QJM: An International Journal of Medicine, 2025, **00(00)**, 1–8
https://doi.org/10.1093/qjmed/hcaf092
Advance Access Publication Date: 15 April 2025
Original Article

OXFORD

Original Article

Association between *Helicobacter pylori* and Epstein–Barr virus co-infection and gastric cancer risk: a systematic review and meta-analysis

Ngoc-Niem Bui [1,2,†], Shih-Chiang Huang[1,3,†], Thi Nhu Le Tran[2], Ngoc Hien Nguyen[4], Hang Nga Do[1], Ya-Fang Chiu[1,5,6,7,8,*] and Chih-Ho Lai [1,5,7,9,10,11,12,*]

[1]Graduate Institute of Biomedical Sciences, Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[2]Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam
[3]Department of Anatomical Pathology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[4]Faculty of Medicine, Nam Can Tho University, Can Tho, Vietnam
[5]Research Center for Emerging Viral Infections, Chang Gung University, Taoyuan, Taiwan
[6]Department of Laboratory Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[7]Department of Microbiology and Immunology, Chang Gung University, Taoyuan, Taiwan
[8]Division of Infectious Diseases, Department of Medicine, New Taipei Municipal Tucheng Hospital, New Taipei, Taiwan
[9]Department of Medical Research, School of Medicine, China Medical University and Hospital, Taichung, Taiwan
[10]Department of Nursing, Asia University, Taichung, Taiwan
[11]Department of Pediatrics, Molecular Infectious Disease Research Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[12]Institute of Immunology and Translational Medicine, Center for the Molecular and Clinical Immunology, Chang Gung University, Taoyuan, Taiwan

*Address correspondence to Y.-F. Chiu, Department of Microbiology and Immunology, Chang Gung University, 259, Wenhua 1st Rd., Guishan Dist., Taoyuan, 33302, Taiwan. Email: yfchiu@mail.cgu.edu.tw; C.-H. Lai, Department of Microbiology and Immunology, Chang Gung University, 259, Wenhua 1st Rd., Guishan Dist., Taoyuan, 33302, Taiwan. Email: chlai@mail.cgu.edu.tw

[†]These contributed equally to this work and should be regarded as co-first authors.

Abstract

Background: Co-infection with *Helicobacter pylori* (*H. pylori*) and Epstein–Barr virus (EBV) has been demonstrated in clinical studies; however, its association with gastric cancer (GC) remains uncertain.

Aims: This study aims to assess and establish evidence linking *H. pylori* and EBV co-infection to an increased risk of GC development.

Design: A meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods: We conducted a meta-analysis study to investigate the pooled odds ratios (ORs) for individual infections and co-infections, and their association with the risk of GC development.

Results: EBV infection was more frequent in patients with GC than in non-GC patients (OR 4.98, 95% confidence interval (CI) 3.17–7.85, $P < 0.0001$). *H. pylori* infection was associated with a significantly increased GC risk compared with a control group excluding gastritis cases (OR 1.42, 95% CI 1.02–1.99, $P = 0.03$). Nevertheless, the random-effects model revealed that the pooled odds of co-infection were significantly elevated (OR 2.57, 95% CI 1.65–4.01, $P < 0.0001$).

Conclusions: Both *H. pylori* and EBV infections increase the risk of developing GC. The co-infection of *H. pylori* and EBV was linked to a 2.57-fold higher risk of GC, indicating the significance of incorporating both infections into diagnostic and treatment approaches for GC.

Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide. Several factors contribute to the development of GC, including diet, tobacco use, environmental and occupational exposure, genetics, family history, obesity, gastroesophageal reflux disease and chronic infections.[1] Chronic *Helicobacter pylori* (*H. pylori*) infection is a well-documented and significant risk factor for GC development.[1] Moreover, Epstein–Barr virus (EBV) has been identified globally in approximately 8.77% of GC cases, establishing it as another infectious agent that contributes to GC development.[2]

Helicobacter infection is thought to induce chronic gastritis in the stomach, leading to DNA damage, progressive gastric mucosal damage and subsequently promoting cancer progression.[1] Moreover, *H. pylori* has several virulence factors that contribute to the development of GC, with CagA being the most notable, as it is strongly associated with an increased GC risk.[3,4] Additionally, EBV infection has been established as a significant

Received: 18 February 2025. **Revised (in revised form):** 31 March 2025.

etiological factor for GC, with a globally pooled prevalence of 7.5% (95% CI 6.9–8.1%).[5] Current evidence suggests that EBV-mediated gastric carcinogenesis involves complex molecular interactions. These include viral protein and microRNA expressions (LMP2A, miR-BART1-3p and miR-BART18-5p) and the activation of the WNT/CTNNB1/TCF7L2 signaling pathway, which together drive the malignant transformation of infected cells.[1,6]

Although several systematic reviews have examined the detection rates of *H. pylori* or EBV infection in GC, comprehensive meta-analyses quantifying the association between co-infection and GC risk remain limited.[2,5,7–10] This study aimed to address this gap by performing a meta-analysis of existing case-control studies to investigate the summary odds ratio (OR) and 95% CI. The results of this study provide valuable insights into the role of individual and dual infections with *H. pylori* and EBV in GC, contributing to more targeted prevention and treatment approaches.

Methods

Literature search strategy

This study was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] A comprehensive literature search was conducted using the PubMed and Web of Science Databases until 30 June 2024. The search terms included '*Helicobacter pylori*', '*H. pylori*', 'Epstein–Barr virus', 'EBV', 'human herpesvirus 4', 'HHV-4', 'co-infection', 'dual infection' and 'association' with Boolean operators (AND, OR) were applied to combine terms and identify relevant studies.

Data were extracted independently by two reviewers (Drs Ngoc-Niem Bui and Thi Nhu Le Tran). Any disagreements were resolved through discussion and, if necessary, adjudicated by a third reviewer (Dr Chih-Ho Lai). The key information extracted included patient characteristics, study design, disease type and methods for detecting EBV and *H. pylori*.

Eligibility criteria

The inclusion criteria for this meta-analysis were restricted to observational studies, specifically case-control and cross-sectional research designs that examined the relationship between *H. pylori* and EBV co-infections and their association with GC development. Eligible studies were required to present findings on GC outcomes, including non-cardia and overall GC risks, and were compared with the control groups. This review was limited to English language publications containing complete, accessible and full-text articles.

Case reports, reviews, animal models or *in vitro* studies were excluded. Studies that did not include a control group or failed to report comparative risk analyses of GC were also excluded. Additionally, studies focusing on non-GC conditions, such as esophageal cancer, or unrelated conditions, such as duodenal ulcers and peptic ulcer disease, were excluded. Studies investigating *H. pylori* or EBV infections individually without exploring their co-infection effects were also excluded.

Statistical analysis

The primary objective was to evaluate the association between individuals and co-infection with *H. pylori* and EBV with GC compared with non-neoplastic controls. After applying the inclusion and exclusion criteria, the data from 13 studies were compiled. These studies included the study year, number of positive diagnoses of *H. pylori* and/or EBV in the case and control groups, nationalities of participants, diagnostic methods for *H. pylori* and EBV, sample types and disease characteristics. OR and 95% CI were calculated for each study using the Metafor R package based on the number of positive and negative diagnoses of *H. pylori* and/or EBV in each group. The random-effects model with the z-score (z) and *P* values were calculated. Study heterogeneity was evaluated using *I*-squared values (%), and pooled OR with 95% CI was estimated using random-effects models. Publication bias was assessed using Egger's test for small study effects and Begg's rank correlation test.

Results

Characteristics of included studies

A total of 1092 studies were initially retrieved as of 30 June 2024, from PubMed (413 studies) and the Web of Sciences Database (679 studies). After excluding 572 duplicates, 520 studies were reviewed based on their titles and abstracts. After applying the exclusion criteria, 476 studies were excluded, leaving 44 eligible studies for a full-text review. Ultimately, 13 studies met the inclusion criteria and were selected for analysis. A detailed protocol for selecting eligible studies is illustrated in Figure 1.

Data from 1061 patients with GCs and 1633 non-GC patients with *H. pylori* and EBV individual and co-infection were analysed across the 13 included studies, as summarized in Table 1. These studies included two papers each from India,[12,13] Iran,[14,15] Turkey[16,17] and Italy,[18,19] and one from Portugal,[20] Brazil,[21] Peru,[22] Mexico[23] and Paraguay.[24] The included studies ranged from the earliest conducted in 2008 to the most recent in 2023, with the number of cases varying from 50 to 540. Two studies from Mexico and Paraguay classified GC into intestinal, diffused and mixed types.[23,24] The control group included patients with normal gastric mucosa, adjacent non-tumor tissues, peptic ulcers, non-ulcer dyspepsia, gastritis, intestinal metaplasia and premalignant lesions. The most common diagnostic method for the detection of *H. pylori* is polymerase chain reaction (PCR) (13/13, 100%), followed by a combination of PCR and urease test (3/13, 23%), serology (2/13, 15.4%) and culture (2/13, 15.4%). EBV was detected using PCR (5/13, 38.5%), reverse transcription PCR (5/13, 38.5%), *in situ* hybridization (2/13, 15.4%), individual (11/13, 84.6%) or in combination with each other (2/13, 15.4%) (Table 1).

The association of *H. pylori* and EBV individual and co-infection in GC development risk

Helicobacter pylori infection is documented as one of the significant risk factors for GC development.[25] Moreover, EBV is classified as a Group I carcinogen and presents approximately 10% of GC,[2,5] suggesting that co-infection with these two Group I carcinogen pathogens may synergistically increase the risk of GC development. To explore this association, we analysed the differences between co-infection in the GC and control (non-GC) groups. The results showed that *H. pylori* co-infection with EBV was associated with a higher risk of GC than in non-GC controls. The pooled odds of co-infection were significantly higher in the random-effects model (OR 2.57, 95% CI 1.65–4.01, $P < 0.0001$) for heterogeneity ($I^2 = 53\%$) (Figure 2, Supplementary Table S1). We analysed the pooled OR of respective *H. pylori* or EBV individual infections in patients with GC and non-GC controls. The EBV individual infection was significantly higher in patients with GC compared with non-GC in the random-effects model (OR 4.99, 95% CI 3.17–7.85, $P < 0.0001$), and heterogeneity resulted significantly different (I^2 53%, $P < 0.01$) (Figure 3). However, the pooled OR of *H. pylori* individual infection showed no significant differences in comparison between GC and non-GC in the random-effects model (OR 1.24, 95% CI 0.92–1.67, $P = 0.15$) (Figure 4A). Since the progression of gastric carcinogenesis, along with the stepwise evolution of chronic gastritis, is initiated by *H. pylori* infection,[1] we further

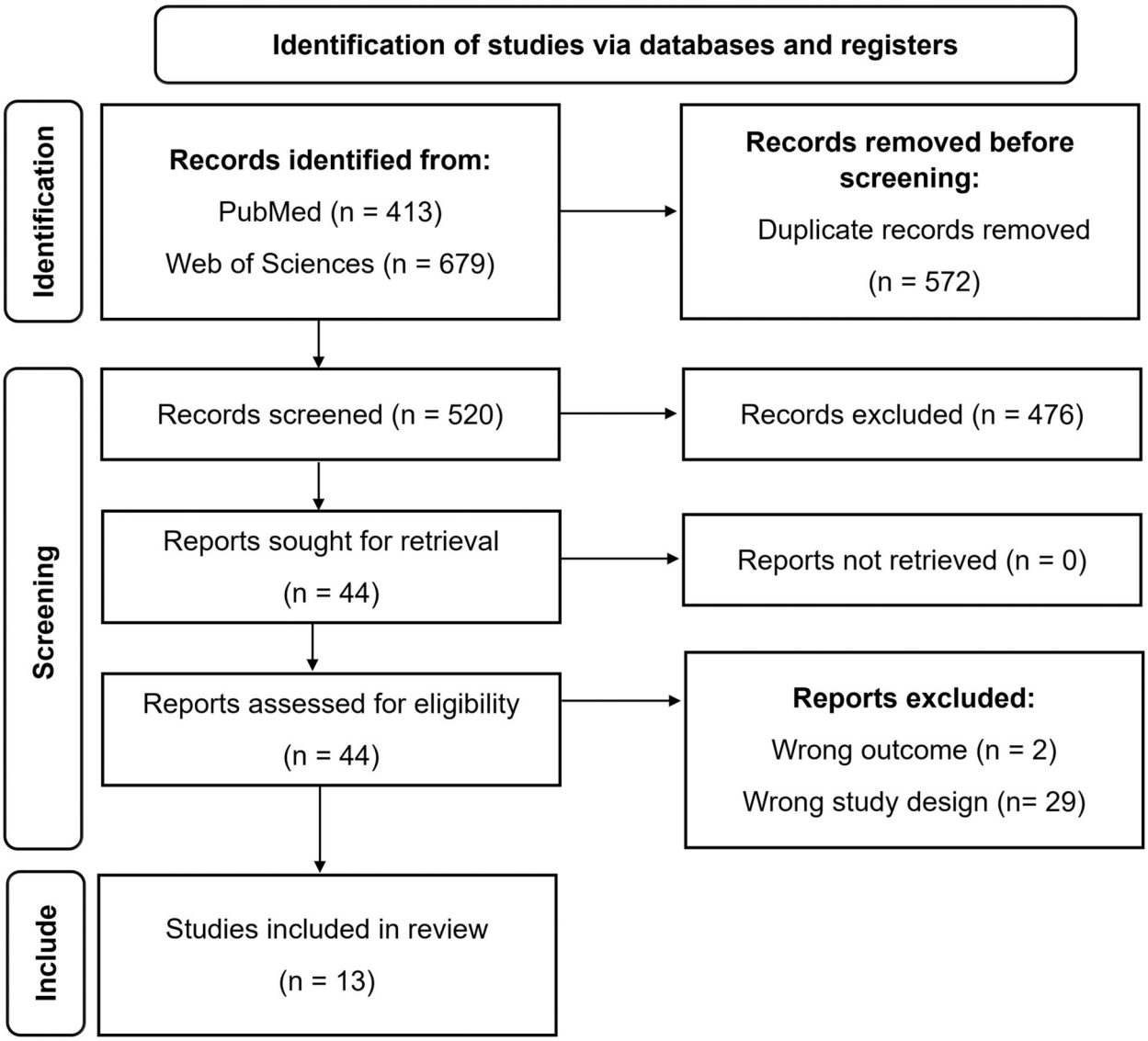


Figure 1. Flow diagram of the articles selected from the literature search examining the association of *H. pylori* and EBV co-infections with the risk of GC development.

excluded studies analysing gastritis in the control group and meta-analyses in this subgroup for GC risk by *H. pylori* individual infection. The results showed a significantly increased GC risk compared with the control group, which included normal tissue, adjacent normal tissue, peptic ulcer and non-peptic ulcer cases (OR 1.49, 95% CI 1.09–2.05, $P = 0.01$) (Figure 4B). These results indicate that *H. pylori* and EBV co-infections play a crucial role in elevating the risk of GC, highlighting the importance of co-infection as a significant factor in GC development.

Reciprocal influences of *H. pylori* and EBV infections on each other's prevalence

Helicobacter pylori infection can enhance the expression of accessory EBV receptors for viral infection of gastric epithelial cells.[26] We next investigated whether *H. pylori* infection increases the rate of EBV infection or, conversely, whether EBV infection promotes *H. pylori* prevalence. To address this, we analysed the risk of EBV or *H. pylori* individual infection in cases in which other infections were present. The results showed no significant correlation between *H. pylori* infection in EBV-positive and EBV-negative cases (OR 1.49, $P = 0.2$) (Supplementary Figure S1A) or EBV infection in *H. pylori*-positive versus *H. pylori*-negative cases (OR 1.43, $P = 0.26$) (Supplementary Figure S1B). A similar pattern was observed when comparing the GC groups. No correlation was found between *H. pylori* infection in EBV-positive or EBV-negative among patients with GC (OR 1.06, $P = 0.87$) (Supplementary Figure S2A). Similarly, no correlation was observed between EBV infection in *H. pylori*-positive and *H. pylori*-negative individuals among patients with GC (OR 1.06, $P = 0.87$) (Supplementary Figure S2B). These results indicated that neither *H. pylori* nor EBV enhanced the infection rate of the other, both in the general population and specifically in GC cases.

Risk of bias across studies

Publication bias was evaluated using multiple complementary approaches. Visual inspection of the funnel plot revealed asymmetry, suggesting potential publication bias (Supplementary Figure S3). This observation was supported by the results of two statistical analyses. A significant bias was detected using Egger's test in the overall analysis ($t = 3.09$, $P = 0.01$) and Begg's rank correlation test ($z = 2.07$, $P = 0.0381$), indicating significant asymmetry.

Table 1 Characteristics of included studies

Studies (country, year) (reference)	Total case	*H. pylori* detection method	EBV detection method	Type of samples	GC (*N*)	Type of control (*N*)
Saxena (India, 2008)[12]	348	Urease test, culture, PCR (*ureA*)	PCR (*EBNA1*)	GC, PUD, NUD	62	NUD (241), PUD (45)
Shukla (India, 2011)[13]	200	Urease test, culture, PCR (*ureA*)	qPCR (*EBNA1*)	GC, PUD, NUD	50	NUD (100), PUD (50)
Souza (Brazil, 2014)[21]	217	Urease test, PCR (*ureA*)	*EBER1* in situ hybridization	GC, GT	125	GT (92)
Cardenas-Mondragon (Mexico vs. Paraguay, 2015)[24]	525	Serology	Serology (viral capsid antigen IgG)	GC, GT, IM, PM	Total (114): IT (50), DT (64)	Total (411): GT (225), PM (186)
Nogueira (Portugal, 2017)[20]	115	Serology, PCR (*flagella*)	*EBER1* in situ hybridization, RT PCR (*BamHIW*)	GC, Non-GC	82	33
Fattahi (Iran, 2018)[15]	63	PCR (*glmM*)	RT PCR (*BamHIW*)	GC, ANC	63	63
Teresa (Italy, 2019)[19]	96	PCR (*ureA*)	RT PCR (*BamHIW*)	GC, GT, NC	24	24
Moral-Hernandez (Mexico, 2019)[23]	138	PCR (*16S rRNA*)	PCR (*EBNA1*)	GC, GT	Total (32): IT (7), DT (18), MT (3), others (4)	GT (106)
Castaneda (Peru, 2019)[22]	540	PCR (*hspA*, *ureA*)	qPCR (*BNRF1*)	GC, GT	375	GT (165)
Gareayaghi (Turkey, 2021)[17]	104	PCR (*glmM*)	RT PCR (*EBER1*), serology (EBNA1 IgG)	GC, PUD, NUD, NC	34	Total (70): PUD (30), NUD (40)
Akkus (Turkery, 2022)[16]	108	PCR (*glmM*)	qPCR (*EBNA1*), serology (EBNA1 IgG)	GC, IM, PUD	25	Total (83): IM (13), PUD (30), NUD (40)
Estaji (Iran, 2022)[14]	150	PCR (*ureA*)	qPCR (*BZLF1*, *EBNA1*, *EBER1*)	GT, MP, GC	50	Total (100): MP (50), GT (50)
Giammanco (Italy, 2023)[18]	50	PCR (*ureA*)	PCR (*BamHIW*)	NC, GT, GC	25	Total (50): NC (25), GT (25)

Abbreviations: GS: gastric cancer; PD, peptic ulcer; NUD: non-ulcer dyspepsia; IM: intestinal metaplasia; GT: gastritis; NC: normal gastric mucosa; ANC: adjacent nontumoral tissues; PM: premalignant lesion; MP: metaplasia; IT: intestinal type; DT: diffuse type; MT: mixed type.

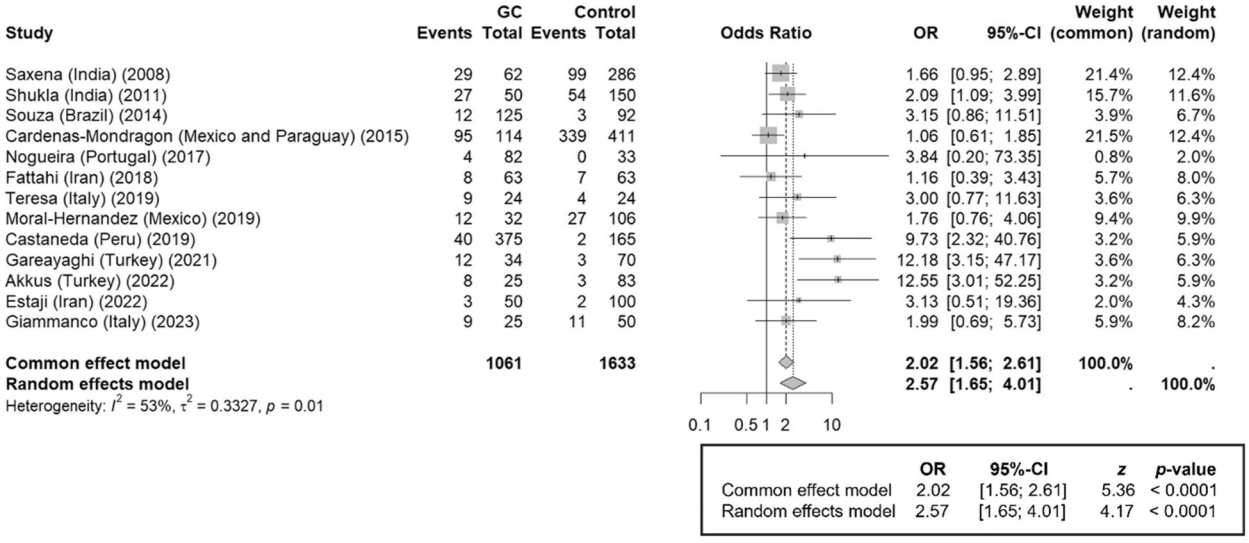


Figure 2. Forest plot of the association between *H. pylori* and EBV co-infections and GC development risk in 13 eligible studies using OR analysis.

A trim-and-fill analysis was conducted to quantify the potential impact of publication bias. The original random-effects model yielded an OR 2.57 (95% CI 1.65–4.01, $P < 0.0001$) with the I^2 53%. After adjustment using the trim-and-fill method, OR was reduced to 1.95 (95% CI 1.42–2.68, $P < 0.0001$) with the I^2 0% (Supplementary Figure S4).

Discussion

Analysis of case-control data from 13 studies indicated that *H. pylori* and EBV co-infection had a significantly positive relationship with GC. This analysis aligned with a previous report showing that individuals with EBV infection displayed substantially higher risks of developing GC, as evidenced by a pooled OR of 4.88.[2,5,7–10] The association between *H. pylori* and GC was well studied, and OR varied from 1.81 (95% CI 1.16–2.84) to 2.04 (95% CI 1.69–2.45).[27–29] As most data from the 13 studies used patients with gastritis as the control group, the relationship between *H. pylori* and EBV showed no significant difference in the association between *H. pylori* infection and GC risk (OR 1.24, $P = 0.15$). The progression of gastric carcinogenesis is a multistep process

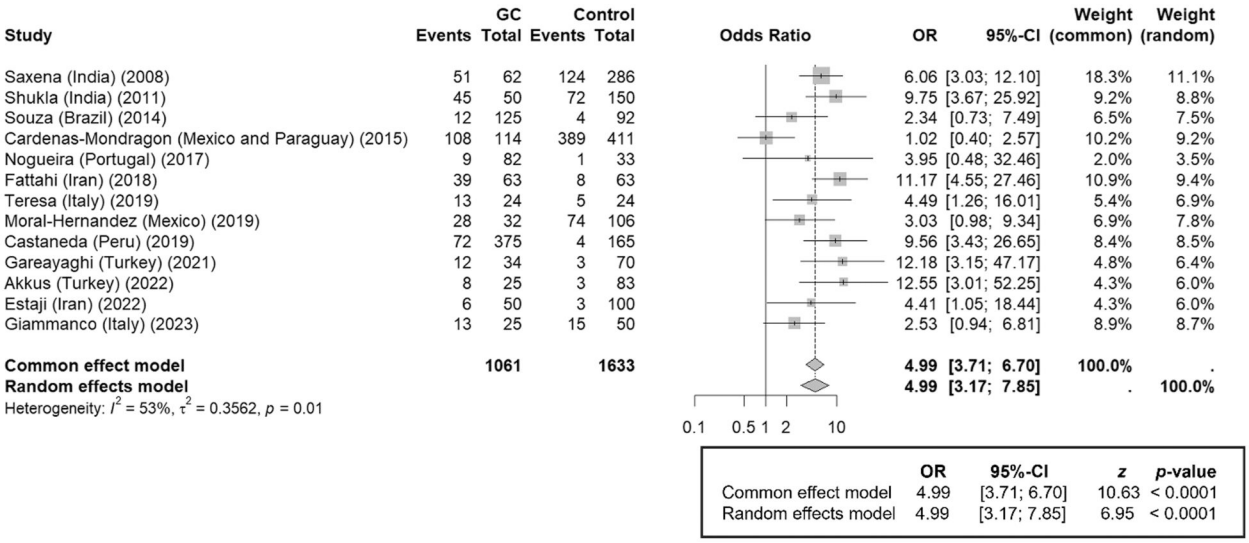
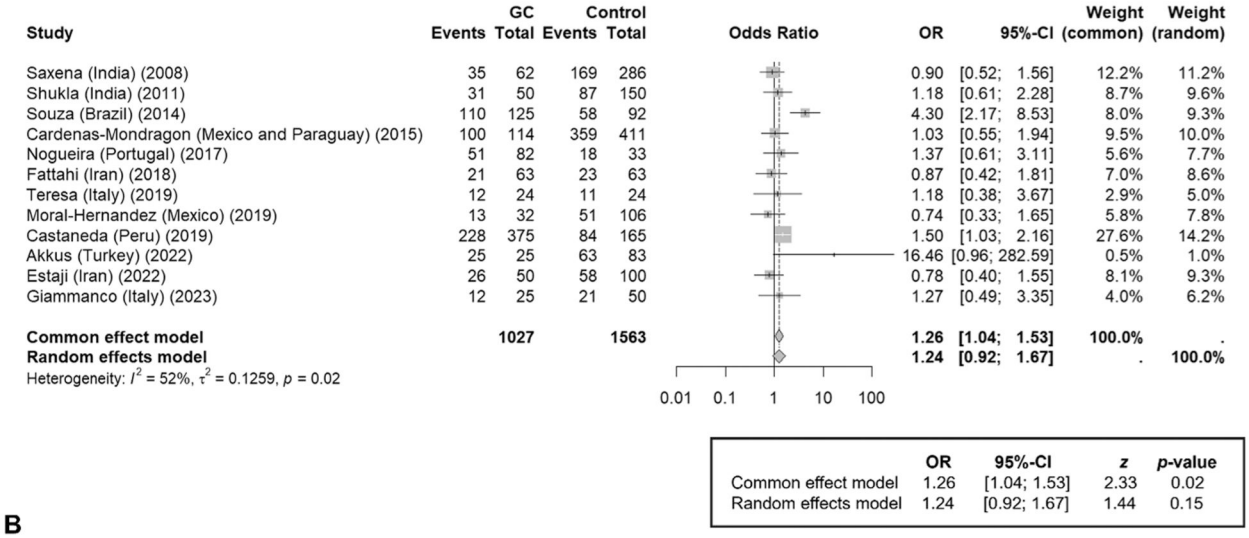


Figure 3. OR analysis of the association between EBV individual infection and GC risk in 13 eligible studies.

A



B

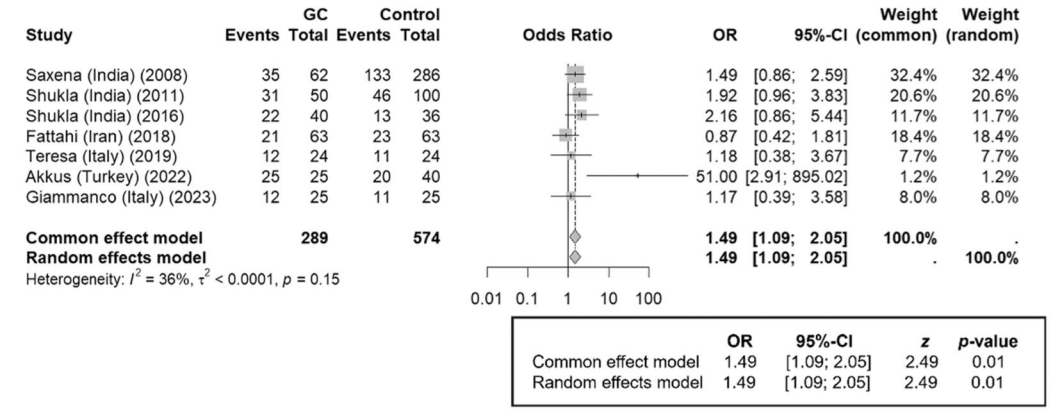


Figure 4. The risk of GC development in *H. pylori* individual infection. Forest plot showing the association between individual *H. pylori* infection and GC development risk compared with two control groups: (**A**) including patients with gastritis and (**B**) excluding patients with gastritis.

that typically begins with chronic gastritis initiated by *H. pylori* infection, subsequently evolving through stages such as atrophic gastritis, intestinal metaplasia and dysplasia, and eventually developing into GC.[1] When we performed a subgroup analysis excluding patients with gastritis from the control group, the results showed a significant association between *H. pylori* infection and GC risk (OR 1.42, $P = 0.03$).

The highest risk of GC development associated with *H. pylori* and EBV co-infection was observed in Turkey (OR 12.18 and 12.55) and Peru (OR 9.56) (Table 1). For EBV individual infection, the association remained consistently highest in Turkey and Peru. However, the association with *H. pylori* individual infection showed a significant positive result in the studies from Turkey (OR 16.46, 95% CI 0.96–282.59) but was comparatively lower in Peru (OR 1.5, 95% CI 1.03–2.16). This variability underscores the potential influence of regional- or population-specific factors on risk dynamics. We also searched for more studies on the prevalence of EBV and the risk of GC in Peru and Turkey. A high prevalence of the distinctive type i/XhoI+, characterized by the BamHI W1/I1 variant (type I) and the presence of the XhoI restriction site in exon 1 of the latent membrane protein 1 gene (XhoI+), was predominantly observed in EBV-positive GC cases in Peru.[30]

A similar observation has been reported in neighboring countries, including Colombia and Chile, where most EBV-associated GC cases harbored a distinctive EBV strain (type I/XhoI+).[31,32] Moreover, the risk of GC development associated with EBV individual infection was significantly higher in India, with ORs of 6.06 and 9.75. In contrast, the risk associated with EBV and *H. pylori* co-infection was comparatively lower, with ORs of 1.66 and 2.09, respectively. Variability in EBV strains and their oncogenic potential seem to play crucial roles in GC development.[33] *H. pylori* infection may further enhance the oncogenic effects of EBV, potentially through interactions that influence viral or host factors. Investigating the gene expression profiles of EBV and the specific characteristics of EBV strains associated with GC in the regions is a priority for better understanding these mechanisms.

In vitro studies demonstrated that EBV infection in gastric epithelial cancer cell lines downregulated SHP1 through promoter hypermethylation, which subsequently enhanced phosphorylation-dependent CagA activity and amplified *H. pylori*'s oncogenic potential.[1] The oncoprotein CagA of *H. pylori* can induce malignant neoplasms in host cells through its phosphorylation by host cell kinases, allowing it to bind with the proto-oncogenic phosphatase SHP-2 and activate multiple signaling pathways.[4] Moreover, among the four CagA EPIYA motifs—A, B, C and D, the EPIYA-D motif, predominantly found in East Asian strains, exhibits a higher affinity for SHP-2 binding compared to the Western CagA variant, leading to more severe gastric diseases and a higher incidence of GC.[4] These findings suggest that co-infection between EBV and *H. pylori* East Asian strains may have a stronger synergistic effect on GC development. However, among 13 studies recruited for this analysis, no case-control data from East Asia. A further case-control study in this region, including a detailed analysis of CagA EPIYA motifs, is needed to investigate *H. pylori* and EBV co-infection in relation to GC development.

The hypothesis that *H. pylori* and EBV influence each other's infectivity has been documented in several *in vitro* studies. For example, *H. pylori* CagA-positive strains can induce interleukin 8 cytokine secretion, which acts as a chemoattractant for EBV-positive B cells and promotes their migration to gastric tissues.[34] Additionally, *H. pylori* infection of gastric epithelial cells stimulates the expression of Ephrin type-A receptor 2 and non-muscle myosin heavy chain IIa receptors, which facilitate EBV entry into these cells.[26] These findings provide *in vitro* evidence that *H. pylori* enhances EBV infection in gastric epithelial cells. However, our meta-analysis on the mutual influence of *H. pylori* and EBV infection prevalence indicates that neither *H. pylori* nor EBV significantly increases the infection rate of others, either in the general population or specifically in GC cases. Further clinical studies that collect samples at different time points may help clarify the chronological order of these infections and their potential impact on GC development.

Conclusions

Our meta-analysis revealed that *H. pylori* and EBV co-infection increased the risk of GC by 2.57-fold. *H. pylori* and EBV individual infections are also associated with an elevated risk of GC. No evidence suggests that individual *H. pylori* and EBV infections influence the prevalence of each other in GC cases. These findings highlight the potential importance of considering *H. pylori* and EBV co-infection in the diagnosis and therapeutic strategies for GC.

Acknowledgements

The authors thank the editor and the reviewers for their editorial assistance and valuable comments. The authors gratefully acknowledge the support from Can Tho University of Medicine and Pharmacy, Vietnam.

Author contributions

Ngoc-Niem Bui (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Software [equal], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Shih-Chiang Huang (Investigation [equal], Methodology [equal], Supervision [equal], Validation [equal], Visualization [equal]), Thi Nhu Le Tran (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Methodology [equal], Software [equal], Supervision [equal], Validation [equal], Writing—original draft [equal]), Ngoc Hien Nguyen (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Methodology [equal], Software [equal], Visualization [equal], Writing—original draft [equal]), Hang Nga Do (Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Software [equal], Validation [equal], Visualization [equal], Writing—original draft [equal]), and Ya-Fang Chiu (Funding acquisition [equal], Investigation [equal], Methodology [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), and Chih-Ho Lai (Conceptualization [equal], Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal])

Supplementary material

Supplementary material is available at *QJMED* online.

Conflict of interest: The authors have no competing interests to declare.

Funding

This study was supported by the National Science and Technology Council [112-2320-B-182-036-MY3, 112-2320-B-182-042-MY3 and 113-2320-B-182-010], Chang Gung Memorial Hospital [CMRPD1K0361, CMRPD1L0321, CMRPD1M0491-2, CMRPD1P0181 and CORPD1M0021-3], Research Center for Emerging Viral Infections from the Featured Areas Research Center Program within the framework of the Higher Education

Sprout Project by the Taiwan Ministry of Education and Tomorrow Medical Foundation.

Data availability

The datasets produced and analysed in this study are available from the corresponding author upon reasonable request.

References

1. Wroblewski LE, Peek RM Jr. Clinical pathogenesis, molecular mechanisms of gastric cancer development. *Curr Top Microbiol Immunol* 2023; **444**:25–52.
2. Tavakoli A, Monavari SH, Solaymani Mohammadi F, Kiani SJ, Armat S, Farahmand M. Association between Epstein–Barr virus infection and gastric cancer: a systematic review and meta-analysis. *BMC Cancer* 2020; **20**:493.
3. Murata-Kamiya N, Kurashima Y, Teishikata Y, Yamahashi Y, Saito Y, Higashi H, *et al. H. pylori* CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene* 2007; **26**:4617–26.
4. Hatakeyama MH. *pylori* CagA and gastric cancer: a paradigm for hit-and-run carcinogenesis. *Cell Host Microbe* 2014; **15**:306–16.
5. Hirabayashi M, Georges D, Clifford GM, de Martel C. Estimating the global burden of Epstein–Barr virus-associated gastric cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2023; **21**:922–30.e921.
6. Zhao Y, Zhang J, Cheng ASL, Yu J, To KF, Kang W. Gastric cancer: genome damaged by bugs. *Oncogene* 2020; **39**:3427–42.
7. Dokanei S, Minai-Tehrani D, Moghoofei M, Rostamian M. Investigating the relationship between Epstein–Barr virus infection and gastric cancer: a systematic review and meta-analysis. *Health Sci Rep* 2024; **7**:e1976.
8. Bae JM, Kim EH. Epstein–Barr virus and gastric cancer risk: a meta-analysis with meta-regression of case-control studies. *J Prev Med Public Health* 2016; **49**:97–107.
9. Liu X, Liu J, Qiu H, Kong P, Chen S, Li W, *et al.* Prognostic significance of Epstein–Barr virus infection in gastric cancer: a meta-analysis. *BMC Cancer* 2015; **15**:782.
10. Zong L, Seto Y. CpG island methylator phenotype, *H. pylori*, Epstein–Barr virus, and microsatellite instability and prognosis in gastric cancer: a systematic review and meta-analysis. *PLoS One* 2014; **9**:e86097.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; **372**:n71.
12. Saxena A, Nath Prasad K, Chand Ghoshal U, Krishnani N, Roshan Bhagat M, Husain N. Association of *H. pylori* and Epstein–Barr virus with gastric cancer and peptic ulcer disease. *Scand J Gastroenterol* 2008; **43**:669–74.
13. Shukla SK, Prasad KN, Tripathi A, Singh A, Saxena A, Ghoshal UC, *et al.* Epstein–Barr virus DNA load and its association with *H. pylori* infection in gastroduodenal diseases. *Braz J Infect Dis* 2011; **15**:583–90.
14. Estaji F, Nasr Esfahani B, Zibaee S, Sanei MH, Moghim S. Epstein–Barr virus/*H. pylori* co-infection and gastric cancer: the possible role of viral gene expression and shp1 methylation. *Iran J Microbiol* 2022; **14**:901–12.
15. Fattahi S, Nikbakhsh N, Taheri H, Ghadami E, Kosari-Monfared M, Amirbozorgi G, *et al.* Prevalence of multiple infections and the risk of gastric adenocarcinoma development at earlier age. *Diagn Microbiol Infect Dis* 2018; **92**:62–8.
16. Akkus S, Gareayaghi N, Saribas S, Demiryas S, Ozbey D, Kepil N, *et al.* Co-infection relationship with Epstein–Barr virus in gastroduodenal diseases with *H. pylori*. Quantitative PCR and EBNA-1 gene-based approach. *Acta Gastroenterol Belg* 2022; **85**:301–8.
17. Gareayaghi N, Akkus S, Saribas S, Demiryas S, Ozbey D, Kepil N, *et al.* Epstein–Barr virus and *H. pylori* co-infection in patients with gastric cancer and duodenale ulcer. *New Microbiol* 2021; **44**:217–26.
18. Giammanco A, Anzalone R, Serra N, Graceffa G, Vieni S, Scibetta N, *et al. H. pylori* and Epstein–Barr virus co-infection in gastric disease: what is the correlation with p53 mutation, genes methylation and microsatellite instability in a cohort of Sicilian population? *Int J Mol Sci* 2023; **24**:8104.
19. Teresa F, Serra N, Capra G, Mascarella C, Gagliardi C, Di Carlo P, *et al. H. pylori* and Epstein–Barr virus infection in gastric diseases: correlation with IL-10 and IL1RN polymorphism. *J Oncol* 2019; **2019**:1785132.
20. Nogueira C, Mota M, Gradiz R, Cipriano MA, Caramelo F, Cruz H, *et al.* Prevalence and characteristics of Epstein–Barr virus-associated gastric carcinomas in Portugal. *Infect Agent Cancer* 2017; **12**:41.
21. de Souza CR, de Oliveira KS, Ferraz JJ, Leal MF, Calcagno DQ, Seabra AD, *et al.* Occurrence of *H. pylori* and Epstein–Barr virus infection in endoscopic and gastric cancer patients from Northern Brazil. *BMC Gastroenterol* 2014; **14**:179.
22. Castaneda CA, Castillo M, Chavez I, Barreda F, Suarez N, Nieves J, *et al.* Prevalence of *H. pylori* infection, its virulent genotypes, and Epstein–Barr virus in Peruvian patients with chronic gastritis and gastric cancer. *J Glob Oncol* 2019; **5**:1–9.
23. Del Moral-Hernandez O, Castanon-Sanchez CA, Reyes-Navarrete S, Martinez-Carrillo DN, Betancourt-Linares R, Jimenez-Wences H, *et al.* Multiple infections by EBV, HCMV and *H. pylori* are highly frequent in patients with chronic gastritis and gastric cancer from Southwest Mexico: an observational study. *Medicine (Baltimore)* 2019; **98**:e14124.
24. Cardenas-Mondragon MG, Torres J, Flores-Luna L, Camorlinga-Ponce M, Carreon-Talavera R, Gomez-Delgado A, *et al.* Case-control study of Epstein–Barr virus and *H. pylori* serology in Latin American patients with gastric disease. *Br J Cancer* 2015; **112**:1866–73.
25. Shirani M, Pakzad R, Haddadi MH, Akrami S, Asadi A, Kazemian H, *et al.* The global prevalence of gastric cancer in *H. pylori*-infected individuals: a systematic review and meta-analysis. *BMC Infect Dis* 2023; **23**:543.
26. Fekadu S, Kanehiro Y, Kartika AV, Hamada K, Sakurai N, Mizote T, *et al.* Gastric epithelial attachment of *H. pylori* induces EphA2 and NMHC-IIA receptors for Epstein–Barr virus. *Cancer Sci* 2021; **112**:4799–811.
27. Wang C, Yuan Y, Hunt RH. The association between *H. pylori* infection and early gastric cancer: a meta-analysis. *Am J Gastroenterol* 2007; **102**:1789–98.
28. Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of *H. pylori* infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol* 1999; **94**:2373–9.
29. Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *H. pylori* seropositivity and gastric cancer. *Gastroenterology* 1998; **114**:1169–79.
30. Ordonez P, Koriyama C, Ding S, Yoshiwara E, Corvalan AH, Takano J, *et al.* Identification of the distinctive type i/XhoI+ strain of Epstein–Barr virus in gastric carcinoma in Peru. *Anticancer Res* 2011; **31**:3607–13.

31. Corvalan A, Ding S, Koriyama C, Carrascal E, Carrasquilla G, Backhouse C, *et al.* Association of a distinctive strain of Epstein–Barr virus with gastric cancer. *Int J Cancer* 2006; **118**:1736–42.
32. Vidal-Realpe A, Dueñas-Cuellar RA, Niño-Castaño VE, Mora-Obando DL, Arias-Agudelo JJ, Bolaños HJ. Clinical and pathologic characteristics of gastric adenocarcinoma associated with Epstein–Barr virus in a region with a high incidence of gastric cancer in Colombia. *Rev Gastroenterol Mex (Engl Ed)* 2023; **88**:256–66.
33. Santos E, Silva M, Canedo NHS, Gaui MFD, Britto A, Silva W, *et al.* Epstein–Barr virus in gastric cancer and association with 30 bp del-latent membrane protein 1 polymorphism. *Rev Assoc Med Bras (1992)* 2023; **69**:e20221571.
34. Dominguez-Martinez DA, Fontes-Lemus JI, Garcia-Regalado A, Juarez-Flores A, Fuentes-Panana EM. IL-8 secreted by gastric epithelial cells infected with *H. pylori* CagA positive strains is a chemoattractant for Epstein–Barr virus infected B lymphocytes. *Viruses* 2023; **15**:651.

QJM: An International Journal of Medicine, 2025, 00, 1–8
https://doi.org/10.1093/qjmed/hcaf092
Original Article