REVIEW

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Epstein-Barr Virus and *Helicobacter pylori* Co-Infection in Gastric Cancer: A Systematic Review and Meta-Analysis of Case-Control and Cross-Sectional Studies

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Abstract

Background: Gastric cancer (GC) is a multifactorial malignancy in which both *Helicobacter pylori* (*H. pylori*) and Epstein-Barr virus (EBV) have been implicated. Given the high prevalence of both pathogens, we performed a systematic review and meta-analysis to estimate the prevalence of *H. pylori*–EBV co-infection (HECo) in GC and to evaluate its association with GC. **Materials and methods:** A systematic literature search was performed using a search strategy consisting of appropriate keywords in online databases including MEDLINE, Embase, and Web of Science from inception to July 2024. Eligible case-control and cross-sectional studies in English reported *H. pylori* and EBV status assessed using validated assays (e.g., PCR, serology, immunohistochemistry/in situ hybridization, rapid urease test), enabling ascertainment of HECo within the same participant. Study quality was assessed using the "Newcastle–Ottawa Quality Assessment Scale" (NOS) and the Appraisal Tool for Cross-Sectional Studies (AXIS tool). Random-effects meta-analyses were used to pool prevalence estimates and odds ratios (ORs) with 95% confidence intervals (CIs), and heterogeneity was quantified using I^2. **Results:** Eighteen studies (n = 4364; 1999–2023) were included. HECo prevalence among GC patients was 21.44% (95% CI: 9.46–33.42). HECo was associated with increased odds of GC (pooled OR = 3.09, 95% CI: 1.66–5.73; I^2 = 69.1%). Subgroup estimates by age (high vs low) were based on two studies per stratum and showed wide CIs (high age: OR = 9.61, 95% CI: 1.90–48.64; low age: OR = 9.52, 95% CI: 1.83–49.54) and should be interpreted cautiously. There was a significant association between the presence of metastasis, the high stage of GC, and HECo. Our results showed no significant association between moderately or poorly differentiated GC, diffuse-type GC, the presence of vessel invasion, and HECo. **Conclusion:** HECo is associated with a higher risk of GC. Future primary studies should report mutually exclusive infection categories (HP only, EBV only, both, neither) and clarify the temporal relationship between infection and GC, to better disentangle independent versus joint effects and to inform prevention strategies.

Keywords: Stomach neoplasms- *Helicobacter pylori*- Epstein-Barr virus- Co-infection

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Introduction

Gastric cancer (GC) is an imperative worldwide issue. It is stated as the fifth most common origin of cancer deaths, with close to 660,000 total mortalities in 2022. Diagnosing about 1 million stomach cancer-related cases per year makes it the fifth most common malignancy incident globally. In countries located in South Central part of Asia such as Iran, Afghanistan, Kyrgyzstan, and Tajikistan, stomach cancer is the most frequent and the most deadly cancer in men [1].

The most predominant risk factor for the development of GC, containing gastric carcinoma and MALT lymphoma, is *Helicobacter pylori* (*H. pylori or HP*) [2, 3]. Nearly half of the world population have this spiral-shaped Gram-negative bacterium colonized in their stomach, with less than 2% progressing to gastric neoplasms [4, 5]. Proliferation of HP in the mucosal layer of the stomach ultimately leads to chronic inflammation called gastritis, [6] turning to gastric ulcer [7, 8] and consequently GC [9]. Besides inflammation, an oncogenic bacterial protein termed Cag A protein plays an important role in carcinogenesis by the deterioration of ongoing HP-related inflammation according to its capacity to disrupt several intracellular signaling pathways [10]. This cancer predisposing protein is encoded by CagA

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(cytotoxin-associated gene A) located in the DNA fragment of most species [11, 12]. Moreover, *H. pylori* strains display polymorphism within multiple genes which relates to severity of the gastric diseases within the host [13, 14]. Altogether, disease progression is the product of complex interaction between HP polymorphisms, host polymorphisms, and environmental factors, with varying prevalence throughout the world [15]. *Helicobacter pylori* is typically transmitted by oral-oral or fecal-oral mode [16] and its infection is simply eradicated by antibiotic therapy [17].

Another risk factor inducing stomach cancer is Epstein-Barr virus (EBV), a γ-herpes-virus with170 kb double-stranded DNA which develops infectious mononucleosis in human [18]. EBV is among the most widespread persistent human infections, establishing latent infection in approximately 95% of the global population, with primary exposure typically occurring in early childhood. [19, 20]. Among widespread malignancies initiated by EBV such as Hodgkin's lymphoma, nasopharyngeal carcinoma (NPC), Burkitt lymphoma, frequency of EBV-associated GC remains the most [21]. Typically, prevalence of EBV infection varies according to geographic region, with more infection rates in underdeveloped countries than developed ones [22, 23].

Owing to the high frequency of colonization of the human community by both microorganisms, to the extent of 80-90% in some populations, several investigations were performed focusing on the effect of *H. pylori* and EBV co-infection (HECo) on gastric lesions. An observational study by Moral-Hernández et al. suggested a possible synergic effect of *H. pylori* and EBV co-infection during chronic inflammation and carcinogenesis [24]. Meanwhile, a study conducted in pediatric patients in Mexico mentioned a potential cooperative effect between *H. pylori* and EBV infection correlating with severe gastritis. Surprisingly, in the absence of EBV colonization, an association even between infection with *H. pylori* cag A+ strains and severe gastric inflammation doesn't exist [25]. While Another research emphasizes rising of GC risk with EBV and HP co-participant, [26] Su et al implied a possibility of antagonism between EBV and *H. pylori* reaction in GC lesions [27]. Although a narrative review article was also conducted to express status on coinfection of both agents and their correlation with GC in 2017, [9] to the best of our knowledge, no thorough meta-analysis or systematic review has been carried out so far to estimate the prevalence of HECo in GC and to examine the association between HECo and the risk of GC. Therefore, we conducted this systematic review and meta-analysis to estimate the prevalence of HECo in GC and assess its association with cancer risk.

Materials and Methods

Search strategy

This systematic review and meta-analysis was conducted in accordance with the protocols of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [28] for guiding the study design, search approach, screening, and reporting. A systematic literature search was performed using a search strategy developed by PECO ("P" stands for Patients, "E" for Exposure, "C" for Comparison, and "O" for Outcome) to identify and retrieve pertinent studies in online databases including MEDLINE (via PubMed), Embase, and Web of Science. The applied key terms used were as follows: "Burkitt Lymphoma Virus" OR "Burkitt's Lymphoma Virus" OR "Burkitts Lymphoma Virus" OR "E-B Virus" OR "E B Virus" OR "E-B Viruses" OR "Infectious Mononucleosis Virus" OR "Infectious Mononucleosis Viruses" OR "Epstein-Barr Virus" OR "Epstein Barr Virus" OR "HHV-4" OR "Human Herpesvirus 4" OR "Burkitt Herpesvirus" OR "EBV" AND "*Helicobacter pylori*" OR "Helicobacter nemestrinae" OR "Campylobacter pylori" OR "Campylobacter pylori subsp. Pylori" OR "Campylobacter pyloridis" OR "*H. pylori*" OR "HP". No filters were applied, and studies from database inception to July 2024 were included. A manual search was also performed; however, it did not yield any additional studies. All of the obtained articles were imported into Endnote X9 software.

Eligibility criteria

Publications that met the eligibility criteria according to the purpose of this study were included: (1) studies with available full text in English; (2) cross-sectional studies which assessed prevalence of HECo among GC patients; (3) case-control studies that identified the prevalence of HECo in GC patients and compared them with a control group; (4) presence of *H. pylori* and EBV infection was confirmed by a validated method containing PCR, ELISA, rapid urease test, immunohistochemistry, Warthin–Starry stain, and microscopic inspection for HP and PCR, ELISA, and ISH for EBV infection; and (4) provided sufficient data for statistical analysis. Exclusion criteria were classified into four groups: (1) publications irrelevant to the scope of our study; (2) publications with inaccessible full test; (3) conference abstracts, letters, commentaries, reviews, in vitro studies, and animal studies that did not meet the eligibility criteria upon full-text screening; and (4) non-English articles. In this review, HECo was defined as concurrent detection/positivity for both *H. pylori* and EBV in the same participant, as reported in the primary study. Detection could be based on tissue- or blood-based specimens and on the validated assays used in each study. Because most included studies were case-control or cross-sectional, infection status was typically measured at or near the time of endoscopy/surgery, and the temporal sequence (i.e., whether infection preceded GC) could not be established.

Study selection

At the beginning of the study selection, we removed the duplicated articles followed by screening the titles and abstracts of the remained studies by two independent researchers (AH AND YZ) based on their appropriateness for inclusion. Afterward, we screened the full text of the previously selected articles according to our inclusion and exclusion criteria. As well, if the full text of related papers was not found, each article's corresponding author was contacted by sending an E-mail. The eligibility of the controversial studies was judged by the third author's opinion (RAN).

Data extraction

The required data were extracted by two investigators (AH AND KR) and were imported from the literature into a pre-designed Excel sheet. The third reviewer (RAN) made the final decision through consultation in case of any discrepancies. We achieved the following information from included studies: the first author's name, publication year, country, study design, cancer type, case and control groups sample sizes, type of controls, demographic information (age and sex), and HP and EBV detection methods. Additionally, data on the prevalence of HP and EBV infection, CagA-positive HP infection, co-infection of EBV and all types of HP, and co-infection of EBV and CagA-positive HP were collected. To conduct subgroup analysis, we gathered the data on HECo prevalence based on gender, age, histopathological differentiation, tumor size, histological type, lymph node metastasis status, lymphatic vessel invasion, and stage of cancer.

Quality assessment

In this study, we utilized two different tools including the "Newcastle–Ottawa Quality Assessment Scale" (NOS) [29] and the Appraisal Tool for Cross-Sectional Studies (AXIS tool) [30] to assess the quality of case-control studies and cross-sectional studies, respectively. Two reviewers (YZ AND KR) in the team evaluated the risk of bias independently, following the advice of (RAN) in the matter of any disagreement as a referee. The NOS appraises selection, comparability, and exposure as potential biases, which assigns a maximum score of 4 points, 2 points, and 3 points for each of the categories, respectively. The AXIS tool consists of a determined questionnaire with 20 items across five main domains (introduction, methods, results, discussion, and other) that rates the publications with yes/no answers to assess their credibility and reliability to the aims. Finally, studies with ratings of (70 to 100%), (60 to 69.9%), and (0 to 59.9%) are considered as high quality, fair quality, and low quality, respectively. We note that our exclusion criteria did not contain low-quality studies based on their quality score.

Statistical analysis

The association between HECo and GC was presented by merging the odds ratios (ORs) and 95% confidence intervals (CIs). The heterogenicity between eligible studies was assessed using the I2 test. To practice a statistical model, we preferred to interpret I-square values, using random effect model in case of considerable heterogenicity (I-square ≥ 50%), and applying the fixed effect model otherwise. Moreover, to explore the source of statistical heterogeneity, subgroup analysis was performed based on age, histopathological differentiation, histological type of cancer, status of metastasis, vessel invasion, and stage of cancer. Considering the number of included studies, Egger's test and Trim-and-Fill analysis were utilized as a statistical method to determine whether there is publication bias. STATA Statistical Software (version 14.0, Stata Corp) was applied to carry out all the statistical analyses. We displayed the results of the meta-analysis on forest plots to provide a visual assessment.

Results

Study selection process

The search strategy on above mentioned databases yielded 1902 publications initially, followed by the removal of 525 duplicated articles. Then based on the title and abstract, the remaining 1377 kinds of literature were screened, which resulted in the exclusion of 1340 articles considered as irrelevant. 37 publications were reviewed for a detailed evaluation of the full text. Among these investigations, 19 studies were excluded, as they did not proffer sufficient data concerning some reasons (listed in Figure 1). Our final systematic review and meta-analysis contained 18 publications and the desired data were collected from these studies [31-47]. The study selection process is presented in Figure 1.

Study characteristics

A total of 18 studies with 4364 participants published from 1999 through 2023 were identified, of which 8 were case-control studies and 10 were cross-sectional ones. The sample sizes of these published studies ranged from 20 to 956, and Japan (one study), Brazil (three studies), Korea (two studies), Hong Kong (one study), China (one study), India (two studies), Türkiye (two studies), Taiwan (one study), Peru (one study), Mexico (two studies), Paraguay (one study), Morocco (one study), Italy (one study) were the variable locations of the studies. All of the approved case-control articles assessed the association between *Helicobacter pylori* and EBV co-infection and GC. The main characteristics of studies entered into our meta-analysis are shown in Table 1.

Quality assessment

According to NOS tool, all the case-control studies had good quality. Besides, four studies had high quality, while quality assessment of six studies revealed fair quality based on AXIS. Qualities of the included studies evaluated by NOS and AXIS are determined in Table 2 and Table 3, respectively.

Meta-analysis

Prevalence of H. pylori and EBV co-infection in GC patients

As demonstrated in figure 2, the pooled data from all eighteen studies indicated that the combined prevalence of HECo among GC patients was 21.44% with a 95% CI of 9.46 to 33.42. According to table 4, we perceived that the prevalence of *H. pylori* and EBV infection among patients with GC was 54.32% (95% CI: 44.85 to 63.80) and 22.03% (95% CI: 11.55 to 32.51), respectively. Furthermore, CagA-positive *Helicobacter pylori* infection was detected in 51.61% (95% CI: 41.10 to 62.11) of individuals with GC due to eight studies. Additionally, the meta-analysis of data from seven studies showed that the pooled prevalence of CagA-positive *H. pylori* and EBV co-infection among GC cases was 22.44% (95% CI: 5.30 to 39.59). In a subgroup analysis performed based

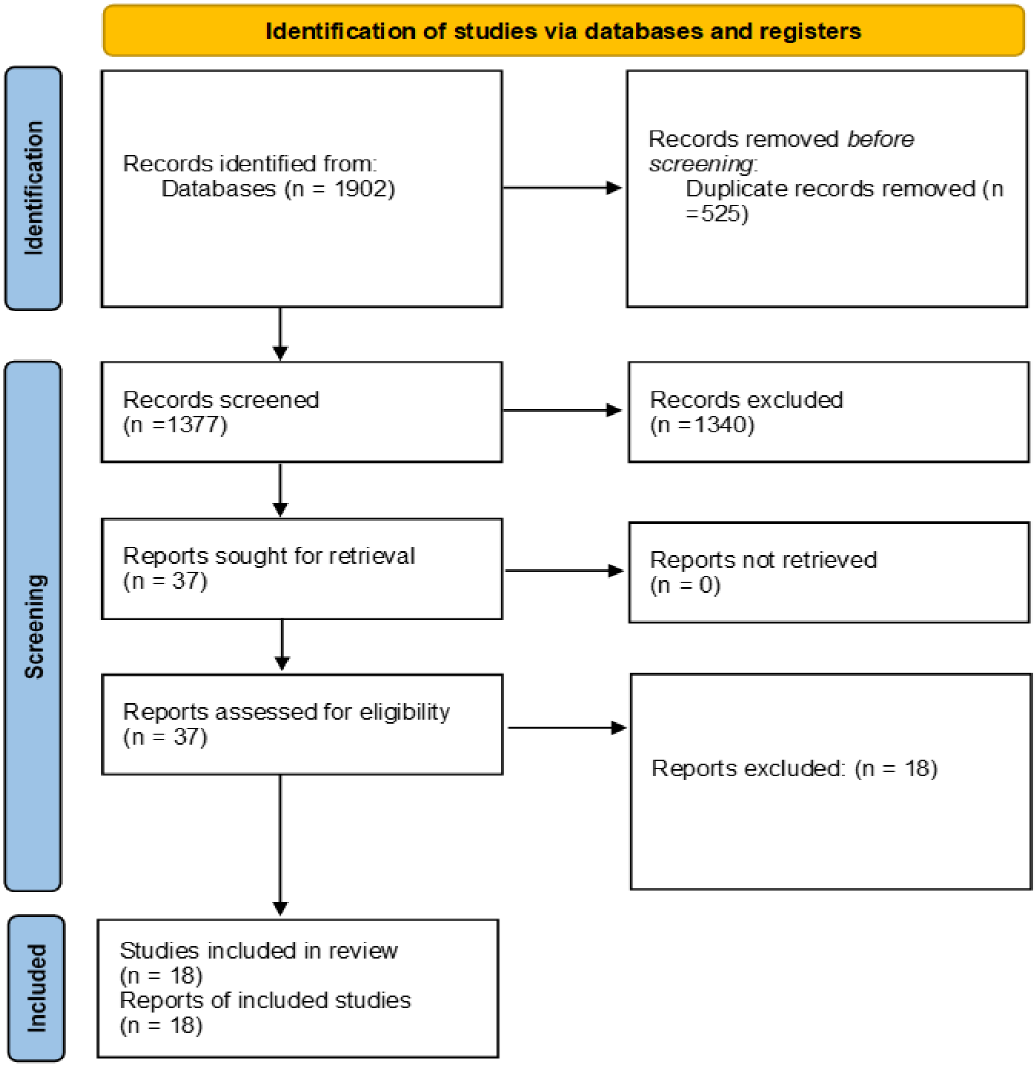

Figure 1. PRISMA Flowchart for the Study Selection Process

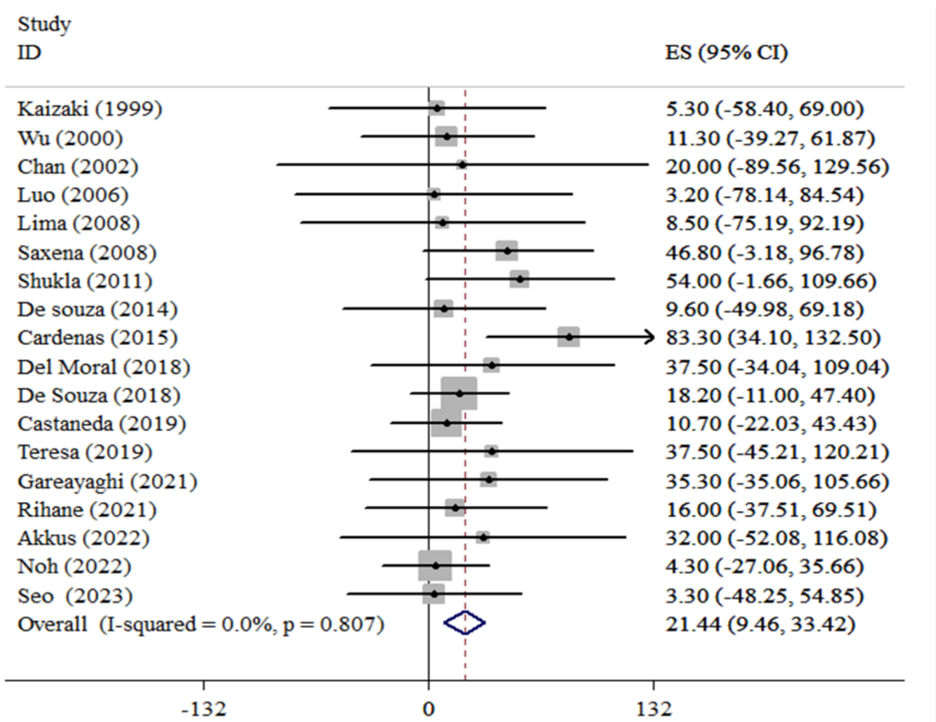

Figure 2. Forest Plot of Prevalence of *H. pylori* and EBV Co-Infection in Gastric Cancer Patients

Table 1. Characteristics of Included Studies

First author	Country	Study type	Cancer type	Case mean (SD) age	Case sample size	Control mean (SD) age	Control sample size	HP detection method	EBV detection method	QA
Kaizaki et al. [43]	Japan	Cross-sectional	Adenocarcinoma	63 (11.98)	189	-	-	IHC	PCR and ISH	12
Wu et al. [39]	Taiwan	Cross-sectional	Adenocarcinoma and LELC	62.48 (10.35)	150	-	-	ELISA	PCR and ISH	13
Chan et al. [41]	Hong Kong	Cross-sectional	Adenocarcinoma and LELC	61.5 (15.6)	20	-	-	ELISA	ISH	13
Luo et al. [45]	China	Cross-sectional	Adenocarcinoma	-	185	-	-	PCR and RUT	PCR and ISH	12
Lima et al. [44]	Brazil	Cross-sectional	Adenocarcinoma	56.5 (11.16)	71	-	-	PCR	ISH	13
Saxena et al. [38]	India	Cross-sectional	Adenocarcinoma	56.6 (15.423)	63	-	-	PCR and RUT	PCR	14
Shukla et al. [46]	India	Case-control	Adenocarcinoma	52.43 (12.378)	50	45.27 (15.31)	150	PCR and RUT	PCR	6
De souza et al. [41]	Brazil	Case-control	Adenocarcinoma	63.16 (13.38)	125	22.55 (17.18)	101	PCR and RUT	ISH	6
Cardenas et al. [32]	Mexico & Paraguay	Case-control	Adenocarcinoma	-	114	-	411	ELISA	ELISA	6
De Souza et al. [34]	Brazil	Cross-sectional	Adenocarcinoma	62 (10.6)	302	-	-	RUT	ISH	14
Del Moral et al. [24]	Mexico	Case-control	unknown	63 (13)	32	50 (17)	106	PCR	PCR	6
Castaneda et al. [33]	Peru	Case-control	Adenocarcinoma	-	114	-	411	ELISA	ELISA	6
Teresa et al. [37]	Italy	Case-control	Adenocarcinoma	69.88 (8.68)	24		48	PCR	PCR	6
Gareayaghi et al. [42]	Türkiye	Case-control	Adenocarcinoma	67.71 (8.916)	34	60.28 (12.30)	40	PCR	PCR	6
Rihane et al. [36]	Morocco	Cross-sectional	Adenocarcinoma	58 (6)	100	-	-	PCR	PCR	13
Noh et al. [35]	Korea	Cross-sectional	unknown	58.6 (11.9)	956	-	-	Microscopic inspection of HP	ISH	15
Akkus et al. 2022 [31]	Türkiye	Case-control	unknown	67.7 (9.053)	25	Four subgroups: 58.15 (12.24) 60.06 (14.76) 60.85 (13.59) 59.7 (9.84)	83	PCR	PCR	5
Seo et al. 2023 [47]	Korea	Cross-sectional	Adenocarcinoma	65.4 (12.2)	460	-	-	IHC	ISH	15

SD, standard deviation; QA, quality assessment; LELC, Lymphoepithelioma-like carcinoma; PCR, polymerase chain reaction; IHC, Immunohistochemistry; ELISA, enzyme-linked immunosorbent assay; RUT, and rapid urease test; ISH, In situ hybridization; EBV, Epstein–Barr virus; HP, Helicobacter pylori; WS, Warthin-Starry stain.

Table 2. Detailed Quality Assessment of Cross-Sectional Studies Based on AXIS

Study	Introduction	Methods	Methods	Methods	Methods	Methods	Methods	Methods	Methods	Methods	Methods	Results	Results	Results	Results	Results	Discussion	Discussion	Other	Other		
	Were the aims/objectives of the study clear?	Was the study design appropriate for the stated aim(s)?	Was the sample size justified?	Was the target/reference population clearly defined?	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Was the selection process likely to select subjects/ participants that were representative of the target/reference population under investigation?	Were measures undertaken to address and categorise non-responders?	Were the risk factor and outcome variables measured appropriate to the aims of the study?	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	Is it clear what was used to determined statistical significance and/or precision estimates?	Were the methods sufficiently described to enable them to be repeated?	Were the basic data adequately described?	Does the response rate raise concerns about non-response bias?	If appropriate, was information about non-responders described?	Were the results internally consistent?	Were the results presented for all the analyses described in the methods?	Were the authors' discussions and conclusions justified by the results?	Were the limitations of the study discussed?	Were there any funding sources or conflicts of interest that may affect the authors interpretation of the results?	Was ethical approval or consent of participants attained?	Score (out of 20)	Quality
Kaizaki et al. [43]	Yes	Yes	No	Yes	No	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	No	Yes	Yes	Yes	No	No	No	12	Fair
Wu et al. [39]	Yes	Yes	NO	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	No	Yes	Yes	Yes	No	N/A	N/A	13	Fair
Chan et al. [41]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	13	Fair
Luo et al. [45]	Yes	Yes	No	Yes	No	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	No	Yes	Yes	Yes	No	N/A	No	12	Fair
Lima et al. [44]	Yes	Yes	No	Yes	No	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	No	Yes	Yes	Yes	No	N/A	Yes	13	Fair
Saxena et al. [38]	Yes	Yes	No	Yes	Yes	Yes	N/A	YES	Yes	Yes	Yes	Yes	N/A	No	Yes	Yes	Yes	No	N/A	Yes	14	High
De Souza et al. [34]	Yes	Yes	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	No	No	Yes	14	High
Rihane et al. [36]	Yes	Yes	No	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	No	No	Yes	13	Fair
Noh et al. [35]	Yes	Yes	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No	Yes	15	High
Seo et al. [47]	Yes	Yes	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No	Yes	15	High

on cancer type, the pooled prevalence of HECo estimated as 24.73% (95% CI: 10.78 to 38.68) in known cases of adenocarcinoma, 12.83% (95% CI: -33.09 to 58.74) in patients with adenocarcinoma and lymphoepithelioma-like carcinoma (LELC), and 11.99% (95% CI: -15.19 to 39.17) in unknown ones. Notably, although pooled prevalences for *H. pylori* infection and EBV infection are also reported (Table 4), most primary studies did not provide mutually exclusive infection categories (HP only, EBV only, both, neither). Therefore, we could not perform a comparative meta-analysis of HECo versus single infections to formally test additive or synergistic effects.

Association between EBV and H. pylori co-infection and GC risk

Overall, we found that patients with HECo had a significantly higher risk of GC compared with subjects without HECo with the pooled OR of 3.09 (95% CI: 1.66 to 5.73) as expressed in Figure 3. The heterogeneity was statistically significant with I2 of 69.1%.

Publication Bias Assessment and Trim-and-Fill Analysis

The potential publication bias was identified using Egger's test, which was significant (bias coefficient = 17.24, p = 0.011). To further explore and adjust for this potential bias, the trim-and-fill method was conducted using a linear trimming estimator under a random-effects model. Using the trim-and-fill procedure, one potentially missing study was imputed to correct for suspected publication bias. Despite this correction, heterogeneity remained high (Q = 522.33, $p < 0.001$; $\tau^2 = 15.444$).

Subgroup analysis

Also, a subgroup analysis based on parameters such as age, histopathological differentiation, histological type, the presence of metastasis, the presence of vessel invasion, and stage of cancer was performed (Table 3). First of all, the subgroup analysis based on age illustrated that HECo in both high (OR: 9.61, 95% CI: 1.90 to 48.64) and low age patients (OR: 9.52, 95% CI: 1.83 to 49.54) increased the risk of GC. Through the synthesis of the data from four studies and using the fixed effect model, it found that there was a significance correlation between high stage of GC and HECo (OR: 1.99, 95% CI: 1.11 to 3.55). We also remarked that there was a significant association between the presence of metastasis and HECo with the OR: 5.05 (95% CI: 1.16 to 21.9). Our results manifested no significant association between the risk of moderately or poor differentiated GC (OR: 1.36, 95% CI: 0.82 to 2.26), diffuse-type GC (OR: 0.80, 95% CI: 0.34 to 1.86), and the presence of vessel invasion (OR: 0.01, 95% CI: 0.00 to 0.02), and HECo.

Discussion

This meta-analysis assessed the epidemiology of HP and EBV infections in patients with GC and the association of GC development and co-infection of HP and EBV (HECo). The present study illustrates that just under one-third of patients with GC had EBV infection, and more than half of them tested positive for HP infection.

Table 3. Detailed Quality Assessment of Case-Control Studies based on Newcastle–Ottawa Scale (NOS)

Study	Selection	Selection	Selection	Selection		Exposure	Exposure	Exposure	Score
	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Shukla et al. [46]	*	*	-	*	*	*	*	-	6
De souza et al. [41]	*	*	-	*	*	*	*	-	6
Cardenas et al. [32]	*	*	-	*	*	*	*	-	6
Del Moral et al. [24]	*	*	-	*	*	*	*	-	6
Castaneda et al. [33]	*	*	-	*	*	*	*	-	6
Teresa et al. [37]	*	*	-	*	*	*	*	-	6
Gareayaghi et al. [42]	*	*	-	*	*	*	*	-	6
Akkus et al. [31]	*	*	-	-	*	*	*	-	5

Table 4. Pooled Prevalence of Infections by Subgroups

Parameters	Number of studies	I-square (%)	Pooled prevalence (95% confidence interval)
HP infection	17	4.2	54.32 (44.85 to 63.80)
CagA-positive HP infection	8	0	51.61 (41.10 to 62.11)
EBV infection	18	0	22.03 (11.55 to 32.51)
HECo*	18	0	21.44 (9.46 to 33.42)
HECo**	7	0.9	22.44 (5.30 to 39.59)
HECo* by type of malignancy			
Adenocarcinoma	13	0	24.73 (10.78 to 38.68)
Adenocarcinoma and LELC	2	0	12.83 (-33.09 to 58.74)
Unknown	3	0	11.99 (-15.19 to 39.17)

EBV, Epstein–Barr virus; HP, Helicobacter pylori; CagA, cytotoxin-associated gene A; HECo, Helicobacter pylori and Epstein–Barr virus co-infection; LELC, Lymphoepithelioma-like carcinoma; *, Co-infection of EBV and all types of HP; **, Co-infection of EBV and CagA-positive HP

Table 5. Pooled Odd Ratios for Gastric Cancer in HECo-Positive Patients by Subgroups

Subgroup		Number of studies	I-square (%)	Pooled Odd ratio (95% confidence interval)
Age	High	2	22.7	9.61 (1.90 to 48.64)
	Low	2	5.9	9.52 (1.83 to 49.54)
Histopathological differentiation	Moderate to poor vs. well differentiated	3	40.0	1.36 (0.82 to 2.26)
Histological type	Diffuse-type vs. intestinal-type	8	54.4	0.80 (0.34 to 1.86)
Lymph node metastasis status	Positive vs. negative	3	15.20	5.05 (1.16 to 21.90)
Lymphatic vessel invasion	Positive vs. negative	2	0.0	0.01 (0.00 to 0.02)
Stage	High vs. low	4	9.70	1.99 (1.11 to 3.55)

Moreover, the prevalence of HECo was similar to that of patients with EBV infection. Notably, EBV and HP CagA co-infection was slightly higher than co-infection of EBV and all type of HP. Additionally, this co-infection was significantly associated with an increased risk of developing GC, both generally and among older and younger patients. Furthermore, this co-infection was a risk factor for diffuse-type Lauren's classification, lymph node metastasis, and a higher stage of cancer.

The observed association may be explained by known mechanisms of EBV persistence and reactivation in the context of chronic gastric inflammation. Chronic *H. pylori* infection can alter inflammatory signaling and immune modulation, potentially facilitating EBV infection and/or reactivation in the gastric mucosa [48, 49]. Several lines of evidence support a biologically plausible interaction

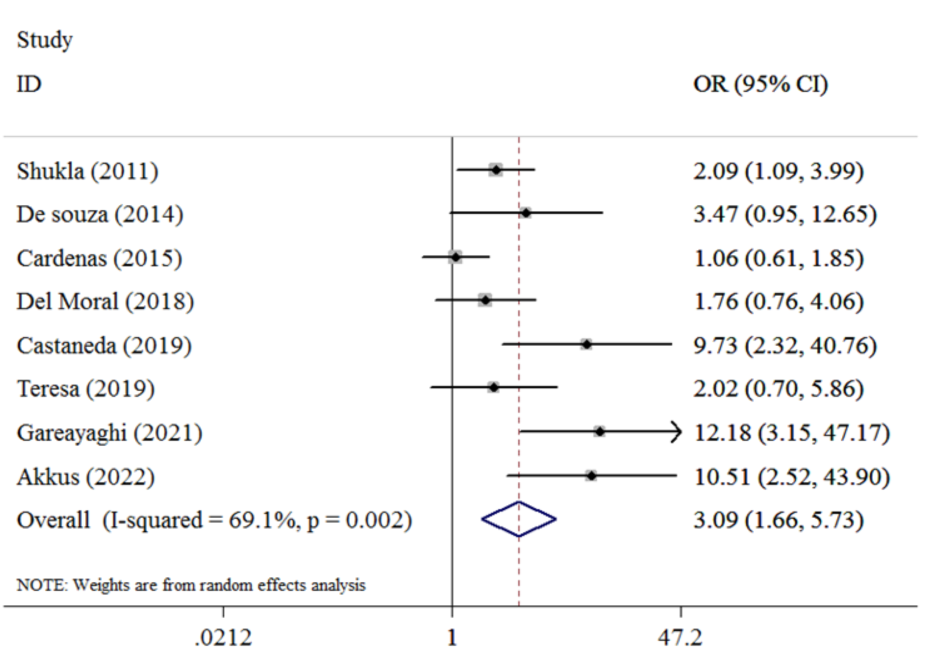

Figure 3. Forest Plot of the Pooled Odd Ratios for Gastric Cancer in HECo-Positive Patients

between *H. pylori* and EBV in the gastric epithelium. Experimental studies suggest that *H. pylori* attachment to gastric epithelial cells may induce the expression of accessory EBV entry receptors such as EphA2 and non-muscle myosin heavy chain IIA (NMHC-IIA), which can facilitate EBV entry even in CD21-negative cells. In addition, *H. pylori* establishes a state of chronic inflammation that is independently implicated in gastric carcinogenesis and may also promote EBV persistence, providing a mechanistic basis for the increased GC risk observed in HECo [50, 51].

The high prevalence of HP and EBV infection has been widely reported in previous studies. To the best of our knowledge there have been no comprehensive meta-analyses that have evaluated the effect of HECo on GC development. In this regard, our findings indicated a notable increase in the risk of GC when compared with the control group (OR: 3.09, 95% CI: 1.66 to 5.73). The exact mechanism of HP infection in the pathogenesis of GC is still unclear. However, HP infection is known as an agent that induces an inflammatory process and has direct effects on epithelial tissues, which could be related to tumorigenesis [5]. Besides, EBV acts as an oncogene in several malignancies, including GC, Hodgkin's lymphoma, nasopharyngeal carcinoma, and Burkitt lymphoma [52]. In fact, the mechanism of EBV infection in gastric carcinogenesis is not yet completely understood, but EBV-infected cells showed monoclonal proliferation and changes in DNA methylation [53, 54]. Likewise, GC patients who have EBV infection showed several specific epigenetic and genetic features in comparison with other GC patients [55]. Some studies have shown that the coexistence of infectious organisms could lead to exacerbated effects. In case of HECo, the HP infection stimulates the reactivation of EBV from its latent phase in epithelial cells of stomach [56]. In addition, some studies found that the EBV could act as an agent that cooperates with HP to initiate an inflammatory process through the gastric epithelial cells [26, 57]. In summary, molecular evidence and our meta-analysis indicate that HECo is associated with elevated GC risk. HECo may represent a potential marker for targeted interventions, although further research is needed.

Previous studies evaluated the association of viral and bacterial infections with GC. Based on the meta-analysis conducted by Huang et al., the prevalence of HP infection in patients with GC was considerably higher in comparison with the control group and it increased the risk of developing GC by 1.64-fold increase (1.21 to 2.24) [58]. This discrepancy between our finding and the mentioned studies may be due to the differences in inclusion criteria of the studies, our review was limited to the original studies that reported the HECo. However, the other studies evaluated all case-control studies in which the EBV infection was reported. Also Yao et al. confirmed the increased risk of GC [59]. Their study showed a greater proportion of CagA sero-positivity was associated with an elevated risk of cardiac and non-cardiac GC. Current meta-analysis illustrates that the HP infection is more prevalent in patients with GC in comparison with the control group.

The overall prevalence of EBV infection in our meta-analysis is lower than three times greater than the proportion presented in patients with gastric adenocarcinoma in meta-analysis of Hirabayashi et al. (7.5%; 95% CI: 6.9–8.1) [60]. Furthermore, other reviews illustrated greater proportion for EBV infection in patients with Gastric diffuse large B cell lymphoma from 7.9% (5.8% to 9.6%) to 11% (5.8% to 20.0%) [61, 62]. In addition, the risk of GC in EBV infected patients was 10-fold higher (5.8% to 17.2%) in comparison with the patients who had no confirmed EBV infection [63]. In the present study, significant heterogeneity was observed across studies, which may reflect variations in study design (e.g., case-control vs. cross-sectional), population demographics (e.g., geographic differences in EBV/HP strains), or methodological disparities (e.g., detection assays for HP/EBV). Although subgroup analyses reduced heterogeneity, residual variability suggests caution in generalizing results.

Limitation of the present study include

1. Due to the small quantity of included papers, therefore, the pooled EBV infection prevalence was calculated regardless of the method of HP and EBV detection, the sample used for detection, and CagA presentation.
2. The number of studies included in our subgroup analysis (by cancer type or histological differentiation) resulted in inconclusive pooled estimates.
3. In this investigation, only the articles published in English were included which may limit the comprehensiveness of the review.
4. The observed heterogeneity across studies remained unresolved despite subgroup analyses, potentially due to unmeasured confounders such as variations in study populations, diagnostic methods, or regional differences, highlighting the necessity for individual participant data (IPD) meta-analyses to address these limitations.
5. Most studies did not report mutually exclusive infection categories (HP only, EBV only, both, neither), which precluded direct comparisons of co-infection versus single infections and limited inference regarding additive or synergistic effects.
6. The apparent age-related differences should be interpreted with caution, as they were based on a small number of studies with wide confidence intervals and may reflect residual confounding or study-level differences rather than true effect modification.

Future comprehensive secondary studies are recommended to estimate more consistent odds ratios (OR) for GC in patients with HECo.

In conclusion, the findings of the present meta-analysis showed a considerable increase in the risk of GC in patients with HECo. These results support the importance of identifying and treating *H. pylori* infection in clinical practice and encourage further investigation of EBV-related pathways in gastric carcinogenesis. However, because mutually exclusive infection categories were inconsistently reported, future well-designed studies are needed to clarify the independent and joint effects of EBV and *H. pylori* and to evaluate preventive strategies.

Author Contribution Statement

Conceptualization: Ghazal Mohseni and Reza Alizadeh-Navaei. Methodology: Ghazal Mohseni and Reza Alizadeh-Navaei. Literature search: Ghazal Mohseni. Study selection / Screening: Aref Hoseini, Younes Zeytounli, Kimia Rasouli. Data extraction and quality (risk of bias) assessment: Aref Hoseini, Younes Zeytounli, Kimia Rasouli. Formal analysis (meta-analysis): Reza Alizadeh-Navaei. Writing-original draft: Ghazal Mohseni and Keyvan Heydari. review & editing: Sina Neshat and Reza Alizadeh-Navaei.

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None.

Ethical issue

According to the ethical regulations of the Iranian Ministry of Health and Medical Education (MOHME), systematic reviews and meta-analyses that use previously published data do not require an ethical approval code.

Data Availability Statement

All data used in this systematic review and meta-analysis were extracted from previously published studies. The extracted dataset is available from the corresponding author upon reasonable request.

Conflict Of Interest

All authors have asserted no potential interest exists.

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