Clinics and Research in Hepatology and Gastroenterology (2019) 43, 216—224

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ORIGINAL ARTICLE

The prognostic role of *Helicobacter pylori* in gastric cancer patients: A meta-analysis

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Available online 22 October 2018

KEYWORDS
Helicobacter pylori;
Gastric cancer;
Prognosis;
Meta-analysis

Summary
Background: The prognostic value of *Helicobacter pylori* (*H. pylori*) infection in gastric cancer patients has been investigated over many years; however, the results remain inconclusive. Thus, we performed a comprehensive review of currently available evidence via a systemic meta-analysis to evaluate the effects of *H. pylori* infection on the prognosis of gastric cancer patients.
Methods: Studies that evaluated the prognostic value of *H. pylori* infection in gastric cancer were extracted in March 2016 by searching PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. We obtained or calculated hazard ratios (HRs) and the associated 95% confidence intervals (CIs) from the identified studies, and conducted random-effects model analyses of overall survival and progression-free survival. Twenty-four studies with a cumulative sample size of 7191 patients were included in our analysis.
Results: Our meta-analysis revealed that *H. pylori* infection is an indicator of improved overall survival in gastric cancer patients (HR, 0.79; 95% CI, 0.64—0.99); however, this was only true for European patients. The benefits of *H. pylori* infection were not detected in Asian gastric cancer patients (HR, 1.01; 95% CI, 0.91—1.12) or those in the United States (HR, 0.88; 95% CI, 0.73—1.05). Subgroup analyses revealed that the prognostic significance of *H. pylori* infection differed with respect to the year of study publication, number of patients, *H. pylori* detection method, tumor stage, *H. pylori*-positive rate, and risk of bias. The prognostic value of *H. pylori* infection on progression-free survival was unclear (HR, 0.84; 95% CI, 0.70—1.01).
Conclusions: These data provide limited, moderate-quality evidence that *H. pylori* infection is an indicator of good prognosis in European gastric cancer patients. However, this is not necessarily true for other populations.

Abbreviations: CI, confidence interval; GC, gastric cancer; *H. pylori*, helicobacter pylori; HR, hazard ratio; IHC, immunohistochemistry; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival.

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https://doi.org/10.1016/j.clinre.2018.08.012
2210-7401/

Background

Gastric cancer (GC) represents the third most common malignancy worldwide and is a major global health threat that causes more than 720,000 deaths per year globally; the majority of deaths occur in East Asia, with almost half of those in China [1,2]. The prognosis for patients with GC is extremely poor even after potentially curative surgery, and survival is often measured in months once recurrence occurs or metastases are detected. Therefore, it is necessary to discover biomarkers that can identify patients who are at-risk of disease recurrence and survival.

Helicobacter pylori (*H. pylori*) was classified as a Group 1 carcinogen by the International Agency for Research on Cancer in 1994. Approximately 89% of non-cardia GC cases, representing 78% of all GC cases, are now estimated to be attributable to chronic *H. pylori* infection [1]. A large amount of evidence links *H. pylori* to gastric adenocarcinoma, and epidemiological studies have shown that the risk of GC is higher in individuals who are *H. pylori*-positive [3,4]. In an animal model using Mongolian gerbils, gastric infection with *H. pylori* led to the development of GC [5]. *H. pylori* infection contributes to the development of GC because of its induction of chronic inflammation, DNA damage, activation of gastric stem cells, impaired gastric acidification, and changes in cell proliferation and apoptosis [6,7].

Whether *H. pylori* infection can be used as a prognostic biomarker has also been investigated. However, there is enormous controversy regarding in the impact of *H. pylori* infection status on the survival of GC patients. One German study reported a better prognosis in patients with positive *H. pylori* infection status compared to those with negative status [8]. Additionally, another study from Italy showed that a negative *H. pylori* infection status in patients with GC was associated with poor prognosis [9]. However, similar research in China found no significant difference in prognosis between *H. pylori*-positive versus -negative patient groups [10]. Our own 2013 study found that *H. pylori* infection is a poor indicator for overall survival (OS) in GC patients; however, we determined *H. pylori* infection status in gastric tumor tissues using immunohistochemistry (IHC), which was different from the detection method used elsewhere [11]. Taken together, the prognostic value of *H. pylori* infection among GC patients remains unclear, and the knowledge gap is wide.

A better understanding of the prognostic role of *H. pylori* infection would be helpful in identifying patients with GC who require more intensive follow-up. Therefore, we conducted this meta-analysis to evaluate the prognostic value of *H. pylori* infection among GC patients.

Methods

Search strategy and selection criteria

We conducted a search of the PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials databases in March 2016. We additionally examined the reference lists of relevant articles and review articles. No language restrictions or time limits were applied to the initial search. The literature search we performed is detailed in Supplementary Table 1. Eligibility criteria for inclusion in this meta-analysis were that the study evaluated the correlation between *H. pylori* infection and survival among GC patients, and that the study provided sufficient information for the estimation of hazard ratios (HRs) and their 95% confidence intervals (CIs). Two reviewers (L.G.H. and Y.S.Z.) independently screened the extracted abstracts for eligibility, then resolved any disagreements by discussion. When multiple publications reported identical or overlapping patient cohorts (e.g., the same authors and/or institutions), only the most informative study was included in the analysis.

Data extraction

Two investigators (L.G.H. and Y.S.J) independently extracted the following data from the eligible articles: first author, year of publication, study location, sample size, proportion of male subjects, patient age, site of disease, stage of disease, *H. pylori* detection method, proportion of *H. pylori*-positive subjects, any administered adjuvant chemotherapy, prognostic outcomes, multivariate models, and study type.

Study quality assessment

The qualities of the included studies were assessed using the modified risk of bias tool that is recommended by the Cochrane Collaboration, as previously described [12,13]. Briefly, answers to specific questions (see Supplementary Table 2) provided scores to reflect low, high, or unclear risks of bias. For summary assessment, a low risk of bias indicated low risk across all domains, an unclear risk of bias indicated that the risk of bias in at least 1 domain was unclear, and a high risk of bias indicated that the risk of bias was high in at least 1 domain.

Statistical analyses

HRs were used to determine the prognostic value of *H. pylori* infection. When unavailable in the cited study, we approximated the HR (and the associated standard error or CI) using the statistical data present in the article [14,15]. The extracted HRs were pooled using a fixed-effects model (weighted with inverse variance) or a random-effects model [16]. The fixed-effects model was employed assuming homogeneity in the individual HRs; heterogeneity between studies was assessed using χ^2 and I^2 statistics. The random-effects model was used if the assumption of homogeneity was rejected [17].

With a minimum of 2 studies required to perform the meta-analyses, an HR > 1 indicated a worse prognosis in *H. pylori* infection-positive patients. Sensitivity analysis was also performed using sequential omission of individual studies to determine the stability of the results. Funnel plot analyses were used to evaluate publication bias [18]. All analyses were performed using STATA version 10.0, and a *P*-value < 0.05 was considered statistically significant.

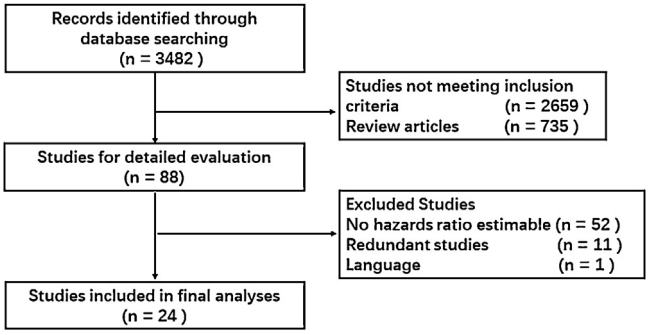

Figure 1 Flow chart showing the study selection process.

Results

Baseline study characteristics

We identified 24 eligible studies with a cumulative sample size of 7191 patients (Fig. 1) [8—11,19—38]. All the included studies were published between 2003 and 2015 (Table 1); the median study sample size was 213 patients (range, 61—802 patients). Eleven studies were excluded owing to the overlap of patient cohorts with those of other selected studies [39—49]. The extracted variables from the included studies are summarized in Table 1.

Among the 24 studies that investigated the influence of *H. pylori* infection on patient prognosis, 2 [11,35] used IHC for detection while 4 [9,10,20,32] used polymerase chain reaction (PCR). Fourteen studies were scored as having a low risk of bias (Supplementary Table 2). According to multivariate analysis, *H. pylori* infection was found to be a prognostic factor in 7 of the studies conducted in European countries, but was not correlated with prognosis in Asia or the United States [8,9,24,25,29,32,34]. HRs for OS and progression-free survival (PFS) were extracted from 24 and 10 studies, respectively. Sensitivity analysis showed that omitting any single study did not significantly influence the calculated HRs. Moreover, funnel plot analyses did not reveal a significant publication bias that would affect our findings for OS (Supplementary Fig. 1); however, we could not exclude a publication bias in our findings in relation to PFS because of the small number of studies.

Prognostic value of *H. pylori* infection

Pooled analysis of OS in all studies using the random-effects model revealed a marginally significant improvement in prognosis in GC patients with *H. pylori* infection (HR, 0.79; 95% CI, 0.64—0.99; $n = 24$; $I^2 = 85.4\%$; Fig. 2A). Heterogeneity was not found to be caused by any single study according to sensitivity analyses. However, our meta-analyses using the random-effects model did not find *H. pylori* infection to be predictive of PFS (HR, 0.84; 95% CI, 0.70—1.01; $n = 10$; $I^2 = 75.7\%$; Fig. 2B), and we observed a significant degree of heterogeneity that was not reduced substantially by the exclusion of any single study. Moreover, meta-regression analysis for OS using the same covariates showed no explanatory variable that influenced HR estimates (Supplementary Table 3).

Subgroup analyses

Despite the limited number of included studies, meta-regression and subgroup analyses of *H. pylori* infection status and its relationship to OS were performed according to study location, year of publication, number of patients, sample size, stage of disease, *H. pylori* detection method, proportion of *H. pylori*-positive cases, study type, and risk of bias. None of these factors were significantly influenced by heterogeneity (Table 2).

Subgroup analysis indicated a significant association between *H. pylori* infection and increased OS among European patients (HR, 0.66; 95% CI, 0.44—0.99) according to 7 studies encompassing 1631 patients. However, no benefits of *H. pylori* infection were detected among patients in Asia (HR, 1.01; 95% CI, 0.91—1.12) or in the United States (HR, 0.88; 95% CI, 0.73—1.05; Table 2). Fifteen studies from Asian countries with 4,199 patients overall were analyzed; the remaining 2 studies with 1361 patients were both performed in the United States [19,33]. The HRs for PFS were available from 2 studies of 276 European patients and 8 studies of 1,946 Asian patients. A protective role for *H. pylori* infection was found among European patients (HR, 0.59; 95% CI, 0.40—0.88) but not among Asian patients (HR, 0.83; 95% CI, 0.52—1.33) (Table 3).

Subgroup analysis was also performed with respect to the *H. pylori* detection method; data on *H. pylori* detection from serum were extracted from 6 studies assessing 2046 patients. GC patients with serum *H. pylori*-positive status exhibited better OS (HR, 0.57; 95% CI, 0.38—0.88), although this effect was not significant among other groups using different detection methods that included urease, histology, IHC, and PCR (Table 2).

Three studies that assessed 701 patients reported the OS of GC patients with relatively early disease stages (I—II). These studies found that *H. pylori* infection was an indicator of longer OS in these patients (HR, 0.45; 95% CI, 0.35—0.57). However, no such significant association was observed for late-stage GC patients (HR, 0.94; 95% CI, 0.48—1.85) or those of all stages analyzed together (HR, 0.83; 95% CI, 0.65—1.06) (Table 2).

In 2005, the Nobel Prize has been awarded to B. Marshall and R. Warren for their discovery that *H. pylori* infection was the reason for peptic ulcer disease. *H. pylori* infection was payed more attention to than ever before. Therefore, we made a subgroup analysis categorizing the studies according the 2005 cut-off. Six studies performed before 2005 analyzed OS in 1376 GC patients with *H. pylori* infection. The results of these studies showed that *H. pylori* infection was protective (HR, 0.79; 95% CI, 0.64—0.99). However, no such protective role for *H. pylori* infection was detected in 8 studies encompassing 1952 patients that were performed after 2005 (HR, 0.90; 95% CI, 0.61—1.32) or in the 10 studies with 3,863 patients that were performed around the year 2005 (HR, 0.96; 95% CI, 0.74—1.26) (Table 2).

Discussion

Our analysis revealed that *H. pylori* infection is an indicator of more favorable prognosis among European GC patients, but not among patients in Asian countries or the United

Table 1 Baseline characteristics of included studies.

First author	Year	Country	Number of patients	Male (%)	Age (median)	Age (range)	Tumor location	Tumor stage	*H. pylori* detection method	*H. pylori* (+) vs. (-) (*n*)	Surgery	Adjuvant chemotherapy	Suvival analysis	Follow-up period (Months)	Outcome report	Study type	Risk of bias
Bautista	2014	USA	802	58	NR	> = 18	Non-cardia	All stages	Serum or endoscopy	594/208	Curative resection	NR	Multivariate	24—132	OS	RSCS	Low
Chen	2012	China	120	66.7	58	25-86	NR	All stages	PCR	20/100	NR	NR	Univariate	36—86	OS (OR)	RSCS	High
Choi	2012	Korea	61	57.4	57	26-83	Cardia 5, non-cardia 56	Inoperable advanced gastric cancer	HE and cresyl violet	19/42	Inoperable	5-FU + platinum-based chemotherapy	Univariate	60	OS	RSCS	High
Fang	2014	China	252	55.9	NR	NR	NR	Gastric cancer patients with malignant ascites	NR	213/39	Gastrectomy	cisplatin taxanes	Multivariate	10.4(0.3—60.1)	OS	RSCS	High
Gan	2011	China	794	69.5	59.6	20-86	Upper 122, middle 244, lower 399, diffuse 29	All stages	Histology (Giemsa)	239/555	Gastrectomy	NR	Multivariate	50(1—110)	OS	RSCS	Low
García-González	2012	Spain	344	67.6	NR	30-96	NR	All stages	Urease test histology	245/99	Gastrectomy	NR	Univariate	9.9(0.4—120.3)	OS	RMCS	High
García-González	2015	Spain	558	68.6	NR	29-96	NR	All stages	Urease test histology	381/117	Gastrectomy	NR	Univariate	12.5(0.3—124)	OS	RMCS	High
Hur	2012	Korea	174	62.7	NR	NR	Upper 30, middle 48, lower 93, diffuse 3	All stages	Serum and histology	111/63	Curative resection	5-FU-based adjuvant chemotherapy	Univariate	5—40	OS PFS	PSCS	LOW
Kang	2012	Korea	274	68.97	54	25—73	Upper 42, middle 89, lower 121, diffuse 22	Locally advanced gastric cancer patients	Histology (HE)	166/108	Curative resection	(5-FU) and doxorubicin (DOX) based	Univariate, multivariate	144 (120—184)	OS	RMCS	LOW
Kim	2014	Korea	726	67	NR	41-61	NR	All stages	Serum or histology	690/36	Endoscopic resection or surgery	NR	Multivariate	3—120	OS PFS	RMCS	LOW
Kurtenkov	2003	Estonia	77	60.7	62	NR	NR	Stage I/II	Serum	NR	Curative resection	NR	Univariate	26—85	OS	RSCS	High
Li, G	2013	China	162	72.8	56	26-87	Proximal 49, distal 113	All stages	IHC	75/87	Curative resection	5-FU-based adjuvant chemotherapy	Multivariate	1.7—71.9	OS PFS	RSCS	Low
Lian, G	2014	China	101	84.2	60.6	NR	Proximal 18, distal 83	All stages	Serum	64/37	Curative resection	5-FU-based adjuvant chemotherapy	Multivariate	2.7—60	OS PFS	RSCS	Low
Ling, Z. Q	2015	China	300	57	56	NR	Proximal 57, distal 243	All stages	NR	165/135	Curative resection	monochemotherapy with S-1	Univariate, Multivariate	11—59	OS PFS	RSCS	Low
Marrelli	2009	Italy	297	58	68	30—92	Cardia 45, non-cardia 252	All stages	Serum and PCR	256/41	Curative resection	No	Multivariate	1—220	OS	RSCS	Low
Meimarakis	2006	Germany	166	60.2	65	NR	Proximal 41 Distal 125	All stages	Serum or histology or culture	125/41	Curative resection	intraoperative radiotherapy OR 5-FU-based adjuvant chemotherapy	Multivariate	1—146	OS PFS	RCT	Low
Posteraro	2014	Italy	110	53.6	67.3	NR	Cardia 17, non-cardia 93	All stages	PCR	86/24	Curative resection	NR	Univariate	1—158	OS PFS	RSCS	Low
Postlewait	2015	USA	559	56	64	NR	Fundus, cardia, or GE junction 143 antrum or body 406	Stage I, II, III	NR	104/455	Curative resection	radiotherapy OR chemotherapy	Multivariate	1—84	OS	RMCS	High
Qiu	2010	China	157	68.1	57.2	27—78	Upper 31 middle or lower 51	All stages	PCR	82/75	Curative or palliative	5-FU-based chemotherapy	Univariate	0.2—81.8	OS PFS	RSCS	Low
Roberts	2014	West Indies	79	47.3	67	36—86	NR	NR	NR	15/64	NR	NR	Multivariate	NR	OS	RSCS	High
Wang, F	2013	China	261	77	61	26—87	Proximal 48 Distal 213	All stages	IHC of tumor and normal tissue	188/261	Curative resection	NR	Univariate, multivariate	NR	OS PFS	RSCS	Low
Zhang	2015	China	65	67.6	66	30—79	NR	Stage I, II	Rapid urease test	70/45	Curative resection	NR	Univariate, multivariate	6.7—40.3	OS PFS	RSCS	Low
Zhao	2015	China	600	71.3	NR	NR	NR	All stages	NR	475/125	Curative resection	NR	Multivariate	NR	OS	RSCS	High
Zhou	2015	China	152	34.90%	33.7	< = 40	Proximal 8 Middle 57 Distal 75 Whole gastric 12	All stages	NR	70/67	Palliative (*n* = 15) Curative-intend (*n* = 137)	NR	Univariate	1.6—118	OS	RSCS	High

FU: fluorouracil; IHC: immunohistochemistry; RCT: randomized controlled trial; NR: not reported; RMCS: retrospective multicenter cohort study; PSCS: prospective single-center cohort study; RSCS: retrospective single-center cohort study.

Table 2 Stratified analysis of pooled hazard ratios of *H. pylori* on overall survival.

			Pooled HR (95% CI)			Heterogeneity	
Stratified analysis	No. of studies	No. of patients	Fixed	Random	Meta-regression *P*-value	I2 (%)	*P*-value
Study location					0.002		
Asia	15	4199	1.01 [0.91, 1.12]	0.88 [0.64, 1.22]		85.5	< 0.001
Europe	7	1631	0.75 [0.67, 0.86]	0.66 [0.44, 0.99]		87.1	< 0.001
Other regions	2	1361	0.88 [0.73, 1.05]	0.76 [0.46, 1.26]		64	0.095
Patients inclusion year					< 0.001		
After 2005	8	1952	1.10 [0.95, 1.27]	0.90 [0.61, 1.32]		73.9	< 0.001
Before 2005	6	1376	0.68 [0.60, 0.77]	0.79 [0.64, 0.99]		93.2	< 0.001
Both	10	3863	0.99 [0.88, 1.11]	0.96 [0.74, 1.26]		67.5	0.001
Number of patients					< 0.001		
≥ 100	20	6909	0.96 [0.89, 1.04]	0.84 [0.67, 1.05]		83.6	< 0.001
< 100	4	282	0.46 [0.37, 0.58]	0.55 [0.35, 0.88]		54.2	0.088
Detection method					< 0.001		
Serum	6	2046	0.66 [0.57, 0.76]	0.57 [0.38, 0.88]		82.3	< 0.001
Urease	3	967	1.03 [0.88, 1.20]	1.03 [0.88, 1.20]		0	0.962
Histology	3	1129	0.77 [0.65, 0.92]	0.60 [0.23, 1.54]		95.2	< 0.001
IHC	2	423	1.11 [0.78, 1.58]	0.93 [0.27, 3.19]		90.9	0.001
PCR	4	684	0.83 [0.62, 1.11]	0.88 [0.50, 1.47]		66.5	0.03
Tumor stage					< 0.001		
Stage I/II	3	701	0.45 [0.35, 0.57]	0.55 [0.32, 0.94]		64	0.062
Stage IV	2	313	1.19 [1.00, 1.41]	0.94 [0.48, 1.85]		81.7	0.019
All stages	18	6098	0.91 [0.84, 1.00]	0.83 [0.65, 1.06]		83.3	< 0.002
H. pylori positive rate(%)					< 0.001		
< 50	7	1927	1.02 [0.86, 1.21]	0.85 [0.57, 1.26]		71.9	0.002
50-75	10	3036	0.85 [0.76, 0.94]	0.75 [0.56, 1.01]		82.1	< 0.001
> 75	6	2151	1.14 [0.98, 1.33]	0.92 [0.53, 1.61]		86.3	< 0.001
Risk of bias					< 0.001		
High	10	2802	0.95 [0.86, 1.05]	0.85 [0.60, 1.20]		88.9	< 0.001
Low	14	4389	0.83 [0.75, 0.93]	0.75 [0.55, 1.02]		82.4	< 0.001

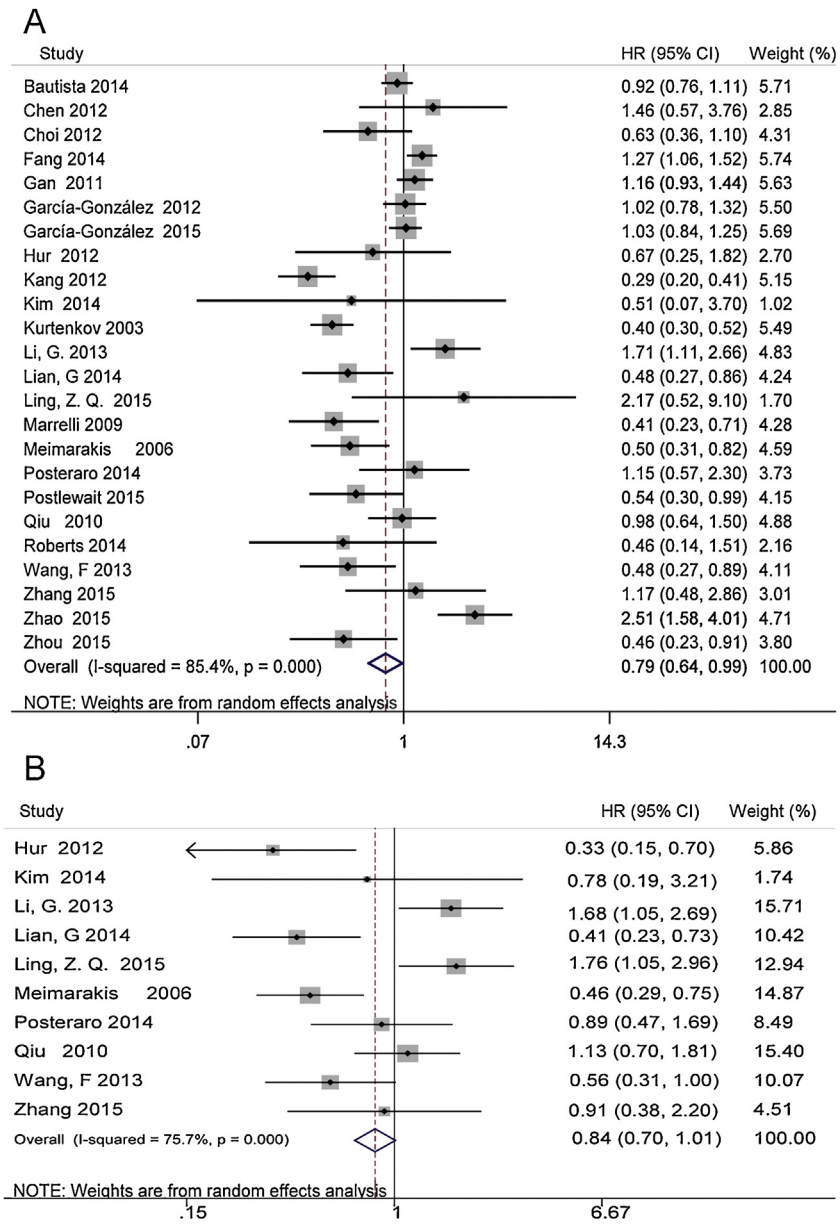

Figure 2 Meta-analyses of the association between *H. pylori* infection and (A) overall survival or (B) progression-free survival. Squares and horizontal bars indicate the point estimates [hazard ratios (HRs)] with 95% confidence intervals (CIs) for each individual study. Diamonds indicate the summary estimates for the hazard ratio. The width of the bar corresponds to the 95% CI.

States. A similar conclusion was also derived regarding the prognostic value of *H. pylori* infection for PFS among GC patients from different geographical areas.

There was significant heterogeneity among the studies included in this meta-analysis. Although we used both random effects and fixed-effects models when pooling the data, neither identified the source of heterogeneity. Moreover, sensitivity analysis did not assist in identifying the source of heterogeneity in this study.

Despite the number of studies that have been conducted on this topic, the prognostic value of *H. pylori* infection among GC patients has remained highly equivocal given these studies' inconsistent results. In the present study, pooled analyses of the available data only revealed a marginally significant association between *H. pylori* infection and improved OS. However, there was insufficient statistical power to determine any such association among patients in Asian countries and the United States. Moreover, these data were derived mostly from low-quality studies that included patients who were unmatched for age and *H. pylori* detection method; hence, these results should be interpreted with caution.

The following limitations exist in the present meta-analysis. First, only 1 study was a randomized controlled trial [8], while the remainder were observational studies. The included studies were performed at clinical centers with varying protocols, and were likely to have different levels of surgical expertise. Second, *H. pylori* detection methods varied between studies, and included serum, urease, histology, PCR, and IHC. Moreover, different criteria for diag-

Table 3 Stratified analysis of pooled hazard ratios of *H. pylori* on progession free survival.

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI) Fixed	Random	Meta-regression *P*-value	Heterogeneity I2 (%)	*P*-value
Study location					0.039		
Asia	8	1946	0.93 [0.76, 1.16]	0.83 [0.52, 1.33]		76.8	< 0.001
Europe	2	276	0.59[0.40, 0.88]	0.62 [0.33, 1.17]		60.8	0.11
Detection method					0.001		
Histology	2	239	0.51 [0.29, 0.92]	0.54 [0.20, 1.45]		65.7	0.088
Serum	3	993	0.46 [0.32, 0.65]	0.46 [0.32, 0.65]		0	0.709
IHC	2	423	1.09 [0.76, 1.58]	0.98 [0.33, 2.89]		87.9	0.004
PCR	2	267	1.04 [0.71, 1.52]	1.04 [0.71, 1.52]		0	0.557
H. pylori positive rate(%)					< 0.001		
< 75	7	1220	0.94 [0.76, 1.16]	0.84 [0.51, 1.37]		80.1	< 0.001
> 75	3	1002	0.60 [0.41, 0.87]	0.62 [0.39, 0.99]		25.8	0.26

nosing *H. pylori* infection were employed among the various studies, even in those using the same detection method. Third, the differences in sample size, patient age, tumor stage, neoadjuvant and adjuvant medical therapy, and other factors among the studies likely contributed to the high heterogeneity. Using a random effects model for OS estimation might minimize, but does not abolish, such heterogeneity. Fourth, the strains of *H. pylori* differ among various countries. For example, several types of strains linked to high GC risk (including the CagA PAI, type s1 forms of vacA, and babA) are present in nearly all East Asian *H. pylori* isolates [50—52]. Conversely, cagA-negative strains containing type s2 vacA alleles and lacking babA are commonly found in the United States and Western Europe, but are rarely isolated in East Asia [50,51]. Fifth, multiple host-related factors, such as gene variations across races and dietary differences are known to play a role in the etiology of *H. pylori*-induced GC [53]. Finally, the nature of this meta-analysis meant that it cannot address or incorporate individual factors at the patient level.

Conclusions

We found marginal, moderate-quality evidence that *H. pylori* infection is indicative of good prognosis among European GC patients; our data showed that this was not true of patients in Asian countries or in the United States. These findings ought to encourage efforts to conduct more randomized controlled trials to determine the prognostic role of *H. pylori* in GC patients in different geographical regions.

Ethical approval

Ethics approval and consent to participate
Not applicable.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Funding

This work was Supported by the Natural Science Foundation of Guangdong Province, China (No. 2016A030310155) and National Natural Science Foundation of China (No. 81602049).

The funders had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

LGH and WZ extracted the data from the literature.
XJB, ZXH, and YJN performed the analysis.
WZ and HYL designed the project.
All authors have read and approved the final manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2018.08.012.

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