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

Wijarnpreecha K *et al.* *H. pylori* and end-stage renal disease

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**Abstract**

***AIM***

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

***METHODS***

A 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 4,546 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 prevalenceof *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](#_ENREF_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](#_ENREF_2)]. Many studies demonstrated that *H. pylori* infection is associated with a peptic and duodenal ulcer, chronic gastritis, and gastric cancer[[3](#_ENREF_3),[4](#_ENREF_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](#_ENREF_5)].

End-stage renal disease (ESRD) is a common and serious chronic disease worldwide that continues to increase in prevalence by approximately 21,000 cases per year in the United States[[8](#_ENREF_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](#_ENREF_9)]. Interestingly, recent investigations have demonstrated an association between H. pylori infection and ESRD[[12-14](#_ENREF_12)]. In addition, an increase in renal resistance index due to systemic inflammation state *H. pylori* infection was also described[[15-18](#_ENREF_15)]. 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](#_ENREF_19)]. 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 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](#_ENREF_43)] and modified Newcastle-Ottawa scale[[44](#_ENREF_44)] for the cross-sectional study.

***Statistical analysis***

MetaXL software ([EpiGear](http://www.epigear.com) International Pty Ltd)[[45](#_ENREF_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](#_ENREF_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 I2 statistic were used to ascertain the between-study heterogeneity. A value of *I2* of 0%-25%, 25%-50%, 50%-75%, and > 75% embodied insignificant, low, moderate and high heterogeneity, respectively[[47](#_ENREF_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](#_ENREF_14),[48](#_ENREF_48)] and 35 cross-sectional studies[[12](#_ENREF_12),[13](#_ENREF_13),[16](#_ENREF_16),[19-42](#_ENREF_19),[49-56](#_ENREF_49)]) 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 prevalenceof *H. pylori* among ESRD patients was 44% (95%CI: 40%-49%, *I2* = 80%), as demonstrated in Figure 2. Subgroup analysis was also performed on thirty-two studies[[12](#_ENREF_12),[13](#_ENREF_13),[16](#_ENREF_16),[19-23](#_ENREF_19),[25-28](#_ENREF_25),[30-42](#_ENREF_30),[49-51](#_ENREF_49),[53-56](#_ENREF_53)] that provided prevalence on adult subjects and three studies[[24](#_ENREF_24),[29](#_ENREF_29),[52](#_ENREF_52)] that provided prevalence on pediatric patients and showed estimated prevalencesof *H. pylori* among adult ESRD patients of 44% (95%CI: 39%-49%, *I2*= 81%), and 47% (95%CI: 24%-71%, *I2* = 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](#_ENREF_12),[13](#_ENREF_13),[16](#_ENREF_16),[19-42](#_ENREF_19),[49-56](#_ENREF_49)] with pooled RR of 0.77 (95%CI: 0.59-1.00, *I2* = 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](#_ENREF_12),[13](#_ENREF_13),[16](#_ENREF_16),[19-23](#_ENREF_19),[25-28](#_ENREF_25),[30-42](#_ENREF_30),[49-51](#_ENREF_49),[53-56](#_ENREF_53)] with pooled RR of 0.71 (95%CI: 0.55-0.94, *I2* = 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](#_ENREF_24),[29](#_ENREF_29),[52](#_ENREF_52)]; pooled RR = 1.93 (95%CI: 0.55-6.82, *I2 =* 77%), (supplementary Figure4).

The data on the risk of ESRD in patients with *H. pylori* were limited. Two cohort[[14](#_ENREF_14),[48](#_ENREF_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 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](#_ENREF_39),[53](#_ENREF_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](#_ENREF_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](#_ENREF_57)] and chronic circulatory failure[[58](#_ENREF_58),[59](#_ENREF_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].

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 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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**D:\WJG\编稿\WJG加工厂\2017-1-4\31120\Figure 1.tif**

**Figure 1 Literature review process.**

**D:\WJG\编稿\WJG加工厂\2017-1-4\31120\Figure 2.tif**

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

**D:\WJG\编稿\WJG加工厂\2017-1-4\31120\Figure 3.tif**

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

**D:\WJG\编稿\WJG加工厂\2017-1-4\31120\Figure 4.tif**

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

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Country** | **Year** | **Study sample** | ***H. pylori* testing** | ***H. pylori* prevalence (%)** | **OR** | **Study quality** |
| Offerhaus *et al*[36] | The Netherland | 1989 | Dialysis | Antibody | 22/50 (44%) | 0.96 (0.42-2.22) | S 3  C 0  O 2 |
| Shousha *et al*[55] | United Kingdom | 1990 | Dialysis | Histology | 12/50 (24%) | 0.43 (0.20-0.90) | S 3  C 0  O 2 |
| Loffeld *et al*[34] | The Netherland | 1991 | HD | Antibody | 13/30 (43%) | 1.24 (0.58-2.64) | S 3  C 1  O 2 |
| Davenport *et al*[22] | United Kingdom | 1991 | HD | Antibody | 27/76 (36%) | 1.29 (0.75-2.22) | S 3  C 1  O 2 |
| Ala-Kaila *et al*[16] | Finland | 1991 | HD | Histology | 3/23 (13%) | 0.68 (0.17-2.64) | S 3  C 0  O 2 |
| Gladziwa *et al*[27] | Germany | 1993 | HD | Cumulative evaluation (urease, test, histology, culture and direct examiniation) | 12/35 (34%) | 0.44 (0.19 -1.00) | S 3  C 0  O 2 |
| Giachino *et al*[25] | Italy | 1994 | HD | Urease test, histology and culture | 13/40 (32%) | 0.51 (0.20-1.28) | S 3  C 0  O 2 |
| De Vecchi *et al*[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) | S 3  C 1  O 2 |
| Jaspersen *et al*[31] | Germany | 1995 | HD | Urease test and histology | 7/34 (21%) | 0.44 (0.18-1.09) | S 3  C 0  O 2 |
| Seyrek *et al*[39] | Turkey | 1996 | HD | Antibody | 13/91 (14%) | 0.56 (0.21-1.50) | S 3  C 1  O 2 |
| Krawczyk *et al*[33] | Poland | 1996 | HD | Urease test and histology | 13/21 (62%) | 0.93 (0.27-3.20) | S 3  C 1  O 2 |
| Ozgür *et al*[38] | Turkey | 1997 | HD | Urease test | 28/47 (60%) | 0.83 (0.41-1.69) | S 3  C 0  O 2 |
| Hruby *et al*[30] | Poland | 1997 | HD | Antibody, culture | 9/26 (35%) by culture  16/26 (62%0 by antibody | 0.68 (0.19-2.44) by culture  0.53 (0.13-2.12) | S 3  C 0  O 2 |
| Yildiz *et al*[42] | Turkey | 1999 | HD | Antibody | 31/47 (66%) | 0.79 (0.34-1.84) | S 3  C 0  O 2 |
| Fabrizi *et al*[23] | United States | 1999 | HD | Antibody | 127/228 (56%) | 1.11 (0.74-1.66) | S 3  C 1  O 2 |
| Tamura *et al*[40] | Japan | 1999 | HD and PD | Urease test, histology, and culture | 25/49 (51%) | 0.88 (0.40-1.96) | S 3  C 0  O 2 |
| Gür *et al*[28] | Turkey | 1999 | HD | Urease test and histolgy | 25/45 (56%) | 1.04 (0.45-2.40) | S 3  C 0  O 2 |
| Araki *et al*[50] | Japan | 1999 | HD and PD | Histology and culture | 29/63 (46%) | 0.45 (0.22-0.91) | S 3  C 1  O 2 |
| Karari *et al*[32] | Kenya | 2000 | CRF  (HD – 36%) | Urease test and histology | 41/77 (53%) | 0.90 (0.48-1.70) | S 3  C 1  O 2 |
| Nakajima *et al*[53] | Japan | 2002 | HD | Urease test, histology, and culture | 14/51 (28%) | 0.30 (0.11-0.81) | S 3  C 0  O 2 |
| Tsukada *et al*[41] | Japan | 2003 | HD | Histology | 9/36 (25%) | 0.28 (0.02-3.82) | S 3  C 2  O 2 |
| Olmos *et al*[37] | Argentina | 2003 | HD | Antibody | 44/93 (47%) | 0.62 (0.35-1.11) | S 3  C 2  O 2 |
| Nakajima *et al*[54] | Japan | 2004 | HD | Antibody | 51/138 (37%) | 0.35 (0.22-0.58) | S 3  C 1  O 2 |
| Nardone *et al*[35] | Italy | 2005 | HD | Urease test, histology, urea breath test and stool antigen | 7/11 (64%) | 3.04 (0.82-11.13) | S 3  C 0  O 2 |
| Blusiewicz *et al*[19] | Poland | 2005 | HD | Urease, histology | 19/30 (63%) | 0.71 (0.24-2.07) | S 3  C 0  O 2 |
| Khedmat *et al*[13] | Iran | 2007 | HD | Urease test | 46/73 (63%) | 3.20 (1.88-5.44) | S 3  C 0  O 2 |
| Khazaei *et al*[52] | Iran | 2008 | HD - children | Urease test, and histology | 16/24 (67%) | 8.00 (2.19-29.25) | S 3  C 0  O 2 |
| Gioè *et al*[26] | Italy | 2008 | HD | Urease test, and histology | 75/142 (53%) | 1.39 (0.86-2.23) | S 3  C 0  O 2 |
| Abdulrahman *et al*[49] | Saudi Arabia | 2008 | ESRD | Histology | 16/40 (40%) | 0.22 (0.09-0.56) | S 3  C 1  O 2 |
| Asl *et al*[12] | Iran | 2009 | HD | Histology | 23/40 (58%) | 2.81 (1.13-6.99) | S 3  C 1  O 2 |
| Sugimoto *et al*[56] | Japan | 2009 | HD | Antibody | 262/539 (49%) | 0.26 (0.19-0.35) | S 3  C 0  O 2 |
| Chang *et al*[21] | South Korea | 2010 | HD | Urease test and histology | 12/33 (36%) | 0.30 (0.12-0.74) | S 3  C 0  O 2 |
| Hooman *et al*[29] | Iran | 2011 | HD - children | Histology | 19/68 (28%) | 1.59 (0.65-3.92) | S 3  C 0  O 2 |
| Genç *et al*[24] | Turkey | 2013 | HD and PD - children | Antibody | 17/33 (52%) | 0.69 (0.26-1.83) | S 3  C 1  O 2 |
| Chang *et al*[20] | Taiwan | 2014 | ESRD | Urease test and histology | 81/144 (56%) | 0.54 (0.38-0.77) | S 4  C 2  O 3 |

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

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

|  |  |  |
| --- | --- | --- |
| **Study** | **Lo *et al*[48]** | **Lin *et al*[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 | *H. pylori*-infected and non-infected patients without ESRD |
| *H. pylori* testing | Antibody  Positive *H. pylori* (Titer > 1.1 U/ml) | Diagnosis of *H. pylori* 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, *H. pylori* 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.