International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Researcher Article *DOI: 10.61336/im/26-07-188*

Association Between Long-Term Proton Pump Inhibitor Use and Risk of Chronic Kidney Disease: A Prospective Cohort Study.

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Received: 14-06-2026
Revised: 24-06-2026
Accepted: 03-07-2026
Published: 06-07-2026

Abstract

Background: Proton pump inhibitors are widely used for acid-related disorders, although prolonged exposure has been linked to adverse renal outcomes. Prospective evidence from Indian clinical settings remains limited. ***Objectives:*** To evaluate the association between long-term proton pump inhibitor use and incident chronic kidney disease and identify independent predictors of renal-function decline. ***Methods:*** This prospective cohort included 100 adults without pre-existing chronic kidney disease: 50 long-term proton pump inhibitor users and 50 non-users. Participants were followed for 24 months. Serum creatinine and estimated glomerular filtration rate were assessed at baseline and follow-up. Incident chronic kidney disease, a reduction of at least 30% in estimated glomerular filtration rate, and acute kidney injury were recorded. Modified Poisson regression with robust standard errors estimated adjusted risk ratios. ***Results:*** Baseline characteristics and renal function were comparable between groups. At 24 months, proton pump inhibitor users had higher serum creatinine (1.18 ± 0.34 versus 1.02 ± 0.23 mg/dL; p=0.007), lower estimated glomerular filtration rate (77.4 ± 16.8 versus 85.9 ± 15.2 mL/min/1.73 m^2; p=0.009), and greater estimated glomerular filtration rate reduction (11.2 ± 8.9 versus 4.5 ± 6.8 mL/min/1.73 m^2; p<0.001). Incident chronic kidney disease occurred in 14 users and four non-users. Long-term use remained independently associated with chronic kidney disease (adjusted risk ratio 3.10; 95% confidence interval 1.15–8.37; p=0.025). ***Conclusion:*** Long-term proton pump inhibitor exposure was associated with greater renal-function decline and a higher risk of incident chronic kidney disease. Regular review of treatment indications and renal monitoring are warranted in chronic users.

Keywords: proton pump inhibitors; chronic kidney disease; estimated glomerular filtration rate; renal safety; prospective cohort; pharmacoepidemiology.

INTRODUCTION

Proton pump inhibitors (PPIs) suppress gastric acid secretion by irreversibly inhibiting the hydrogen-potassium adenosine triphosphatase pump in gastric parietal cells. Their potent and sustained acid suppression has established them as central therapies for gastro-oesophageal reflux disease, peptic ulcer disease, Helicobacter pylori eradication regimens, prevention of non-steroidal anti-inflammatory drug-related ulcers, and selected hypersecretory disorders. Despite substantial clinical benefit, PPIs are frequently continued beyond the recommended duration or prescribed without a clearly documented indication. Such exposure is important because even uncommon adverse effects can produce a meaningful population burden when a drug class is used extensively and for prolonged periods.1,2

Renal injury linked to PPI treatment was initially recognised through reports of acute interstitial nephritis. This reaction often has a subacute presentation, lacks the classic hypersensitivity features, and can remain undetected until serum creatinine has increased substantially. Population-based investigations subsequently reported higher rates of acute interstitial nephritis and acute kidney injury among PPI users.5,6 Incomplete recovery after an unrecognised or recurrent renal insult provides a biologically plausible pathway from acute tubular-interstitial injury to chronic loss of kidney function.

Large observational studies have extended this concern to incident chronic kidney disease (CKD). Lazarus and colleagues reported a higher risk of CKD among PPI users in both a community-based cohort and a replication cohort.3 Xie et al. similarly found associations with incident CKD, substantial estimated glomerular filtration rate (eGFR) decline, disease progression, and end-stage renal disease when PPI users were compared with histamine-2 receptor antagonist users.4 Later studies identified possible exposure-response relationships involving treatment duration or cumulative use, while findings

in diabetic populations strengthened concern among patients already susceptible to renal injury.7-10 More recent prospective analyses and meta-analyses have generally supported a modest increase in CKD risk, although heterogeneity and residual confounding remain important limitations.11-13

The clinical interpretation of this evidence requires caution. PPI users commonly have greater comorbidity, polypharmacy, health-care contact, and exposure to potentially nephrotoxic drugs. Confounding by indication and surveillance bias therefore complicate causal attribution. Moreover, Indian prospective data describing serial changes in serum creatinine and eGFR among chronic PPI users are scarce. Locally generated evidence is relevant because prescribing patterns, access to over-the-counter PPIs, comorbidity profiles, and laboratory follow-up differ across health systems.

The present study aimed to determine whether long-term PPI use was associated with a higher incidence of CKD during 24 months of follow-up among adults without baseline CKD. Secondary objectives were to compare changes in serum creatinine and eGFR between long-term users and non-users, assess the occurrence of acute kidney injury and a reduction of at least 30% in eGFR, and identify independent predictors of incident CKD after adjustment for major clinical confounders.

MATERIALS AND METHODS

Study design and setting: This prospective cohort study was conducted at Prathima Institute of Medical Sciences, Karimnagar, Telangana, India. To accommodate the prespecified 24-month follow-up, recruitment was undertaken from October 2023 to April 2024, and follow-up was completed by April 2026. The manuscript was prepared in accordance with accepted reporting principles for observational cohort studies.

Study population: Adults aged 18 years or older who had normal baseline kidney function and were receiving care at the institute were screened consecutively. Long-term PPI users were defined as participants with documented continuous use of pantoprazole, omeprazole, or esomeprazole for at least 12 months before enrolment. Non-users had no PPI exposure during the preceding 12 months. Fifty eligible participants were included in each cohort. Individuals with pre-existing CKD, previous kidney replacement therapy, acute kidney injury within three months before enrolment, structural renal disease, active malignancy receiving nephrotoxic chemotherapy, incomplete baseline renal data, pregnancy, or inability to complete follow-up were excluded.

Data collection and follow-up: Demographic characteristics, body mass index, smoking status, diabetes mellitus, hypertension, regular non-steroidal anti-inflammatory drug use, PPI type, and duration of exposure were recorded using a structured case-record form. Serum creatinine was measured at baseline and at 6, 12, 18, and 24 months. eGFR was calculated using the 2021 CKD Epidemiology Collaboration creatinine equation without a race coefficient.14 Investigators reviewing renal outcomes used the same laboratory definitions in both cohorts.

Outcome definitions: The primary outcome was incident CKD, defined as an eGFR below 60 mL/min/1.73 m^2 on at least two measurements separated by three months in a participant without CKD at baseline. Secondary outcomes were serum creatinine and eGFR at 24 months, absolute eGFR reduction, a decline of at least 30% from baseline eGFR, and acute kidney injury. Acute kidney injury was defined as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours or at least 1.5 times the baseline value within seven days.

Statistical analysis: Continuous variables were expressed as mean ± standard deviation or median with interquartile range, according to distribution, and categorical variables as frequencies and percentages. Independent-samples t tests compared continuous variables, while chi-square or Fisher exact tests compared categorical variables. Cumulative incidence and unadjusted risk ratios with 95% confidence intervals were calculated. Modified Poisson regression with robust standard errors estimated adjusted risk ratios for incident CKD. The model included PPI exposure, diabetes mellitus, hypertension, age of at least 60 years, and baseline eGFR. A two-sided p-value below 0.05 indicated statistical significance. Analyses included all enrolled participants, and no outcome data were missing.

Ethical considerations: Necessary Permissions were obtained before starting the study. Written informed consent was obtained from every participant, and study data were analysed without personal identifiers.

RESULTS

Participant recruitment and follow-up

During the study period, 108 adults were assessed for eligibility. Eight individuals were excluded: four had pre-existing chronic kidney disease, two had incomplete baseline renal-function data, and two declined participation. The remaining 100 participants were enrolled in the prospective cohort. Of these, 50 were long-term PPI users and 50 were non-users. All participants completed the 24-month follow-up and were included in the final analysis.

Among long-term PPI users, the median duration of treatment before enrolment was 22 months (interquartile range: 14–36 months). Pantoprazole was the most frequently used agent, reported in 29 (58.0%) participants, followed by omeprazole in 13 (26.0%) and esomeprazole in 8 (16.0%).

Baseline characteristics

The mean age of the study population was 55.0 ± 10.9 years, and 56 (56.0%) participants were males. The mean age was 55.8 ± 10.6 years among PPI users and 54.1 ± 11.2 years among non-users (p=0.438). Baseline demographic characteristics, comorbidities, body mass index, serum creatinine, and eGFR were comparable between the groups. Diabetes mellitus was present in 14 (28.0%) PPI users and 12 (24.0%) non-users, while hypertension was documented in 20 (40.0%) and 18 (36.0%) participants, respectively. No statistically significant between-group differences were observed in smoking status or regular non-steroidal anti-inflammatory drug use (Table 1).

Table 1. Baseline characteristics of the study groups

Characteristic	Long-term PPI users (n=50)	Non-users (n=50)	p-value
Age, years, mean ± SD	55.8 ± 10.6	54.1 ± 11.2	0.438
Age ≥60 years	11 (22.0)	9 (18.0)	0.617
Male sex	29 (58.0)	27 (54.0)	0.687
Body mass index, kg/m², mean ± SD	25.9 ± 3.8	25.2 ± 3.6	0.347
Diabetes mellitus	14 (28.0)	12 (24.0)	0.648
Hypertension	20 (40.0)	18 (36.0)	0.680
Current smoking	11 (22.0)	9 (18.0)	0.617
Regular NSAID use	13 (26.0)	12 (24.0)	0.817
Serum creatinine, mg/dL, mean ± SD	0.91 ± 0.16	0.88 ± 0.15	0.336
Baseline eGFR, mL/min/1.73 m², mean ± SD	88.6 ± 13.9	90.4 ± 14.2	0.523

Values are presented as n (%) unless otherwise specified. PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Changes in renal function during follow-up

At 24 months, participants receiving long-term PPI therapy had a significantly higher mean serum creatinine than non-users (1.18 ± 0.34 versus 1.02 ± 0.23 mg/dL; p=0.007). Correspondingly, mean eGFR was significantly lower among PPI users (77.4 ± 16.8 versus 85.9 ± 15.2 mL/min/1.73 m²; p=0.009).

The mean reduction in eGFR from baseline was 11.2 ± 8.9 mL/min/1.73 m² in the PPI group compared with 4.5 ± 6.8 mL/min/1.73 m² among non-users (p<0.001). A decline of at least 30% from baseline eGFR occurred in 11 (22.0%) PPI users and 3 (6.0%) non-users (p=0.041). Acute kidney injury was recorded in 8 (16.0%) PPI users and 2 (4.0%) non-users. Although acute kidney injury was more frequent among PPI users, the difference did not reach statistical significance (p=0.092) (Table 2).

Table 2. Renal outcomes during the 24-month follow-up

Outcome	Long-term PPI users (n=50)	Non-users (n=50)	p-value
Serum creatinine at 24 months, mg/dL	1.18 ± 0.34	1.02 ± 0.23	0.007
eGFR at 24 months, mL/min/1.73 m²	77.4 ± 16.8	85.9 ± 15.2	0.009
Reduction in eGFR, mL/min/1.73 m²	11.2 ± 8.9	4.5 ± 6.8	<0.001
≥30% reduction in eGFR	11 (22.0)	3 (6.0)	0.041
Acute kidney injury	8 (16.0)	2 (4.0)	0.092
New-onset chronic kidney disease	14 (28.0)	4 (8.0)	0.017

Continuous variables are presented as mean ± standard deviation and categorical variables as n (%). PPI, proton pump inhibitor; eGFR, estimated glomerular filtration rate.

Incidence of chronic kidney disease

New-onset CKD developed in 18 of the 100 participants, corresponding to an overall cumulative incidence of 18.0%. CKD occurred in 14 (28.0%) long-term PPI users compared with 4 (8.0%) non-users. Long-term PPI use was associated with a 3.5-fold higher unadjusted risk of CKD compared with non-use (risk ratio: 3.50; 95% confidence interval: 1.24–9.90; p=0.018). The absolute difference in CKD risk between the groups was 20.0 percentage points (95% confidence interval: 5.5–34.5 percentage points).

Among the 18 participants who developed CKD, 7 (38.9%) had diabetes mellitus, 9 (50.0%) had hypertension, and 7 (38.9%) were aged 60 years or older.

Predictors of chronic kidney disease

Modified Poisson regression with robust standard errors was performed to identify factors independently associated with incident CKD. Variables entered into the multivariable model were PPI exposure, diabetes mellitus, hypertension, age of at least 60 years, and baseline eGFR.

After adjustment for potential confounders, long-term PPI use remained independently associated with CKD, with an adjusted risk ratio of 3.10 (95% confidence interval: 1.15–8.37; p=0.025). Diabetes mellitus was associated with an adjusted risk ratio of 2.91 (95% confidence interval: 1.38–6.15; p=0.005), and age of at least 60 years was associated with an adjusted risk ratio of 2.47 (95% confidence interval: 1.18–5.19; p=0.017). For every 10 mL/min/1.73 m² lower baseline eGFR, the adjusted risk of CKD increased by approximately 74% (adjusted risk ratio: 1.74; 95% confidence interval: 1.36–2.24; p<0.001). Hypertension was not independently associated with the outcome (Table 3).

Table 3. Regression analysis of factors associated with incident chronic kidney disease

Predictor	Unadjusted RR (95% CI)	p-value	Adjusted RR (95% CI)	p-value
Long-term PPI use	3.50 (1.24–9.90)	0.018	3.10 (1.15–8.37)	0.025
Diabetes mellitus	1.81 (0.79–4.18)	0.164	2.91 (1.38–6.15)	0.005
Hypertension	1.63 (0.71–3.75)	0.248	1.45 (0.69–3.05)	0.333
Age ≥60 years	2.55 (1.13–5.73)	0.024	2.47 (1.18–5.19)	0.017
Each 10 mL/min/1.73 m² lower baseline eGFR	1.68 (1.35–2.10)	<0.001	1.74 (1.36–2.24)	<0.001

RR, risk ratio; CI, confidence interval; PPI, proton pump inhibitor; eGFR, estimated glomerular filtration rate.

DISCUSSION

In this prospective cohort, long-term PPI users experienced a greater deterioration in renal function than non-users over 24 months. Serum creatinine was higher, eGFR was lower, and the absolute reduction in eGFR was more pronounced in the exposed cohort. Incident CKD occurred in 28.0% of PPI users compared with 8.0% of non-users. After adjustment for age, diabetes, hypertension, and baseline eGFR, long-term PPI exposure remained independently associated with incident CKD. Diabetes, older age, and lower baseline eGFR were additional independent predictors.

These findings are directionally consistent with major population-based studies. Lazarus et al. observed a higher incidence of CKD among PPI users across two cohorts, with adjusted estimates indicating a modest elevation in risk.3 In a large cohort of United States veterans, Xie and colleagues reported associations between PPI exposure and incident CKD, eGFR decline, disease progression, and end-stage renal disease.4 Klatte et al. also found that PPI initiation and cumulative exposure were associated with CKD progression when compared with histamine-2 receptor antagonist therapy.7 Studies examining duration and dose, as well as diabetic populations, have further suggested that cumulative exposure and underlying metabolic risk influence renal outcomes.8-10

The adjusted risk ratio in the present study was larger than the pooled estimates reported in recent meta-analyses.12,13 Several factors can explain this difference. The cohort was small, producing a wide confidence interval, and long-term exposure was defined by documented continuous treatment before enrolment. The observed estimate could also reflect local prescribing patterns, concurrent nephrotoxic exposures, or unmeasured differences between users and non-users. Accordingly, the magnitude should not be interpreted as proof of a threefold causal effect.

A plausible pathway involves PPI-associated acute interstitial nephritis, which can present without fever, rash, or eosinophilia and remain clinically unrecognised.6 Population data have also linked PPI initiation to acute kidney injury.5 Recurrent or unresolved tubular-interstitial inflammation can result in fibrosis and incomplete restoration of glomerular filtration. Nevertheless, long-term kidney decline has also been reported without a recorded intervening acute kidney injury, suggesting that unrecognised episodes or other mechanisms contribute.4 Hypomagnesaemia, endothelial dysfunction, altered gut-derived metabolites, and oxidative stress have been proposed, but direct mechanistic confirmation remains incomplete.

The identification of diabetes, age of at least 60 years, and lower baseline eGFR as independent predictors is clinically coherent. These characteristics reduce renal reserve and increase vulnerability to medication-related injury. The results support periodic reassessment of PPI indications, avoidance of unnecessary continuous therapy, and renal-function

surveillance in patients requiring prolonged treatment. However, PPIs should not be discontinued solely because of observational associations when a valid indication exists. The therapeutic benefit, gastrointestinal bleeding risk, and availability of dose reduction or alternative acid suppression should guide individual decisions.2,13

LIMITATIONS

This study was limited by its single-centre setting, modest sample size, and non-randomised exposure allocation. Residual confounding from PPI indication, adherence, dietary factors, hydration, and unrecorded nephrotoxic medicines remained possible. Albuminuria and cystatin C were not assessed, and the cohort lacked sufficient power for agent-specific comparisons. The 24-month observation period also restricted evaluation of end-stage kidney disease and long-term reversibility.

CONCLUSION

Long-term proton pump inhibitor use was associated with a greater decline in estimated glomerular filtration rate and a higher cumulative incidence of chronic kidney disease during 24 months of observation. The relationship persisted after adjustment for age, diabetes mellitus, hypertension, and baseline renal function. Older age, diabetes, and lower initial estimated glomerular filtration rate identified participants at increased risk. These findings support confirmation of the treatment indication, use of the lowest effective dose, and renal-function assessment during prolonged therapy. Because exposure was not randomised and the cohort was small, the results demonstrate association rather than causation. Larger multicentre prospective studies should clarify dose-response patterns, agent-specific effects, and reversibility after deprescribing.

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