Research Square

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Proton pump inhibitor use and upper gastrointestinal bleeding in ICU patients receiving high-flow nasal cannula or noninvasive positive pressure ventilation: A nationwide cohort study

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Abstract

Background

Stress ulcer prophylaxis (SUP) with proton pump inhibitors (PPIs) reduces upper gastrointestinal bleeding in critically ill patients. However, its role in patients receiving noninvasive respiratory support remains uncertain. We evaluated the association between PPI use and gastrointestinal bleeding events among ICU patients receiving noninvasive positive pressure ventilation (NPPV) or high-flow nasal cannula (HFNC).

Methods

We conducted a retrospective cohort study using the Japanese Diagnosis Procedure Combination inpatient database from April 2018 to March 2024. Adult ICU patients who received NPPV or HFNC, but not invasive mechanical ventilation, within two days of admission were included. Patients who received PPIs were compared with those who received no SUP. The primary outcome was upper gastrointestinal bleeding requiring endoscopic hemostasis or surgery. Propensity-score overlap weighting and competing risk models were used to estimate cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs). Subgroup analyses were performed by severe illness with bleeding risk factors, early enteral nutrition, respiratory support modality, and circulatory failure.

Results

Among 9,176 patients, 5,941 received PPIs, and 3,235 received no SUP. Upper gastrointestinal bleeding occurred in 53 patients (0.9%) in the PPI group and 28 (0.9%) patients in the no-SUP group. After overlap weighting, PPI use was not significantly associated with upper gastrointestinal bleeding (cause-specific HR, 0.77; 95% CI, 0.46–1.27), 90-day mortality (cause-specific HR, 0.91; 95% CI, 0.80–1.03), or discharge alive within 90 days (cause-specific HR, 0.98; 95% CI, 0.91–1.07). No significant differences were observed in *Clostridioides difficile* infection, pneumonia, or red blood cell transfusion volume. Subgroup analyses suggested heterogeneity in the association by respiratory support modality, with PPI use associated with a lower risk of upper gastrointestinal bleeding among patients receiving HFNC (cause-specific HR, 0.50; 95% CI, 0.27–0.92), but not among those receiving NPPV (cause-specific HR, 1.80; 95% CI, 0.83–3.92).

Conclusions

Among ICU patients receiving NPPV or HFNC, PPI use was not associated with a lower risk of upper gastrointestinal bleeding. These findings do not support routine PPI-based SUP for all patients receiving noninvasive respiratory support.

Background

In critically ill patients, mucosal hypoperfusion and physiologic stress can cause stress-related gastric and duodenal mucosal injury, leading to ulcer formation and bleeding.[1] Stress ulcer prophylaxis (SUP) with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists is routinely used in intensive care units (ICUs) to prevent clinically important gastrointestinal bleeding.[2] PPI-based SUP reduced the risk of upper gastrointestinal bleeding, although no significant mortality benefits were demonstrated.[3,4] PPI use was associated with potential adverse effects, increased risks of pneumonia and *Clostridioides difficile* infection (CDI), and the current guideline recommended limiting SUP to patients with appropriate indications.[5]

Traditionally, mechanical ventilation for more than 48 h was considered as an indication for SUP.[6] However, a recent study suggested that mechanical ventilation reflected overall severity of illness rather than an independent risk factor for stress-related mucosal bleeding.[7] The recent guideline recommended SUP primarily for critically ill patients with established risk factors of circulatory failure, coagulopathy, or chronic liver disease.[5] Previous studies evaluating SUP mainly focused on patients with invasive mechanical ventilation or populations largely composed of such patients.[8,9] The balance between the benefits and harms of SUP in patients who do not require invasive mechanical ventilation therefore remains unclear.

To our knowledge, no studies have specifically investigated patients receiving noninvasive respiratory support, such as noninvasive positive pressure ventilation (NPPV) or high-flow nasal cannula (HFNC).[5] Whether patients receiving NPPV and HFNC require SUP remains uncertain because they differ from patients with invasive mechanical ventilation in illness severity, feeding tolerance, and physiologic stress from devices.[10,11] We hypothesized that PPI-based SUP would reduce the risk of gastrointestinal bleeding among patients receiving NPPV or HFNC. Using a nationwide inpatient database in Japan, we evaluated the association between PPI use and gastrointestinal bleeding events comparing patients receiving PPIs with those who did not receive PPIs, potassium-competitive acid blockers, or histamine-2 receptor antagonists.

Methods

Data source

This study used patient-level data from the Japanese Diagnosis Procedure Combination inpatient database. This database contains administrative claims data from more than 1,700 acute-care hospitals and covers over 90% of tertiary-care hospitals in Japan. The database includes patient demographics, daily records of procedures and medications, diagnoses and comorbidities coded according to the International Classification of Diseases, 10th Revision (ICD-10), and discharge status. The details of the database have been described elsewhere.[12]

We obtained data on patient demographics, baseline functional status, consciousness level at admission, comorbidities, the Sequential Organ Failure Assessment (SOFA) score at ICU admission, primary diagnosis, hospital characteristics, and discharge status. Moreover, we extracted daily treatment and procedural data, including respiratory support, transfusions, organ support, initiation of enteral nutrition, and medications. The validity of the database has been previously evaluated, demonstrating moderate sensitivity and high specificity for diagnoses as well as high sensitivity and specificity for procedures.[13]

This study was approved by the Institutional Review Board of the authors' institution. The requirement for informed consent was waived because the study used anonymized administrative claims data.

Study cohort and exposure definition

We identified patients aged ≥ 18 years who were admitted to ICU and received NPPV or HFNC within 2 days of admission between April 2018 and March 2024. The exclusion criteria were: (1) invasive mechanical ventilation within 2 days of admission, (2) prior gastrectomy, (3) gastrointestinal bleeding present at admission, (4) endoscopic gastrointestinal hemostasis within 2 days of admission, (5) upper gastrointestinal endoscopy within 2 days of admission, (6) dual antiplatelet therapy within 2 days of admission, (7) concomitant antiplatelet and anticoagulant therapy within 2 days of admission, (8) percutaneous cardiopulmonary support within 2 days of admission, (9) PPI administration only on hospital day 1, (10) use of histamine-2 receptor antagonists or potassium-competitive acid blockers within 2 days of admission, and (11) death or discharge within 2 days of admission.

The PPI group consisted of patients who received any PPI within 2 days of admission, including omeprazole, lansoprazole, esomeprazole, and rabeprazole, administered orally or intravenously. The comparison group consisted of patients who did not receive PPIs, potassium-competitive acid blockers, or histamine-2 receptor antagonists within 2 days of admission. Patients who received PPIs only on hospital day 1 were excluded because this exposure was unlikely to represent ongoing prophylactic treatment. Detailed definitions of the exclusion criteria are presented in Supplementary Table 1.

To address immortal time bias, we adopted a landmark design, with follow-up beginning on hospital day 3.

Outcomes

The primary outcome was upper gastrointestinal bleeding, defined as endoscopic hemostasis for upper gastrointestinal bleeding or surgical intervention for gastric or duodenal ulcer bleeding. Detailed procedure codes for outcome identification are provided in Supplementary Table 2. Secondary outcomes included 90-day mortality, discharge alive within 90 days, *Clostridioides difficile* infection (CDI), pneumonia occurring after admission, and cumulative red blood cell transfusion volume administered after hospital day 3. CDI was defined as either a diagnosis of CDI (ICD-10 code: A04.7) recorded after

admission or initiation of CDI-related treatment following a diagnostic test for *Clostridioides difficile* (antigen test or toxin B gene detection test). Treatment for CDI was defined as the administration of metronidazole, oral vancomycin, or fidaxomicin. Pneumonia was defined using ICD-10 codes J13–18 or J69, or Japanese diagnostic terms indicating pneumonia recorded after admission.

Covariates

Covariates in this study included age, sex, body mass index, Japanese Coma Scale, Charlson Comorbidity Index, SOFA scores at ICU admission (including each component score), admission to a tertiary or teaching hospital, coronavirus disease 2019 infection, Barthel Index at admission, smoking history, and primary diagnosis categories according to major ICD-10 chapters (Supplementary Table 3). The Japanese Coma Scale is a widely used measure of impaired consciousness in Japan, and well correlated with the Glasgow Coma Scale.[14]

Furthermore, we collected data on treatment and procedures administered within 2 days of admission: deep vein thrombosis prophylaxis, rehabilitation, HFNC or NPPV, renal replacement therapy, initiation of enteral nutrition, 5% albumin administration, and 25% albumin infusion; transfusion volume of red blood cells, platelets, and fresh frozen plasma; antiplatelet agents and anticoagulation therapy (direct oral anticoagulants and warfarin); reversal agents for anticoagulation therapy; hemostatic therapies; probiotics; gastroprotective agents; nonsteroidal anti-inflammatory drugs; corticosteroids; vasoactive agents, and dobutamine. Antibiotics were classified according to their reported risk of CDI as high-risk, moderate-risk or low-risk, based on previous literature.[15,16] Gastrointestinal bleeding risk factors were defined as circulatory failure, coagulopathy, and chronic liver disease.[5] Detailed definitions of covariates are provided in Supplementary Table 4.

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD), and categorical variables as numbers with percentages. Group differences were assessed using the Student's *t*-test for continuous variables and the chi-square test for categorical variables. Missing data were handled using multiple imputations with chained equations, and the estimates from 20 imputed datasets were combined using Rubin's rules.[17]

We assessed the association between PPI use and gastrointestinal bleeding using propensity score overlap weighting and competing risk models.[18] Propensity scores were estimated for each patient using a logistic regression model predicting the probability of receiving PPIs. Overlap weights were calculated as 1 minus the propensity score for patients receiving PPIs and the propensity score for patients in the comparison group. Covariate balance was evaluated using absolute standardized differences, with values < 10% indicating adequate balance.[19] To account for within-hospital clustering, these models applied cluster-robust variance estimators at the hospital level. As death prevented

subsequent observation of the event of interest, we modeled death as a competing risk in the survival analysis and estimated cause-specific hazard ratios (HRs) and their 95% confidence intervals (CIs).

Subgroup analyses were conducted for the primary outcome and the key secondary outcome of 90-day mortality according to the following prespecified factors: (i) patients with severe illness (total SOFA score ≥ 9) and at least one major risk factor for gastrointestinal bleeding (circulatory failure, coagulopathy or chronic liver disease), for whom the recent guideline recommended consideration of SUP;[5] (ii) initiation of enteral nutrition within 2 days of admission; (iii) respiratory support modality (NPPV versus HFNC); (iv) presence of circulatory failure. The cutoff of a total SOFA score ≥ 9 was selected because it approximated the median SOFA score reported in the SUP-ICU trial,[8] in which the study population consisted mainly of mechanically ventilated patients who were more severely ill than those in the present study. The interaction between the treatment effect and subgroup was assessed using the Wald test.

Five sensitivity analyses were performed: (1) Fine–Gray sub-distribution hazard models to account for competing risks;[20] (2) complete-case analysis to evaluate the impact of missing data assumptions; (3) redefining the primary outcome as gastrointestinal bleeding occurring within 30 days of admission; (4) redefining exposure as receipt of any SUP agent, including PPIs, potassium-competitive acid blockers, or histamine-2 receptor antagonists; and (5) redefining PPI exposure as administration on hospital days one or two. All statistical tests were two-sided, and *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using the Stata version 19.5 software (Stata Corp, College Station, TX, USA).

Use of generative artificial intelligence

ChatGPT (GPT-5.5 Thinking; OpenAI) was used only to assist with English grammar and phrasing during manuscript drafting, and no extensions or plugins were used. Its contribution was limited to a minor proportion of the writing process and did not involve study design, data analysis, interpretation of results, or generation of scientific conclusions. The draft was reviewed and revised by the authors and a native English-language editor, and the authors take full responsibility for the final manuscript.

Results

Figure 1 shows a flowchart of the patient selection process. During the study period, 17,580 adults were admitted to the ICU and received NPPV or HFNC within 2 days of admission. We finally identified 9,176 patients who were eligible for inclusion in the main analysis: 5,941 patients (64.7%) received PPIs and 3,235 patients (35.3%) did not receive SUP. Details of the PPIs administered within 2 days of admission are shown in Supplementary Table 5.

Table 1 summarizes patient characteristics before and after propensity score overlap weighting. Before weighting, patients who received PPIs had greater illness severity and treatment intensity, including higher SOFA scores and more frequent use of renal replacement therapy, albumin administration, blood

transfusion, probiotics, and antibiotics. Infections including COVID-19, circulatory failure, and coagulopathy were more common in the PPI group. The median SOFA score in the overall cohort was 5 (interquartile range, 3–7). Antiplatelet therapy and corticosteroid use were more frequent in the PPI group. HFNC was administered more frequently in the PPI group, whereas NPPV and early enteral nutrition were more common in the no-SUP group. After overlap weighting, covariate balance was achieved, with all absolute standardized differences below 10%. The missing values are summarized in Supplementary Table 6. Individual SOFA component scores had the highest proportion of missing values (33–38%).

Table 1
Baseline characteristics before and after propensity score overlap weighting

Characteristics	Unweighted cohort					After adjustment		
	PPI group (n = 5,941)		No SUP group (n = 3,235)		ASD	PPI group	No SUP group	ASD
Age, years, mean (SD)	72.6	(14.0)	73.6	(14.9)	5.7	72.7 (14.3)	73.5 (14.8)	5.1
Male, n (%)	3,928	(66.1)	1,968	(60.8)	11.0	(63.6)	(62.8)	1.6
Body mass index, n (%)					4.8			1.6
< 18.5	851	(15.6)	501	(16.3)		(17.1)	(17.2)	
18.5–24.9	2,971	(54.5)	1,544	(52.3)		(52.3)	(52.6)	
25.0–29.9	1,160	(21.3)	643	(21.8)		(21.5)	(21.5)	
≥ 30.0	471	(8.6)	265	(9.0)		(9.1)	(8.7)	
Japanese Coma Scale, n (%)					11.4			1.6
0 (alert)	3,888	(65.4)	2,286	(70.7)		(68.1)	(68.4)	
1-digit (dizziness)	1,401	(23.6)	662	(20.5)		(22.1)	(21.6)	
2-digit (somnolence)	421	(7.1)	185	(5.7)		(6.4)	(6.4)	
3-digit (coma)	231	(3.9)	102	(3.2)		(3.4)	(3.6)	
Charlson Comorbidity Index, n (%)					4.8			3.7
0	3,014	(50.7)	1,567	(48.4)		(50.6)	(48.9)	
1	842	(14.2)	464	(14.3)		(14.0)	(14.1)	
2	1,324	(22.3)	765	(23.6)		(22.8)	(23.5)	
≥ 3	761	(12.8)	439	(13.6)		(12.6)	(13.5)	
SOFA score at ICU admission, mean (SD)								
Total	5.4	(3.0)	4.9	(2.9)	14.6	5.1(3.0)	5.1(3.0)	0.3

ASD, absolute standardized difference; CDI, *Clostridioides difficile* infection; HFNC, high-flow nasal cannula; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUP, stress ulcer prophylaxis.

Characteristics	Unweighted cohort					After adjustment		
	PPI group (n = 5,941)		No SUP group (n = 3,235)		ASD	PPI group	No SUP group	ASD
Respiratory	2.3	(1.1)	2.2	(1.1)	3.6	2.3 (1.1)	2.2 (1.1)	2.0
Cardiovascular	0.5	(0.8)	0.4	(0.8)	8.4	0.4 (0.8)	0.4 (0.8)	0.2
Hepatic	0.3	(0.7)	0.3	(0.6)	4.5	0.3 (0.6)	0.3 (0.6)	0.7
Coagulation	0.7	(1.2)	0.5	(1.1)	13.0	0.6 (1.2)	0.6 (1.2)	0.4
Renal	0.6	(1.0)	0.6	(1.0)	5.1	0.6 (1.0)	0.6 (1.0)	1.2
Neurological	1.0	(1.3)	0.9	(1.3)	7.1	0.9 (1.3)	0.9 (1.3)	0.1
Emergency admission to tertiary hospitals, n (%)	209	(3.5)	67	(2.1)	8.8	(3.2)	(2.4)	4.5
Admission in a teaching hospital, n (%)	5,444	(91.6)	2,876	(88.9)	9.2	(91.4)	(89.4)	6.8
COVID-19 infection, n (%)	970	(16.3)	251	(7.8)	26.6	(12.3)	(9.9)	7.5
Primary diagnosis category, n (%)								
Infection	364	(6.1)	110	(3.4)	12.8	(4.1)	(4.2)	0.9
Neoplasm	232	(3.9)	129	(4.0)	0.4	(4.1)	(3.9)	1.1
Hematologic and immune disorders	70	(1.2)	22	(0.7)	5.2	(0.8)	(0.8)	0.6
Cardiovascular disease	2,226	(37.5)	1,688	(52.2)	29.9	(46.1)	(46.9)	1.6
Respiratory disease	1,319	(22.2)	689	(21.3)	2.2	(21.1)	(22.4)	3.3
Gastrointestinal disease	274	(4.6)	84	(2.6)	10.8	(3.2)	(3.5)	2.0
Neurological disease	37	(0.6)	22	(0.7)	0.7	(0.7)	(0.7)	0.1
External causes	101	(1.7)	61	(1.9)	1.4	(1.8)	(1.9)	0.7
Renal disease	185	(3.1)	116	(3.6)	2.6	(3.6)	(3.4)	0.6

ASD, absolute standardized difference; CDI, *Clostridioides difficile* infection; HFNC, high-flow nasal cannula; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUP, stress ulcer prophylaxis.

Characteristics	Unweighted cohort					After adjustment		
	PPI group (n = 5,941)		No SUP group (n = 3,235)		ASD	PPI group	No SUP group	ASD
Other category	1,133	(19.1)	312	(9.6)	26.9	(14.6)	(12.1)	7.4
Circulatory failure	1,540	(25.9)	613	(18.9)	16.8	(26.0)	(26.1)	0.3
Coagulopathy	405	(6.8)	104	(3.2)	16.6	(4.2)	(3.9)	1.4
Chronic liver disease	184	(3.1)	74	(2.3)	5.0	(2.5)	(2.6)	0.8
Barthel Index at admission, mean(SD)	34.3	(42.8)	38.5	(44.2)	9.7	36.8 (43.8)	36.3 (43.6)	1.1
Non-smoker, n (%)	2,677	(45.1)	1,649	(51.0)	11.9	(47.6)	(48.8)	2.6
Treatments and procedures within 2 days of admission								
Deep vein thrombosis prophylaxis, n (%)	2,530	(42.6)	1,206	(37.3)	10.8	(40.6)	(37.8)	5.8
Rehabilitation, n (%)	2,743	(46.2)	1,331	(41.1)	10.1	(44.3)	(41.8)	5.0
High-flow nasal cannula, n (%)	3,844	(64.7)	1,623	(50.2)	29.7	(56.9)	(55.7)	2.3
Noninvasive positive pressure ventilation, n (%)	2,105	(35.4)	1,615	(49.9)	29.6	(43.3)	(44.4)	2.4
Renal replacement therapy, n (%)	686	(11.5)	270	(8.3)	10.7	(9.4)	(9.2)	1.0
Initiation of enteral nutrition, n (%)	3,149	(53.0)	2,161	(66.8)	28.4	(60.3)	(61.5)	2.4
5% Albumin administration, n (%)	448	(7.5)	112	(3.5)	18.0	(4.8)	(4.6)	1.2
25% Albumin administration, n (%)	259	(4.4)	58	(1.8)	14.9	(2.6)	(2.4)	1.8
Total red blood cell units transfused, mean (SD)	0.5	(1.8)	0.2	(1.1)	18.4	0.3 (1.2)	0.3 (1.2)	2.1

ASD, absolute standardized difference; CDI, *Clostridioides difficile* infection; HFNC, high-flow nasal cannula; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUP, stress ulcer prophylaxis.

Characteristics	Unweighted cohort					After adjustment		
	PPI group (n = 5,941)		No SUP group (n = 3,235)		ASD	PPI group	No SUP group	ASD
Total platelet units transfused, mean (SD)	0.5	(3.4)	0.1	(1.8)	12.3	0.2 (2.2)	0.2 (2.2)	1.2
Total fresh frozen plasma units transfused, mean (SD)	0.4	(3.3)	0.1	(1.5)	12.3	0.2 (1.8)	0.2 (1.8)	0.8
Antithrombotic therapies, n (%)								
Antiplatelet therapy	974	(16.4)	260	(8.0)	25.7	(10.7)	(10.4)	1.1
Direct oral anticoagulants	606	(10.2)	409	(12.6)	7.7	(12.0)	(12.7)	2.1
Reversal agents for anticoagulation therapy	253	(4.3)	119	(3.7)	3.0	(3.2)	(3.6)	2.5
Hemostatic therapy, n (%)	244	(4.1)	87	(2.7)	7.8	(3.3)	(3.3)	0.3
Antibiotics, n (%)								
High-risk antibiotics for CDI	2,390	(40.2)	1,013	(31.3)	18.7	(34.3)	(34.3)	0.1
Intermediate-risk antibiotics for CDI	1,747	(29.4)	787	(24.3)	11.5	(27.4)	(26.2)	2.7
Low-risk antibiotics for CDI	1,500	(25.2)	486	(15.0)	25.7	(18.5)	(17.8)	2.0
No antibiotics	1,876	(31.6)	1,435	(44.4)	26.6	(39.1)	(40.0)	1.8
Probiotics, n(%)	545	(9.2)	130	(4.0)	20.9	(5.8)	(5.2)	2.6
Other gastroprotective agents, n(%)	113	(1.9)	80	(2.5)	3.9	(2.1)	(2.3)	1.2
Non-steroidal anti-inflammatory drugs, n(%)	273	(4.6)	145	(4.5)	0.5	(4.5)	(4.5)	0.4

ASD, absolute standardized difference; CDI, *Clostridioides difficile* infection; HFNC, high-flow nasal cannula; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUP, stress ulcer prophylaxis.

Characteristics	Unweighted cohort					After adjustment		
	PPI group (n = 5,941)		No SUP group (n = 3,235)		ASD	PPI group	No SUP group	ASD
Corticosteroids, n (%)	2,701	(45.5)	702	(21.7)	52.0	(31.0)	(29.1)	4.1
Dobutamine, n (%)	569	(9.6)	346	(10.7)	3.7	(10.3)	(10.8)	1.5

ASD, absolute standardized difference; CDI, *Clostridioides difficile* infection; HFNC, high-flow nasal cannula; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUP, stress ulcer prophylaxis.

Table 2 presents the primary and secondary outcomes. The crude and adjusted cumulative incidence function curves are shown in Figs. 2 and 3, respectively. Upper gastrointestinal bleeding occurred in 53 patients (0.9%) in the PPI group and 28 patients (0.9%) in the no-SUP group. Two patients underwent surgical interventions, consisting of laparoscopic gastric suturing and laparoscopic gastrectomy. After propensity-score overlap weighting, PPI administration was not significantly associated with the incidence of upper gastrointestinal bleeding (cause-specific HR, 0.77; 95% CI, 0.46 to 1.27).

Table 2
Crude outcome and adjusted estimates after propensity score overlap weighting

	PPI group		No SUP group		Adjusted analysis	
	(n = 5,941)		(n = 3,235)		Estimate	95% CI
Primary outcome					Cause-specific HR	
Upper gastrointestinal bleeding, n (%)	53	(0.9)	28	(0.9)	0.77	0.46–1.27
Secondary outcomes						
90-day mortality, n (%)	1,095	(18.4)	459	(14.2)	0.91	0.80–1.03
Discharge alive within 90 days, n (%)	4,672	(78.6)	2,698	(83.4)	0.98	0.91–1.07
					Risk ratio	
Clostridioides difficile infection, n (%)	126	(2.1)	39	(1.2)	1.31	0.88–1.96
Pneumonia, n (%)	506	(8.5)	221	(6.8)	1.08	0.90–1.28
					Difference	
Total RBC units transfused within 14 days after hospital day 3, units (SD)	1.7	(6.6)	1.0	(5.0)	0.2	−0.1 to 0.5

CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor; RBC, red blood cell; SD, standard deviation; SUP, stress ulcer prophylaxis.

Crude and adjusted cumulative incidence function curves for 90-day mortality and discharge alive within 90 days are shown in Supplementary Figs. 1–4. In the crude analysis, 90-day mortality was 18.4% in the PPI group and 14.2% in the no-SUP group. After overlap weighting, PPI use was not significantly associated with 90-day mortality (cause-specific HR, 0.91; 95% CI, 0.80–1.03) and discharge alive within 90 days (cause-specific HR, 0.98; 95% CI, 0.91–1.07). No significant differences were observed between groups in CDI (risk ratio, 1.31; 95% CI, 0.88–1.96), in-hospital pneumonia occurrence (risk ratio, 1.08; 95% CI, 0.90–1.28), and total red blood cell transfusion volume within 14 days after hospital day 3 (difference, 0.2 units; 95% CI, − 0.1 to 0.47).

Table 3 and Supplementary Table 7 include the results of the subgroup analyses. For upper gastrointestinal bleeding, the interaction was statistically significant across the respiratory support modality strata. PPI administration was not associated with a reduced incidence of gastrointestinal bleeding among patients receiving NPPV, whereas PPI administration was associated with a reduced risk among patients receiving HFNC. No clear effect modification was observed in the strata of severe illness with risk factors for gastrointestinal bleeding, initiation of enteral nutrition within 2 days of

admission, or circulatory failure. For the 90-day mortality, a statistically significant interaction was observed according to initiation of enteral nutrition within 2 days of admission. PPI use was associated with a lower 90-day mortality only among patients who did not receive enteral nutrition within 2 days of admission. No clear effect modifications were observed in the other subgroup analyses.

Table 3
Subgroup analyses for upper gastrointestinal bleeding

Subgroups	PPI		No SUP		Cause-specific HR	95% CI	*P*-value for interaction
	Number	Event	Number	Event			
Severe illness with bleeding risk factors							0.71
Yes	744	14	288	3	0.95	0.26–3.49	
No	5,197	39	2,947	25	0.73	0.42–1.27	
Enteral nutrition							0.18
Yes	3,149	23	2,161	14	1.08	0.55–2.12	
No	2,792	30	1,074	14	0.54	0.26–1.13	
Respiratory support modality							0.01
NPPV	2,105	17	1,615	8	1.80	0.83–3.92	
HFNC	3,844	36	1,623	20	0.50	0.27–0.92	
Circulatory failure							0.37
Yes	1,799	22	785	10	0.57	0.23–1.41	
No	4,142	31	2,450	18	0.92	0.50–1.68	

CI, confidence interval; HFNC, high-flow nasal cannula; HR, hazard ratio; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SUP, stress ulcer prophylaxis.

Supplementary Table 8 presents the results of the sensitivity analyses. These findings were consistent with those in the main analyses. PPI use was not significantly associated with a reduced incidence of upper gastrointestinal bleeding in the Fine–Gray competing-risk analysis, complete-case analysis,

analysis considering a 30-day outcome window, analysis redefining exposure as any SUP use, or analysis redefining PPI exposure as any administration on hospital days one or two.

Discussion

In this retrospective cohort study, we examined the association between PPI use and upper gastrointestinal bleeding in ICU patients receiving noninvasive respiratory support with NPPV or HFNC, excluding those who required invasive mechanical ventilation. PPI administration was not associated with a reduced risk of upper gastrointestinal bleeding.

Previous studies reported that PPI-based SUP was associated with a reduction in upper gastrointestinal bleeding in critically ill patients.[8,9] Several explanations could account for the difference in the results between these previous studies and the present study. First, we restricted patients to those receiving noninvasive respiratory support, and the illness severity in our study was lower than that in previous studies.[8,9] Patients receiving noninvasive respiratory support, therefore, may not correspond to the critically ill population for whom the guideline recommends SUP administration.[5] Second, our primary outcome was defined as upper gastrointestinal bleeding requiring endoscopic hemostasis or surgery. In contrast, previous trials included patients with overt bleeding accompanied by hemodynamic instability, hemoglobin decrease, transfusion requirement, or therapeutic intervention.[8,9] Therefore, our definition focused on severe bleeding events and may not be directly comparable with those used in previous studies.[8,9] Third, the incidence of gastrointestinal bleeding in critically ill patients has decreased over time, which likely reflects improvements in ICU care, including earlier enteral nutrition and overall advances in critical care management.[21] As the baseline risk decreased, the benefit of routine SUP possibly became less apparent.

PPI use was not significantly associated with 90-day mortality, discharge alive within 90 days and red blood cell transfusion volume. These findings were consistent with those in previous reports.[8,9] PPI use was not significantly associated with increased CDI or pneumonia. Although these adverse events have been considered potential harms of SUP, our findings are consistent with those of a recent meta-analysis.[4]

In subgroup analyses, we observed a statistically significant interaction for upper gastrointestinal bleeding according to respiratory support modality, with the association favoring PPI use among patients receiving HFNC but not among those receiving NPPV. Although HFNC was considered more tolerable than NPPV,[22] both discomfort and physiological stress during HFNC depend on flow settings, cannula size, and patient tolerance.[11,23,24] Current evidence does not clearly establish whether HFNC or NPPV imposes greater stress on patients.[25] Alternatively, this finding may reflect differences in patient characteristics related to the selection of respiratory support modality. For 90-day mortality, PPI use appeared to be associated with lower mortality only in patients who did not receive early enteral nutrition. Early enteral nutrition possibly reduced stress-related mucosal injury,[26] and the benefits of SUP

may differ according to the feeding status. These findings suggest that selected patients receiving noninvasive respiratory support may still benefit from PPI-based SUP. However, given the small number of bleeding events within each subgroup, the findings in subgroup analyses should be interpreted with caution.

To the best of our knowledge, this is the first study to examine PPI-based SUP for the prevention of upper gastrointestinal bleeding in ICU patients receiving NPPV or HFNC. These findings provide evidence for the uncertain role of SUP in patients receiving noninvasive respiratory support.

Several limitations should be acknowledged. First, the database lacked detailed clinical information on gastrointestinal bleeding symptoms, endoscopic findings, hemoglobin levels, and hemodynamic consequences of bleeding. Our outcome definition possibly missed milder bleeding events but focused on the most clinically relevant bleeding events. Second, PPI treatment was not randomly assigned, but was determined by clinicians. Although the overlap weighting achieved a good balance in the measured covariates, confounding by indication remains possible. Third, CDI and pneumonia were identified using administrative diagnostic codes and disease names in the claims data, which may have led to outcome misclassification.

Conclusions

In this nationwide cohort study, PPI use was not associated with a lower risk of upper gastrointestinal bleeding in ICU patients receiving NPPV or HFNC. Although subgroup analyses suggested potential heterogeneity among patients receiving HFNC and those without early enteral nutrition, routine PPI-based SUP may not be warranted for all patients receiving noninvasive respiratory support.

Abbreviations

CDI, Clostridioides difficile infection

CI, confidence interval

HFNC, high-flow nasal cannula

HR, hazard ratio

ICD-10, International Classification of Diseases, 10th Revision

ICU, intensive care unit

NPPV, noninvasive positive pressure ventilation

PPI, proton pump inhibitor

SD, standard deviation

SOFA, Sequential Organ Failure Assessment

SUP, stress ulcer prophylaxis

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The University of Tokyo(approval number: 3501). The requirement for informed consent was waived because the study used anonymized administrative claims data.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest related to this work.

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Author Contribution

WY: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration.SA: Methodology, Validation, Formal analysis, Writing – review & editing.HM: Resources, Data curation, Writing – review & editing.KY: Resources, Data curation, Writing – review & editing.HY: Conceptualization, Methodology, Supervision, Writing – review & editing.All authors read and approved the final manuscript.

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Availability of data and materials

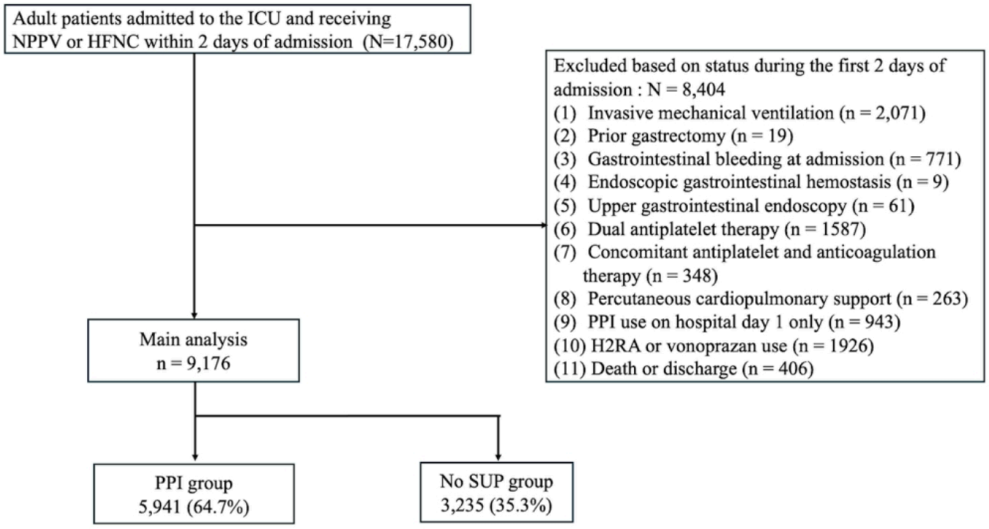
The data analyzed in this study are not publicly available because they were obtained from the Japanese Diagnosis Procedure Combination database under restrictions imposed by the data provider.

References

1. Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med*. 2018;378(26):2506–2516.
2. Borthwick M, Barton G, Boxall E, et al. Stress ulcer prophylaxis practice in UK critical care units: A comparison of cross-sectional surveys between 2020 and 2024. *J Intensive Care Soc*. 2025;26(4):466–471.
3. Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. *BMJ*. 2020;368:l6744.
4. Wang Y, Parpia S, Ge L, et al. Proton pump inhibitors to prevent gastrointestinal bleeding — an updated meta-analysis. *NEJM Evid*. 2024;3(7):EVIDoa2400134.
5. MacLaren R, Dionne JC, Granholm A, et al. Society of Critical Care Medicine and American Society of Health-System Pharmacists guideline for the prevention of stress-related gastrointestinal bleeding in critically ill adults. *Crit Care Med*. 2024;52(8):e421-e430.
6. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med*. 1994;330(6):377–381.
7. Granholm A, Krag M, Marker S, Alhazzani W, Perner A, Møller MH. Predictors of gastrointestinal bleeding in adult ICU patients in the SUP-ICU trial. *Acta Anaesthesiol Scand*. 2021;65(6):792–800.
8. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379(23):2199–2208.
9. Cook D, Deane A, Lauzier F, et al. Stress ulcer prophylaxis during invasive mechanical ventilation. *N Engl J Med*. 2024;391(1):9–20.
10. Cammarota G, Simonte R, De Robertis E. Comfort during non-invasive ventilation. *Front Med (Lausanne)*. 2022;9:874250.
11. Li J, Albuainain FA, Tan W, Scott JB, Roca O, Mauri T. The effects of flow settings during high-flow nasal cannula support for adult subjects: a systematic review. *Crit Care*. 2023;27(1):78.
12. Yasunaga H. Updated information on the Diagnosis Procedure Combination data. *Ann Clin Epidemiol*. 2024;6(4):106–110.
13. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol*. 2017;27(10):476–482.
14. Shigematsu K, Nakano H, Watanabe Y. The eye response test alone is sufficient to predict stroke outcome—reintroduction of Japan Coma Scale: a cohort study. *BMJ Open*. 2013;3(4):e002736.
15. Brown KA, Langford B, Schwartz KL, Diong C, Garber G, Daneman N. Antibiotic prescribing choices and their comparative C. difficile infection risks: A longitudinal case-cohort study. *Clin Infect Dis*.

2021;72(5):836–844.
16. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(4):881–891.
17. Rubin DB. Multiple imputation after 18 + years. *J Am Stat Assoc*. 1996;91(434):473–489.
18. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. *Am J Epidemiol*. 2019;188(1):250–257.
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107.
20. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol*. 2009;170(2):244–256.
21. Al-Dorzi HM, Arabi YM. Prevention of gastrointestinal bleeding in critically ill patients. *Curr Opin Crit Care*. 2021;27(2):177–182.
22. Artaud-Macari E, Bubenheim M, Le Bouar G, et al. High-flow oxygen therapy versus noninvasive ventilation: a randomised physiological crossover study of alveolar recruitment in acute respiratory failure. *ERJ Open Res*. 2021;7(4):00373–2021.
23. Zhao E, Zhou Y, He C, Ma D. Factors influencing nasal airway pressure and comfort in high-flow nasal cannula oxygen therapy: a volunteer study. *BMC Pulm Med*. 2023;23(1):449.
24. Ye H, Xiang D, Zhu X, et al. High-flow nasal cannula oxygen therapy versus non-invasive ventilation in healthy respiratory physicians: a non-randomized study. *Front Med (Lausanne)*. 2025;11:1506877.
25. Ovtcharenko N, Ho E, Alhazzani W, et al. High-flow nasal cannula versus non-invasive ventilation for acute hypercapnic respiratory failure in adults: a systematic review and meta-analysis of randomized trials. *Crit Care*. 2022;26(1):348.
26. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. *Crit Care*. 2018;22(1):20.

Figures



Unless otherwise specified, exclusion criteria were assessed within 2 days of admission. Abbreviations: HFNC, high-flow nasal cannula; H2RA, histamine-2 receptor antagonist; ICU, intensive care unit; NPPV, noninvasive positive pressure ventilation; PPI, proton pump inhibitor; SUP, stress ulcer prophylaxis.

Figure 1

Flowchart of patient selection.

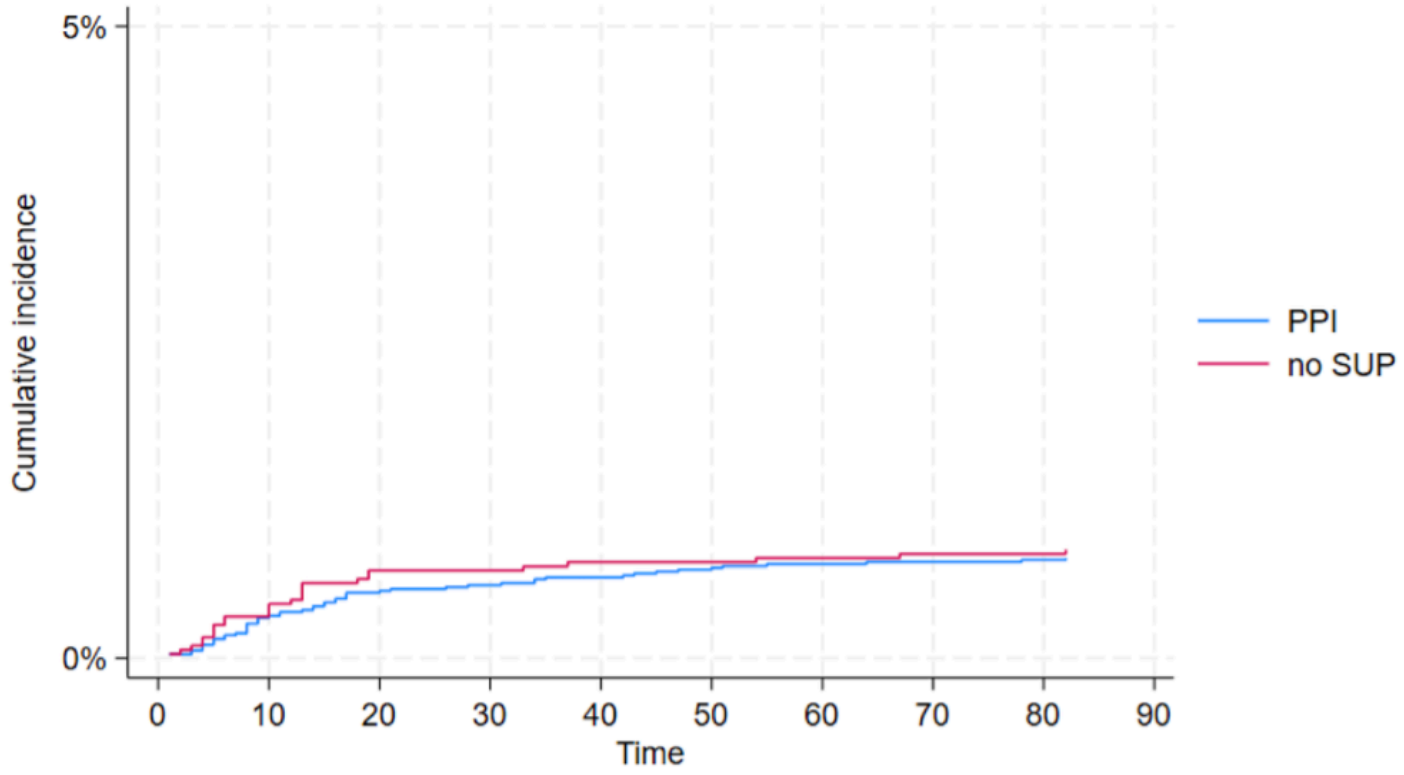


Figure 2

Crude cumulative incidence function curves for upper gastrointestinal bleeding.

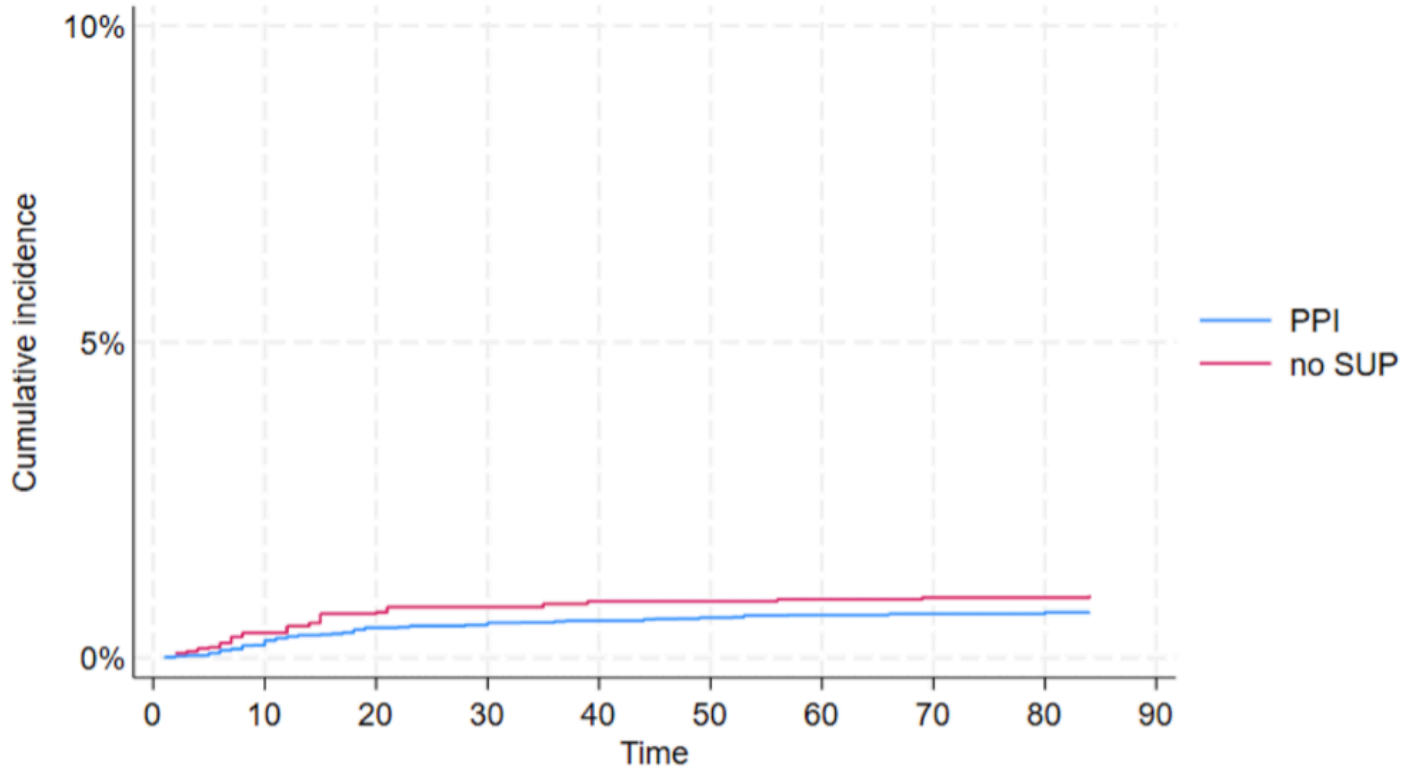


Figure 3

Weighted cumulative incidence function curves for upper gastrointestinal bleeding.

Weighted curves were estimated after propensity score overlap weighting.

Supplementary Files

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- AdditionalFileNIVPPIwyfinal.docx