

Proton pump inhibitor usage associates with higher risk of first episodes of pneumonia and peritonitis in peritoneal dialysis patients

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ABSTRACT

Background: A large number of studies have shown that proton pump inhibitors (PPIs) are associated with infection events. Therefore, we retrospectively evaluated the association of PPI therapy with the occurrence of first pneumonia and peritoneal dialysis(PD)-related peritonitis events in the maintenance PD patients.

Methods: We collected PD patients in two large hospitals from January 1, 2012 to December 31, 2016, and divided them into the PPI group and the non-PPI group. Multivariate Cox proportional hazards models were applied to evaluate the cumulative incidence and hazard ratios (HRs). Inverse probability of treatment weight (IPTW) method was used to adjust for covariate imbalance between the two groups and further confirm our findings.

Results: Finally, 656 PD patients were included for data analysis, and the results showed that PPI usage was associated with an increased risk of pneumonia [HR 1.71; 95% CI 1.06-2.76; $p = 0.027$] and peritonitis [HR 1.73; 95% CI 1.24-2.40; $p = 0.001$]. IPTW-adjusted HRs for the association of PPIs with pneumonia and peritonitis were 1.58 (95% CI:1.18-2.12; $p = 0.002$) and 2.33 (95% CI:1.91-2.85; $p < 0.001$), respectively. Moreover, the competitive risk model proved that under the conditions of competition for other events(including transfer to hemodialysis therapy, kidney transplant, transfer from our research center, loss to follow-up, and death), the differences in endpoints events between the two groups were still statistically significant ($p = 0.009$, $p < 0.001$, respectively).

Conclusions: PPIs was associated with an increased risk of first pneumonia and PD-related peritonitis events in PD patients, which reminds clinicians to be cautious when prescribing acid-suppressing drugs for PD patients.

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Introduction

Infection is one of the most common complications in dialysis patients. According to the National Kidney Registry of the United States, infection has become the second cause of hospitalization and death in patients with kidney disease, and one-quarter of them were due to lung infections [1]. Peritonitis is another common and serious infectious event in peritoneal dialysis (PD) patients, which causes a mortality rate of about 16%

[2–7]. In addition, frequent or severe peritonitis can also lead to failure of PD techniques, peritoneal damage or failure, transfer to hemodialysis (HD), and even death [8]. Therefore, it is vital to reduce and prevent infection for PD patients.

Since the advent of acid inhibitor drugs, they have gradually become one of the most widely used drugs in the world. Due to the extremely high frequency of acid inhibitors in clinical application, the adverse effects

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brought by them have attracted people's attention. An early study evaluated the correlation between any type of acid inhibitors therapy and the development of hospital-acquired pneumonia (HAP), and found that patients receiving acid suppression therapy were more likely to develop HAP than patients not taking acid inhibitor drugs [9]. Further analysis of the different types of acid inhibitor drugs found that this correlation existed in patients treated with proton pump inhibitors (PPIs), but not in patients treated with histamine-2 receptor antagonists (H2RAs) [10]. In addition, a meta-analysis study has demonstrated that the use of acid inhibitors was a risk factor for enteroperitonitis [11].

A recent questionnaire on outpatient prescriptions for hemodialysis patients in Japan found that because the risk of gastrointestinal bleeding in dialysis patients was higher than that of the general population, clinicians often prescribe acid inhibitor drugs to dialysis patients, of which proton pump inhibitors was one of the most commonly used [12]. As a special population, there are few studies on whether the use of PPI is related to the infection event in PD population. Therefore, we conducted this study to explore the relationship between PPIs and the first infectious events in PD patients.

Materials and methods

Study design and participants

This study recruited patients who received PD treatment at two centers from January 1, 2012 to December 31, 2016. Of the 707 patients, 51 were excluded due to the following reasons: younger than 18 years ($n=11$), maintaining PD for less than 3 months ($n=8$), and excessive data loss ($n=32$). Ultimately, this study included 656 patients. The institutional review boards of the two PD centers approved this retrospective study (IRB approval number 2022-hg-ks-01) and exempted informed consent because all our medical records were collected retrospectively.

Data collection

The demographic data such as center, gender, age, weight, height, comorbidities, and medication history were collected at the start of PD treatment, whereas laboratory parameters were collected within 90 days of PD treatment initiation. We retrospectively collect comorbidities from the medical records, such as hypertension, diabetes, and cardiovascular disease (CVD). The definition of CVD included ischemic heart disease, congestive heart failure, angioplasty, coronary artery

bypass surgery, cerebrovascular disease, or peripheral vascular disease. Pneumonia was diagnosed if one of the pneumonia ICD codes was existed and there was evidence of infection on chest radiography or chest CT. The organisms isolated from peritoneal dialysis effluent were tested, and the diagnosis of PD-related peritonitis was based on at least the following two criteria [13]: (1) abdominal pain or cloudiness of PD effluent; (2) white blood cell count in PD effluent $>100/\mu\text{L}$, with $>50\%$ polymorphonuclear leukocytes; or (3) a positive culture from PD effluent.

Clinic outcomes

During the follow-up period, the main exposure was the use of PPI, and the primary endpoint was the first occurrence of pneumonia and peritonitis. Similar to previous studies, patients who used PPIs continuously for more than 1 week were classified as PPI group, and the remaining patients were classified as Non-PPI group [14, 15]. It is worth noting that only patients who took PPIs before the onset of pneumonia or peritonitis were included in the PPI group. All patients were followed until pneumonia/peritonitis, death, transfer to hemodialysis therapy, kidney transplantation, transfer from two centers, or censoring on December 31, 2017.

Statistical analysis

Continuous variables were all described as median (25th to 75th percentile), and the differences between the two groups were tested by Mann-Whitney because of their skewed distribution. Categorical data was given as percentages, and the χ^2 test was used for comparison between groups. In our study, survival was calculated using Kaplan–Meier method and differences between distributions of survival were assessed by log-rank test. An IPTW model was established to evaluate the relationship between the use of PPI and first pneumonia and peritonitis events using the estimated propensity score as weights. Multivariable Cox regression model was constructed to estimate the relationships between the use of PPI and first pneumonia or peritonitis event adjusting for covariates that were associated with events of pneumonia or peritonitis ($p < 0.05$) and potential confounders as judged by our team. Moreover, competitive risk models were performed to explore whether other follow-up endpoint events had an effect on the first event of pneumonia or peritonitis. Forest plots were used to show the differences between PPI treatment and these two infectious events in different subgroups. The SPSS (version 22.0), and R software

Table 1. Baseline data characteristics.

	Total (n = 656)	Group1 Non-PPI (n = 467)	Group2 PPI (n = 189)	p Value
No. of C1/C2	365/469	225/242	39/150	<0.001
No. of men/women	367/289	274/193	93/96	0.027
Demographics				
Age(y)	53 (43, 63)	52 (42, 62)	57 (44, 66)	0.010
BMI(kg/m ²)	22.8 (20.7, 25.0)	22.9 (20.7, 25.2)	22.6 (20.7, 24.6)	0.385
Comorbid				
Hypertension	367 (55.9%)	231 (49.5%)	136 (72.0%)	<0.001
Systolic BP(mmHg)	145 (136, 165)	144 (137, 160)	150 (132, 172)	0.379
Diastolic BP(mmHg)	85 (79, 94)	85 (80, 93)	84 (75, 96)	0.184
Diabetes	164 (25.0%)	106 (22.7%)	58 (30.7%)	0.032
Cardiovascular disease	145 (22.1%)	89 (19.1%)	56 (29.6%)	0.003
Gastrointestinal bleeding	48 (7.3%)	25 (5.4%)	23 (12.2%)	0.002
Smoke	60 (9.1%)	43 (9.2%)	17 (9.0%)	0.932
Laboratory variables				
WBC (4.0-10.0, × 10 ⁹ /L)	6.7 (5.6-8.1)	6.7 (5.6, 7.8)	7.1 (5.6, 8.6)	0.054
Hemoglobin (130-175, g/L)	95 (83, 108)	96 (84, 110)	91 (83, 104)	0.047
Albumin (40-55, g/L)	33.0 (29.8, 35.9)	33.3 (30.0, 36.2)	32.5 (28.6, 35.0)	0.006
Creatinine (53-115, umol/L)	780 (559, 999)	769 (550, 963)	816 (599, 1124)	0.028
BUN (3.1-8.8, mmol/L)	19.0 (14.5, 24.6)	19.0 (14.8, 24.7)	19.1(13.6, 23.9)	0.311
Uric acid(150-350, umol/L)	427 (369, 491)	432 (369, 494)	413 (367, 491)	0.232
FBG (3.9-6.1, mmol/L)	4.5 (4.0, 5.6)	4.6 (4.1, 5.6)	4.5 (3.9, 5.6)	0.161
Cholesterol (3.0-5.2, mmol/L)	4.4 (3.8, 5.1)	4.4 (3.8, 5.1)	4.4 (3.8, 5.2)	0.973
Triglycerides (0.5-1.7, mmol/L)	1.4 (1.0, 2.0)	1.4 (1.0, 1.9)	1.5 (1.0, 2.3)	0.133
Sodium (137-147, mmol/L)	141.0 (138.5, 143.0)	141.0 (138.5, 143.0)	141.2 (138.6, 143.1)	0.577
Chlorine (99-110, mmol/L)	100.3 (97.3, 103.0)	100.4 (97.6, 103.2)	99.5 (96.5, 102.9)	0.094
Calcium (2.1-2.5, mmol/L)	2.1 (1.9, 2.2)	2.1 (2.0, 2.2)	2.0 (1.9, 2.2)	0.001
Potassium (3.5-5.3, mmol/L)	3.9 (3.5, 4.5)	3.9 (3.5, 4.5)	3.9 (3.4, 4.4)	0.916
Phosphorus (0.8-1.5, mmol/L)	1.6 (1.2, 1.9)	1.5 (1.2, 1.9)	1.6 (1.2, 2.1)	0.185
Total KT/V	2.3 (1.9, 2.7)	2.3 (2.0, 2.7)	2.2 (1.8, 2.6)	0.186
RRF (mL/min)	9.9 (3.1, 32.4)	7.5 (2.9, 29.7)	17.9 (4.1, 38.5)	<0.001
Treatments				
CCB (yes VS no)	547 (83.4%)	386 (82.7%)	161 (85.2%)	0.430
ACEI/ARB (yes VS no)	346 (52.7%)	264 (56.5%)	82 (43.4%)	0.002
EPO (yes VS no)	348 (53.0%)	232 (49.7%)	116 (61.4%)	0.007
Aspirin (yes VS no)	65 (9.9%)	48 (10.3%)	17 (9.0%)	0.618
Insulin (yes VS no)	106 (16.2%)	69 (14.8%)	37 (19.6%)	0.130
Statin (yes VS no)	135 (20.6%)	84 (18.0%)	51 (27.0%)	0.010

All continuous variables are skewed distribution, the values for continuous variables are given as median(P25, P75).

C1: center 1; C2: center 2; BMI: Body mass index; WBC: white blood cell; BUN: Blood urea nitrogen; FBG: fasting blood-glucose; KT/V: K-dialyzer clearance of urea, T-dialysis time, V-volume of distribution of urea; RRF: residual renal function; CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; EPO: erythropoietin.

(version R-3.5.2) were performed for Statistical analyses. $p < 0.05$ was considered statistically significant.

Results

Baseline demographic and clinical characteristics of the cohort were given in Table 1, one hundred and eighty-nine patients were exposed to PPIs and 467 patients did not receive PPIs (Figure 1).

As shown in Table 1, compared with the non-PPI group, patients in the PPI group were usually older, with higher levels of white blood cells and creatinine, and lower levels of hemoglobin and albumin. The use of ACEI/ARB, EPO, and statins was more common in the PPI group. Among patients receiving PPIs therapy, they were more likely to have a history of hypertension, diabetes, CVD, and gastrointestinal bleeding. During the follow-up period, 85 cases of pneumonia (12.4%) and 176 cases of peritonitis (26.8%) occurred. Among them, the first pneumonia event was 32 cases (16.9%) in the PPI group and 53 cases (11.3%) in the non-PPI group;

while 68 (36.0%) and 108 (23.1%) developed first peritonitis in PPI and non-PPI groups, respectively.

The cumulative incidence of first pneumonia and peritonitis events was represented by the Kaplan–Meier curve and tested by log-rank test. The results showed that compared to the non-PPI group, the cumulative incidence of first pneumonia and peritonitis in the PPI group was higher (log-rank test: $p = 0.0048$, $p < 0.001$, respectively)(Figure 2).

The Cox proportional hazards model was used to test the difference in the results of the first infectious event between the two groups. In the unadjusted cohort, after including possible confounding factors related to pneumonia or peritonitis, the use of PPI was associated with the occurrence of the first pneumonia event (HR 1.71; 95% CI 1.06-2.76; $p = 0.027$) and the first peritonitis event (HR 1.73; 95% CI 1.24-2.40; $p = 0.001$) (Table 2).

Similar to the results of the unadjusted model, the IPTW-adjusted model also showed that PPIs was related to the occurrence of the first pneumonia events (HR

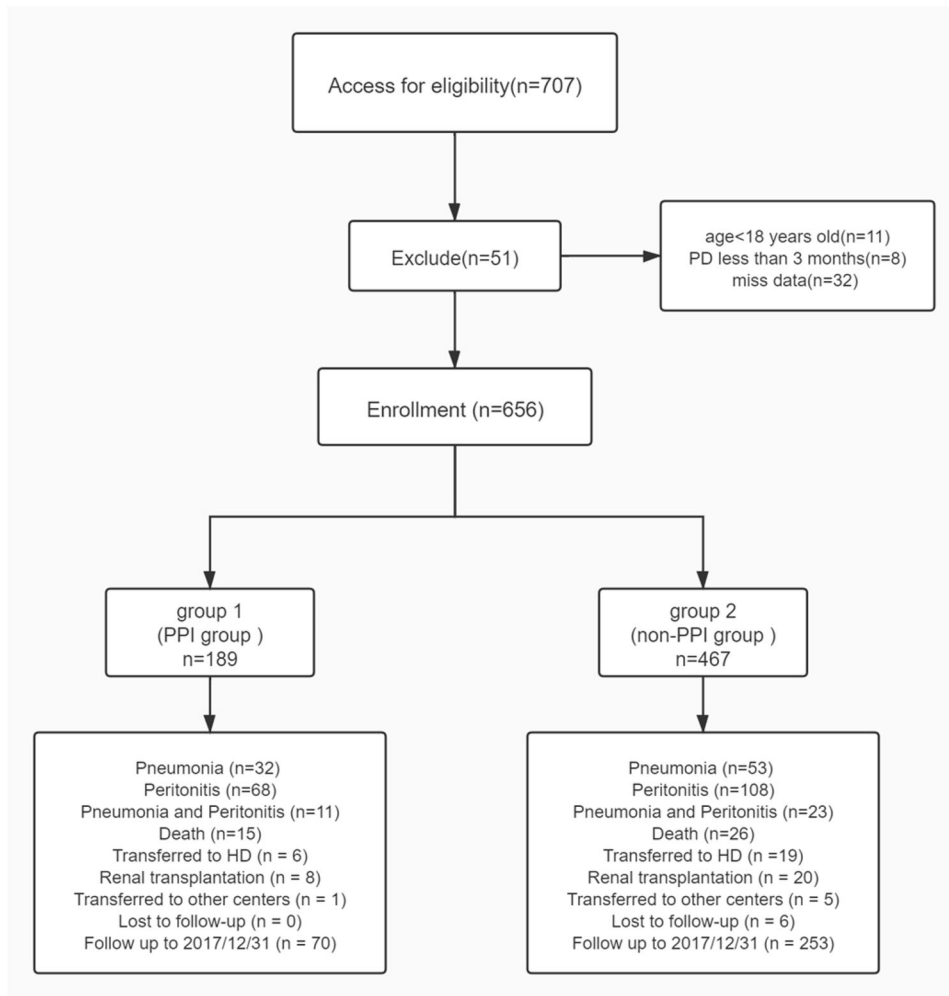


Figure 1. Flow chart- including patient enrollment and outcomes.

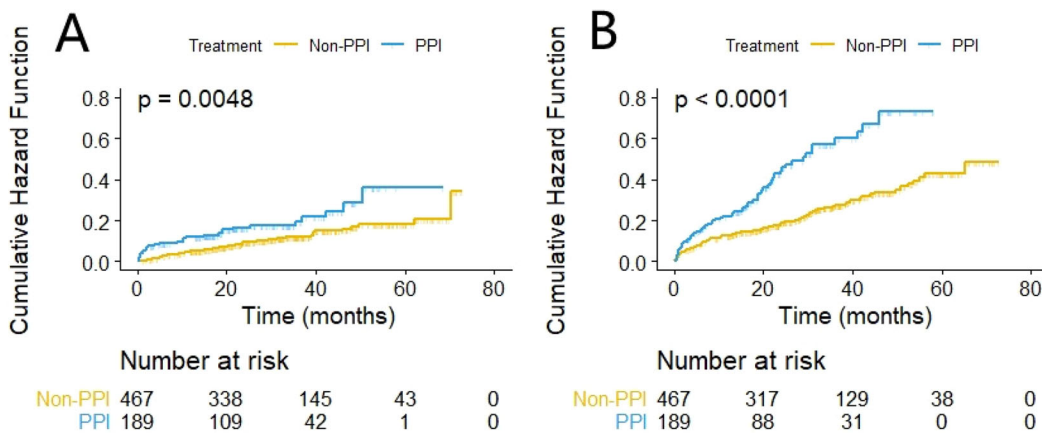


Figure 2. Comparison of the first occurrence of the Pneumonia disease (A) and the Peritonitis disease (B), using Kaplan–Meier method, between patients in the PPI group (n = 189) and the non-PPI group (n = 467).

1.58, 95% CI [1.18-2.12], $p = 0.002$) and the first occurrence of peritonitis (HR 2.33, 95% CI [1.91-2.85], $p < 0.001$) (Table 2). In addition, the cumulative incidence of first pneumonia and peritonitis events after IPTW-adjusted was also statistically different between

the two groups (log-rank test: $p = 0.002$, $p < 0.001$, respectively) (Figure 3).

In the competitive risk model, the difference in the cumulative incidence function (CIF) of first pneumonia and peritonitis event between the PPI group and

non-PPI group was statistically significant ($p = 0.009$, $p < 0.001$, respectively), and the difference in other end-points was not statistically significant (Figure 4).

We investigated the relationship between PPIs and the first occurrence of pneumonia and peritonitis in different subgroups of interest, including gender, age, and history of diabetes. Used COX analysis to explore whether there were statistical differences in the subgroups, and expressed them by forest plot. After analysis, no interaction was found in these subgroups (Figure 5).

Discussion

In the PD population, PPIs was mainly used to treat or prevent peptic ulcers, gastrointestinal bleeding, severe gastrointestinal reactions during dialysis, and preventive stomach protection with anti-platelet drugs or non-steroidal drugs [16, 17]. In this retrospective observational study, we used the IPTW method to test the effect of PPI usage on the first episode of pneumonia

and peritonitis in PD patients. Our results showed that in PD patients, PPIs was associated with an increased risk of first pneumonia and peritonitis events.

Existing studies on PPIs and pneumonia were mainly for the general population, stroke population or people with diabetes, while the research on PPIs and peritonitis was mainly focused on people with hepatic cirrhosis. Few researches have been conducted on this specific population of dialysis. In a large retrospective cohort study of the stroke population in Taiwan, it was found that the use of acid-suppressing drugs was an independent risk factor of pneumonia, and only the use of PPI could increase the risk of chronic stroke-associated pneumonia (SAP) [18]. Lin *et al.* found that PPI usage increased the incidence of pneumonia in patients with type 2 diabetes, and this effect was more significant in patients taking high-dose PPIs [19]. Consistent with previous research results, our findings suggested that in the adjusted model, the risk of first pneumonia events was 1.58 times higher in the PPI group than in the non-PPI group.

The mechanism of PPIs associated with pneumonia may be explained by the following reasons. As we all know, gastric acid acted as an important barrier to prevent pathogens from invading due to its lowering of the PH value of the gastrointestinal tract. PPIs inhibited the secretion of gastric acid mainly by irreversibly binding the H-K-ATPase on the cell membrane of the gastric parietal to inactivate it, thus increasing the pH value of the stomach, which in turn led to the excessive growth and colonization of pathogens [20–22]. And PPIs also reduced the acidity of the upper gastrointestinal tract, which changed the oral flora and further led to respiratory infections [23, 24]. In addition, a basic study in mice has found that the intestinal microbiota acts as a protective mediator during pneumococcal pneumonia, and the gut microbiota enhances the function of primary alveolar macrophages [25]. In a large cohort study

Table 2. The relationship between PPI and the Pneumonia disease and Peritonitis disease.

	Pneumonia		Peritonitis	
	HR(95%CI)	p Value	HR(95%CI)	p Value
Unadjusted	1.87 (1.20-2.92)	0.006	2.07 (1.53-2.82)	<0.001
Model1	2.33 (1.44-3.75)	0.001	1.91 (1.38-2.65)	<0.001
Model2	1.66 (1.04-2.66)	0.035	1.66 (1.20-2.29)	0.002
Model3	1.71 (1.06-2.76)	0.027	1.73 (1.24-2.40)	0.001
IPTW	1.58 (1.18-2.12)	0.002	2.33 (1.91-2.85)	<0.001

Note: Reference group is Non-PPI group.

Model 1: center, sex, age, BMI.

Model 2: Model 1 plus Comorbid conditions ((HBP, DM, Cardiovascular diseases, Gastrointestinal bleeding), Medications (CCB, statin, EPO, Insulin, Aspirin).

Model 3: Model 2 plus albumin, BUN, p, KTV, RRF.

PPI: proton pump inhibitor; HR: hazard ratio; CI: confidence interval; IPTW: inverse probability of treatment weighting; HBP: high blood pressure; DM: diabetes mellitus; CVE: cardiovascular events; EPO: erythropoietin; CCB: calcium channel blocker; BUN: blood urea nitrogen; KT/V, K-dialyzer clearance of urea, T-dialysis time, V-volume of distribution of urea; RRF: residual renal function.

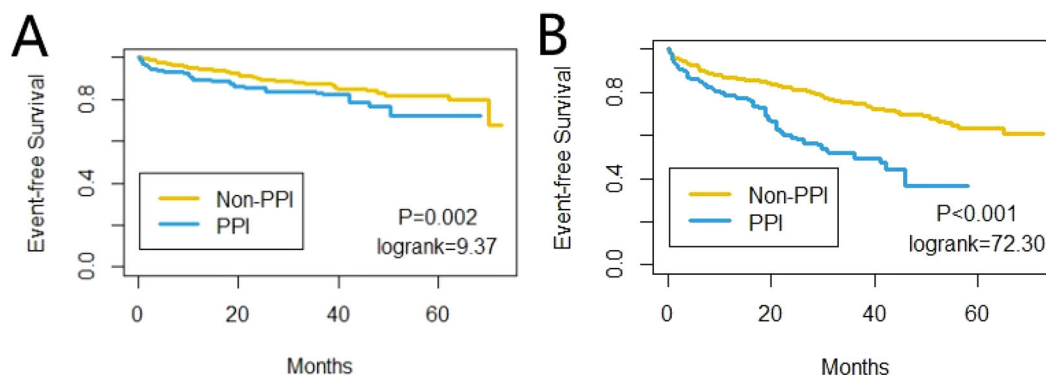


Figure 3. Comparison of the first occurrence of the Pneumonia disease (A) and the Peritonitis disease (B), adjusted using inverse-probability of treatment weighting, between patients in the PPI group and the non-PPI group.

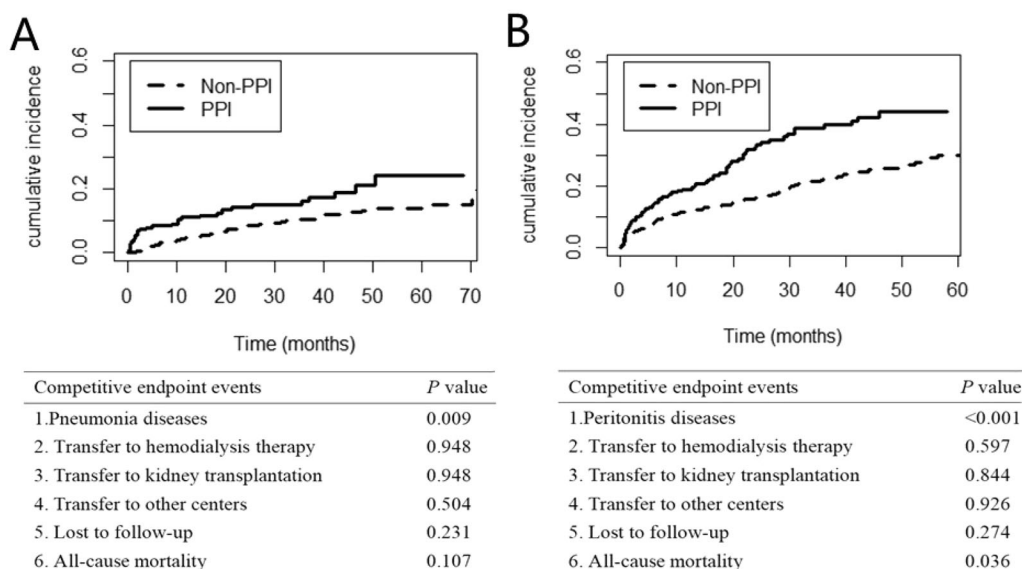


Figure 4. (A) Estimated cumulative incidence curves between the Pneumonia diseases and other competing events. (B) Estimated cumulative incidence curves between the Peritonitis diseases and other competing events.

of healthy people, it was found that PPI use significantly increased the growth of streptococci [26], while studies on streptococcal pneumonia confirmed that PPIs were associated with an increased risk of CAP caused by streptococcus pneumonia infection [27]. There was also evidence that acid inhibitors may damage immune cell function, including T lymphocytes, neutrophils, or natural killer cells [28–32], which may increase the body's susceptibility to infection [33].

In patients with liver cirrhosis, the use of PPI was closely related to the occurrence of peritonitis, which has been confirmed in many studies [34, 35]. However, there was less literature on the relationship between acid inhibitors and peritonitis associated with peritonitis in PD population, and the results were conflicting. A single-center retrospective analysis compared the use of acid inhibitors in PD patients with peritonitis and non-peritonitis, and the results showed that only H2RAs, rather than PPIs, was associated with an increased risk of PD-associated peritonitis [36]. Caravaca *et al.* found that the use of gastric acid suppression was an independent risk factor for intestinal peritonitis [37]. A recent Japanese study indicated that the use of PPI was significantly related to PD-related peritonitis [15].

Our study concluded that PD patients using PPIs were more likely to suffer from the PD-related peritonitis event. The pathophysiological mechanism was still under investigation. In addition to the several mechanisms mentioned above, that is, PPIs promoted the growth and colonization of intestinal bacteria by reducing the pH value of the gastrointestinal tract and directly affected the susceptibility of the body to the inflammatory cells. PPIs can also promote the

occurrence of peritonitis by affecting the types of gastrointestinal flora. Genetic sequencing revealed that PPIs significantly increased certain bacterial groups, including *Streptococcus* and *Enterococcus*, which were risk factors for intestinal disease [38]. Takagi T *et al.* found that the population of *Faecalibacterium* genera among PPI users was excessively reduced [21]. Besides, studies have found that butyrate, a product of the *Faecalibacterium*, enhanced the intestinal mucosal barrier function and immune function [39]. The combination of these factors may explain the use of PPIs to allow bacteria to easily translocate through the damaged barrier of the intestine to the peritoneal cavity to cause infection [11].

Elderly PD patients had multiple comorbidities, increased catabolism, high protein energy consumption, severe daily protein loss through PD, and were more prone to infection events [40]. The most common infectious event in PD patients was peritonitis. The same is true in our study, where the incidence of peritonitis was 26.8% higher than the incidence of pneumonia at 12.4%. In addition, many retrospective reports have identified diabetes mellitus, old age, comorbidities, and hypoalbuminemia as independent risk factors for PD-related peritonitis, which was why peritonitis was more likely to occur [41].

Our article has several advantages. First of all, our study included long-term PD populations from two large hospitals, so our sample size was large and the average follow-up time was long. Moreover, we used the statistical method of IPTW to eliminate the bias caused by confounding factors. In addition, we defined the use of PPI as the use of drugs for at least 1 week to

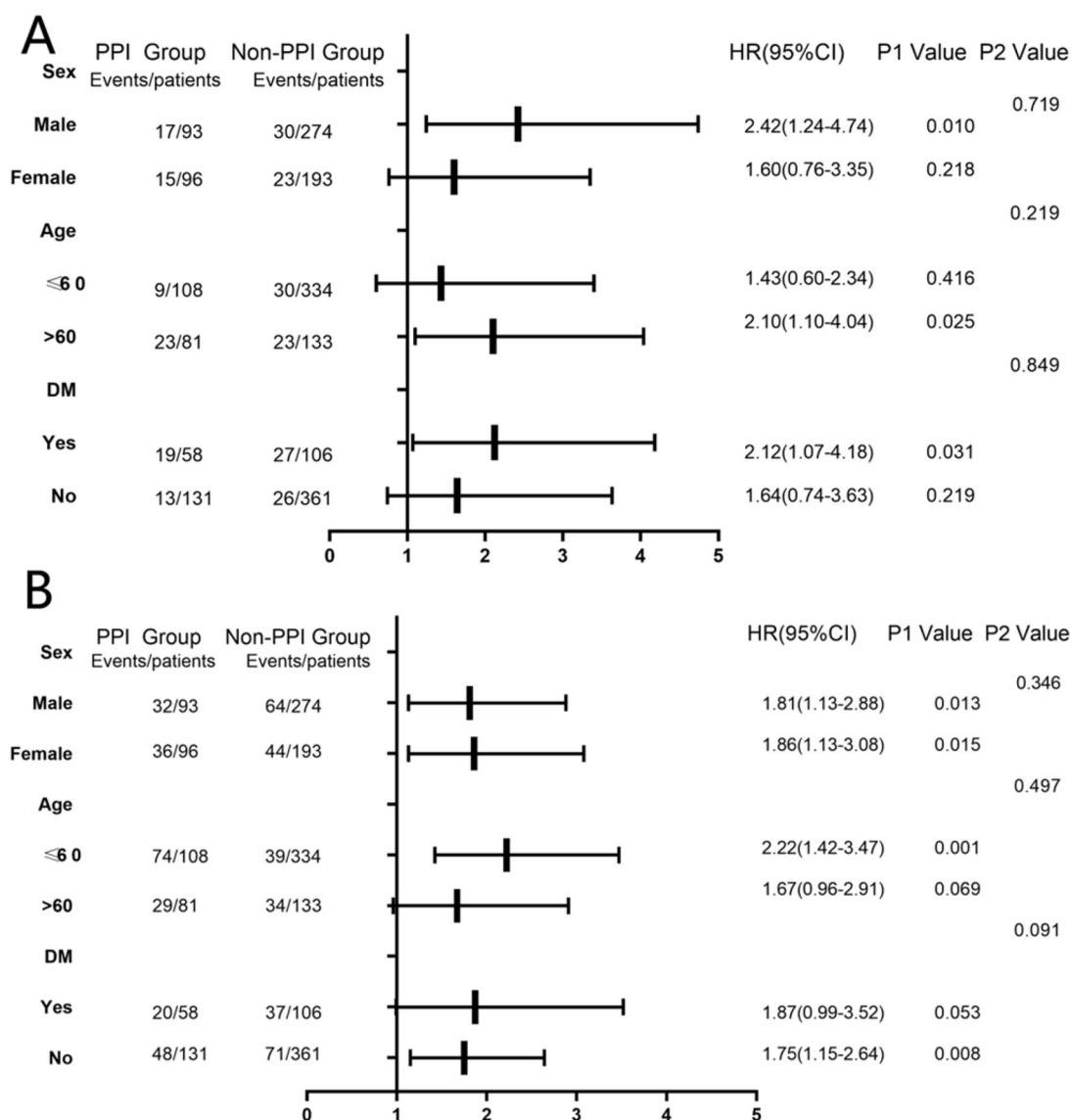


Figure 5. (A) Forest plot of relationship between PPI and the pneumonia diseases in different subgroups. (B) Forest plot of relationship between PPI and the peritonitis diseases in different subgroups. The P1 value corresponds to the relationship between PPI and the pneumonia diseases(A) or peritonitis diseases(B) in different subgroups. The P2 value corresponds to the interaction test between the PPI and the subgroups variable of interest. **Adjusted model:** center, sex, age, BMI, the history of hypertension, diabetes mellitus, cardiovascular events and gastrointestinal bleeding, the use of statin, Insulin, Aspirin, EPO and CCB, albumin, BUN, p, KTV, RRF (In particular, the adjustment model should exclude its own factors in different subgroups. For example, in the age subgroup, the adjustment model does not include age), HR: hazard ratio; CI: confidence interval.

prevent the protopathic bias to avoid reverse causality. Finally, we found that the use of PPIs may increase the incidence of first pneumonia and PD-related peritonitis in PD population. Although the relationship between PPIs and PD-related peritonitis is still controversial, considering the differences in intestinal flora caused by dietary habits, living environment and genes between Asian and Western populations [42, 43], it may further affect the occurrence of peritonitis [11]. So our study has certain clinical significance [15].

There were three main limitations in our article. First, we did not record the type, dose and specific course of PPIs in our data, nor did we record the relevant information of over-the-counter PPIs drugs, so the impact of PPIs may be underestimated. Second, we did not include the types of microorganisms that cause peritonitis infection, so it was impossible to study the relationship between flora and peritonitis. Third, our study was a retrospective study, prone to bias associated with confounding variable adjustment. Although our study used propensity matching to control for known

confounders as much as possible, such biases may still exist if there were unmeasured or unknown confounders.

Conclusions

The results of this population-based retrospective cohort study indicate that PPIs may be associated with an increased risk of first pneumonia and PD-related peritonitis events in PD patients, and nephrologists should be cautious when prescribing PPIs. Prospective clinical trials are needed to further clarify the association of PPIs with increased risk of infection as a guideline for clinicians.

Human and animal rights

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 2022-hg-ks-01), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data was obtained with the consent of all centers, and the data in this study are true and reliable.

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