other causes, were reported to increase and have been drawing attention.[32,33] IPU is refractory to treatment compared with simple *H.pylori* ulcers.[34,35] To the extent that we can investigate, this study had sixty-nine patients who were *H.pylori*-negative and NSAIDs-negative, and the number of rebleeding in these patients was five (7.5%), which rate was higher than that in *H.pylori*-positive patients (p = 0.07). Many of *H.pylori*-negative ulcers may be categorized as IPUs, and these ulcers might have had an effect on the high rebleeding rate under PPI treatment after endoscopic hemostasis. There were more *H. pylori*-negative patients among those with renal dysfunction with eGFR < 30 mL/min/1.73 m^2. Previous reports showed that the prevalence of *H. pylori* in patients undergoing HD was lower than that in patients with normal kidney function.[36] The reason for this is still unclear. One hypothesis is that *H. pylori* has already been eradicated in patients undergoing HD due to the more frequent use of antibiotics.[25] Another suggestion is that patients undergoing HD have proinflammatory cytokine upregulation and gastric atrophy progression,[37] making the gastric mucosa an unhabitable environment for *H. pylori*.

With the decrease in the number of *H. pylori*-positive patients caused by *H. pylori* eradication and the decreased infection rate, the etiology of PUB has shifted from *H. pylori* to comorbidities.[38] The present study has shown that renal dysfunction is an independent risk factor for rebleeding among comorbidities. In the future, with the decreasing prevalence of *H. pylori* infection,

attention should be focused on comorbidities such as renal dysfunction.

In the analysis of endoscopic hemostasis, patients with combination therapy showed a higher rebleeding risk. Forrest I, which had a high risk of rebleeding in a previous report,[6] was also associated with rebleeding. One possible reason for the high rebleeding risk in patients with combination therapy is that the patients of Forrest I had the higher rate of combination therapy (28.6% vs. 18.5%, p = 0.08), although no statistically significant difference was observed. Another reason might be that we mainly applied monotherapy when hemostasis could be achieved without difficulty. Indicators of hemostasis difficulty such as procedure time could not be evaluated accurately. In some patients with difficulty in hemostasis, hemostasis could not be achieved; however, one patient who failed to achieve endoscopic hemostasis was excluded from this study. In patients with eGFR < 30 mL/min/1.73 m^2, the rate of use of combination therapy did not differ from that in other patients. In a previous report by Cheung et al., the method of hemostasis did not differ among patients with ESRD, CKD, and normal renal function.[8]

This study had several limitations. First, this was a retrospective, single-institution study. Nevertheless, the quality of the collected data is high because all data were reviewed and updated. Second, the number of rebleeding patients was small. Third, most patients were tested for *H. pylori* using serology alone, which cannot accurately determine an *H. pylori*-negative status. Fourth, most patients had no data, such as previous blood test results and medical history regarding renal function except hemodialysis.

In conclusion, this study demonstrated that renal dysfunction might be an independent factor for rebleeding after endoscopic hemostasis in patients with PUB. Therefore, patients with PUB and renal dysfunction need to be observed more carefully. Further studies are required to confirm the importance of renal dysfunction in risk stratification.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Itami City Hospital (Decision date July 25, 2019. Decision number 677).

Informed Consent: All patients were provided opportunities to decline participation in this study by the opt-out method . Moreover, the requirement for obtaining informed consent was waived.

Peer-review: Externally peer-reviewed.

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