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Original Article

ORIGINAL ARTICLE

Prophylactic proton pump inhibitor usage and new-onset acute kidney injury in critically ill patients: a retrospective analysis

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ABSTRACT

Background. Proton pump inhibitors (PPIs) are widely prescribed for stress ulcer prophylaxis (SUP) in intensive care unit (ICU) patients. However, the potential association between prophylactic PPIs and the development of new-onset acute kidney injury (AKI) remains unclear.

Methods. Patients without AKI or end-stage renal disease and not undergoing renal replacement therapy upon admission to the ICU were identified from the Medical Information Mart for Intensive Care (MIMIC-IV) database. The exposure factor for the study was the initiation of prophylactic PPIs within 48 h of admission, with the primary outcome being the occurrence of new-onset AKI after 48 h. Multivariable regression models were employed to investigate the association between prophylactic PPIs and the risk of new-onset AKI. Various propensity score analyses, along with stratified and subgroup analyses and E-value calculations, were conducted to further evaluate the reliability of the results.

Results. A total of 7498 ICU patients were analyzed. The multivariable analysis showed a higher incidence of new-onset AKI in the PPI group (30.7%) compared with the control group (24.1%), yielding an adjusted odds ratio (OR) of 1.43 (95% confidence interval 1.22–1.67). Propensity score analyses confirmed these results, with ORs ranging from 1.34 to 1.49 ($P \leq .005$). Results from multiple sensitivity analyses further supported these findings, with an E-value of 2.34 indicating robustness against unmeasured confounders.

Conclusions. Prophylactic PPI use is associated with an increased risk of new-onset AKI in ICU patients. Indiscriminate use of PPIs should be avoided.

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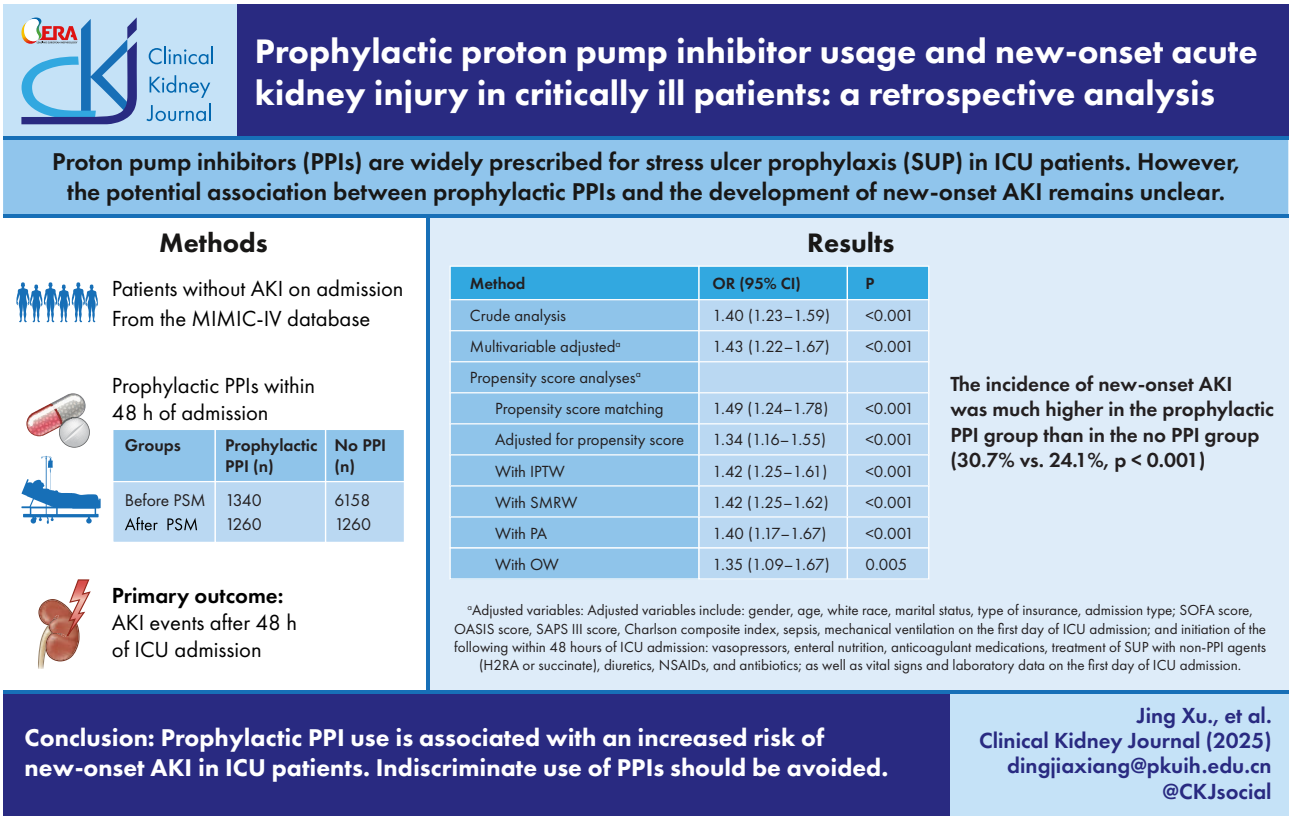
GRAPHICAL ABSTRACT



Keywords: acute kidney injury (AKI), intensive care unit (ICU), proton pump inhibitors (PPIs), stress ulcer prophylaxis (SUP)

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) are at high risk for stress ulcer bleeding, which can lead to negative outcomes [1, 2]. Consequently, stress ulcer prophylaxis (SUP) is routinely administered in ICUs. A survey across 97 adult ICUs in 11 countries indicated that nearly all ICUs implement SUP, with 26% prescribing it universally [3]. Proton pump inhibitors (PPIs) are the most commonly used agents for this purpose. Although current guidelines recommend PPIs as the preferred choice for SUP, this is classified as a weak recommendation [4]. Systematic evaluations and network meta-analyses have shown that while PPIs reduce the risk of clinically significant bleeding, they do not seem to influence critical outcomes in ICU patients, such as mortality, length of hospital stay or duration of mechanical ventilation [5]. Therefore, the potential adverse effects of PPIs warrant closer scrutiny.

Numerous large observational studies outside the ICU have consistently linked PPI use to an increased risk of AKI. For example, a population-based cohort study by Antonio *et al.* involving 290 592 Ontario residents found that older adults (>65 years) initiating PPI therapy faced a higher risk of hospital admission with AKI [6]. Similarly, Svanström *et al.* reported a greater incidence of AKI events among PPI users in a cohort of 24 579 rheumatoid arthritis patients [7]. Other studies, including a retrospective cohort analysis of 1284 Korean patients undergoing percutaneous coronary intervention, also noted elevated AKI risks associated with PPI use [8]. Additionally, research by Hart *et al.* in a large health maintenance organization confirmed these findings [9]. A study involving 42 232 hospitalized children across multiple Chinese centers further demonstrated an increased risk of hospital-acquired AKI among PPI users [10]. However, the impact of PPI use on AKI risk specifically in ICU patients remains unclear.

AKI is a common complication in critically ill patients, with incidence rates exceeding 50% [11]. New-onset AKI in ICU patients during hospitalization ranges from 5.4% to 30% [12, 13]. Moreover, AKI presence significantly affects patient prognosis, correlating with higher in-hospital mortality and an increased risk of chronic kidney disease and end-stage renal disease (ESRD) [12–15].

This study aims to explore the potential association between PPI use for SUP and the risk of new-onset AKI in ICU patients.

MATERIALS AND METHODS

Sources of data

Data for this study were extracted from the Medical Information Mart for Intensive Care (MIMIC-IV version 2.0), an electronic health record dataset covering admissions from 2008 to 2019 [16]. MIMIC-IV is a collaboration between Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Institute

of Technology (MIT). Data collected at BIDMC during routine clinical care is deidentified and made available to researchers who have completed human research training and signed a data use agreement. The BIDMC Institutional Review Board waived informed consent and approved data sharing. J.X. received access approval (certification number 40398740). This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17].

Selection of participants

The study included adult patients (18 years or older) admitted to the ICU for the first time. Exclusion criteria were: (i) diagnosis of ESRD or renal replacement therapy at ICU admission; (ii) AKI onset within 48 h of ICU admission; (iii) ICU stay shorter than 48 h; (iv) receipt of therapeutic PPIs; (v) initiation of prophylactic PPIs more than 48 h after ICU admission.

Ethics approval and consent to participate

The establishment of this database was approved by MIT (Cambridge, MA, USA) and BIDMC (Boston, MA, USA) and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Data extraction

Data from MIMIC-IV were extracted using SQL queries in Navicat Premium (version 15.0.12). The following data were collected:

(i) Demographic and admission information: age, gender, weight, race, marital status, insurance type, admission time, admission type (emergency or not), ICU admission time and ICU discharge time.
(ii) Renal function diagnoses: diagnoses based on International Classification of Diseases-9 and -10 codes, including chronic kidney disease (CKD) stage 5 or ESRD.
(iii) Clinical data on ICU admission day: data included the Sequential Organ Failure Assessment (SOFA) score, Oxford Acute Severity of Illness Score (OASIS), Simplified Acute Physiology Score III (APS III), Charlson Comorbidity Index (CCI), presence of sepsis, congestive heart failure or renal disease, renal replacement therapy status, mechanical ventilation use, vital signs (mean arterial pressure, heart rate, temperature, respiration rate, SpO_2) and laboratory values [serum creatinine, urea nitrogen, glucose, white blood cell count, hematocrit, hemoglobin, platelets, potassium, sodium, chloride, calcium, anion gap, bicarbonate, international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (APTT)]. Vital signs were recorded as average values, while laboratory data were taken as maximum values.
(iv) Medication information: included PPIs and non-PPIs for SUP, vasoactive drugs (vasopressin, phenylephrine, norepinephrine, epinephrine, dopamine, dobutamine), anticoagulants, enteral nutrition, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and antibiotics. Prescription details included drug name, route of administration, dosage, and start and end times. Specifics about PPIs and non-PPI SUP drugs were extracted to confirm prophylactic use.
(v) AKI events: any AKI events occurring within 2 days of ICU admission.

According to KDIGO criteria, AKI is defined as an increase in serum creatinine (SCr) of ≥26.5 μmol/L (0.3 mg/dL) within 48 h, an increase in SCr of ≥50% within 7 days or urine output of <0.5 mL/(kg·h) for 6 h or more [18]. The study population excluded patients receiving therapeutic PPIs; thus, prophylactic PPI exposure was defined as the initiation of any PPI from 6 h before ICU admission to 48 h after admission. Patients were categorized into a prophylactic PPI group and a no PPI control group.

Endpoint

The primary endpoint of the study was the development of AKI after 48 h of ICU admission. An SQL script was created to extract relevant information regarding endpoint events. Measurements of creatinine and urine output used to diagnose AKI were limited to the period following 48 h of ICU admission and prior to transfer out of the ICU.

Statistical analysis

Categorical variables were expressed as proportions (%). Continuous data were expressed as mean and standard deviation or median and interquartile range, as appropriate. One-way analysis of variance (for normal distribution), Kruskal–Wallis H test (for skewed distribution), chi-square tests or Fisher's exact test (for categorical variables) were used to determine any statistical differences between the means and proportions of two groups.

Multivariable logistic regression analyses were conducted to evaluate the independent relationship between prophylactic PPIs and the risk of new-onset AKI. An extended logistic model approach was used for covariate adjustment. Model 1 adjusts for the use of prophylactic PPIs. Model 2 incorporates further adjustments for demographic characteristics, such as gender, age, race, marital status, type of insurance and admission type. Model 3 incorporates further adjustments for variables related to disease severity and bleeding tendency, including the first day SOFA score, OASIS score, SAPS III score, CCI, diagnosis of sepsis, mechanical ventilation, vasopressor use, enteral nutrition use, anticoagulant use and the administration of H2RA or sucralfate. Model 4 accounts for other medications initiated within 2 days of ICU admission that may be associated with AKI, including diuretics, NSAIDs and antibiotics. Finally, Model 5 includes additional adjustments for first-day vital signs and laboratory data.

Propensity score–matched analysis (PSM) was employed to minimize the imbalance between groups. A logistic regression model was used to compute the propensity score for each patient, followed by 1:1 matching of the two groups with a caliper width of 0.2. The variables utilized to generate the propensity scores align with those outlined in Model 5 of the multivariable logistic regression analysis. Standardized mean difference (SMD) was computed to assess the effectiveness of PSM in minimizing the disparities between the two groups, with a threshold of <0.1 deemed acceptable [19]. In addition, we employed inverse probability of treatment weighting (IPTW), standardized mortality ratio weighting (SMRW), pairwise algorithmic (PA) and overlap weight (OW) models to create weighted cohorts [20].

Stratified analyses were conducted within the matched cohort after PSM to explore the relationship between prophylactic PPIs and the risk of new-onset AKI in different subgroups based on age (≥60 years), sex, SOFA score (≥4), sepsis, congestive heart failure, renal disease, mechanical ventilation, and use of non-PPI prophylaxis, enteral nutrition, NSAIDs, diuretics or

Table 1: Baseline characteristics of the study participants.

	Original cohort			Propensity score–matched cohort			
Covariate	Control group	PPI group	SMD	Control group	PPI group	SMD	Missing data (%)
N	6158	1340		1260	1260		NA
Female (%)	3251 (52.8)	756 (56.4)	0.073	732 (58.1)	708 (56.2)	0.038	0.00
Age (years)	61.74 (18.3)	63.08 (16.7)	0.077	62.98 (17.9)	63.13 (16.6)	0.009	0.00
Married (%)	4327 (70.3)	962 (71.8)	0.034	909 (72.1)	903 (71.7)	0.011	0.00
White race (%)	3899 (63.3)	910 (67.9)	0.097	864 (68.6)	854 (67.8)	0.017	0.00
Insurance (%)			0.121			0.047	0.00
Medicaid	494 (8.0)	123 (9.2)		98 (7.8)	114 (9.0)		0.00
Medicare	2254 (36.6)	556 (41.5)		516 (41.0)	516 (41.0)		0.00
Other	3410 (55.4)	661 (49.3)		646 (51.3)	630 (50.0)		0.00
Admission, emergency (%)	4835 (78.5)	1199 (89.5)	0.302	1117 (88.7)	1122 (89.0)	0.013	0.00
SOFA score	3.71 (2.76)	4.67 (3.11)	0.327	4.51 (3.11)	4.52 (3.05)	0.002	0.00
OASIS score	29.09 (7.78)	30.92 (8.14)	0.229	30.29 (7.90)	30.53 (7.99)	0.030	0.00
SAPS III score	39.19 (17.6)	46.34 (19.9)	0.381	45.29 (19.6)	45.11 (19.0)	0.009	0.00
CCI	4.87 (3.00)	5.42 (2.98)	0.184	5.36 (3.14)	5.42 (3.00)	0.019	0.00
Sepsis (%)	2615 (42.5)	761 (56.8)	0.290	688 (54.6)	691 (54.8)	0.005	0.00
Congestive heart failure (%)	1111 (18.0)	284 (21.2)	0.079	259 (20.6)	265 (21.1)	0.012	0.00
Renal disease (%)	619 (10.1)	173 (12.9)	0.09	174 (13.8)	163 (13.0)	0.026	0.00
Mechanical ventilation (%)	1609 (26.1)	445 (33.2)	0.155	366 (29.0)	388 (30.8)	0.038	0.00
Vasopressors use[a] (%)	830 (13.5)	255 (19.0)	0.151	237 (18.8)	227 (18.0)	0.020	0.00
H2RAs or sucralfate (%)	2342 (38.0)	181 (13.5)	0.584	180 (14.3)	181 (14.4)	0.002	0.00
Anticoagulant[a] (%)	2460 (39.9)	754 (56.3)	0.331	724 (57.5)	692 (54.9)	0.051	0.00
Enteral nutrition[a] (%)	631 (10.2)	204 (15.2)	0.15	158 (12.5)	167 (13.3)	0.021	0.00
NSAIDs[a] (%)	1344 (21.8)	300 (22.4)	0.014	284 (22.5)	286 (22.7)	0.004	0.00
Diuretic[a] (%)	1092 (17.7)	261 (19.5)	0.045	261 (20.7)	251 (19.9)	0.020	0.00
Antibiotics[a] (%)	3174 (51.5)	897 (66.9)	0.317	845 (67.1)	825 (65.5)	0.034	0.00
Weight (kg)	76.39 (19.74)	76.01 (19.44)	0.019	76.47 (19.23)	75.93 (19.49)	0.027	1.63
Heart rate (bpm)	84.05 (16.24)	87.98 (16.51)	0.24	87.63 (16.94)	87.51 (16.26)	0.007	0.37
SBP (mmHg)	122.5 (16.57)	119.7 (17.37)	0.163	119.3 (16.70)	119.8 (17.39)	0.031	0.63
DBP (mmHg)	67.08 (11.50)	63.92 (10.40)	0.288	63.92 (10.99)	64.05 (10.41)	0.012	0.63
MAP (mmHg)	82.56 (11.53)	79.10 (10.76)	0.311	78.96 (11.04)	79.20 (10.81)	0.021	0.41
Respiratory rate (bpm)	19.01 (3.67)	19.48 (3.97)	0.124	19.57 (3.95)	19.43 (3.97)	0.036	0.72
Temperature (°C)	37.01 (0.48)	36.97 (0.62)	0.08	36.99 (0.53)	36.97 (0.59)	0.034	1.83
SpO_2 (%)	96.95 (1.96)	97.05 (1.95)	0.05	96.94 (1.94)	97.00 (1.95)	0.033	0.39
WBC ($\times 10^9$/L)	13.41 (11.64)	13.62 (8.43)	0.021	13.47 (8.64)	13.53 (8.43)	0.007	0.92
Hematocrit (%)	36.51 (5.94)	34.03 (6.10)	0.412	34.19 (6.27)	34.22 (6.06)	0.004	0.91
Hemoglobin (g/L)	12.10 (2.08)	11.29 (2.13)	0.385	11.36 (2.17)	11.35 (2.12)	0.005	0.96
Platelets ($\times 10^9$/L)	234.3 (106.1)	236.7 (121.6)	0.021	231.5 (121.0)	234.8 (119.7)	0.027	0.96
BUN (mmol/L)	20.73 (16.67)	26.11 (22.64)	0.271	25.61 (21.63)	25.43 (22.05)	0.008	0.91
SCr (mg/dl)	1.04 (0.81)	1.15 (0.88)	0.126	1.16 (0.80)	1.14 (0.88)	0.022	0.87
Glucose (mmol/L)	158.4 (98.9)	170.8 (104.2)	0.122	173.1 (117.4)	169.7 (102.1)	0.031	1.16
Potassium (mmol/L)	4.39 (0.75)	4.39 (0.68)	0.004	4.38 (0.73)	4.39 (0.68)	0.012	1.00
Sodium (mmol/L)	140.1 (4.98)	140.1 (5.14)	0.001	139.8 (5.81)	140.1 (4.95)	0.035	0.98
Chloride (mmol/L)	105.5 (6.07)	106.6 (6.46)	0.169	106.3 (6.91)	106.4 (6.23)	0.018	1.03
Calcium (mmol/L)	8.69 (0.81)	8.48 (0.72)	0.282	8.48 (0.72)	8.49 (0.72)	0.013	5.85
Anion gap (mmol/L)	15.71 (4.16)	16.04 (4.66)	0.073	16.15 (5.26)	16.04 (4.61)	0.022	1.07
Bicarbonate (mmol/L)	24.52 (3.79)	24.86 (4.32)	0.084	24.72 (4.22)	24.79 (4.18)	0.015	1.01
INR	1.36 (0.68)	1.57 (1.23)	0.204	1.48 (0.82)	1.51 (0.94)	0.038	9.56
PT (s)	14.90 (7.29)	16.93 (11.51)	0.211	16.09 (8.41)	16.43 (9.26)	0.038	9.56
APTT (s)	38.88 (25.06)	40.06 (25.43)	0.047	39.49 (22.82)	39.84 (25.42)	0.014	9.98

For all continuous covariates, the mean values and standard deviations are reported.

[a]Initiated within 48 h of ICU admission

SBP, systolic blood pressure; DBP, diastolic blood pressure, MBP, mean arterial pressure; BUN, blood urea nitrogen; WBC, white blood cell count.

antibiotics. Subgroup analyses were performed to address potential selection bias by excluding patients with missing baseline data or those on H2RAs or sucralfate. Furthermore, the E-value was calculated to assess the possibility of unmeasured confounding [21]. Finally, to account for the competing risks of death and AKI, we performed an analysis of composite outcome encompassing either AKI or ICU mortality.

In this study, all variables exhibited <10% missing data (see Table 1 for details). Assuming that the missing data are missing at random, we employed the K-nearest neighbor (KNN) method

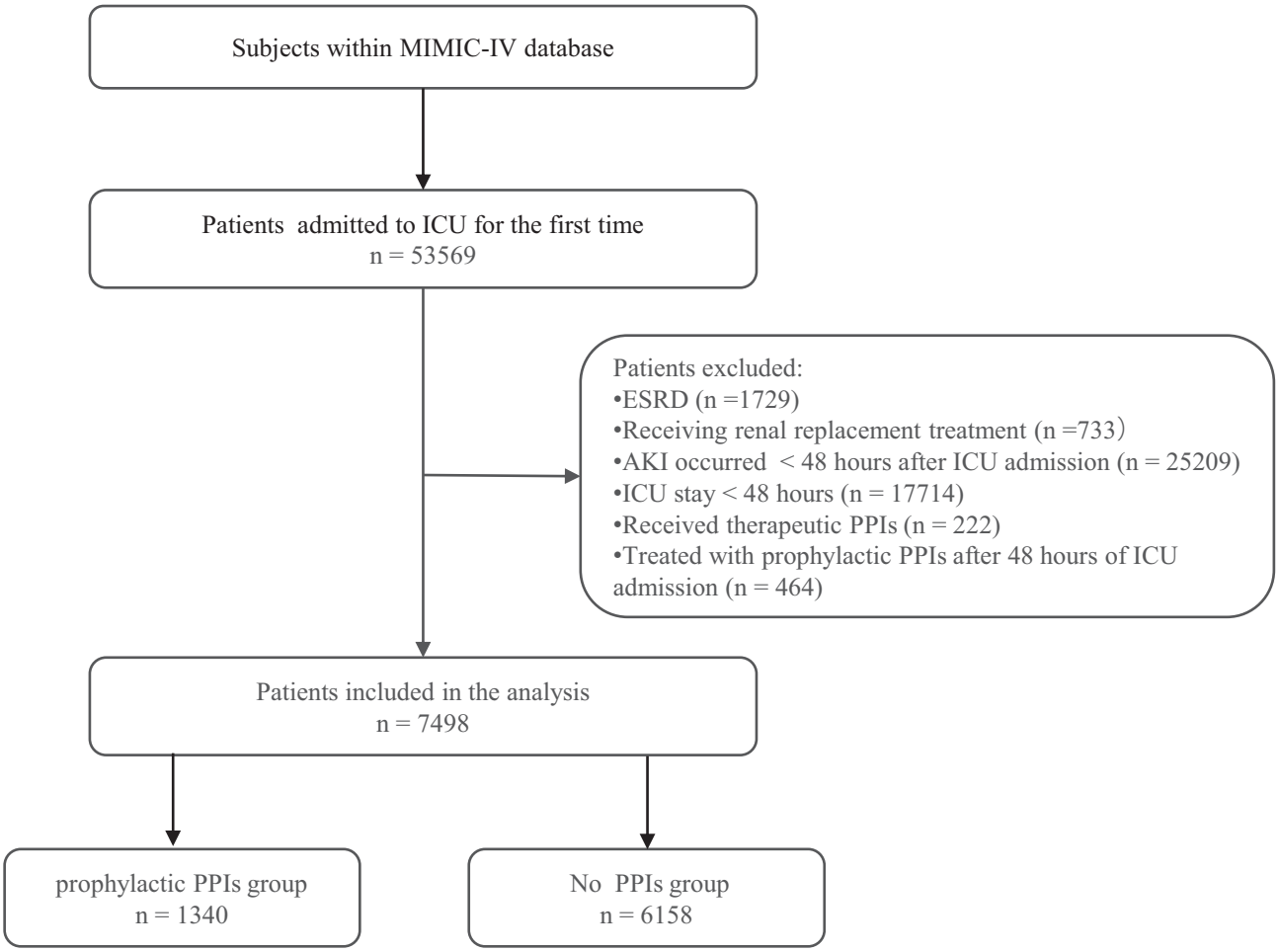


Figure 1: Flowchart of patient selection.

[22] to interpolate these missing values. All analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.9.2. A two-tailed test was performed and $P < .05$ was considered statistically significant.

RESULTS

Basic characteristics

Among the 53 569 adult patients who experienced their first hospital and ICU admission in MIMIC-IV between 2008 and 2019, a total of 7498 eligible patients were included in the study. This cohort comprised 1340 patients in the PPI group and 6158 patients in the control group, which did not receive PPIs. The flow chart of patient selection is presented in Fig. 1. PPIs initiated within 48 h of ICU admission included pantoprazole, omeprazole, lansoprazole and esomeprazole, with pantoprazole being the most frequently prescribed, accounting for 81.6% of patients, followed by omeprazole at 14.4%. While most patients received only one prophylactic PPI, a subset transitioned to a second PPI following the initiation of the first. Details regarding PPI usage are presented in Supplementary data, Table S1, which categorizes patients based on the type of PPI administered at the time of initiation. Non-PPI SUP medications, such as H2RAs like famotidine and ranitidine, as well as sucralfate, were initiated within 48 h of ICU admission in 2532 patients, with the majority (86.7%) receiving famotidine. The median length of stay in the ICU for 7498 observations was 3.3 days (interquartile range 2.5 to 5.1 days), with a minimum duration of 2.01 days and a maximum of 74.31 days.

Baseline characteristics are summarized in Table 1. Prior to PSM, patients receiving prophylactic PPIs exhibited significantly higher scores in SOFA, OASIS, SAPS and CCI compared with control patients not on PPIs. The prophylactic PPI group also had a higher percentage of patients diagnosed with sepsis, as well as those undergoing mechanical ventilation, vasopressor therapy and receiving treatments such as enteral nutrition, anticoagulation and antibiotics. Furthermore, differences were observed between the two groups regarding insurance status, admission type, vital signs and certain laboratory test results. Additionally, in the prophylactic PPI group, 13.5% of patients were treated with non-PPI SUP drugs, compared with 38.0% in the no PPI group. After PSM, 1260 paired patients were obtained, with all variables being well balanced between the two groups, as indicated by SMD values <0.1 (Table 1).

Primary outcomes

Among the 7498 patients, 1892 experienced an AKI event 48 h after admission, resulting in an overall incidence of 25.2%. The median time to AKI occurrence was 2.8 days (interquartile range

Table 2: Association between prophylactic PPIs use and new-onset AKI using an extended model approach.

	OR of prophylactic PPIs use	95% CI	P-value
Model 1	1.40	1.23–1.59	<.001
Model 2	1.36	1.19–1.55	<.001
Model 3	1.29	1.11–1.49	<.001
Model 4	1.36	1.17–1.58	<.001
Model 5	1.43	1.22–1.67	<.001

Model 1: adjusted for prophylactic PPI use.
Model 2: adjusted for Model 1 plus gender, age, White race, marital status, type of insurance and admission type.
Model 3: adjusted for Model 2 plus SOFA score, OASIS score, SAPS III score, CCI, sepsis, mechanical ventilation on the first day of ICU admission, and initiation of vasopressin, enteral nutrition, anticoagulant medications, and treatment of SUP with non-PPI agents (H2RA or succinate) within 48 h of ICU admission.
Model 4: adjusted for Model 3 plus diuretics, NSAIDs and antibiotics initiated within 48 h of ICU admission.
Model 5: adjusted for Model 4 plus vital signs and laboratory data on the first day of ICU admission, including body weight, respiratory rate, temperature, heart rate, mean arterial pressure, SCr, urea nitrogen, glucose, white blood cell count, hematocrit, hemoglobin, platelets, potassium, sodium, chloride, calcium, anion gap, bicarbonates, INR, PT and APTT.

Table 3: Associations between prophylactic PPIs use and new-onset AKI in the crude analysis, multivariable analysis and PS analyses.

Method	OR (95% CI)	P
Crude analysis	1.40 (1.23–1.59)	<.001
Multivariable adjusted[a]	1.43 (1.22–1.67)	<.001
Propensity score analyses[a]		
Propensity score matching	1.49 (1.24–1.78)	<.001
Adjusted for propensity score	1.34 (1.16–1.55)	<.001
With IPTW	1.42 (1.25–1.61)	<.001
With SMRW	1.42 (1.25–1.62)	<.001
With PA	1.40 (1.17–1.67)	<.001
With OW	1.35 (1.09–1.67)	.005

[a]Adjusted variables are the same as those in Model 5 of Table 2.

2.3 to 4.1 days) following ICU admission, with a minimum of 2.01 days and a maximum of 34.52 days. The incidence of new-onset AKI was significantly higher in the PPI group compared with the no PPI group (30.7% vs 24.1%, $P < .001$). In the extended multivariable logistic models (Table 2), the odds ratio (OR) for prophylactic PPI use remained consistently significant across all five models (ORs ranging from 1.29 to 1.43, $P < .001$ for all).

The results of multiple propensity score (PS) analyses, including PSM, adjusting for PS as a covariate, IPTW, SMRW, PA and OW regression analysis, were consistent with those from the multivariable logistic regression models (ORs ranging from 1.34 to 1.49, $P \leq .005$ for all; see Table 3).

Stratified analysis demonstrated consistent and stable results when patients were categorized by age (≥60 years), SOFA score (≥4), presence of sepsis, congestive heart failure, renal disease, requirement for mechanical ventilation, administration of enteral nutrition, and use of anticoagulants, NSAIDs, diuretics or antibiotics (P-values for all interactions >.05; see Fig. 2). However, an interaction was observed between gender and prophylactic PPI exposure (P for interaction = 0.014). PPIs were associated with a significantly higher risk of AKI in male patients [OR 1.97, 95% confidence interval (CI) 1.52–2.56], whereas no such association was found in female patients (OR 1.2, 95% CI 0.88–1.64) (refer to Fig. 2).

The results of the subgroup analyses indicate that the association between prophylactic PPIs and the risk of new-onset AKI remained significant even after excluding individuals with missing baseline data or who were on non-PPI prophylactics (H2RAs or sucralfate) (Supplementary data, Tables S2 and S3). During the ICU hospitalization, death occurred in 280 patients, resulting in a mortality rate of 3.7%. The composite outcome, which included AKI or ICU mortality, was observed in 2011 patients, yielding an incidence rate of 26.8%. Patients in the PPI group exhibited a significantly higher risk of reaching the composite endpoint compared with the control group (OR 1.33, 95% CI 1.14–1.55; $P < .001$) (Supplementary data, Table S4). However, the risk of death did not differ statistically between the two groups (OR 0.98, 95% CI 0.69–1.40; $P = .919$) (Supplementary data, Table S5).

The cohort had an E-value of 2.34, suggesting that residual confounding could explain the observed association if there exists an unmeasured covariate with a relative risk association of at least 2.34 with both the use of prophylactic PPIs and the occurrence of new-onset AKI, even after controlling for known confounders.

Of the 7498 patients, 280 patients died during ICU hospitalization, with a mortality rate of 3.7%; the composite endpoint including AKI or death occurred in 2011 patients, with an incidence rate of 26.8%. Patients in the PPI group had a significantly higher risk of the composite endpoint compared with the control group, while the risk of death was not statistically different between the two groups.

DISCUSSION

The study indicated that among 7498 critically ill patients admitted to the ICU, 25.2% developed new-onset AKI after 48 h of admission. Both multivariable logistic regression models and PS analyses consistently demonstrated that the use of prophylactic PPIs was associated with an elevated risk of new-onset AKI (OR 1.34–1.49; $P \leq .005$ for all). Furthermore, multiple sensitive analyses and an assessment of unmeasured confounding (E-value of 2.34) supported the robustness and reliability of these findings.

Acute interstitial nephritis (AIN) is widely recognized as the most common histopathologic change associated with PPI-associated AKI. Ruffenach *et al.* were among the first to suggest a potential increased risk of AIN in individuals using omeprazole [23]. Subsequent case reports and series have further confirmed this class effect of PPIs, including omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole [24–29]. According to existing literature, PPIs mediate AIN with a range of clinical features. The time interval between PPI use and AIN diagnosis typically spans from weeks to months; however, some cases have been reported with a rapid onset of symptoms as soon as 1–2 days or even a few hours after initiation [26, 28]. The renal impairment degree is usually mild or asymptomatic, although severe cases may necessitate dialysis [26, 27, 29]. Importantly, AIN induced by PPI use is not dose-dependent and may recur or worsen rapidly upon re-exposure to the same or related drugs [30, 31]. Patients may experience complete reversal of renal function after discontinuing the offending agent, but there is also a risk of progression to CKD or ESRD [27]. Renal biopsy is considered the gold standard for diagnosing AIN; however, the pathological features of PPI-induced AIN are often nonspecific, making differentiation from AIN caused by other medications challenging. Convincing evidence of causation includes the exclusion of a history of exposure to other drugs, improvement in renal function following the cessation of PPIs, and the recurrence of AIN upon rechallenge with the same medication. Diagnosing

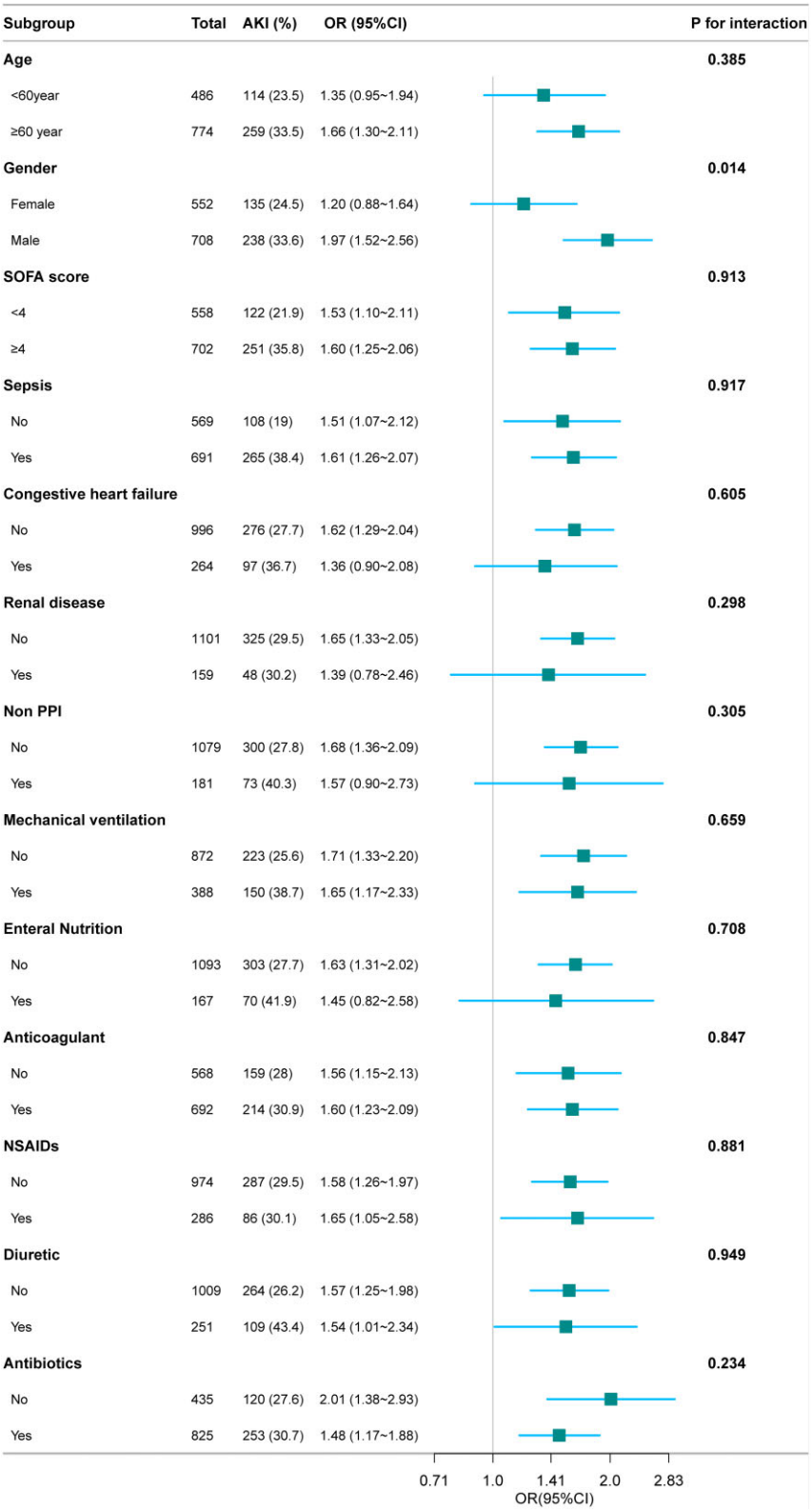


Figure 2: The association between prophylactic PPIs use and new-onset AKI in subgroups. The P-value for interaction represents the likelihood of interaction between the variable and the PPIs.

PPI-induced AIN in the ICU is particularly challenging due to the patients' critical conditions, which render renal biopsy unfeasible, coupled with the complexity of their medication regimens.

The exact pathogenesis of PPI-associated AKI remains unclear. Some *in vitro* and animal studies suggest that PPIs may down-regulate or inhibit the PI3K–Akt signaling pathway [32, 33], while other research has linked abnormalities in this pathway to AKI development [34–37]. For instance, studies by Fahmy *et al*. and Li *et al*. found that activation of the PI3K–Akt signaling pathway could mitigate or prevent cisplatin-induced AKI [34, 35]. Additionally, Yue *et al*. observed that enhancing this signaling pathway could reduce contrast-induced apoptosis in renal tubular epithelial cells [36], while Zhang *et al*. noted that blocking the PI3K–Akt signaling pathway could lead to programmed cell death, potentially worsening renal ischemia–reperfusion injury [37]. Patients in the ICU are often face multiple AKI risk factors, and the use of PPIs might hinder the expression of the PI3K–Akt signaling pathway, thereby increasing susceptibility to AKI. However, more research is needed to confirm this hypothesis.

Our study revealed an interaction between gender and PPIs. PPI exposure was significantly associated with a higher risk of developing AKI in male patients, but not in females. Previous studies support the existence of gender differences in AKI susceptibility, with men generally experiencing a higher incidence of AKI than women [38–40]. Gender differences in AKI have also been noted in animal models [41–43]. However, the underlying mechanisms remain poorly understood. In an experiment by Hwang *et al*., male rats showed greater sensitivity to cisplatin-induced nephrotoxicity [43]. To identify potential genetic factors contributing to this sex difference, the researchers performed RNA sequencing analysis on renal tissues collected before and after cisplatin treatment. The results indicated that gene expression related to the PI3K–Akt signaling pathway and redox processes was significantly lower in male rats than in female controls before cisplatin treatment. These findings lead us to postulate that both PPIs and gender may negatively impact the PI3K–Akt signaling pathway, and that these factors interact to influence AKI occurrence. Thus, additional studies are warranted to explore this interaction further.

Our study has several limitations that should be acknowledged. First, as an observational study, we could only establish an association between prophylactic PPI exposure and AKI risk, without proving causality. Second, due to its retrospective design, unmeasured confounding factors were inevitable, despite strict exclusion criteria and careful propensity score matching. However, we calculated an E-value of 2.34, suggesting that a significant unmeasured confounder would need to have a strong effect to invalidate our findings. Third, there were instances of missing baseline data, which we addressed using KNN interpolation. Sensitivity analyses conducted after excluding cases with missing data yielded results consistent with our initial findings. Lastly, this study was conducted at a single center, highlighting the need for further validation through multicenter clinical trials.

CONCLUSIONS

Our study suggests that the use of prophylactic PPIs may increase the risk of new-onset AKI in ICU patients during hospitalization. Given the widespread use of PPIs for SUP in ICU populations, the debate regarding their benefits and risks remains ongoing. These findings may assist in informing clinical decision-making when evaluating the risks and benefits of prophylactic PPIs in the ICU setting.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

J.X. designed the study, extracted data from the MIMIC-IV database, participated in data analysis and contributed to the writing of this manuscript. Z.Z. and Y.P. processed and analyzed the data, and also contributed to the manuscript's writing. X.L. assisted with data processing and analysis. J.D. designed and supervised the study, as well as drafting the manuscript. M.W. also contributed to the design and supervision of the study. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

MIMIC-IV database v2.0 is freely-available on PhysioNet (10.13026/7vcr-e114). The code for data query and extraction is available from the MIMIC Code Repository (https://github.com/MIT-LCP/mimic-code).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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