ORIGINAL ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Evaluation of Proton Pump Inhibitor Prescribing Practices for Stress Ulcer Prophylaxis in ICU Patients: A Retrospective Cross-Sectional Study

Doaa H. El-Farook[1], Ahmed Essam Abou Warda[2], Nada Hazem Farrag[3], Sayed Gaber[4], Mahmoud Tammam[5], Ramy M. El Sabaa[6], Asmaa S. Mohamed[7,8*]

[1] Clinical Pharmacy Department, Faculty of pharmaceutical sciences and drug manufacturing, Misr University for science and technology, Giza, Egypt; [2] Clinical Pharmacy Department, Faculty of Pharmacy, October 6 University, Giza, Egypt; [3] University of Hertfordshire hosted by global academic foundation, new capital, Cairo, Egypt; [4] Critical Care Medicine, Faculty of Medicine, Cairo University, Giza, Egypt; [5] IQVIA, Cairo, Egypt; [6] Clinical Pharmacy Department, Faculty of Pharmacy, Menoufia University; Menoufia, Egypt; [7] Clinical Pharmacy and Pharmacy Practice Department, Faculty of Pharmacy, Port Said University, Port Said, Egypt; [8] Clinical Pharmacy and Pharmacy Practice Department, Faculty of Pharmacy, East Port Said National University, Port Said, Egypt.

Received: 1. 8. 2025

Revised: 12. 8. 2025

Accepted: 15. 8. 2025

*Correspondence Author:

E-mail address:

asmaa.mohamed@pharm.psu.edu.eg

Abstract

Background: Stress ulcer prophylaxis (SUP) with proton pump inhibitors (PPIs) is widely used in intensive care units (ICUs) to prevent gastrointestinal bleeding in critically ill patients. This study evaluates PPI prescribing patterns in ICU patients, their appropriateness based on clinical risk factors, and associated outcomes, including therapeutic failure and adverse events.

Methods: This retrospective cross-sectional study analyzed data from 158 adult ICU patients at El Moalmeen Private Hospital in Cairo, Egypt. Researchers collected demographic, clinical, and laboratory data using a structured form. The study evaluated PPI prescribing practices based on recognized major and minor risk factors for stress-related mucosal bleeding, along with instances of therapeutic failure and adverse effects.

Results: In a study of 158 ICU patients (mean age 63.8 years, 57% male), hypertension (60.1%) and diabetes (41.8%) were prevalent comorbidities, with pneumonia (41.1%) as the leading cause of admission, followed by acute kidney injury and altered consciousness (10.1% each). Only 44.9% of PPI prescriptions were appropriate, with 22.2% supported by major indications and 24.1% by two or more minor indications. However, 55.1% of PPI use lacked clear justification. Therapeutic failure occurred in 12.7% of cases, and *Clostridioides difficile* infection was noted in 5.1%. Logistic regression identified older age (OR 1.04) and chronic kidney disease (OR 4.98) as significant predictors of PPI overprescription.

Conclusion: Inappropriate PPI use for SUP remains prevalent in ICU patients. Advanced age and chronic kidney disease are key predictors, highlighting the need for evidence-based guidelines and increased prescriber awareness to optimize therapy and reduce adverse outcomes.

Keywords: Proton pump inhibitors; Prescription; Intensive care units; Stress ulcer prophylaxis; Acid-suppressive therapy.

1. Introduction

Stress-induced gastrointestinal ulcers are a common complication among patients admitted to intensive care units (ICUs), contributing significantly to both morbidity and mortality **(Jufan & Wisudarti, 2021; Agarwal & Agarwal, 2022)**. As a result, stress ulcer prophylaxis (SUP) has become a widely adopted practice among healthcare providers managing critically ill patients. Over the past four decades, various strategies for SUP have been proposed, with acid-suppressive therapies being the most commonly employed in ICU settings. Among these, proton pump inhibitors (PPIs) have emerged as one of the most frequently prescribed agents for stress ulcer prevention due to their potent and sustained acid-suppressive effects **(Pham et al., 2006; Grube & May, 2007; Savarino et al., 2018; Barbateskovic et al., 2019)**.

Identifying patients at risk for stress-related mucosal bleeding is essential to guide appropriate use of SUP. Risk factors can be classified into major and minor categories. Major risk factors include mechanical ventilation for more than 48 hours, coagulopathy (defined as a platelet count <50,000/mm³ or an international normalized ratio [INR] >1.5), spinal cord injury, severe burns covering more than 30% of total body surface area, or a history of gastrointestinal bleeding within the past 12 months. Minor risk factors include severe sepsis or septic shock, an ICU stay exceeding one week, occult gastrointestinal bleeding persisting for at least six days, use of antiplatelet agents, and administration of high-dose glucocorticoids (e.g., ≥250 mg of hydrocortisone or equivalent). Current guidelines recommend initiating SUP in patients with at least one major risk factor or two or more minor risk factors **(Grube & May, 2007; Barletta et al., 2016)**.

Gastric acidity serves as a natural physiological barrier that protects the body against ingested pathogens. However, the use of acid-suppressing medications disrupts this defence mechanism, leading to an increased risk of both gastric and duodenal bacterial overgrowth **(Thorens et al., 1996)**. Two clinically significant complications associated with this disruption are pneumonia and *Clostridioides difficile* (*C. difficile*) –associated diarrhea **(Agastya et al., 2000; Castellana et al., 2021; Inghammar et al., 2021; Tawam et al., 2021; Maideen, 2023)**.

Proton pump inhibitors help prevent stress ulcers by irreversibly blocking the proton pump in gastric parietal cells, which is responsible for the final step in acid secretion. This inhibition reduces stomach acid levels, raises intragastric pH, and protects the stomach lining, aiding mucosal healing and reducing the risk of gastrointestinal bleeding in critically ill patients **(Carlman & Joby, 2020; Clarke et al., 2022) (Figure 1)**.

Although there is strong evidence supporting the effectiveness of SUP as a preventive measure, inadequate education regarding the appropriate indications for PPI therapy has contributed to their overuse, leading to an increased risk of adverse effects and unnecessary healthcare costs **(Eom et al., 2011; Kwok et al., 2012; Willems et al., 2020)**.

The main objective of this study is to evaluate PPI prescribing patterns in ICU patients, their appropriateness based on clinical risk factors, and associated outcomes, including therapeutic failure and adverse events.

2. Methods

2.1. Study Design

This retrospective observational cross-sectional study included 158 adult patients (aged over 18 years) who were admitted to the ICU at El Moalmeen Private Hospital in Cairo, Egypt, which is affiliated with the Syndicate of Educational Professions **(Figure 2)**. Exclusion criteria included age under 18 years, pregnancy, lactation, hepatic impairment classified as Child-Pugh class C, and severe renal impairment defined as creatinine clearance <10 mL/min.

2.2. Sample size

The sample size was calculated prior to the start of the study. Using a 95% confidence level, a margin of error of 0.08 (8%), and an estimated population proportion of 50%, the required minimum sample size was determined to be approximately 150

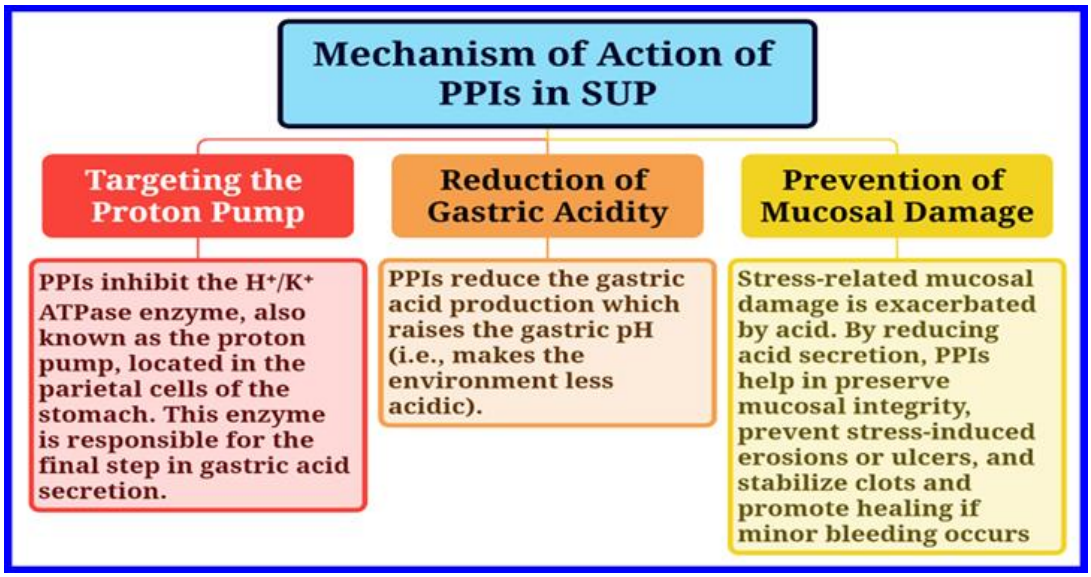

Figure 1. Mechanism of action of PPIs in SUP

patients. This level of precision was considered appropriate given the available ICU population. Consecutive sampling was employed, and a total of 158 adult ICU patients who met the inclusion criteria were included in the study.

2.3. Patient Data Collection

A structured patient data collection form was used to gather essential information for assessing each patient's risk of requiring SUP. The form included: (1) demographic data, such as age, gender, allergies, and length of hospital stay; (2) clinical information, including chief complaint, history of present illness, diagnosis, and prescribed medications; (3) details of the SUP regimen, including the agents used, dosage, route of administration, frequency, and duration; and (4) relevant laboratory results, particularly complete blood count (CBC) and INR.

2.4. Pattern of PPI Prescription and Patient Follow-Up

All patients were assessed for risk factors associated with the use of a SUP regimen. We determined the proportion of patients receiving PPIs as SUP who were considered at high risk for developing stress ulcers, as well as those who received PPIs despite having no identifiable risk factors or clear indication for prophylaxis. In addition, we evaluated the rate of therapeutic failure and the incidence of adverse effects associated with PPI use. In this study, therapeutic failure was defined as the inability of PPI therapy to effectively prevent clinically significant gastrointestinal (GI) bleeding among ICU patients receiving SUP. This included the development of upper GI bleeding symptoms such as hematemesis, melena, or occult bleeding evidenced by unexplained anemia or a drop in hemoglobin levels.

All prescriptions containing PPIs for the studied patients were analyzed. Any PPI, regardless of its specific type or route of administration, was considered eligible for inclusion in the analysis.

2.5. Outcomes

This study evaluated the appropriateness of PPI use for stress ulcer prophylaxis based on clinical risk factors. Secondary outcomes included rates of therapeutic failure, adverse events such as C. difficile infection. Predictors of PPI overprescription were also analyzed.

2.6. Statistical Analysis

Data were analyzed using SPSS v26. Descriptive statistics were employed to summarize patient characteristics, admission diagnoses, PPI prescription patterns, and adverse outcomes. Continuous variables, such as age and length of hospital stay, were expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR) as appropriate. Categorical variables, including gender, comorbidities, indications for PPI use, and adverse events, were summarized as frequencies and

percentages. To identify predictors of PPI overprescription, binary logistic regression analysis was performed. A p-value of less than 0.05 was considered statistically significant.

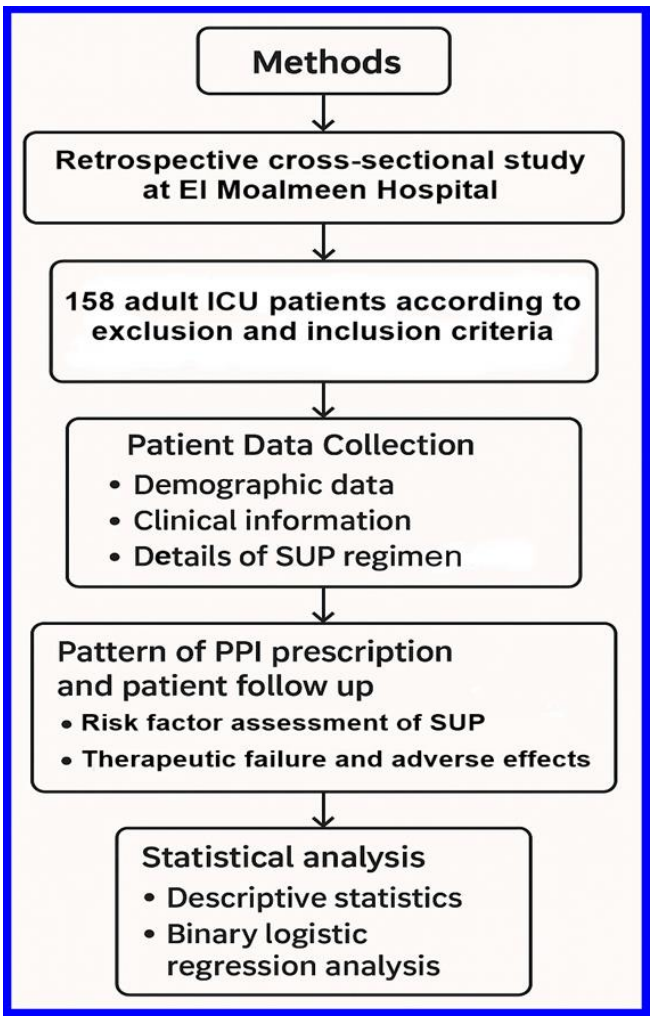

Figure 2. Study methods

3. Results

A total of 158 patients admitted to the ICU during the study period were included in the analysis. **Table 1** summarizes the baseline demographic and clinical characteristics of the study population.

The demographic data presented in table 1 offers a comprehensive overview of the study population, which included 158 patients with a mean age of 63.8 years, slightly more males (57%) than females (43%). The median hospital stay was 7 days (IQR: 4–11). Comorbidities were common, with hypertension (60.1%) and diabetes (41.8%) being the most prevalent. Chronic kidney disease (25.3%) and ischemic heart disease (20.9%) were also frequent. Other conditions such as atrial fibrillation, stroke, COPD, and asthma were less common. In addition to the listed conditions, 50% of patients had at least one other comorbidity not individually specified, such as liver disease, malignancy, metabolic, endocrine, inflammatory, or neurologic disorders. Overall, the population was predominantly older adults with a high burden of chronic diseases.

Figure 3 presents the distribution of chief complaints on admission among the 158 patients included in the study. Pneumonia was the most common reason for admission (41.1%), followed by acute kidney injury and disturbed consciousness (each 10.1%). Stroke accounted for 8.2% of admissions, while sepsis and dehydration were less frequent at 7% and 3.8%, respectively. A diverse range of other complaints made up 19.6% of admissions. Overall, respiratory infections, neurological conditions, and acute organ dysfunction were the predominant causes of hospitalization in this population.

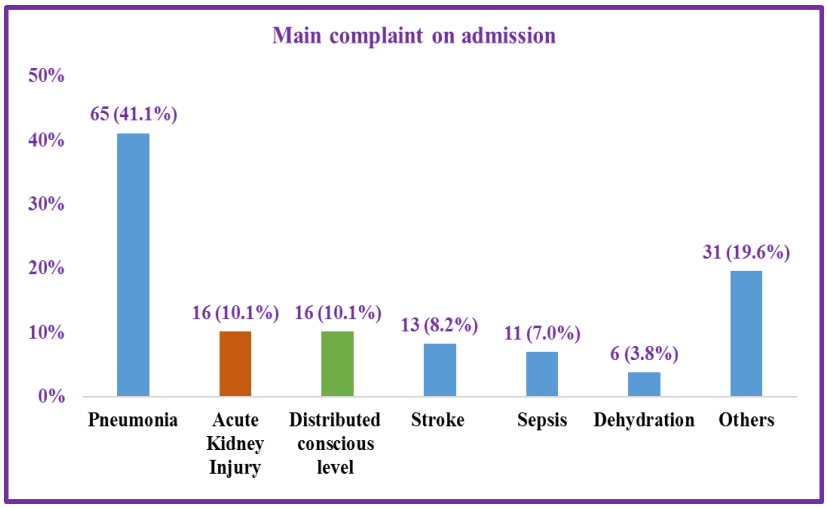

Figure 3. Main Complaint on Admission

Table 1. **Patients' demographics data**

Age, gender, and length of hospital stay, n=158	
Age mean (SD)	63.8 (15.5)
Male, n (%)	90 (57%)
Female, n (%)	68 (43%)
Length of hospital stay days, Median (IQR)	7 (4-11)
Comorbidities	**n (%)**
Diabetes	66 (41.8%)
Hypertension	95 (60.1%)
Stroke	11 (7%)
Chronic Kidney Disease (CKD)	40 (25.3%)
Ischemic Heart Disease (AF)	33 (20.9%)
Atrial Fibrillation	16 (10.1%)
Chronic obstructive pulmonary disease (COPD)	6 (3.8%)
Asthma	6 (3.8%)
Others	79 (50%)

Table 2. Proton Pump Inhibitors Prescription for Stress Ulcer Prophylaxis

Proton Pump Inhibitors Prescription Indications	**n (%)**
Indicated no. (%)	71 (44.9%)
Major Indication no. (%)	35 (22.2%)
2 or more Minor Indications	38 (24.1%)
Major Indications for PPI Prescription	
Coagulopathy	2 (1.3%)
Mechanical Ventilation > 48 Hrs.	33 (20.9%)
Minor Indications for PPI Prescription	
Sepsis	6 (3.8%)
History of GI Ulceration or Bleeding	5 (3.2%)
Thermal Injury	1 (0.6%)
Renal Transplantation	1 (0.6%)
Glasgow Coma score <10	23 (14.6%)
ICU admission > 1 week	66 (41.8%)
Occult or Overt Bleeding	3 (1.9%)
High Dose of Corticosteroids	58 (36.7%)
Side Effects & Therapeutic Failure	
C. Difficile	8 (5.1%)
Therapeutic Failure	20 (12.7%)

The data presented in **Table 2** summarizes the use of PPIs for SUP in critically ill patients. Out of the 158 patients, PPI use was deemed appropriate in 44.9% (n=71), with major indications accounting for 22.2% (n=35) and cases with two or more minor indications making up 24.1% (n=38). This suggests that a significant portion of PPI prescriptions were based on accepted clinical criteria, although there may be some overlap between major and minor indications.

Among the major indications, prolonged mechanical ventilation for more than 48 hours was the most frequent, reported in 20.9% of cases (n=33), while coagulopathy was rarely documented (1.3%). As for minor indications, the most common were ICU stays exceeding one week (41.8%) and use of high-dose corticosteroids (36.7%), followed by a Glasgow Coma Score of less than 10 (14.6%). Other minor factors, including sepsis, previous gastrointestinal bleeding, and occult bleeding, were less prevalent.

Despite appropriate use in many cases, adverse outcomes were noted. *C. difficile* infection occurred in 5.1% of patients (n=8), and therapeutic failure was documented in 12.7% (n=20).

These findings highlight both the widespread use of PPIs in the ICU and the need to balance benefits with potential risks, particularly in cases where the indication is unclear or not strongly supported by evidence.

Table 3 shows the key predictors of PPI overprescription, with age and CKD showing statistically significant associations. Each one-year increase in age raised the odds of PPI overprescription by 4% (OR 1.04, 95% CI 1.01–1.07). Notably, CKD had the strongest effect, increasing the odds nearly fivefold (OR 4.98, 95% CI 1.94–12.77). While asthma also showed a high odds ratio (OR 4.74), its wide confidence interval (0.51–44.17) suggests uncertainty. Other comorbidities, including hypertension, diabetes, stroke, and COPD, did not demonstrate significant associations. Gender also had no meaningful impact (OR 0.94, 95% CI 0.44–2.0). These findings highlight CKD and advancing age as the most robust predictors of PPI overprescription, warranting closer scrutiny in clinical practice to avoid unnecessary use.

4. Discussion

The demographic profile of the present study, comprising 158 patients with a mean age of 63.8 years and a slight male predominance, aligns with patient populations commonly observed in ICUs **(Simpson et al., 2021; Al-Otaiby et al., 2022)**. In addition, Jha et al., which also reported a higher rate of PPI use among males (54.36%) **(Goyal & Gor, 2020)**. The median hospital stay of 7 days further reflects the acute nature of critical illness requiring intensive care. The high prevalence of comorbidities, particularly hypertension and diabetes, is consistent with the increasing burden of chronic diseases in critically ill patients **(Forte & van der Horst, 2019)**.

Table 3. Associations and predictors of proton pump inhibitor over prescription

Predictor	Odds Ratio	95% CI		p
		Lower	Upper	
Age	**1.04**	1.01	1.07	**0.008**
Gender	0.94	0.44	2	0.87
Hypertension	1.53	0.65	3.57	0.33
Diabetes	0.64	0.3	1.4	0.26
Stroke	2.01	0.43	9.38	0.37
Chronic Kidney Disease (CKD)	**4.98**	1.94	12.77	**< 0.001**
Ischemic Heart Disease	0.85	0.32	2.25	0.74
Atrial Fibrillation (AF)	0.69	0.21	2.35	0.55
COPD	1.54	0.27	8.67	0.63
Asthma	4.74	0.51	44.17	0.17
Other Comorbidities	1.02	0.49	2.1	0.95

COPD, chronic obstructive pulmonary disease

These findings underscore that ICU admissions frequently involve older adults with complex medical histories, making them particularly vulnerable to complications such as stress ulcers. The significant presence of CKD and ischemic heart disease within this study is also noteworthy. Chronic kidney disease is a known risk factor for adverse outcomes in critically ill patients and is often associated with a higher prevalence of cardiovascular diseases, including ischemic heart disease **(Wright & Hutchison, 2009; Burnier & Damianaki, 2023)**. The co-occurrence of these conditions can complicate patient management and contribute to increased morbidity and mortality in the ICU setting **(Rai et al., 2023)**. The observation that 50% of patients had additional comorbidities beyond those specifically enumerated further emphasizes the polymorbidity characteristic of this patient group, highlighting the challenges in providing comprehensive care and the importance of tailored prophylactic strategies.

Regarding the choice of acid-suppressive agents, PPIs were the only medications prescribed in this study. According to the American Society of Health-System Pharmacists (ASHP), PPIs, H_2 receptor blockers (H2RBs), antacids, and sucralfate are all recommended options for SUP. However, antacids are no longer considered viable due to their labor-intensive dosing schedules and potential adverse effects. Additionally, both sucralfate and H2RBs have been largely replaced by PPIs in clinical practice due to their comparative efficacy and practicality **(Alshamsi et al., 2016; Krag et al., 2018)**. The predominance of PPI use over H2RBs in the current study can be attributed to their superior potency as acid-suppressive agents. PPIs are at least as effective as H2RBs in preventing stress ulcers and offer greater flexibility in administration. They can be delivered via nasogastric or jejunal tubes or administered parenterally in patients who cannot tolerate oral medications. Furthermore, PPIs are associated with a relatively low incidence of adverse effects, further supporting their widespread use in ICU settings **(Richardson et al., 2002; Spirt, 2004; Reeve et al., 2015)**.

The current study indicates that while a substantial proportion of PPI prescriptions for SUP in these critically ill patients were deemed appropriate, a notable percentage lacked clear justification. This aligns with broader concerns regarding the overuse of PPIs in ICUs without strict adherence to established guidelines **(Saeed et al., 2022)**. The prevalence of major indications such as prolonged mechanical ventilation (>48 hours) in the study cases is consistent with current recommendations for SUP, as mechanical ventilation is a well-recognized risk factor for stress-related mucosal bleeding **(MacLaren et al., 2024)**. However, the low documentation of coagulopathy, another significant risk factor, suggests potential under-recognition or under-reporting of this indication.

Among minor indications, the high frequency of ICU stays exceeding one week and high-dose corticosteroid therapy further highlights the complexity of patient profiles in the ICU. While these factors contribute to increased risk, their individual contribution to the need for SUP, especially in the absence of major risk factors, remains a subject of ongoing debate and guideline evolution **(Buendgens et al., 2016)**. The observation that more than half of patients received PPIs without clear justification underscores the need for more rigorous adherence to evidence-based prescribing practices to mitigate unnecessary exposure and potential adverse effects. These results align with previous studies conducted internationally. For example, a multicenter prospective chart review by **Zeitoun et al. (2011)** evaluating SUP practices in Lebanon (n = 1004) found that 67% of patients who received prophylaxis did not meet the criteria for SUP. Also, in a prospective study conducted by **Frandah et al. (2014)**, which aimed to evaluate the effect of medications used for stress-related mucosal disease prophylaxis and their usage patterns in the ICU, 82% of 51 patients received SUP without a justified indication. Similarly, an observational study by **Alsaleh et al. (2021)**, involving 661 patients, investigated the inappropriate use of pantoprazole and ranitidine. The findings revealed that 43% of patients received these medications without proper indication.

The reported incidence of *C. difficile* infection and therapeutic failure are critical outcomes to consider. The association between PPI use and increased risk of *C. difficile* infection in critically ill patients has been a subject of extensive research, with some studies indicating a heightened risk due to altered gut microbiota and reduced gastric acidity (**Barletta & Sclar, 2014; Ro et al., 2016)**. While some literature presents conflicting views on this association **(Finke et al., 2025)**, the findings in this study warrant careful consideration of the risk-benefit profile of PPIs, particularly in patients without strong indications. Therapeutic failure, as observed in this study, further emphasizes the

importance of appropriate patient selection and ongoing monitoring to ensure the efficacy of SUP strategies and to prevent adverse clinical and economic consequences.

The logistic regression analysis presented in the current study identifies age and CKD as significant predictors of PPI overprescription. The finding that each one-year increase in age raised the odds of PPI overprescription is consistent with existing literature highlighting a higher prevalence of inappropriate PPI use in older adult populations **(Voukelatou et al., 2019; Koggel et al., 2022)**. This trend may be attributed to polypharmacy, multiple comorbidities, and a general tendency to continue medications initiated during acute care admissions without re-evaluation in elderly patients **(Farrell at al., 2017)**.

The overprescription of PPIs in ICU patients with CKD may be driven by a combination of clinical concerns and risk perceptions. CKD is a known contributor to anemia due to reduced erythropoietin production, iron deficiency, chronic inflammation, and uremia-induced platelet dysfunction **(Awdishu et al., 2025)**. In critically ill patients, this baseline anemia is often compounded by factors such as frequent blood sampling, hemodilution, and nutritional deficits **(Xu et al., 2025)**. Stress-related mucosal bleeding, though less common with modern ICU care, remains a potential source of acute blood loss, particularly in high-risk patients. Given this context, clinicians may be more inclined to prescribe PPIs preemptively in CKD patients to mitigate the risk of gastrointestinal bleeding and prevent further hemoglobin decline **(Buendgens et al., 2016)**. Moreover, CKD patients are frequently exposed to anticoagulants and have multiple comorbidities, which may increase their perceived bleeding risk **(Dos Santos et al., 2023)**. This cautious approach, while understandable, may lead to PPI use even in the absence of clear indications. Compounding this issue, patients with CKD frequently experience polypharmacy and prolonged ICU stays, both of which are associated with increased exposure to PPIs. However, emerging evidence suggests that inappropriate PPI use may itself contribute to adverse renal outcomes, including acute interstitial nephritis and progression of CKD **(Ang et al., 2024)**. These findings highlight the need for careful risk-benefit assessment and adherence to evidence-based guidelines when prescribing PPIs in this vulnerable population.

In the current study, CKD emerged as the strongest predictor, increasing the odds of PPI overprescription. This association is particularly concerning given the potential for PPIs to negatively impact kidney function, especially with long-term use **(Dos Santos et al., 2023; Parmar et al., 2023)**. While the exact mechanisms are still being investigated, studies suggest a link between PPI use and increased risk of acute kidney injury and progression of CKD **(Klatte et al., 2017; Wu et al., 2021)**. The strong correlation observed in this study underscores the critical need for careful scrutiny of PPI prescriptions in patients with CKD to avoid exacerbating renal issues and to minimize unnecessary drug exposure.

While asthma also showed a high odds ratio, its wide confidence interval indicates considerable uncertainty and suggests that this association may not be statistically robust in a larger population. The lack of significant associations with other common comorbidities such as hypertension, diabetes, stroke, and COPD, as well as gender, further emphasizes the specific and potent predictive roles of age and CKD in PPI overprescription within this study. These findings highlight the importance of targeted interventions and stricter adherence to evidence-based guidelines, particularly for older patients and those with compromised renal function, to optimize PPI prescribing practices and reduce associated risks and healthcare costs.

Based on these considerations, it was important to thoroughly review each patient's complete medication history, including the duration of PPI use, the various prescribed doses, and the routes of administration employed.

5. Limitations

This study has several limitations that should be considered when interpreting the findings. First, the retrospective and cross-sectional design limits the ability to establish causality between PPI use and clinical outcomes such as therapeutic failure or *C. difficile* infection. Second, the study was conducted in a single tertiary care hospital, which may restrict the generalizability of the results to other ICU settings with different prescribing practices or patient populations. Third, the reliance on medical records may have led to incomplete data capture or documentation bias, particularly regarding adverse effects and non-documented clinical risk factors.

6. Conclusion

This retrospective cross-sectional study evaluated the appropriateness of PPI prescribing practices for SUP. While PPI use for SUP was deemed appropriate in 44.9% of patients, most often due to prolonged mechanical ventilation, extended ICU stays, or high dose corticosteroid therapy, the study also revealed a substantial proportion of inappropriate prescriptions. Adverse outcomes, including *C. difficile* infection and therapeutic failure, underscore the risks associated with PPI use. Notably, advanced age and chronic kidney disease emerged as robust predictors of PPI overprescription. These findings highlight the continued prevalence of inappropriate PPI use in the ICU setting and emphasize the critical need for evidence-based guidelines and enhanced prescriber awareness to optimize SUP utilization, minimize adverse effects, and reduce unnecessary healthcare expenditures.

7. Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

This study was approved by the Ethics Committee of Faculty of Pharmacy, Port Said University (Approval number. PHARM.PSU.30).

Consent for publication

Not applicable.

Data availability

All data generated or analysed during this study are included in this published article.

Funding

This research did not receive any funds.

Acknowledgments

The authors thank all participants of this study.

Authors' contributions

D.H.E, S.G., and A.S.M. contributed to the study conception and design. A.E.A performed data collection and investigation. M.T. conducted the statistical analysis and data interpretation. R.M.E and N.H.F drafted the original manuscript. D.H.E, S.G., and A.S.M. critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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