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Risk of Chronic Kidney Disease after Early and Late *Helicobacter Pylori* Eradication in Patients with Peptic Ulcer Disease: A Population-Based Cohort Study in Taiwan

Guei-Fen Chiu[1*], Yu-Han Chang[1], Den-Chang Wu[1,2,4], Ming-Tsang Wu[4] and Hugo You-Hsien Lin[1,3]

[1]*Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Taiwan*

[2]*Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan*

[3]*Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan*

[4]*Division of Family Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan*

[*]**Corresponding author:** Guei Fen Chiu, Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Taiwan, Tel: 0929659621; E-mail: 0870023@gmail.com

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Abstract

Background: *Helicobacter pylori* play a central role in the development of chronic gastritis, gastric and duodenal ulcers, and gastric cancer. The risk of upper gastrointestinal bleeding in patients with chronic kidney disease (CKD) or end stage renal disease is reportedly higher than that in the general population. The effects of early and late *H. pylori* eradication on kidney disease rates warrant further investigation.

Methods: We conducted a population-based study by using Taiwan's National Health Insurance Research Database of 1 million beneficiaries. The enrolled-date of this database is from January 1, 2000 to December 31, 2009. We compared the incidence and risk of CKD in 3,689 patients in the early *H. pylori* eradication cohort with those in 4,298 patients in the late *H. pylori* eradication cohort.

Results: The adjusted hazard ratio (HR; 95% confidence interval (CI)=1.17–1.77) for subsequent CKD was 1.44-fold higher in the late eradication cohort than in the early eradication cohort. In subgroup analysis, in patients aged 40–65 years, the HR was 1.55 (95% CI=1.14–2.10) and in those aged >65 years, the HR was 1.41 (95% CI=1.03–1.93).

Conclusion: This nationwide population-based cohort study provides evidence that patients with late eradication of *H. pylori* are at higher risk of CKD than those with early eradication of *H. pylori*.

Keywords: *Helicobacter pylori*; Chronic kidney disease; Nationwide population-based cohort study

Introduction

Chronic kidney disease (CKD) is a growing public health problem worldwide [1,2]. It is crucial to evaluate risk factors in patients with CKD because of higher all-cause mortality and cardiovascular disease [3]. In addition, it is unclear how the major causes of CKD [4], hypertension and type 2 diabetes mellitus (DM), account for its development or progression. Hyperuricemia, dyslipidemia, obesity, and inflammation were the other risk factors but only partially accounted for individual differences [5-8]. Some epidemiological studies have reported a significant association between *Helicobacter pylori* infection and certain cardiovascular disease risk factors, suggesting that chronic inflammation caused by *H. pylori* promotes atherosclerosis and cardiovascular disease [9]. However, no study has investigated the relationship between *H. pylori* and CKD. We evaluated the effects of the time of *H. pylori* eradication and development of CKD in Taiwan. This nationwide population-based cohort study assessed the possibilities patients with increasing risk of CKD. The original data were derived from Taiwan's National Health Insurance Research Database (NHIRD).

Methods

Study population

This retrospective cohort study analyzed data from the NHIRD, which was established by the NHI Bureau of the Department of Health. A random sample of one million beneficiaries was created by the National Health Research Institutes in 2000, and the reimbursement data between 1996 and 2010 (Longitudinal Health Insurance Database (LHID) 2000) are available. This database is contracted with 97% of hospitals and clinics in Taiwan which covers 99% of the 23 million Taiwanese residents (Figure 1).

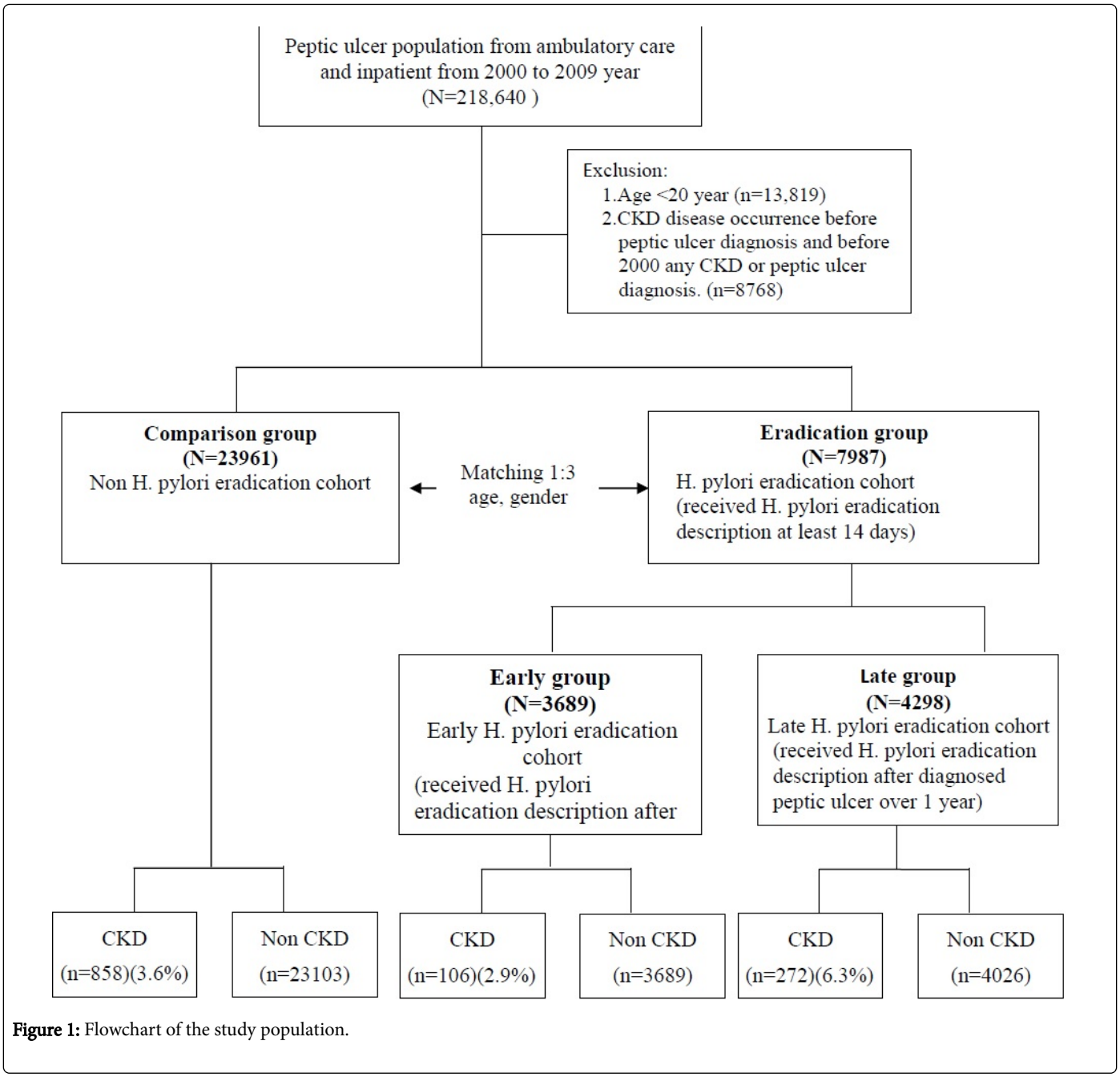

Figure 1: Flowchart of the study population.

Study patients

We first analyzed patients aged >20 years who were diagnosed as having peptic ulcer disease according to International Classification of Disease Ninth Modification, Clinical Modification (ICD-9-CM; 531 (gastric ulcer), 532 (duodenal ulcer), 533 (nonspecific peptic ulcer), and 534 (gastrojejunal ulcer)] between Jan 1, 2000 and Dec 31, 2009. The date of the first diagnosis was considered the index date. The *H. pylori* eradication cohorts comprised patients from the LHID2000; these patients had *H. pylori* infection and had received triple or quadruple therapy for *H.pylori* eradication lasting between 7 and 14 days. Furthermore, we analyzed a comparison cohort that comprised randomly selected patients with peptic ulcer disease who were matched for age, gender, and the index year. One year was selected as the cut-off period on the basis of the distribution of the *H. pylori* eradication date after the index date. Patients who received *H. pylori* eradication therapy within the first year of the index admission were included in the early eradication cohort, whereas those who received the therapy for 1 year or more after the index date were included in the late eradication cohort. From both cohorts, we excluded patients diagnosed as having CKD or end stage renal disease (ESRD; ICD-9-CM 585) before the index date, whose age- or sex-related information was unavailable, and those who experienced CKD events before the index date. Moreover, we analyzed the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-platelet agents. Patients who received NSAIDs or antiplatelet agents for at least 3 months within 1 year were defined as regular users of these medications. The Charlson comorbidity index score (CCIS) was defined as the disease

severity of patients on admissions before the index date. The ICD-9-CM codes for *H. pylori* infection (041.86) and ESRD (585), as obtained from the NHIRD, are highly reliable based on large amount of previous studies making use of the same codes [10].

Outcome measures and comorbidities

The study outcome was new-onset CKD (ICD-9-CM 581–587) diagnosed twice at outpatient visits within 1 year of hospitalization. The person-years of follow-up were estimated from the index date to the date of CKD diagnosis; censoring because of death during hospitalization; loss to follow-up; withdrawal from the insurance system; or December 31, 2010. Patients with CKD were followed from the index date to the study endpoint. The baseline comorbidity history of each patient was according to their inpatient database. These comorbidities included hypertension (ICD-9-CM 401–405), DM (ICD-9-CM 250), coronary artery disease (CAD; ICD-9-CM 410–412, 428), cerebrovascular disease (CVD; ICD-9-CM 430–438), malignancy (ICD-9-CM 346), liver cirrhosis (ICD-9-CM 571), chronic pulmonary disease (ICD-9-CM 491, 492, and 494), and connective tissue disease (ICD-9-CM code 710, 714, and 725).

Statistical analysis

We compared the distribution of risk factors between the comparison and eradication cohorts by using independent t, chi-squared, or Fisher's exact test. We performed Cox proportional hazard regression analyses to calculate the crude and adjusted hazard ratios (HRs) for CKD development risk. Multiple Cox proportional hazard regression analysis was performed to estimate the adjusted HR after adjustment for age, gender, the CCIS, comorbidities, medications (NSAIDs or anti-platelet agents). We used Kaplan–Meier curves to estimate the probability of CKD onset, and we also did the log-rank or Gehan–Breslow–Wilcoxon test to evaluate the differences among the comparison and eradication cohorts. All of the statistical analyses were performed by SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA). The statistical significance was set at $p<0.05$.

Results

Baseline characteristics of the study cohorts

For the period 2000–2009, we analyzed the LHID2000 and recruited and enrolled 7,787 and 23,961 patients with peptic ulcer disease in the eradication and comparison cohorts. The mean age of patients in the eradication cohort was 54.60 ± 16.37 years, and 43.9% were women. The distribution of age, sex, insurance range, hypertension, CAD, CVD, malignancy, liver cirrhosis, connective tissue disease, and medications was similar in the comparison and eradication cohorts (Table 1).

	Eradication group (n=7987)	Comparison group (n=23961)	p value*
Age (mean ± SD)	54.6 (± 16.37)	54.57 (± 16.41)	0.868
40	1621 (20.3)	4863 (20.3)	1.000
41-65	3976 (49.8)	11928 (49.8)	
>65	2390 (29.9)	7170 (29.9)	
Gender			
Female	3509 (29.9)	10527 (43.9)	1.000
Male	4478 4478 (56.1)	13434 (56.1)	
Urbanization			
Urban	2150 (26.9)	6749 (28.2)	0.096
Suburban	3521 (44.1)	10409 (43.4)	
Rural	2316(29.0)	6803 (28.4)	
Region			
Northern	3428 (42.9)	10663 (28.4)	<0.001
Central	1816 (22.7)	6360 (26.5)	
Southern	2385 (29.9)	6136 (25.6)	
Eastern	358 (4.5)	802 (25.6)	
Insurance range			
<NT15,000	2386 (29.9)	7467 (31.2)	0.094
NT 15,000-29,999	3941 (49.3)	11579 (48.3)	
NT 30,000	1660 (20.8)	4915 (20.5)	
Comorbidity			
Hypertension	2418 (30.3)	7316 (30.5)	0.663
Diabetes mellitus	117 (14.0)	2894 (12.1)	<0.001
Coronary artery disease	69 (0.9)	161 (0.7)	0.079
Cerebrovascular disease	278 (3.5)	866 (3.6)	0.578
Malignancy	201 (2.5)	574 (2.4)	0.543
Liver cirrhosis	1499 (18.8)	4515 (18.8)	0.882
Chronic pulmonary disease	1832 (22.9)	5061 (21.1)	0.001
Connective tissue disease	142 (1.8)	424 (1.8)	0.961
CCIS score	1.49 (± 1.56)	1.43 (± 1.54)	0.001
0	2390 (29.9)	7512 (31.4)	<0.001
1	2458 (30.8)	7637 (31.9)	
2	3139 (39.3)	8812 (36.8)	
Medication			
NSAID	5468 (68.5)	16757 (69.9)	0.013
Aspirin	42 (0.5)	120 (0.5)	0.785
Warfarin	40 (0.5)	122 (0.5)	0.928
Clopidogrel	66 (0.5)	210 (0.9)	0.675
Cilostazol	18 (0.2)	57 (0.2)	0.841
*Comparison of the eradication and comparison cohorts			

Table 1: Demographic characteristics of the eradication and control cohorts (N=31948).

Relative risk of chronic kidney disease

We observed that the 10-year cumulative incidence of CKD was significantly higher in the eradication cohort than in the comparison cohort (4.7% vs. 3.6%; log-rank test, p<0.001; Figure 2a), and higher risk existed between late eradication and early eradication cohorts (6.3% vs. 2.9%; log-rank test, p<0.006; Figure 2b). After the follow-up period, the overall incidence of CKD was higher in the eradication cohorts than in the comparison cohort. After adjustment for covariates, the risk of CKD was significant in the eradication cohort (HR=1.21; 95% confidence interval (CI)=1.07–1.37, p=0.002); the incidence of CKD was higher in the late eradication cohort than in the comparison cohort (HR=1.34; 95% CI=1.16–1.53, p<0.001) (Table 2).

Comorbidities

Table 3 shows a higher risk of CKD in patients aged >65 years in the late eradication cohort than in those aged <40 years in the comparison cohort (HR=1.95; 95% CI=1.22–3.12, p=0.005). Furthermore, the risk was higher in the late eradication cohort with hypertension than in the comparison cohort without hypertension (HR=2.00; 95% CI=1.63–2.46, p<0.001) and higher in the late eradication cohort with NSAID use than in the comparison cohort without NSAID use (HR=1.58; 95% CI=1.30–1.92, p<0.001).

	Overall		Male		Female	
	Adjusted HR (95% CI.)	**p value**	**Adjusted HR (95% CI.)**	**p value**	**Adjusted HR (95% CI.)**	**p value**
Overall						
Comparison group	Ref.		Ref.		Ref.	
Eradication group	1.21 (1.07-1.37)	0.002	1.14 (0.98-1.34)	0.098	1.32 (1.09-1.59)	0.004
Early eradication	0.98 (0.80-1.19)	0.799	0.93 (0.72-1.21)	0.573	1.07 (0.77-1.47)	0.699
Late eradication	1.34 (1.16-1.53)	<0.001	1.27 (1.06-1.52)	0.011	1.44 (1.17-1.77)	0.001
Age<40 years old						
Comparison group	Ref.		Ref.		Ref.	
Eradication group	1.15 (0.73-1.82)	0.535	1.44 (0.79-2.63)	0.239	0.89 (0.43-1.84)	0.749
Early eradication	0.75 (0.34-1.65)	0.478	1.02 (0.39-2.65)	0.972	0.51 (0.12-2.17)	0.363
Late eradication	1.42 (0.85-2.37)	0.178	1.74 (0.86-3.45)	0.113	1.09 (0.49-2.41)	0.236
Age 40-65 years old						
Comparison group	Ref.		Ref.		Ref.	
Eradication group	1.26 (1.05-1.52)	0.015	1.15 (0.88-1.50)	0.304	1.44 (1.10-1.88)	0.008
Early eradication	1.16 (0.88-1.54)	0.296	1.13 (0.78-1.65)	0.517	1.25 (0.82-1.90)	0.299
Late eradication	1.33 (1.07-1.66)	0.012	1.16 (0.84-1.61)	0.368	1.55 (1.14-2.10)	0.005
Age> 65 years old						
Comparison group	Ref.		Ref.		Ref.	
Eradication group	1.17 (0.99-1.39)	0.067	1.1 (0.89-1.37)	0.374	1.33	0.055
Early eradication	0.89 (0.65-1.23)	0.491	0.81 (0.54-1.21)	0.303	1.08	0.745
Late eradication	1.29 (1.07-1.55)	0.009	1.23 (0.97-1.55)	0.087	1.41	0.031
Adjusted age, gender, residential region, comoribidities (hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, malignancy, liver cirrhosis, chronic pulmonary disease, and connective tissue disease), and medication (NSAID, aspirin, warfarin, clopidogrel, cilostazol).						

Table 2: Risk of chronic kidney disease in the eradication and comparison cohorts.

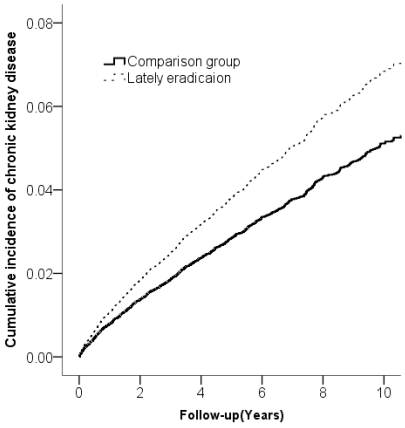

Figure 2a: Cumulative incidence of CKD in the late *H. pylori* eradication and control cohorts Kaplan-Meir Curves estimated the probability new onset of chronic kidney disease between comparison group and the lately eradication group.

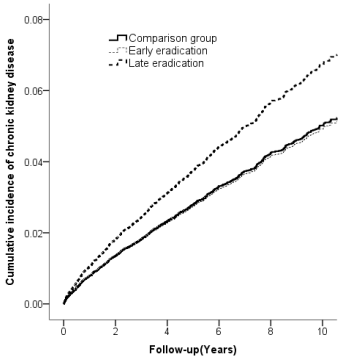

Figure 2b: Cumulative incidence of CKD in the late *H. pylori* eradication and control cohorts Kaplan-Meir Curves estimated the probability new onset of chronic kidney disease among comparison group and early eradication and late eradication.

Comorbidities	Comparison group		Eradication group			
			Early eradication		Late eradication	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age						
40	Ref.		0.73 (0.33-1.59)	0.421	1.65 (1.00-2.72)	0.048
41-65	1.33 (0.95-1.85)	0.097	1.5 (1.00-2.25)	0.049	1.85 (1.28-2.69)	0.001
>65	1.56 (0.99-2.44)	0.053	1.36 (0.80-2.33)	0.261	1.95 (1.22-3.12)	0.005
Gender						
Male	Ref.		0.91 (0.70-1.18)	0.456	1.28 (1.07-1.53)	0.008
Female	0.75 (0.65-0.86)	<0.001	0.83 (0.60-1.13)	0.228	1.05 (0.86-1.28)	0.636
Hypertension						
No	Ref.		0.95 (0.71-1.26)	0.702	1.48 (1.21-1.79)	<0.001
Yes	1.65 (1.42-1.91)	<0.001	1.68 (1.25-2.27)	0.001	2 (1.63-2.46)	<0.001
Diabetes mellitus						
No	Ref.		0.86 (0.67-1.09)	0.211	1.33 (1.14-1.56)	<0.001
Yes	1.45 (1.22-1.73)	<0.001	2 (1.42-2.81)	<0.001	1.96 (1.52-2.52)	<0.001
Coronary artery disease						
No	Ref.		0.96 (0.79-1.18)	0.726	1.34 (1.17-1.54)	<0.001
Yes	1.11 (0.62-1.98)	0.725	2.31 (0.74-7.21)	0.151	0.96 (0.31-3.00)	0.946
NSAID						
No	Ref.		1.07 (0.74-1.55)	0.72	1.28 (0.97-1.68)	0.085
Yes	1.17 (1.00-1.37)	0.049	1.11 (0.85-1.44)	0.46	1.58 (1.30-1.92)	<0.001

Adjusted age, gender, residential region, comoribidities (hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, malignancy, liver cirrhosis, chronic pulmonary disease, and connective tissue disease), and medication (NSAID, aspirin, warfarin, clopidogrel, cilostazol).

Table 3: Interaction effect on the risk of chronic kidney disease in the comparison, early eradication, and late eradication cohorts.

Risk factors associated with chronic kidney disease

Table 4 shows multiple Cox proportional hazard regression model of the risk of CKD in the comparison and eradication cohorts. The risk of CKD was higher in patients aged >65 years in the late eradication cohort than in those aged <40 years in the comparison cohort (HR=1.95; 95% CI=1.22–3.12, p=0.005). The risk was higher in the late eradication cohort with hypertension than in the comparison cohort without hypertension (HR=1.65; 95% CI=1.45–1.87, p<0.001) and higher in the late eradication cohort with DM than in the comparison cohort without hypertension (HR=1.52; 95% CI=1.31–1.76, p<0.001). Furthermore, the risk of CKD was higher the late eradication cohort with connective tissue disease than in the comparison cohort without hypertension (HR=1.48; 95% CI=1.07–2.05, p<0.017); higher in the late eradication with NSAID use than in the comparison cohort without NSAID use (HR=1.18; 95% CI=1.03–1.34, p<0.017), and higher risk in the late eradication with clopidogrel use than in the comparison cohort without NSAID use (HR=1.18; 95% CI=1.03–1.34, p<0.017).

	Adjusted HR (95% CI)	**p value***
Comparison group	Ref.	
Early Eradication	0.97 (0.80-1.19)	0.799
Late Eradication	1.34 (1.16-1.53)	<0.001
Age		
40	Ref.	
41-65	1.98 (1.56-2.50)	<0.001
>65	3.24 (2.54-4.13)	<0.001
Gender		
Male	Ref.	
Female	0.78 (0.69-0.87)	<0.001
Urbanization		
Urban	Ref.	
Suburban	0.95 (0.82-1.11)	0.547
Rural	0.91 (0.76-1.09)	0.304
Region		
Northern	Ref.	
Central	1.07 (0.92-1.25)	0.36
Southern	1.02 (0.86-1.19)	0.859
Eastern	0.88 (0.63-1.22)	0.434
Monthly income		
< NT15,000	Ref.	
NT 15,000-29,999	1.08 (0.95-1.24)	0.241
NT 30,000	0.9 (0.74-1.08)	0.247
Comorbidity		
Hypertension	1.65 (1.45-1.87)	<0.001
Diabetes mellitus	1.52 (1.31-1.76)	<0.001
Coronary artery disease	1.14 (0.71-1.84)	0.58
Cerebrovascular disease	0.84 (0.63-1.10)	0.207
Malignancy	1.01 (0.72-1.41)	0.96
Liver cirrhosis	0.97 (0.83-1.13)	0.669
Chronic pulmonary disease	0.94 (0.82-1.08)	0.415
Connective tissue disease	1.48 (1.07-2.05)	0.017
CCIS score		
0	Ref.	
1	1.2 (1.01-1.41)	0.033
2	1.37 (1.37-1.65)	0.001
Medication		
NSAID	1.18 (1.03-1.34)	0.017
Aspirin	1.27 (0.70-2.30)	0.432
Warfarin	1.47 (0.83-2.62)	0.187
Clopidogrel	0.4 (0.18-0.89)	0.025
Cilostazol	0.29 (0.04-2.05)	0.214
*comparison between the eradication and comparison cohorts		

Table 4: Multiple Cox proportional hazard regression model of the risk of chronic kidney disease between the comparison and eradication cohorts (N=34,580).

Discussion

The present study investigated the association between early and late eradication *H. pylori* and CKD. According to our review of relevant literature, this large nationwide cohort study is the first to demonstrate an increased risk of CKD in patients who received *H. pylori* eradication. In this study, CKD was more likely in patients who received late eradication than in controls after adjustments for potential confounders and competing mortality.

H. pylori is a gram-negative microaerophilic spiral shaped bacterium. Most *H. pylori* colonize in the antral mucosa of the stomach and recruit neutrophils and monocytes to the infected area. *H. pylori* colonization triggers the release of proinflammatory and procoagulant cytokines, which may cause extraintestinal diseases [9].

Similar to CVD, chronic infections have been suggested as an example of inflammatory risk factors. Moreover, *H. pylori* was reported as a risk factor for kidney disease [10]. It is rational to hypothesize that the difference in *H. pylori* eradication time could promote kidney disease.

CVD is an established risk factor for CKD. A study compared 111 patients with CAD and 74 controls from a general practice health screening clinic and reported significantly different *H. pylori* seropositivity between both cohorts [11]. Many epidemiological studies have investigated this relationship [12]. A prospective cohort study recruited 135 patients with myocardial infarction and 136 controls from a longitudinal study of CAD that randomly recruited 7735 middle-aged men from 24 British towns [13]. The odds ratio was significant for myocardial infarction. These results may link to the pathogenesis of CKD after *H. pylori* infection.

Previous exposure of an individual to chronic infections is considered a risk factor for artherosclerosis. Numerous previously reported infectious agents were attributed to the risk of subsequent CKD events [14]. Another possible mechanism for the pathogenesis of CKD is the relationship between chronic *H. pylori* infection and glucose metabolism. DM is a classical risk factor for CKD, and impairment in glucose metabolism because of *H. pylori* infection may be an etiological factor for chronic liver disease in patients with *H. pylori* infection. The incidence of CKD and CVD was higher in patients with diabetes comorbid with chronic *H. pylori* infection than in individuals without *H. pylori* infection [15]. Renal function may interfere in the development of atherosclerosis.

Our results are consistent with previous studies that hypertension, DM, hypertension, hyperlipidemia and CAD are independent risk factors for ESRD [16-18]. Besides of these findings, we also demonstrated a synergistic interaction between *H. pylori* infection and the risk factors for ESRD. However, the mechanism of the synergistic interaction between *H. pylori* infection and risk factors for CVD and CKD remains unknown and these may require further investigation. According to previous studies, *H. pylori* infection may increase risk of shifting lipid profiles, increasing proinflammatory cytokines and increasing insuin resistance. These relationship may increase trend of atherogenic and reduce endothelial function upon *H. pylori* infection [19,20]. In our study, the risk ESRD was up to 20.5-fold when *H. pylori* eradication and DM existed concomitantly. These results may suggest that patients with *H. pylori* infection and any CKD or CVD risk factor have a higher risk of ESRD than those with only a single CKD or CVD risk factor.

H. pylori, an intracellular organism, can invade macrophages and reach the vascular site away from its primary colonization site. The direct involvement of *H. pylori* can also elicit inflammation, which is essential for the development of atherosclerosis. *H. pylori* may continue its effect on kidney inflammation. Low-grade systemic inflammation differs from acute phase of infection. The human immune system cannot eliminate *H. pylori* from gastric mucosa; thus, infection persists and is suggested to cause low-grade systemic inflammation. The relationship between chronic *H. pylori* infection and extragastrointestinal diseases is based on this theory.

Limitations

This study has several limitations. First, we had no information on the severity of *H. pylori* infection, whether *H. pylori* was eradicated, and the persistence of *H. pylori* infection. However, we made the diagnosis of *H. pylori* infection basing on all administrative and claims data available in the NHIRD, ensuring the reliability of the diagnosis. Second, individual information, such as family history, smoking, obesity, socioeconomic status, blood pressure, and plasma glucose levels, all of which may contribute to ESRD, were unavailable in the administrative data set. Despite our meticulous study design, which ensured adequate control of confounders, these limitations could have influenced our findings. Besides these limitations, the NHIRD cohort study was followed for >15 years which can make us establish the relative time scale of *H. pylori* eradication and subsequent ESRD events. Second, this is the largest and longest follow-up population-based epidemiological study reported until now on the association between *H. pylori* eradication and ESRD risk. Summarization of this study, we observed a higher risk of subsequent ESRD in the *H. pylori* eradication cohort than in the comparison cohort. Moreover, *H. pylori* eradication was associated with common CKD and CVD risk factors, thereby contributing to ESRD development. The association between *H. pylori* eradication and ESRD should be observed and managed cautiously in clinical settings. Physicians should address the need for both primary and secondary *H. pylori* prevention in patients with high risks of CKD and ESRD. Early detection and appropriate therapy for *H. pylori* infection may prevent subsequent renal failure events. Therefore, we added the CCIS into the propensity score in multivariate and stratified analyses to control confounding by these variables. Our findings may benefit future studies on the aforementioned association.

Conclusion

In this nationwide population-based cohort study conducted in Taiwan, *H. pylori* eradication was significantly associated with increased risks of CKD. Future studies for further evaluation may be required.

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Author Contributions

GFC participated in the study design and data acquisition and entry, prepared the database, and performed the statistical analyses. In addition, he prepared the first draft, and edited and finalized the manuscript. DCW, MTL, and YHC participated in the interpretation of data, contributed to discussions, and critically reviewed drafts of the manuscript. DCW, MTL, and YHC provided expert advice on biostatistics. YHL initiated and planned the study; participated in the data acquisition; and drafted, critically reviewed, commented on, and edited various versions of the manuscript. GFC and YHL are the guarantors of this study. All the authors have read and approved the final version of the manuscript.

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