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Original Article

Lower *Helicobacter pylori* infection rate in chronic kidney disease and end-stage renal disease patients with peptic ulcer disease

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Abstract

Background: Distinguishing the rates of *Helicobacter pylori* infection in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients with peptic ulcer disease (PUD) from that in PUD patients without CKD is critical.
Methods: We first stratified the original 1 million study population according to CKD or ESRD. We retrospectively investigated the incidence of *H. pylori* infection in PUD patients with or without CKD or ESRD between 2000 and 2008 in a nationwide, population-based cohort using data from the Taiwan National Health Insurance Research Database. The comparison cohort consisted of PUD patients without CKD. A logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals, to determine whether the occurrence of *H. pylori* infection in CKD or ESRD patients with PUD differed from that of PUD patients without CKD.
Results: Among the CKD patients, 261 patients had *H. pylori*-positive and 185 *H. pylori*-negative peptic ulcers. Among the ESRD patients, 81 had *H. pylori*-positive and 63 *H. pylori*-negative peptic ulcers. Among the non-CKD control patients, 1658 patients had *H. pylori*-positive and 702 *H. pylori*-negative peptic ulcers. Our results revealed a lower *H. pylori* infection rate in CKD (OR = 0.64, $p < 0.001$) and ESRD (OR = 0.54, $p = 0.001$) patients with PUD than in PUD patients without CKD.
Conclusion: The *H. pylori* infection rate is lower in PUD patients with CKD and ESRD than in those without CKD.

Keywords: chronic kidney disease; end-stage renal disease; *H. pylori*; lower; peptic ulcers

1. Introduction

Uremic patients exhibit a higher incidence of peptic ulcer disease (PUD) than nonuremic patients.[1–3] *Helicobacter pylori* plays a central role in the development of chronic gastritis, gastric ulcers, duodenal ulcers, and gastric cancer.[4–6] The difference in *H. pylori* infection rates between uremic and nonuremic patients with PUD warrants further investigation.

Increased gastrin level,[7] gastric acid hypersecretion,[8] and gastric acid hyposecretion[9] are relevant to the pathology of gastrointestinal lesions in uremic patients. Interactions among hosts, pathogens, and environmental factors are crucial to *H. pylori* colonization.[10,11] Studies on *H. pylori* infection in uremic patients have reported infection rates to vary from 27% to 73.0%.[1,3,12–18] The variation might have been caused by small sample size, nonuniform duration of dialysis, varying methodologies, and different enrollment criteria.

Distinguishing the rates of *H. pylori* infection in chronic kidney disease (CKD) and end-stage renal disease (ESRD)

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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patients with PUD from those in PUD patients without CKD is critical. Neither a large clinical trial nor a nationally representative observational study has been conducted to address this health care concern. Therefore, we analyzed *H. pylori* infection in patients with PUD, and grouped the participants as CKD, ESRD, and non-CKD patients. The objective of our study was to determine whether the risk of *H. pylori* infection among CKD and ESRD patients with PUD differs from that of non-CKD patients with PUD.

2. Methods

2.1. Ethics statement

In our study, all data that could be used to identify patients were obtained from the National Health Insurance (NHI) files. To ensure confidentiality of the data presented in our study, which was approved by the National Health Research Institute (NHRI), Taiwan, we adhered to the regulations of the Bureau of National Health Insurance, Taiwan. The Institutional Review Board (IRB) of Taipei City Hospital, Taipei, Taiwan approved this study (IRB Number: TCHIRB-1020424-E).

2.2. Study population

Our nationwide, population-based cohort consisted of patients selected from the National Health Insurance Database (NHID) from claims records collected between January 1, 2000 and December 31, 2008. The NHID, which is managed by the NHRI, contains health care data for approximately 23 million people, who constitute 99% of the residents of Taiwan. The National Health Insurance Research Database (NHIRD) is also managed by the NHRI, is updated annually, and consists of comprehensive data for a randomly selected sample of 1 million NHI beneficiaries, representing approximately 5% of all enrollees. The NHIRD contains comprehensive patient data, including demographic data, dates of clinical visits, diagnostic codes, and the details of medical prescriptions. The diagnoses used in the NHIRD are coded according to the diagnostic criteria of the International Classifications of Diseases, Revision 9, Clinical Modification (ICD-9-CM).

2.3. Study participants

We conducted a retrospective cohort study based on ambulatory care and inpatient discharge records in the NHIRD recorded between 2000 and 2008. We first stratified the original 1 million study population according to CKD or ESRD, and then analyzed the prevalence of *H. pylori* infection among the groups. We used ICD-9-CM codes (531.xx, 532.xx, or 533.xx) after the endoscopic examination to identify peptic ulcer patients. All patients with peptic ulcers that were endoscopically confirmed and clinically tested for the presence of *H. pylori*, based on the rapid urease test or hematoxylin and eosin histological staining, were considered for inclusion in our PUD cohort.

The PUD patients who were endoscopically diagnosed with peptic ulcers between January 1, 1997 and December 31, 1999 were identified as those having a history of peptic ulcer. Patients who had undergone gastrectomy or vagotomy, received a diagnosis of gastric cancer or Zollinger–Ellison syndrome between 1997 and 2008, and patients who had undergone *H. pylori* eradication therapy between 1997 and 1999 were excluded.

According to the reimbursement policy of the NHI, patients with a confirmed diagnosis of *H. pylori*-positive peptic ulcers are reimbursed for 7–14 days of *H. pylori* eradication therapy. In Taiwan, *H. pylori* infection is treated by performing a triple or quadruple therapy, consisting of proton pump inhibitors (PPIs) or histamine receptor-2 blockers (H_2 blockers), clarithromycin or tetracycline, and amoxicillin or metronidazole with or without bismuth. The PPIs used by the patients in our cohort included lansoprazole, esomeprazole, omeprazole, pantoprazole, and rabeprazole, and the H_2 blockers used included cimetidine, famotidine, nizatidine, ranitidine, and roxatidine.[19] Fig. 1 shows a flow chart depicting participant selection in our study.

2.4. H. pylori-associated peptic ulcers

Physicians are more likely to treat and test patients with PUDs according to clinical practice guidelines.[20] Therefore, patients diagnosed with PUD with *H. pylori* infection were defined as those who received 7–14 days of triple or quadruple therapy during the same outpatient treatment period or during the same hospitalization period. Patients without *H. pylori* infection were defined as those who were prescribed PPIs or H_2 blockers for a minimum of 3 consecutive months after undergoing gastroscopy and *H. pylori* diagnostic tests, but did not receive the other components of *H. pylori* eradication therapy during PPI or H_2 blocker treatment. We also excluded patients receiving PPIs, H_2 blockers, clarithromycin, tetracycline, amoxicillin, metronidazole, bismuth, levofloxacin, and refabutin 4 weeks prior to *H. pylori* testing from January 1, 2000 to December 31, 2008.

2.5. Definition of CKD and ESRD

In Taiwan, ESRD patients requiring dialysis can apply to receive a catastrophic illness card. Cardholders are exempt from the cost sharing required by the NHI program. ESRD patients were defined as the patients who had received a catastrophic illness card and claimed for hemodialysis or peritoneal dialysis for at least 3 months (ICD-9-CM 585). CKD patients were defined as the non-ESRD patients who were hospitalized at least once or presented for three or more outpatient visits, in which one or more of the following ICD-9-CM diagnostic codes were used: 585-589, 250.4, 274.1, 283.11, 403.x1, 404.x2, 404.x3, 440.1, 442.1, 447.3, 572.4, 642.1x, 646.2x, and 794.4.

2.6. Definition of the control group

To be defined as a non-CKD patient (control group), a person could not have the following ICD-9-CM codes in his or her

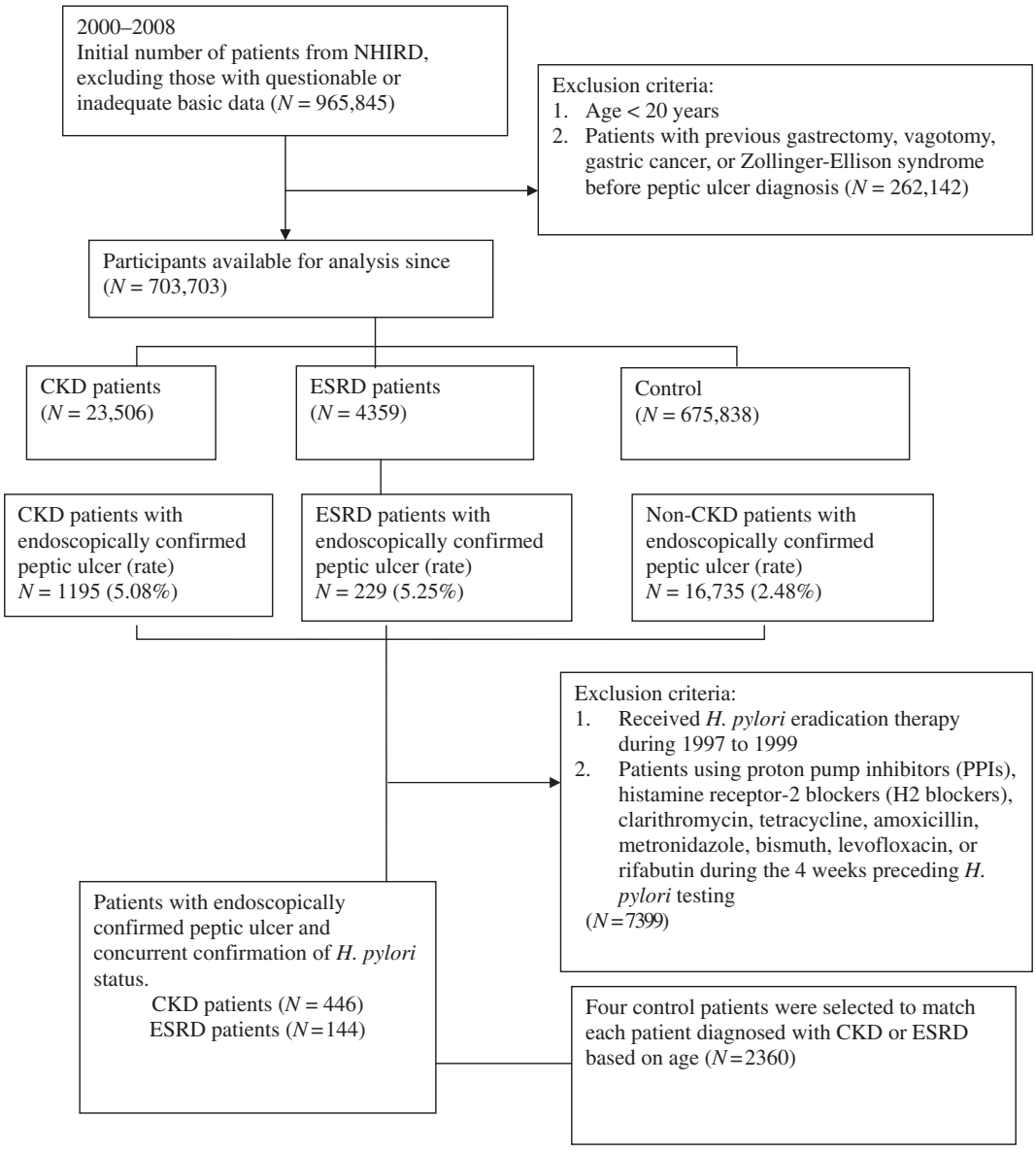

Fig. 1. Flowchart depicting the selection of participants.

inpatient records or in the ambulatory care claims: 580-589, 250.4, 274.1, 283.11, 403.x1, 404.x2, 404.x3, 440.1, 442.1, 447.3, 572.4, 642.1x, 646.2x, and 794.4. Four control patients were matched to each CKD or ESRD patient based on sex and age group (20–49 years and ≥50 years). The participants were categorized into CKD, ESRD, and control groups, based on when the ulcer events were identified using ICD-9-CM diagnosis codes.

2.7. Definition of peptic ulcer history

All CKD, ESRD, and non-CKD patients endoscopically diagnosed to have peptic ulcers during 1997–1999, based on ambulatory care and inpatient discharge records, were defined as those having a peptic ulcer history. Peptic ulcers were classified as gastric ulcers (ICD-9-CM 531.xx), duodenal ulcers (ICD-9-CM 532.xx), and nonspecific peptic ulcers (ICD-9-CM 533.xx) after endoscopic examination claim.

2.8. Comorbidities

Comorbidities were defined based on diagnostic codes identified in at least one inpatient discharge record or three or more ambulatory care claims. Comorbidities examined in our study included the following conditions: diabetes mellitus, ICD-9-CM 250; hypertension, ICD-9-CM 401-405; congestive heart failure, ICD-9-CM 428; coronary artery disease, ICD-9-CM 410-414; cerebral vascular disease, ICD-9-CM 430-438; and liver cirrhosis, ICD-9-CM 571.2, 571.5, and 571.6.

2.9. Medication use

Patients who used aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2-specific inhibitors, steroids, selective serotonin-reuptake inhibitors, clopidogrel, ticlopidine, or warfarin within 28 days prior to *H. pylori*

Table 1
Demographic and clinical characteristics of patients with peptic ulcer disease stratified according to CKD and ESRD status.

Variables	Control[b]		CKD[b]		ESRD[b]		*p*
	n = 2360	%	*n* = 446	%	*n* = 144	%	
Age (y)							0.102
20–49	276	11.69	45	10.09	24	16.67	
≥50	2084	88.31	401	89.91	120	83.33	
Sex							0.093
Male	1380	58.47	174	39.01	71	49.31	
Female	980	41.53	272	60.99	73	50.69	
Peptic ulcer history	169	7.16	29	6.50	5	3.47	0.223
Medication							
Aspirin	161	6.82	65	14.57	15	10.42	<0.001
NSAIDs	60	2.54	18	4.04	2	1.39	0.124
COX-2 inhibitors	87	3.69	19	4.26	7	4.86	0.680
Steroid	22	0.93	13	2.91	4	2.78	0.001
SSRIs	21	0.89	7	1.57	4	2.78	0.050
Other medications[a]	35	1.48	15	3.36	3	2.08	0.023
Comorbidities							
DM	379	16.06	229	51.35	65	45.14	<0.001
Hypertension	1090	46.19	316	70.85	104	72.22	<0.001
CHF	114	4.83	53	11.88	22	15.28	<0.001
CAD	512	21.69	173	38.79	53	36.81	<0.001
CVD	325	13.77	116	26.01	20	13.89	<0.001
Liver cirrhosis	70	2.97	16	3.59	5	3.47	0.756
H. pylori status							<0.001
H. pylori (−)	702	29.75	185	41.48	63	43.75	
H. pylori (+)	1658	70.25	261	58.52	81	56.25	

CAD = cardiovascular disease; CHF = congestive heart failure; CKD = chronic kidney disease; COX-2 inhibitors = cyclooxygenase-2-specific inhibitors; CVD = cerebral vascular disease; DM = diabetes mellitus; ESRD = end-stage renal disease; *H. pylori* (+) = *Helicobacter pylori* infection; *H. pylori* (−) = no *H. pylori* infection; *n* = number of patients; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin-reuptake inhibitors.

[a] Other medications were clopidogrel, ticlopidine, or warfarin.

[b] The raw ulcer rates were 2.48% in the control group, 5.08% in the CKD group, and 5.25% in the ESRD group.

testing between 2000 and 2008 were defined, respectively, as aspirin users, NSAID users, cyclooxygenase-2-specific inhibitors users, steroid users, selective serotonin-reuptake inhibitor users, clopidogrel users, ticlopidine users, or warfarin users.

2.10. Statistical analysis

The number and percentage of patients were calculated for the categorical variables, including age group, sex, medication use, peptic ulcer history, and comorbidities. The differences between the CKD, ESRD, and non-CKD study groups were compared using a χ^2 test. A logistic regression model was used to calculate the odds ratios (ORs) and the 95% confidence intervals (CIs) for the occurrence of *H. pylori* infection to determine whether CKD or ESRD was an independent factor in *H. pylori* infection in PUD patients. Risk factors with $p < 0.1$ in univariate logistic analysis were entered into the multivariate analysis. Age, sex, peptic ulcer history, medications, and comorbidities were included as variables in the model. All statistical analyses were performed using SAS for Windows, version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

Among the CKD patients, 261 had *H. pylori*-positive and 185 *H. pylori*-negative peptic ulcers. Among the ESRD patients, 81 had *H. pylori*-positive and 63 had *H. pylori*-negative peptic ulcers. Among the non-CKD control patients, 1658 had *H. pylori*-positive and 702 had *H. pylori*-negative peptic ulcers. A lower *H. pylori* infection rate was observed among the CKD (58.52%) and ESRD (56.25%) patients with PUD, compared with the non-CKD patients with PUD (70.35%). Table 1 lists other demographic data, including age, sex, peptic ulcer history, medication use, and comorbidities. Multivariate logistic regression analysis showed that CKD (OR = 0.64, $p < 0.001$) and ESRD (OR = 0.54, $p = 0.001$) were associated with a lower incidence of *H. pylori* infection in PUD patients, compared with that in PUD patients without CKD (Table 2). A peptic ulcer history (OR = 0.53, $p < 0.001$), NSAID use (OR = 0.62, $p = 0.043$), and liver cirrhosis (OR = 0.45, $p < 0.001$) were also associated with a lower incidence of *H. pylori* infection in PUD patients, compared with those in PUD patients without the respective comorbidity. The incidence of *H. pylori* infection is higher in PUD patients aged 20–49 years (OR = 2.28, $p < 0.001$) than in older patients.

4. Discussion

Our data showed a lower *H. pylori* infection rate in CKD and ESRD patients with PUD than in PUD patients without CKD. High serum urea nitrogen contributes to hypoacid secretion, and high gastric pH has been proposed as the cause

Table 2
Uni- and multivariate logistic regression results for predicting *Helicobacter pylori* infection in patients with peptic ulcer disease.

Variables	Univariate			Multivariate*		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (y)						
20–49 vs. ≥50	2.52	1.88–3.37	<0.001	2.28	1.68–3.10	<0.001
Sex						
Male vs. female	1.04	0.89–1.21	0.659	—	—	—
Kidney disease						
CKD vs. control	0.60	0.49–0.74	<0.001	0.64	0.51–0.81	<0.001
ESRD vs. control	0.54	0.39–0.77	<0.001	0.54	0.38–0.77	<0.001
Peptic ulcer history						
Yes vs. no	0.53	0.39–0.70	<0.001	0.53	0.40–0.72	<0.001
Aspirin						
User vs. nonuser	0.99	0.75–1.32	0.955	—	—	—
NSAIDs						
User vs. nonuser	0.54	0.35–0.85	0.007	0.62	0.40–0.99	0.043
COX-2 inhibitors						
User vs. nonuser	0.77	0.52–1.13	0.176	—	—	—
Steroid						
User vs. nonuser	0.45	0.24–0.84	0.012	0.58	0.30–1.11	0.101
SSRIs						
User vs. nonuser	0.91	0.44–1.89	0.792	—	—	—
Other medications[a]						
User vs. nonuser	0.53	0.31–0.91	0.021	0.61	0.35–1.07	0.086
DM						
Yes vs. no	0.75	0.63–0.90	0.002	1.02	0.83–1.24	0.876
Hypertension						
Yes vs. no	0.68	0.59–0.80	<0.001	0.89	0.75–1.06	0.198
CHF						
Yes vs. no	0.64	0.48–0.87	0.004	0.88	0.64–1.20	0.411
CAD						
Yes vs. no	0.69	0.58–0.83	<0.001	0.89	0.74–1.08	0.256
CVD						
Yes vs. no	0.88	0.71–1.08	0.211	—	—	—
Liver cirrhosis						
Yes vs. no	0.45	0.30–0.69	<0.001	0.45	0.29–0.69	<0.001

Variables where *$p < 0.1$ were put into multivariate analysis.
CAD = cardiovascular disease; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; COX-2 inhibitors = cyclooxygenase-2-specific inhibitors; CVD = cerebral vascular disease; DM = diabetes mellitus; ESRD = end-stage renal disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; SSRIs = selective serotonin-reuptake inhibitors.
[a] Other medications were clopidogrel, ticlopidine, or warfarin.

of lower *H. pylori* infection rates in CKD patients.[16] Sugimoto et al[18] reported an *H. pylori* infection rate of 38.3% in ESRD patients receiving dialysis for 4 years, suggesting that longer durations of dialysis reduce the risk of *H. pylori* infection. Prostaglandin is a crucial factor for protecting the gastric mucosa against injury, and uremic patients often experience a reduction in mucosal prostaglandin.[1] Therefore, a reduction in mucosal prostaglandin and hypergastrinemia[7] may contribute to the development of peptic ulcers in the absence of *H. pylori* in CKD patients.

Findings of previous studies on the prevalence of *H. pylori* infection in uremic patients vary. Such variation may be attributed to the use of different methodologies and enrollment criteria. Our findings differ from those of Luzza et al,[15] who showed a higher *H. pylori* infection rate in uremic patients. However, they used the method of measuring serum anti-*H. pylori* immunoglobulin G antibody levels to confirm *H. pylori* infection, which have a lower specificity than those of the rapid urease and histological methods that were used in our study. The 2007 Maastricht III Consensus Report on diagnosis and treatment of *H. pylori* infection does not recommend the serological determination of *H. pylori* infection in routine clinical practice.[20] In addition, this study enrolled uremia patients, and analyzed dyspepsia and dyspeptic symptoms based on the results of a questionnaire, without confirming peptic ulcer endoscopically. However, our study enrolled only patients with peptic ulcers confirmed by conducting endoscopic examination. Thus, the differences in the methodologies and enrollment criteria may explain the discrepancies between our findings and those of Luzza et al.[15]

Our nationwide, population-based observational study revealed *H. pylori* infection rates of 58.52% and 56.25% in CKD and ESRD patients with PUD, respectively, whereas 70.35% of the PUD patients without CKD were *H. pylori*-positive. Previous studies[1,18] have reported lower *H. pylori* infection rates, ranging from 22.6% to 42.9% (in Asian countries) in uremic patients with gastrointestinal mucosal lesions and peptic ulcers. These previous studies have used rapid urease tests or hematoxylin and eosin staining to diagnose *H. pylori* infection. Uremic patients are at a high risk of damage to the gastric mucosa because of fluctuations in the gastric blood supply[17] and increased inflammation. Thus, uremic patients are likely to be at an increased risk for peptic ulcers and gastric erosions in the absence of *H. pylori*. However, the *H. pylori* infection rate varies from region to region. Therefore, caution must be taken in extrapolating our results to Western developed countries, which have lower *H. pylori* prevalence rates.

In our analysis, patients with a history of peptic ulcer had significantly lower *H. pylori* infection rates, for which we propose two possible explanations. First, physicians are more likely to treat and test patients with PUDs according to clinical practice guidelines.[20] Therefore, non-CKD patients with a peptic ulcer history are likely to have received *H. pylori* eradication therapy prior to 1997. A recent multicenter study in Taiwan[21] reported a PPI-based *H. pylori* eradication rate of approximately 87.1%, and Cameron et al[22] reported an annual *H. pylori* reinfection rate of 0.4%, suggesting that the rate of *H. pylori* infection is lower in patients with recurrent peptic ulcers. Second, CKD and ESRD patients exhibit a higher incidence of PUD than non-CKD patients,[1,2] and are at an increased risk of developing ulcerative conditions through pathogenic mechanisms other than *H. pylori* infection. The presence of comorbidities, such as malignancy, diabetes

mellitus, chronic obstructive pulmonary disease, cerebral vascular disease, and liver cirrhosis, are independent predictors for non-*H. pylori* peptic ulcers.[23−25] Therefore, factors other than *H. pylori* infection play essential roles in the development of peptic ulcers in patients with ESRD or liver cirrhosis,[1,25] which is consistent with our findings (OR = 0.45, $p < 0.001$ for liver cirrhosis).

Several limitations to our findings should be noted. First, pathological classification is crucial for distinguishing between inflammation (gastritis) and *H. pylori* infection. Patients with a confirmed diagnosis of atrophic gastritis with concurrent *H. pylori* infection are not reimbursed by the NHI for *H. pylori* eradication therapy. Therefore, caution should be exercised when extending our findings to other patient populations, such as nonulcer dyspepsia patients, patients with atrophic gastritis, or the general population. Second, because certain laboratory data, such as serum creatinine and urine creatinine levels, were not recorded in the NHIRD, we used ICD-9-CM code 585 and the catastrophic illness card-holder status to identify ESRD patients, rather than basing the identification on the glomerular filtration rate. Third, the NHIRD does not contain data regarding patients' antibiotic allergy status. Therefore, because patients with relevant antibiotic allergies do not receive *H. pylori* eradication therapy, they may have been misclassified as *H. pylori*-negative patients.

In conclusion, our data showed that the *H. pylori* infection rate among CKD and ESRD patients with PUD is lower than that in PUD patients without CKD. Whether *H. pylori* eradication therapy can reduce the recurrence of peptic ulcers in CKD and ESRD patients in a manner similar to that achieved in the general population[26] warrants further study.

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