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【 ORIGINAL ARTICLE 】

Characteristics, Outcomes, and Risk Factors for Upper Gastrointestinal Bleeding in Inpatients - A Comparison with Outpatients

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Abstract:

Objective The study objectives were to clarify the clinical findings and the causes of intractability and mortality of upper gastrointestinal (UGI) bleeding in inpatients.

Methods The patients were divided into Inpatient (Ip) and Outpatient (Op) onset groups, and their characteristics, clinical and bleeding data, and outcomes were compared.

Patients or Materials Our study included 375 patients who developed UGI bleeding during hospitalization or were admitted after being diagnosed with UGI bleeding in an outpatient setting from January 1, 2015, to June 30, 2020.

Results The Ip group had worse general condition; increased percentages of comorbidities; and more common use of proton pump inhibitor, anti-coagulant, and steroid than the Op group. Compared with the Op group, the Ip group had lower serum albumin levels and platelet counts at the onset of bleeding, whereas rebleeding, mortality, and bleeding-related death rates were higher. Multivariate analysis of the Ip group revealed that the risks of rebleeding included endoscopic high-risk stigmata, maintenance dialysis, and duodenal bleeding, whereas the risks of mortality were gastric ulcer and a Charlson Comorbidity Index update score of ≥3.

Conclusion UGI bleeding in the Ip group was associated with higher rebleeding and mortality rates. Because of their poor general health condition, the pathology of UGI bleeding in these patients may differ from that of patients with common UGI bleeding. A different approach for the care and prevention of UGI bleeding in inpatients is required.

Key words: Upper gastrointestinal bleeding, Inpatients, Risk factor, Mortality, Rebleeding

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Introduction

Upper gastrointestinal (UGI) bleeding is a common medical emergency, and most patients with UGI bleeding are diagnosed in an outpatient setting. There are numerous reports on the clinical presentation and treatment outcomes of UGI bleeding; however, these reports have focused on outpatients with UGI bleeding (1, 2). Prevention of gastroduodenal (GD) ulcers, the major cause of UGI bleeding, includes eradication therapy for patients positive for *Helicobacter pylori*, discontinuation of the causative drug, and prophylactic use of gastric acid secretion inhibitors for drug-induced ulcers, as recommended by the Japanese Clinical Guidelines (3). However, these preventive methods are only effective for outpatients with UGI bleeding.

In contrast, there are only a few reports on patients who experienced UGI bleeding after hospital admission. Furthermore, there are differences in patient characteristics and prognoses between UGI bleeding cases of inpatients and

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outpatients. Although previous studies have indicated that several factors are involved in the poor prognosis of inpatient bleeding cases, there is no consensus on its pathophysiology and prognosis (4-9).

Based on the gap of knowledge stated above, this study aimed to compare the clinical background, endoscopic findings, treatment course, and outcomes between the inpatient (Ip) and outpatient (Op) onset groups for UGI bleeding. Further analysis was conducted to elucidate the causes of intractability and mortality in the Ip group.

Materials and Methods

Study design and population

A total of 1,187 patients underwent UGI endoscopy due to suspected UGI bleeding at the Tokyo Women's Medical University Hospital between January 1, 2015, and June 30, 2020. Among them, the bleeding sites of 375 patients was identified during endoscopy and these patients required several treatments. A retrospective review of the medical records of these patients was conducted. Patients with esophageal and gastric varices and post-endoscopic bleeding were excluded because they were greatly affected by the underlying liver disease and the corresponding treatment procedures.

Patients were categorized into two groups; 100 patients who developed UGI bleeding while they were hospitalized for another disease were assigned to the Ip group, and the remaining 275 patients who presented to an outpatient clinic due to new-onset UGI bleeding and were subsequently admitted were assigned to the Op group.

Materials

Patient characteristics, such as sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS) at the onset of initial UGI bleeding (10), length of hospital stay before onset, presence of comorbidities, *H. pylori* infection, and type of oral medication taken prior to UGI bleeding, were retrospectively compared and analyzed between the two groups. Clinical and endoscopic findings, such as pulse and systolic blood pressure recorded at the time of bleeding, bleeding symptoms, location of bleeding organ, type of bleeding lesion, platelet count, prothrombin time (international normalized ratio), serum albumin level, endoscopic high-risk stigmata, and number of red blood cell (RBC) transfusions, were also collected and evaluated. Furthermore, treatment initiated at the time of bleeding and patient outcomes after diagnosis (such as the incidence of rebleeding, in-hospital death, and bleeding-related death) were also examined between the two groups. Hemostasis was performed in patients with bleeding lesions that exhibited high-risk stigmata (Forrest I and IIa) (11).

To identify the risk factors for rebleeding and death in the Ip group, univariate and multivariate analyses were performed on patient characteristics, clinical and endoscopic findings, treatment initiated at the time of bleeding, and outcomes. Comorbidity was scored using the updated Charlson Comorbidity Index (CCI) (12).

Rebleeding was defined as bleeding symptoms that occurred within 30 days after the confirmation of hemostasis at the first examination. These bleeding symptoms were as follows: melena, hematochezia, hematemesis, decreased blood pressure, and decreased serum hemoglobin levels. All deaths that occurred within 30 days of onset were regarded as inpatient deaths, whereas death due to hemorrhagic shock caused by blood loss and organ failure triggered by bleeding was considered as bleeding-related death.

Statement of ethics

This study was reviewed and approved by the Institutional Review Board of Tokyo Women's Medical University Hospital (No. 2021-0163) and conducted in accordance with the Declaration of Helsinki. The Tokyo Women's Medical University Ethics Committee approved the opt-out system for informed consent for this study.

Statistical analysis

The results for categorical variables are presented as number of cases (%) and continuous variables as median (interquartile range). Pearson's chi-square test and Mann-Whitney U test were performed for between-group comparisons. Univariate and multivariate analysis using logistic regression was performed to examine risk factors for rebleeding and in-hospital mortality. A p-value of <0.05 was considered statistically significant. JMP pro 15 software program (SAS institute Inc., Cary, NC, USA) was used for all analyses.

Results

Comparison between the Ip and Op groups

Table 1 shows the comparison of the characteristics between the Ip and Op groups. There were no significant differences in sex or age between the groups (Table 1-a). However, compared with the Op group, the Ip group showed a higher percentage of patients with a poor ECOG performance status (≥2) and comorbidities, such as chronic heart failure, ischemic heart disease, maintenance dialysis, malignancies, and infectious diseases. In addition, the number of anti-coagulant, steroid, and proton pump inhibitor (PPI) users was significantly higher in the Ip group than in the Op group. In contrast, the *H. pylori* infection rate tended to be higher in the Op group than in the Ip group.

Clinical findings at the time of bleeding showed significantly more cases with systolic blood pressure of <100 mmHg in the Ip group than in the Op group (Table 1-b). In terms of symptoms, melena was significantly more prevalent in the Op group, whereas hematemesis was significantly more common in the Ip group. Endoscopic findings showed that the esophagus was a significantly more common lesion site in the Ip group, whereas lesion site was found more

Table 1. Comparison of the Characteristics between the Outpatient and Inpatient Onset Groups.

a) Baseline characteristics

	Op group, n=275	Ip group, n=100	p value
Male (%)	175 (63.6%)	65 (65%)	ns
Age, median (IQR)	70 (58-80)	73 (64.3-78)	ns
ECOG Performance status ≥ 2	81 (29.5%)	90 (90%)	<0.001
Length of hospital stay, days, median(IQR)	15 (7-37)		
Comorbidities			
Ischemic heart disease	44 (16%)	26 (26%)	0.032
Chronic heart disease	58 (21.1%)	39 (39%)	<0.001
Cerebrovascular disorder	43 (15.6%)	19 (19%)	ns
Diabetes	83 (30.2%)	26 (26%)	ns
Chronic renal disease	88 (32.0%)	44 (44%)	0.033
Maintenance dialysis	32 (11.6%)	20 (20%)	0.045
Liver cirrhosis	23 (8.4%)	10 (10%)	ns
Collagen disease	24 (8.7%)	13 (13%)	ns
Chronic respiratory disease	13 (4.7%)	7 (7%)	ns
Malignancies	51 (18.5%)	32 (32%)	0.007
Infection	14 (5.1%)	27 (27%)	<0.001
History of transplantation	11 (4%)	9 (9%)	0.057
Helicobacter pylori, positive	66/156 (42.3%)	6/24 (25%)	0.098
Medication before bleeding			
Anti-coagulant	64 (23.3)	43 (43%)	<0.001
Anti-platelet	91 (33.1)	29 (29%)	ns
NSAIDs	59 (21.5)	17 (17%)	ns
Steroid	36 (13.1)	26 (26%)	0.004
PPI	79 (28.7)	49 (49%)	<0.001

IQR: interquartile range, ECOG: Eastern Cooperative Oncology Group, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor, Op: outpatient, Ip: inpatient, ns: not significant

b) Clinical and endoscopic findings and treatment

	Op group, n=275	Ip group, n=100	p value
Vital signs at onset			
Systolic blood pressure <100 mmHg	78 (28.4%)	50 (50%)	<0.001
Pulse rate>100/min	88 (32%)	34 (34%)	ns
Symptoms			
Melena	178 (64.7%)	47 (47%)	0.002
Hematochezia	17 (6.2%)	7 (7%)	ns
Hematemesis	89 (32.4%)	44 (44%)	0.039
Anemia	117 (42.6%)	42 (42%)	ns
Location of bleeding			
Esophagus	29 (10.6%)	23 (23%)	0.003
Stomach	169 (61.5%)	46 (46%)	0.008
Duodenum	82 (29.8%)	40 (49%)	0.066
Anastomosis	6 (2.2%)	1 (1%)	ns
Etiology of bleeding			
Esophageal mucosal disorder	13 (4.7%)	10 (10%)	0.073
Iatrogenic esophageal mucosal disorder	0 (0%)	4 (4%)	0.001
Mallory-Weiss tear	16 (5.8%)	16 (16%)	0.003
Polyp	6 (2.2%)	3 (3%)	ns
Angioectasia	32 (11.6%)	10 (10%)	ns
GDU	172 (62.5%)	55 (55%)	ns
PPI user in patients with GDU	33 (12%)	20 (20%)	0.049
Post-bulbar duodenal ulcer	13 (4.7%)	14 (14%)	0.002
Malignancies	34 (12.4%)	4 (4%)	0.010
Others	9 (3.3%)	6 (6%)	ns
Blood test findings at onset			
Serum albumin, g/dL, median (IQR)	3.2 (2.8-3.6)	2.4 (2.1-2.8)	<0.001
Platelets, $\times 10^4/\mu L$, median (IQR)	20 (15.3-27.5)	17.1 (10.2-28.4)	0.045
Prothrombin time, INR, median (IQR)	1.09 (1-1.31)	1.21 (1.07-1.4)	0.002
Endoscopic high-risk stigmata	144 (52.4%)	55 (55%)	ns
Treatment			
Endoscopic treatment	140 (50.9%)	52 (52%)	ns
IVR	2 (0.7%)	3 (3%)	ns
Surgical intervention	3 (1.1%)	2 (2%)	ns
RBC transfusion	227 (82.6%)	89 (89%)	ns
Transfusion units, median (IQR)	7 (6-8)	10 (8-12)	0.024

GDU: gastroduodenal ulcer, PPI: proton pump inhibitor, IQR: interquartile range, INR: international normalized ratio, IVR: interventional radiology, RBC: red blood cells, Op: outpatient, Ip: inpatient, ns: not significant

c) Outcomes

	Op group, n=275	Ip group, n=100	p value
Rebleeding	21 (7.6%)	18 (18%)	<0.001
In-hospital death	6 (2.2%)	17 (17%)	<0.001
Bleeding-related death	3 (1.1%)	9 (9%)	<0.001

Op: outpatient, Ip: inpatient

often in the stomach in the Op group. In both groups, the most common etiology of bleeding was GD ulcer. Mallory-Weiss tear, iatrogenic esophageal mucosal injury, GD ulcers in spite of taking PPIs and post-bulbar duodenal ulcer were significantly more common in the Ip group. In comparison, bleeding from malignant tumors occurred more often in the Op group than in the Ip group. Blood test findings at the onset of UGI bleeding showed that, in the Ip group, serum albumin levels and platelet counts were significantly lower, and prothrombin time was significantly prolonged compared with those in the Op group. There were no significant differences between the two groups in the ratio of treatment endoscopy to treatment modality. The number of RBC transfusion units used after onset was significantly higher in the Ip group than in the Op group. Regarding clinical outcomes, rebleeding, in-hospital death, and bleeding-related mortality were significantly higher in the Ip group than in the Op group (Table 1-c).

Comparison of rebleeding cases and non-rebleeding cases in the Ip group

Table 2 shows the results of the univariate comparison of the 18 cases with rebleeding and 82 cases without rebleeding in the Ip group. Compared with the group without rebleeding, in the rebleeding group, the percentage of older patients (≥70 years old) was significantly higher, but there were no significant differences in sex or ECOG performance status. Rebleeding tended to be less in long-term (≥3 weeks) hospitalization cases, but not significant. Regarding comorbidities, the prevalence of maintenance dialysis was significantly higher in the rebleeding group than in the non-rebleeding group (Table 2-a). There were no differences in oral medication use between the groups. Regarding bleeding location, rebleeding occurred more often in the duodenum than in the esophagus (Table 2-b). In particular, post-bulbar duodenal ulcers tended to be more common in the rebleeding group. Blood test findings from the onset of the initial UGI bleeding showed that albumin levels tended to be low in patients with rebleeding than in those without rebleeding. The incidence of endoscopic high-risk stigmata was significantly higher in the rebleeding group than in the non-rebleeding group. There were no significant differences in mortality outcomes between the two groups.

Univariate analysis showed significant differences in age (≥70 years), prevalence of maintenance dialysis, duodenal bleeding, and endoscopic high-risk stigmata between the two groups. These significant variables were subsequently inputted in multivariate analysis to assess their effect on rebleeding. The results showed that endoscopic high-risk stigmata, maintenance dialysis, and duodenal bleeding were independent risk factors for rebleeding (Table 3).

Comparison of inpatient death and surviving patients in the inpatient onset group

Table 4 shows a comparison of in-hospital deaths and survivors in the Ip group. In relation to the CCI update score, which indicates the comorbidity level, a score of ≥3 was significantly more common in the in-hospital death group than in the survivor group (Table 4-a). There was no difference in length of hospital stay before onset and oral medication use between the two groups. Regarding the etiology of bleeding, gastric ulcers were more common while duodenal ulcers were less common in the in-hospital death group than in the survivor group (Table 4-b). Two cases of duodenal ulcer in the in-hospital death group were both post-bulbar duodenal ulcers. Blood test findings showed that platelet counts tended to be lower in the in-hospital death group than in the survivor group.

Univariate analysis showed significant differences in the prevalence of an updated CCI score of ≥3 and gastric ulcers. These significant variables and age as a general prognostic factor were inputted in multivariate analysis to assess their effect on in-hospital mortality. The results showed that an updated CCI score of ≥3 and gastric ulcer were independent risk factors for in-hospital mortality (Table 5).

A detailed review of in-hospital deaths in the Ip group revealed nine bleeding-related deaths (Table 6). Hemorrhagic shock due to UGI bleeding was the cause of death in three cases. In the other six cases, organ failure triggered by bleeding was the cause of death. Further breakdown of the cause of death in the six cases revealed that liver failure occurred in one case, respiratory failure in one case, and multiple organ failure in one case, while the remaining three cases were due to heart failure. The origin of bleeding was gastroduodenal ulcer in eight cases. Of these, seven cases were treated with anti-coagulant or anti-platelets, four cases were treated with PPI, an anti-ulcer drug.

Discussion

Previous reports have suggested that the pathophysiology and prognosis of UGI bleeding differ depending on whether it develops during hospitalization. Herein, we compared the clinical background, endoscopic findings, treatment course, and outcomes between the Ip and Op groups for UGI bleeding. A detailed comparison of the groups revealed significant differences in several factors. The causal relationship between these results and the pathophysiology of UGI bleeding during hospitalization (i.e., underlying cause of intractability and poor prognosis of UGI bleeding onset during hospitalization) was further analyzed.

In the present study, the rebleeding and mortality rates were significantly higher in the Ip group than in the Op group. Similar studies have reported increased mortality in hospitalized patients (4-9). Several studies have also reported that the incidence of rebleeding was higher in the Ip group, which is similar to the results shown in our study (4, 7), while others have shown that the incidence of rebleeding was similar in both Ip and Op groups (6, 9).

GD ulcers are the primary cause of UGI bleeding (3). *H. pylori* infection and drug-induced mucosal injury, such as non-steroidal anti-inflammatory drugs (NSAIDs), are well-

Table 2. Comparison of Clinical Characteristics between Patients with and without Rebleeding in the Inpatient Onset Group.

a) Baseline characteristics

	Rebleeding, n=18	Non-rebleeding, n=82	p value
Male (%)	13 (72.2%)	52 (63.4%)	ns
Age ≥ 70 years old	15 (83.3%)	48 (58.5%)	0.049
ECOG Performance Status ≥ 2	17 (94.4%)	73 (89.0%)	ns
Length of stay before onset ≥ 14days	6 (33.3%)	48 (58.5%)	0.052
Comorbidities			
Ischemic heart disease	7 (38.9%)	19 (23.2%)	ns
Chronic heart failure	7 (38.9%)	32 (39.0%)	ns
Cerebrovascular disease	4 (22.2%)	15 (18.3%)	ns
Diabetes	7 (38.9%)	19 (23.2%)	ns
Maintenance dialysis	7 (38.9%)	13 (15.9%)	0.037
Liver cirrhosis	0 (0%)	10 (12.2%)	ns
Collagen disease	3 (16.7%)	10 (12.2%)	ns
Chronic respiratory disease	2 (11.1%)	5 (6.1%)	ns
Malignancies	7 (38.9%)	25 (30.5%)	ns
CCI update score ≥ 3	10 (55.6%)	41 (50.0%)	ns
Medication before bleeding			
Anti-coagulant	5 (27.8%)	38 (46.3%)	ns
Anti-platelet	9 (50.0%)	30 (36.6%)	ns
NSAIDs	2 (11.1%)	15 (18.3%)	ns
Steroid	5 (27.8%)	21 (25.6%)	ns
PPI	7 (38.9%)	42 (51.2%)	ns

ECOG: Eastern Cooperative Oncology Group, CCI: Charlson Comorbidity Index, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor, ns: not significant

b) Bleeding characteristics, treatment, and outcomes

	Rebleeding, n=18	Non-rebleeding, n=82	p value
Vital sign at onset			
Systolic blood pressure <100 mmHg	10 (55.6%)	40 (48.8%)	ns
Pulse rate ≥ 100/min	6 (33.3%)	28 (34.2%)	ns
Location of bleeding			
Esophagus	0 (0%)	23 (28.1%)	0.01
Stomach	7 (38.9%)	39 (47.6%)	ns
Duodenum	12 (66.7%)	28 (34.2%)	0.011
Etiology of bleeding			
Esophageal mucosal disease	0 (0%)	10 (12.2%)	ns
Angioectasia	3 (16.7%)	7 (8.5%)	ns
Gastric ulcer	4 (22.2%)	23 (28.1%)	ns
Duodenal ulcer	9 (50%)	23 (28.1%)	0.071
Post-bulbar duodenal ulcer	5 (27.8%)	9 (11.0%)	0.063
Malignancies	2 (11.1%)	4 (4.9%)	ns
Diverticulum	1 (5.5%)	1 (1.2%)	ns
Blood test findings at onset			
Serum albumin ≤ 2.8g/dL	17 (94.4%)	60 (73.2%)	0.052
Platelets ≤ 5×10^4/μL	2 (11.1%)	5 (6.1%)	ns
Prothrombin time (INR) ≥ 2.0	2 (11.1%)	12 (15.2%)	ns
Endscopic high-risk stigmata	15 (83.3%)	40 (48.8%)	0.008
Treatment			
Endoscopic treatment	14 (77.8%)	38 (46.3%)	0.016
IVR	1 (5.6%)	0 (0%)	0 .032
Surgery intervension	0 (0%)	2 (2.4%)	ns
In-hospital death	2 (11.1%)	15 (18.3%)	ns
Bleeding-related death	1 (5.6%)	6 (7.3%)	ns

INR: international normalized ratio, IVR: interventional radiology, ns: not significant

Table 3. Multivariate Analysis of the Risk Factors for Rebleeding.

	Odds ratio	95% CI	p value
Endoscopic high-risk stigmata	11.61	2.29-58.80	0.0031
Maintenance dialysis	7.29	1.64-32.34	0.0089
Duodenum	4.80	1.35-17.12	0.0156
Age ≥ 70 years old	4.57	0.99-21.05	0.0511

CI: confidence interval

known causes of GD ulcers (13, 14). In this study, the *H. pylori* infection rate tended to be lower in the Ip group than in the Op group, whereas the number of anti-coagulant use, including the use of NSAIDs and low-dose aspirin, was similar between the groups. These results suggest that although bleeding gastric and duodenal ulcers were prevalent in both the Ip and Op groups, the pathogenesis and bleeding mechanism may be different between the groups. Furthermore, our results showed that the Ip group had worse ECOG PS and vital signs and lower serum albumin levels, platelet counts, and coagulation activity than the Op group. The Ip group also had a higher comorbidity rate than the Op group. Not surprisingly, the general health condition of the patients was worse in the Ip group than in the Op group. Breakdown of the mucosal defense mechanism due to microcirculatory disorders and visceral hypoperfusion is involved in the development of peptic ulcers, especially gastric ulcers, associated with aggravation of the general health condition of a patient. In addition, physical and mental stress trigger vagal stimulation, which may lead to the development of stress ulcers (15). Therefore, it is postulated that the mechanism of peptic ulcer formation during hospitalization is different from that in outpatients.

In a study examining idiopathic ulcers that were neither *H. pylori*-positive or drug-induced ulcers, these ulcers were shown to be associated with old age, gastric ulcer, high American Society of Anesthesiologists score, and in-hospital condition. High rebleeding and mortality rates have also been reported in patients with idiopathic ulcers (16). These findings suggest that, to prevent peptic ulcers and bleeding during hospitalization, standard therapies such as *H. pylori* eradication and PPI therapy are insufficient. In this study, 50% of bleeding-related deaths with gastroduodenal ulcer were receiving PPI treatment before bleeding. The management of the primary disease and nutritional status, improvement of the general health condition, control of anticoagulation therapy, and reduction of physical and mental stresses are important and should be taken into consideration when treating UGI bleeding for inpatients.

In addition, the Ip group had significantly more cases of bleeding from the esophageal lesions than the Op group. Significant differences were also observed in the incidence of Mallory-Weiss tears and iatrogenic bleeding between the two groups. Vomiting due to side effects related to drugs and treatments is common during hospitalization, and medical procedures that directly stimulate the esophageal mucosa, such as endoscopy, transesophageal echocardiography, and nasogastric tube insertion, are performed. In addition, heart disease, renal failure, and hypoxemia are known risk factors for acute esophageal mucosal injury, such as acute necrotizing esophagitis, (17) and may occur during inpatient treatment of the underlying disease.

Previous studies have reported an overall mortality rate of 8.9%-29% for inpatient-onset bleeding and 2%-39% for rebleeding (4, 6-9, 18). In our study, the Ip group had 17% of all-cause deaths with 8% that were bleeding-related deaths and a rebleeding rate of 18%. Our results are comparable to previous reports. Furthermore, the median length of hospital stay before bleeding was 15days, as previously reported (4, 9). The long-term hospitalization (≥14days) did not significantly affect rebleeding or in-hospital death.

Multivariate analysis showed that endoscopic high-risk stigmata, maintenance dialysis, and duodenal bleeding were independent risk factors for rebleeding in the Ip group. Other studies have also reported that the presence of endoscopic high-risk stigmata (Forrest I and IIa) is a risk factor for rebleeding (6, 19). If active bleeding or a visible vessel is identified during the initial endoscopic examination, clinicians should ensure adequate hemostasis because these lesions have a high risk of rebleeding.

Patients with chronic renal failure have been reported to have a significantly higher incidence (i.e., 10-12 times higher) of GD ulcer bleeding, and patients undergoing dialysis have a particularly high rebleeding rate. This can be attributed to the aspects of dialysis treatment, including the use of anti-coagulants and hypotension during dialysis, which cause ischemia due to decreased peripheral circulating blood flow, leading to gastrointestinal mucosal damage and UGI bleeding (20, 21).

Furthermore, studies have reported that duodenal ulcers, especially post-bulbar duodenal ulcers, are associated with a high risk of rebleeding (19, 22, 23). In this study, post-bulbar duodenal ulcers occurred more frequently in the rebleeding group. Anatomically, the duodenum has a narrow lumen; therefore, endoscopic hemostasis in the duodenum is challenging due to difficulties in visualizing the bleeding point and manipulating the endoscope. In addition, healing may be delayed by the presence of bile and pancreatic juice, leading to an increased risk of rebleeding.

Although our study did not show a significant association between rebleeding and death, previous large-scale studies have reported that rebleeding is associated with increased mortality (19, 24, 25). Clinicians should be made aware that prevention of rebleeding leads to improved patient survival.

Table 4. Comparison of Clinical Characteristics between In-hospital Deaths and Survivors in the Inpatient Onset Group.

a) Baseline characteristics

	In-hospital death, n=17	Survivors, n=83	p value
Male (%)	10 (58.8%)	55 (66.3%)	ns
Age ≥ 70 years old	11 (64.7%)	52 (62.7%)	ns
ECOG performance status ≥ 2	16 (94.1%)	74 (89.2%)	ns
Length of stay before onset ≥ 14days	11 (64.7%)	43 (51.8%)	ns
Comorbidities			
Ischemic heart disease	4 (23.5%)	22 (26.5%)	ns
Chronic heart failure	10 (58.8%)	29 (34.9%)	ns
Cerebrovascular disease	5 (29.4%)	14 (16.9%)	ns
Diabetes	2 (11.8%)	24 (28.9)	ns
Maintenance dialysis	5 (29.4%)	15 (18.1%)	ns
Liver cirrhosis	2 (11.8%)	8 (9.6%)	ns
Connective tissue disease	2 (11.8%)	11 (13.3%)	ns
Chronic respiratory disease	3 (17.7%)	4 (4.8%)	0.059
Malignancies	4 (23.5%)	28 (33.7%)	ns
CCI update score ≥ 3	14 (82.4%)	37 (44.6%)	0.005
Medication before bleeding			
Anti-coagulant	9 (52.9%)	34 (40.9%)	ns
Anti-platelet	8 (47.1%)	31 (37.4%)	ns
NSAIDs	1 (5.9%)	16 (19.3%)	ns
Steroid	7 (41.2%)	19 (22.9%)	ns
PPI	7 (41.2%)	42 (50.6%)	ns

ECOG: Eastern Cooperative Oncology Group, CCI: Charlson Comorbidity Index, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor, ns: not significant

b) Bleeding characteristics, treatment, and outcomes

	In-hospital death, n=17	Survivors, n=83	p value
Vital sign at onset			
Systolic blood pressure <100mmHg	9 (52.4%)	41 (49.4%)	ns
Pulse rate ≥ 100/min	8 (47.1%)	26 (31.3%)	ns
Location of bleeding			
Esophagus	5 (29.4%)	18 (21.7%)	ns
Stomach	11 (64.7%)	35 (42.2%)	ns
Duodenum	3 (17.7%)	37 (44.6%)	0.039
Etiology of bleeding			
Esophageal mucosal disorder	3 (17.7%)	7 (8.4%)	ns
Mallory-Weiss tear	5 (29.4%)	11 (13.3%)	0.098
Angioectasia	0 (0%)	10 (12.1%)	ns
Gastric ulcer	9 (53.0%)	18 (21.7%)	0.008
Duodenal ulcer	2 (11.8%)	30 (36.1%)	0.049
Post-bulbar duodenal ulcer	2 (11.8%)	12 (14.5%)	ns
Malignancies	1 (5.9%)	3 (3.6%)	ns
Blood test findings at onset			
Serum albumin ≤ 2.8 g/dL	14 (82.4%)	63 (75.9%)	ns
Platelets ≤ $5\times10^4/\mu L$	3 (17.7%)	4 (4.8%)	0.059
Prothrombin time (INR) ≥ 2.0	4 (17.4%)	10 (13.5%)	ns
Endoscopic high-risk stigmata	8 (47.1%)	47 (56.6%)	ns
Treatment			
Endoscopic hemostasis	8 (47.1%)	44 (53.0%)	ns
IVR	0 (0%)	4 (4.8%)	ns
Surgical intervention	0 (0%)	2 (2.4%)	ns
Rebleeding	2 (11.7%)	16 (19.3%)	ns

INR: international normalized ratio, IVR: interventional radiology, ns: not significant

Multivariate analysis showed that an updated CCI score of ≥3 and gastric ulcer were independent risk factors for in-hospital death in the Ip group. Various scoring systems such as Rockall score (26), Glasgow-Blatchford score (GBS) (27), and AIMS65 (28) have been developed for the management and prognostic evaluation of UGI bleeding. These scorings require vital signs, blood test data, and endoscopic findings at onset. In this study, we considered that it is important to perform risk management before bleeding, especially in hospitalized patients. Therefore, we used the CCI update score as an index to evaluate comorbidity, which does not include information on bleeding (12, 29). Although multiple studies to date have discussed the risk factors for mortality, many have reported the presence of multiple comorbidities as one of the key risk factors for mortality. The CCI update score significantly correlates with prognosis compared with other multiple scoring systems. A CCI score of ≥3 has been reported to be useful for predicting mortality (30). Patients with multiple comorbidities may be more prone to death because bleeding may easily aggravate their general health condition.

Table 5. Multivariate Analysis of the Risk Factors for In-hospital Mortality.

	Odds ratio	95% CI	p value
Gastric ulcer	5.62	1.65-19.16	0.0057
CCI update score ≥ 3	7.65	1.84-31.73	0.0050
Age ≥ 70 years	1.45	0.42-5.04	0.5555

CCI: Charlson comorbidity index, CI: confidence interval

The presence of gastric ulcers is also an independent risk factor for mortality. In general, the symptoms of UGI can be well controlled; however, in hospitalized patients with a poor general health condition, healing of ulcers is often delayed due to peripheral circulatory disturbance and/or poor nutritional status. Bleeding can lead to further nutritional difficulties, and this vicious cycle may lead to increased mortality.

In our study, six patients died due to organ failure-induced UGI bleeding, which suggested that UGI bleeding can exacerbate comorbidity. Thus, it is important to not only treat the bleeding of UGI but also manage other comorbidities when caring for patients with UGI bleeding and comorbidities. In a study investigating the long-term prognosis after UGI bleeding, Crooks et al. reported that mortality was higher in the bleeding group than in the non-bleeding control group up to 3 years after bleeding onset; bleeding-related mortality and mortality due to comorbidities in-

Table 6. Details of Nine In-hospital Deaths Cases in the Inpatient Onset Group.

	Age Sex	Origin of bleeding ① location, ② number, ③ size, ④ Forrest classification, ⑤ treatment, ⑥ result	Comorbidities	Cause of death	Medication
1	78 Male	Gastroduodenal ulcer ① M/L/P-B, ② multiple, ③ 30mm, ④ IIc, ⑤ no treatment, ⑥ failure	Chronic heart failure Maintenance dialysis Post-renal transplantation ARDS	Hemorrhagic shock	Anti-platelet Steroid
2	73 Female	Gastric ulcer ① L, ② single, ③ 20mm, ④ Ib, ⑤ no treatment, ⑥ failure	Lung cancer Interstitial pneumonia DVT	Hemorrhagic shock	Steroid PPI
3	78 Male	Gastric ulcer ① M, ② single, ③ 50mm, ④ IIa, ⑤ electrocoagulation, ⑥ failure	Ischemic heart disease Chronic heart failure Chronic renal failure Chronic lung disease	Hemorrhagic shock	Anti-coagulant Anti-platelet PPI
4	85 Male	Gastric ulcer ① U, ② multiple, ③ 10mm, ④ IIa, ⑤ electrocoagulation, ⑥ success	Chronic heart failure Eosinophilic lung disease DVT	Heart failure	Anti-coagulant Steroid PPI
5	89 Female	Gastric ulcer ① L, ② single, ③ 10mm, ④ Ib, ⑤ electrocoagulation, ⑥ success	Chronic heart failure Chronic renal failure	Heart failure pneumonia	Anti-coagulant Anti-platelet
6	68 Male	Gastric ulcer ① L, ② single, ③ 15mm, ④ IIa, ⑤ electrocoagulation, ⑥ success	Chronic heart failure Maintenance dialysis Post-liver transplantation	Heart failure pneumonia	Anti-coagulant Anti-platelet PPI
7	42 Female	GAVE ① L, ② diffuse, ⑤ APC, ⑥ success	Liver cirrhosis Chronic renal failure	Liver failure	PPI
8	76 Male	Duodenal ulcer ① B/P-B, ② mulitple, ③ 15mm, ④ IIc, ⑤ no treatment, ⑥ success	Ischemic heart disease Maintenance dialysis Liver cirrhosis	Pneumonia	Anti-platelet
9	62 Male	Gastric ulcer ① M, ② single, ③ 50mm, ④ IIb, ⑤ no treatment, ⑥ success	Chronic heart failure (artificial heart) Maintenance dialysis	Multi-organ failure	Anti-coagulant Anti-platelet

U: upper of the stomach, M: middle of the stomach, L: lower of the stomach, B: duodenal bulb, P-B: postbulbus of the duodenum, GAVE: gastric antral vascular ectasia, APC: algonplasma coagulation, ARDS: acute respiratory distress syndrome, DVT: deep venous thrombosis, PPI: proton pump inhibitor

creased in the bleeding group (31). Based on the above findings, we should be concerned about the potential exacerbation of comorbidities in inpatients with UGI bleeding.

The limitations of this study include its retrospective nature, single-center design, and small sample size. The small number of patients with bleeding-related death did not allow us to perform a comparative analysis; thus, risk factors associated with bleeding-related death was not analyzed.

This study demonstrated that UGI bleeding in the Ip group had a different pathology, higher rebleeding and mortality rates, and poorer prognosis than that in the Op group. Therefore, to minimize the number of fatal cases due to UGI bleeding, it is important to implement measures against and prevent UGI bleeding in inpatients, which differs from UGI bleeding in the general outpatient population. Furthermore, poor hemodynamics due to bleeding, as well as exacerbation of comorbidities due to bleeding, lead to death. Therefore, it is important to not only treat the bleeding but also improve the management of comorbidities and general health conditions of inpatients with UGI bleeding.

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

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