

# Effectiveness of Proton Pump Inhibitors as a Gastrointestinal Bleeding Prophylaxis in Intensive Care Unit: Systematic Review and Meta-Analysis

Fonny Cokro<sup>1\*</sup>, Jenny Jokimawidjaja<sup>1</sup>

<sup>1</sup>Department of Pharmacy, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, North Jakarta, Indonesia

\*Corresponding author: Fonny Cokro (fonny.cokro@atmajaya.ac.id)

## Abstract

**Introduction:** GI bleeding is a serious illness that can lengthen the time spent in the Intensive Care Unit (ICU) and increase morbidity and death by up to four times. Proton Pump Inhibitors (PPIs) are agents commonly used in patients to prevent Gastrointestinal (GI) bleeding in ICU. However, nowadays, the use of PPIs to prevent GI bleeding is being concerned due to the emergence of various studies regarding the side effects caused by PPIs. We conducted a systematic review and meta-analysis to see the magnitude of the effectiveness and validate the safety of PPIs.

**Methods:** We searched through PubMed, ScienceDirect, GARUDA Portal, Clinical Key, and Google Scholar databases to identify randomized controlled trials (RCTs) that compared the effects of PPI administration on the PPI and placebo groups in adults ICU patients. Fixed effect was used if the data were homogenous.

**Results:** From a total of 8 studies, this meta-analysis shows the effectiveness of PPIs as prophylactic GI bleeding significantly with  $p < 0.0001$ ,  $RR = 0.52$  (95% CI 0.38-0.71). Regarding safety, PPIs did not significantly increase the risk of pneumonia ( $p = 0.30$ ,  $RR = 1.31$  (95% CI 0.78-2.20)); and *C. difficile* infection ( $p = 0.90$ ,  $RR = 0.91$  (95% CI 0.21-3.85)); and it does not impact on the mortality event ( $p = 0.78$ ;  $RR 1.01$  (95% CI 0.93-1.10)).

**Conclusions:** PPIs reduce GI bleeding in ICU patients over the age of 18. PPIs are also safe to use as preventative GI bleeding with no increased risk of pneumonia and *C. difficile* infection. PPI does not, however, significantly affect the death rates.

**Keywords:** gastrointestinal bleeding - intensive care unit - prophylaxis - proton pump inhibitor

## INTRODUCTION

Patients in the Intensive Care Unit (ICU) with critical illness, within 24 hours, can be at high risk for Gastrointestinal bleeding (GI bleeding). GI bleeding is a severe condition, where this condition can increase morbidity and mortality by up to 4 times and prolong the stay in the ICU

for 4-8 days.<sup>1</sup> Factors that can cause GI bleeding in the ICU include the presence of use of mechanical ventilation, patients with coagulopathy, and liver or renal failure.<sup>2</sup> However, the most common cause of GI bleeding is the presence of Peptic Ulcer Disease (PUD), where PUD is the cause of more than

60% of GI bleeding events. PUD can arise due to several things, including hypoperfusion and ischemia, which occur mainly in critically ill patients admitted to the ICU, where hypoperfusion and ischemia can damage the cyclooxygenase 2 (COX-2) and lipoxygenase pathways, thereby reducing the levels of prostaglandins produced, which is the component of the gastric mucosa defense.<sup>3</sup> One type of PUD that causes GI bleeding in ICU patients is Stress-Related Mucosal Disease (SRMD). SRMD occurs only in critically ill patients, such as patients who have experienced severe trauma, patients who have undergone major surgery, and patients with burns covering up to one-third of the body SRMD can cause acute erosive gastropathy in patients after surgery and during organ failure, sepsis, and respiratory failure, leading to GI bleeding.<sup>4</sup>

With the high incidence of GI bleeding and the number of deaths that can be caused, it is necessary to have prophylaxis to prevent GI bleeding. Proton Pump Inhibitors (PPIs) are one of gastrointestinal medicine's most commonly used drug classes.<sup>5</sup> However, a study by Kurlander et al. on 799 internal medicine physicians showed that 79% discontinued PPI administration in patients with a high risk of upper GI bleeding due to a large number of studies on the side effects of PPIs in circulation.<sup>6</sup> Some side effects that PPIs can cause include pneumonia and *C. difficile* infection.<sup>7-10</sup> Therefore, this study aimed to validate the

effectiveness of PPIs in preventing GI bleeding, reducing mortality in ICU patients, and validating the safety of PPIs against pneumonia and *C. difficile* infection.

## METHODS

This study is retrospective, using the Systematic Review method. This research was conducted from January to May 2021.

### Search Strategy

Data were collected from several databases using predefined keywords. The PubMed database was searched through MeSH using keywords (((("Intensive Care Units"[Mesh])) AND "Proton Pump Inhibitors"[Mesh]) OR "Omeprazole"[Mesh]) OR "Lansoprazole"[ Mesh]) OR "Pantoprazole"[Mesh]) AND "prevention and control" [Subheading]) AND "Gastrointestinal Hemorrhage"[Mesh]. In the ScienceDirect database, a search was conducted with the keywords: "Intensive Care Units AND Proton Pump Inhibitors AND Prophylaxis OR Prevention AND Gastrointestinal Bleeding." The Garuda Portal, the keywords are as follows: "Proton Pump Inhibitor Prophylaxis." We also use Clinical Key with the keywords: "Proton Pump Inhibitor AND Prophylaxis AND Intensive Care Unit." To add to the literature search, we also conducted a Google Scholar search with the keywords: "ICU Proton Pump Inhibitor Prophylaxis Bleeding." Filters used on each

database include age >18 years, human subject, article type RCT, and Systematic Review.

### **Inclusion and Exclusion Criteria**

This study analyzed various Randomized Controlled Trials (RCTs) that compared the effectiveness of prophylaxis between PPIs and placebo or no PPIs. The inclusion criteria in this study were RCTs with following criteria: 1) patients aged  $\geq 18$  years, 2) ICU patients or patients receiving mechanical ventilators, and 3) a comparison of the effectiveness and safety of PPI and placebo. Meanwhile, the exclusion criteria set were: 1) studies including patients experiencing recurrent GI bleeding, 2) patients receiving H2RA or other prophylactic drugs, and 3) full texted articles could not be obtained.

### **Data Extraction and Quality Assesment**

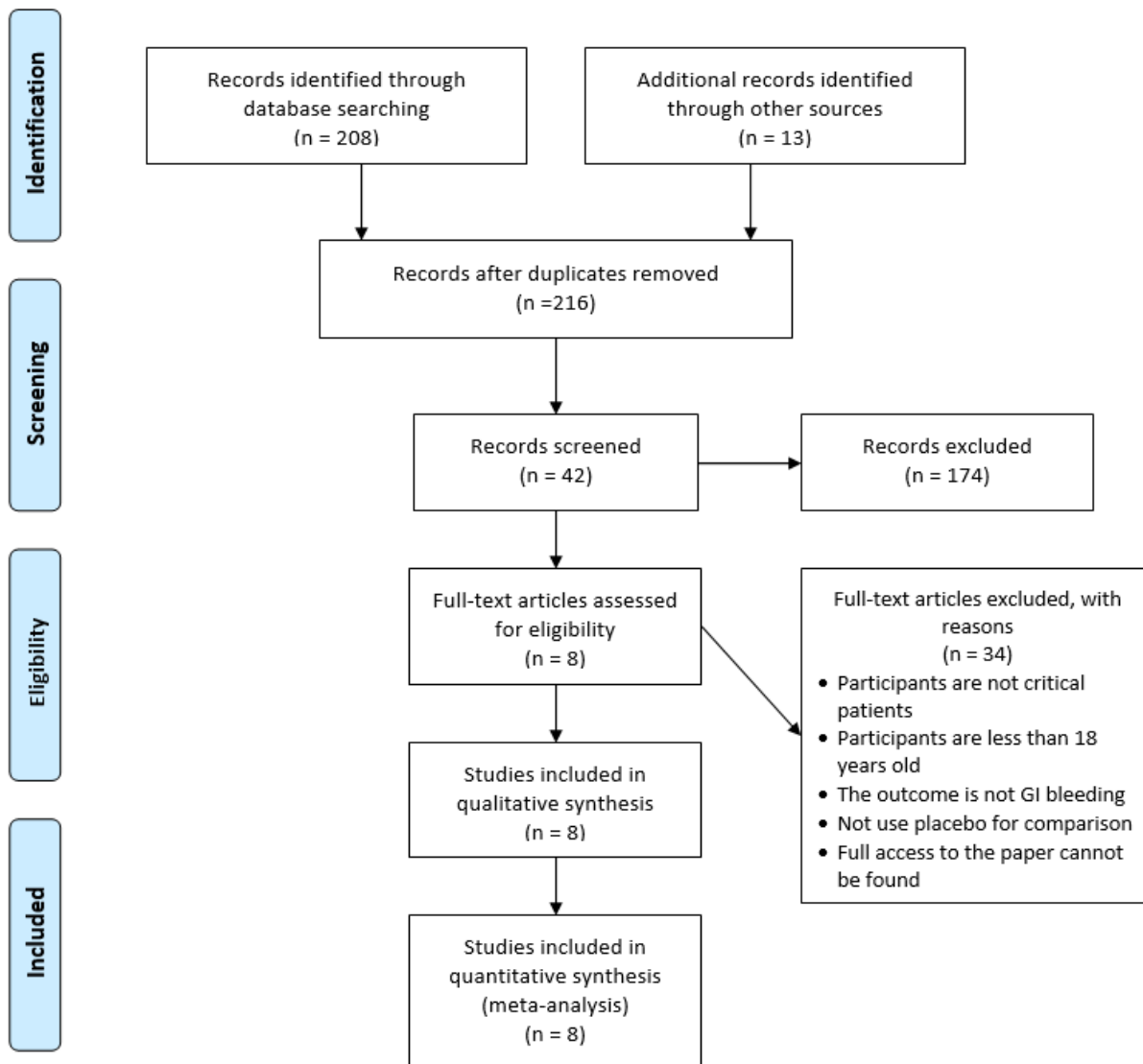
Data collection was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. The quality of each study obtained was analyzed qualitatively using The Critical Appraisal Skills Program (CASP) checklist for RCT studies to see quality of each study. Good quality studies met all the criteria in the CASP checklist for RCT studies. Quality assessment was conducted by two reviewers independently. Different results from assessment were discussed until agreement achieved.

### **Statistical Analysis**

The selected final articles were analyzed using the Review Manager application version 5.4, where the analysis was carried out per outcome measured. The primary outcome was Risk Ratio (RR) of GI bleeding events, while the secondary outcome included were incidence RR of pneumonia, *C. difficile* infection, and mortality rates. Suppose the study data had high heterogeneity (p-value heterogeneity <0.05), then a random effect model was used. However, if the study data was homogeneous (p-value heterogeneity > 0.05), then the fixed effect model was used. If the overall effect value was  $p < 0.05$ , it was considered statistically significant. The confidence interval (CI) used is 95%.

### **RESULTS**

The article search from 6 databases yielded 221 studies that were candidates for further analysis. Of the six sources, no studies could be found in the Garuda Portal database. Thus, only five database sources were used. After selecting the studies by looking at the titles and their abstracts, a total of 42 studies were obtained, which would then be re-selected by reading the full-text article. However, 32 studies with irrelevant subject criteria and outcomes were excluded from this study. Furthermore, two studies have not been able to get full access to date.<sup>11-12</sup> Thus, both studies were excluded from this study. From reading the full-text articles,



**Fig 1.** PRISMA Flow Chart as Study Selection Protocol

we obtained a final total of 8 studies that could be used in qualitative and quantitative analysis, of which six studies came from the PubMed database, one from the ScienceDirect database, and 1 study came from Google Scholar. The flow of the study search can be seen in Figure 1. The three studies included in the final study in this study came from the same trial, The Stress Ulcer Prophylaxis-ICU (SUP-ICU) trial.<sup>13-15</sup> Although derived from the same trial, the three studies

analyzed different outcomes, so the three studies were still used in qualitative and quantitative analysis. The studies analyzed were from the 2013-2019 publication year. The total participants in this study were 3931 patients aged 18 years with one or more risk factors for GI bleeding. The highest number of participants was taken in the three studies originating from the SUP-ICU trial. The

**Table 1.** Characteristics of Included Articles

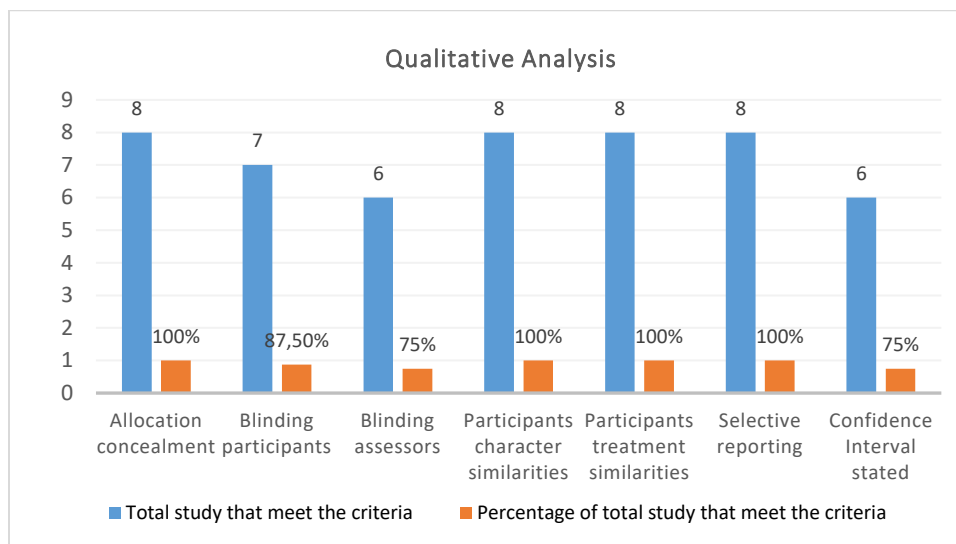
| Study                        | Participant  | Intervention                                       | Comparator                              | Outcome   | Treatment Duration  |
|------------------------------|--|--|---|---|---|
| Scheffold et al., 2019 (13)  | 3291 ICU patients >18 years with or without RRT, and at least one risk factor for GI bleeding                                  | Pantoprazole 40 mg IV once daily                   | Placebo IV once daily                   | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding in RRT and non-RRT patients</li> <li>90-day mortality rate in both RRT and non-RRT patients</li> </ul>   | Until the patient is discharged from the ICU or dies, a maximum of 90 days                        |
| Marker et al., 2019 (14)     | 3291 ICU patients >18 years with at least one risk factor for GI bleeding  | Pantoprazole 40 mg IV 1x1 once daily               | Placebo IV once daily                   | Mortality rate in 1 year  | During the time of stay in the ICU  |
| Krag et al., 2018 (15)       | 3298 ICU patients 18 years had at least one risk factor for GI bleeding  | Pantoprazole 40 mg IV 1x1 once daily               | Placebo of 10ml NaCl 0.9% IV once daily | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding in RRT and non-RRT patients</li> <li>90-day mortality rate in both RRT and non RRT patients</li> <li>Number of patients with infection (<i>C. difficile</i> or pneumonia)</li> </ul> | Until the patient was discharged from the ICU or dies, a maximum of 90 days                       |
| Selvanderan et al., 2016(17) | 209 ICU patients at Adelaide Hospital who used mechanical ventilator >24 hours and received enteral nutrition within 48 hours  | Pantoprazole 40 mg IV 1x1 once daily               | Placebo of 10ml NaCl 0.9% IV once daily | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding</li> <li>Number of patients infected with <i>C. difficile</i></li> <li>Number of patients with pneumonia</li> <li>90-day mortality rate</li> </ul>                                   | Until the patient did not use a mechanical ventilator or a maximum of 14 days                     |
| Lin et al., 2016 (19)        | 120 ICU patients on a mechanical ventilator  | Lansoprazole 30 mg once daily via nasogastric tube | No gastric medication was given         | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding</li> <li>Number of patients with pneumonia</li> </ul>  | 14 days   |
| El-Kersh et al., 2017 (21)   | 102 ICU patients 18 years requiring mechanical ventilation >48 hours   | Pantoprazole 40 mg IV + EN once daily              | Normal saline once daily                | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding</li> <li>Number of patients infected with <i>C. difficile</i></li> </ul>   | First 24 hours after intubation   |
| Liu et al., 2013 (20)        | 111 ICU patients >18 years who had CT-proven intracerebral hemorrhage (ICH) within 72 hours of jaundice requiring neurosurgery | Omeprazole 40 mg IV every 12 hours                 | Placebo every 12 hours                  | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding</li> <li>Number of patients with pneumonia</li> <li>Patient mortality rate within one month</li> </ul>   | Seven days or until upper GI bleeding occurred  |
| Alhazzani et al., 2017 (18)  | 91 ICU patients 18 years who were expected to receive 48 hours of mechanical ventilation                                       | Pantoprazole 40mg in 0.9% NaCl 50mL                | Placebo (0.9% NaCl, 50mL)               | <ul style="list-style-type: none"> <li>Number of patients experiencing GI bleeding</li> <li>Number of patients with pneumonia</li> <li>Number of patients infected with <i>C. difficile</i></li> <li>Number of patients who died in the ICU</li> </ul>                  | When the patient was on a mechanical ventilator or until GI bleeding or death occurred in the ICU |

characteristics of each study can be seen in Table 1. The results of the study search were

followed by a qualitative analysis using the CASP checklist for RCT studies to see the quality

of each study. After that, The Cochrane Tool for Assessing Risk of Bias<sup>16</sup> was used to analyze the risk of possible bias in each study by interpreting the results obtained from the analysis using the CASP checklist for RCT

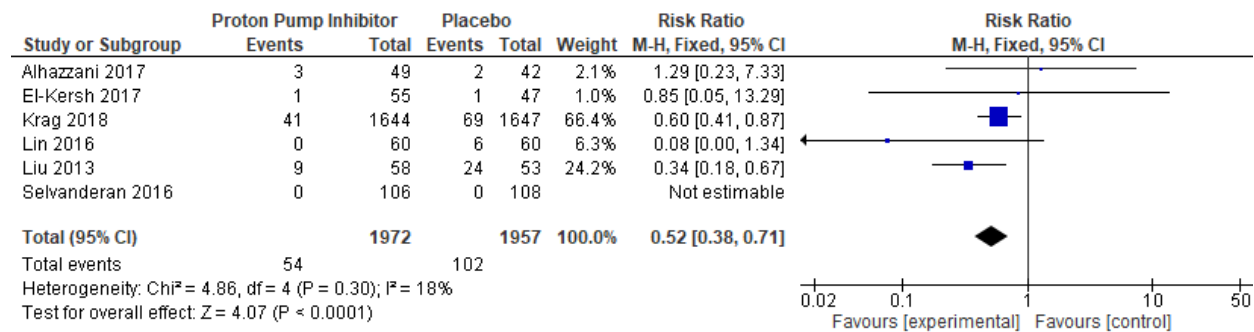
studies. Of the eight studies obtained, four studies met all of the criteria, Schefold et al.<sup>13</sup>, Krag et al.<sup>15</sup>, Selvanderan et al.<sup>17</sup>, and Alhazzani et al.<sup>18</sup>. The number of studies that meet each criterion can be seen in Figure 2.



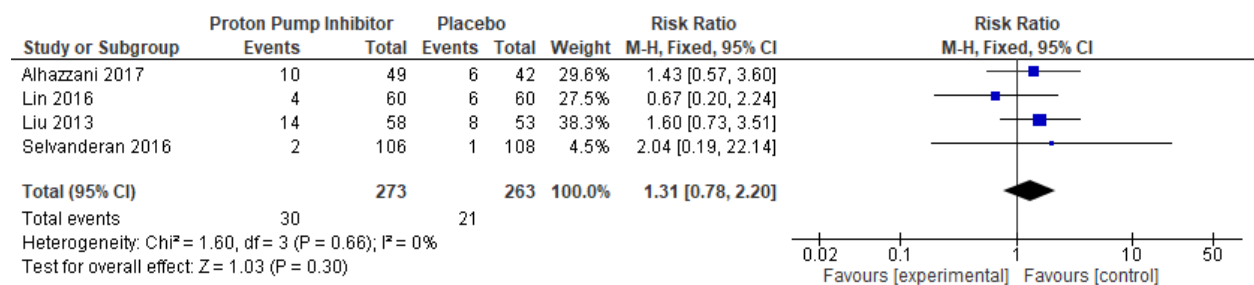
**Fig 2.** Number of Studies that Meet Each Criterion

A quantitative analysis was also carried out, using the Review Manager application version 5.4 to see the forest plot. After the selection process, six studies were selected to be used in the quantitative analysis, namely Marker et al.<sup>14</sup>, Krag et al.<sup>15</sup>, Selvanderan et al.<sup>17</sup>, Lin et al.<sup>19</sup>, El-Kersh et al.<sup>20</sup>, Liu et al.<sup>20</sup>, and Alhazzani et al.<sup>18</sup>. The results of the meta-analysis of GI bleeding in 6 studies showed heterogeneity between studies with  $p = 0.30$ , so the fixed effect model was used. One of the studies, Selvanderan et al.<sup>17</sup>, was not included in the forest plot because the number of patients experiencing GI bleeding in both groups was 0. The largest study effect

was in the study by Krag et al.<sup>15</sup>, which was 66.4%. Although the three studies were not statistically significant, the overall effect was statistically significant, with  $p < 0.0001$ , RR 0.52 (95% CI 0.38-0.71). The results of the meta-analysis of each incidence of pneumonia, *C. difficile* infection, and death showed that the heterogeneity values between studies were homogeneous ( $p > 0.05$ ), then a fixed model was used, and the results obtained were not significant with sequential results:  $p = 0.30$ , RR 1.31 (95% CI 0.78-2.20);  $p = 0.90$ , RR 0.91 (95% CI 0.21-3.85); and  $p = 0.78$ ; RR 1.01 (95% CI 0.93-1.10).



**Fig 3.** Forest plot Comparison of PPI and Placebo on the Incidence of GI bleeding



**Fig 4.** Forest plot Comparison of PPI and Placebo on the Incidence of Pneumonia

## DISCUSSION

PPIs are prophylactic agents commonly used in patients to prevent GI bleeding. Liu et al. stated that omeprazole was effective and safe in significantly reducing the morbidity of upper GI bleeding.<sup>20</sup> However, on the other hand, other studies found no evidence that offering PPI prophylaxis was beneficial.<sup>17,18,21</sup> Although most studies show similar results that there is no significant difference in preventing GI bleeding, the final result is that PPIs can prevent GI bleeding after conducting a quantitative analysis. In addition, administering a PPI can affect gastric pH to 4, lowering the risk of GI bleeding.<sup>20</sup>

Studies examining the adverse effects of pneumonia in patients receiving a PPI and

placebo found no significant difference between a PPI and a placebo in the incidence of pneumonia (17–20). Selvanderan et al. stated that the administration of pantoprazole did not clearly increase the risk of ventilator-associated pneumonia (VAP).<sup>17</sup> However, there is a trend toward an increased incidence of pneumonia associated with the use of omeprazole.<sup>20</sup> The results of the data in the study by Liu et al. and Alhazzani et al. showed that pneumonia occurred in the group of patients receiving a PPI higher than placebo by up to 40%.<sup>18,20</sup> Future studies with larger samples are needed to validate this. In addition, there was no significant difference between the PPI and placebo groups in the incidence of *C. difficile* infection.<sup>17,20,21</sup> However, similar research is still

needed to validate this due to the lack of data on research on this outcome.

Studies conducted to analyze the associated mortality rates varied from 30 days, 90 days, and 1 year. Researchers combined different periods of mortality rates due to the lack of studies examining mortality rates over the same period. However, all studies showed no significant difference in mortality rates between PPI and placebo administration.<sup>14,15,17,19-21</sup> Liu et al. stated that omeprazole failed to reduce mortality and that upper GI bleeding could be a marker of a high mortality rate.<sup>20</sup> Since 1981, several severity scores have been proposed for intensive care unit patients. One of them is the Simplified Acute Physiology Score (SAPS II). SAPS II is a measure of severity score in ICU patients aged 18 years, with a range of 0 to 163 points, from a total sum of 12 physiological variables collected within 24 hours after the patient was admitted to the ICU. SAPS II was used to measure the mortality rate of each patient. The more severe the patient's illness, the higher the points earned and the higher the mortality risk.<sup>22</sup> Krag et al. stated that they found an interaction between the effect of the intervention and disease severity indicating a higher 90-day mortality rate among patients who had more severe disease and received pantoprazole.<sup>15</sup> However, the study by Marker et al. did not show any harmful effect of pantoprazole administration among ICU

patients in patients with SAPS II scores >53 points.<sup>14</sup>

Previously, several similar studies conducted a systematic review and meta-analysis on the effect of PPIs as prophylaxis of GI bleeding in ICU patients 18 years of age. However, most studies do not compare PPIs with placebo but with H2RA or other drugs such as sucralfate. The meta-analysis by Alhazzani et al. includes studies from 1993 to 2016.<sup>18</sup> Thus, this systematic review is more up-to-date, including recent studies from 2017 to 2019.

The results of Alhazzani et al. study showed that PPIs were not significantly effective in preventing GI bleeding ( $p = 0.95$ ; OR 0.96; (95% CI 0.24-3.82)), with no significant event of pneumonia ( $p = 0.41$ ; OR 1.32 (95% CI 0.68-2.55)).<sup>18</sup> The results obtained by Alhazzani et al. on the outcome of GI bleeding are different from the results of this research because some of the latest studies that the researchers used in this study had a lower incidence of GI bleeding in the PPI group, so when added to the meta-analysis, the results showed a significant difference where PPIs were more effective in preventing GI bleeding.

There are some limitations exist in this study. At the beginning of the study, there were two studies with non-obtainable full-text versions. Thus, it affects the lack of research data. In addition, studies that examine similar topics are still very lacking, especially the three studies



that the researchers got from the same trial. Another limitation is the lack of research examining events of pneumonia and *C. difficile* infection. This results in a wide confidence interval on the forest plot.

## CONCLUSIONS

Based on the results of systematic review and meta-analysis that have been carried out, it can be concluded that PPIs are significantly effective in preventing GI bleeding in ICU patients aged 18 years. In addition, PPIs do not significantly cause pneumonia and *C. difficile* infection. Thus, PPIs are safe to use for prophylactic GI bleeding. However, PPI does not have a significant effect on reducing mortality rates. Additional large RCTs are needed to confirm these results.

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## CONFLICT OF INTEREST

No conflict of interest is found in this study.

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