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Association between *Helicobacter pylori* Infection and Early Kidney Damage in a Healthy Population

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Abstract

Background: The relationship of renal damage with *Helicobacter pylori* infection remains unclear.

Objectives: Our objective was to determine the correlation of early renal dysfunction with *H. pylori* infection in a healthy population.

Methods: This retrospective study was conducted at the Physical Examination Center of the First Hospital of Jilin University, China. The 5594 healthy individuals were included based on strict predefined inclusion and exclusion criteria from 8821 participants who received health examinations between January 2019 and April 2019. *H. pylori* infection was detected using a commercial carbon-14 urea breath test. Logistic regression analysis was used to determine the relationships of biomarkers of early kidney dysfunction with *H. pylori* infection, after adjusting for age, sex, and metabolic factors.

Results: A total of 43.0% participants had *H. pylori* infections. Infected individuals had increased levels of retinol-binding protein (RBP) and cystatin C (Cys-C), and decreased estimated glomerular filtration rate (eGFR) (all $P<0.05$). Calculation of crude odds ratios (ORs) indicated that *H. pylori* infection was associated with RBP (OR=1.164, 95%CI=1.020–1.329) and eGFR (OR=0.851, 95%CI=0.754–0.961). However, after adjusting for confounding, none of the examined variables were associated with *H. pylori* infection. Subgroup analysis of subjects without hypertension or diabetes mellitus indicated a significant relationship of eGFR and *H. pylori* infection based on the crude OR, but there were no significant variables after adjustment for confounding.

Conclusions: Our results indicated no significant relationships between markers of early kidney damage and *H. pylori* infection. These results imply that *H. pylori* is not a major factor affecting the onset of renal damage.

Keywords: *Helicobacter pylori*; Retinol-binding protein (RBP); Cystatin C (Cys-C); Kidney insufficiency; Kidney Disease

Introduction

Numerous studies indicated that alterations in certain gut microbiome-host interactions [1] may contribute to the pathogenesis of various kidney diseases, such as chronic kidney disease (CKD), immunoglobulin (Ig) A nephropathy (IgAN), and acute kidney injury [2]. Furthermore, there is evidence that *H. pylori* infection leads to dramatic changes in the gastric microenvironment, affects the composition of the gastric microbiota, and is likely associated with the changes in colonic microbiota [3].

H. pylori is a common pathogen in the human stomach, and infections are usually asymptomatic, but can sometimes lead to malignant or non-malignant diseases [4]. *H. pylori* infection usually occurs early in life, and if untreated can persist throughout an individual's life [5]. *H. pylori* infection is the major risk factor for gastric cancer, the fifth most commonly diagnosed cancer worldwide and the third leading cause of cancer deaths [6]. There is also evidence that *H. pylori* infections can cause extragastric diseases, such as neurological, metabolic [7], and allergic diseases. For many patients, eradication therapy provides clear benefits [8]. However, the route of *H. pylori* transmission remains unclear [9].

During recent decades, many epidemiological and clinical studies analyzed the relationships of *H. pylori* infection with non-gastrointestinal diseases, including kidney diseases, and related risk factors [10]. Some studies showed that kidney diseases were associated with *H. pylori* infection, but this remains controversial [11]. For example, some studies reported that *H. pylori* infection was associated with CKD, end-stage renal disease (ESRD), and the need for hemodialysis [12,13], and other studies reported that eradication of *H. pylori* may reduce kidney damage and ameliorate renal insufficiency [14,15]. However, other studies reported no relationship of *H. pylori* infection with renal diseases [16,17]. Due to the high incidence of *H. pylori* infection in the general population and the challenges in treating kidney diseases [18], determining the connection of these conditions may provide new strategies for treatment of kidney diseases. Therefore, it is necessary to precisely analyze the nature of the relationship between *H. pylori* infection and kidney diseases.

There is currently a limited understanding of the relationship of *H. pylori* infection with alterations of early biomarkers of kidney damage. We therefore investigated the relationship between *H. pylori* infection and the presence of alterations of early markers of kidney damage in a large asymptomatic population, with control for potential confounders.

Materials and Methods

Study population

From January to April 2019, 8821 subjects were selected for testing using the carbon-14 (^{14}C)-urea breath test while attending the Physical Examination Department of a grade-A tertiary hospital in Jilin province, China. After exclusion of 3227 subjects for various predefined reasons, 5594 subjects were eligible for inclusion (Figure 1).

Blood biochemistry and biometric parameters

Serum and urine samples were collected from healthy participants at the Physical Examination Center and sent to the clinical laboratory for testing. Fasting blood glucose, uric acid, blood urea nitrogen (BUN), cystatin C (Cys-C), retinol-binding protein (RBP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), and triglycerides (TG) were measured using an automatic biochemistry analyzer (HITACHI Automatic Biochemistry Analyzer 7600-210). Urinary protein was measured using the semiquantitative dipstick test, and defined as negative, trace, 1+, 2+, 3+, or 4+. A subject was diagnosed with diabetes mellitus (DM) if fasting blood glucose was 7.0 mmol/L or more, if glycosylated hemoglobin was more than 6.5%, or if there was a history of using a hypoglycemic agent, DM, or both [19]. Blood pressure was measured using an automatic sphygmomanometer, and three measurements were taken, with at least 5-min intervals between measurements. The mean of the

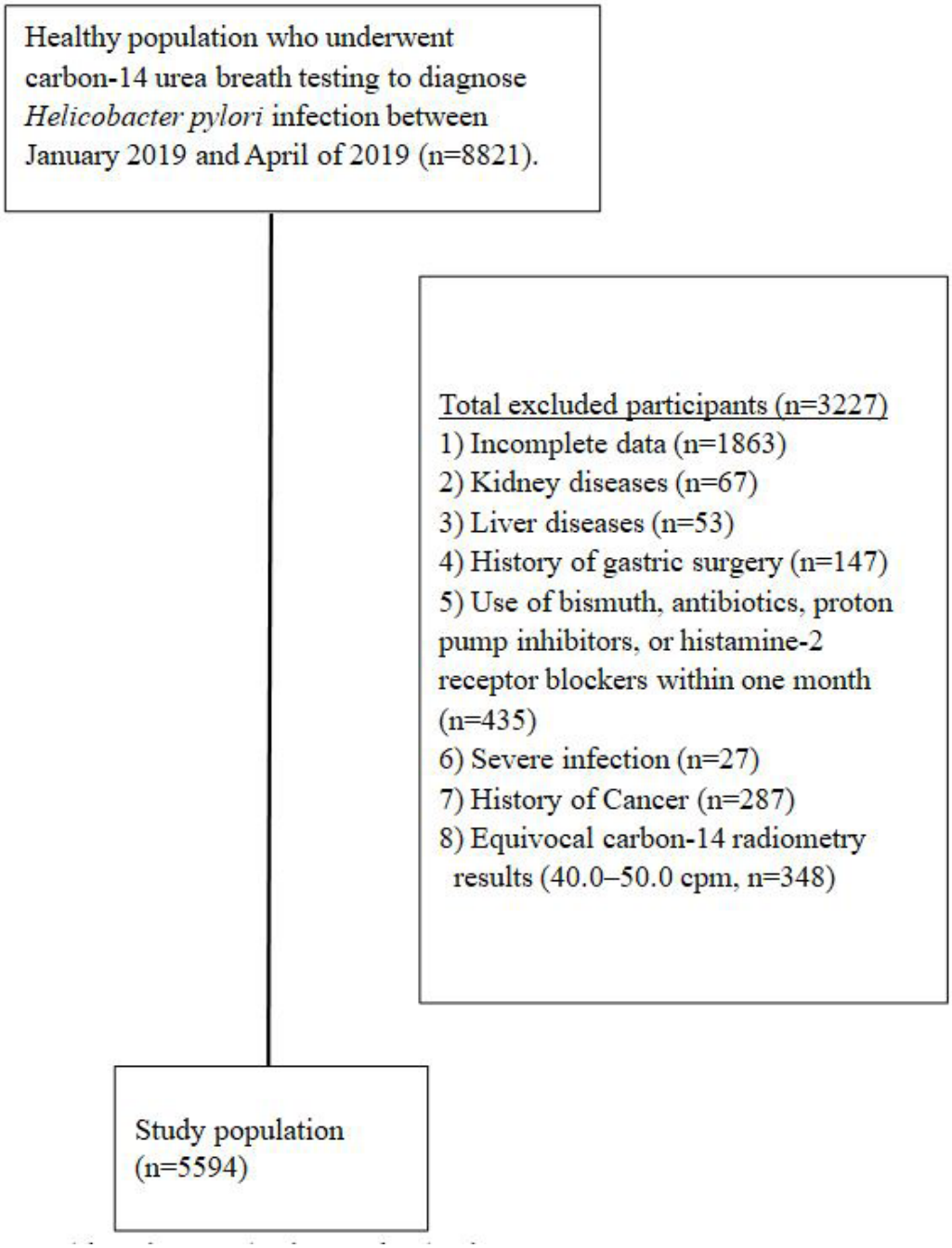

Figure 1: Criteria used for inclusion and exclusion of study subjects

three measurements was recorded; if measurements were substantially different between readings, the mean was determined for the two closest results. Hypertension was defined as systolic blood pressure (SBP) of 140 mmHg or more, diastolic blood pressure (DBP) of 90 mmHg or more, or a history of hypertension. An estimated glomerular filtration rate (eGFR) below 90 mL/min/1.73 m^2 was considered abnormal. The eGFR was calculated using the revised Modification of Diet in Renal Disease formula:

$eGFR = 175 \times (\text{serum creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female})$

where serum creatinine is in μmol/L and age is in years.

Demographic information was collected from the electronic medical records. These data included age, sex, body mass index (BMI), waist circumference, and laboratory data (listed above). Approval for this study was provided by the Institutional Review Board and Ethics Committee of the First Hospital of Jilin University, China. Because all medical records were anonymized prior to

collection, the ethics committee did not require informed consent from participants.

Identification of H. pylori infection

The manufacturer's instructions for the ^{14}C-urea breath test (HUBT-20A2, HEADEWAY Medical Instrument, Shenzhen China) require fasting for at least 3 h prior to the test. The instructions require drinking 20 mL of lukewarm water when taking the ^{14}C-urea capsule (0.75 μCi), and then sitting for 15 min. Then, the participant was asked to blow onto a "Breath Test Card" for breath sample collection. When the display turned from orange to yellow, it indicated the collection was complete. Radioactivity (due to the presence of radioactive CO_2) was measured within 250 s using the breath test machine. A reading of at least 50 counts per minute (cpm) indicated *H. pylori* infection and a reading below 40.0 cpm indicated no *H. pylori* infection. Subjects with readings between 40.0 and 50.0 cpm were excluded.

Statistical analysis

Data are presented as proportions (categorical variables) or as medians and interquartile ranges (continuous variables). The significance of differences between groups was tested using the chi-square test (categorical variables) or a nonparametric test for two independent samples (continuous variables). The meaningful independent variables were adjusted in the above models. Multivariate logistic regression analysis was used to determine the significance of associations between *H. pylori* infection and indicators of kidney damage. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Subgroup analysis of participants without hypertension or DM (n = 3688) was performed using the same logistic regression model to determine the relationship between *H. pylori* infection and biomarkers of kidney damage. All statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) version 24.0 (IBM Corp., Armonk, NY). All *P* values less than 0.05 were considered significant.

Results

We analyzed 5594 healthy participants from January to April 2019 (Table 1). The median age was 47 years (range: 36-56 years), 53.2% of the participants were men, and the *H. pylori* infection rate was 43.03% (2407/5594). Participants with *H. pylori* infections were more likely to have hypertension (33.6% *vs.* 30.0%, $P < 0.05$) and had a lower eGFR (100.78 [range: 89.87–113.97] *vs.* 101.72 [range: 88.99–113.12] mL/min/1.73 m^2, $P < 0.05$). In addition, the *H. pylori*-positive group was older (48 [range: 38–56] *vs.* 46 [range: 35–55] years, $P < 0.001$), had more males (55.7% *vs.* 51.4%, $P < 0.05$), and had higher levels of TG (1.39 [range: 0.97–2.06] *vs.* 1.32 [range: 0.92–1.98] mmol/L, $P < 0.05$), TC (5.25 [range: 4.65–5.99] *vs.* 5.14 [4.56–5.85] mmol/L, $P < 0.001$), and LDL cholesterol (3.13 [range: 2.64–3.69] *vs.* 3.02 [range: 2.53–3.56] mmol/L, $P < 0.001$). The two groups also had significant differences in BMI, waist circumference, serum uric acid, SCr, RBP, and Cys-C (Table 1).

Calculation of the crude ORs for all participants (Table 2) indicated significant associations of RBP (OR = 1.164 [95% CI = 1.020–1.329]) and eGFR (OR = 0.851 [95% CI = 0.754–0.961]) with *H. pylori* infection. However, after adjusting for age, sex, BMI, waist circumference, uric acid, TC, TG, LDL, SCr, and Cys-C, there were no significant associations.

Calculation of the crude ORs for the subgroup of participants without hypertension or DM (Table 2) also indicated no significant association of RBP or CysC with *H. pylori* infection. The eGFR had a nearly significant association with *H. pylori* infection (OR = 0.867 [95% CI = 0.738–1.019]). As above, there were no significant associations with *H. pylori* infection after adjusting for age, sex,

	All	Hp (+)	Hp (−)	Z/χ^2	P-value
Participants, n	5594	2407	3187		
Age, years	47 (36–56)	48 (38–56)	46 (35–55)	−6.133	**<0.001**
Male, n (%)	2977 (53.2)	1340 (55.7)	1637 (51.4)	10.213	**0.001**
Hypertension, n (%)	1766 (31.6)	809 (33.6)	957 (30.0)	8.145	**0.004**
Diabetes, n (%)	307 (5.5)	137 (5.7)	170 (5.3)	0.338	0.561
Waist Circumference (cm)	85 (78–92)	85 (78–92)	84 (77–91)	−3.577	**<0.001**
BMI (kg/m^2)	25.07 (22.75–27.55)	25.18 (22.89–27.62)	24.98 (22.61–27.46)	−2.541	**0.011**
Uric acid (μmol/L)	322 (263–387)	326 (269–389)	318 (259–385)	−2.468	0.014
TG (mmol/L)	1.35 (0.94–2.02)	1.39 (0.97–2.06)	1.32 (0.92–1.98)	−2.683	0.007
TC (mmol/L)	5.19 (4.59–5.90)	5.25 (4.65–5.99)	5.14 (4.56–5.85)	−4.326	<0.001
LDL (mmol/L)	3.07 (2.57–3.62)	3.13 (2.64–3.69)	3.02 (2.53–3.56)	−5.241	<0.001
HDL (mmol/L)	1.42 (1.21–1.70)	1.42 (1.20–1.70)	1.42 (1.21–1.71)	−0.030	0.976
SCr (μmol/L)	65.4 (54.9–76.1)	66.0 (55.7–76.3)	64.9 (54.3–76.0)	−2.522	0.012
Proteinuria (n, %)	98 (1.8)	50 (2.1)	48 (1.6)	2.599	0.107
BUN (mmol/L)	4.97 (4.17–5.88)	4.98 (4.19–5.90)	4.96 (4.14–5.86)	−1.142	0.254
Cys-C (mg/L)	0.75 (0.66–0.86)	0.75 (0.67–0.86)	0.74 (0.66–0.85)	−2.368	**0.018**
RBP (mg/L)	47.3 (39.4–56.5)	48.1 (40.0–57.7)	46.7 (38.9–55.6)	−4.440	**<0.001**
eGFR (mL/min/1.73 m^2)	101.36 (89.87–113.97)	100.78 (88.99–113.12)	101.72 (90.44–114.78)	−3.079	**0.002**

*Data are given as median (range) or as indicated

HP: Helicobacter pylori; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; TC: Total Cholesterol; TG: Triglyceride; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; Scr: Serum Creatinine; BUN: Blood Urea Nitrogen; Cys-C: Cystatin C; RBP: Retinol-Binding Protein; eGFR: estimated Glomerular Filtration Rate

Table 1: Baseline characteristics of participants with (+) and without (−) of Helicobacter pylori (Hp) infections*

Participants	Crude OR (95% CI)	Age- and sex-adjusted OR (95% CI)	Multivariable adjusted OR1*(95% CI)	Multivariable adjusted OR2† (95% CI)
All (*n*=5594)				
RBP	**1.164 (1.020–1.329)**	1.062 (0.926–1.218)	1.061 (0.925–1.217)	1.027 (0.893–1.180)
Decreased eGFR	**0.851 (0.754–0.961)**	0.976 (0.858–1.110)	0.979 (0.861–1.113)	0.916 (0.767–1.094)
Cys-C	**0.926 (0.626–1.269)**	0.777 (0.564–1.070)	0.779 (0.565–1.073)	0.790 (0.570–1.096)
Subgroup (n=3688)				
RBP	1.132 (0.967–1.325)	0.992 (0.839–1.172)	––	0.974 (0.820–1.157)
Decreased eGFR	0.867 (0.738–1.019)	1.041 (0.878–1.234)	––	0.946 (0.746–1.200)
Cys-C	1.157 (0.721–1.855)	1.047 (0.650–1.688)	––	1.057 (0.654–1.706)

OR: Odds Ratio; CI: Confidence Interval; RBP: Retinol-Binding Protein; eGFR: estimated Glomerular Filtration Rate; Cys-C: Cystatin C

*OR1 was adjusted for age, sex, hypertension, and diabetes

†OR2 was adjusted for age, sex, hypertension, diabetes, body mass index, waist circumference, uric acid, total cholesterol, triglycerides, low-density lipoprotein, and serum creatinine

Subgroup‡: n = 3688, including participants without hypertension and diabetes. The ORs were adjusted for age, sex, hypertension, diabetes, body mass index, waist circumference, uric acid, total cholesterol, triglycerides, low-density lipoprotein, and serum creatinine

Table 2: Association of RBP, eGFR, and Cys-C with Helicobacter pylori infection in all subjects (top) and in a subgroup of subjects without hypertension or DM (bottom)

BMI, waist circumference, uric acid, TC, TG, LDL, Scr, and Cys-C.

Discussion

H. pylori infections are present in about half of the world's population [8]. These infections increase the risk of gastric diseases and can also have negative impacts on other organ systems, leading to neurological, dermatological, hematologic, cardiovascular, metabolic, and allergic diseases [10]. Notably, all of these conditions are characterized by persistent and low-grade systemic inflammation [20]. Our results indicated that the TC, TG, and LDL levels had statistically significant differences in healthy individuals who were *H. pylori*-positive and *H. pylori*-negative. Similar results were also reported in previous studies [4,5]. However, the association between *H. pylori* infection and kidney diseases remains controversial because of the high prevalence and social burdens of both conditions. This motivated us to determine the nature of the relationship of *H. pylori* infection and kidney diseases.

CKD is a major global disease [21] that includes all degrees of renal insufficiency and is associated with an increased incidence and prevalence of kidney failure. Furthermore, as the GFR decreases, health-related quality of life also decreases [22]. Persistent low-grade inflammation [23] and altered immune responses [24] are considered important components of the pathogenesis of CKD, and are also associated with renal pathology and increased all-cause mortality in these patients. *H. pylori* infection can cause diverse extragastric diseases that may also be related to increased inflammation and altered immune responses. Previous research reported the presence of *H. pylori* antigens in the glomeruli of patients with membranous nephropathy, and a higher *H. pylori* infection rate in patients with membranous nephropathy than in those without this condition [25]. Another study compared 22 patients with primary IgAN, 20 patients with non-IgAN primary glomerulonephritis, and 30 healthy controls, and concluded that *H. pylori* infection might contribute to the pathogenesis of IgAN by increasing the mucosal immune response, thus damaging the renal tubules [12]. This motivated us to examine the role of *H. pylori* infection in the early pathogenesis of kidney damage.

Several previous studies evaluated the association of *H. pylori* infection with CKD, ESRD, and kidney transplantation. One study reported that long-term use of antibiotics, proton pump inhibitors, or histamine-2 receptor antagonists in patients with kidney disease decreased the rate of infection by *H. pylori* [11]. However, to our knowledge, no previous study evaluated the association between early kidney damage and *H. pylori* infection. RBP and Cys-C are well-established early markers of kidney damage [26,27]. Our study was the first to evaluate the association between serum levels of these two markers with *H. pylori* infection in healthy individuals undergoing physical examinations. Our major finding is that the levels of these markers had no significant association with *H. pylori* infection.

A previous case-control study examined 241 patients with type 2 DM and 69 non-diabetic individuals (controls) who had symptoms of dyspepsia. Based on urinary albumin excretion (UAE), these researchers classified the DM patients into three groups: a DM group (UAE < 30 mg/day); a diabetic nephropathy (DN) group-1 (UAE = 30–300 mg/day); and a DN group-2 (UAE ≥ 300 mg/day). Their results indicated the levels of interleukin-8, tumor necrosis factor-α, and UAE were higher in those with *H. pylori* infection, thus supporting a relationship between *H. pylori* infection and DN [28]. However, a systematic review and meta-analysis of 47 observational studies (from inception to April 2018) that examined 4084 patients with CKD (2470 on dialysis and 1916 on hemodialysis specifically) and 6908 controls without CKD indicated a lower prevalence of *H. pylori* infection in CKD patients [29]. Another meta-analysis that examined 37 observational studies of adults found that ESRD was associated with a reduced risk of *H. pylori* infection [30]. A large-scale cross-sectional study of 22,044 Chinese adults reported that *H. pylori* infection was unrelated to CKD [16]. Furthermore, a 2016 meta-analysis of 9 cross-sectional studies concluded that *H. pylori* infection was not correlated with non-dialysis-dependent kidney diseases or CKD [17].

In agreement with these meta-analyses, our results also indicated no significant correlation of *H. pylori* infection with the level of Cys-C, RBP, or eGFR after adjusting for age, sex, BMI, waist circumference, uric acid, TG, TC, and LDL. In addition, eGFR was not significantly associated with *H. pylori* infection after adjusting for age and sex (Table 2). Our results also indicated that proteinuria and BUN level were not significantly different among the participants with and without *H. pylori* infections (P =

1.521 and $P = 0.254$, respectively; Table 1). We suggest three possible reasons for our negative results, which differ from those of some other studies. First, different strains of *H. pylori* have varying degrees of virulence [31]. It is possible that many of our study subjects were infected by strains that had low virulence, although we had no data on the *H. pylori* strains in our subjects and no data on virulence-related factors (vacA, cagA, dupA, oipA, iceA, and babA). Second, most infected individuals are asymptomatic, and only a small number of people develop gastric diseases, including gastric cancers. It is possible that many of our subjects had healthy immune systems that inhibited disease progression [32]. Third, the duration of *H. pylori* infection is a key factor underlying extragastric organ damage, and we had no data on duration of infection. Thus, further research is needed to determine if there are specific factors of the patient or of *H. pylori* that contribute to renal injury.

Two studies that examined the impact of *H. pylori* eradication reported reductions of proteinuria in patients with membranous nephropathy [30] and in those with type 2 DM [7]. Similarly, Pan et al. showed that successful eradication of *H. pylori* significantly reduced the urine albumin-to-creatinine ratio [14]. Therefore, eradication of *H. pylori* may improve the prognosis of patients with renal disease. Further studies are therefore needed to clarify the relationship between *H. pylori* infection and renal dysfunction and the impact of *H. pylori* eradication.

There are some limitations to this study. First, this was a single-center retrospective study. Second, we did not evaluate *H. pylori* virulence factors. Third, we have no data on long-term follow-up. Finally, we did not examine the effect of *H. pylori* eradication on kidney function.

Conclusion

We conducted a retrospective study of a healthy population to assess the association between infection by *H. pylori* and markers of early kidney damage. Our findings indicated that kidney damage was not correlated with *H. pylori* infection. Future cohort studies and randomized clinical trials are therefore needed to verify the relationship between *H. pylori* infection and renal disease, and to examine the underlying pathogenesis. A better understanding of this relationship may help clinicians to implement measures that prevent the progression to severe kidney disease.

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Footnotes

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of The First hospital of Jilin University.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after de-identification processing by the Information Center.

Conflict of interest statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data sharing statement: No additional data are available.

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