



Gastrointestinal bleeding increases the risk of subsequent cardiovascular events in patients with acute cardiovascular diseases requiring intensive care

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Abstract

Gastrointestinal (GI) bleeding worsens the outcomes of critically ill patients in the intensive care unit (ICU). Owing to a lack of corresponding data, we aimed to investigate whether GI bleeding during cardiovascular-ICU (C-ICU) admission in acute cardiovascular (CV) disease patients is a risk factor for subsequent CV events. Totally, 492 consecutive C-ICU patients (40.9% acute coronary syndrome, 22.8% heart failure) were grouped into GI bleeding ($n=27$; 12 upper GI and 15 lower GI) and non-GI bleeding ($n=465$) groups. Thirty-nine patients died or developed CV events during hospitalization, and 453 were followed up from the date of C-ICU discharge to evaluate subsequent major adverse CV events. The GI bleeding group had a higher Acute Physiology and Chronic Health Evaluation II score (20.2 ± 8.2 vs. 15.1 ± 6.8 , $p < 0.001$), higher frequency of mechanical ventilator use (29.6% vs. 13.1%, $p = 0.039$), and longer C-ICU admission duration (8 [5–16] days vs. 5 [3–8] days, $p < 0.001$) than the non-GI bleeding group. The in-hospital mortality rate did not differ between the groups. Of those who were followed-up, CV events after C-ICU discharge were identified in 34.6% and 14.3% of patients in the GI and non-GI bleeding groups, respectively, during a median follow-up period of 228 days (log rank, $p < 0.001$). GI bleeding was an independent risk factor for subsequent CV events (adjusted hazard ratio: 2.23, 95% confidence interval: 1.06–4.71; $p = 0.035$). GI bleeding during C-ICU admission was independently associated with subsequent CV events in such settings.

Keywords Gastrointestinal bleeding · Cardiovascular event · Cardiovascular-intensive care unit

Introduction

Gastrointestinal (GI) bleeding is a commonly reported complication in critical care settings and occurs predominantly due to stress-related mucosal damage of the GI tract [1–3]. Moreover, aggressive anti-thrombotic therapies for patients with acute cardiovascular (CV) diseases, such as acute coronary syndrome (ACS), heart failure, and pulmonary embolism, aggravate the degree of GI bleeding in

cardiovascular-intensive care units (C-ICU). Furthermore, GI bleeding may decrease the mortality rate of critically ill patients [4] and increase the risk of subsequent CV events in ACS patients [5, 6]. However, it is still unclear whether GI bleeding in patients with acute CV diseases, including non-ACS disease, in the C-ICU is a risk factor for subsequent CV events. Therefore, this study aimed to investigate the association between GI bleeding during C-ICU admission and CV events after C-ICU discharge in patients with acute CV disease.

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Methods

Study population

We retrospectively reviewed hospital records and enrolled 492 consecutive patients who were emergently admitted

to the C-ICU of Nippon Medical School Hospital for suspected acute CV disease between January 2018 and December 2018. The medical ethics committee of Nippon Medical School Hospital reviewed and approved this clinical study (B-2020-156). Opt-out consent by posting the research information in our hospital was utilized instead of obtaining informed consent from each patient because of our retrospective study design.

The 492 C-ICU patients comprised 201 (40.9%) with ACS (126 with ST elevation myocardial infarction, 46 with non-ST elevation myocardial infarction, and 29 with unstable angina), 112 (22.8%) with heart failure, 33 (6.7%) with acute aortic dissection, 31 (6.3%) with emergency arrhythmias, 12 (2.4%) with Takotsubo cardiomyopathy, 7 (1.4%) with acute myocarditis, 4 (0.8%) with pulmonary embolism, and 92 (18.7%) with other diseases. The patients were grouped according to the presence of GI bleeding during C-ICU admission into the GI bleeding group ($n = 27$) and the non-GI bleeding group ($n = 465$).

Thirty-four patients died, and 5 developed CV disease during the index hospitalization, and the remaining 453 patients were followed-up from the date of C-ICU discharge in order to evaluate subsequent CV events. The median follow-up period was 228 (interquartile range [IQR]: 30–353) days.

Diagnosis of GI bleeding

According to the Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria [7], clinically apparent signs of bleeding, including imaging findings, with a reduction in the hemoglobin level, during C-ICU admission, were regarded as bleeding complications in this study. GI bleeding was defined as a bleeding complication that met the TIMI bleeding criteria and was observed by upper or lower GI endoscopy, or an episode of coffee ground emesis, hematemesis, melena, or red blood per rectum [5]. The severity of the bleeding complications was classified as follows: major, minor, or minimal, based on the TIMI bleeding criteria [7], and the bleeding complication onset date was determined as the day on which the TIMI bleeding criteria were satisfied. When a patient experienced multiple bleeding complications, the most severe bleeding event, as assessed by the TIMI bleeding criteria, was taken as the bleeding complication for the purpose of this analysis.

Patient disease severity

For the evaluation of disease severity on C-ICU admission, we applied two scoring systems: The Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II score. The SOFA score was used to quantitatively assess the presence

of major organ dysfunction, including that of the respiratory, CV, hepatic, coagulation, renal, and neurological systems. For each patient, the general disease severity was assessed according to the APACHE II score, based on 12 physiologic variables, age, and underlying health.

Patient treatments

C-ICU admission and discharge were determined by the full-time attending CV intensivists. Treatment strategies, including intensive care for patients with emergency CV disease, in our C-ICU were planned and performed as indicated by guidelines. A stress ulcer prophylaxis strategy with oral or intravenous administration of proton pump inhibitors (PPIs) was applied for all patients admitted to our C-ICU unless they had contraindications according to recent ACS guidelines [8, 9].

Endpoint and in-hospital adverse events

For the evaluation of subsequent CV events after C-ICU discharge, the primary endpoint of the current analysis was defined as a composite of major adverse CV events (all-cause mortality, non-fatal myocardial infarction or stroke, admission for heart failure, unstable angina, or other CV events) [10].

Nosocomial pneumonia and *Clostridium difficile* infection during hospitalization were selected as in-hospital infectious adverse events related to GI bleeding and PPI administration. In-hospital mortality was defined as short-term mortality of C-ICU patients.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics version 25.0 software (SPSS Inc., Chicago, IL). Dichotomous variables were tested using the Fisher's exact test. Numeric values are presented as the means \pm standard deviations or the medians [IQR] and were tested using the Student's t test or the Mann–Whitney U test when the data had a non-normal distribution. The Kaplan–Meier method was used to estimate the cumulative incidence of the outcomes, and the differences were compared using the log-rank test. For multivariate analysis, hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of each outcome were determined by Cox proportional hazards modeling, and covariates including the APACHE II score, which served as the severity score at admission, use of mechanical support devices during the C-ICU stay (ventilator, renal replacement therapy, intra-aortic balloon pump, percutaneous cardiopulmonary support, and Impella[®]), and length of C-ICU stay were selected through consideration of their impact on the outcomes at each time-point, in addition to age, sex, primary

disease, and GI bleeding. A probability (p) value < 0.05 was considered indicative of a statistically significant difference.

Results

Frequency and severity of GI bleeding

Bleeding complications developed in 64 of the 492 patients (13.0%) during C-ICU admission. Among those with bleeding complications, GI bleeding was the most frequently reported bleeding type, as observed in 27 of the 492 patients (5.5%; 12 with upper GI bleeding and 15 with lower GI bleeding), followed by puncture site bleeding (4.7%), cardiac origin bleeding (1.0%), intra-cranial bleeding (0.8%), respiratory tract bleeding (0.4%), major blood vessel bleeding (0.2%), and others (0.4%).

GI bleeding was observed by upper GI endoscopy in 11 patients and by lower GI endoscopy in 6 patients. The clinical episodes of GI bleeding included 3 with coffee ground emesis or hematemesis, 9 with melena, and 15 with red blood per rectum. In terms of the severity of GI bleeding, the rates of major, minor, and minimal bleeding were 25.9, 44.4, and 29.6%, respectively. Minor upper GI bleeding and minimal lower GI bleeding were most frequent (upper GI bleeding: major 33.3%, minor 58.3%, minimal 8.3%; lower GI bleeding: major 20.0%, minor 33.3%, minimal 46.7%). The frequencies of GI bleeding, with their severity for each primary disease, are shown in Fig. 1a. Details on the timing of complications of GI bleeding during C-ICU admission are presented in Fig. 1b. The frequencies of GI bleeding on the first day and within 5 days of hospitalization were 33.3% ($n=9$) and 77.8% ($n=21$), respectively.

Patient characteristics and treatments

We compared the characteristics and co-interventions used during the C-ICU admission period between the patients in the GI bleeding and non-GI bleeding groups (Table 1). There was no statistical difference in patient demographics between the groups (age, 72.3 ± 14.9 vs. 70.8 ± 14.6 , $p=0.592$; female sex, 44.4 vs. 34.8%, $p=0.309$). The use of anti-platelet drugs before admission was not associated with the occurrence of GI bleeding. The administration rate of anti-peptic ulcer drugs, including PPIs and histamine type 2 receptor antagonists (H_2 Ras), before admission, which were considered for prophylaxis against low-dose aspirin ulcers or treatment of peptic comorbidities, such as gastritis and gastric ulcer, showed no statistically significant difference between the groups (PPIs, 33.3 vs. 29.5%, $p=0.668$; H_2 Ras, 3.7 vs. 3.9%, $p=1.000$). Furthermore, when the administration rates were compared between patients with upper and lower GI bleeding among the GI bleeding group, no

statistically significant difference was observed (PPIs, 25.0 vs. 40.0%, $p=0.683$; H_2 Ras, 0 vs. 6.7%, $p=1.000$). The GI bleeding group showed higher proportions of out-of-hospital cardiac arrest (18.5 vs. 3.2%, $p=0.003$) and shock vitals on arrival (25.9 vs. 10.8%, $p=0.027$). The severity scores on admission were significantly higher in patients with GI bleeding than in those without (SOFA score: 4.3 ± 3.6 vs. 2.8 ± 3.2 , $p=0.016$; APACHE II score, 20.2 ± 8.2 vs. 15.1 ± 6.8 , $p<0.001$). The rate of PPI administration in the GI bleeding group increased to 100% during the C-ICU stay, regardless of upper or lower GI bleeding; patients without GI bleeding also had a high rate of PPI administration (82.6%) based on the stress ulcer prophylaxis strategy in our C-ICU.

Blood transfusions were more frequently performed in patients with GI bleeding than in those without (81.5 vs. 17.6%, $p<0.001$). Mechanical ventilators were more commonly used in the GI bleeding group than in the non-GI bleeding group (29.6 vs. 13.1%, $p=0.039$). Patients with GI bleeding had longer durations of C-ICU stay than those without (8 [IQR 5–16] days vs. 5 [IQR 3–8] days, $p<0.001$). However, there were no differences in infectious complications, including pneumonia and *Clostridium difficile* infection, during hospitalization and in-hospital mortality between the groups.

Impact of GI bleeding on subsequent CV events

After the exclusion of 39 patients who died or developed CV events during the index hospitalization, we assessed the rate of GI bleeding during C-ICU admission as a risk factor for subsequent CV events through follow-up of the remaining 453 patients from the date of C-ICU discharge. CV events were identified in 34.6% (9 of 26) of the patients in the GI bleeding group (25.0 and 46.7% of those with upper and lower GI bleeding, respectively) and 14.3% (61 of 427) of those in the non-GI bleeding group. Kaplan–Meier analyses showed that the cumulative incidence of CV events was higher in the GI bleeding group than in the non-GI bleeding group (log-rank test, $p<0.001$) (Fig. 2). Upon evaluation of CV disease outcomes, statistically significant differences were observed in other CV events between the two groups (all-cause mortality: 3.8 vs. 1.9%, $p=0.415$; non-fatal MI or stroke: 0.0 vs. 0.2%, $p=1.000$; admission for heart failure: 15.4 vs. 5.6%, $p=0.068$; unstable angina: 0.0 vs. 0.5%, $p=1.000$; other CV events: 15.4 vs. 4.9%, $p=0.047$). In the GI bleeding group, the patients who did not receive blood transfusion experienced no CV events, while 42.9% of those who received blood transfusion developed CV events ($p=0.129$).

In the subgroup analysis of ACS ($n=190$) and non-ACS ($n=263$) patients, the incidence of GI bleeding did not differ significantly (6.0 vs. 5.2%, $p=0.693$), and the cumulative incidence of CV events in both subgroups was

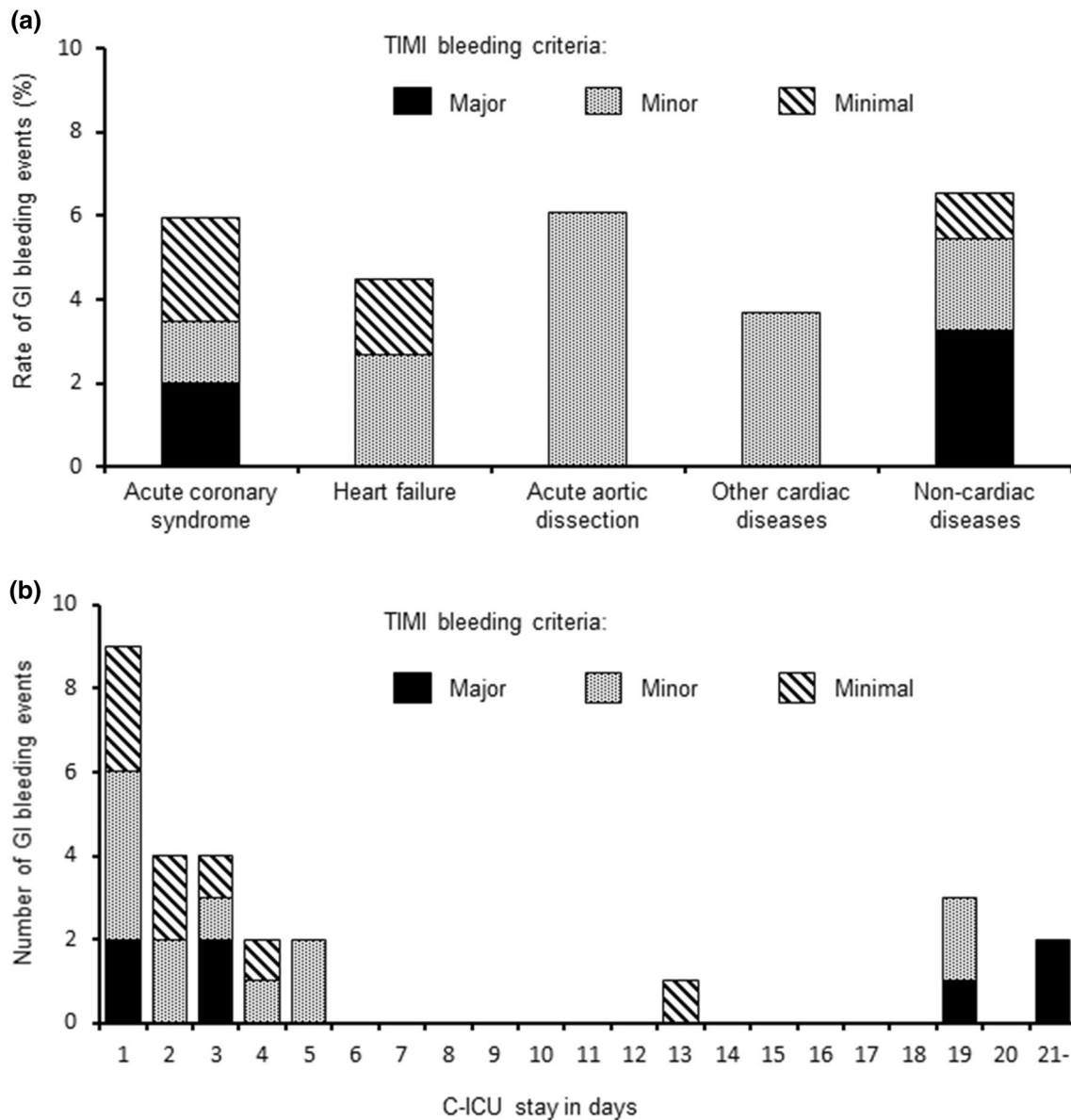


Fig. 1 **a** Incidence rate of GI bleeding for each primary disease, and **b** timing of GI bleeding complications during C-ICU admission. *TIMI* thrombolysis in myocardial infarction, *GI* gastrointestinal, *C-ICU* cardiovascular-intensive care unit

significantly higher in patients with GI bleeding than in those without (log-rank test, ACS: $p = 0.002$; and non-ACS: $p = 0.022$, respectively).

Multivariable analysis employing Cox proportional hazards models revealed GI bleeding to be an independent risk factor for CV events, after adjustment for age, sex, primary disease, APACHE II score, use of mechanical support devices, and length of C-ICU stay (adjusted HR: 2.23, 95% CI 1.06–4.71; $p = 0.035$) (Table 2).

Discussion

The principal finding of our study was that GI bleeding during C-ICU admission in patients with CV diseases requiring intensive care was associated with subsequent CV events after C-ICU discharge. The patients' characteristics differed significantly between the GI bleeding and non-GI bleeding groups, with a higher prevalence

Table 1 Clinical characteristics and co-interventions in patients with and without GI bleeding

	GI bleeding (<i>n</i> =27)	Non-GI bleeding (<i>n</i> =465)	<i>p</i> value
Demographics			
Age (years)	72.3 ± 14.9	70.8 ± 14.6	0.592*
Female sex, <i>n</i> (%)	12 (44.4)	162 (34.8)	0.309
Medical history, <i>n</i> (%)			
Diabetes	9 (33.3)	169 (36.3)	0.839
Hypertension	21 (77.8)	363 (78.1)	1.000
Dyslipidemia	15 (55.6)	263 (56.6)	1.000
Chronic kidney disease (≥ grade 3)	19 (70.4)	264 (56.8)	0.161
Myocardial infarction	2 (7.4)	75 (16.1)	0.286
Atrial fibrillation	7 (25.9)	69 (14.8)	0.164
Heart failure	5 (18.5)	115 (24.7)	0.645
Hepatic disorders	2 (7.4)	8 (1.7)	0.099
Gastroesophageal reflux disease	0 (0.0)	15 (3.2)	1.000
Gastroduodenal ulcer	2 (7.4)	17 (3.7)	0.280
Gastrointestinal bleeding	2 (7.4)	12 (2.6)	0.176
Malignancy	5 (18.5)	71 (15.3)	0.589
Smoking habit	16 (59.3)	269 (57.8)	1.000
Percutaneous coronary intervention	6 (22.2)	67 (14.4)	0.266
Coronary artery bypass grafting	2 (7.4)	20 (4.3)	0.343
Medications before admission, <i>n</i> (%)			
Anticoagulant drugs	6 (22.2)	54 (11.6)	0.124
Aspirin	9 (33.3)	88 (18.9)	0.081
Clopidogrel	1 (3.7)	33 (7.1)	1.000
Prasugrel	1 (3.7)	7 (1.5)	0.365
Other anti-platelet drugs	1 (3.7)	8 (1.7)	0.401
Steroids	1 (3.7)	24 (5.2)	1.000
Proton pump inhibitors	9 (33.3)	137 (29.5)	0.668
Histamine type 2 receptor antagonists	1 (3.7)	18 (3.9)	1.000
Primary diseases, <i>n</i> (%)			
Acute coronary syndrome	12 (44.4)	189 (40.6)	0.693
Heart failure	5 (18.5)	107 (23.0)	0.813
Acute aortic dissection	2 (7.4)	31 (6.7)	0.701
Emergency arrhythmia	1 (3.7)	30 (6.5)	1.000
Pulmonary embolism	1 (3.7)	3 (0.6)	0.203
Acute myocarditis	0 (0.0)	7 (1.5)	1.000
Takotsubo cardiomyopathy	0 (0.0)	12 (2.6)	1.000
Others	6 (22.2)	86 (18.5)	0.614
Clinical features, <i>n</i> (%)			
Out-of-hospital cardiac arrest	5 (18.5)	15 (3.2)	0.003
Cardiopulmonary arrest on arrival	3 (11.1)	15 (3.2)	0.069
Shock vital (SBP < 90 mmHg)	7 (25.9)	50 (10.8)	0.027
Severity score at admission (score)			
SOFA score	4.3 ± 3.6	2.8 ± 3.2	0.016*
APACHE II score	20.2 ± 8.2	15.1 ± 6.8	< 0.001*
Treatments during C-ICU admission, <i>n</i> (%)			
Anticoagulant drugs	16 (59.3)	256 (55.1)	0.696
Single anti-platelet therapy	3 (11.1)	91 (19.6)	0.448
Dual anti-platelet therapy	10 (37.0)	161 (34.6)	0.836
Proton pump inhibitors	27 (100)	384 (82.6)	0.013
Blood transfusion	22 (81.5)	82 (17.6)	< 0.001

Table 1 (continued)

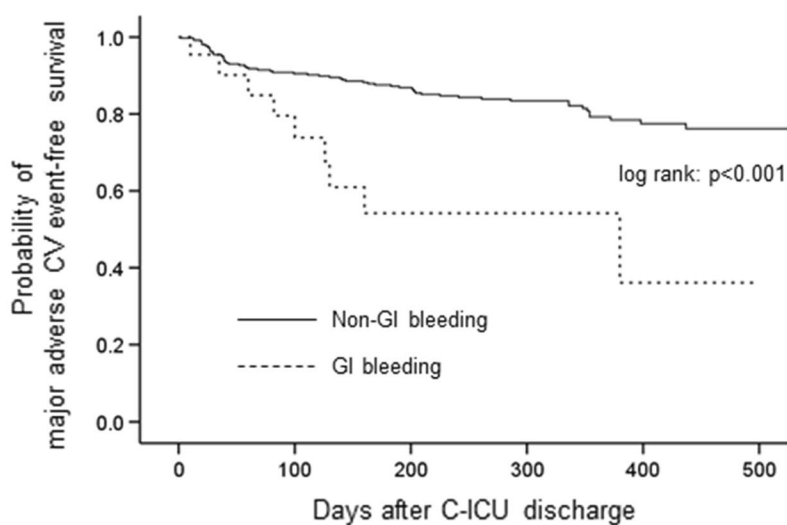
	GI bleeding (<i>n</i> =27)	Non-GI bleeding (<i>n</i> =465)	<i>p</i> value
Percutaneous coronary intervention	10 (37.0)	149 (32.0)	0.673
Coronary artery bypass grafting	0 (0.0)	19 (4.1)	0.615
Other surgical interventions	4 (14.8)	27 (5.8)	0.081
Noninvasive positive pressure ventilation	6 (22.2)	120 (25.8)	0.822
Mechanical ventilator	8 (29.6)	61 (13.1)	0.039
Renal replacement therapy	5 (18.5)	43 (9.2)	0.169
Intra-aortic balloon pump	4 (14.8)	53 (11.4)	0.539
Percutaneous cardiopulmonary support	2 (7.4)	15 (3.2)	0.238
Impella®	2 (7.4)	11 (2.4)	0.156
Length of C-ICU stay (days)	8 [5–16]	5 [3–8]	<0.001 [†]
In-hospital adverse events			
Nosocomial pneumonia, <i>n</i> (%)	3 (11.1)	18 (3.9)	0.101
<i>Clostridium difficile</i> infection, <i>n</i> (%)	1 (3.7)	0 (0.0)	0.055
In-hospital mortality, <i>n</i> (%)	0 (0.0)	34 (7.3)	0.244

Data are presented as mean ± standard deviation, *n* (%), or median [interquartile range]. Chronic kidney disease (stage G3), based on an estimated glomerular filtration rate < 60 ml/min/1.73 m²

*Compared by Student's *t* test; [†]compared by Mann–Whitney *U* test

GI gastrointestinal, *SBP* systolic blood pressure, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation, *C-ICU* cardiovascular-intensive care unit

Fig. 2 Cumulative incidences of CV events as estimated by Kaplan–Meier analysis. *CV* cardiovascular, *GI* gastrointestinal, *C-ICU* cardiovascular-intensive care unit



of unfavorable characteristics noted in the GI bleeding group, including a higher severity on admission, higher frequency of mechanical ventilators usage, and a longer C-ICU admission duration. GI bleeding occurs more frequently in ACS patients with severe clinical symptoms and is associated with more advanced age, baseline anemia, diabetes, and chronic renal insufficiency [5, 11–15]. These findings, in combination with ours, raise the possibility

that GI bleeding is a clinical feature of severe primary disease conditions associated with poor CV outcomes.

We also considered that GI bleeding in C-ICU patients was independently associated with long-term CV outcomes, as multivariate analyses demonstrated that GI bleeding was an independent risk factor for subsequent CV events, after adjustment for severity score, use of mechanical support devices, and length of C-ICU stay, all of which are known

Table 2 Multivariable analysis with a Cox proportional hazards model for subsequent cardiovascular events

Variables	Adjusted HR (95% CI)	<i>p</i> value
Age (years)	1.03 (1.00–1.05)	0.024
Male sex	1.34 (0.77–2.31)	0.298
Primary diseases (vs. acute coronary syndrome)		
Heart failure	2.01 (1.13–3.57)	0.017
Acute aortic dissection	1.50 (0.57–3.97)	0.414
Other cardiac diseases	0.80 (0.27–2.35)	0.681
Non-cardiac diseases	1.75 (0.78–3.91)	0.175
APACHE II score	1.03 (0.98–1.07)	0.239
Use of mechanical support devices	0.91 (0.48–1.73)	0.762
Gastrointestinal bleeding	2.23 (1.06–4.71)	0.035
Length of C-ICU stay (days)	1.03 (1.01–1.04)	0.010

HR hazard ratio, CI confidence interval, APACHE Acute Physiology and Chronic Health Evaluation, C-ICU cardiovascular-intensive care unit

to be associated with poorer outcomes [4, 16]. Furthermore, the in-hospital mortality rates, which are reportedly more strongly associated with a patient's disease severity, did not differ between the GI bleeding and non-GI bleeding groups. Although the impact of bleeding on short-term mortality was significant and directly explained the fatal course of bleeding events with anemia or hypotension [17], the effects of bleeding on long-term prognoses remain controversial, and the mechanisms by which bleeding affects CV outcomes long after the bleeding events themselves remains unclear [18, 19]. Blood transfusion is a possible reason for the association of bleeding events with long-term mortality and CV events, as it is linked to adverse effects such as the following: (1) increased platelet reactivity and procoagulant protein levels, (2) impaired oxygenation capability, (3) reduced transport rate of nitric oxide by transfused red blood cells, and (4) altered deformability of red blood cells during storage [20]. In the present study, blood transfusion was performed in more than 80% of patients with GI bleeding, and subsequent CV events were identified only in those who received blood transfusions. Although major bleeding is likely to require blood transfusion and is associated with poor outcomes, our results show that only 11% of the patients with GI bleeding who developed subsequent CV events had been categorized as having major bleeding. Previous reports also indicated that provision of blood transfusion to patients with GI bleeding negatively affects their long-term CV outcomes, regardless of the severity of bleeding [21, 22]. The formulation of a restrictive blood transfusion strategy should be considered for the treatment of anemia [23, 24]. On the other hand, the presence of anemia is known to increase the risks of death and CV events in patients with cardiac disease after surgery, critically ill patients, and ACS patients [25–27]. Appropriate blood transfusion criteria is required for such cases.

The incidence rates of GI bleeding in our C-ICU, as real world data, did not differ between primary diseases, and were higher than those reported in a prospective randomized study limited to ACS patients [5]. Initially, we expected that ACS patients would have a higher rate of GI bleeding than patients with other CV diseases, as all ACS patients receive anti-platelet drugs, usually as dual anti-platelet therapy, immediately after diagnosis. However, our results differed from this initial expectation, and the type of anti-platelet therapy used, such as single or dual anti-platelet therapy, did not affect the incidence of GI bleeding. This may be attributed to the high usage rate of prophylactic PPIs (82.6% in the non-GI bleeding group) in our C-ICU based on our stress ulcer prophylaxis strategy, which potentially reduces the risk of GI bleeding due to anti-platelet drugs [28].

The prophylactic use of PPIs for stress ulcers in critically ill patients is still controversial [29]. In this study, we could not determine whether PPI administration was effective in preventing both GI bleeding and subsequent CV events in our specific C-ICU setting with a high rate of prophylactic PPI administration. It was also unclear whether PPI administration to outpatients could prevent GI bleeding after C-ICU admission. Stress-related mucosal erosions and subepithelial hemorrhage occurred within 24 h after admission in more than 70% of critically ill patients in the ICU [3]. Taken together with our dataset, in which GI bleeding occurred most frequently on the first day, the prompt administration of PPIs after C-ICU admission or a potassium-competitive acid blocker that can rapidly raise blood concentrations of PPIs may be effective in preventing the incidence of GI bleeding complications in patients with CV diseases requiring intensive care [30, 31]. On the other hand, prophylactic administration of PPIs has not demonstrated a reduction in the mortality rate after 90 days in ICU patients who were at risk of GI bleeding, although it did reduce the incidence of clinically important GI bleeding [29]. Subsequent CV events after GI bleeding during C-ICU admission may not be reduced by the administration of PPIs in patients with acute CV diseases. Physicians should recognize GI bleeding as a risk factor of CV outcomes regardless of PPI administration in such cases.

The GI tract, including the upper and lower tracts, was the most frequently reported site of bleeding complications in patients admitted to the C-ICU in this study. In a previous report, vascular access sites were the most commonly noted sources of bleeding in patients with acute myocardial infarction who underwent percutaneous coronary intervention (PCI) [32]. Several factors have been suggested to underlie this difference. First, our study included several CV diseases, such as heart failure and acute aortic dissection, in addition to ACS requiring PCI. Second, changing the access site for PCI from the femoral to the radial artery may reduce the rates of bleeding complications involving the puncture

site. Third, critically ill patients in the C-ICU were subjected to high levels of stress, increasing the risk of stress-related mucosal damage and resulting in gastroduodenal ulceration and GI bleeding [3, 33].

This study has several limitations owing to its retrospective design, small sample size, and single-center nature. We enrolled all patients admitted to the C-ICU, including non-cardiac patients with suspicions of CV disease at the time of admission. This population heterogeneity may have affected the outcomes of patients in this study, although the incidence rates of both GI bleeding complications while in the C-ICU and subsequent CV events were similar in our ACS and non-ACS patient groups. Heart failure was the main cause of both C-ICU admission and subsequent CV events. Therefore, as a co-variate of GI bleeding, it may have affected the result of the multivariate analysis in the present study, which showed a low incidence rate of the outcome. Second, we could not collect information on those who were transferred to other hospitals or who went to other hospitals after discharge. Thus, the outcomes of this study may have been underestimated. Third, the number of GI bleeding events may not have been accurately determined, as not all patients underwent GI endoscopy for the diagnosis of GI bleeding. However, GI bleeding events were documented as accurately as possible by the application of the TIMI bleeding criteria. Notably, the incidence of GI bleeding in this study was higher than that observed in a previous study [5]. Fourth, the mechanism by which GI bleeding is associated with CV events, unlike other bleeding complications, is yet to be fully clarified. The GI tract may merely be a source of bleeding. Furthermore, it was unclear whether GI bleeding after C-ICU discharge was a risk factor for subsequent CV events.

In conclusion, we demonstrated that GI bleeding during C-ICU admission was independently associated with subsequent CV events in C-ICU patients who required care for acute CV disease. Therefore, reduction of the risk of GI bleeding is crucial in C-ICU settings.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

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