

Effect of Proton Pump Inhibitors on the Development of Acute Kidney Injury in Critically Ill Patients: A Clinical Trial Emulation

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Abstract

Background: This study aimed to determine whether the administration of proton pump inhibitors (PPIs) increases the risk of acute kidney injury (AKI) in critically ill patients admitted to intensive care units (ICUs).

Methods: We conducted a retrospective cohort study using data from patients admitted to the Beth Israel Deaconess Medical Center obtained from the MIMIC IV database. Odds ratios were calculated using a multivariate logistic regression model to obtain more robust and adjusted estimates.

Results: A total of 8,161 patients were included, with 3,592 (44%) who received PPI prophylaxis, while 4,569 (56%) did not. Acute kidney injury (AKI) developed in 855 (10.48%) patients, 486 (13.5%) of whom were exposed to PPIs, and 369 (8.1%) were not exposed ($p < 0.001$). The OR (odds ratio) for AKI risk, calculated using inverse probability weighting (IPW), among PPI-exposed patients was 1.78 (95% CI: 1.54–2.05).

The variables that had the strongest association with AKI were vancomycin with an OR of 2.40 (95% CI: 1.93–2.99), aminoglycosides with an OR of 1.55 (95% CI: 1.17–2.05), and contrast media with an OR of 1.44 (95% CI: 1.14–1.81).

Conclusion: The results support previous evidence of the association between PPI exposure in critically ill patients and the development of acute kidney injury. Prophylaxis should be carefully considered in the presence of other factors contributing to renal injury.

Introduction

Acute kidney injury (AKI) poses a significant challenge in the healthcare domain, particularly among critically ill patients admitted to intensive care units (ICUs). The incidence of AKI in these patients is remarkable, ranging from 30% to 70%, depending on the definitions used for classification (1–3). This phenomenon not only carries medical ramifications but also exerts considerable strain on healthcare resources, as approximately 10% of ICU AKI cases necessitate renal replacement therapy (RRT), incurring substantial expenses that are estimated between \$11,016 and \$42,077 per patient (4, 5).

The mortality associated with kidney failure in ICU admitted patients range from 15% to 60%, depending on associated illnesses and the acute condition for which they are admitted to the ICU (6, 7). Several factors contribute to the development of AKI in ICU patients, including exposure to different medications, such as antibiotics, contrast agents, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors (8–10). Notably, proton pump inhibitors (PPIs), commonly employed for gastrointestinal bleeding prophylaxis, have garnered increased attention as a potential contributor to AKI development (11).

The administration of PPIs in critically ill patients, who are at a higher risk of gastrointestinal bleeding due to factors such as mechanical ventilation, sepsis, shock, and coagulopathies, has raised concerns

about its impact on renal function. Despite a significant proportion (30–40%) of these patients receiving PPI formulations (12, 13), the results of studies examining the association between PPIs and AKI have been contradictory. While some studies have not found an increased risk of AKI associated with PPIs (14), others, such as the study involving cardiac surgery patients (15), have identified an increased incidence of kidney injury in those previously exposed to proton pump inhibitors.

In the context of this controversy and considering its clinical relevance, the main objective of this study is to determine the association between PPI exposure in critically ill patients and the development of acute kidney injury in the first seven days of exposure using established criteria for AKI by emulating a randomized clinical trial and employing causal inference methods.

Methods

Study Population

The study cohort comprised adults aged 18 and above admitted to the ICUs at Beth Israel Deaconess Medical Center (BIDMC) from 2008 to 2019 for various medical reasons. Patient records were obtained from the MIMIC IV version 2.2 database, a joint creation of the Massachusetts Institute of Technology (MIT) Computational Physiology Lab and the Department of Medicine at Beth Israel Deaconess Medical Center (BIDMC). The database contains information on 53,569 individual ICU patients (16).

Study Design

From an observational cohort, we emulated a target clinical trial, adhering to criteria encompassing eligibility, treatment strategies, conditional assignment based on baseline characteristics, the establishment of a temporal reference point, follow-up, and causal contrasts. This emulation followed the guidelines outlined by Hernan for conducting a clinical trial emulation (17). The propensity score for treatment assignment was calculated considering variables such as comorbidities and demographic characteristics. Follow-up was conducted during the first seven days, and the occurrence of renal dysfunction was assessed based on the AKI classification (18). Utilizing the propensity score, we calculated the inverse probability weight (IPW) to create a weighted pseudopopulation (19). This approach aimed to achieve a more balanced distribution of initial characteristics between the exposed and unexposed groups.

Exposure Variables

Patients who received PPIs during their stay in the ICU were considered "exposed," whereas those who did not receive this class of medication were labeled "unexposed." Care was taken to ensure that none of the selected patients had a history of prior PPI or H2 blockers use upon hospitalization. The initiation of treatment in the ICU was defined as time zero.

Outcomes

The primary outcome was the occurrence of renal dysfunction of any degree, assessed using the AKI classification in its three stages (AKI I, AKI II, and AKI III). This assessment considered the changes in serum creatinine levels relative to baseline levels (18). The baseline creatinine measurement was established using the value recorded on the day of ICU admission, and subsequent creatinine levels were compared every 48 hours up to the seventh day of hospitalization. To assess residual confounding, patients who developed ventilator-associated pneumonia were identified as negative controls. Odds ratios representing the unadjusted association with PPIs and those adjusted through multivariate analysis and IP weighting were also calculated (20, 21). Additional outcomes examined included ICU mortality and the average length of stay in the unit for patients who developed acute kidney injury and those who did not.

Covariates

Key covariates included demographic factors (gender and age) and concurrent medical conditions defined by the Charlson comorbidity index (22). Other factors related to ICU stay, such as admission due to trauma and sepsis, as well as severity scores like SAPS II (23) and SOFA (24), were also considered. These calculations were conducted on the initial day of ICU admission, and exposure to antibiotics (vancomycin, meropenem, aminoglycosides, piperacillin-tazobactam) and contrast agents were also evaluated. The causal relationship of these variables concerning PPIs and the AKI outcome was established using directed acyclic graphs (DAGs) (Fig. 1). (25).

Statistical Analysis

Initially, the baseline characteristics of both the exposed and unexposed groups were meticulously detailed, and the unadjusted odds ratio was determined to assess the relationship between PPI exposure and the development of kidney injury according to the AKI classification.

Odds ratios were calculated using a multivariate logistic regression model to obtain more robust and adjusted estimates. This model included the confounding variables identified during the analysis, excluding variables exclusively associated with the intervention or acting as intermediaries in the causal relationship between exposure and outcome. Additionally, these results were compared with the odds ratio obtained through inverse propensity score weighting. This approach aimed to balance the baseline characteristics of the groups.

To evaluate residual confounding, ventilator-associated pneumonia outcome was selected as a negative control. Unadjusted and adjusted odds ratios were calculated through multivariate analysis and weighting, incorporating the same confounding variables shared with the renal injury outcome, allowing for a more comprehensive evaluation of confounding factors.

Statistical analyses were performed using Stata version 17 and R version 4.3 with the following packages: weightIt, cobalt, and marginal effects. Data preprocessing, transformation, and loading were conducted in BigQuery using the SQL (Structured Query Language) programming language.

Results

The study initially considered a population of 53,569 patients admitted to the ICU. After excluding 45,425 patients for the following reasons: 39,728 due to stays shorter than 96 hours, 4,965 with a history of prior renal insufficiency, 245 due to concomitant use of proton pump inhibitors and H2 blockers, and 487 due to incomplete records, the final sample consisted of 8,161 patients. Among these, 3,592 (44%) were exposed to PPIs, while 4,569 (56%) were not exposed. Out of a total of 5,868 patients who had an indication for PPI prophylaxis, only 2,733 (46.6%) received PPIs, while 3,135 (53.4%) did not receive PPI prophylaxis despite the indication (Fig. 2).

A total of 855 (10.48%) patients developed AKI, of which 486 (13.5%) were exposed to PPIs and 369 (8.1%) were not exposed ($p < 0.001$).

The main reasons for admission to the ICU were trauma and sepsis, representing 16% and 18% of cases, respectively. Higher severity scores (SAPS II and SOFA) were observed on the first day of admission to the ICU for patients who received PPIs compared to those who did not receive prophylaxis, and these differences were statistically significant. The most prevalent coexisting diseases were COPD, cerebrovascular disease, hypertension, and diabetes. Among the diagnoses associated with exposure, sepsis was the most prevalent, with 859 (23.9%) patients in the exposed group and 616 (13.5%) in the nonexposed group ($p < 0.001$). Additionally, liver disease occurred in 778 (21.6%) exposed patients and 470 (10.29%) nonexposed patients ($p < 0.001$). (Table 1).

Table 1
General characteristics of patients admitted to the ICU.

Baseline characteristics	Full sample n = 8,161	PPI n = 3,592	No PPI n = 4,569	P Value
Age, mean (SD)	63,3 (16.0)	63,2 (15.5)	63,4 (16.4)	0.739
Male gender, n (%)	4,502 (55.16)	1,958 (54.51)	2,544 (55.68)	0.292
18–39 years	713 (8.74)	289 (8.05)	424 (9.28)	0.736
40–49 years	804 (9.85)	349 (9.72)	455 (9.96)	0.715
50–59 years	1,507 (18.47)	702 (19.54)	805 (17.62)	0.026
60–69 years	2,012 (24.65)	904 (25.17)	1,108 (24.25)	0.340
70–79 years	1,734 (21.25)	770 (21.44)	964 (21.10)	0.711
>= 80 years.	1,391 (17.04)	578 (16.09)	813 (17.79)	0.042
Trauma	1,304 (15.98)	515 (14.34)	789 (17.27)	0.001
Sepsis	1,475 (18.07)	859 (23.91)	616 (13.48)	0.001
Myocardial infarction	1,014 (12.42)	488 (13.59)	526 (11.51)	0.005
Congestive heart failure	1,808 (22.15)	872 (24.28)	936 (20.49)	0.000
Contrast medium	648 (7.94)	340 (9.47)	308 (6.74)	0.001
Diabetes	1,686 (16.92)	740 (20.6)	946 (20.7)	0.909
Hypertension	1,671 (20.8)	598 (16.65)	1,073 (23.48)	0.001
Cerebrovascular disease	1,916 (23.48)	553 (15.40)	1,363 (29.83)	0.000
Chronic pulmonary disease	2,084 (25.54)	1,060 (29.51)	1,024 (22.41)	0.001
Connective tissue disease	240 (2.94)	124 (3.45)	116 (2.54)	0.015
Ulcer disease	175 (2.14)	143 (3.98)	32 (0.70)	0.001
Liver disease	1,248 (15.29)	778 (21.66)	470 (10.29)	0.001
Cancer	1,043 (12.78)	532 (14.81)	511 (11.18)	0.001
AIDS	58 (0.71)	30 (0.84)	28 (0.61)	0.235
Acute kidney injury	855 (10.48)	486 (13.53)	369 (8.08)	0.001
AKI I	655 (8.03)	356 (9.91)	299 (6.54)	0.001
Notes: PPI: proton pump inhibitor; SD: standard deviation; ICU: intensive care unit; AKI: acute kidney injury; AIDS: acquired immunodeficiency syndrome.				

Baseline characteristics	Full sample n = 8,161	PPI n = 3,592	No PPI n = 4,569	P Value
AKI II	251 (3.08)	167 (4.65)	84 (1.84)	0.001
AKI III	119 (1.46)	78 (2.17)	41 (0.90)	0.001
Indication of prophylaxis (mechanic ventilation, sepsis, bleeding)	5,868 (72)	2,733 (76)	3,135 (68.6)	0.001
Ventilator-associated pneumonia	515 (6.31)	251 (6.99)	264 (5.78)	0.026
ICU mortality	1,441 (17.66)	735 (20.46)	706 (15.45)	0.001
Notes: PPI: proton pump inhibitor; SD: standard deviation; ICU: intensive care unit; AKI: acute kidney injury; AIDS: acquired immunodeficiency syndrome.				

The variables associated with the outcome of acute kidney injury were, first, the administration of antibiotics such as vancomycin, with an OR of 2.40 (95% CI: 1.93–2.99), followed by aminoglycosides, with an OR of 1.55 (95% CI: 1.17–2.05), and the administration of contrast media, with an OR of 1.44 (95% CI: 1.14–1.81). Sepsis had an OR of 1.47 (95% CI: 1.24–1.76), metastatic tumors had an OR of 1.59 (95% CI: 1.17–2.16) and exposure to proton pump inhibitors had an OR of 1.27 (95% CI: 1.09–1.48). In terms of age, an increased risk was observed from the age of 60 (**Supplementary Table 1**).

Supplementary Fig. 1 presents the odds ratio for exposure to PPI, while Supplementary Fig. 2 illustrates the odds ratios of factors associated with AKI.

Association Between PPI, AKI, and Residual Confounding

The association between PPI exposure and the development of renal dysfunction, as determined by the crude OR, was 1.78 (95% CI: 1.54–2.05). For the multivariable logistic regression analysis adjusted for demographic variables and coexisting diseases, the adjusted OR was 1.27 (95% CI: 1.09–1.48). Finally, with propensity score weighting and inverse probability weighting, an OR of 1.27 (95% CI: 1.08–1.48) was obtained. Prior to this, the balance of baseline characteristics in each of the PPI-exposed and non-PPI-exposed groups was assessed, revealing an imbalance in most of the variables (Fig. 3). Regarding the association between proton pump inhibitors and pneumonia as a negative control, the calculated crude OR was 1.24 (95% CI: 1.04–1.47), the OR adjusted by multivariable logistic regression was 1.01 (95% CI: 0.83–1.22), and the OR calculated using IPW was 1.08 (95% CI: 0.89–1.30) (Table 2).

Table 2
Risks of outcome with proton pump inhibitors exposure

Outcome	OR (95% CI) Unadjusted	OR (95% CI) Adjusted*	OR (95% CI) IPW**
AKI with PPI	1.78 (1.54–2.05)	1.27 (1.09–1.48)	1.27 (1.08–1.48)
Pneumonia	1.24 (1.04–1.47)	1.01 (0.83–1.22)	1.08 (0.89–1.30)
*Adjusted by age, sex, trauma, sepsis, myocardial infarct, congestive heart failure, contrast medium, vancomycin, piperacillin-tazobactam, hypertension, diabetes, cerebrovascular disease, chronic pulmonary disease, ulcer disease, liver disease, cancer, SOFA score at admission.			
** IPW: Inverse probability weighting.			

Mortality and Length of Stay in the ICU for Patients with AKI

The overall ICU mortality rate in the entire cohort was 17.6%. Among the 855 patients who developed renal injury, 340 (39.6%) died during their ICU stay, while among the 7,306 patients who did not develop renal injury, 1101 (15.1%) died ($p < 0.001$). Among survivors, the average length of stay for those who developed AKI was 11.9 days, while for those who did not develop AKI, it was 8.0 days ($p < 0.001$).

Discussion

This study reveals that a substantial proportion (44%) of patients admitted to the intensive care unit (ICU) received prophylaxis with proton pump inhibitors (PPIs) for at least 48 hours. This aligns with the high incidence of 66% of patients requiring mechanical ventilation and having sepsis as the primary indications for prophylaxis. However, importantly, 53.4% of patients with valid indications did not receive prophylaxis, and 37.4% of exposed patients did not have a clear indication. This suggests a potential deviation from current recommendations for PPI prophylaxis, reflecting a trend observed in previous research (1–5).

The incidence of acute kidney failure in this cohort was 10.5%, a figure that falls within the broad range reported in the literature, which ranges from 5% to 30% (6). While our results align with most studies on renal failure in the ICU, they differ with others, such as Hoste's study (7), which reported an incidence between 30% and 60%. It is essential to highlight that this relatively low incidence could be partly explained by the exclusion of patients with a history of renal impairment.

The precise mechanism by which exposure to PPIs can lead to kidney injury is not yet fully understood. Some authors (5) (8) suggest that acute interstitial nephritis may play a significant role, characterized by inflammatory infiltrates, edema, and tubulointerstitial inflammation. This condition is commonly associated with nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs, and antibiotics. Immune reactions to medications, influenced by critically ill conditions like decreased plasma albumin levels and sepsis, are major contributors. Brewster UC (9) reported 64 cases of PPI-induced acute interstitial nephritis,

confirmed by renal biopsy, primarily linked to omeprazole exposure. However, importantly, omeprazole allergy may cause cross-reactions with this class of drugs. In our study, we did not differentiate specifically by PPI class, including omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole, which are the drugs most commonly connected with acute interstitial nephritis.

The overall ICU mortality was 17%, and for patients with sepsis, it reached 33%, similar to the findings of Fleischmann in 2016 (10, 11).

Our results reinforce the association between acute kidney injury and PPI exposure, supported by adjusted odds ratios through multivariate analysis and by inverse probability weighting. These results are consistent with the study by Koh (12) in patients undergoing cardiac surgery who received PPIs before surgery. A notable aspect of our study is defining the time of onset of PPI exposure upon ICU admission. Patients already receiving PPIs were excluded, thereby avoiding prevalence and immortal time biases. Additionally, our patient cohort encompassed various diagnoses upon ICU admission.

Importantly, our research focused exclusively on PPI exposure, unlike the study by Lee J (14), which grouped H2 blockers and PPIs into the same exposure category. Furthermore, we found no available evidence regarding the association of H2 blockers with kidney injury, unlike PPIs, which have a more robust evidence base (15–17).

A distinctive feature of our study lies in that it emulated a randomized clinical trial as per the criteria established by Hernán M. (18). This involved defining a time zero coinciding with eligibility and exposure assignment, excluding patients with previous renal injury, and it included a continuous follow-up until the outcome, with meticulous adjustment for identified confounding variables. These variables included coexisting diseases that partly determine the patients' preexisting renal reserve. We did not consider including physiological variables and biomarkers, most of which were included in the SAPSII severity score. This is because some of these variables were individually considered in the model, such as age, COPD, and HIV presence, as well as other variables such as creatinine, which is part of the outcomes. Assessing residual confounding bias through a negative control outcome strengthened our findings (19). The choice of ventilator-associated pneumonia as a negative control outcome could be questioned because gastric prophylaxis has been implicated to be associated with an increased risk of ventilator-associated pneumonia. However, despite the numerous studies evaluating the increased risk of pneumonia with PPI use, Fang Li recently evaluated 6,921 patients receiving only PPI therapy and found no association with the incidence of ventilator-associated pneumonia; instead, they did find an association with the combination of PPIs and H2 blockers (20–22). Moreover, the presentation of ventilator-associated pneumonia shares many of the confounding variables present in the association between PPIs and AKI, which is one of the requirements for an appropriate negative control.

In summary, this study elucidates the importance of precise and personalized administration of proton pump inhibitors in critically ill patients in the ICU. Although there is a clear association between PPI exposure and acute kidney injury, other risk factors and comorbidities also play a fundamental role in this outcome. The administration of antibiotics such as vancomycin and piperacillin-tazobactam,

exposure to contrast media, and the presence of diseases such as sepsis and liver disease significantly contributed to kidney injury.

It is important to recognize the potential limitations of this study. While a rigorous approach was taken to adjust and control for confounding variables, exposure to PPIs before hospital admission was not considered, which could introduce a prevalence bias. Despite applying inverse probability weighting methods for adjustment, it is crucial to acknowledge that there may still be unidentified confounding factors affecting the results.

Conclusion

This study highlights the importance of a more precise and personalized administration of proton pump inhibitors in critically ill patients in the ICU. While there is a clear association between PPI exposure and acute kidney injury, other risk factors and comorbidities also play a fundamental role in this outcome.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained/exempted by the corresponding Institutional Review Board due to the retrospective use of de-identified data. Human Research and Data or Specimens Only Research training from the CITI Program was completed prior to accessing and handling electronic medical records from the MIMIC-IV database. The MIMIC-IV database contains fully de-identified patient information, and informed consent was waived. All procedures were conducted in accordance with relevant institutional guidelines and the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

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Author Contribution

H.O., J.B., J.K., E.G.-G., H.R.-A., E.T.-Q., and L.F.R. contributed to the conception and design of the study. H.O., J.B., J.K., and E.T.-Q. performed the statistical analysis, analyzed and interpreted the results, conducted the literature search, and drafted the manuscript. All authors critically revised the manuscript, read and approved the final version, and agreed to be accountable for all aspects of the work, ensuring

that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

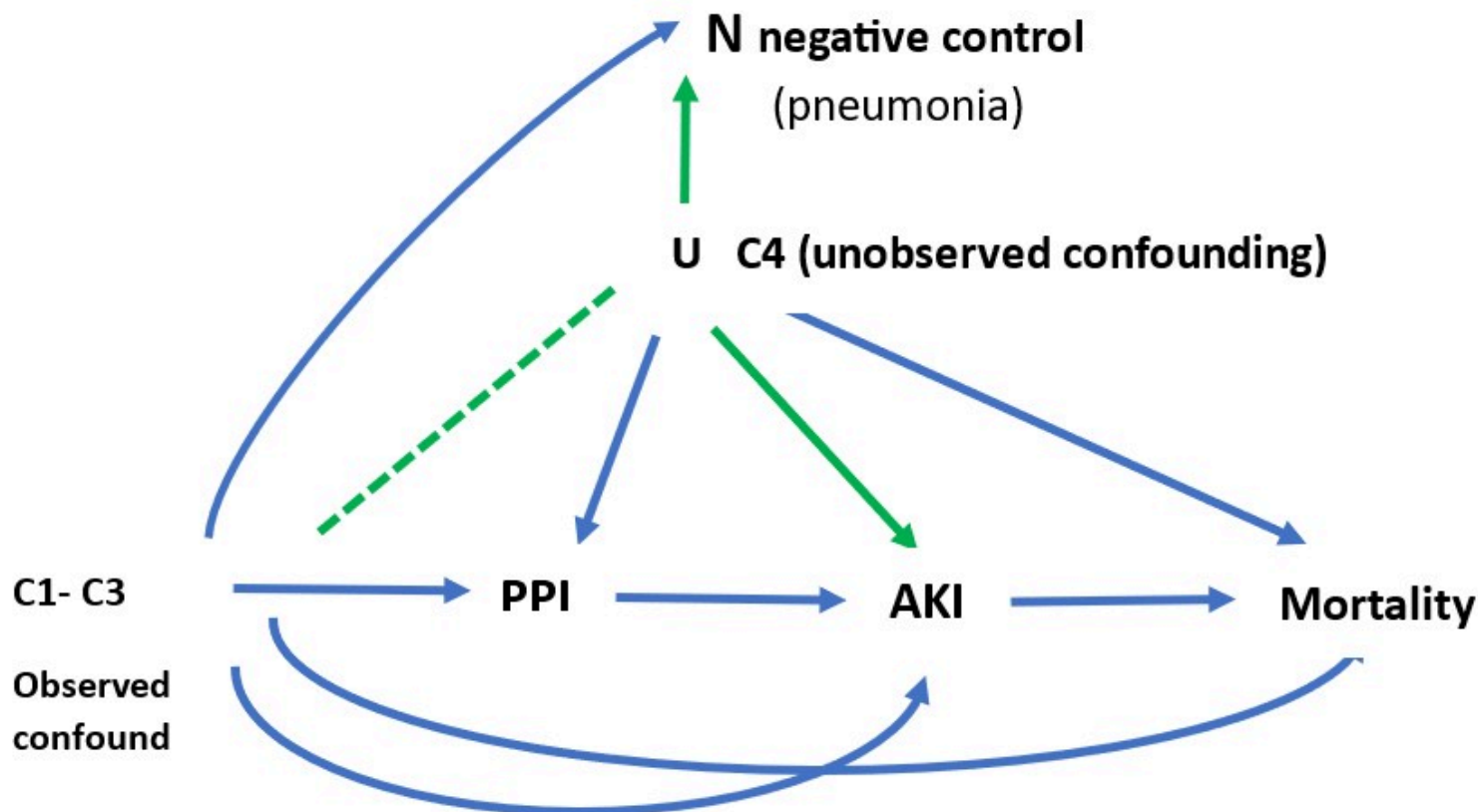


Figure 1

Causal pathway between PPI and AKI and the relationship with confounding variables

Notes: **C1:** Trauma, Sepsis, Myocardial infarction, Congestive heart failure; **C2:** Age, Sex, Hypertension, Diabetes, Cerebrovascular disease, Chronic pulmonary disease, Peptic ulcer disease, Liver disease, Cancer; **C3:** Concomitant antibiotics, contrast medium; **C4:** Liquid balance, Hypotension, vasopressors.

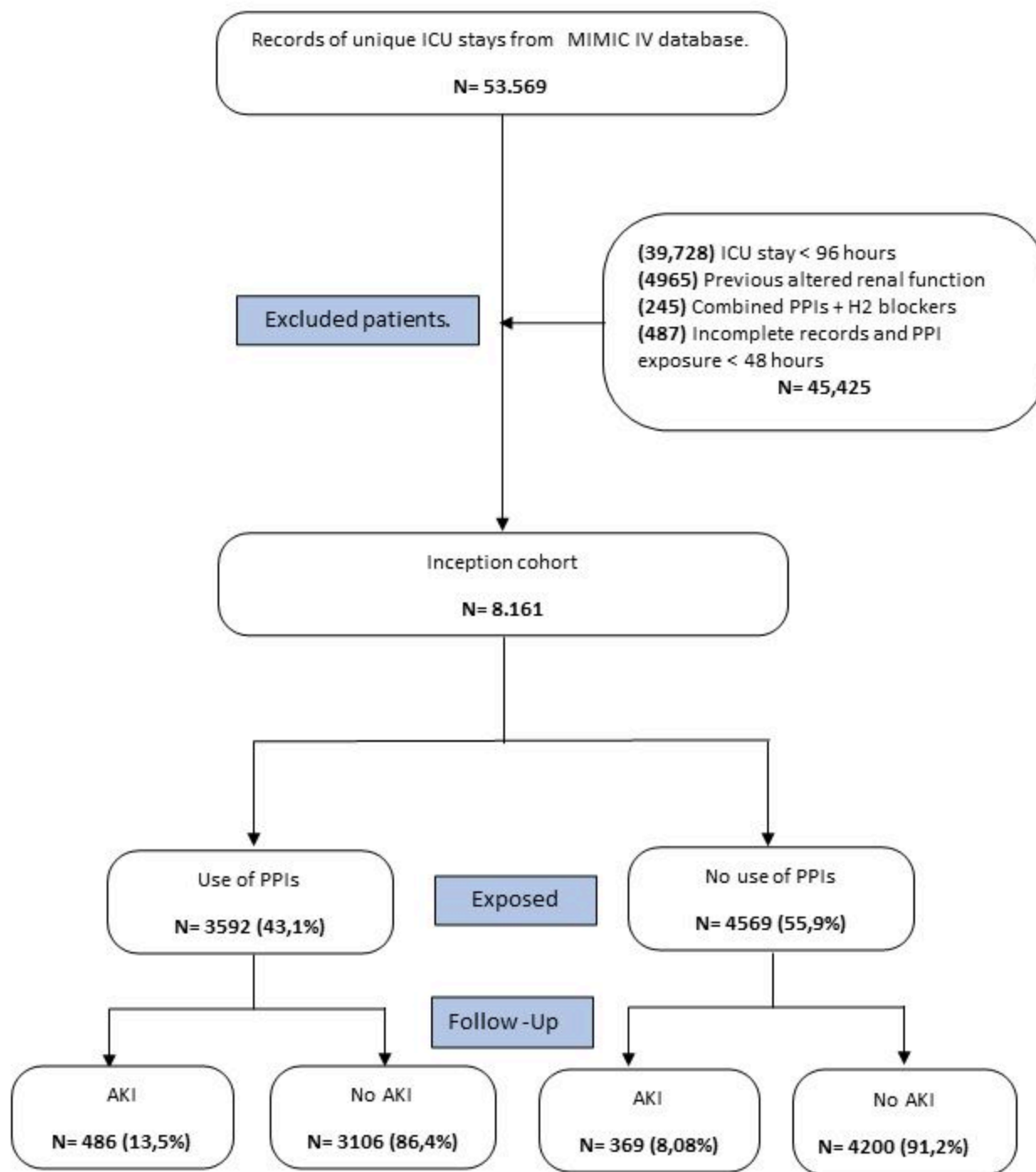


Figure 2

Flowchart of the subjects included from electronic medical records.

Covariate Balance

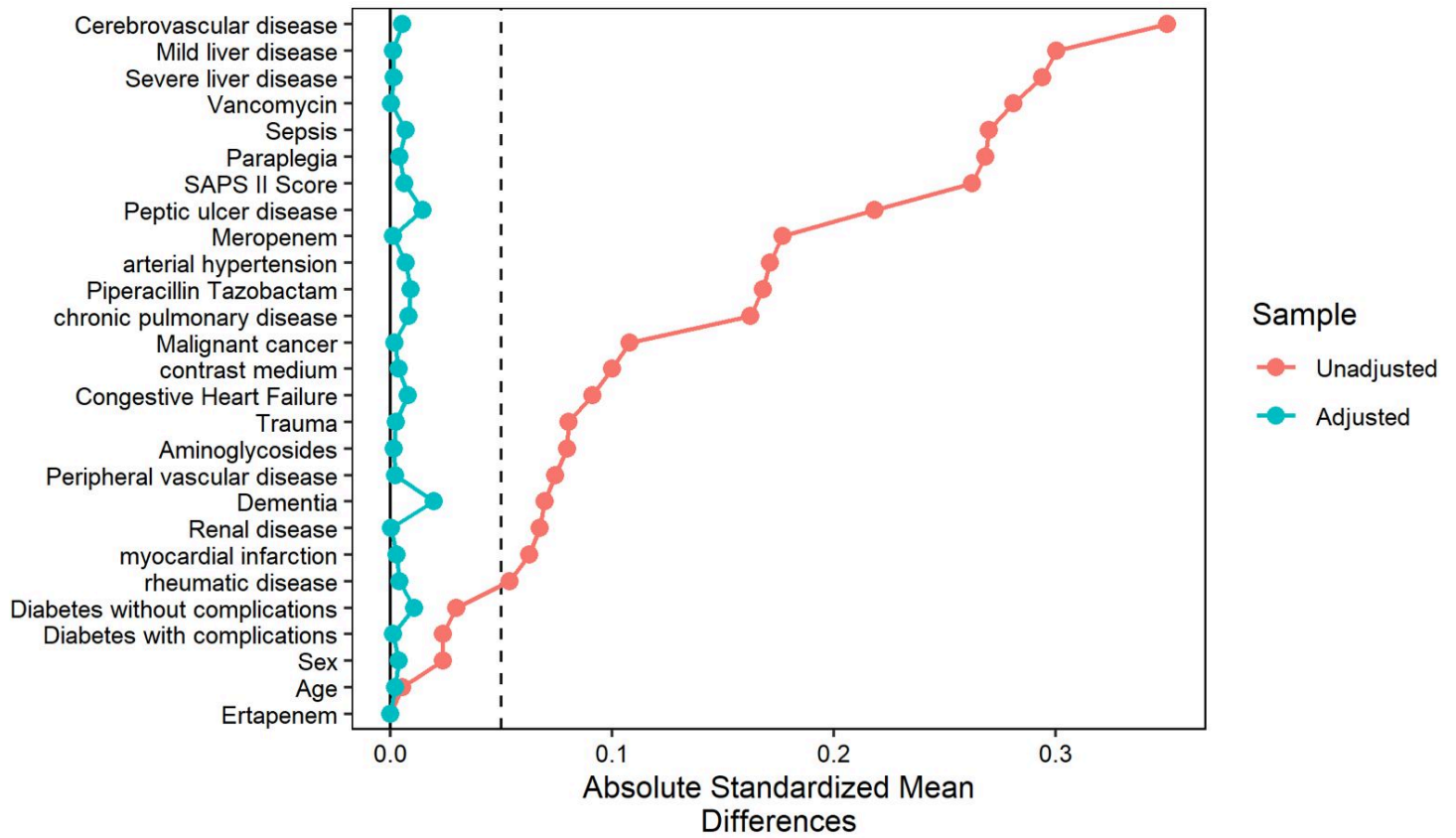


Figure 3

Covariate Balance

Supplementary Files

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- [Supplementaryfile26052026.pdf](#)