Protective Role of *Helicobacter pylori* Infection in Prognosis of Gastric Cancer: Evidence from 2454 Patients with Gastric Cancer

Fang Wang¹, Guoping Sun¹*, Yanfeng Zou², Fei Zhong¹, Tai Ma¹, Xiaoqiu Li¹

¹ Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China, ² Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, Anhui, China

Abstract

**Background:** A number of studies have investigated the association between *Helicobacter pylori* (*H. pylori*) infection and the prognosis of gastric cancer (GC), with inconsistent and inconclusive results. We performed a meta-analysis to derive a more precise estimation of the association.

**Methodology/Principal Findings:** A systematic search of PubMed, EMBASE, Cochrane and Chinese wanfang databases was performed with the last search updated on February 19, 2013. The hazard ratio (HR) and its 95% confidence interval (95%CI) were used to assess the strength of association. A total of 12 studies including 2454 patients with GC were involved in this meta-analysis. The pooled HR was 0.71 (95%CI: 0.57–0.87; \( P = 0.001 \)) for OS and 0.60 (95%CI: 0.30–1.18; \( P = 0.139 \)) for DFS in GC patients, respectively. The protective role of *H. pylori* infection in the prognosis of GC was also observed among different subgroups stratified by ethnicity, statistical methodology, *H. pylori* evaluation method and quality assessment. There was no evidence of publication bias.

**Conclusions/Significance:** This meta-analysis suggests a protective role for *H. pylori* infection in the prognosis of GC. The underlying mechanisms need to be further elucidated, which could provide new therapeutic approaches for GC.

Introduction

Gastric cancer (GC) remains the fourth most common malignancy and the second most common cause of cancer-related deaths throughout the world [1]. Despite recent advances in surgical techniques combined with neoadjuvant chemotherapy and radiotherapy approaches, patients with advanced disease still have a poor outlook [2]. Most cases have locally advanced disease when diagnosed, with a 5-year survival rate of only 20% to 25% [3]. In the era of personalized medicine, it is necessary to find prognostic and predictive factors that can be used to modify treatment strategies.

*Helicobacter pylori* (*H. pylori*) is a Gram-negative, microaerophilic bacterium which is the major causative agent of gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and GC [4]. Moreover, International Agency for Research on Cancer categorized *H. pylori* as a group 1 carcinogen for GC in 1994 [5]. To date, an increasing body of evidence indicates that *H. pylori* infection increases the risk of developing adenocarcinoma of the distal stomach [6–7]. Meanwhile, some researchers have focused on the association between *H. pylori* status and the prognosis of GC patients [8–19]. Several studies suggested that patients with GC who are negative for *H. pylori* have a poor outlook than those positive [9–11,16,18]. However, some other studies did not provide evidence of a better prognosis in patients with *H. pylori* infection compared with negative subjects [9,12–15,17,19].

These reported results were inconsistent and conflicting with no clear consensus. Therefore, we performed a meta-analysis to derive a more precise estimation of the association between *H. pylori* infection and the prognosis of GC.

Materials and Methods

Identification of Studies

We conducted a comprehensive search of medical literature on studies evaluating the effect of *H. pylori* infection on the prognosis of GC. We searched the US National Library of Medicine’s PubMed database, Excerpta Medica Database (EMBASE), the Cochrane Central Register of Controlled Trials and Chinese wanfang database using the keywords “*Helicobacter pylori*”, “*H. pylori*”, “gastric cancer”, “gastric carcinoma”, “prognosis”, “survival”, “recurrence”, and “relapse” with the last search updated on February 19, 2013. There is no restriction on language or publication years in the selection process. All of the references from review papers and original reports were checked for further
relevant studies in the systematic review. Search was performed independently by two reviewers (WF and ZYF), and disagreement was resolved by discussion with our research team.

Eligibility Criteria
Studies were eligible if survival was analyzed in GC patients stratified by H. pylori status. The primary outcome of interest was overall survival (OS). The secondary outcome of interest was disease-free survival (DFS). Criteria for eligibility of a study to the present meta-analysis were: to present a proven diagnosis of GC in humans; to evaluate the association between H. pylori status and patient survival; to provide hazard ratios (HRs) with its corresponding 95% confidence intervals (CIs) or sufficient data for estimating HR with 95%CI.

Data Extraction
Data extraction was performed independently by two reviewers (WF and ZYF). Disagreement was resolved by discussion with our research team. For each study the following information were collected: the first author's name, ethnicity, year of publication, definition of cases, sample size, H. pylori evaluation method, number of patients with positive H. pylori status and prognostic information. If the required information were unavailable in relevant articles, a request was sent to the corresponding author for additional data. If a study reported the results on different ethnicities, we treated them as separate studies.

Quality Assessment
Quality assessment was performed with the Newcastle-Ottawa quality assessment scale (NOS) for cohort studies. Each study was judged on three broad perspectives: selection, comparability and outcome. The maximum score was 9 and a high-quality study was defined as one with a score of ≥6. Quality assessment was performed independently by two reviewers (MT and LXQ), and disagreement was resolved by discussion with our research team.

Statistical Analysis
We used the PRISMA checklist as protocol of the meta-analysis and followed the guideline (Table S1) [20]. The HR and its 95%CI were used to assess the strength of association. Heterogeneity among studies was assessed by using the chi-square test, with a value indicating better methodology (see Table S2). Ten studies were excluded for duplicate reports [28–32]. There were two studies from the same population, both reported by Lee et al. [8,33]. Under this circumstance, the study with larger sample size was included [8], while the other study was excluded due to overlapping data-set [33]. The study by Zhang et al. [34] was excluded because it focused on patients with proximal gastric carcinoma involving the esophagus (PGCE).

Study Characteristics and Quality Assessment
The main characteristics for the studies included in our meta-analysis are summarized in Table 1. Among these studies, 7 studies were performed in Asians [8,12,13,15,16,18,19], 4 studies were performed in Caucasians [9–11,17] and 1 study was performed in Brazilian [14]. Sample sizes ranged from 61 [10,19] to 794 patients [13], with a total of 2454 GC patients. The positive rate of H. pylori varied from 17.5% [15] to 86.2% [11]. H. pylori status was evaluated by different methods in these studies, which mainly included serologic detection, histological analysis and polymerase chain reaction (PCR). We were able to extract overall survival (OS) information from all the studies on GC. Nevertheless, we were able to extract disease-free survival (DFS) information from only 3 studies [10,12,19].

The range of quality scores was from 4 to 9 stars, with a higher value indicating better methodology (see Table S2). Ten studies that had ≥6 awarded stars were categorized as high quality studies [8–14,16,17,19], while 2 studies that had <6 awarded stars were categorized as low quality studies [15,19].

Overall Analysis
The main results of this meta-analysis and the heterogeneity test are presented in Table 2. Among the 12 studies eligible for pooling of OS data, 7 studies provided estimated HR associated with its 95%CI [8,10–14,16]. In the remaining studies, these data points were calculated from data presented [9,15,17] or reconstructed from survival curve [18,19]. Figure 2 shows the forest plot of HR for OS from each study. The pooled HR for OS in GC patients was 0.71 (95%CI: 0.57–0.87; P = 0.001), with significant evidence of heterogeneity between the contributing studies (P = 0.0001). The funnel plot of HR showed no evidence of publication bias from
Figure 1. The flow chart of the included studies in the meta-analysis.
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Table 1. Characteristics of studies that evaluated the impact of *H. pylori* infection on the prognosis of gastric cancer.

| Study ID | Authors | Year | Ethnicity | Sample Size | Patients positive for *H. pylori* (%) | *H. pylori* Evaluation Method | Prognostic information | Quality Score |
|----------|---------|------|-----------|-------------|-------------------------------------|-----------------------------|------------------------|--------------|
| 1        | Lee et al. [8] | 1995 | Asian     | 151         | 92(60.9)                             | Serologic detection         | OS:0.91(0.51–1.62)    | 7/9          |
| 2        | Kurtenkov et al. [9] | 2003 | Caucasian | 87          | NA                                  | Serologic detection         | OS:0.74(0.63–0.87)    | 6/9          |
| 3        | Meimarakis et al. [10] | 2006 | Caucasian | 166         | 125(75.3)                           | Serologic detection, Histological analysis, Bacterial culture | OS:0.50(0.31–0.82) DFS:0.46(0.29–0.75) | 8/9          |
| 4        | Marrelli et al. [11] | 2009 | Caucasian | 297         | 256(86.2)                           | Serologic detection, PCR    | OS:0.40(0.23–0.71)    | 9/9          |
| 5        | Qiu et al. [12] | 2010 | Asian     | 157         | 82(52.2)                             | PCR                         | OS:1.09(0.70–1.68) DFS:1.13(0.67–1.92) | 8/9          |
| 6        | Gan et al. [13] | 2011 | Asian     | 794         | 239(30.1)                           | Histological analysis       | OS:0.87(0.70–1.08)    | 8/9          |
| 7        | Santos et al. [14] | 2011 | Brazilian | 68          | 34(50.0)                             | Histological analysis       | OS:0.68(0.40–1.16)    | 8/9          |
| 8        | Chen et al. [15] | 2012 | Asian     | 120         | 21(17.5)                             | PCR                         | OS:1.50(0.75–3.00)    | 5/9          |
| 9        | Kang et al. [16] | 2012 | Asian     | 274         | 166(60.6)                           | Histological analysis       | OS:0.29(0.20–0.41)    | 8/9          |
| 10       | Syrios et al. [17] | 2012 | Caucasian | 218         | 76(34.9)                             | Serologic detection         | OS:0.88(0.66–1.16)    | 7/9          |
| 11       | Choi et al. [18] | 2012 | Asian     | 61          | 19(31.1)                             | Histological analysis       | OS:0.78(0.63–0.97)    | 5/9          |
| 12       | Hur et al. [19] | 2012 | Asian     | 61          | 40(65.6)                             | Serologic detection, Histological analysis | OS:0.62(0.25–1.54) DFS:0.37(0.16–0.84) | 7/9          |

Abbreviations: *H. pylori*, Helicobacter pylori; OS, overall survival; DFS, disease-free survival; PCR, Polymerase chain reaction; HR, hazard ratio; CI, confidence interval; u, univariate result; m, multivariate result; NA, not available.

**HR = 1 for negative *H. pylori* status.**

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Subgroup and Sensitivity Analyses

Subgroup and sensitivity analyses were further performed to evaluate the effect of *H. pylori* infection on OS in GC patients. Statistically significant heterogeneity was observed in all the subgroup analyses except for the subgroup analysis of univariate results. The results of Begg's test and Egger's test showed no evidence of publication bias for all subgroup analyses. When stratified by ethnicity, the subgroup analysis in Asians yielded a HR of 0.66 (95%CI: 0.50–0.87; P = 0.003), whereas the subgroup analysis in Caucasians yielded a HR of 0.80 (95%CI: 0.72–0.87; P = 0.019), with evidence of study heterogeneity (I² = 64.3%).

Statistical methodology

Univariate analysis results

| Statistic | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-----------|------------|---|---------|-------|----|---------|-------|
| OS Overall | 0.71 (0.57–0.87) | 3.27 | 0.001 | R | 44.79 | <0.0001 | 75.4 |

Ethnicity

| Ethnicity | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-----------|------------|---|---------|-------|----|---------|-------|
| Asian | 0.77 (0.54–1.10) | 1.46 | 0.145 | R | 36.08 | <0.0001 | 83.4 |
| Caucasian | 0.66 (0.50–0.87) | 2.95 | 0.003 | R | 8.39 | 0.039 | 64.3 |

Subgroup analysis in Caucasians

| Subgroup analysis | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-------------------|------------|---|---------|-------|----|---------|-------|
| OS Overall | 0.77 (0.54–1.10) | 1.46 | 0.145 | R | 36.08 | <0.0001 | 83.4 |

Discussion

Meta-analysis was originally developed to combine the results of randomized controlled trials. Nowadays, this approach has been widely applied for identification of prognostic indicators in patients with malignant diseases [35,36]. The reports about the prognostic signification of *H. pylori* infection in GC were controversial, thus the combination of data to reach a reasonable conclusion is necessary. As far as we know, this is the first meta-analysis to investigate the association between *H. pylori* infection and the prognosis of GC. Findings from the current meta-analysis suggest that positive *H. pylori* status is associated with better OS in GC patients, which may provide a new light of therapeutic and prophylactic targets in *H. pylori*-related GC.

When stratified by ethnicity, the protective role of *H. pylori* infection in the prognosis of GC was identified in subgroup analysis of Caucasians. In contrast, there was no association between *H. pylori* infection and patient survival in subgroup analysis of Asians. So far, reasons for ethnic differences remain unclear. Population differences of genetic factors, dietary behavior, environmental exposures and other factors may help explain part of the ethnic differences in patient survival with GC. Furthermore, more and larger studies in Asians, Caucasians as well as Africans are warranted in the future. The method used for the assessment of *H. pylori* status differed among these studies. In order to minimize the effects resulting from *H. pylori* evaluation methods, we investigated the effects of *H. pylori* infection on survival in three categorized groups: serologic detection group, histological analysis group and PCR group. We observed improved survival among either Begg's test (P = 0.999) or Egger's test (P = 0.634), which was shown in Figure 3.

When assessing *H. pylori* infection on DFS in GC patients, only three studies presented data valuable for analysis [10,12,19]. The pooled HR was 0.60 (95%CI: 0.30–1.18; P = 0.005) and the HR for the 6 studies using serologic detection method was 0.73 (95%CI: 0.64–0.83; P = 0.0001), whereas the pooled HR for the multivariable analysis results was 0.66 (95%CI: 0.50–0.85; P = 0.003).

Sensitivity analyses showed that the HR and 95%CI did not alter substantially by removing any one study, ranged from a low of 0.68 (95%CI: 0.55–0.84; P = 0.001) to a high of 0.78 (95%CI: 0.68–0.90; P = 0.001) via omission of the study by Chen et al. [15] and the study by Kang et al. [16], respectively.

### Abbreviations

- *H. pylori*
- Helicobacter pylori
- OS, overall survival
- DFS, disease-free survival
- PCR, Polymerase chain reaction
- HR, hazard ratio
- CI, confidence interval
- R, random-effects model
- F, fixed-effects model

### Quality assessment

| Evaluation Method | No. of Studies | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-------------------|----------------|------------|---|---------|-------|----|---------|-------|
| Serologic detection | 6 | 0.73 (0.64–0.83) | 4.92 | <0.0001 | F | 9.10 | 0.105 | 45.0 |
| Histological analysis | 6 | 0.60 (0.42–0.85) | 2.82 | 0.005 | R | 29.74 | <0.0001 | 83.2 |
| PCR | 3 | 0.86 (0.41–1.81) | 0.40 | 0.690 | R | 10.69 | 0.005 | 81.3 |

### Statistical methodology

| Test of association | Test of heterogeneity |
|---------------------|-----------------------|
| Pooled HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
| OS Overall | 0.71 (0.57–0.87) | 3.27 | 0.001 | R | 44.79 | <0.0001 | 75.4 |

| Ethnicity | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-----------|------------|---|---------|-------|----|---------|-------|
| Asian | 0.77 (0.54–1.10) | 1.46 | 0.145 | R | 36.08 | <0.0001 | 83.4 |
| Caucasian | 0.66 (0.50–0.87) | 2.95 | 0.003 | R | 8.39 | 0.039 | 64.3 |

| Subgroup analysis | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-------------------|------------|---|---------|-------|----|---------|-------|
| OS Overall | 0.77 (0.54–1.10) | 1.46 | 0.145 | R | 36.08 | <0.0001 | 83.4 |

| Stratified analysis | No. of Studies | Test of association | Test of heterogeneity |
|---------------------|----------------|---------------------|-----------------------|
| OS Overall | 12 | 0.71 (0.57–0.87) | 3.27 | 0.001 | R | 44.79 | <0.0001 | 75.4 |

| Ethnicity | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-----------|------------|---|---------|-------|----|---------|-------|
| Asian | 0.77 (0.54–1.10) | 1.46 | 0.145 | R | 36.08 | <0.0001 | 83.4 |
| Caucasian | 0.66 (0.50–0.87) | 2.95 | 0.003 | R | 8.39 | 0.039 | 64.3 |

| Subgroup analysis | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-------------------|------------|---|---------|-------|----|---------|-------|
| OS Overall | 0.77 (0.54–1.10) | 1.46 | 0.145 | R | 36.08 | <0.0001 | 83.4 |

| Evaluation Method | No. of Studies | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-------------------|----------------|------------|---|---------|-------|----|---------|-------|
| Serologic detection | 6 | 0.73 (0.64–0.83) | 4.92 | <0.0001 | F | 9.10 | 0.105 | 45.0 |
| Histological analysis | 6 | 0.60 (0.42–0.85) | 2.82 | 0.005 | R | 29.74 | <0.0001 | 83.2 |
| PCR | 3 | 0.86 (0.41–1.81) | 0.40 | 0.690 | R | 10.69 | 0.005 | 81.3 |

| Quality assessment | HR (95%CI) | Z | P-value | Model | I² | P-value | I² (%) |
|-------------------|------------|---|---------|-------|----|---------|-------|
| High quality | 10 | 0.66 (0.52–0.85) | 3.31 | 0.001 | R | 40.20 | <0.0001 | 77.6 |
| Low quality | 2 | 0.90 (0.54–1.84) | 0.02 | 0.980 | R | 3.12 | 0.077 | 67.9 |

| DFS Overall | 3 | 0.60 (0.30–1.18) | 1.48 | 0.139 | R | 8.00 | 0.018 | 75.0 |

*HR* = 1 for negative *H. pylori* status.
patients with positive *H. pylori* status in both serologic detection group and histological analysis group, consistent with the overall analysis result. With regard to the statistical methodology, the results of the meta-analysis suggested an association between positive *H. pylori* status and better survival in either a univariate setting or a multivariate setting. Thus, even after adjustment for conventional prognostic factors of survival, the association observed in the univariable analysis seemed still hold in the multivariable analysis. Moreover, the significant protective effect of *H. pylori* on patient survival with GC was still observed even after excluding low quality studies or in sensitivity analysis. No improvements in terms of DFS were observed in the present meta-analysis. This result should be interpreted with caution due to the small number of contributing studies.

There is continued controversy with regard to whether *H. pylori* infection can lead to improved outcomes for GC patients. *H. pylori* is thought to be an important pathogen for GC, which indirectly promote carcinogenesis through induction of chronic inflammatory states. Once cancer has developed, persistent infection with *H. pylori* and infiltration with some leucocyte subsets seem to correlate with a favorable prognosis in *H. pylori*-related GC patients [37]. This seems paradoxical but might have a biological basis. The plausible explanations and theoretical bases may be elucidated as follows. Microbe-induced inflammation might modulate antitumor immunity. The presence of *H. pylori* acts as an adjuvant for the induction of the cellular immune response which displays a type-1 T-helper-cell (Th1) type, and a local B-cell response in gastric mucosa [38,39]. Wherever, the relation between inflammation-related immune response and antitumor activity still needs further evidences. If further related basic experiments confirm the hypothesis, *H. pylori* might contribute to an improved antitumor immune response. Microsatellite instability may also play certain role in *H. pylori* positive GC. Microsatellite instability is a hallmark of the DNA mismatch repair deficiency that is one of the pathways of gastric carcinogenesis. Microsatellite alterations were related with a higher rate of *H. pylori* infection and a better postoperative survival [40,41].

Despite considerable efforts to explore the possible association between *H. pylori* infection and the prognosis of GC, some limitations should be addressed. Firstly, significant between-study heterogeneity was detected in overall and subgroup analyses, which may be distorting the meta-analysis. There is no common threshold value to assign *H. pylori* status. That might account for part of the heterogeneities of all analyses. Other factors, such as ethnicity, study design and patient selection, may also be possible explanations for the heterogeneities across the studies. In this case, the random-effect model, which took heterogeneity into account, was used to analyze the studies with heterogeneity. Additionally, we did sensitivity testing and found that the HR and 95%CI did not alter substantially after removing any one study. Secondly, in the manuscript, we only discussed the protective effect of *H. pylori* and Prognosis of Gastric Cancer.
Other strong carcinogens and hereditary factors may contribute to the tumorigenesis of GC with non-*H. pylori* infection. The interactions between these factors and *H. pylori* infection should be elucidated in further studies. Thirdly, the secondary outcome of interest was DFS. Lacking sufficient eligible studies limited our further stratified analysis on DFS. Fourthly, only a few prospective studies were included in this meta-analysis [10,11,16,19]. We have performed a subgroup analysis for the 4 prospective studies. The pooled HR was 0.38 (95%CI: 0.29–0.48; *P*<0.0001) for OS, consistent with the overall analysis result.

In conclusion, our results suggest a protective role for *H. pylori* infection in the prognosis of GC. More large-scale and well-designed prospective cohort studies from various ethnic populations are necessary to validate our findings in the future. The underlying mechanisms need to be further elucidated, which could provide new therapeutic approaches for GC.

**Supporting Information**

*Table S1* PRISMA checklist. (DOC)

*Table S2* Methodologic quality of studies included in the meta-analysis. (DOC)

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**Author Contributions**

Conceived and designed the experiments: FW GS YZ. Performed the experiments: FW GS YZ FZ TM XL. Analyzed the data: FW GS YZ FZ TM XL. Contributed reagents/materials/analysis tools: FW GS YZ FZ TM XL. Wrote the paper: FW GS YZ FZ TM XL.
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