

***Helicobacter pylori* Infection in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis**

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Background/Aims: Insufficient systematic reviews were conducted in the previous meta-analyses about the prevalence of *Helicobacter pylori* infection in patients with chronic kidney disease (CKD). The aim of this study was to evaluate the prevalence of *H. pylori* infection in patients with CKD. **Methods:** A systematic review of studies that evaluated the prevalence of *H. pylori* infection in patients with CKD compared to a control group was performed. Only studies with adult patients were included, and studies with renal transplant recipients or diabetic nephropathy patients were excluded. Random-effects model meta-analyses with sensitivity analyses and subgroup analyses were conducted to confirm the robustness of the main result. A meta-regression analysis was conducted to explore the influence of potential heterogeneity on the outcomes. The methodological quality of the included publications was evaluated using the Risk of Bias Assessment tool for Nonrandomized Studies. Publication bias was also assessed. **Results:** In total, 47 studies were identified and analyzed. The total prevalence of *H. pylori* infection was 48.2% (1,968/4,084) in patients with CKD and 59.3% (4,097/6,908) in the control group. Pooled analysis showed a significantly lower prevalence of *H. pylori* infection in patients with CKD (vs control group: odds ratio, 0.64; 95% confidence interval, 0.52 to 0.79). Sensitivity analyses revealed consistent results, and meta-regression analysis showed no significant confounders. No publication bias was detected. **Conclusions:** The results of this study suggest a lower prevalence of *H. pylori* infection in patients with CKD. (Gut Liver 2019;13:628-641)

Key Words: *Helicobacter pylori*; Meta-analysis; Chronic kidney disease

INTRODUCTION

Helicobacter pylori is the most common chronic bacterial infection in humans and is related to various gastrointestinal diseases such as gastritis, peptic ulcer, gastric cancer, and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.^{1,2} The extraintestinal linking of *H. pylori* to various conditions, including hematologic, cardiovascular, metabolic, neurologic, and dermatologic disorders, has been investigated and recently published; the Maastricht V/Florence Consensus Report recommends eradication for patients who have iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency, although it is a weak grade recommendation.³⁻⁵

Patients with chronic kidney disease (CKD) often complain of dyspepsia due to various causes, and *H. pylori* infection should now be excluded for the diagnosis of functional dyspepsia.³ However, epidemiologic studies have shown inconsistent results about the association between *H. pylori* infection and CKD.^{6,7} The increased interest in the relationship between *H. pylori* infection and CKD is due to extraintestinal associations such as insulin resistance or metabolic syndrome associated with *H. pylori* infection, which is expected to be highly relevant because diabetes and hypertension are the most common causes of CKD.^{5,8}

Three meta-analyses have been conducted for the association of *H. pylori* infection and CKD.^{6,7,9} Wijarnpreecha *et al.*⁷ found no significant association between non-dialysis-dependent CKD and *H. pylori* infection. Gu *et al.*⁶ also revealed no evidence of association between dialysis-dependent CKD and *H. pylori* infection. Although these studies commonly claim no association, many articles were omitted during the literature search, and since both meta-analyses included only a subgroup (Wijarnpreecha *et al.* only included non-dialysis-dependent CKD, and

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Gu *et al.* only included dialysis-dependent CKD), an integrated analysis and subsequent sensitivity and subgroup analyses confirming the main result are needed. Another meta-analysis by Wijarnpreecha *et al.*⁹ found no association between end-stage renal disease (ESRD) and *H. pylori* infection. However, this meta-analysis included several studies with pediatric patients and also many articles were omitted during the literature search. Moreover, the method of dialysis (hemodialysis or peritoneal dialysis), ethnicity of the enrolled population, and methodological quality of the included studies were not considered as confounding factors in the previous meta-analyses (Table 1). Therefore, this study aimed to evaluate the prevalence of *H. pylori* infection in patients with CKD with systematic review, meta-analysis, and meta-regression.

MATERIALS AND METHODS

This systematic review and meta-analysis fully adhered to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table 1).¹⁰

1. Literature searching strategy

MEDLINE (through PubMed), the Cochrane library, and Em-

base were searched using common keywords associated with *H. pylori* infection or CKD (from inception to April 2018) by two independent evaluators (C.S.B. and S.P.S.). Medical Subject Heading (MeSH) or Emtree keywords were selected for searching electronic databases. The abstracts of all identified studies were reviewed to exclude irrelevant articles. Full-text reviews were performed to determine whether the inclusion criteria were satisfied in the remaining studies, and the bibliographies of relevant articles were rigorously reviewed to identify additional studies. Disagreements between the evaluators were resolved by discussion. The detailed searching strategy is described in Supplementary Table 2.

2. Selection criteria

We included studies that met the following criteria: (1) studies designed to evaluate the prevalence of *H. pylori* infection in patients with CKD (vs. a control group without kidney diseases); (2) studies of human subjects; and (3) full-text publications. Studies that met the all of the inclusion criteria were sought and selected. The exclusion criteria were as follows: (1) publications with incomplete data; (2) review articles; (3) pediatric studies; (4) letters or case articles; (5) abstract-only publications; and (6) studies with CKD including DM nephropathy or renal transplant recipient (meta-analysis with DM nephropathy or renal trans-

Table 1. Comparison of Previous Meta-Analyses with the Current Analysis

Parameters	Current study	Gu <i>et al.</i> ⁶	Wijarnpreecha <i>et al.</i> ⁷	Wijarnpreecha <i>et al.</i> ⁹
No. of included studies	47 Studies in systematic review (46 studies for meta-analysis)	15 Studies	9 Studies	37 Studies in systematic review (35 studies for meta-analysis)
Main outcome	Lower prevalence of <i>H. pylori</i> infection in patients with CKD compared to control group (OR, 0.64; 95% CI, 0.52–0.79)	No significant difference in the prevalence of <i>H. pylori</i> infection between patients with dialysis and control group (OR, 0.86; 95% CI, 0.52–1.42)	No significant difference in the prevalence of <i>H. pylori</i> infection between patients with CKD and control group (OR, 1.2; 95% CI, 0.73–1.97)	No significant difference in the prevalence of <i>H. pylori</i> infection between patients with ESRD and control group (RR, 0.77; 95% CI, 0.59–1.00)
Whether dialysis patients were included or not	Included dialysis patients (ESRD) and non-dialysis patients with CKD	Only patients with dialysis-dependent CKD (ESRD)	Only patients with non-dialysis-dependent CKD	Only patients with ESRD
Whether pediatric patients were included or not	Excluded	Included	Excluded	Included
Whether diabetic nephropathy or renal transplant recipient were included or not	Excluded	Included	Included	Included
Whether analysis based on modifiers were included or not (meta-regression)	Included	Not included	Not included	Not included

H. pylori, *Helicobacter pylori*; CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; ESRD, end-stage renal disease; RR, risk ratio.

plant recipient is different topic of interest and already published^{11,12}). Studies meeting at least one of the exclusion criteria were excluded from this analysis.

3. Methodological quality

The methodological quality of the included publications was assessed using the Risk of Bias Assessment tool for Nonrandomized Studies (RoBANS).¹³ The RoBANS tool contains six domains, including the selection of participants, confounding variables, measurement of intervention (exposure), blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.¹³ RoBANS is a validated tool that is reliable and feasible for the assessment of the methodological quality of nonrandomized studies. Review Manager version 5.3.3 (RevMan for Windows 7; the Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate the summary of RoBANS results. Studies with matched participants (e.g., age or sex) and the diagnosis of *H. pylori* infection with two or more methods were ranked with low risk of bias in the selection of participants and incomplete outcome date variable, respectively. Two of the evaluators (C.S.B. and S.P.S.) independently assessed the methodological quality of all included studies, and any disagreements between the evaluators were resolved by discussion or consultation with a third evaluator (G.H.B.).

4. Primary and modifier-based analysis

Two evaluators (C.S.B. and S.P.S.) independently used the same data fill-in form to collect the primary summary outcome and modifiers in each study. The outcome was the prevalence of *H. pylori* infection in patients with CKD and the control groups. These ratios were extracted and evaluated using odds ratios (ORs). Sensitivity analyses, including cumulative and one-study-removed analyses, were performed to confirm the robustness of the main analysis results. These analyses were calculated in the order of publication year or effect size to find whether the time trend exists or which study is more or less influential in the pooled estimate and to find the small-study effect (to ensure no changes in the effect size if more small-effect size studies were added). We also performed subgroup and meta-regression analyses to identify the source of heterogeneity based on the multiple modifiers identified during the systematic review. These modifiers include the ethnicity of the study population, classification of CKD (ESRD on dialysis vs CKD not on dialysis), dialysis method among ESRD population (hemodialysis or not), duration of dialysis (more than 4 years or not) and methodological quality.

5. Statistical analysis

Comprehensive Meta-Analysis software version 3 (Borenstein M, Hedges L, Higgins J and Rothstein H; Biostat, Englewood, NJ, USA) was used for this meta-analysis. We calculated the ORs with 95% confidence intervals (CIs) using 2x2 tables from

the original articles to compare the prevalence of *H. pylori* infection between the patients with CKD and the control group whenever possible. Heterogeneity was determined using the I^2 test developed by Higgins, which measures the percentage of total variation across studies.¹⁴ I^2 was calculated as follows: I^2 (%) = $100 \times (Q - df) / Q$, where Q is Cochran's heterogeneity statistic and df signifies the degrees of freedom. Negative values for I^2 were set to zero, and an I^2 value over 50% was considered to be of substantial heterogeneity (range, 0% to 100%).¹⁵ Pooled-effect sizes with 95% CIs were calculated using a random effects model and the method of DerSimonian and Laird due to methodological heterogeneity.¹⁶ These results were confirmed by the I^2 test. Significance was set at $p=0.05$. Publication bias was evaluated using Begg's funnel plot, Egger's test of the intercept, Begg and Mazumdar's rank correlation test, and Duval and Tweedie's trim and fill method.¹⁷⁻²¹

RESULTS

1. Identification of relevant studies

Fig. 1 presents a flow diagram showing how relevant studies were identified. In total, 1,296 articles were identified by a search of three databases. In all, 347 were duplicate studies, and an additional 732 studies were excluded during the initial screening through a review of titles and abstracts. The full texts of the remaining 219 studies were then thoroughly reviewed. Among these studies, 171 articles were excluded from the final analysis. The reasons for study exclusion during the final review were as follows: narrative review article ($n=7$), meta-analysis or systematic review ($n=5$), letters, comment, editorial or reply to questions ($n=15$), abstract-only article ($n=4$), case study ($n=5$), duplicated data ($n=1$), and incomplete data ($n=134$). Forty-eight studies²²⁻⁶⁹ were included in the systematic review; however, study by Kong *et al.*⁴⁰ showed no crude rate of *H. pylori* infection, therefore, this was excluded in the final meta-analysis. The remaining 47 studies^{22-39,41-69} were included in the final quantitative analysis.

2. Characteristics of included studies

In the 47 case-control or cross-sectional studies, we identified a total of 4,084 patients with CKD (2,470 patients on dialysis and 1,916 patients on hemodialysis) and 6,908 controls without CKD. The total prevalence of *H. pylori* infection in patients with CKD was 48.2% (1,968/4,084), and it was 59.3% (4,097/6,908) in the control group. The included studies were published between 1989 and 2017. Only one study included an African population,²² whereas the remaining studies included Asian (17 studies),²³⁻³⁹ Western (16 studies),⁴¹⁻⁵⁶ Middle Eastern (11 studies),⁵⁷⁻⁶⁷ and South American populations (two studies).^{68,69} Most articles were written in English, except for two Spanish,^{68,69} one Japanese,²³ one Korean,²⁷ one Czech,⁵¹ and one Turkish⁵⁹ studies. The age of the enrolled population ranged from 32.5±5.3

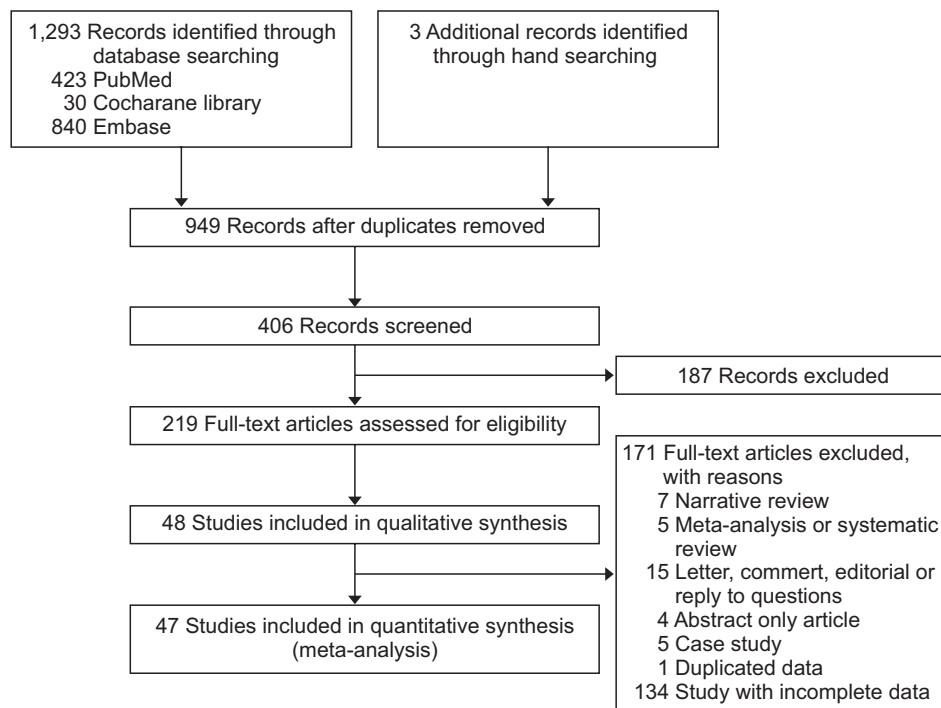


Fig. 1. Flow diagram for identification of relevant studies.

to 69.5 ± 13.8 years (mean \pm standard deviation). The diagnostic method of *H. pylori* infection varied according to each study, and included histology (Warthin–Starry, H&E, Giemsa, alcian blue–periodic acid Schiff’s, Loeffler’s methylene blue stain), culture, serology (IgG antibody against *H. pylori*), urease testing, phase-contrast microscopy, analysis for the stool antigen for *H. pylori*, and a urea breath test. The duration of dialysis in the enrolled population ranged from at least 6 months to 8.4 ± 0.3 years (mean \pm standard deviation). Most studies presented a crude rate of *H. pylori* infection in patients with CKD versus a control group, and two studies^{37,40} presented adjusted ORs, which were adjusted for age, sex, peptic ulcer history, steroid or medication use, diabetes, hypertension, chronic heart failure, coronary artery disease, and liver cirrhosis in Chang and Hu³⁷ and for sex, age, hypertension, diabetes, body mass index, uric acid, smoking, drinking, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in Kong *et al.*⁴⁰ The clinical characteristics of the included studies are shown in Table 2 (study by Kong *et al.* is described in the Table 2, but was not included in the final meta-analysis).

3. Prevalence of *H. pylori* infection in patients with CKD

The pooled meta-analysis of 34 studies exhibited a significantly lower prevalence of *H. pylori* infection in patients with CKD (vs a control group) (OR, 0.64; 95% CI, 0.52 to 0.79; $I^2=79.53\%$) in a random effect model analysis (Fig. 2).

4. Sensitivity meta-analysis

A cumulative meta-analysis of the included studies based on publication year showed no specific trend over time (Supple-

mentary Fig. 1A). A cumulative meta-analysis based on effect size showed no small study bias (Supplementary Fig. 1B). A one-study-removed meta-analysis revealed a stable feature (Supplementary Fig. 1C). Overall, the sensitivity meta-analyses revealed robust results.

5. Subgroup analyses according to the modifiers

The ESRD on dialysis subgroup showed robust lower prevalence of *H. pylori* (vs a control group) (OR, 0.58; 95% CI, 0.51 to 0.66) (Supplementary Fig. 2A). The hemodialysis subgroup also showed lower prevalence of *H. pylori* (OR, 0.60; 95% CI, 0.52 to 0.69) (Supplementary Fig. 2B). This effect was intensified in a subgroup of hemodialysis for more than 4 years (OR, 0.34; 95% CI, 0.27 to 0.43) (Supplementary Fig. 2C).

However, analysis of the ethnicity of the enrolled population showed a different result. Asian (OR, 0.46; 95% CI, 0.41 to 0.52) and Western population (OR, 0.78; 95% CI, 0.66 to 0.92) showed a lower prevalence; the African (OR, 0.90; 95% CI, 0.48 to 1.70), Middle Eastern (OR, 1.1; 95% CI, 0.87 to 1.34), and South American populations (OR, 0.76; 95% CI, 0.46 to 1.27) showed no significant difference of *H. pylori* infection in patients with CKD (vs a control group) (Supplementary Fig. 2D).

In terms of the methodological quality of the included studies, high-quality studies (defined as having no negative component in the RoBANS evaluation) showed a significantly lower prevalence of *H. pylori* infection in patients with CKD (OR, 0.57; 95% CI, 0.49 to 0.67). However, low-quality studies (defined as having any negative component in the RoBANS evaluation) showed no significant difference (OR, 0.66; 95% CI, 0.59 to 0.73) (Supplementary Fig. 2E). The detailed quality evaluation is described in Fig. 3.

Table 2. Clinical Data of Included Studies on the Prevalence of *H. pylori* Infection in Patients with CKD (vs Control Group)

Study	Nationality	Age, mean±SD, yr	Study format	<i>H. pylori</i> test	Duration of dialysis, mean±SD, mo	CKD (infected/total)	Control (infected/total)
Offerhaus <i>et al.</i> (1989) ⁴¹	Netherlands	ESRD: 52 (24–78), control: 47 (39–61)	Case-control	IgG antibody against <i>H. pylori</i>	NS	22/50 (ESRD)	18/40
Shousha <i>et al.</i> (1990) ⁴²	UK	ESRD: 49.7±14.3 (26–78), control: 52.6±18.5 (20–84)	Case-control	Warthin-Starry, Giemsa	NS	12/50 (ESRD)	51/120
Davenport <i>et al.</i> (1991) ⁴³	UK	HD: median 54 (22–75) (age-matched control)	Case-control	IgG antibody against <i>H. pylori</i>	Median 38 (1–76)	27/76 (HD)	74/247
Loffeld <i>et al.</i> (1991) ⁴⁴	Netherlands	HD: 58 (20–82) (age-matched control)	Case-control	IgG antibody against <i>H. pylori</i>	Median 4.2 yr (2–16 yr)	13/30 (HD)	230/500
Nieves <i>et al.</i> (1992) ⁴⁵	Venezuela	ESRD: 39±16 (18–72), control: 36±17 (17–74)	Case-control	H&E, Giemsa	NS	15/26 (ESRD)	12/26
Gladziwa <i>et al.</i> (1993) ⁴⁶	Germany	HD: 55.1±12.0, CKD without dialysis: 61.2±13.8, control: 53.8±13.2	Case-control	Urease test, Warthin-Starry, culture, phase-contrast microscopy	43.8±47.2 (5–200)	21/45 (CKD with or without dialysis)	45/83
Tokushima (1995) ⁴⁷	Japan	ESRD: 57.1±1.54, control: 53.6±1.41	Case-control	H&E, culture	33.8±4.56	23/43 (dialysis)	21/34
Jaspersen <i>et al.</i> (1995) ⁴⁸	Germany	HD: 54.6±11.8, control: 58.2±12.6	Case-control	Urease test, modified Giemsa	NS	7/34 (HD)	47/127
De Vecchi <i>et al.</i> (1995) ⁴⁹	Italy	HD: median 49 (26–69), PD: median 36 (21–84)	Case-control	IgG antibody against <i>H. pylori</i>	NS	37/67 (ESRD)	51/67
Krawczyk <i>et al.</i> (1996) ⁵⁰	Poland	HD: 36.8±13.2 (21–55), control: 34.8±12.1 (age-matched control)	Case-control	Urease test, modified Giemsa	28±12.2	13/21 (HD)	14/22
Abu Farsakh <i>et al.</i> (1996) ⁵¹	Jordan	HD: 40.3 (21–60), control: 39.4	Case-control	H&E or culture	18 (2 wk to 108 mo)	45/92 (HD)	73/100
Seyrek <i>et al.</i> (1996) ⁵²	Turkey	HD: 41.4±1.4 (16–70) (age-matched control)	Case-control	IgG antibody against <i>H. pylori</i>	22.9±2.2 (6–120)	13/91 (HD)	8/35
Luzza <i>et al.</i> (1996) ⁵³	Italy	HD: 60±13 (age, sex matched control)	Case-control	IgG antibody against <i>H. pylori</i>	Median 46 (mean, 74±63)	75/103 (HD)	80/103
Vardar <i>et al.</i> (1997) ⁵⁴	Turkey	CKD: 55±10.08, HD: 45.65±14.09, control: 48.47±13.78	Case-control	IgG antibody against <i>H. pylori</i> , urease test, histology	NS	27/40	29/40
Ozgür <i>et al.</i> (1997) ⁵⁵	Turkey	HD: 37.27±14.08, control: 40.51±13.60	Case-control	Urease test	28.87±28.92	28/47 (HD)	64/100

Table 2. Continued

Study	Nationality	Age, mean±SD, yr	Study format	<i>H. pylori</i> test	Duration of dialysis, mean±SD, mo	CKD (infected/total)	Control (infected/total)
Gür et al. (1999) ⁶¹	Turkey	Infected: 32.50±5.30, non-infected: 35.10±4.20	Case-control	Urease test, histology	Infected: 21.80±11.64, non-infected: 21.20±16.40	25/45 (HD)	24/44
Araki et al. (1999) ²⁴	Japan	ESRD: 57.4±12.8 (33-87), control: 57.8±17.3 (20-88) (age, sex-matched control)	Case-control	H&E, culture, IgG antibody against <i>H. pylori</i>	7.6±5.2 yr	29/63 (ESRD)	42/64
Yildiz et al. (1999) ⁶²	Turkey	HD: 36.6±15.2 (18-83), control: 33.4±9.6 (21-58)	Cross-sectional	IgG antibody against <i>H. pylori</i>	32.5±27.7 (1-100)	31/47 (HD)	39/55
Tamura et al. (1999) ²⁵	Japan	ESRD: 52.2±1.8, control: 48.6±1.6	Case-control	Urease test, histology, culture	29.3±5.4	25/49 (ESRD)	26/48
Fabrizi et al. (1999) ⁵⁰	US	HD: 61.8±13.8, control: 58.9±13.9 (sex, race-matched control)	Case-control	RIBATM <i>H. pylori</i> strip immunoblot assay	Median 29 (6-331)	127/228 (HD)	84/158
Misra et al. (1999) ²⁶	India	CKD: 35.4±14.6 (18-65), control: 33.33±13.9 (14-70)	Case-control	Urease test, histology	NS	28/50 (CKD with or without dialysis)	39/50
Karani et al. (2000) ²²	Kenya	CKD: 38.70±14.16 (18-70), control: 41.90±14.95 (18-87) (age, sex-matched control)	Prospective study	Urease test, histology	NS	41/77 (CKD with or without dialysis)	43/77
Kim et al. (2000) ²⁷	Korea	ESRD: 41±2, control: 46±2 (age-matched control)	Case-control	Urease test, histology, culture	NS	19/49 (CKD with or without dialysis)	29/41
Wang et al. (2001) ²⁸	Taiwan	HD: median 53.7 (20-66), control: median 50.4 (25-68)	Case-control	Histology, culture, IgG antibody against <i>H. pylori</i> , stool antigen for <i>H. pylori</i>	NS	40/80 (HD)	48/60
Cekin et al. (2002) ⁶³	Turkey	ESRD: 39±13, control: 41±11 (age, sex-matched control)	Case-control	Urease test, histology (H&E, modified Giemsa)	NS	16/42 (ESRD)	31/46
Závada et al. (2002) ⁵¹	Czech	NS	Case-control	Urease test, histology	NS	4/37 (CKD)	6/22
Tsukada et al. (2002) ²⁹	Japan	HD: 62.1±2.9, control: 55.4±3.0	Case-control	Giemsa stain, urea breath test	NS	14/47 (HD)	31/55
Olimos et al. (2003) ⁶⁹	Argentina	ESRD: 57.5±17.2 (matched control)	Case-control	IgG antibody against <i>H. pylori</i>	NS	44/93 (ESRD)	55/93
Tsukada et al. (2003) ³⁰	Japan	Infected: 63±5, non-infected: 69±2	Case-control	Immunochemically with a rabbit anti- <i>H. pylori</i> antibody	Infected: 592±176 times, non-infected: 483±92 times	9/36 (HD)	44/81

Table 2. Continued

Study	Nationality	Age, mean±SD, yr	Study format	<i>H. pylori</i> test	Duration of dialysis, mean±SD, mo	CKD (infected/total)	Control (infected/total)
Misra et al. (2004) ³¹	India	CKD: 38.5±13.2, control: 37.9±11.15	Case-control	Histology (H&E, alcian blue-periodic acid Schiff's, Loeffler's methylene blue)	NS	20/34 (CKD)	41/50
Al-Mueilo (2004) ⁶⁴	Saudi Arabia	HD: 42.4±18.8 (16–85), control: 38.9±13.3	Case-control	Histology	17±12.3 (3–48)	34/54 (HD)	38/60
Nakajima et al. (2004) ³²	Japan	CKD: 67.7±10.3, dialysis: 63.2±11.5, control: 62.8±11.7 (age-matched control)	Case-control	IgG antibody against <i>H. pylori</i>	57.3±61.7	16/30 (CKD without dialysis), 51/138 (dialysis)	86/138
Blusiewicz et al. (2005) ⁵²	Poland	HD: 50.8±2.9, control: 61.3±2.2 (age-matched control)	Case-control	Urease test, histology	At least 6 mo	19/30 (HD)	22/31
Simunić et al. (2005) ⁵³	Croatia	HD: 52.2±14.8 (19–77), CKD without dialysis: 56.6±14.0 (21–78), control: 54.6±14.1 (23–79)	Prospective study	Urease test, histology, culture, IgG antibody against <i>H. pylori</i>	NS	24/51 (CKD without dialysis), 23/55 (HD)	37/63
Nardone et al. (2005) ⁵⁴	Italy	CKD: 52.4±10, control: 54±7	Prospective study	Urease test, histology, urea breath test, stool antigen for <i>H. pylori</i>	NS	19/39 (CKD without dialysis), 7/11 (HD)	34/93
Moriyama et al. (2006) ³³	Japan	Membranous nephropathy: 54±12, control: 45±11 (age-matched control)	Case-control	HM-CAP serological test	NS	21/32 (membranous nephropathy)	108/243
Khedmat et al. (2007) ⁶⁵	Iran	CKD: 43.9±2.7, HD: 47.9±3.5, control: 45±2.3	Case-control	Urease test	46.9±10.7	47/71 (CKD), 46/73 (HD)	106/305
Stolic et al. (2008) ⁵⁵	Serbia	CKD: 60.65±12.74, control: 53.4±11.2	Prospective study	Urease test, histology (H&E)	NS	29/124	72/120
Abdulrahman et al. (2008) ³⁴	Saudi Arabia	ESRD: 46.4±15.7, control: 48.6±12.3 (age, sex-matched control)	Prospective study	Histology	CKD duration: 39±18.6	16/40 (ESRD)	33/44
Gioè et al. (2008) ⁵⁶	Italy	Range 42–85	Case-control	Urease test, histology (Giemsa)	NS	75/142 (HD)	59/132
Sugimoto et al. (2009) ³⁵	Japan	HD: 58.8±0.4, control: 58.4±0.6	Case-control	IgG antibody against <i>H. pylori</i>	8.4±0.3 yr	262/539 (HD)	314/400
Asl and Nasri (2009) ⁶⁶	Iran	HD: 56±14, control: 47±15	Cross-sectional	Histology (Giemsa)	At least 6 mo	23/40 (HD)	13/40
Chang et al. (2010) ³⁶	Korea	HD: 62.0±9.8, control: 60.2±7.7	Case-control	Urease test, histology (H&E, Wright stain)	<i>H. pylori</i> infected: 56.8±26.9, <i>H. pylori</i> non-infected: 66.4±26.1	12/33 (HD)	36/55

Table 2. Continued

Study	Nationality	Age, mean±SD, yr	Study format	<i>H. pylori</i> test	Duration of dialysis, mean±SD, mo	CKD (infected/total)	Control (infected/total)
Chang and Hu (2014) ³⁷	Taiwan	NS	Retrospective cohort study	Urease test, histology	NS	261/446 (CKD), 81/144 (ESRD), ESRD vs control (OR, 0.54; 95% CI, 0.38-0.77), CKD vs control (OR, 0.64; 95% CI, 0.51-0.81)*	1,658/2,360
Bunchohrtavakul and Aisawarungruangkit (2014) ³⁸	Thailand	ESRD: median 38.7 (15.9-65), 39.4±10.3 (sex and age-matched control)	Retrospective and prospective cohort study	Urease test, histology (H&E)	Median 2.1 yr (0.2-15.3 yr)	29/107	41/105
Zhu et al. (2016) ³⁹	China	IgA nephropathy: 33.25±9.67 (serum IgG antibody against <i>H. pylori</i> positive), 33.30±14.05 (negative), non-IgA nephropathy: 34.50±13.96 (positive), 36.53±11.48 (negative), control: 38.96±9.22 (age, sex-matched control)	Case-control	¹⁴ C urea breath test	NS	12/42 (IgA and non-IgA nephropathy)	10/30
Can et al. (2016) ⁶⁷	Turkey	Uremia patients: 69.5±13.8, non-uremic patients: 69±13.6	Case-control	Unknown	77.4±64.6 (patients with uremic GI bleeding, HD)	11/51 (uremic GI bleeding)	31/101 (non-uremic GI bleeding)
Kong et al. (2017) ⁴⁰	China	48.6±14.3 (18-92) (total 22,044 patients with health checkup, 604 CKD patients were included)	Cross-sectional	IgG antibody against <i>H. pylori</i>	NS	CKD vs. control (OR, 0.92; 95% CI, 0.75-1.12) [†]	-

Helicobacter pylori, *H. pylori*; CKD, chronic kidney disease; ESRD, end-stage renal disease; IgG, immunoglobulin G; NS, no significant; HD, hemodialysis; PD, peritoneal dialysis; OR, odds ratio; CI, confidence interval; GI, gastrointestinal.

*Adjusted for age, sex, peptic ulcer history, steroid or medication use, diabetes, hypertension, chronic heart failure, coronary artery disease, liver cirrhosis; †Adjusted for sex, age, hypertension, diabetes, body mass index, uric acid, smoking, drinking, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol.

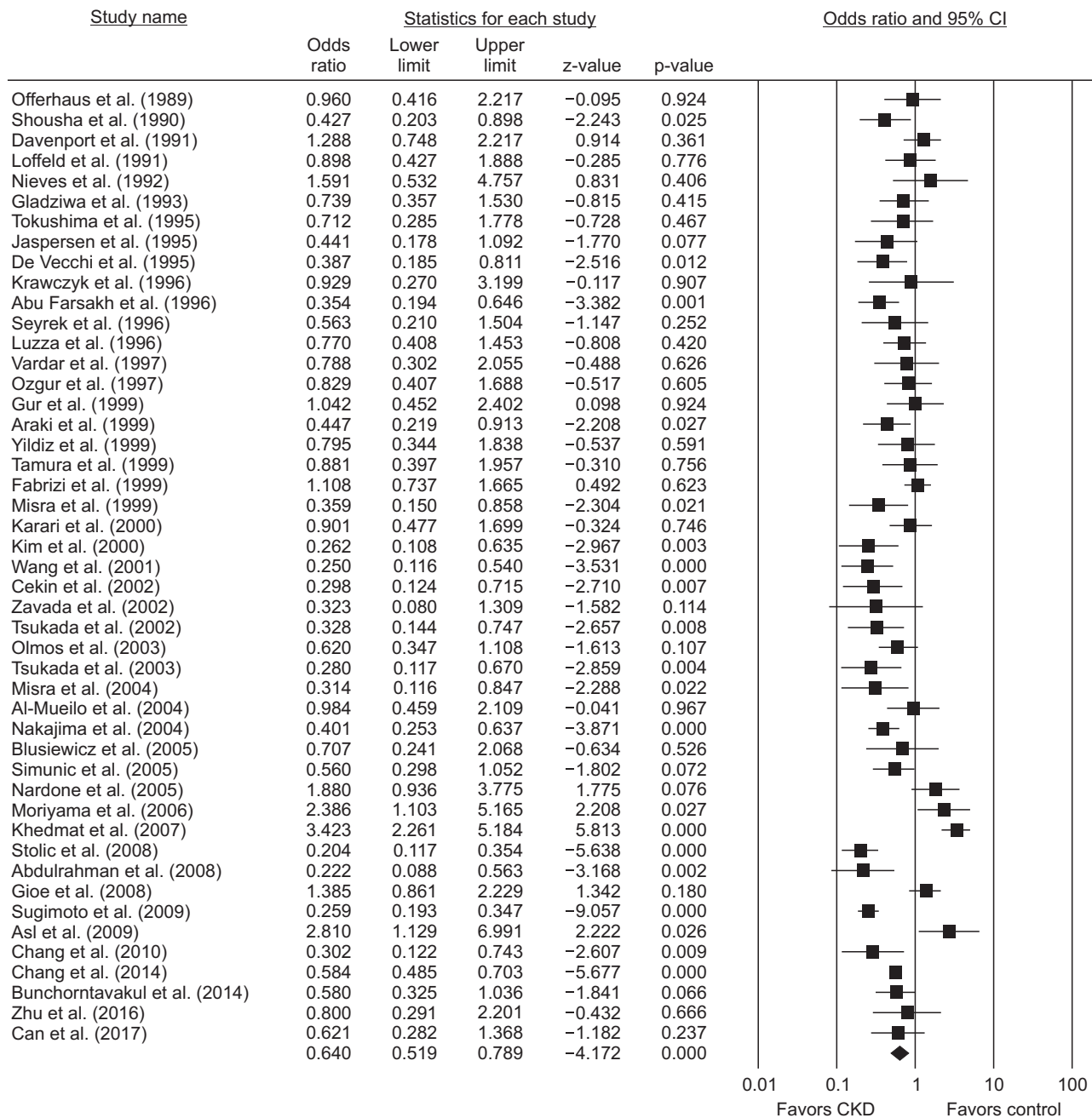


Fig. 2. Prevalence of *Helicobacter pylori* infection in patients with CKD (vs control group). The size of each square is proportional to the study's weight. Diamond is the summary estimate from the pooled studies (random-effects model). Heterogeneity: $\chi^2=224.693$, $df=46$ ($p<0.001$), $I^2=79.582\%$. Test for overall effect: $Z=-4.172$ ($p<0.001$). CKD, chronic kidney disease; CI, confidence interval.

6. Meta-regression analyses

Among the potential confounding factors, including whether the population was on dialysis or not, ethnicity, dialysis method, dialysis duration (more than 4 years), and methodological quality, there were no covariates that explained heterogeneity in the meta-regression tests (Table 3).

7. Analysis of publication bias

A funnel plot for the included studies is illustrated in Fig. 4 and shows a symmetrical shape. Egger's regression test revealed that the intercept was 0.23 (95% CI, -1.23 to 1.68; t-value, 0.31; $df=45$, $p=0.38$ [1-tailed] and $p=0.76$ [2-tailed]). A trim and fill analysis showed that no study was missed or trimmed. The rank correlation test showed Kendall's tau was -0.04 with a continuity correction ($p=0.33$ [1-tailed] and $p=0.66$ [2-tailed]). Overall,

there was no evidence of publication bias in this meta-analysis.

DISCUSSION

This meta-analysis confirmed the lower prevalence of *H. pylori* infection in patients with CKD (The total prevalence of *H. pylori* infection was 48.2% in patients with CKD vs 59.3% in the control group). Although the previous three meta-analyses claimed no significant association, the current study is the first meta-analysis representing the real prevalence because many articles were omitted during systematic review process in the previous systematic review (47 studies were included in the current study, whereas Wijarnpreecha *et al.*⁷ included nine studies, Gu *et al.*⁶ included 15 studies, and Wijarnpreecha *et al.*⁹ included 37 studies), and these studies enrolled a subgroup of patients with CKD according to whether patients were on dialysis or not. Many articles were omitted in these systematic reviews because searching strategy was unclear.^{6,7,9} Studies with renal transplant recipients or diabetic nephropathy, and pediatric population was included in the meta-analysis because inclusion criteria was vague (Table 1).⁹

Although most subgroup analyses verified according to the modifiers in the current study showed consistent results with main outcome, the ethnicity of the study population showed inconsistent results. Analyses with an Asian and Western population showed a significant lower prevalence and analyses of African, Middle Eastern, and South American populations commonly showed no significant difference. Considering most studies with an African, Middle Eastern, and South American population were included in the low-quality methodology group, these inconsistencies indicate and favor a significant lower prevalence of *H. pylori* infection in patients with CKD.

The most important factor for the determination of the methodological quality was an incomplete outcome of each study, especially the method of diagnosing *H. pylori* infection (Fig. 3). Included studies used various methods, including a urease test, histology, culture, a urea breath test, serology, or a stool antigen test. Although the urease test, histology, urea breath test, and stool antigen test have a high diagnostic value, with sensitivity and specificity exceeding 90% for the determination of *H. pylori* infection status, each diagnostic method has some considerations.^{3,70,71} False-negative results in the urease test, histology, urea breath test, and stool antigen test can be detected when patients are taking antibiotics, proton pump inhibitors, or bismuth, which are frequently prescribed drugs in patients with CKD.^{3,71,72} Therefore, the Maastricht V/Florence Consensus Report recommends that proton pump inhibitors should be discontinued at least 2 weeks before testing, and antibiotics and bismuth should be discontinued at least 4 weeks before testing.³ The serology test, which detects an IgG antibody against *H. pylori*, needs local validation before clinical application, and its overall sensitivity and specificity from published studies was less than 90%,

	Selection of participants	Confounding variables	Intervention measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Abdulrahman et al.	(+)	(+)	(+)	(+)	(-)	(+)
Abu Farsakh et al.	(-)	(+)	(+)	(+)	(+)	(+)
Al-Mueilo et al.	(-)	(+)	(+)	(+)	(-)	(+)
Araki et al.	(+)	(+)	(+)	(+)	(+)	(+)
Asl et al.	(-)	(+)	(+)	(+)	(-)	(+)
Blusiewicz et al.	(-)	(+)	(+)	(+)	(+)	(+)
Bunchorntavakul et al.	(+)	(+)	(+)	(+)	(+)	(+)
Can et al.	(-)	(+)	(+)	(+)	(-)	(+)
Cekin et al.	(+)	(+)	(+)	(+)	(+)	(+)
Chang et al.	(+)	(+)	(+)	(+)	(+)	(+)
Davenport et al.	(+)	(+)	(+)	(+)	(-)	(+)
De Vecchi et al.	(-)	(+)	(+)	(+)	(-)	(+)
Kim et al.	(+)	(+)	(+)	(+)	(+)	(+)
Fabrizi et al.	(+)	(+)	(+)	(+)	(-)	(+)
Gioè et al.	(-)	(+)	(+)	(+)	(+)	(+)
Gladziwa et al.	(-)	(+)	(+)	(+)	(+)	(+)
Gür et al.	(-)	(+)	(+)	(+)	(+)	(+)
Jaspersen et al.	(-)	(+)	(+)	(+)	(+)	(+)
Karari et al.	(+)	(+)	(+)	(+)	(+)	(+)
Khedmat et al.	(-)	(+)	(+)	(+)	(-)	(+)
Kong et al.	(+)	(+)	(+)	(+)	(-)	(+)
Krawczyk et al.	(+)	(+)	(+)	(+)	(+)	(+)
Loffeld et al.	(+)	(+)	(+)	(+)	(-)	(+)
Luzza et al.	(+)	(+)	(+)	(+)	(-)	(+)
Misra et al.	(-)	(+)	(+)	(+)	(+)	(+)
Misra et al.(2)	(-)	(+)	(+)	(+)	(+)	(+)
Moriyama et al.	(+)	(+)	(+)	(+)	(-)	(+)
Nakajima et al.	(+)	(+)	(+)	(+)	(-)	(+)
Nardone et al.	(-)	(+)	(+)	(+)	(+)	(+)
Nieves et al.	(-)	(+)	(+)	(+)	(-)	(+)
Offerhaus et al.	(-)	(+)	(+)	(+)	(-)	(+)
OlmosA et al.	(+)	(+)	(+)	(+)	(-)	(+)
Ozgür et al.	(-)	(+)	(+)	(+)	(-)	(+)
Seyrek et al.	(+)	(+)	(+)	(+)	(-)	(+)
Shousha et al.	(-)	(+)	(+)	(+)	(-)	(+)
Simunić et al.	(-)	(+)	(+)	(+)	(+)	(+)
Stolic et al.	(-)	(+)	(+)	(+)	(+)	(+)
Sugimoto et al.	(-)	(+)	(+)	(+)	(-)	(+)
Tamura et al.	(-)	(+)	(+)	(+)	(+)	(+)
Tokushima et al.	(-)	(+)	(+)	(+)	(+)	(+)
Tsukada et al.	(-)	(+)	(+)	(+)	(+)	(+)
Tsukada et al.(2)	(-)	(+)	(+)	(+)	(-)	(+)
Vardar et al.	(-)	(+)	(+)	(+)	(+)	(+)
Wang et al.	(-)	(+)	(+)	(+)	(+)	(+)
Chang WC et al.	(-)	(+)	(+)	(+)	(+)	(+)
Yildiz et al.	(-)	(+)	(+)	(+)	(-)	(+)
Závada et al.	(-)	(+)	(+)	(+)	(+)	(+)
Zhu et al.	(+)	(+)	(+)	(+)	(-)	(+)

Fig. 3. Risk of Bias Assessment tool for Nonrandomized Studies (Ro-BANS) for the assessment of methodological quality for all included studies. (+) Denotes low risk of bias, blank denotes unclear risk of bias, (-) denotes high risk of bias.

Table 3. Results of Meta-Regression Analyses

Model	Modifier	Coefficient	Standard error	p-value	
Model 1	ESRD on dialysis vs CKD	-0.35	0.49	0.48	
		Ethnicity	Asian: -0.62	0.76	0.41
			Middle Eastern: 0.10	0.80	0.90
			South American: 0.23	0.99	0.82
			Western: -0.14	0.79	0.86
					0.09 (Q: 8.00, df: 4)
	HD or not	HD: 0.06	0.34	0.86	
		No HD: -0.01	0.47	0.98	
					0.98 (Q: 0.04, df: 2)
	Model 2	ESRD on dialysis vs CKD	0.11	0.34	0.74
Ethnicity			Asian: -0.34	0.48	0.47
			Middle Eastern: 0.19	0.71	0.79
			South American: 0.34	0.89	0.70
			Western: -0.04	0.70	0.95
				0.10 (Q: 7.76, df: 4)	
HD or not		HD: 0.12	0.31	0.71	
		No HD: -0.001	0.45	0.99	
				0.93 (Q: 0.14, df: 2)	
Model 3		Dialysis more than 4 years	-0.17	0.34	0.63
	ESRD on dialysis vs CKD		-0.17	0.50	0.23
		HD or not	HD: 0.17	0.33	0.60
No HD: 0.15	0.51		0.77		
					0.87 (Q: 0.29, df: 2)
Methodological quality	ESRD on dialysis vs CKD	0.23	0.34	0.51	

ESRD, end-stage renal disease; CKD, chronic kidney disease; HD, hemodialysis; df, degrees of freedom.

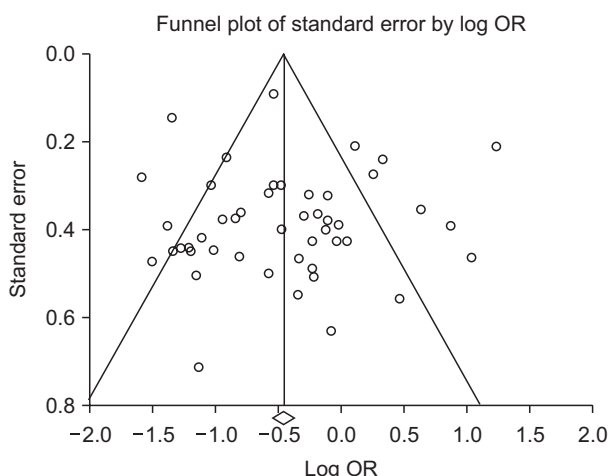


Fig. 4. Funnel plot of included studies. The line in the center is the natural logarithm of the pooled odds ratio (OR), and the two oblique lines are pseudo 95% confidence limits.

which shows lower diagnostic value than the other tests.⁷³ The diagnostic value of histology is higher than the other tests, but it is dependent on where the biopsies were conducted and how

many specimens were obtained. The degree of atrophic gastritis or intestinal metaplasia is also important for obtaining biopsy tissue for histology, influencing the accurate determination of *H. pylori* infection status.³ In the previous meta-analysis, subgroup analysis revealed a trend of decreased risk of *H. pylori* infection in patients with CKD that was diagnosed with histology, excluding other diagnostic methods, and it had a marked decrease in heterogeneity between studies.⁷ This indicates that the diagnostic values of all currently available methods are not perfect and are only valid and accurate in certain situations. Taking into account all of the above considerations, only a single diagnostic method is insufficient, and combining diagnostic methods is expected to have a high diagnostic yield. Therefore, studies combining diagnostic methods were included in the low-risk group, and studies with single diagnostic method were included in the high-risk group of the incomplete outcome category of RoBANS in the current study.

Although the pathogenesis of a lower prevalence of *H. pylori* infection in patients with CKD is not completely understood, several hypotheses have been proposed to explain the mechanism. First, frequent use of antacids or antibiotics in patients

with CKD might be associated with decreased prevalence.⁴⁶ The subgroup analysis of the current study showed that the subgroup with a dialysis duration of more than 4 years showed a more intensified lower prevalence (OR, 0.34; 95% CI, 0.27 to 0.43), and a previous meta-analysis also showed a consistent result, indicating frequent antacid or antibiotic consumption might be associated with this finding.⁶ Second, high blood urea nitrogen level was suspected as the cause of inhibited growth of *H. pylori*.⁴⁵ However, this was not consistent in other studies.^{44,74} Lastly, increased inflammatory cytokines in patients with CKD leads to gastric mucosal damage, which in turn makes it difficult for *H. pylori* to survive.^{7,75}

This meta-analysis included the largest number of articles identified by a comprehensive literature search, and potential confounding modifiers were searched within each study whenever possible. Sensitivity analyses, subgroup analyses, and meta-regression tests were performed to demonstrate robustness or to identify the reason of heterogeneity. Despite the strengths, several limitations were detected during the systematic review. First, only two studies presented adjusted outcomes.^{37,40} These two studies presented different associations between *H. pylori* infection and CKD (CKD vs control: OR, 0.64; 95% CI, 0.51 to 0.81 in Chang *et al.* vs OR, 0.92; 95% CI, 0.75 to 1.12 in Kong *et al.*). Considering the high methodological quality of Chang *et al.*, the inverse association is consistent with the main result of current study, but more studies with adjusted variables are needed to explain this inconsistent result. Second, only case-control or cross-sectional studies were found during systematic review of this topic. Because the overall quality of the evidence is influenced by individual studies, future addition of high-quality studies would enhance the level of evidence. Third, it is not possible to determine the causality of the interaction-whether *H. pylori* influences the progression of kidney disease or CKD influences the *H. pylori* prevalence.

In conclusion, the results of this study suggest that there is a lower prevalence of *H. pylori* infection in patients with CKD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception and design of the study: C.S.B. Generation, col-

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