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ORIGINAL RESEARCH

Effects of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: A randomized control trial

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ABSTRACT:

Background: Critically ill patients are prone to gastrointestinal bleeding, leading to hemodynamic instability, transfusions, and prolonged hospitalization. Stress ulcer prophylaxis with proton pump inhibitors (PPIs) is commonly used in intensive care, but their benefit is uncertain and may increase hospital-acquired pneumonia risk. This study aimed to evaluate the efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis, focusing on the occurrence of gastrointestinal bleeding and pneumonia.

Method: An open label, randomized controlled trial was conducted at Chiangrai Prachanukroh Hospital between January and October 2022. Critically ill patients were randomly assigned to receive a once-daily dose of omeprazole 40 mg intravenously or without prophylaxis; all received enteral nutrition. The primary outcome was the rate of gastrointestinal bleeding at 30 days, and hospital-acquired pneumonia was a safety outcome.

Result: One hundred thirty patients were enrolled (65 per group). Baseline characteristics, disease severity, laboratory values, and feeding parameters were comparable between groups. The duration of mechanical ventilation was longer in the PPI group, and all patients received enteral nutrition with similar feeding profiles. Gastrointestinal bleeding occurred in 6.15% of patients in the proton pump inhibitor group and 3.08% of controls, with no statistically significant difference. Hospital-acquired pneumonia occurred more frequently in the PPI group than in the control group (23.08% vs. 9.23%) in the crude analysis; however, PPI use was not independently associated with hospital-acquired pneumonia after multivariate adjustment. Mortality was higher in the PPI group (9.23% vs. 1.54%), but the difference was not statistically significant.

Conclusion: Critically ill patients on PPIs have comparable rates of gastrointestinal bleeding. Although the incidence of hospital-acquired pneumonia is higher in the PPI group, the multivariable analysis shows no statistically significant difference.

Trial registration: TCTR20260116007

Keywords: Stress ulcer prophylaxis; Critically ill patient; Hospital-acquired pneumonia

INTRODUCTION

Patients with critical illnesses face a heightened risk of gastrointestinal bleeding, which includes mucosal damage, ulceration, and bleeding. The potential consequences of this bleeding include hemodynamic instability that may necessitate blood transfusions, increased mortality, and prolonged hospitalization [1]. The reported incidence of gastrointestinal (GI) bleeding in intensive care unit (ICU) patients varies from 0.6% to 8.1% [2-6]. To mitigate the risk of significant gastrointestinal hemorrhage, stress ulcer prophylaxis is recommended for patients with risk factors such as mechanical ventilation, coagulopathy, and renal and liver failure [7]. Commonly used prophylactic agents include proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs) [8].

However, the supporting evidence for the prophylactic use of PPIs and H2RAs is unclear. Various RCTs and meta-analyses found similar gastrointestinal bleeding rates in the prophylaxis group compared with the placebo [7,9-10], raising concerns about the adverse effects of acid suppressants. Firstly, these agents alter the gastrointestinal microbiome, increasing the prevalence of Clostridioides difficile infection [6]. Furthermore, patients on acid suppressants face a higher risk of hospital-acquired pneumonia due to changes in respiratory and gastric flora, which can lead to increased micro-aspiration and pneumonia risk [11].

Several studies indicate an increased adjusted odds of ventilator-associated pneumonia in patients receiving acid suppressants [8,12]. Additionally, evidence suggests that PPIs impair immune cell function, contributing to pneumonia risk. Contrary to expectations, enteral nutrition as stress ulcer prophylaxis in critically ill patients did not significantly differ from proton pump inhibitors regarding the incidence of significant gastrointestinal hemorrhage [12-13]. Considering the adverse effects of acid suppressants, their routine use as stress ulcer prophylaxis warrants careful consideration. In addition, most existing randomized trials were conducted in highly controlled settings, and evidence from real-world intensive care units in Southeast Asia remains limited.

Furthermore, enteral nutrition, which may itself reduce stress-related mucosal injury, has not been consistently administered across previous studies. This study aimed to evaluate the effects and adverse events associated with the prophylactic use of proton pump inhibitors as stress ulcer prophylaxis in critically ill patients. This study was conducted in a real-world ICU setting in which all enrolled patients received enteral feeding, with the additional objective of describing local epidemiology and identifying risk factors for hospital-acquired pneumonia in this population.

KEY MESSAGES:

- Proton pump inhibitors did not significantly reduce gastrointestinal bleeding in critically ill patients on enteral nutrition.
- An increased incidence of hospital-acquired pneumonia was observed in the PPI group without statistical significance after adjustment.
- Routine stress ulcer prophylaxis with PPIs should be individualized rather than routinely applied, and further research in high-risk populations is warranted.

MATERIALS AND METHODS

This open-label randomized controlled trial was conducted at Chiangrai Prachnukroh Hospital. Adult patients aged 18 years or older who were critically ill and admitted to the intensive care unit (ICU) at Chiang Rai Hospital were screened for eligibility. Patients were included if they received enteral feeding during their ICU admission, either via oral feeding or tube feeding through any enteral route, between January 1 and October 31, 2022. Patients were excluded if they had contraindications to enteral feeding, overt gastrointestinal bleeding, pneumonia at ICU admission, were receiving antiplatelet or anticoagulant therapy, had thrombocytopenia (platelet count <100,000 cells/mm^3), or had coagulopathy defined as an international normalized ratio (INR) greater than 1.5.

The sample size was calculated using STATA software with a two-sided alpha of 0.05 and a power of 80%. Based on preliminary study data, the incidence of hospital-acquired pneumonia was 20.7% in the proton pump inhibitor group and 3.6% in the non–proton pump inhibitor group, resulting in a required sample size of 61 patients per group [11]. Although gastrointestinal bleeding was defined as the primary outcome due to its clinical relevance, its low incidence limited the feasibility of powering the study for this outcome. Therefore, the study was not powered to detect small differences in gastrointestinal bleeding.

Patients were randomly assigned to either the control group (n=65) or the PPI group (n=65) using a computerized randomization system with sealed opaque envelopes to ensure blinding. All patients received enteral nutrition and standard care. Patients in the proton pump inhibitor group received omeprazole 40 mg intravenously once daily throughout admission without switching to oral therapy. The primary outcome assessed was the incidence of gastrointestinal bleeding. Hospital-acquired pneumonia was a safety outcome. Hospital-acquired pneumonia was diagnosed according to the Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) surveillance criteria for pneumonia (PNEU), including both ventilator-associated and non–ventilator-associated pneumonia. Gastrointestinal bleeding was defined as clinically significant gastrointestinal hemorrhage, characterized by overt bleeding manifestations (e.g., melena or coffee-ground nasogastric aspirate), with or without associated hemodynamic or laboratory changes. All diagnoses were made by the attending physicians based on routine clinical practice, without any intervention or influence from the researchers. Mortality rate was defined as a secondary outcome.

Patients were followed from ICU admission until a 30-day period or hospital discharge (Figure 1). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee/Institutional Review Board (EC CRH 075/65 In). This study has been reviewed and approved by the Thai Clinical Trials Registry Committee (TCTR20260116007).

Statistical analysis

Descriptive statistics were used to summarize the data. Continuous variables were assessed for normality and are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables are presented as frequencies and percentages. Comparisons of continuous variables were performed using the student's t-test or Mann–Whitney U test, as appropriate, while categorical variables were analyzed using the chi-square test. Survival analysis was performed using the Kaplan-Meier method, and Cox proportional hazards models were used to determine the variable-associated predictors of hospital-acquired pneumonia and gastrointestinal bleeding events. Data comparisons between hospital-acquired pneumonia and gastrointestinal bleeding events were conducted within a 30-day follow-up period. Variables included in the multivariable Cox models were selected based on clinical relevance and prior evidence. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using a standard statistical software package.

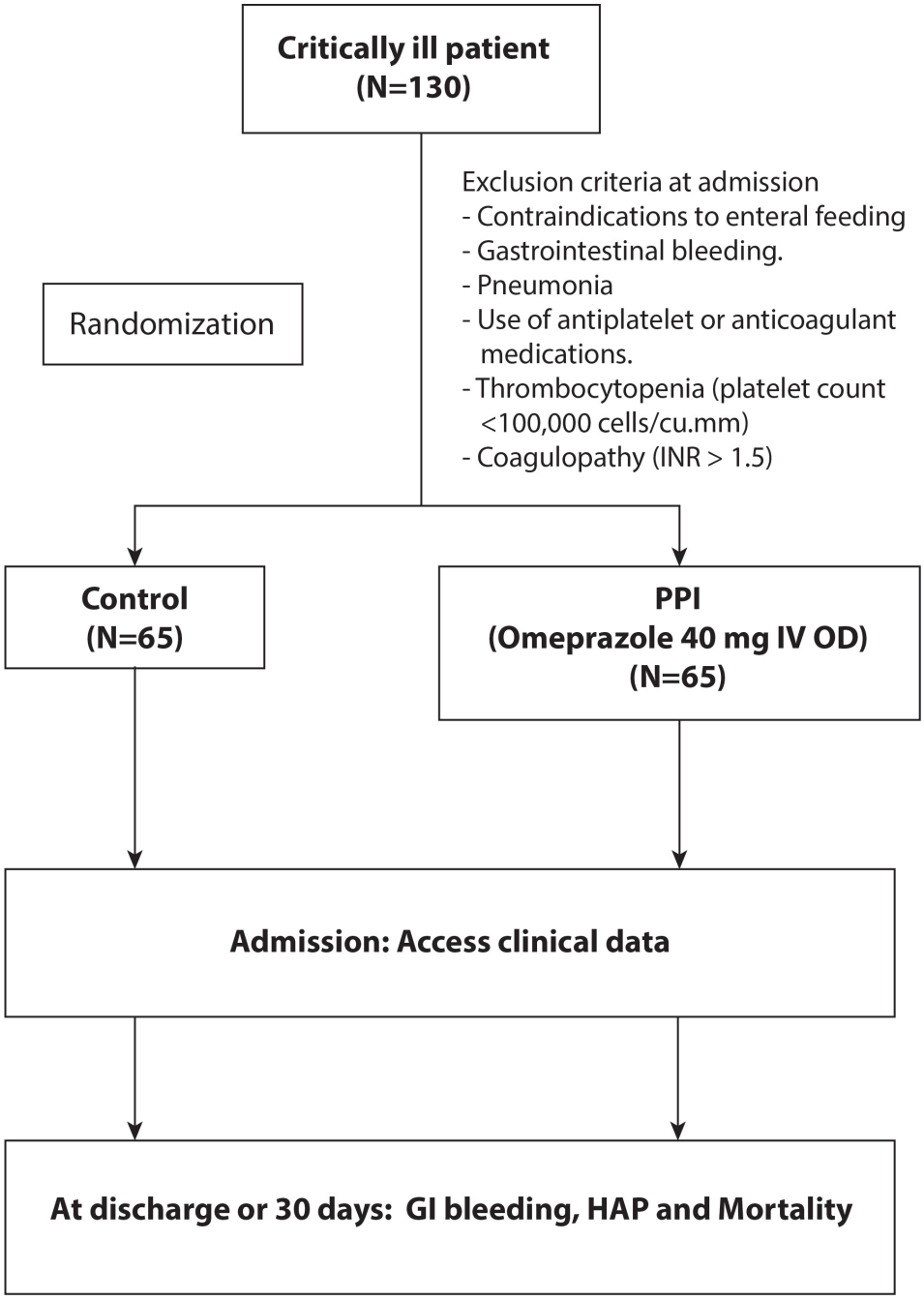

Figure 1. Study flow

RESULTS

As shown in Table 1, baseline demographic characteristics, comorbidities, primary diagnoses, severity indicators, laboratory values, and feeding parameters were generally comparable between the control and PPI groups.

There were no statistically significant differences between groups in age, sex distribution, body weight, or the prevalence of major comorbidities, including diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, cirrhosis, steroid use, and HIV infection.

Regarding disease severity, the proportion of patients requiring mechanical ventilation and vasopressor support did not differ significantly between groups. However, the duration of mechanical ventilation was significantly longer in the PPI group compared with the control group (5.30 ± 6.46 vs. 2.58 ± 4.13 days, P = 0.005). Antibiotic use and Modified Early Warning Score (MEWS) on admission were similar between groups. Baseline laboratory values, including hemoglobin, platelet count, and serum creatinine, showed no significant differences.

Outcomes related to hospital-acquired pneumonia, gastrointestinal bleeding, and mortality are presented in Table 2. The analysis of outcomes between the control and PPI groups revealed notable differences. The incidence of gastrointestinal bleeding (GI bleed) was slightly higher in the PPI group (6.15%) compared to the control group (3.08%), although this difference was not statistically significant (P-value=0.680).

The prevalence of hospital-acquired pneumonia (HAP) was significantly higher in the PPI group (23.08%) compared to the Control group (9.23%), with a statistically significant P-value of 0.032. Regarding mortality, the percentage of deceased patients was higher in the PPI group (9.23%) compared to the Control group (1.54%), but this difference did not reach statistical significance (P-value = 0.052).

Survival analysis of hospital-acquired pneumonia, gastrointestinal bleeding and hospital mortality outcomes is demonstrated Figure 2, 3 and 4. Among the 130 patients included in the follow-up, which extended for 30 days, pneumonia events occurred in 6 patients in the Control group and 15 patients in the PPI group. The median time to pneumonia events in this study was 4 days (IQR 4-10 days). Regarding gastrointestinal (GI) bleeding events, 2 patients in the Control group and 4 patients in the PPI group experienced such incidents. The median time to GI bleeding events was 5 days (IQR 3-17 days).

Factors associated with hospital-acquired pneumonia (HAP) are demonstrated in Table 3, examined through crude hazard ratios and adjusted hazard with their respective 95% confidence intervals. Among the assessed factors, a duration of mechanical ventilation of less than 48 hours showed a significant association with HAP as a protective factor, with a crude hazard ratio of 0.05 (95% CI: 0.00-0.79, P-value=0.034), however, adjusted hazard ratio does not show statistically significant with adjust hazard ratio of 0.04 (95% CI: 0.00-1.67, P-value=0.091). Other variables, including male gender, diabetes mellitus (DM), hypertension (HT), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cirrhosis, human immunodeficiency virus (HIV) status, age over 50 years, Modified Early Warning Score (MEWS) over 4, vasopressor use, prokinetic use, anemia, feeding calories below 1500 kcal, and PPI use did not show statistically significant associations with hospital-acquired pneumonia.

Factors associated with gastrointestinal (GI) bleeding are presented in Table 4, examined through crude hazard ratios and adjusted hazard with their respective 95% confidence intervals. None of the evaluated variables demonstrated associations with GI bleeding. Including age over 50 years, male gender, chronic kidney disease (CKD) and congestive heart failure (CHF).

DISCUSSION

The prevalence of gastrointestinal bleeding did not significantly differ between the control and PPI groups, aligning with prior research [3-4,13]. Our findings are also relevant to previous studies that found the prevalence of gastrointestinal bleeding to be around 0.6% to 8.1% [2-6]. This is consistent with earlier RCTs and meta-analyses, which showed that stress ulcer prophylaxis with a proton pump inhibitor was not associated with the risk of gastrointestinal bleeding in critically ill patients [16]. These findings highlight the importance of carefully evaluating the regular use of acid-suppressive medications for preventing stress ulcers in critically ill patients.

Our results indicate a significantly higher prevalence of hospital-acquired pneumonia in patients using PPIs compared to the control group, consistent with previous studies [3-4,11-12]. Potential contributing factors include gastrointestinal bacterial overgrowth, increased microaspiration of bacteria, and impaired immune cell function associated with PPI use [14-15]. However, after multivariate adjustment, PPI use was not independently associated with hospital-acquired pneumonia, suggesting that the observed difference may be influenced by baseline illness severity or other clinical factors. In addition, no significant difference in the incidence of gastrointestinal bleeding was observed between the PPI and control groups. This finding is consistent with previous studies, which suggest that routine stress ulcer prophylaxis may provide limited additional benefit in patients receiving early enteral nutrition [12,13].

From our survival analysis, the duration of mechanical ventilation tended to be associated with the risk of developing hospital-acquired pneumonia. The longer duration of mechanical ventilation relates to an increased risk of hospital-acquired pneumonia, consistent with several studies that reported an association between prolonged mechanical ventilation and the incidence of hospital-acquired pneumonia [17]. However, larger cohorts with a number of events are needed to emphasize this correlation.

According to our research, survival analysis revealed associations between certain patient characteristics and a higher risk of gastrointestinal bleeding, although statistical significance was not achieved.

Table 1. Baseline characteristics

	Control (N=65)	PPI (N=65)	P-value
Demographic			
Mean age: yr±SD	66.63±15.59	66.52±14.89	0.967
Female (n%)	23 (35.38)	34 (52.31)	0.052
Weight: kg± SD	51.89±12.59	50.40±12.11	0.655
Underlying			
Diabetes mellitus (n%)	14 (21.54)	11 (16.92)	0.504
Hypertension (n%)	43 (66.15)	32 (49.23)	0.051
Chronic kidney disease (n%)	10 (15.38)	6 (9.23)	0.286
Chronic obstructive pulmonary disease (n%)	28 (43.08)	28 (43.08)	1.000
Congestive heart failure (n%)	12 (18.46)	6 (9.23)	0.128
Cirrhosis (n%)	2 (3.08)	1 (1.54)	0.559
On steroid (n%)	0 (0)	1 (1.54)	0.315
HIV (n%)	2 (3.08)	2 (3.08)	1.000
Diagnosis			0.190
Septic shock (n%)	7 (10.77)	15 (23.08)	
Renal failure (n%)	7 (10.77)	4 (6.15)	
Acute heart failure (n%)	16 (24.62)	9 (13.58)	
Acute coronary syndrome (n%)	1 (1.54)	0 (0)	
COPD with AE (n%)	27 (41.54)	27 (41.54)	
Alteration of consciousness (n%)	7 (10.77)	10 (15.38)	
Antibiotic on admission			
Yes (n%)	61 (93.85)	61 (93.85)	1.000
No (n%)	4 (6.15)	4 (6.15)	1.000
Duration of ETT (SD)	2.584 (4.137)	5.307 (6.466)	0.005
Severity			
Mechanical ventilator (n%)	59 (90.77)	62 (95.38)	0.300
Vasopressor (n%)	9 (13.85)	13 (20.00)	0.349
MEWS score: mean±SD	3.23±1.73	3.00±1.72	0.448
Lab on admission			
Hemoglobin (g/dL): mean±SD	11.0±52.76	10.99±2.59	0.895
Platelet (cell/mm3): mean±SD	$256.34x10^3$± 89.28 $x10^3$	$258.83x10^3$± 10.79 $x10^3$	0.886
BUN (mg/dL): mean±SD	38.44±42.98	34.21±30.89	0.521
Creatinine (mg/dL): mean±SD	3.89±6.00	2.88±3.84	0.254
Feeding			
Feeding calories (kcal): mean±SD	1243.07±265.73	1156.92±335.04	0.113
Feeding volume (mL): mean±SD	1083.07±356.88	1010.76±343.29	0.241
Prokinetic (n%)	1 (1.54)	4 (6.15)	0.171

P values for individual diagnoses were not calculated due to small cell counts in several categories.
*Significant consider as P<0.05
Abbreviations: HIV: Human immunodeficiency virus; COPD with AE: Chronic obstructive pulmonary disease with acute exacerbation; MEWS: Modified Early Warning Score

Table 2. Primary and secondary outcomes

	Control	PPI	P-value
Gastrointestinal bleeding (n%)	2 (3.08)	4 (6.15)	0.680
Hospital-acquired pneumonia (n%)	6 (9.23)	15 (23.08)	0.032
Hospital mortality (n%)	1 (1.54)	6 (9.23)	0.052

*Significant consider as P<0.05

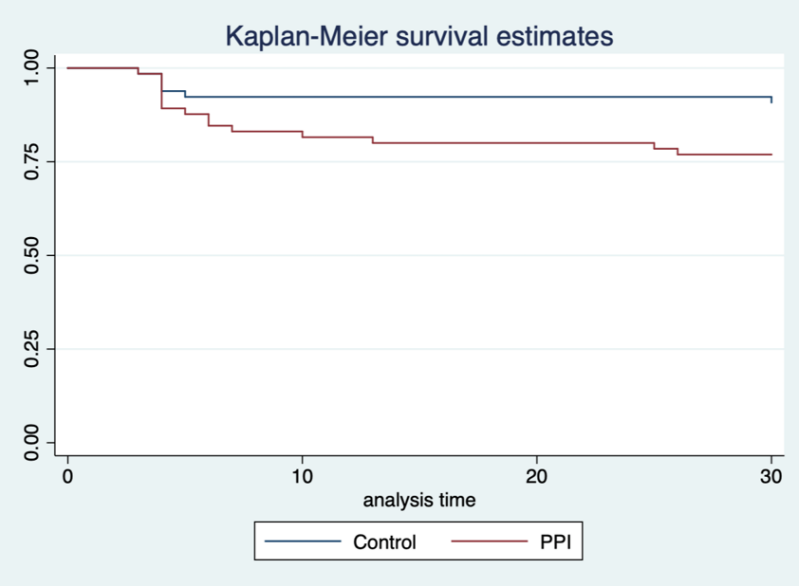

Figure 2. Kaplan-Meier curve of hospital-acquired pneumonia events.

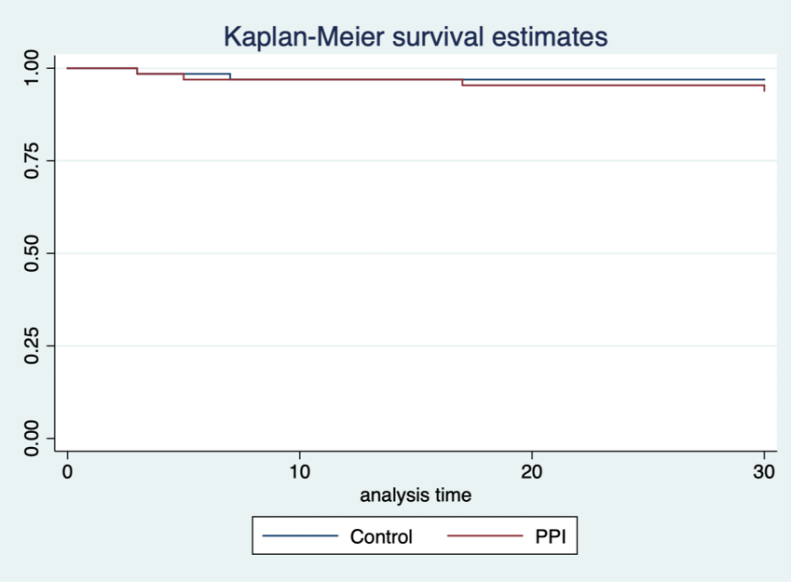

Figure 3. Kaplan-Meier curve of GI bleeding events.

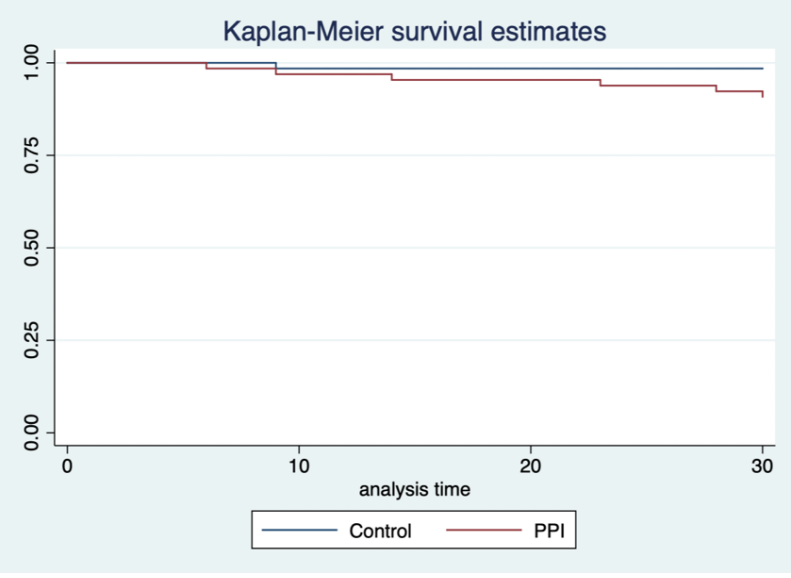

Figure 4. Kaplan-Meier curve of hospital mortality.

Table 3. Factors associated with Hospital-acquired pneumonia

Factor	Crude hazard ratio (95% confidence interval)	P-value	Adjusted hazard ratio (95% confidence interval)	P-value
Male	0.94 (0.37-2.39)	0.903	0.49 (0.00-1.67)	0.460
Diabetes mellitus	2.56 (0.77-8.52)	0.124	24.21 (0.98-598.68)	0.052
Hypertension	1.10 (0.41-2.45)	0.981	0.56 (0.27-11.42)	0.706
Chronic kidney disease	1.66 (0.21-12.89)	0.626	4.28 (0.02-655.47)	0.571
Chronic obstructive pulmonary disease	1.16 (0.46-2.89)	0.745	3.73 (0.15-93.22)	0.423
Cirrhosis	1.66 (0.21-12.89)	0.626	4.68 (0.26-838.77)	0.559
HIV	1.66 (0.21-12.89)	0.626	0.28 (0.00-60.20)	0.649
Age > 50 yr	2.89 (0.35-23.34)	0.318	8.35 (0.01-4850.21)	0.513
Anemia (Hb<10g /dl)	1.98 (0.73-5.34)	0.176	1.24 (0.18-8.14)	0.821
MEWS >4	0.96 (0.34-2.69)	0.95	0.15 (0.00-8.10)	0.353
Vasopressor	0.79 (0.18-3.52)	0.768	2.34 (0.12-44.08)	0.569
Prokinetic use	1.55 (0.43-5.59)	0.496	3.29 (0.09-120.28)	0.569
Feeding calories < 1500 kcal	0.99 (0.99-1.00)	0.488	1.00 (0.90-120.28)	0.516
Duration of MV < 48 hr	0.05 (0.00-0.79)	0.034	0.04 (0.00-1.67)	0.091
PPI	0.42 (0.14-1.23)	0.117	0.19 (0.00-4.05)	0.293

*Significant consider as P<0.05
Abbreviations: HIV: Human immunodeficiency virus; Hb: Hemoglobin; MEWS: Modified Early Warning Score

Table 4. Factors associated with GI bleeding

Factor	Crude hazard ratio (95% confidence interval)	P-value	Adjusted hazard ratio (95% confidence interval)	P-value
Age > 50 yr	1.33 (0.21-8.47)	0.758	1.90 (0.27-131.37)	0.766
Male	1.31 (0.21-8.01)	0.764	2.10 (0.09-48.36)	0.641
Chronic kidney disease	4.60 (0.41-51.31)	0.214	4.91 (0.17-136.73)	0.348
Congestive heart failure	1.12 (0.11-11.17)	0.920	2.11 (0.09-48.36)	0.641
PPI	0.45 (0.06-3.23)	0.429	0.52 (0.00-36.26)	0.766

*Significant consider as P<0.05

This study, conducted according to a randomized controlled trial protocol, contributes to the strength of our findings. However, there are limitations. First, this was an open-label study. Second, there was a low prevalence of primary endpoints—hospital-acquired pneumonia and gastrointestinal bleeding, limits the strength of conclusions regarding efficacy and making it challenging to provide statistically significant hazard ratios among the associated factors. The small number of outcome events, especially gastrointestinal bleeding, limited the robustness of multivariable analyses and resulted in wide confidence intervals. Accordingly, these findings should be interpreted as exploratory rather than definitive. Third, patient with coagulopathy or certain bleeding risk were exclude from this study. Results from this study may mainly apply to low-to-moderate bleeding-risk ICU patients receiving enteral nutrition. Therefore, a multicenter study with a larger population is warranted.

CONCLUSION

This randomized controlled trial found that the risk of gastrointestinal bleeding was comparable between critically ill patients receiving PPIs and those in the control group. Although a higher incidence of hospital-acquired pneumonia was observed in the PPI group, PPI use was not independently associated with hospital-acquired pneumonia after multivariate adjustment. Larger multicenter studies are warranted to further validate these findings.

CONFIDENTIALITY

Written informed consent was obtained from all participants. Participant confidentiality was strictly maintained throughout the study. All data were anonymized prior to analysis, and access was restricted to authorized members of the research team. The study was approved by the Institutional Review Board.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Than Akkharawanasakun and Piyaporn Sirijanchun Data curation: Than Akkharawanasakun; (II) Formal analysis: Piyaporn Sirijanchun; (III) Methodology: Than Akkharawanasakun and Piyaporn Sirijanchun; (IV) Project administration: Than Akkharawanasakun; (V) Visualization: Than Akkharawanasakun; (VI) Writing – original draft: Than Akkharawanasakun; (VII) Writing – review & editing: Than Akkharawanasakun and Piyaporn Sirijanchun.

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