

Association between *Helicobacter pylori* and end-stage renal disease: A meta-analysis

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Abstract

AIM

To investigate the prevalence and association of *Helicobacter pylori* (*H. pylori*) with end-stage renal disease (ESRD).

METHODS

SA comprehensive literature search was completed from inception until October 2016. Studies that reported prevalence, relative risks, odd ratios, hazard ratios or standardized incidence ratio of *H. pylori* among ESRD patients were included. Participants without *H. pylori* were used as comparators to assess the association between *H. pylori* infection and ESRD. Pooled risk ratios and 95%CI was calculated using a random-effect model. Adjusted point estimates from each study were combined by the generic inverse variance method of DerSimonian and Laird.

RESULTS

Of 4546 relevant studies, thirty-seven observational studies met all inclusion criteria. Thirty-five cross-sectional studies were included in the analyses to assess the prevalence and association of *H. pylori* with ESRD. The estimated prevalence of *H. pylori* among ESRD patients was 44% (95%CI: 40%-49%). The pooled RR of *H. pylori* in patients with ESRD was 0.77 (95%CI: 0.59-1.00) when compared with the patients without ESRD. Subgroup analysis showed significantly reduced risk of *H. pylori* in adult ESRD patients with pooled RR of 0.71 (95%CI: 0.55-0.94). The data on the risk of ESRD in patients with *H. pylori* were limited. Two cohort studies were included to assess the risk of ESRD in patients with *H. pylori*. The pooled risk RR of ESRD in patients with *H. pylori* was 0.61 (95%CI: 0.03-12.20).

CONCLUSION

The estimated prevalence of *H. pylori* in ESRD patients is 44%. Our meta-analysis demonstrates a decreased risk of *H. pylori* in adult ESRD patients.

Key words: *Helicobacter pylori*; Kidney failure; Renal disease; Renal insufficiency; End stage kidney disease; Meta-analysis

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Core tip: *Helicobacter pylori* (*H. pylori*) is the most common chronic bacterial infection in gastrointestinal tract of humans. The prevalence and association of *H. pylori* with end-stage renal disease (ESRD), however, are still unclear. To further investigate this potential relationship, we conducted this systematic review and meta-analysis of observational studies reporting the association between *H. pylori* infection and ESRD and prevalence in ESRD patients. We found an estimated prevalence of *H. pylori* in ESRD patients of 44%. In addition, our meta-analysis demonstrates a 0.71-fold decreased risk of *H. pylori* in adult ESRD patients.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is the most common chronic bacterial infection in the gastrointestinal tract of humans^[1]. It has been estimated that the prevalence of *H. pylori* infection is up to thirty percent in adult aged 18 to 30 years and to fifty percent in those older

than 60 years old^[2]. Many studies demonstrated that *H. pylori* infection is associated with a peptic and duodenal ulcer, chronic gastritis, and gastric cancer^[3,4]. Recently, epidemiologic studies have demonstrated associations between *H. pylori* infection and extra-gastrointestinal organ involvements including coronary artery disease, dyslipidemia, insulin resistance, and hematologic disorders^[5-7].

End-stage renal disease (ESRD) is a common and serious chronic disease worldwide that continues to increase in prevalence by approximately 21000 cases per year in the United States^[8]. Although there is no visible evidence demonstrated that *H. pylori* infection is directly associated with renal disease, patients with ESRD usually have gastrointestinal problems such as gastritis, dyspeptic symptoms or ulcers^[9-11]. Interestingly, recent investigations have demonstrated an association between *H. pylori* infection and ESRD^[12-14]. In addition, an increase in renal resistance index due to systemic inflammation state *H. pylori* infection was also described^[15-18]. However, many studies reported the conflict data regarding the association between *H. pylori* infection in ESRD and also the prevalence of *H. pylori* infection in ESRD patients^[19-42]. Thus, we conducted the systematic review and meta-analysis that summarized all available evidence to determine the prevalence of *H. pylori* infection among ESRD patients and the association between *H. pylori* infection and ESRD.

MATERIALS AND METHODS

Literature search

Three investigators (Wijarnpreecha K, Thongprayoon C and Cheungpasitporn W) independently reviewed published studies indexed in MEDLINE and EMBASE database from their inception to October 2016 using the search strategy that included the terms for "Helicobacter", "hemodialysis", and "renal disease" as described in Item S1 in online Supplementary Data 1. A search for additional articles utilizing references from included studies was also performed. There was no confinement on language in the literature search. We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Selection criteria

The inclusion criteria were: (1) observational studies appraising the association between *H. pylori* and ESRD and prevalence in hemodialysis; (2) prevalence, odds ratios, relative risks, or hazard ratios with 95%CI were presented; and (3) individuals without *H. pylori* were used as comparators in cohort studies while individuals without ESRD were used as comparators in the cross-sectional and case-control studies. Wijarnpreecha K, Thongprayoon C and Cheungpasitporn W individually examined the titles and abstracts of the studies. After

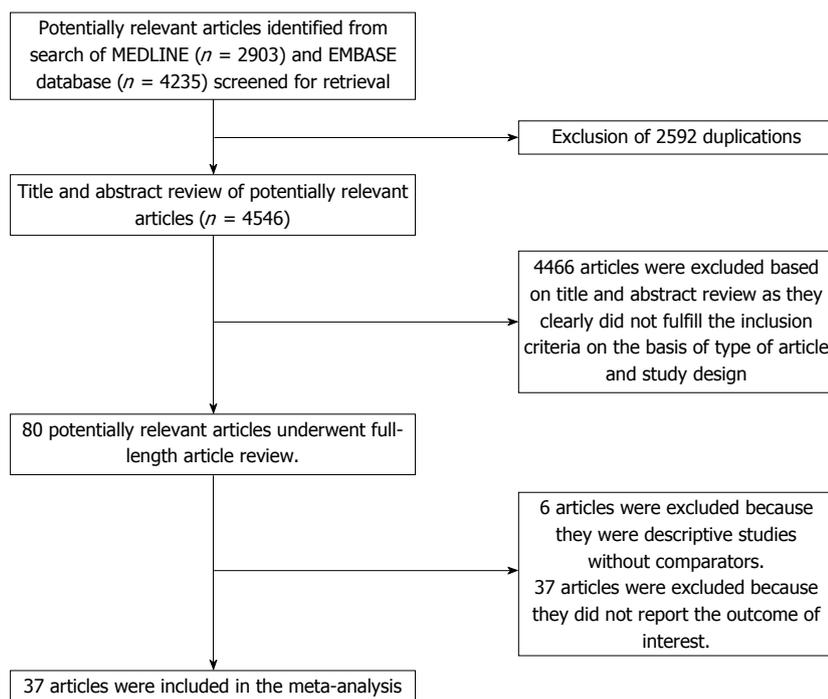


Figure 1 Literature review process.

the first phase, the full text of the included studies was subsequently examined to ascertain if they met the inclusion criteria. Discrepancies were also settled by discussion with all investigators.

Data abstraction

A structured data collection form was utilized to obtain the data from included studies including title of the study, year of publication, country where the study was conducted, name of the first author, demographic of subjects, method used to diagnose *H. pylori*, prevalence of *H. pylori*, effect estimates (hazard ratios, odds ratios, relative risks) with 95%CI, and factors adjusted in the multivariate analysis. To ensure the certainty, this data extraction process was reviewed by all investigators. The quality of each study was individually appraised by each investigator. We utilized the validated Newcastle-Ottawa quality assessment scale for cohort and case-control studies^[43] and modified Newcastle-Ottawa scale^[44] for the cross-sectional study.

Statistical analysis

MetaXL software (EpiGear International Pty Ltd)^[45] was used for meta-analysis of prevalence. Otherwise, data analysis was performed using the Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Adjusted point estimates from each study were combined by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study based on its variance^[46]. We used a random-effect model due to the high likelihood of between-study variance from different study designs, populations, and *H. pylori* testing. Cochran's *Q* test and

I^2 statistic were used to ascertain the between-study heterogeneity. A value of I^2 of 0%-25%, 25%-50%, 50%-75%, and > 75% embodied insignificant, low, moderate and high heterogeneity, respectively^[47].

RESULTS

Of 4546 potentially relevant articles, 4466 articles were excluded due to the title and abstract not meeting inclusion criteria. Subsequently, 43 articles were excluded (6 articles were not observational studies, and 37 articles did not describe the outcomes of interest). Finally, thirty-seven observational studies (2 cohort^[14,48] and 35 cross-sectional studies^[12,13,16,19-42,49-56]) met all inclusion criteria. The literature retrieval, review, and selection process are shown in Figure 1. The characteristics and quality assessment of the included cross-sectional studies are presented in Table 1 while the characteristics of the included cohort studies are shown in Table 2.

The prevalence of *H. pylori* among ESRD patients

Thirty-five cross-sectional studies were included in the analyses to assess the prevalence and association of *H. pylori* with ESRD. The estimated prevalence of *H. pylori* among ESRD patients was 44% (95%CI: 40%-49%, $I^2 = 80%$), as demonstrated in Figure 2. Subgroup analysis was also performed on thirty-two studies^[12,13,16,19-23,25-28,30-42,49-51,53-56] that provided prevalence on adult subjects and three studies^[24,29,52] that provided prevalence on pediatric patients and showed estimated prevalences of *H. pylori* among adult ESRD patients of 44% (95%CI: 39%-49%, I^2

Table 1 Main characteristics of the cross-sectional studies included in this meta-analysis

Study	Country	Year	Study sample	<i>H. pylori</i> testing	<i>H. pylori</i> prevalence (%)	OR	Study quality
Offerhaus <i>et al</i> ^[36]	The Netherland	1989	Dialysis	Antibody	22/50 (44%)	0.96 (0.42-2.22)	S3 C0 O2
Shousha <i>et al</i> ^[55]	United Kingdom	1990	Dialysis	Histology	12/50 (24%)	0.43 (0.20-0.90)	S3 C0 O2
Loffeld <i>et al</i> ^[34]	The Netherland	1991	HD	Antibody	13/30 (43%)	1.24 (0.58-2.64)	S3 C1 O2
Davenport <i>et al</i> ^[22]	United Kingdom	1991	HD	Antibody	27/76 (36%)	1.29 (0.75-2.22)	S3 C1 O2
Ala-Kaila <i>et al</i> ^[16]	Finland	1991	HD	Histology	3/23 (13%)	0.68 (0.17-2.64)	S3 C0 O2
Gladziwa <i>et al</i> ^[27]	Germany	1993	HD	Cumulative evaluation (urease, test, histology, culture and direct examination)	12/35 (34%)	0.44 (0.19 -1.00)	S3 C0 O2
Giachino <i>et al</i> ^[25]	Italy	1994	HD	Urease test, histology and culture	13/40 (32%)	0.51 (0.20-1.28)	S3 C0 O2
De Vecchi <i>et al</i> ^[51]	Italy	1995	HD and PD	Antibody	HD and PD 37/67 (55%) HD 17/29 (59%) PD 20/38 (53%)	HD and PD 0.39 (0.18-0.81) HD 0.54 (0.18-1.62) PD 0.30 (0.11-0.81)	S3 C1 O2
Jaspersen <i>et al</i> ^[31]	Germany	1995	HD	Urease test and histology	7/34 (21%)	0.44 (0.18-1.09)	S3 C0 O2
Seyrek <i>et al</i> ^[39]	Turkey	1996	HD	Antibody	13/91 (14%)	0.56 (0.21-1.50)	S3 C1 O2
Krawczyk <i>et al</i> ^[33]	Poland	1996	HD	Urease test and histology	13/21 (62%)	0.93 (0.27-3.20)	S3 C1 O2
Ozgür <i>et al</i> ^[38]	Turkey	1997	HD	Urease test	28/47 (60%)	0.83 (0.41-1.69)	S3 C0 O2
Hruby <i>et al</i> ^[30]	Poland	1997	HD	Antibody, culture	9/26 (35%) by culture 16/26 (62%) by antibody	0.68 (0.19-2.44) by culture 0.53 (0.13-2.12)	S3 C0 O2
Yildiz <i>et al</i> ^[42]	Turkey	1999	HD	Antibody	31/47 (66%)	0.79 (0.34-1.84)	S3 C0 O2
Fabrizi <i>et al</i> ^[23]	United States	1999	HD	Antibody	127/228 (56%)	1.11 (0.74-1.66)	S3 C1 O2
Tamura <i>et al</i> ^[40]	Japan	1999	HD and PD	Urease test, histology, and culture	25/49 (51%)	0.88 (0.40-1.96)	S3 C0 O2
Gür <i>et al</i> ^[28]	Turkey	1999	HD	Urease test and histology	25/45 (56%)	1.04 (0.45-2.40)	S3 C0 O2
Araki <i>et al</i> ^[50]	Japan	1999	HD and PD	Histology and culture	29/63 (46%)	0.45 (0.22-0.91)	S3 C1 O2
Karari <i>et al</i> ^[32]	Kenya	2000	CRF (HD - 36%)	Urease test and histology	41/77 (53%)	0.90 (0.48-1.70)	S3 C1 O2
Nakajima <i>et al</i> ^[53]	Japan	2002	HD	Urease test, histology, and culture	14/51 (28%)	0.30 (0.11-0.81)	S3 C0 O2

Tsukada <i>et al</i> ^[41]	Japan	2003	HD	Histology	9/36 (25%)	0.28 (0.02-3.82)	S3 C2 O2
Olmos <i>et al</i> ^[37]	Argentina	2003	HD	Antibody	44/93 (47%)	0.62 (0.35-1.11)	S3 C2 O2
Nakajima <i>et al</i> ^[54]	Japan	2004	HD	Antibody	51/138 (37%)	0.35 (0.22-0.58)	S3 C1 O2
Nardone <i>et al</i> ^[35]	Italy	2005	HD	Urease test, histology, urea breath test and stool antigen	7/11 (64%)	3.04 (0.82-11.13)	S3 C0 O2
Blusiewicz <i>et al</i> ^[19]	Poland	2005	HD	Urease, histology	19/30 (63%)	0.71 (0.24-2.07)	S3 C0 O2
Khedmat <i>et al</i> ^[13]	Iran	2007	HD	Urease test	46/73 (63%)	3.20 (1.88-5.44)	S3 C0 O2
Khazaei <i>et al</i> ^[52]	Iran	2008	HD - children	Urease test, and histology	16/24 (67%)	8.00 (2.19-29.25)	S3 C0 O2
Gioè <i>et al</i> ^[26]	Italy	2008	HD	Urease test, and histology	75/142 (53%)	1.39 (0.86-2.23)	S3 C0 O2
Abdulrahman <i>et al</i> ^[49]	Saudi Arabia	2008	ESRD	Histology	16/40 (40%)	0.22 (0.09-0.56)	S3 C1 O2
Asl <i>et al</i> ^[12]	Iran	2009	HD	Histology	23/40 (58%)	2.81 (1.13-6.99)	S3 C1 O2
Sugimoto <i>et al</i> ^[56]	Japan	2009	HD	Antibody	262/539 (49%)	0.26 (0.19-0.35)	S3 C0 O2
Chang <i>et al</i> ^[21]	South Korea	2010	HD	Urease test and histology	12/33 (36%)	0.30 (0.12-0.74)	S3 C0 O2
Hooman <i>et al</i> ^[29]	Iran	2011	HD - children	Histology	19/68 (28%)	1.59 (0.65-3.92)	S3 C0 O2
Genç <i>et al</i> ^[24]	Turkey	2013	HD and PD - children	Antibody	17/33 (52%)	0.69 (0.26-1.83)	S3 C1 O2
Chang <i>et al</i> ^[20]	Taiwan	2014	ESRD	Urease test and histology	81/144 (56%)	0.54 (0.38-0.77)	S4 C2 O3

H. pylori: *Helicobacter pylori*; HD: Hemodialysis; PD: Peritoneal dialysis.

= 81%), and 47% (95%CI: 24%-71%, $I^2 = 84%$) among ESRD children, respectively as demonstrated in Supplementary Figures 1 and 2.

The association between *H. pylori* and ESRD

We found a marginal but not significantly decreased risk of *H. pylori* infection in overall ESRD subjects compared with non-ESRD subjects^[12,13,16,19-42,49-56] with pooled RR of 0.77 (95%CI: 0.59-1.00, $I^2 = 79%$) (Figure 3). Subgroup analysis based on ageing as described above, we found a significant decreased risk of *H. pylori* infection among adult ESRD patients^[12,13,16,19-23,25-28,30-42,49-51,53-56] with pooled RR of 0.71 (95%CI: 0.55-0.94, $I^2 = 79%$) compared with non-ESRD patients (Supplementary Figure 3). Nevertheless, we did not find a significant association between *H. pylori* infection and ESRD among ESRD children^[24,29,52]; pooled RR = 1.93 (95%CI: 0.55-6.82,

$I^2 = 77%$), (Supplementary Figure 4).

The data on the risk of ESRD in patients with *H. pylori* were limited. Two cohort^[14,48] studies were included to assess the risk of ESRD in patients with *H. pylori*. The pooled risk RR of ESRD in patients with *H. pylori* was 0.61 (95%CI: 0.03-12.20).

Evaluation for publication bias

A funnel plot assessing publication bias for the association between *H. pylori* infection in overall ESRD subjects was demonstrated in Figure 4. The funnel plot of the association between *H. pylori* infection in overall ESRD subjects was symmetric and suggested no publication bias.

DISCUSSION

In this meta-analysis summarizing all presently

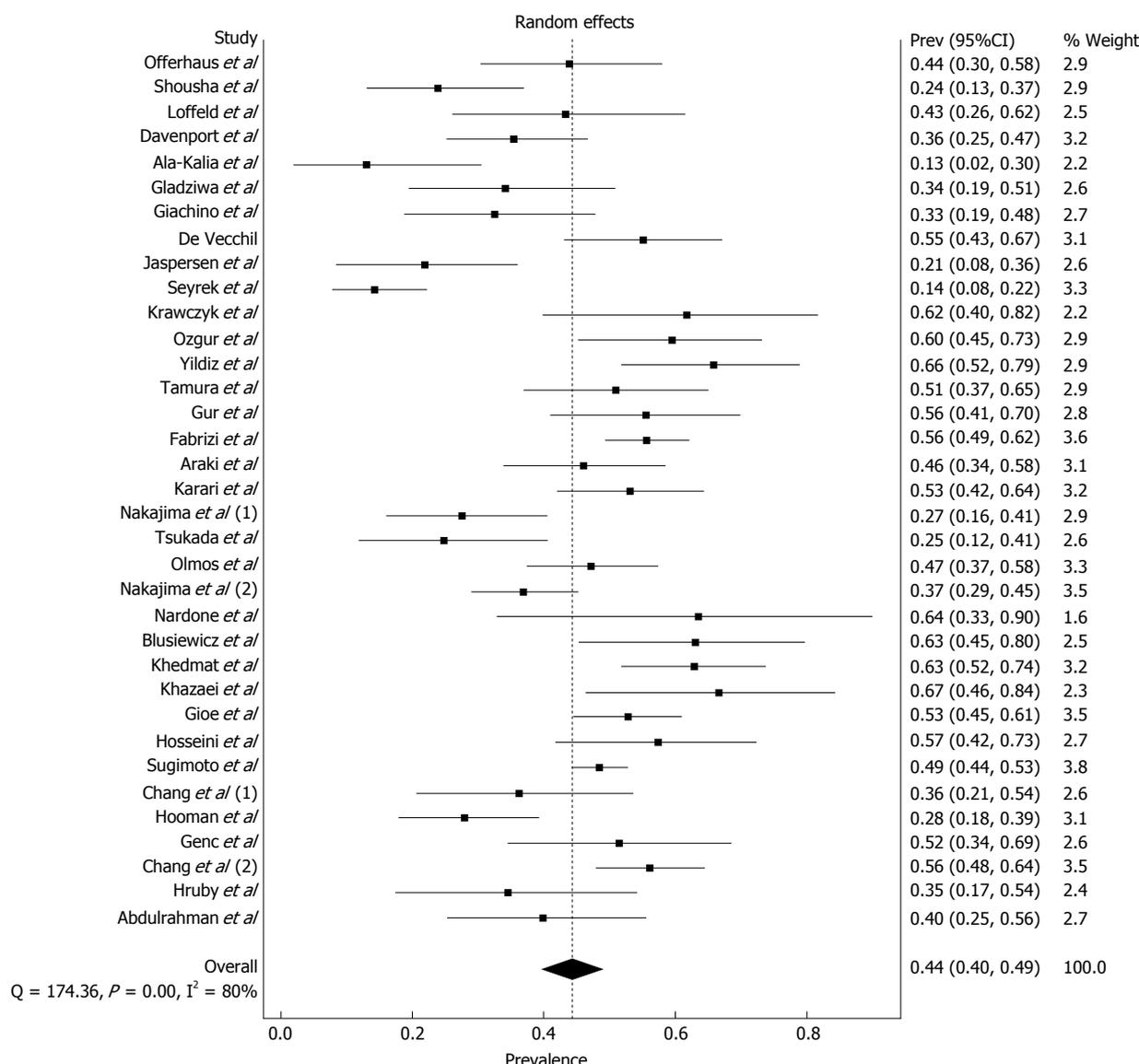


Figure 2 Forest plot of overall prevalence of *Helicobacter pylori* infection among end-stage renal disease patients.

Table 2 Main characteristics of the cohort studies included in this meta-analysis

Study	Lo <i>et al</i> ^[48]	Lin <i>et al</i> ^[14]
Country	Hong Kong	Taiwan
Study design	Cohort study	Cohort study
Year	2004	2015
Study sample	Type 2 diabetic patients with clinical proteinuria and renal insufficiency	<i>H. pylori</i> -infected and non-infected patients without ESRD
<i>H. pylori</i> testing	Antibody Positive <i>H. pylori</i> (Titer > 1.1 U/mL)	Diagnosis of <i>H. pylori</i> infection (ICD-9 041.86) was used from inpatient database of The Taiwan National Health Insurance Research Database
ESRD definition	Doubling of baseline serum creatinine concentration or need for dialysis or serum creatinine ≥ 500 μmol/L	ESRD was identified from Registry for Catastrophic Illness Patient Database
Adjusted HR	0.12 (0.03, 0.52)	2.58 (2.33, 2.86)
Confounder adjustment	Sex, <i>H. pylori</i> status, serum creatinine, hemoglobin, systolic blood pressure, ACE inhibitors, Hepatitis B surface antigen status	Age, sex, comorbidity
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

H. pylori: *Helicobacter pylori*; HD: Hemodialysis; PD: Peritoneal dialysis; ESRD: End-stage renal disease.

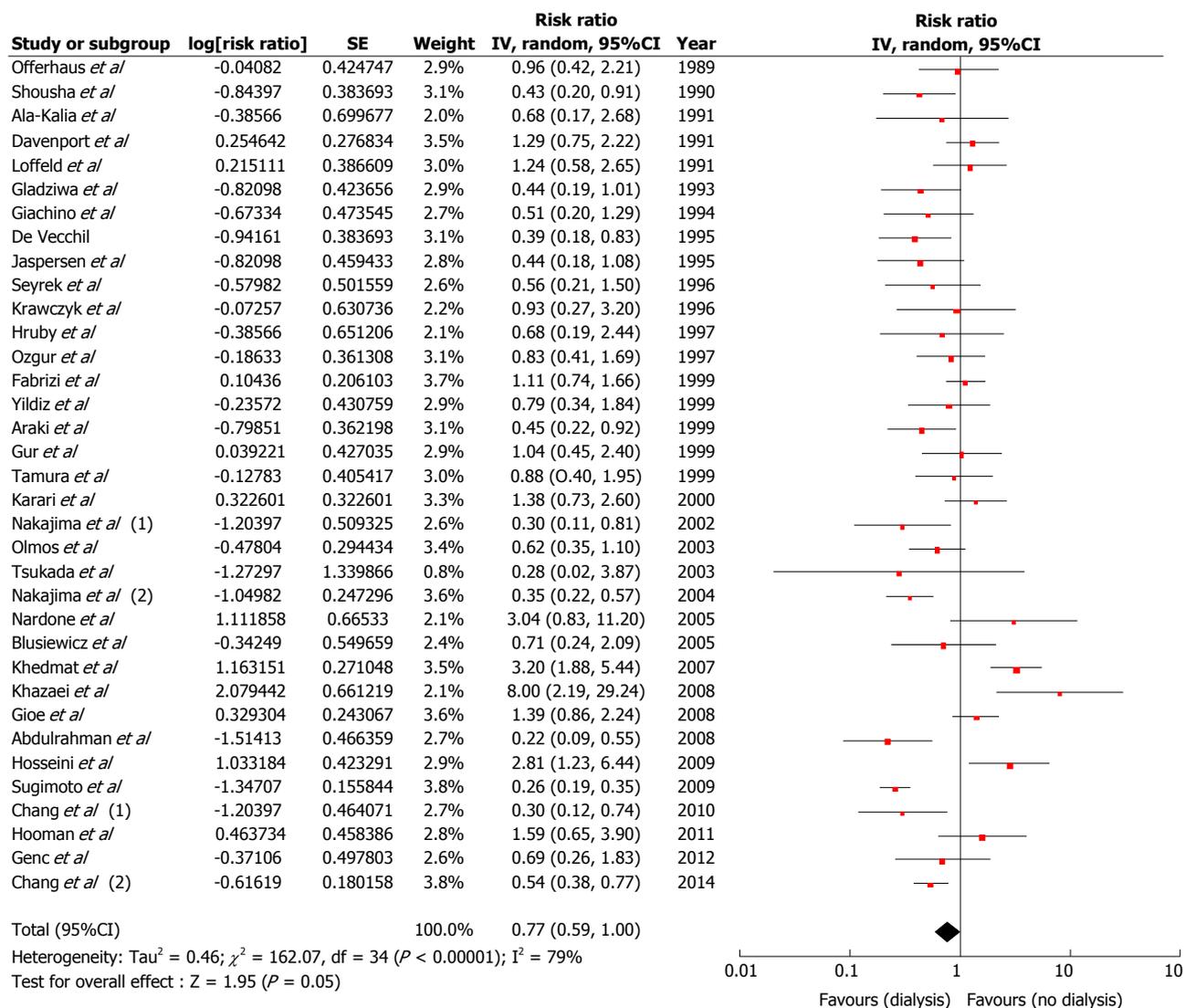


Figure 3 Forest plot of the association between *Helicobacter pylori* infection and end-stage renal disease.

available data on the prevalence of *H. pylori* infection among ESRD patients and the association between *H. pylori* infection and ESRD, we demonstrated an estimated prevalence of *H. pylori* in ESRD patients of 44%. In addition, we found a 0.71-fold decreased risk of *H. pylori* in adult ESRD patients.

Although the precise explanation of reduced risk of *H. pylori* among adult ESRD patients is still unclear, there are several plausible explanations for this association. First, it has been postulated in previous studies that administering antibiotics and antacid more frequently in ESRD patients may contribute to lower the prevalence of *H. pylori* infection^[39,53]. Previous study proposed that ESRD patients may have a lower risk of *H. pylori* infection from routinely used of antacids to prevent renal osteodystrophy by reducing intestinal phosphate absorption^[16]. Second, patients with ESRD have higher levels of inflammatory cytokines including tumor necrotic factor, interleukin-6 and -8 from infiltrative inflammatory cells in gastric mucosa^[57] and chronic circulatory failure^[58,59] could

lead to gastric mucosal damage and progress to gastric atrophy or atrophic gastritis, increased in gastric pH mucosa, and eventually eradication of *H. pylori* infection^[60-62].

Although the included studies in this meta-analysis are almost of good quality, there are several limitations to this study that need to be addressed. Firstly, there was a statistical heterogeneity in the completed analysis. Possible sources of this heterogeneity include differences in confounder-adjusted methods (e.g., age, gender, ethnicity and socioeconomic status), different test to detect *H. pylori* infection in each study, various grades of uremia. Secondly, our subgroup analysis revealed significantly decreased the risk of *H. pylori* infection among adult subjects with ESRD but not in children likely due to a limitation in some studies. Although the number of study assessing *H. pylori* in children was limited and the insignificant finding in ESRD children could be from the lack of power, further studies are required to determine the role of aging in the underlying pathogenesis of *H. pylori* infection

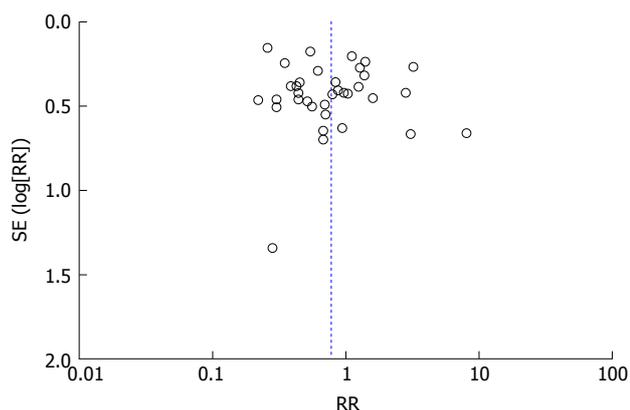


Figure 4 Funnel plot of the association between *Helicobacter pylori* infection and end-stage renal disease.

among ESRD patients. Lastly, this study is a meta-analysis of observational studies. Thus, our study demonstrated an association, but could not establish causality as unknown confounders could play a role in the association between prevalence of *H. pylori* among hemodialysis and association between *H. pylori* and ESRD.

In conclusion, our meta-analysis demonstrated an estimated prevalence of *H. pylori* in ESRD patients of 44%. In addition, our meta-analysis demonstrates a decreased risk of *H. pylori* in adult ESRD patients. ESRD could be a potential protective factor for *H. pylori* infection.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) is the most common chronic bacterial infection in the gastrointestinal tract of humans. Epidemiologic studies showed the link between *H. pylori* infection and extra-gastrointestinal tract including end-stage renal disease (ESRD). However, many studies reported the conflict data regarding the association between *H. pylori* infection in ESRD and also the prevalence of *H. pylori* infection in ESRD patients.

Research frontiers

The results of those epidemiologic studies were inconsistent. To further investigate this possible association of *H. pylori* infection and ESRD and determine the prevalence of *H. pylori* among ESRD patients, the authors conducted this systematic review and meta-analysis of observational studies reporting the association between *H. pylori* and ESRD and prevalence of *H. pylori* among ESRD patients.

Innovations and breakthroughs

The authors found an estimated prevalence of *H. pylori* in ESRD patients of 44% (95%CI: 40%-49%). Moreover, the authors also found a decreased risk of *H. pylori* infection among adult ESRD patients with pooled RR of 0.71 (95%CI: 0.55-0.94).

Applications

This study demonstrated a significantly decreased risk of *H. pylori* infection among ESRD patients. This finding suggests that ESRD may be an independent potential protective factor for *H. pylori* infection.

Peer-review

This meta-analysis investigated the prevalence and association of *H. pylori*

with end-stage renal diseases and demonstrated a decreased risk of *H. pylori* in adult ESRD patients. The context is well organized and the conclusion is of interest.

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