Estimating the Global Burden of Epstein-Barr Virus–Associated Gastric Cancer: A Systematic Review and Meta-Analysis

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BACKGROUND & AIMS: **Evidence suggests that a fraction of new gastric cancer cases may be etiologically associated with Epstein-Barr virus (EBV), a known carcinogenic agent. We aimed to systematically explore the proportion of EBV-positive gastric cancer.**

METHODS: **We did a systematic review (PROSPERO CRD42020164473) from January 1990 to August 2021. For each country and geographical region with available data, pooled prevalence and corresponding 95% confidence intervals (CIs) of EBV in gastric tumors were calculated for 3 subtypes of gastric adenocarcinoma (conventional adenocarcinoma, lymphoepithelioma-like gastric carcinoma, and remnant/stump carcinoma). For conventional adenocarcinoma, prevalence ratios (PRs) were presented for sex, Lauren's classification, gastric cancer stage, and anatomical location of the stomach.**

RESULTS: **In 220 eligible studies including over 68,000 cases of conventional gastric adenocarcinoma, EBV prevalence in tumor cells was 7.5% (95% CI, 6.9%–8.1%) and was higher in men compared with women (PR, 2.1; 95% CI, 1.9–2.4), in diffuse type compared with intestinal type (PR, 1.3; 95% CI, 1.1–1.5), and in the proximal region compared with the distal region (PR, 2.5; 95% CI, 2.0–3.1). There was no difference in EBV prevalence by gastric cancer stage. EBV prevalence was 75.9% (95% CI, 62.8%–85.5%) among lymphoepithelioma-like gastric carcinoma and 26.3% (95% CI, 22.2%–32.0%) among remnant or stump carcinoma.**

CONCLUSIONS: **Assuming a causal association between EBV and gastric cancer, our findings, when applied to the GLOBOCAN 2020 gastric cancer incidence, suggest that primary prevention such as the development of an effective EBV vaccine might prevent 81,000 EBV-associated gastric cancer cases worldwide annually.**

Keywords: Epstein-Barr Virus–Associated Gastric Cancer; Herpesvirus; Prevalence; Meta-Analysis.

Gastric cancer is the fourth most common and fourth most lethal cancer worldwide, with over 1 million new cases and 770,000 deaths in 2020. According to GLOBOCAN 2020, which estimates annual cancer incidence in 185 countries, the highest age-standardized incidence rates (ASIRs) for gastric cancer per 100,000 person-years are observed in eastern Asia (32.5 for men; 13.2 for women), followed by central and eastern Europe (17.4 for men; 7.1 for women), and South America (12.1 for men; 6.1 for women).[1] Given this high global burden, identifying modifiable gastric cancer risk factors is crucial for better-targeted prevention.

Over 90% of noncardia gastric cancers worldwide are estimated to be attributable to *Helicobacter pylori,* as well as a fraction of cardia gastric cancers in high *H. pylori* prevalence regions, such as eastern Asia.[2] Increasing evidence suggests an etiological role for Epstein-Barr virus (EBV) in gastric cancer. EBV is a ubiquitous gamma herpesvirus found in tumor tissue in a proportion of stomach cancer.[3,4] In adenocarcinoma, terminal repeat analysis shows tumor cells to carry the same monoclonal virus genome, suggesting tumor development from a single EBV-infected cell, rather than infection after malignant transformation.[5,6] A causal association has also been suggested between EBV and

Abbreviations used in this paper: **ASIR, age-standardized incidence rate; CI, confidence interval; EBER, EBV-encoded RNA; EBV, Epstein-Barr virus; ISH, in situ hybridization; LELC, lymphoepithelioma-like gastric carcinoma; PR, prevalence ratio.**

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lymphoepithelioma-like gastric carcinoma (LELC), which constitutes 1%–5% of all gastric carcinoma,[7–9] and gastric remnant or stump adenocarcinoma in which EBV prevalence varied from 6% to 30%.[10,11]

A 2009 systematic review estimated the global prevalence of EBV in gastric cancer to be 8.7%.[11] In 2014, the Cancer Genome Atlas program reported specific molecular features associated with EBV-associated gastric cancer,[12] further boosting research on this topic. Here, we aimed to describe the prevalence of EBV in gastric cancer by geographical region, sex, tumor location, histology, and subtype.

What You Need to Know

Background

Emerging evidence suggests that a fraction of gastric cancer, one of the most common cancers worldwide, may be associated with a known carcinogenic agent, Epstein-Barr virus (EBV).

Findings

Among over 68,000 gastric adenocarcinoma patients, we found EBV in 7.5% of tumor cells. This finding was consistent globally.

Implication

Development of an effective EBV vaccine could prevent up to 81,000 gastric cancer cases each year in addition to preventing up to 150,000 other EBV-related cancers.

Materials and Methods

Data Collection

We conducted a systematic review and meta-analysis to determine the prevalence of EBV-associated gastric cancer worldwide, according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) recommendations (PROSPERO CRD42020164473). We searched PubMed (MEDLINE), Scopus, Web of Science, Embase, SciELO, CNKI, Wan Fang, and J-STAGE, without language restriction (see Supplementary Data 1 for search strategies) from January 1, 1990, when in situ hybridization (ISH) for EBV-encoded RNA 1 and 2 was introduced,[13] until August 31, 2021. After removal of duplicate records, titles and abstracts were screened, and full texts were reviewed (M.H. and C.d.M.). Any disagreements regarding inclusion criteria were resolved through discussion. References listed in included articles were reviewed for additional publications.

Eligibility Criteria

Articles were eligible if they reported original data with more than 20 unselected or representative gastric adenocarcinoma cancer cases, published in peer-reviewed journals, assessing EBV in tumor tissue using ISH.

Data Extraction and Quality Assessment

Two researchers (M.H. and C.d.M.) extracted the following data, if available: first author, publication year, journal, country, United Nations geographical region[14], hospital name, median study year, sample size, average age, sex, gastric cancer stage (early 0–IIb/advanced III–IV)[15], Lauren's classification (intestinal/diffuse), tumor subsite (proximal [upper one-third of stomach]/distal [lower two-thirds], and cardia/noncardia), tumor subtype (conventional adenocarcinoma, LELC, stump/remnant adenocarcinoma), and proportion of EBV-positive samples by ISH.

Each study was given a quality score assessing 11 methodological points based on modified STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Supplementary Data 2).[16]

Statistical Analysis

Pooled EBV prevalence, 95% confidence intervals (CIs), 95% prediction intervals, heterogeneity (I^2), and between-study variance (τ^2), were calculated using the random intercept logistic regression model,[17,18] with R command "metaprop."[19] Estimates were calculated separately for conventional adenocarcinoma, LELC, and stump or remnant adenocarcinoma. For conventional adenocarcinoma, prevalence was also estimated by United Nations region,[14] individual country with over 30 studies, sex, Lauren's classification, and tumor location. Differences in EBV prevalence between groups were assessed using Cochran's Q test,[20] and publication bias was evaluated by Egger's test.[21] EBV prevalence in conventional gastric adenocarcinoma, LELC, and stump or remnant adenocarcinoma was compared by a 2-proportions z test.

Variations in EBV prevalence were further investigated by 2019 Human Development Index,[22] 2020 country gastric cancer ASIRs,[1] quality score, and median study year, categorized into tertiles. We conducted a sensitivity analysis by excluding outliers using R's *dmetar* leave-one-out package (R statistical software version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria).[23] A study was defined as an outlier when its 95% CI lay outside the 95% CI of the pooled effect.

Among subsets of studies with relevant information, we calculated the prevalence ratio (PR) for sex, Lauren's classification (diffuse/intestinal), cancer stage (early/advanced), and tumor location (proximal/distal, cardia/noncardia) using DerSimonian and Laird's random effect model[24] with the Stata "metan" command (Stata version 15; StataCorp, College Station, TX).[25]

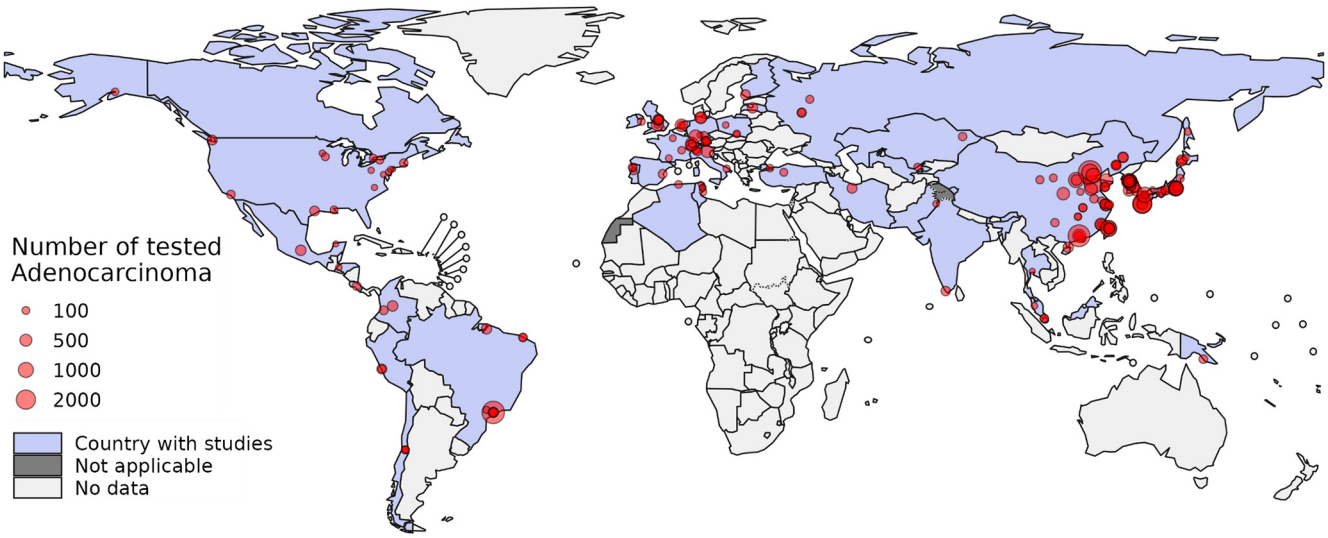

Figure 1. Study area map. Purple: countries represented; red dot: geolocation of studies; light gray: countries with no included data.

We estimated the global fraction of conventional adenocarcinoma associated with EBV for each sex by applying estimated EBV prevalence to 2020 GLOBOCAN gastric cancer incidence.

Analyses were performed using Stata version 15 or R statistical software version 4.0.4.

Results

We identified 7306 papers from 8 search engines (Supplementary Figure 1). After excluding studies not fulfilling our criteria, 775 full articles were retrieved, of which 229 articles were included (Supplementary Table 1).

Conventional Adenocarcinoma

A total of 220 case series with over 68,000 cases from 37 countries reported EBV prevalence in conventional adenocarcinoma (Figure 1). Over half the studies were from eastern Asia: China (n = 51), Japan (n = 38), and the Republic of Korea (n = 33) (Table 1). Studies were also available from Europe (n = 44), South America (n = 21), and North America (n = 16) (Table 1). Only 1 study (Melanesia) was available from Oceania, and none were available from sub-Saharan Africa. Owing to the limited number of studies, we pooled northern Africa; central, southeastern, and southwestern Asia; and Melanesia. EBV prevalence in conventional adenocarcinoma was 7.5% (95% CI, 6.9%–8.1%) globally (Table 1, Supplementary Figure 2) and was similar across regions ($P = .1$ for Cochran's Q test).

Heterogeneity analysis for EBV prevalence in gastric adenocarcinoma by Human Development Index, ASIRs, median study year, or quality score found no statistically significant differences between groups (Supplementary Table 2). Egger's test was also not statistically significant (Supplementary Figure 3). The leave-one-out analysis identified 67 outlier studies. In the remaining 153 studies, global EBV prevalence in conventional adenocarcinoma was 7.0% (95% CI, 6.7%–7.3%) (Supplementary Figure 4), consistent with the overall result.

Of 220 studies, 108 provided EBV prevalence by sex (10.2% [95% CI, 9.2%–11.3%] men, 3.9% [95% CI, 3.1%–4.7%] women) (Table 1, Supplementary Figures 5 and 6). Fifteen studies found no EBV in adenocarcinoma among women.

We calculated PRs for sex (n = 108), Lauren's classification (n = 74) (Table 2), cancer stage (n = 29) (Table 2), and tumor location (n = 54) (Table 3). Globally, men (PR, 2.1; 95% CI, 1.9–2.3) or diffuse type (PR, 1.3; 95% CI, 1.1–1.5) (Table 2) had a higher risk of presence of EBV. We saw no difference in EBV prevalence by cancer stage (PR, 1.0; 95% CI, 0.8–1.3) (Table 2). EBV prevalence was higher (PR, 2.5; 95% CI, 2.0–3.1) in tumors of the proximal region and was similar among the 23 studies reporting cardia or noncardia region (PR, 2.1; 95% CI, 1.7–2.6) (Table 3).

Global Burden of EBV-Related Gastric Cancer

By applying sex-specific conventional adenocarcinoma EBV prevalence to 2020 GLOBOCAN gastric cancer incidence, we found 81,000 cases (71,000 men/10,000 women) to be associated with EBV.

LELC and Stump or Remnant Adenocarcinoma

Global prevalence of EBV in LELC (21 studies) was 75.9% (95% CI, 62.8%–85.5%), significantly higher than in conventional adenocarcinoma ($P < .001$) (Figure 2). In eastern Asia (n = 17), prevalence reached 82.5% (95%

Table 1. Global EBV Prevalence in Conventional Gastric Adenocarcinoma

	All Studies					Studies Reporting on Sex							
								Men			Women		
Study Area	Number of Studies	Total Population	EBV Prevalence (95% CI) (%)	I^2 (%), *P Value*	*P* Value[a]	Number of Studies	Total Population: Men/Women	EBV Prevalence (95% CI) (%)	I^2 (%), *P* Value	*P* Value[a]	EBV Prevalence (95% CI) (%)	I^2 (%), *P* Value	*P* Value[a]
Eastern Asia	122	53,025	7.4 (6.7–8.1)	86, <.001	.1	54	18,752/8431	9.3 (8.1–10.7)	84, <.001	0.2	3.6 (2.8–4.5)	56, <.001	.3
China	51	22,689	6.8 (5.7–8.1)	90, <.001		25	11,173/4721	7.6 (6.2–9.2)	76, <.001		3.0 (2.2–3.9)	51, <.001	
Japan	38	18,326	7.4 (6.5–8.5)	76, <.001		16	5271/2650	10.1 (8.2–12.5)	72, <.001		4.3 (3.0–6.1)	53, <.001	
Republic of Korea	33	12,070	8.2 (7.0–9.6)	84, <.001		13	2308/1000	11.7 (8.3–16.4)	87, <.001		3.8 (2.0–7.2)	47, .03	
Europe	44	9063	6.8 (5.5–8.4)	82, <.001		22	2477/1589	10.2 (7.2–14.4)	81, <.001		3.6 (2.0–6.4)	82, <.001	
South America	21	3444	9.9 (8.0–12.1)	73, <.001		14	1630/1099	12.1 (9.4–15.5)	63, <.001		6.1 (3.7–9.8)	66, <.001	
North America	16	1576	7.7 (5.3–11.1)	74, <.001		8	578/289	14.1 (9.0–21.4)	67, <.001		3.1 (0.9–10.5)	57, .18	
Others[b]	17	1800	7.2 (4.2–12.2)	84, <.001		10[c]	734/410	11.1 (8.0–15.2)	45, .05		2.7 (0.9–7.8)	52, .13	
Total	220	68,908	7.5 (6.9–8.1)	85, <.001		108	24,171/11,818	10.2 (9.2–11.3)	81, <.01		3.8 (3.1–4.7)	72, <.01	

Values are n or prevalence (%), with 95% CI in brackets, unless otherwise indicated.

CI, confidence interval; EBV, Epstein-Barr virus.

[a]For Cochran's Q test.

[b]Algeria (n = 1); India: 1; Iran: 1; Kazakhstan: 1; Malaysia: 1; Pakistan: 1; Papua New Guinea: 1; Singapore: 2; Thailand: 1; Tunisia: 4; Turkey: 2; Uzbekistan: 1.

[c]Algeria (n = 1); India: 1; Iran: 1; Kazakhstan: 1; Malaysia: 1; Singapore: 1; Tunisia: 2; Turkey: 1; Uzbekistan: 1.

CI, 75.2%–88.0%), while in other studies (Italy, Portugal, United States) it was 29.5% (95% CI, 6.4%–72.0%) (*P* for Cochran's Q test < .001) (Figure 2).

Global prevalence of EBV in stump or remnant adenocarcinoma (9 studies: 8 in eastern Asia, 1 in Europe) was 26.3% (95% CI, 21.2%–32.0%), significantly higher than in conventional adenocarcinoma (*P* < .001). Prevalence in eastern Asia was 25.1% (95% CI, 19.9%–31.2%) (Figure 3).

Discussion

We conducted a systematic review and meta-analysis estimating global, regional, and country-specific pooled EBV prevalence in gastric cancer based on studies published in the past 30 years. We found global prevalence for conventional adenocarcinoma to be 7.5% in 220 studies from 37 countries. Higher EBV prevalence was associated with being male (PR, 2.1), having a diffuse-type tumor (PR, 1.3), or having a tumor in the proximal region (PR, 2.5). EBV prevalence in LELC and stump or remnant adenocarcinoma was 10 and 4 times higher compared with conventional adenocarcinoma, respectively. Our findings for EBV prevalence in conventional gastric adenocarcinoma were in line with previous studies by Murphy et al (men: 11% [95% CI, 8.7%–14.1%]; women: 5.2% [95% CI, 3.6%–7.4%]; overall: 8.7% [95% CI, 7.5%–10.0%])[11] as well as the Cancer Genome Atlas Research Network (overall: 8.8%).[12]

In our review of conventional adenocarcinoma, some of the included studies did not specify whether LELC subtype was included in their series. Because EBV prevalence in LELC adenocarcinoma is higher than in conventional adenocarcinoma, our global EBV prevalence (7.5) may be an overestimation. However, despite the differences in gastric cancer risk,[1] our regional estimates of EBV prevalence remained remarkably consistent, and therefore, seem robust.

Of 54 studies, 23 distinguished between cardia and noncardia gastric cancer with a similar PR (2.1; 95% CI, 1.7–2.6) to our finding for proximal compared with distal region (PR, 2.5; 95% CI, 2.0–3.1), supporting our finding that EBV is more prevalent in tumors arising in the upper region of the stomach. This might imply a distinct etiology for EBV-associated gastric cancer. There is no consensus on cardia region definition,[26] and the definitions of cardia or proximal region varied between studies, when provided. Of note, most studies providing tumor location were from eastern Asia, where *H. pylori* has been found to be associated with a fraction of cardia gastric cancer.[27]

Globally, the prevalence of gastric cancer is known to be twice as high in men.[1] The reasons for this difference in prevalence are largely unknown. One possible explanation is the protective effect of estrogen[28] and its immunomodulatory effects. Our study

Table 2. EBV PR Presented for Sex (Men vs Women) and Lauren's Classification (Diffuse vs Intestinal) in Conventional Gastric Adenocarcinoma

	Men vs Women				Diffuse vs Intestinal				Early vs Advanced Stage of Gastric Cancer			
Study Area	Number of Studies	Total Population: Men/Women	EBV PR (95% CI) (%)	I^2 (%), *P* Value	Number of Studies	Total Population: Diffuse/Intestinal	EBV PR (95% CI) (%)	I^2 (%), *P* Value	Number of Studies	Total Population: Early/Advanced	EBV PR (95% CI) (%)	I^2 (%), *P* Value
Eastern Asia	54	18,752/8431	2.2 (1.9–2.5)	0, .7	27	7923/8624	1.5 (1.2–1.8)	51, .1	13	4498/6570	1.2 (0.9–1.5)	69, .1
Europe	22	2477/1589	2.4 (1.8–3.3)	26, .1	18	1157/2078/	7.3 (0.5–1.1)	28, <.0001	8	1054/936	1.2 (0.9–1.7)	0, .8
South America	14	1630/1099	1.7 (1.2–2.3)	20, .2	14	1381,1540	1.4 (1.0–2.0)	52, <.001	4	137/291	0.8 (0.4–1.8)	0, .4
North America	8	578/289	2.8 (1.3–6.0)	28, .2	4	146/305	1.1 (0.6–2.2)	2.0, .1	4	1236/249	0.4 (0.1–1.4)	74, .01
Others	10[a]	734/410	2.4 (1.3–4.2)	6.1, .4	11[a,b]	796/806	1.3 (0.8–2.0)	35, .4	N/A	—	—	—
Total	108	24,171/11 818	2.1 (1.9–2.3)	4.1, .3	74	10,639/13,353	1.3 (1.1–1.5)	45, <.001	29	6925/8046	1.0 (0.8–1.3)	59, <.001

CI, confidence interval; EBV, Epstein-Barr virus; N/A, not available; PR, prevalence ratio.
[a]Algeria (n = 1); India: 1; Iran: 1; Kazakhstan: 1; Malaysia: 1; Singapore: 1; Tunisia: 2; Turkey: 1; Uzbekistan: 1.
[b]Includes Papua New Guinea: 1.

Table 3. EBV PR Presented for Anatomical Locations (Proximal vs Distal and Cardia vs Noncardia) in Conventional Gastric Adenocarcinoma

	Proximal vs Distal				Cardia vs Noncardia			
Study Area	Number of Studies	Total Population: Proximal/Distal	EBV PR (95% CI) (%)	I^2 (%), *P* Value	Number of Studies	Total Population: Cardial/Noncardia	EBV PR (95% CI) (%)	I^2 (%), *P* Value
Eastern Asia	27	6191/5570	3.0 (2.4–3.8)	44, .01	10	610/4178	2.3 (1.7–3.1)	27, .2
Europe	9	553/646	2.8 (1.3–6.3)	51, .03	8	194/867	2.1 (1.3–3.3)	0, .4
South America	10	762/1143	1.8 (1.4–2.4)	0, .4	1	27/140	1.9 (0.5–6.9)	N/A
North America	3	122/97	1.5 (0.3–7.0)	48, .3	1	45/59	0.5 (0.1–2.6)	N/A
Others	5[a]	365/384	1.0 (0.7–1.5)	9.5, .1	3[b]	57/255	1.3 (0.5–3.3)	0, .8
Total	54	7991/7731	2.5 (2.0–3.1)	64, <.001	23	933/5499	2.1 (1.7–2.6)	8.1, .3

CI, confidence interval; EBV, Epstein-Barr virus; N/A, not available; PR, prevalence ratio.
[a]Algeria (n = 1); India: 1; Iran: 1; Tunisia: 1; Turkey: 1.
[b]India (n = 1); Tunisia: 1; Turkey: 1.

found higher EBV prevalence in men (PR, 2.1; 95% CI, 1.9–2.3), suggesting a protective role for estrogen in EBV-associated gastric cancer. Another hypothesis is that biallelic expression of tumor-suppressor genes on the X chromosomes better protects women against EBV carcinogenesis.[29]

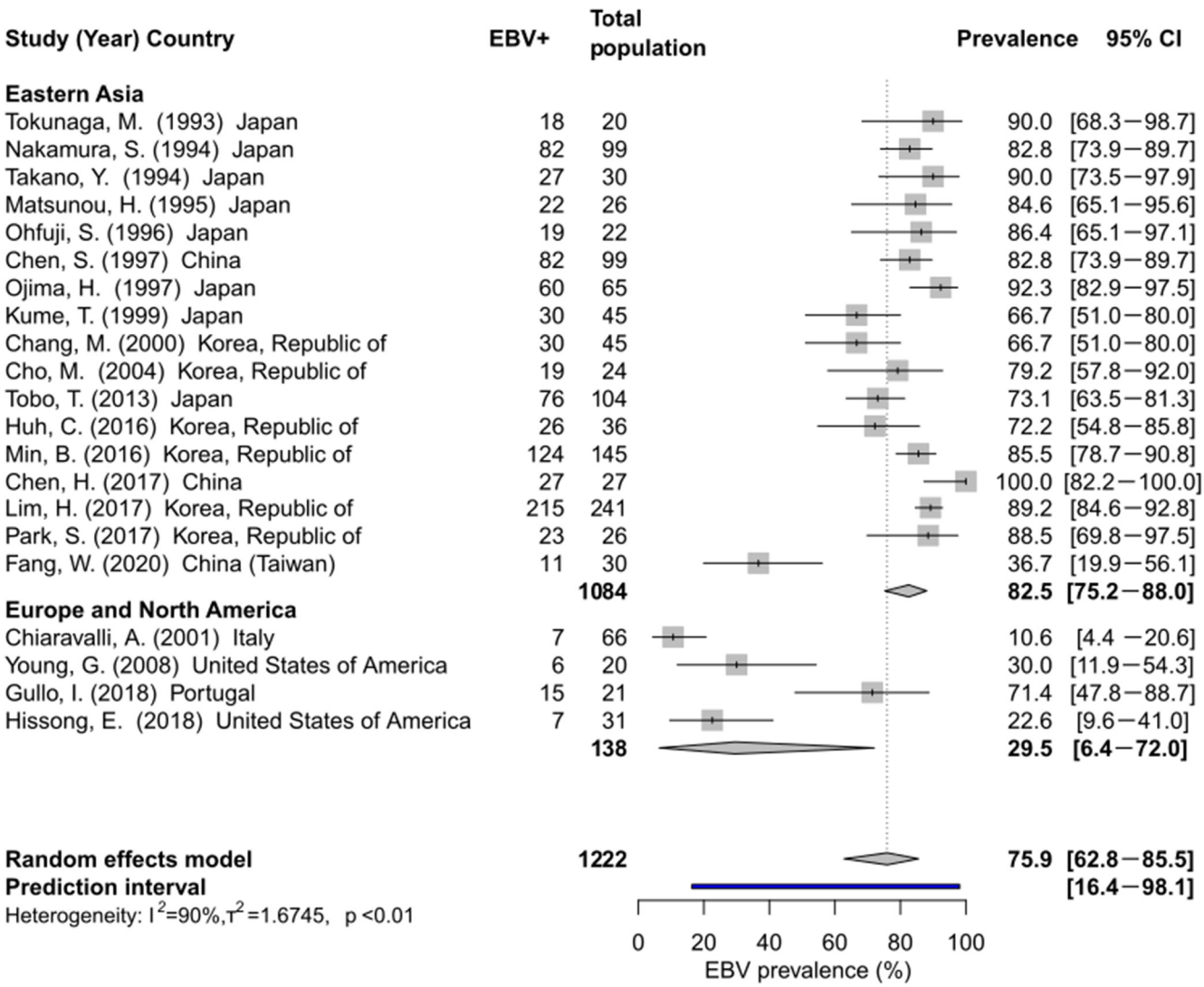

Figure 2. Global EBV prevalence in lymphoepithelioma-like gastric carcinoma.

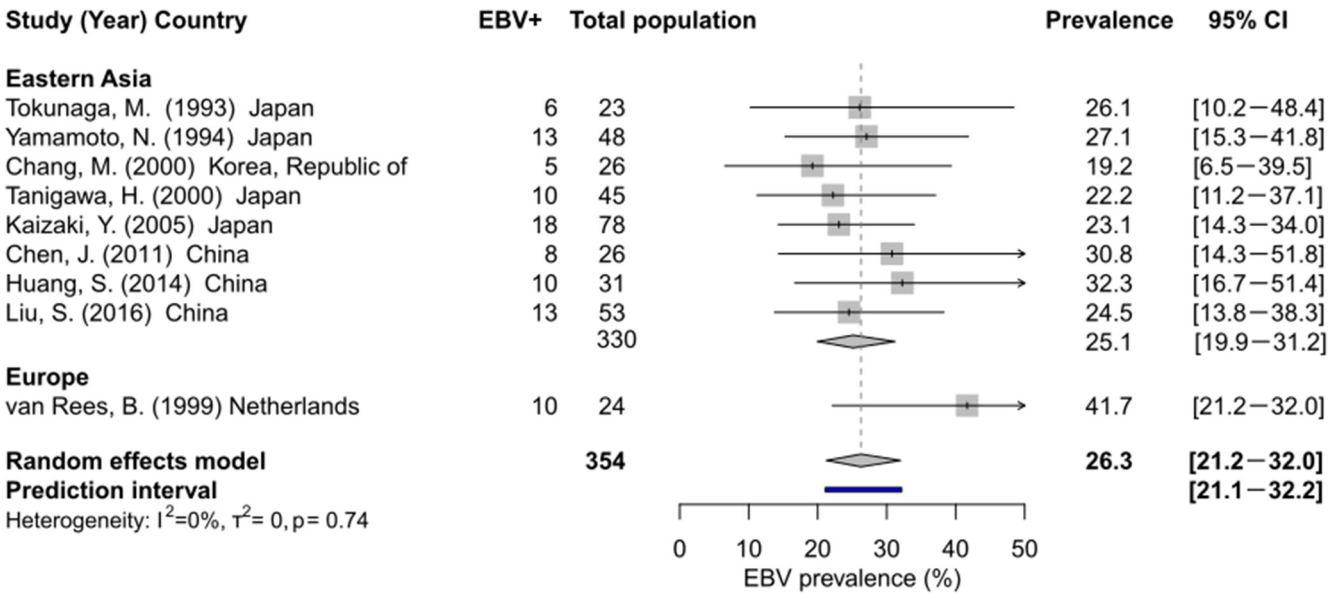

Figure 3. Global *EBV* prevalence in gastric remnant or stump adenocarcinoma.

While some studies demonstrated a strong association between EBV and diffuse type,[30,31] others described equal EBV prevalence in both intestinal and diffuse types.[32,33] In our study, EBV prevalence was marginally higher (PR, 1.3; 95% CI, 1.1–1.5) in diffuse-type tumors. Findings on EBV prevalence and cancer stage have also been inconsistent. A previous meta-analysis[34] showed higher EBV prevalence in advanced gastric cancer. We found no statistical difference in EBV prevalence by clinical stage, in agreement with another study.[10]

Regional differences in EBV prevalence in LELC were found between eastern Asia (82.5%; 95% CI, 75.2%–88.0%) and others (29.5%; 95% CI, 9.4%–72.0%). The high prevalence in eastern Asia is comparable to that of nasopharyngeal carcinoma, a cancer histologically similar to LELC and etiologically linked to EBV. Our estimate was lower than a previous meta-analysis[11] because we included only studies with over 20 patients, while the previous study used single case reports or small case series that were all positive for EBV, probably leading to a slight overestimation of EBV prevalence in this subtype of gastric adenocarcinoma.

A strength of our research is that we included only studies using EBV-encoded RNA by ISH, the gold standard for detecting and localizing EBV.[35–38] A further strength is the absence of language restrictions, allowing the inclusion of a large number of studies. Additionally, we applied predefined eligibility criteria, found no strong geographical variation, and conducted sensitivity analyses.

A limitation of our review is that over 50% of the included studies were from eastern Asia. In Oceania or sub-Saharan Africa, almost no studies were found. We pooled data for certain countries due to lack of studies. While results may not be representative of any of the individual regions, they were consistent with the global estimation. Excluding any of the regions did not shift our findings. A further limitation was the high heterogeneity between studies, which could be expected for studies by different researchers, in various countries, and using different methods, pooled under a single parameter.[39] We were unable to analyze the effect of potential confounders such as age and smoking due to the limited data on comparable groups. For LELC and remnant or stump adenocarcinoma, there may have been a selection or ascertainment bias despite our efforts to include representative cases.

How EBV infects human gastric epithelial cells while interacting with *H. pylori* remains unclear. Stomach inflammation and atrophy in gastric epithelial cells due to long-established *H. pylori* infection may attract B lymphocytes harboring latent EBV, initiating B cell lytic cycle, and facilitating viral transmission.[40] Lymphocyte attraction in a postsurgery damaged gastric epithelium could also explain the high number of EBV-positive stump or remnant adenocarcinomas found in this review.

EBV may increase the risk of malignant transformation in the stomach through microRNAs such as BARF1, which are strongly expressed in gastric cancer cells and have been shown to act as oncogenes, promoting cell proliferation by upregulating transcription factor signals and reducing cell cycle inhibitors.[41,42] DNA methylation is also crucial to the oncogenetic process,[43] induced by EBV LMP2A (latent membrane protein 2A), often expressed in EBV-associated gastric cancer.[41]

Our study showed that 81,000 conventional gastric adenocarcinoma (71,000 men and 10,000 women) are potentially attributable to EBV worldwide in addition to 150,000 cases of other cancers causally associated with EBV such as nasopharyngeal cancer, non-Hodgkin lymphoma, and Burkitt lymphoma.[2] Since 2011, there has been a consensus on implementing EBV vaccination

trials with the aim of preventing infectious mononucleosis and EBV-related cancers.[44] With recent advances in the understanding of virology, vaccine technology, and synthetic biology,[45] particularly in the context of COVID-19, new opportunities for vaccine development have emerged. Development of an EBV vaccine may be the key to EBV-associated cancer prevention.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2022.07.042.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–249.
2. de Martel C, Georges D, Bray F, et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 2020;8:e180–e190.
3. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet 1964;1:702–703.
4. Burke AP, Yen TS, Shekitka KM, et al. Lymphoepithelial carcinoma of the stomach with Epstein-Barr virus demonstrated by polymerase chain reaction. Mod Pathol 1990;3:377–380.
5. Raab-Traub N, Flynn K. The structure of the termini of the Epstein-Barr virus as a marker of clonal cellular proliferation. Cell 1986;47:883–889.
6. Tavakoli A, Monavari SH, Solaymani Mohammadi F, et al. Association between Epstein-Barr virus infection and gastric cancer: a systematic review and meta-analysis. BMC Cancer 2020; 20:493.
7. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol 1995; 103:308–315.
8. Shibata D, Tokunaga M, Uemura Y, et al. Association of Epstein-Barr virus with undifferentiated gastric carcinomas with intense lymphoid infiltration. Lymphoepithelioma-like carcinoma. Am J Pathol 1991;139:469–474.
9. Nakamura S, Ueki T, Yao T, et al. Epstein-Barr virus in gastric carcinoma with lymphoid stroma. Special reference to its detection by the polymerase chain reaction and in situ hybridization in 99 tumors, including a morphologic analysis. Cancer 1994;73:2239–2249.
10. Lee JH, Kim SH, Han SH, et al. Clinicopathological and molecular characteristics of Epstein-Barr virus-associated gastric carcinoma: a meta-analysis. J Gastroenterol Hepatol 2009; 24:354–365.
11. Murphy G, Pfeiffer R, Camargo MC, et al. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. Gastroenterology 2009;137:824–833.
12. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513:202–209.
13. Gulley ML, Glaser SL, Craig FE, et al. Guidelines for interpreting EBER in situ hybridization and LMP1 immunohistochemical tests for detecting Epstein-Barr virus in Hodgkin lymphoma. Am J Clin Pathol 2002;117:259–267.
14. International Organization for Standardization. International Standard ISO 3166-1, Codes for the representation of names of countries and their subdivisions–part 1: country codes, ISO 3166-1. Available at: http://www.iso.org/iso/home/standards/country_codes.htm. Accessed August 11, 2021.
15. Washington K. 7th Edition of the AJCC Cancer Staging Manual: stomach. Ann Surg Oncol 2010;17:3077–3079.
16. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–1457.
17. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med 2010; 29:3046–3067.
18. De Lima MAP, Ferreira MVP, Barros MAP, et al. Epstein-Barr virus (EBV) detection in gastric carcinomas from Ceará and São Paulo states, in Brazil. J Brasileiro Patol Med Lab 2011; 47:171–179.
19. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
20. Cochran WG. The comparison of percentages in matched samples. Biometrika 1950;37:256–266.
21. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315: 629–634.
22. United Nations Development Programme. Human Development Report 2020. The Next Frontier: Human Development and the Anthropocene. New York, NY: United Nations Development Programme; 2020.
23. Harrer M, Cuijpers P, Furukawa T, et al. dmetar: Companion R package for the guide Doing Meta-Analysis in R. Available at: http://dmetar.protectlab.org/. Accessed August 11, 2021.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
25. Harris RJ, Deeks JJ, Altman DG, et al. Metan: fixed-and random-effects meta-analysis. Stata J 2008;8:3–28.
26. Ichihara S, Uedo N, Gotoda T. Considering the esophagogastric junction as a 'zone. Dig Endosc 2017;29:3–10.
27. Yang L, Kartsonaki C, Yao P, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. Lancet Public Health 2021;6:e888–e896.
28. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol 2019; 14:26–38.
29. Dunford A, Weinstock DM, Savova V, et al. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. Nat Genet 2017;49:10–16.
30. Chang MS, Lee HS, Kim CW, et al. Clinicopathologic characteristics of Epstein-Barr virus-incorporated gastric cancers in Korea. Pathol Res Pract 2001;197:395–400.
31. Corvalan A, Koriyama C, Akiba S, et al. Epstein-Barr virus in gastric carcinoma is associated with location in the cardia and with a diffuse histology: a study in one area of Chile. Int J Cancer 2001;94:527–530.
32. Yoshiwara E, Koriyama C, Akiba S, et al. Epstein-Barr virus-associated gastric carcinoma in Lima, Peru. J Exp Clin Cancer Res 2005;24:49–54.

33. Galetsky SA, Tsvetnov VV, Land CE, et al. Epstein-Barr-virus-associated gastric cancer in Russia. Int J Cancer 1997; 73:786–789.
34. Camargo MC, Kim WH, Chiaravalli AM, et al. Improved survival of gastric cancer with tumour Epstein-Barr virus positivity: an international pooled analysis. Gut 2014;63:236–343.
35. Gulley ML. Molecular diagnosis of Epstein-Barr virus-related diseases. J Mol Diagn 2001;3:1–10.
36. Ambinder RF, Mann RB. Detection and characterization of Epstein-Barr virus in clinical specimens. Am J Pathol 1994; 145:239–252.
37. Hamilton-Dutoit SJ, Pallesen G, Franzmann MB, et al. AIDS-related lymphoma. Histopathology, immunophenotype, and association with Epstein-Barr virus as demonstrated by in situ nucleic acid hybridization. Am J Pathol 1991; 138:149–163.
38. Brousset P, Meggetto F, Chittal S, et al. Assessment of the methods for the detection of Epstein-Barr virus nucleic acids and related gene products in Hodgkin's disease. Lab Invest 1993;69:483–490.
39. Higgins JPT. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. Int J Epidemiol 2008;37:1158–1160.
40. Hutt-Fletcher LM. The long and complicated relationship between Epstein-Barr virus and epithelial cells. J Virol 2016;91: e01677-16.
41. Ribeiro J, Oliveira C, Malta M, et al. Epstein-Barr virus gene expression and latency pattern in gastric carcinomas: a systematic review. Future Oncol 2017;13:567–579.
42. Chang MS, Kim DH, Roh JK, et al. Epstein-Barr virus-encoded BARF1 promotes proliferation of gastric carcinoma cells through regulation of NF-κB. J Virol 2013;87:10515–10523.
43. Tahara T, Arisawa T. DNA methylation as a molecular biomarker in gastric cancer. Epigenomics 2015;7:475–486.
44. Cohen JI, Fauci AS, Varmus H, et al. Epstein-Barr virus: an important vaccine target for cancer prevention. Sci Transl Med 2011;3:107fs7.
45. Sun C, Chen XC, Kang YF, et al. The status and prospects of Epstein-Barr virus prophylactic vaccine development. Front Immunol 2021;12:677027.

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Damien Georges, MSc (Formal analysis: Supporting; Validation: Supporting; Visualization: Supporting; Writing – review & editing: Supporting)
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Conflicts of Interest
The authors disclose no conflicts.

Supplementary Appendix

Supplementary Data 1: Search Terms

Embase.

Search Number	Search terms
#17	#15 OR #16
#16	('epstein barr virus associated gastric cancer':ti,ab,kw OR 'epstein barr virus associated gastric carcinoma':ti,ab,kw OR 'ebvagc':ti,ab,kw)
#15	#8 AND #14
#14	#12 OR #13
#13	epstein barr virus'/de
#12	#9 OR #10 OR #11
#11	('infectious mononucleosis':ti,ab,kw OR 'infectious mononucleosis virus*':ti,ab,kw)
#10	('human herpesvirus 4*':ti,ab,kw OR 'human herpes virus 4*':ti,ab,kw OR 'hhv 4*':ti,ab,kw)
#9	('epstein barr virus*':ti,ab,kw OR 'ebv*':ti,ab,kw OR 'epv*':ti,ab,kw OR 'eb virus*':ti,ab,kw OR 'epstein virus*':ti,ab,kw)
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7	('stomach tumor'/de OR 'stomach cancer'/de)
#6	('gastric adenocarcinoma*':ti,ab,kw OR 'stomach adenocarcinoma*':ti,ab,kw)
#5	('gastric tumor*':ti,ab,kw OR 'gastric tumour*':ti,ab,kw OR 'stomach tumor*':ti,ab,kw OR 'stomach tumour*':ti,ab,kw)
#4	('gastric neoplasia*':ti,ab,kw OR 'stomach neoplasia*':ti,ab,kw)
#3	('gastric neoplasm*':ti,ab,kw OR 'stomach neoplasm*':ti,ab,kw)
#2	('gastric carcinoma*':ti,ab,kw OR 'stomach carcinoma*':ti,ab,kw)
#1	('gastric cancer*':ti,ab,kw OR 'stomach cancer*':ti,ab,kw)

PubMed

((((((epstein barr virus associated gastric cancer*[Title/Abstract]) OR epstein barr virus associated gastric cancer*[Text Word])) OR ((epstein barr virus associated gastric carcinoma[Title/Abstract]) OR epstein barr virus associated gastric carcinoma[Text Word])) OR ((ebvagc [Title/Abstract]) OR ebvagc[Text Word]))) OR ((((((((((((((epstein barr virus[Title/Abstract]) OR epstein barr virus[Text Word])) OR ((human herpesvirus 4[Title/Abstract]) OR human herpesvirus 4[Text Word])) OR ((infectious mononucleosis[Title/Abstract]) OR infectious mononucleosis[Text Word])) OR ((human herpes virus 4[Text Word]) OR human herpes virus 4[Title/Abstract])) OR ((epstein virus[Title/Abstract]) OR epstein virus[Text Word])) OR ((ebv[Title/Abstract]) OR ebv [Text Word])) OR ((epv[Title/Abstract]) OR epv[Text Word])) OR ((eb virus[Title/Abstract]) OR eb virus[Text Word])) OR ((infectious mononucleosis virus[Title/Abstract]) OR infectious mononucleosis virus[Text Word]))) OR Herpesvirus 4, Human[MeSH Terms])) AND ((stomach neoplasms[MeSH Terms]) OR ((((((((((((((gastric cancer* [Title/Abstract]) OR gastric cancer*[Text Word])) OR ((stomach cancer*[Title/Abstract]) OR stomach cancer* [Text Word])) OR ((stomach carcinoma*[Text Word]) OR stomach carcinoma*[Title/Abstract])) OR ((gastric carcinoma*[Title/Abstract]) OR gastric carcinoma*[Text Word])) OR ((gastric neoplasm*[Text Word]) OR gastric neoplasm*[Title/Abstract])) OR ((stomach neoplasm* [Title/Abstract]) OR stomach neoplasm*[Text Word])) OR ((stomach neoplasia*[Title/Abstract]) OR stomach neoplasia*[Text Word])) OR ((gastric neoplasia*[Title/ Abstract]) OR gastric neoplasia*[Text Word])) OR ((((gastric tumor*[Title/Abstract]) OR gastric tumor* [Text Word]) OR gastric tumour*[Text Word]) OR gastric tumour*[Title/Abstract])) OR ((((stomach tumor*[Title/ Abstract]) OR stomach tumor*[Text Word]) OR stomach tumour*[Title/Abstract]) OR stomach tumour*[Text Word])) OR ((stomach adenocarcinoma*[Title/Abstract]) OR stomach adenocarcinoma*[Text Word])) OR ((gastric adenocarcinoma*[Title/Abstract]) OR gastric adenocarcinoma*[Text Word]))))

Scopus

"((TITLE-ABS-KEY("epstein barr virus associated gastric cancer") OR TITLE-ABS-KEY("epstein barr virus associated gastric carcinoma")OR TITLE-ABS-KEY("ebvagc"))) OR ((((TITLE-ABS-KEY("epstein barr virus") OR TITLE-ABS-KEY("ebv") OR TITLE-ABS-KEY("epv") OR TITLE-ABS-KEY("eb virus") OR TITLE-ABS-KEY("epstein virus"))) OR ((TITLE-ABS-KEY("human herpesvirus 4") OR TITLE-ABS-KEY("human herpes virus 4")OR TITLE-ABS-KEY("hhv 4"))) OR ((TITLE-ABS-KEY("infectious mononucleosis") OR TITLE-ABS-KEY("infectious mononucleosis virus")))) AND (((TITLE-ABS-KEY("gastric cancer") OR TITLE-ABS-KEY("stomach cancer"))) OR ((TITLE-ABS-KEY("-stomach carcinoma") OR TITLE-ABS-KEY("gastric carcinoma"))) OR ((TITLE-ABS-KEY("stomach neoplasia") OR TITLE-ABS-KEY("gastric neoplasia"))) OR ((TITLE-ABS-KEY("stomach neoplasm") OR TITLE-ABS-KEY("gastric neoplasm"))) OR ((TITLE-ABS-KEY("stomach tum*") OR TITLE-ABS-KEY("gastric tum*"))) OR ((TITLE-ABS-KEY("stomach adenocarcinoma") OR TITLE-ABS-KEY("gastric adenocarcinoma")))))

SciELO

((ab:(epstein barr associated gastric carcinoma)) OR (ti:(epstein barr associated gastric carcinoma)) OR (ab:(epstein barr associated gastric cancer)) OR (ti:(epstein barr associated gastric cancer)) OR OR (ab:(ebvagc)) OR (ti:(ebvagc))) OR (((((ab:(gastric cancer*)) OR (ti:(gastric cancer*)) OR (ti:(gastric lymphoma*)) OR (ab:(gastric lymphoma*)) OR (ti:(gastric neoplasm*)) OR (ab:(gastric neoplasm*)) OR (ti:(gastric neoplasia*)) OR (ab:(gastric neoplasia*)) OR (ti:(stomach cancer*)) OR (ab:(stomach cancer*)) OR (ti:(stomach lymphoma*)) OR (ab:(stomach lymphoma*)) OR (ti:(stomach neoplasm*)) OR (ab:(stomach neoplasm*)) OR (ti:(stomach neoplasia*)) OR (ab:(stomach neoplasia*)) OR (ti:(stomach tumor*)) OR (ab:(stomach tumor*)) OR (ti:(stomach tumour*)) OR (ab:(stomach tumour*)) OR (ti:(gastric tumour*)) OR (ab:(gastric tumour*)) OR (ti:(gastric tumor*)) OR (ab:(gastric tumor*)))AND ((ab:(epstein barr virus)) OR (ti:(epstein barr virus)) OR (ab:(human herpesvirus 4)) OR (ti:(human herpesvirus 4)) OR (ab:(human herpes virus 4)) OR (ti:(human herpes virus 4)) OR (ab:(hhv 4)) OR (ti:(hhv 4)) OR (ab:(ebv)) OR (ti:(ebv)) OR (ab:(epv)) OR (ti:(epv)) OR (ab:(eb virus)) OR (ti:(eb virus)) OR (ab:(epstein virus)) OR (ti:(epstein virus)) OR (ab:(infectious mononucleosis virus)) OR (ti:(infectious mononucleosis virus)) OR (ab:(infectious mononucleosis)) OR (ti:(infectious mononucleosis)))))

World of Science

Search number	Search terms
30	#29 OR #25
29	#28 OR #27 OR #26
28	TS=(ebvagc) OR TI=(ebvagc)
27	TS=(epstein barr virus associated gastric carcinoma*) OR TI=(epstein barr virus associated gastric carcinoma*)
26	TS=(epstein barr virus associated gastric cancer*) OR TI=(epstein barr virus associated gastric cancer*)
25	#24 AND #13
24	#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14
23	TS=(infectious mononucleosis virus) OR TI=(infectious mononucleosis virus)
22	TS=(infectious mononucleosis) OR TI=(infectious mononucleosis)
21	TS=(epstein virus) OR TI=(epstein virus)
20	TS=(eb virus) OR TI=(eb virus)
19	TS=(epv) OR TI=(epv)
18	TS=(ebv) OR TI=(ebv)
17	TS=(hhv 4) OR TI=(hhv 4)
16	TS=(human herpes virus 4) OR TI=(human herpes virus 4)
15	TS=(human herpesvirus 4) OR TI=(human herpesvirus 4)
14	TS=(epstein barr virus) OR TI=(epstein barr virus)
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
12	TS=(gastric tumor*) OR TI=(gastric tumor*) OR TS=(gastric tumour*) OR TI=(gastric tumour*)
11	TS=(stomach tumor*) OR TI=(stomach tumor*) OR TS=(stomach tumour*) OR TI=(stomach tumour*)
10	TS=(gastric neoplasia*) OR TI=(gastric neoplasia*)
9	TS=(stomach neoplasia*) OR TI=(stomach neoplasia*)
8	TS=(gastric neoplasm*) OR TI=(gastric neoplasm*)
7	TS=(stomach neoplasm*) OR TI=(stomach neoplasm*)
6	TS=(stomach adenocarcinoma*) OR TI=(stomach adenocarcinoma*)
5	TS=(gastric adenocarcinoma*) OR TI=(gastric adenocarcinoma*)
4	TS=(stomach carcinoma*) OR TI=(stomach carcinoma*)
3	TS=(gastric carcinoma*) OR TI=(gastric carcinoma*)
2	TS=(stomach cancer*) OR TI=(stomach cancer*
1	TS=(gastric cancer*) OR TI=(gastric cancer*)

CNKI

((TI='EBV' or TI='Epstein Barr virus' or TI='eb virus' or TI='human herpesvirus 4' or TI='hh4' or TI='人类疱疹病毒第4型' or TI='人类疱疹病毒4' or TI='EB病毒' or TI='传染性单核细胞增多症' or KY='EBV' or KY='Epstein Barr virus' or KY='eb virus' or KY='human herpesvirus 4' or KY='hh4' or KY='infectious mononucleosis' or KY='人类疱疹病毒第4型' or KY='人类疱疹病毒4' or KY='EB病毒' or KY='传染性单核细胞增多症') and (TI='胃癌' or TI='胃肿瘤' or TI='胃部癌' or TI='胃部肿瘤' or KY='胃癌' or KY='胃肿瘤' or KY='胃部癌' or

KY=’胃部肿瘤’)) or (TI=’EBV相关胃癌’ or TI=’HH4相关胃癌’ or TI=’EBV相关胃肿瘤’ or TI=’HH4相关胃肿瘤’ or KY=’EBV相关胃癌’ or KY=’HH4相关胃癌’ or KY=’EBV相关胃肿瘤’ or KY=’HH4相关胃肿瘤’)

Wanfang

题名或关键词: (((“EBV” or “Epstein Barr virus” or “eb virus” or “human herpesvirus 4” or “hh4” or “人类疱疹病毒第4型” or “人类疱疹病毒4” or “EB病毒” or “传染性单核细胞增多症”) and (“胃癌” or “胃肿瘤” or “胃部癌” or “胃部肿瘤”)) or (“EBV相关胃癌” or “HH4相关胃癌” or “EBV相关胃肿瘤” or “HH4相关胃肿瘤” or “EBV相关胃癌” or “HH4相关胃癌” or “EBV相关胃肿瘤” or “HH4相关胃肿瘤”))

J-Stage

(((“EBV” or “Epstein Barr virus” or “eb virus” or “human herpesvirus 4” or “hh4” or “EBウイルス” “エプスタインバーウイルス”and ”胃がん”or”胃癌”or”胃の悪性腫瘍“)))

Supplementary Data 2: Quality Score Questionnaires

Variable name	Description of the variable	Note
1. Publication	Whether the study was a full article (1=Y, 0=N)	For meeting abstracts, coded 0
2. Study aim	Whether the authors specifically indicated that the aim of the study was to estimate EBV prevalence (1=Y, 0=N)	
3. Study period	Whether the authors described the year(s) the study samples were collected (1=Y, 0=N)	
4. Representativity	Whether the study methods indicated that the samples were likely to be representative, eg, using words such as “randomly selected,” “all patients,” “representative,” “consecutive” (1=Y, 0=N)	
5. Age and sex	Whether the study provided mean/median age and number of men/women for the population (1=Y, 0=N)	*To be assigned 1, the paper had to provide both age and gender
6. EBER testing	Whether the study described the ISH process in sufficient details, made a reference to a process described in a previous paper, or used a commercial tool kit (1=Y, 0=N)	
7. Definition of EBV	Whether the study gave an acceptable definition of how they classified a tumour as EBV positive by ISH (1=Y, 0=N)	This might be a % of positive tumour cells or all positive tumour cells
8. Anatomical location	Whether the study provided the information on anatomical location of the tumour for the study population (at least cardia vs non-cardia) (1=Y, 0=N)	If the study initially reported only cardia or only non-cardia, score 1.
9. Lauren class	Whether the study provided the information on Lauren’s classification (or equivalent) of the tumour for the whole population (at least intestinal vs diffuse) (1=Y, 0=N)	If the study initially reported only intestinal or diffuse, score 1.
10. EBV sex	Whether the study provided the information on gender by EBV status (1=Y, 0=N)	
11. EBV age	Whether the study provided the information on age by EBV status (1=Y, 0=N)	
Total score	Sum of variables 1–11, 11 being the highest score	

EBV, Epstein-Barr virus; N, no; Y, yes.

Supplementary References

1. Shibata D, Weiss LM. Epstein-Barr Virus-Associated Gastric Adenocarcinoma. Am J Pathol 1992;140:769–774.
2. Rowlands DC, Ito M, Mangham DC, et al. Epstein-Barr virus and carcinomas: rare association of the virus with gastric adenocarcinomas. Br J Cancer 1993;68:1014–1019.
3. Tokunaga M, Uemura Y, Tokudome T, et al. Epstein-Barr virus related gastric cancer in Japan: a molecular patho-epidemiological study. Acta Pathol Jpn 1993;43:574–581.
4. Manivel JC, Jessurun J, Bolio A, et al. Epstein-Barr-Virus (E-Bv) in Gastric Adenocarcinoma and Lymphoid-Cells - Comparative-Study between 2 Different Populations. Lab Invest 1994;70:A64.
5. Mori M, Watanabe M, Tanaka S, et al. Epstein-Barr Virus-Associated Carcinomas of the Esophagus and Stomach. Arch Pathol Lab Med 1994;118:998–1001.
6. Nakamura S, Ueki T, Yao T, et al. Epstein-Barr-Virus in Gastric-Carcinoma with Lymphoid Stroma. Cancer 1994; 73:2239–2249.
7. Ott G, Kirchner T, Muller-Hermelink HK. Monoclonal Epstein-Barr virus genomes but lack of EBV-related protein expression in different types of gastric carcinoma. Histopathology 1994;25:323–329.
8. Takano Y, Kato Y, Sugano H. Epstein-Barr-Virus-Associated Medullary Carcinomas with Lymphoid Infiltration of the Stomach. J Cancer Res Clin Oncol 1994;120:303–308.
9. Wang M, Tokunaga M, Jia XS. [Observations on the relation of gastric carcinoma to Epstein-Barr virus]. Zhonghua Bing Li Xue Za Zhi 1994;23:285–287.
10. Yamamoto N, Tokunaga M, Uemura Y, et al. Epstein-Barr-Virus and Gastric Remnant Cancer. Cancer 1994;74:805–809.
11. Yuen ST, Chung LP, Leung SY, et al. In situ detection of Epstein-Barr virus in gastric and colorectal adenocarcinomas. Am J Surg Pathol 1994;18:1158–1163.
12. Harn HJ, Chang JY, Wang MW, et al. Epstein-Barr Virus-Associated Gastric Adenocarcinoma in Taiwan. Hum Pathol 1995;26:267–271.
13. Matsunou H, Konishi F, Hori H, et al. Characteristics of Epstein-Barr virus-associated gastric carcinoma with lymphoid stroma in Japan. Cancer 1996;77:1998, –2004.
14. Moritani S, Kushima R, Sugihara H, et al. Phenotypic characteristics of Epstein-Barr-virus-associated gastric carcinomas. J Cancer Res Clin Oncol 1996;122:750–756.
15. Ohfuji S, Osaki M, Tsujitani S, et al. Low frequency of apoptosis in Epstein-Barr virus-associated gastric carcinoma with lymphoid stroma. J Cancer 1996;68:710–715.
16. Saiki Y, Ohtani H, Naito Y, et al. Immunophenotypic characterization of Epstein-Barr virus-associated gastric carcinoma: Massive infiltration by proliferating CD8(+) T-lymphocytes. Lab Invest 1996;75:67–76.
17. Selves J, Bibeau F, Brousset P, et al. Epstein-Barr virus latent and replicative gene expression in gastric carcinoma. Histopathology 1996;28:121–127.
18. Shin WS, Kang MW, Kang JH, et al. Epstein-Barr-Virus (Ebv) Associated Gastric Carcinomas (Ebvagc) among Koreans. Anatom Pathol 1996;105:174–181.
19. 陈世荣, 谢作煊. 广州市淋巴样间质胃癌与EB病毒的关系. 中华病理学杂志 1996;26:48.
20. Clark GD, Lee YS, Min KW, et al. Epstein-Barr virus in gastric carcinomas from Singapore. Int J Surg Pathol 1997; 4:149–158.
21. Galetsky SA, Tsvetnov VV, Land CE, et al. Epstein-Barr-virus-associated gastric cancer in Russia. J Cancer 1997; 73:786–789.
22. Ko HM, Lee YJ, Lee JS, et al. Expression of oncogenes and tumor suppressor genes in Epstein-Barr virus-associated gastric carcinoma. Lab Invest 1997;76:324.
23. Ojima H, Fukuda T, Nakajima T, et al. Infrequent overexpression of p53 protein in Epstein-Barr virus-associated gastric carcinomas. Jpn J Cancer Res 1997;88:262–266.
24. Qiu K, Tomita Y, Hashimoto M, et al. Epstein-Barr virus in gastric carcinoma in Suzhou, China and Osaka, Japan: Association with clinico-pathologic factors and HLA-subtype. J Cancer 1997;71:155–158.
25. Yanai H, Nishikawa J, Mizugaki Y, et al. Endoscopic and pathologic features of Epstein-Barr virus-associated gastric carcinoma. Gastrointest Endosc 1997;45:236–242.
26. Baas IO, van Rees BP, Musler A, et al. Helicobacter pylori and Epstein-Barr virus infection and the p53 tumour suppressor pathway in gastric stump cancer compared with carcinoma in the non-operated stomach. J Clin Pathol 1998;51:662–666.
27. 万榕 高美钦, 高凌云 陈碧芬. 蔡乾坤. 胃癌组织中EB病毒编码的RNA原位杂交检测. *福建医科大学学报* 1998;2:33–35.
28. Ioachim HL, Hajdu C, Giancotti FR, et al. Lymphoid proliferations and lymphomas associated with gastric metaplasia, dysplasia, and carcinoma. Hum Pathol 1999; 30:833–842.
29. Kaizaki Y, Sakurai S, Chong JM, et al. Atrophic gastritis, Epstein-Barr virus infection, and Epstein-Barr virus-associated gastric carcinoma. Gastric Cancer 1999;2:101–108.
30. Kume T, Oshima K, Shinohara T, et al. Low rate of apoptosis and overexpression of bcl-2 in Epstein-Barr virus-associated gastric carcinoma. Histopathology 1999;34:502–509.
31. Kume T, Oshima K, Yamashita Y, et al. Relationship between Fas-ligand expression on carcinoma cell and cytotoxic T-lymphocyte response in lymphoepithelioma-like cancer of the stomach. J Cancer 1999;84:339–343.
32. Takano Y, Kato Y, Saegusa M, et al. The role of the Epstein-Barr virus in the oncogenesis of EBV(+) gastric carcinomas. Virchows Arch 1999;434:17–22.
33. Tanaka M, Kawaguchi Y, Yokofujita J, et al. Sequence variations of Epstein-Barr virus LMP2A gene in gastric carcinoma in Japan. Virus Genes 1999;19:103–111.
34. van Rees BP, Musler A, Caspers E, et al. K-ras mutations in gastric stump carcinomas and in carcinomas from the non-operated stomach. Hepatogastroenterology 1999; 46:2063–2068.
35. Wan R, Gao MQ, Gao LY, et al. In situ detection of Epstein-Barr virus in gastric carcinoma tissue in China high-risk area. World J Gastroenterol 1999;5:531–532.
36. Chang MS, Kim WH, Kim CW, et al. Epstein-Barr virus in gastric carcinomas with lymphoid stroma. Histopathology 2000;37:309–315.
37. Chang MS, Lee JH, Kim JP, et al. Microsatellite instability and Epstein-Barr virus infection in gastric remnant cancers. Pathol Int 2000;50:486–492.
38. Chapel F, Fabiani B, Davi F, et al. Epstein-Barr virus and gastric carcinoma in Western patients: comparison of pathological parameters and p53 expression in EBV-positive and negative tumours. Histopathology 2000;36:252–261.
39. Gurtsevich VE, Novikova EV, Borisova EI, et al. Molecular biological and clinical-morphological studies of gastric

tumors associated with Epstein-Barr virus. Vestn Ross Akad Med Nauk 2000;3:27–31.
40. Tanigawa H, Uesugi H, Mitomi H, et al. Possible association of active gastritis, featuring accelerated cell turnover and p53 overexpression, with cancer development at anastomoses after gastrojejunostomy - Comparison with gastroduodenostomy. Am J Clin Pathol 2000;114:354–363.
41. Wu MS, Shun CT, Wu CC, et al. Epstein-Barr virus - Associated gastric carcinomas: Relation to H-pylori infection and genetic alterations. Gastroenterology 2000;118:1031–1038.
42. zur Hausen A, Brink A, Craanen ME, et al. Unique transcription pattern of Epstein-Barr virus (EBV) in EBV-carrying gastric adenocarcinomas: Expression of the transforming BARF1 gene. Cancer Res 2000;60:2745–2748.
43. 闵永芬, 贾心善. 胃癌EB病毒编码小RNA的原位杂交研究. *中国医科大学学报* 2000;1:11–12.
44. Chiaravalli A, Cornaggia M, Furlan D, et al. The role of histological investigation in prognostic evaluation of advanced gastric cancer. Virchows Arch 2001;439:158–169.
45. Ishii H, Gobe G, Kawakubo Y, et al. Interrelationship between Epstein-Barr virus infection in gastric carcinomas and the expression of apoptosis-associated proteins. Histopathology 2001;38:111–119.
46. Koriyama C, Akiba S, Iriya K, et al. Epstein-Barr virus-associated gastric carcinoma in Japanese Brazilians and non-Japanese Brazilians in Sao Paulo. Jpn J Cancer Res 2001;92:911–917.
47. Koriyama C, Shinkura R, Hamasaki Y, et al. Human leukocyte antigens related to Epstein-Barr virus-associated gastric carcinoma in Japanese patients. Eur J Cancer Prev 2001; 10:69–75.
48. Lo YMD, Chan WY, Ng EKW, et al. Circulating Epstein-Barr virus DNA in the serum of patients with gastric carcinoma. Clin Chem 2001;47:366.
49. Luqmani YA, Linjawi SO, Shousha S. Detection of Epstein-Barr virus in gastrectomy specimens. Oncol Rep 2001; 8:995–999.
50. 殷智榕 高冬玲, 徐晓丽 郝志芳. 宋一民. 胃癌组织中EB病毒的检测. *广西医科大学学报* 2001;6:803–805.
51. Burgess DE, Woodman CB, Flavell KJ, et al. Low prevalence of Epstein-Barr virus in incident gastric adenocarcinomas from the United Kingdom. Br J Cancer 2002;86:702–704.
52. Grogg KL, Lohse CM, Pankratz VS, et al. Lymphocyte-rich gastric cancer: Associations with Epstein-Barr virus, microsatellite instability, histology and survival. Lab Invest 2002; 82:128A.
53. Hao ZF, Koriyama C, Akiba S, et al. The Epstein-Barr virus-associated gastric carcinoma in Southern and Northern China. Oncol Rep 2002;9:1293–1298.
54. Hoshikawa Y, Satoh Y, Murakami M, et al. Evidence of lytic infection of Epstein-Barr virus (EBV) in EBV-positive gastric carcinoma. J Med Virol 2002;66:351–359.
55. Kang GH, Lee S, Kim WH, et al. Epstein-Barr virus-positive gastric carcinoma demonstrates frequent aberrant methylation of multiple genes and constitutes CpG island methylator phenotype-positive gastric carcinoma. Am J Pathol 2002; 160:787–794.
56. Kattoor J, Koriyama C, Akiba S, et al. Epstein-Barr virus-associated gastric carcinoma in southern India: A comparison with a large-scale Japanese series. J Med Virol 2002; 68:384–389.
57. Vo QN, Geradts J, Gulley ML, et al. Epstein-Barr virus in gastric adenocarcinomas: association with ethnicity and CDKN2A promoter methylation. J Clin Pathol 2002; 55:669–675.
58. Carrascal E, Koriyama C, Akiba S, et al. Epstein-Barr virus-associated gastric carcinoma in Cali, Colombia. Oncol Rep 2003;10:1059–1062.
59. Czopek JP, Stojak M, Sińczak A, et al. EBV-positive gastric carcinomas in Poland. Polish J Pathol 2003;54:123–128.
60. Karim N, Pallesen G. Epstein-Barr virus (EBV) and gastric carcinoma in Malaysian patients. Malaysian J Pathol 2003; 25:45–47.
61. Kijima Y, Ishigami S, Hokita S, et al. The comparison of the prognosis between Epstein-Barr virus (EBV)-positive gastric carcinomas and EBV-negative ones. Cancer Lett 2003; 200:33–40.
62. Oda K, Koda K, Takiguchi N, et al. Detection of Epstein-Barr virus in gastric carcinoma cells and surrounding lymphocytes. Gastric Cancer 2003;6:173–178.
63. Cho MY, Kim TH, Yi SY, et al. Relationship between Epstein-Barr virus-encoded RNA expression, apoptosis and lymphocytic infiltration in gastric carcinoma with lymphoid-rich stroma. Med Princ Pract 2004;13:353–360.
64. Kerroucha R, Hervieu V, Chambonneire ML, et al. [Incidence and phenotypic characteristics of EBV-assiociated adenocarcinomas of the upper digestive tract in Lyons area, France]. Ann Pathol 2004;24:228–235.
65. Koriyama C, Akiba S, Corvalan A, et al. Histology-specific gender, age and tumor-location distributions of Epstein-Barr virus-associated gastric carcinoma in Japan. Oncol Rep 2004;12:543–547.
66. Lopes LF, Bacchi MM, Elgui-de-Oliveira D, et al. Epstein-Barr virus infection and gastric carcinoma in São Paulo State, Brazil. Braz J Med Biol Res 2004;37:1707–1712.
67. Morewaya J, Koriyama C, Akiba S, et al. Epstein-Barr virus-associated gastric carcinoma in Papua New Guinea. Oncol Rep 2004;12:1093–1098.
68. van Beek J, zur Hausen A, Kranenbarg EK, et al. EBV-positive gastric adenocarcinomas: A distinct clinicopathologic entity with a low frequency of lymph node involvement. J Clin Oncol 2004;22:664–670.
69. 王云, 罗兵, 王笑峰. 阎丽平. 胃癌组织中EB病毒的检测及其增殖期基因的表达. *中国癌症杂志* 2004;3:17–21.
70. 阎丽平, 罗兵, 王笑峰, 赵鹏, 黄葆华. EBV相关胃癌组织中bcl-2和Ki–67蛋白表达的检测. 青岛大学医学院学报 2004;1:57–59.
71. Alipov G, Nakayama T, Nakashima M, et al. Epstein-Barr virus-associated gastric carcinoma in Kazakhstan. World J Gastroenterol 2005;11:27–30.
72. Anwar M, Koriyama C, Naveed IA, et al. Epstein-Barr virus detection in tumors of upper gastrointestinal tract. An in situ hybridization study in Pakistan. J Exp Clin Cancer Res 2005; 24:379–385.
73. Corvalan A, Akiba S, Valenzuela MT, et al. [Clinical and molecular features of cardial gastric cancer associated to Epstein Barr virus]. Rev Med Chile 2005;133:753–760.
74. Herrera-Goepfert R, Akiba S, Koriyama C, et al. Epstein-Barr virus-associated gastric carcinoma: Evidence of age-dependence among a Mexican population. World J Gastroenterol 2005;11:6096–6103.
75. Kaizaki Y, Hosokawa O, Sakurai S, et al. Epstein-Barr virus-associated gastric carcinoma in the remnant stomach: de

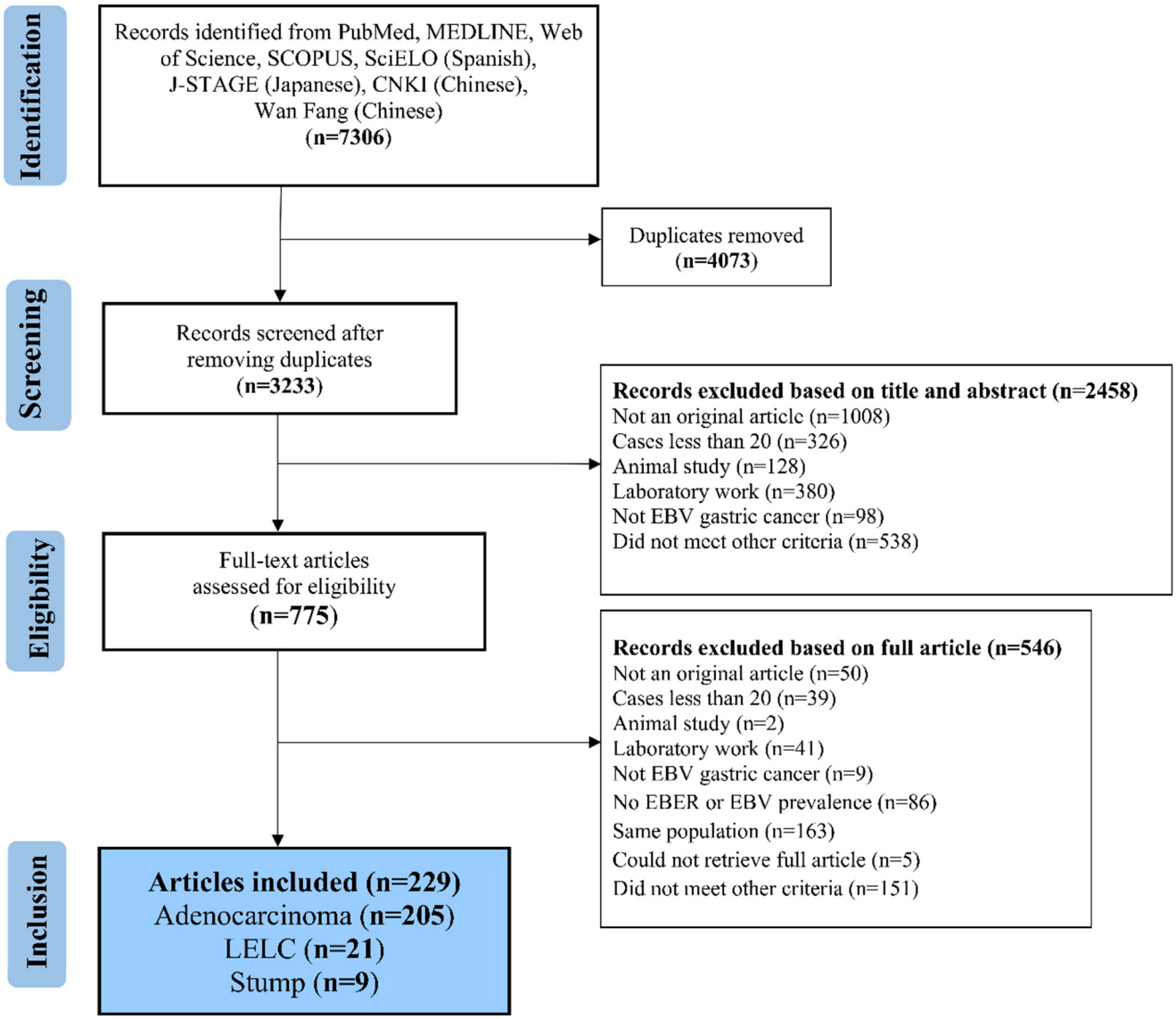
novo and metachronous gastric remnant carcinoma. J Gastroenterol 2005;40:570–577.
76. Kim MA, Lee HS, Yang HK, et al. Clinicopathologic and protein expression differences between cardia carcinoma and noncardia carcinoma of the stomach. Cancer 2005; 103:1439–1446.
77. Sakuma K, Uozaki H, Chong JM, et al. Cancer risk to the gastric corpus in Japanese, its correlation with Interleukin-1 beta gene polymorphism (+3953*T) and Epstein-Barr virus infection. J Cancer 2005;115:93–97.
78. Yoshiwara E, Koriyama C, Akiba S, et al. Epstein-Barr virus-associated gastric carcinoma in Lima, Peru. J Exp Clin Cancer Res 2005;24:49–54.
79. Begnami MD, Montagnini AL, Vettore AL, et al. Differential expression of apoptosis related proteins and nitric oxide synthases in Epstein Barr associated gastric carcinomas. World J Gastroenterol 2006;12:4959–4965.
80. Campos FI, Koriyama C, Akiba S, et al. Environmental factors related to gastric cancer associated with epstein-barr virus in Colombia. Asian Pac J Cancer Prev 2006;7:633–6337.
81. Kim HY, Lee JI, Shim KY, et al. Detection of Epstein-Barr virus by in situ hybridization and polymerase chain reaction in gastric carcinoma. Ann Oncol 2006;17:312.
82. Qian J, Li DQ, Zhong F, et al. [Significance of the expression of P53 protein and P21WAF1 protein in the gastric carcinoma tissues associated with Epstein-Barr virus (EBV) infections]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2006; 20:1–3.
83. von Rahden BHA, Langner C, Brucher B, et al. No association of primary adenocarcinomas of the small bowel with Epstein-Barr virus infection. Mol Carcinog 2006;45:349–352.
84. Zazula M, Ferreira AM, Czopek JP, et al. CDH1 gene promoter hypermethylation in gastric cancer - Relationship to Goseki grading, microsatellite instability status, and EBV invasion. Diagn Mol Pathol 2006;15:24–29.
85. Abdirad A, Ghaderi-Sohi S, Shuyama K, et al. Epstein-Barr virus associated gastric carcinoma: a report from Iran in the last four decades. Diagn Pathol 2007;2:25.
86. Enomoto S, Maekita T, Tsukamoto T, et al. Lack of association between CpG island methylator phenotype in human gastric cancers and methylation in their background non-cancerous gastric mucosae. Cancer Sci 2007; 98:1853–1861.
87. Jung IM, Chung JK, Kim YA, et al. Epstein-Barr virus, beta-catenin, and E-cadherin in gastric carcinomas. J Korean Med Sci 2007;22:855–861.
88. Moncef M, Mounir T, Feriel K, et al. Epstein-Barr virus (EBV) and gastric carcinoma: An in situ hybridization study in tunisian patients. Ann Oncol 2007;18:VII55.
89. 李淑英 胡金华. 周天戟. 唐山地区EB病毒感染与胃癌相关性分析. *中国老年学杂志* 2007;23:2323–2325.
90. Kang J, Ko Y, Roh S, et al. Both VEGF and bFGF play an important role in distinctive angiogenic feature of micro-envirnment surrounding EBV positive gastric cancer. J Clin Oncol 2008;26:15551.
91. Limaiem F, Mekni A, Chelly I, et al. Epstein-Barr virus in gastric carcinoma in situ hybridization study of 25 Tunisian cases. Virchows Arch 2008;452:S196.
92. Nakamura Y, Yanai H, Kitoh T, et al. The clinical meaning of mucin phenotype and Epstein-Barr virus infection in gastric cancer. Hepatogastroenterology 2008;55:41–45.
93. Young GQ, Shia J, Tang LH, et al. Gastric carcinomas with lymphoid stroma show distinct molecular features that reflect their Epstein-Barr virus (EBV) and microsatellite instability (MSI) status. Lab Invest 2008;88:142A.
94. Park ES, Do IG, Park CK, et al. Cyclooxygenase-2 Is an Independent Prognostic Factor in Gastric Carcinoma Patients Receiving Adjuvant Chemotherapy and Is Not Associated with EBV Infection. Clin Cancer Res 2009; 15:291–298.
95. Ramirez V, Malespin W, Agenhen J, et al. Association of Epstein-Barr Virus with Gastric Adenocarcinoma in a Population at High Risk of Gastric Cancer in Costa Rica. Helicobacter 2009;14:385–386.
96. Ryan JL, Morgan DR, Dominguez RL, et al. High levels of Epstein-Barr virus DNA in latently infected gastric adenocarcinoma. Lab Invest 2009;89:80–90.
97. Szkaradkiewicz A, Karpinski T, Majewski P, et al. EBV infection in patients with gastric carcinoma. Int J Antimicrob Agents 2009;34:S99.
98. Truong CD, Feng W, Li W, et al. Characteristics of Epstein-Barr virus-associated gastric cancer: A study of 235 cases at a comprehensive cancer center in USA. J Exp Clin Cancer Res 2009;28:14.
99. 刘换新 赵荡, 袁怀文 刘梅. EB病毒感染及C-erbB-2基因表达与胃癌的相关性. 武警医学 2009;20:122–1224+93.
100. Carrasco G, Diaz J, Valbuena JR, et al. Overexpression of p73 as a Tissue Marker for High-Risk Gastritis. Clin Cancer Res 2010;16:3253–3259.
101. Chen JN, Ding YG, Feng ZY, et al. Association of Distinctive Epstein-Barr Virus Variants With Gastric Carcinoma in Guangzhou, Southern China. J Med Virol 2010;82:658–667.
102. Kim RH, Chang MS, Kim HJ, et al. Medical History and Lifestyle Factors Contributing to Epstein-Barr Virus-Associated Gastric Carcinoma and Conventional Gastric Carcinoma in Korea. Anticancer Res 2010;30:2469–2475.
103. Park SY, Kook MC, Kim YW, et al. Mixed-type gastric cancer and its association with high-frequency CpG island hypermethylation. Virchows Arch 2010;456:625–633.
104. Song HJ, Srivastava A, Lee J, et al. Host Inflammatory Response Predicts Survival of Patients With Epstein-Barr Virus-Associated Gastric Carcinoma. Gastroenterology 2010;139:84–U123.
105. Wang L, Cheong J, Lim KH, et al. Patients with EBV positive gastric cancers have a dense T cell infiltrate and have better prognosis after surgery compared with patients with EBV negative cancers. J Gastroenterol Hepatol 2010;25:A142.
106. Wang Y, Zhang X, Chao Y, et al. New Variations of Epstein-Barr Virus-Encoded Small RNA Genes in Nasopharyngeal Carcinomas, Gastric Carcinomas, and Healthy Donors in Northern China. J Med Virol 2010;82:829–836.
107. BenAyed-Guerfali D, Ayadi W, Miladi-Abdennadher I, et al. Characteristics of epstein barr virus variants associated with gastric carcinoma in Southern Tunisia. Virol J 2011;8:500.
108. Chen JN, Jiang Y, Li HG, et al. Epstein-Barr virus genome polymorphisms of Epstein-Barr virus-associated gastric carcinoma in gastric remnant carcinoma in Guangzhou, southern China, an endemic area of nasopharyngeal carcinoma. Virus Res 2011;160:191–199.
109. De Lima MAP, Ferreira MVP, Barros MAP, et al. Epstein-Barr virus (EBV) detection in gastric carcinomas from Ceará and São Paulo states, in Brazil. J Bras Patol Med Lab 2011;47:171–179.

110. Haas M, Buttner M, Rau TT, et al. Inflammation in gastric adenocarcinoma of the cardia: how do EBV infection, Her2 amplification and cancer progression influence tumor-infiltrating lymphocytes? Virchows Arch 2011;458:403–141.
111. Lee JM, Kim H, Noh SH, et al. Expression of Epstein-Barr Virus Gene and Clonality of Infiltrated T Lymphocytes in Epstein-Barr Virus-associated Gastric Carcinoma. Immune Netw 2011;11:50–58.
112. Matsusaka K, Kaneda A, Nagae G, et al. Classification of Epstein-Barr Virus-Positive Gastric Cancers by Definition of DNA Methylation Epigenotypes. Cancer Res 2011; 71:7187–7197.
113. Peng J, Chen H-L, Zhu X-B, et al. Detection of Epstein-Barr virus infection in gastric carcinomas using quantum dot-based fluorescence in-situ hybridization. J Nanosci Nanotechnol 2011;11:9725–9730.
114. 何影娟, 白光辉, 郭云娣. EB病毒感染与血管生成在胃癌组织芯片中的关系. *世界华人消化杂志* 2011;19:3172–3176.
115. 郭云娣 李明. 胃癌及EB病毒相关胃癌组织中P16和CyclinD1的表达及意义. *山东医药* 2011;51:92–93+120.
116. 顾学文, 肖芹 王翠梅, 陈月香 张真稳. 江苏省扬州地区胃癌组织中EB病毒感染与p53蛋白表达的相关性. *实用临床医药杂志* 2011;15:37–39.
117. Abe H, Maeda D, Hino R, et al. ARID1A expression loss in gastric cancer: pathway-dependent roles with and without Epstein-Barr virus infection and microsatellite instability. Virchows Arch 2012;461:367–377.
118. Chiaravalli AM, Klersy C, Vanoli A, et al. Histotype-based prognostic classification of gastric cancer. World J Gastroenterol 2012;18:896–904.
119. Genitsch V, Cathomas M, Terracciano L, et al. Epstein-Barr virus and p53 in the development of gastric cancer. Virchows Arch 2012;461:S8.
120. He YY, Zhao XD, Gao J, et al. Quantum Dots-Based Immunofluorescent Imaging of Stromal Fibroblasts Caveolin-1 and Light Chain 3B Expression and Identification of Their Clinical Significance in Human Gastric Cancer. Int J Mol Sci 2012; 13:13764–13780.
121. Lima MAPd, Ferreira MVP, Barros MAP, et al. Epstein-Barr virus-associated gastric carcinoma in Brazil: comparison between in situ hybridization and polymerase chain reaction detection. Braz J Microbiol 2012;43:393–404.
122. Park HY, Kang SY, Kang GH, et al. EBV infection and mismatch repair deficiency mediated by loss of hMLH1 expression contribute independently to the development of multiple synchronous gastric carcinomas. J Surg Oncol 2012; 106:777–782.
123. Sukawa Y, Yamamoto H, Nosho K, et al. Alterations in the human epidermal growth factor receptor 2-phosphatidylinositol 3-kinase-v-Akt pathway in gastric cancer. World J Gastroenterol 2012;18:6577–6586.
124. Mitsuhashi K, Sukawa Y, Nakazawa M, et al. Association Between EBV Infection and HER2 Expression in Gastric Cancer. Gastroenterology 2013;144:S353.
125. Tobo T, Hirahashi M, Yao T, et al. Ezrin expression and its phosphorylation in gastric carcinoma with lymphoid stroma and Epstein-Barr virus infection. Mol Clin Oncol 2013; 1:220–224.
126. Warneke VS, Behrens HM, Haag J, et al. Prognostic and Putative Predictive Biomarkers of Gastric Cancer for Personalized Medicine. Diagn Mol Pathol 2013;22:127–137.
127. 于传亭 荆永正, 邱清芳 罗兵. 王云. 烟台地区EBV相关胃癌临床病理特征及病毒基因分型. *青岛大学医学院学报* 2013; 49:377–380+385.
128. 张雅琴 李小宁. 郭云娣. 胃癌组织芯片中EB病毒感染与核PTEN的关系. *江苏医药* 2013;39:537–539.
129. 杨艳丽 胡建国. 司岑. EBV、Hp感染与胃癌的关系及相互作用研究. *天津医药* 2013;41:1048–1051.
130. Huang SC, Ng KF, Chen KH, et al. Prognostic factors in Epstein-Barr virus-associated stage I-III gastric carcinoma: Implications for a unique type of carcinogenesis. Oncol Rep 2014;32:530–538.
131. Ksiaa E, Ziadi S, Gacem RB, et al. Correlation between DNA methyltransferases expression and Epstein-Barr virus, JC polyomavirus and Helicobacter pylori infections in gastric carcinomas. Neoplasma 2014;61:710–717.
132. Uozaki H, Morita S, Kumagai A, et al. Stromal miR-21 is more important than miR-21 of tumour cells for the progression of gastric cancer. Histopathology 2014;65:775–783.
133. Wiegand KC, Sy K, Kalloger SE, et al. ARID1A/BAF250a as a prognostic marker for gastric carcinoma: a study of 2 cohorts. Hum Pathol 2014;45:1258–1268.
134. Yuan H, Liu W, Jiang N, et al. Correlation of Epstein-Barr virus infection with the expression of miR-101, EZH2, and COX-2 in gastric cancer. Chinese J Clin Oncol 2014;41:420–424.
135. Choi E, Byeon SJ, Kim SH, et al. Implication of Leptin-Signaling Proteins and Epstein-Barr Virus in Gastric Carcinomas. PLoS One 2015;10:e0130839.
136. Genitsch V, Novotny A, Seiler CA, et al. Epstein Barr virus in gastro-esophageal adenocarcinomas - single center experiences in the context of current literature. Front Oncol 2015;5:73.
137. Ozmen I, Karagoz B, Yilmaz I, et al. The Epstein-Barr virus-associated gastric carcinoma in Turkey. J Clin Oncol 2015;33: e15107.
138. Aslane M, Al Haj A, Henneb A, et al. Characteristics of gastric carcinoma associated with epstein barr virus in Algeria. Der Pharm Lett 2016;8:169–178.
139. Dai CQ, Geng RX, Wang CC, et al. Concordance of immune checkpoints within tumor immune contexture and their prognostic significance in gastric cancer. Mol Oncol 2016; 10:1551–1558.
140. Fu HL, Ma Y, Yang M, et al. Persisting and Increasing Neutrophil Infiltration Associates with Gastric Carcinogenesis and E-cadherin Downregulation. Sci Rep 2016;6:29762.
141. Gonzalez RS, Messing S, Tu X, et al. Immunohistochemistry as a surrogate for molecular subtyping of gastric adenocarcinoma. Hum Pathol 2016;56:16–21.
142. Han N, Kim MA, Lee HS, et al. Loss of ARID1A Expression is Related to Gastric Cancer Progression, Epstein-Barr Virus Infection, and Mismatch Repair Deficiency. Appl Immunohistochem Mol Morphol 2016;24:320–325.
143. Huh CW, Jung DH, Kim H, et al. Clinicopathologic Features of Gastric Carcinoma With Lymphoid Stroma in Early Gastric Cancer. J Surg Oncol 2016;114:769–772.
144. Kim HS, Shin SJ, Beom SH, et al. Comprehensive expression profiles of gastric cancer molecular subtypes by immunohistochemistry: implications for individualized therapy. Oncotarget 2016;7:44608–44620.
145. Liu SZ, Zhao ZZ, Han L, et al. Epstein-Barr Virus Infection in Gastric Remnant Carcinoma and Recurrent Gastric Carcinoma in Qingdao of Northern China. PLoS One 2016;11: e0148342.

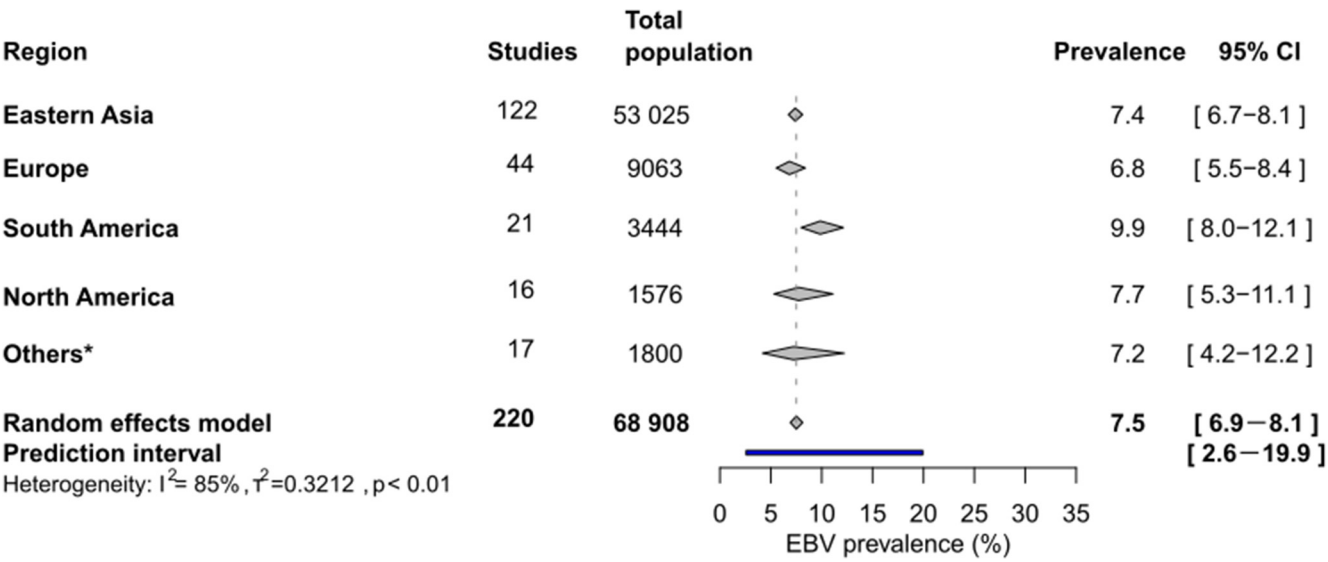
146. Ma CQ, Patel K, Singhi AD, et al. Programmed Death-Ligand 1 Expression Is Common in Gastric Cancer Associated With Epstein-Barr Virus or Microsatellite Instability. Am J Surg Pathol 2016;40:1496–1506.
147. Min B-H, Tae CH, Ahn SM, et al. Epstein-Barr virus infection serves as an independent predictor of survival in patients with lymphoepithelioma-like gastric carcinoma. Gastric Cancer 2016;19:852–859.
148. Park CK, Park JS, Kim HS, et al. Receptor tyrosine kinase amplified gastric cancer: Clinicopathologic characteristics and proposed screening algorithm. Oncotarget 2016; 7:72099–72112.
149. Setia N, Agoston AT, Han HS, et al. A protein and mRNA expression-based classification of gastric cancer. Mod Pathol 2016;29:772–784.
150. Song YS, Kim Y, Cho NY, et al. Methylation status of long interspersed element-1 in advanced gastric cancer and its prognostic implication. Gastric Cancer 2016;19:98–106.
151. Zhang ZX, Guo DL, Jin M, et al. Invasion-related signal pathways in Epstein-Barr virus (EBV)-associated gastric carcinoma. Int J Clin Exp Med 2016;9:3544–3550.
152. Ahn S, Lee SJ, Kim Y, et al. High-throughput Protein and mRNA Expression-based Classification of Gastric Cancers Can Identify Clinically Distinct Subtypes, Concordant With Recent Molecular Classifications. Am J Surg Pathol 2017;41:106–115.
153. Boger C, Kruger S, Behrens HM, et al. Epstein-Barr virus-associated gastric cancer reveals intratumoral heterogeneity of PIK3CA mutations. Ann Oncol 2017;28:1005–1014.
154. Chen BZ, Lin XD, Chen G, et al. [Expression of long non-coding RNA SNHG8 in Epstein-Barr virus-related gastric cancer and clinical outcome]. Zhonghua Bing Li Xue Za Zhi 2017;46:84–87.
155. Irkkan C, Balci S, Tezel GG, et al. Comparison of Clinicopathologic Parameters and Survivals Between Epstein-Barr Virus-positive and Her2-positive Gastric Cancers. Appl Immunohistochem Mol Morphol 2017;25:609–614.
156. Jenkins TM, Tondon R, Wang LP, et al. Mismatch repair deficiency (MMR-D) and programmed death ligand-1 (PD-l1) expression in gastric adenocarcinomas. Lab Invest 2017; 97:178A.
157. Kawazoe A, Kuwata T, Kuboki Y, et al. Clinicopathological features of programmed death ligand 1 expression with tumor-infiltrating lymphocyte, mismatch repair, and Epstein-Barr virus status in a large cohort of gastric cancer patients. Gastric Cancer 2017;20:407–415.
158. Kim JY, Bae BN, Kang G, et al. Cytokine expression associated with Helicobacter pylori and Epstein-Barr virus infection in gastric carcinogenesis. APMIS 2017;125:808–815.
159. Kwon MJ, Kim KC, Nam ES, et al. Programmed death ligand-1 and MET co-expression is a poor prognostic factor in gastric cancers after resection. Oncotarget 2017; 8:82399–82414.
160. Lim H, Lee IS, Lee JH, et al. Clinical application of early gastric carcinoma with lymphoid stroma based on lymph node metastasis status. Gastric Cancer 2017;20:793–801.
161. Ma J, Li JH, Hao YM, et al. Differentiated tumor immune microenvironment of Epstein-Barr virus-associated and negative gastric cancer: implication in prognosis and immunotherapy. Oncotarget 2017;8:67094–67103.
162. Na SJ, Park HL, Hyun OJ, et al. Correlation Between Infection Status of Epstein-Barr Virus and F-18-Fluorodeoxyglucose Uptake in Patients with Advanced Gastric Cancer. *In* Vivo 2017;31:749–753.
163. Narita Y, Sasaki E, Yatabe Y, et al. PD-L1 immunohistochemistry (IHC) by three different assays and molecular profiling in tissue microarray (TMA) of gastric cancer. Ann Oncol 2017;28:v230.
164. Nogueira C, Mota M, Gradiz R, et al. Prevalence and characteristics of Epstein-Barr virus-associated gastric carcinomas in Portugal. Infect Agents Cancer 2017;12:41.
165. Park S, Lee D, Lee KM, et al. Clinical usefulness of F-18 FDG PET in lymphoepithelioma-like gastric carcinoma. Eur J Radiol 2017;94:160–166.
166. Ribeiro J, Oliveira A, Malta M, et al. Clinical and pathological characterization of Epstein-Barr virus-associated gastric carcinomas in Portugal. World J Gastroenterol 2017;23:7292–7302.
167. Thompson ED, Zahurak M, Murphy A, et al. Patterns of PD-L1 expression and CD8 T cell infiltration in gastric adenocarcinomas and associated immune stroma. Gut 2017;66:794–801.
168. Tsai CY, Liu YY, Liu KH, et al. Comprehensive profiling of virus microRNAs of Epstein-Barr virus-associated gastric carcinoma: highlighting the interactions of ebv-Bart9 and host tumor cells. J Gastroenterol Hepatol 2017;32:82–91.
169. Wu YH, Cao DH, Qu LM, et al. PD-1 and PD-L1 co-expression predicts favorable prognosis in gastric cancer. Oncotarget 2017;8:64066–64082.
170. Zhou ZH, Ji CD, Zhu J, et al. The prognostic value and pathobiological significance of Glasgow microenvironment score in gastric cancer. J Cancer Res Clin Oncol 2017; 143:883–894.
171. 陈瑚, 蒋逸婷, 陈永钦, et al. 胃淋巴上皮瘤样癌27例临床病理分析. 临床与实验病理学杂志 2017;33:1016–1018.
172. Baek DW, Kang BW, Kim JG. [The Predictive Value of Epstein-Barr Virus-Positivity in Patients Undergoing Gastrectomy Followed by Adjuvant Chemotherapy]. Chonnam Med J 2018;54:173–177.
173. Birkman EM, Mansuri N, Kurki S, et al. Gastric cancer: immunohistochemical classification of molecular subtypes and their association with clinicopathological characteristics. Virchows Archiv 2018;472:369–382.
174. De Rosa S, Sahnane N, Tibiletti MG, et al. EBV+ and MSI Gastric Cancers Harbor High PD-Li/PD-1 Expression and High CD8(+) Intratumoral Lymphocytes. Cancers (Basel) 2018;10:102.
175. de Souza CRT, Almeida MCA, Khayat AS, et al. Association between Helicobacter pylori, Epstein-Barr virus, human papillomavirus and gastric adenocarcinomas. World J Gastroenterol 2018;24:4928–4938.
176. Gullo I, Carvalho J, Martins D, et al. The Transcriptomic Landscape of Gastric Cancer: Insights into Epstein-Barr Virus Infected and Microsatellite Unstable Tumors. Int J Mol Sci 2018;19:2079.
177. Hewitt LC, Inam IZ, Saito Y, et al. Epstein-Barr virus and mismatch repair deficiency status differ between oesophageal and gastric cancer: A large multi-centre study. Eur J Cancer 2018;94:104–114.
178. Hissong E, Ramrattan G, Zhang P, et al. Gastric Carcinomas With Lymphoid Stroma: An Evaluation of the Histopathologic and Molecular Features. Am J Surg Pathol 2018;42:453–462.
179. Murai K, Kakushima N, Sugino T, et al. Epstein-Barr virus positivity among surgically resected intramucosal gastric cancer. Dig Endosc 2018;30:667–671.

180. Pereira MA, Ramos M, Faraj SF, et al. Clinicopathological and prognostic features of Epstein-Barr virus infection, microsatellite instability, and PD-L1 expression in gastric cancer. J Surg Oncol 2018;117:829–839.
181. Son BK, Kim DH, Min KW, et al. Smad4/Fascin index is highly prognostic in patients with diffuse type EBV-associated gastric cancer. Pathol Res Pract 2018;214:475–481.
182. Yun S, Koh J, Nam SK, et al. Clinical significance of overexpression of NRG1 and its receptors, HER3 and HER4, in gastric cancer patients. Gastric Cancer 2018;21:225–236.
183. 李红 谈顺, 邢璐 李乾. 周欢. 胃癌组织中EB病毒、ARID1A及PIK3CA的表达及意义. *海南医学* 2018;29:1344–1347.
184. 郑珂 张声, 黄贞 陈余朋. 肿瘤浸润淋巴细胞与EBV相关性胃癌侵袭及预后分析. *临床与实验病理学杂志* 2018;34:1063–1068.
185. Beltrán Gárate B, Camara A, Kapsoli Sánchez MDC, et al. [Impact of the Epstein Barr virus on gastric cancer in Peru]. Rev Gastroenterol Peru 2019;39:319–322.
186. Bosch F, Todorova R, Link H, et al. Molecular subtyping of gastric cancer with respect to the growth pattern of lymph-node metastases. J Cancer Res Clin Oncol 2019;145:2689–2697.
187. Cho J, Kang SY, Kim KM. MMR protein immunohistochemistry and microsatellite instability in gastric cancers. Pathology 2019;51:110–113.
188. Coati I, Lotz G, Fanelli GN, et al. Claudin-18 expression in oesophagogastric adenocarcinomas: a tissue microarray study of 523 molecularly profiled cases. Br J Cancer 2019;121:257–263.
189. Cordova-Delgado M, Pinto MP, Retamal IN, et al. High Proportion of Potential Candidates for Immunotherapy in a Chilean Cohort of Gastric Cancer Patients: Results of the FORCE1 Study. Cancers (Basel) 2019;11:1275.
190. De Castria TB, Amorim LC, Ramos MFKP, et al. Impact of adjuvant treatment according to gastric cancer molecular subtypes. J Clin Oncol 2019;37:e15513.
191. Gasenko E, Isajevs S, Camargo MC, et al. Clinicopathological characteristics of Epstein-Barr virus-positive gastric cancer in Latvia. Eur J Gastroenterol Hepatol 2019;31:1328–1333.
192. Huang SC, Ng KF, Yeh TS, et al. Subtraction of Epstein-Barr virus and microsatellite instability genotypes from the Lauren histotypes: Combined molecular and histologic subtyping with clinicopathological and prognostic significance validated in a cohort of 1,248 cases. *In* J Cancer 2019;145:3218–3230.
193. Kawazoe A, Shitara K, Kuboki Y, et al. Clinicopathological features of 22C3 PD-L1 expression with mismatch repair, Epstein-Barr virus status, and cancer genome alterations in metastatic gastric cancer. Gastric Cancer 2019;22:69–76.
194. Kim TS, da Silva E, Coit DG, et al. Intratumoral Immune Response to Gastric Cancer Varies by Molecular and Histologic Subtype. Am J Surg Pathol 2019;43:851–860.
195. Kim YB, Ahn JM, Bae WJ, et al. Functional loss of ARID1A is tightly associated with high PD-L1 expression in gastric cancer. In J Cancer 2019;145:916–926.
196. Kohlruss M, Grosser B, Krenauer M, et al. Prognostic implication of molecular subtypes and response to neoadjuvant chemotherapy in 760 gastric carcinomas: role of Epstein-Barr virus infection and high- and low-microsatellite instability. J Pathol Clin Res 2019;5:227–239.
197. Martinez-Ciarpaglini C, Fleitas-Kanonnikoff T, Gambardella V, et al. Assessing molecular subtypes of gastric cancer: microsatellite unstable and Epstein-Barr virus subtypes. Methods for detection and clinical and pathological implications. ESMO Open 2019;4:e000470.
198. Mishima S, Kawazoe A, Nakamura Y, et al. Clinicopathological and molecular features of responders to nivolumab for patients with advanced gastric cancer. J Immunother Cancer 2019;7:24.
199. Nakayama I, Shinozaki E, Sakata S, et al. Enrichment of CLDN18-ARHGAP fusion gene in gastric cancers in young adults. Cancer Sci 2019;110:1352–1363.
200. Osumi H, Kawachi H, Murai K, et al. Risk stratification for lymph node metastasis using Epstein-Barr virus status in submucosal invasive (pT1) gastric cancer without lymphovascular invasion: a multicenter observational study. Gastric Cancer 2019;22:1176–1182.
201. Osumi H, Kawachi H, Yoshio T, et al. Epstein-Barr virus status is a promising biomarker for endoscopic resection in early gastric cancer: proposal of a novel therapeutic strategy. J Gastroenterol 2019;54:774–783.
202. Sun YQ, Yu WW, Guan WB, et al. Integrated assessment of PD-L1 expression and molecular classification facilitates therapy selection and prognosis prediction in gastric cancer. Cancer Manage Res 2019;11:6397–6410.
203. Valentini AM, Di Pinto F, Coletta S, et al. Tumor microenvironment immune types in gastric cancer are associated with mismatch repair however, not HER2 status. Oncol Lett 2019;18:1775–1785.
204. Wanvimonsuk S, Thitiwanichpiwong P, Keelawat S, et al. Distribution of the Epstein-Barr virus in the normal stomach and gastric lesions in Thai population. J Med Virol 2019;91:444–449.
205. Wei M, Wang X, Luo B. Association between lncRNA H19 polymorphisms and susceptibility to gastric carcinoma and EBV-associated gastric carcinoma in han population in qingdao. Chinese J Cancer Biother 2019;26:676–682.
206. Yanagi A, Nishikawa J, Shimokuri K, et al. Clinicopathologic Characteristics of Epstein-Barr Virus-Associated Gastric Cancer Over the Past Decade in Japan. Microorganisms 2019;7:305.
207. Yang Y, Liu YQ, Wang XH, et al. [Clinicopathological and molecular characteristics of Epstein-Barr virus associated gastric cancer: a single center large sample case investigation]. Beijing Da Xue Xue Bao Yi Xue Ban 2019;51:451–458.
208. Yoon J-Y, Sy K, Brezden-Masley C, et al. Histo- and immunohistochemistry-based estimation of the TCGA and ACRG molecular subtypes for gastric carcinoma and their prognostic significance: A single-institution study. PLoS One 2019;14:e0224812.
209. Zhou H, Tan S, Li H, et al. Expression and significance of EBV, ARID1A and PIK3CA in gastric carcinoma. Mol Med Rep 2019;19:2125–2136.
210. 马艺文, 谭继超, 张宇, et al. 新抑癌基因INPP4B在EB病毒相关胃癌中的表达及其临床意义. *中国医科大学学报* 2019;48:587–590+600.
211. Aversa JG, Song M, Hu N, et al. Low Epstein–Barr Virus Prevalence in Cardia Gastric Cancer Among a High-Incidence Chinese Population. Dig Dis Sci 2021;66:1220–1226.
212. Choi E, Chang MS, Byeon SJ, et al. Prognostic perspectives of PD-L1 combined with tumor-infiltrating lymphocytes, Epstein-Barr virus, and microsatellite instability in gastric carcinomas. Diagn Pathol 2020;15:69.

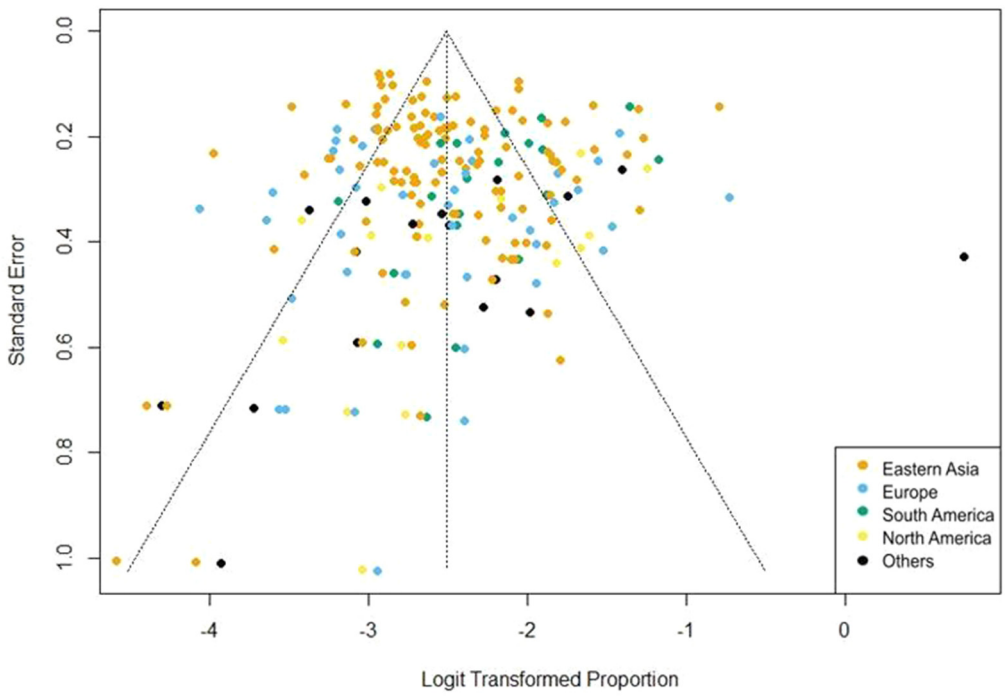
213. Corallo S, Fuca G, Morano F, et al. Clinical Behavior and Treatment Response of Epstein-Barr Virus-Positive Metastatic Gastric Cancer: Implications for the Development of Future Trials. Oncologist 2020;25:780–786.
214. Dislich B, Blaser N, Berger MD, et al. Preservation of Epstein–Barr virus status and mismatch repair protein status along the metastatic course of gastric cancer. Histopathology 2020;76:740–747.
215. Fang WL, Chen MH, Huang KH, et al. The clinicopathological features and genetic alterations in epstein–barr virus-associated gastric cancer patients after curative surgery. Cancers (Basel) 2020;12:1517.
216. Kwon M, Hong JY, Kim ST, et al. Association of serine/threonine kinase 11 mutations and response to programmed cell death 1 inhibitors in metastatic gastric cancer. Pathol Res Pract 2020;216:152947.
217. Lu S, Wang LJ, Lombardo K, et al. Expression of Indoleamine 2, 3-dioxygenase 1 (IDO1) and Tryptophanyl-tRNA Synthetase (WARS) in Gastric Cancer Molecular Subtypes. Appl Immunohistochem Mol Morphol 2020;28:360–368.
218. Martinson HA, Mallari D, Richter C, et al. Molecular classification of gastric cancer among alaska native people. Cancers (Basel) 2020;12:198.
219. Pinto MP, Córdova-Delgado M, Retamal IN, et al. A molecular stratification of chilean gastric cancer patients with potential clinical applicability. Cancers (Basel) 2020;12:1863.
220. Qiu MZ, He CY, Lu SX, et al. Prospective observation: Clinical utility of plasma Epstein-Barr virus DNA load in EBV-associated gastric carcinoma patients. *In* J Cancer 2020; 146:272–280.
221. Tsai JH, Jeng YM, Chen KH, et al. An Integrative Morphomolecular Classification System of Gastric Carcinoma with Distinct Clinical Outcomes. Am J Surg Pathol 2020;44:1017–1030.
222. 杨斌 郭江红, 白玮 孙瑞. 高宁. EB病毒相关性胃癌临床病理特征及磷脂酰肌醇3激酶α基因突变分析. *中国药物与临床* 2020; 20:1921–1923.
223. Challoner BR, von Loga K, Woolston A, et al. Computational Image Analysis of T-Cell Infiltrates in Resectable Gastric Cancer: Association with Survival and Molecular Subtypes. J Natl Cancer Inst 2021;113:88–98.
224. Daun T, Nienhold R, Paasinen-Sohns A, et al. Combined Simplified Molecular Classification of Gastric Adenocarcinoma, Enhanced by Lymph Node Status: An Integrative Approach. Cancers (Basel) 2021;13:3722.
225. Jia XX, Guo T, Li ZM, et al. Clinicopathological and Immunomicroenvironment Characteristics of Epstein-Barr Virus-Associated Gastric Cancer in a Chinese Population. Front Oncol 2021;10:3722.
226. Liu Y, Zang FL, Qiu ZQ, et al. [Association of status of mismatch repair protein expression and EB virus infection with clinicopathological parameters in 886 gastric adenocarcinoma patients]. Zhonghua Wei Chang Wai Ke Za Zhi 2021; 24:440–448.
227. Tanabe H, Mizukami Y, Takei H, et al. Clinicopathological characteristics of Epstein-Barr virus and microsatellite instability subtypes of early gastric neoplasms classified by the Japanese and the World Health Organization criteria. J Pathol Clin Res 2021;7:397–409.
228. Weadick C, McLaughlin RA, Ramsey M, et al. The incidence of Epstein-Barr Virus-associated gastric cancer in an Irish population. J Clin Oncol 2021;39:236.
229. Yang N, Wu Y, Jin M, et al. Microsatellite instability and epstein-barr virus combined with pd-l1 could serve as a potential strategy for predicting the prognosis and efficacy of postoperative chemotherapy in gastric cancer. PeerJ 2021;9: e11481.



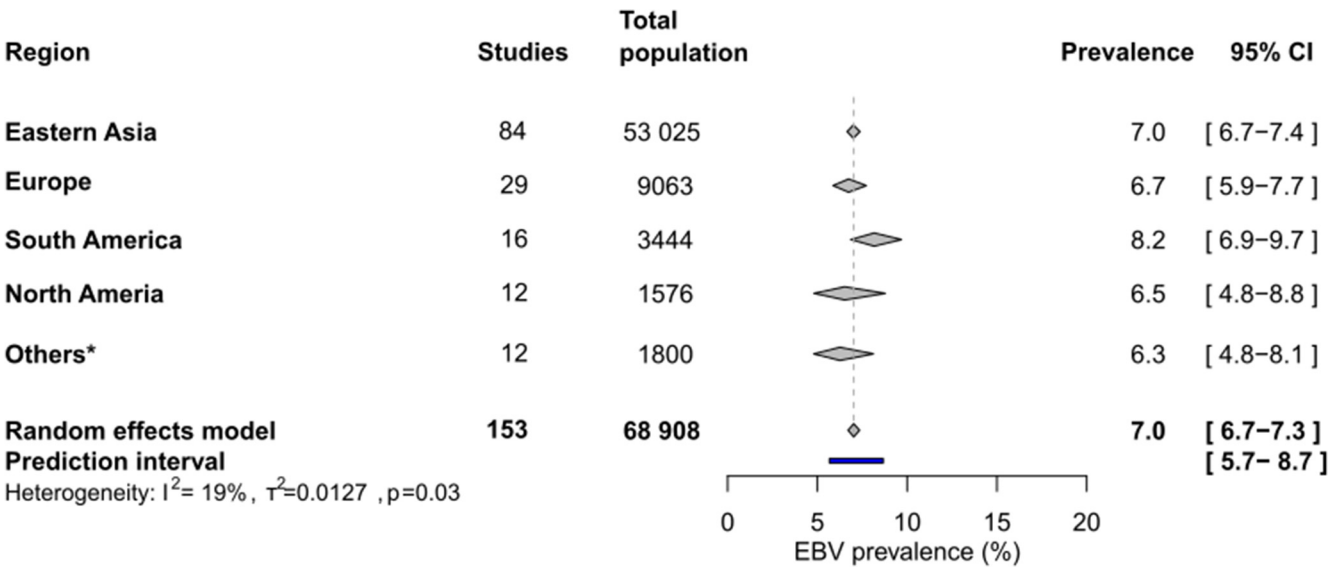
Supplementary Figure 1. Flowchart showing the successive steps of literature search and selection process. EBER, Epstein-Barr virus–encoded RNA; EBV, Epstein-Barr virus; LELC, lymphoepithelioma-like gastric carcinoma.



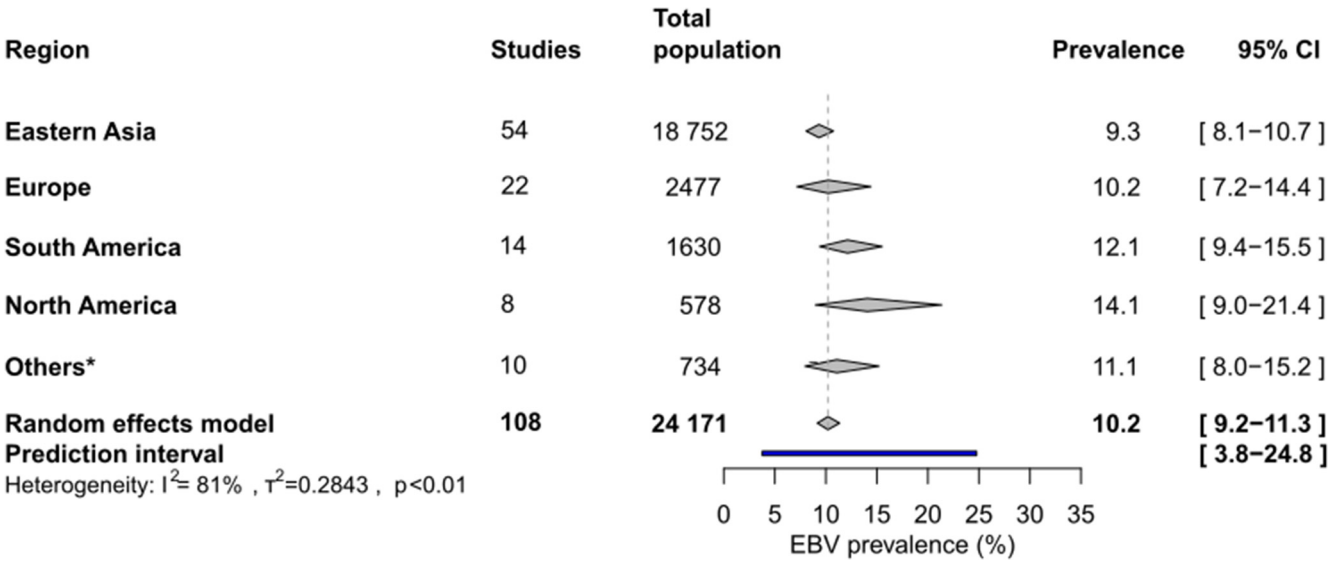
Supplementary Figure 2. Global Epstein-Barr virus (EBV) pooled prevalence in conventional gastric adenocarcinoma. CI, confidence interval. *Includes Algeria (n = 1); India (1); Iran (1); Kazakhstan (1); Malaysia (1); Pakistan (1); Papua New Guinea (1); Singapore (2); Thailand (1); Tunisia (4); Turkey (2); and Uzbekistan (1). I^2=percentage of variation across studies due to heterogeneity rather than chance.



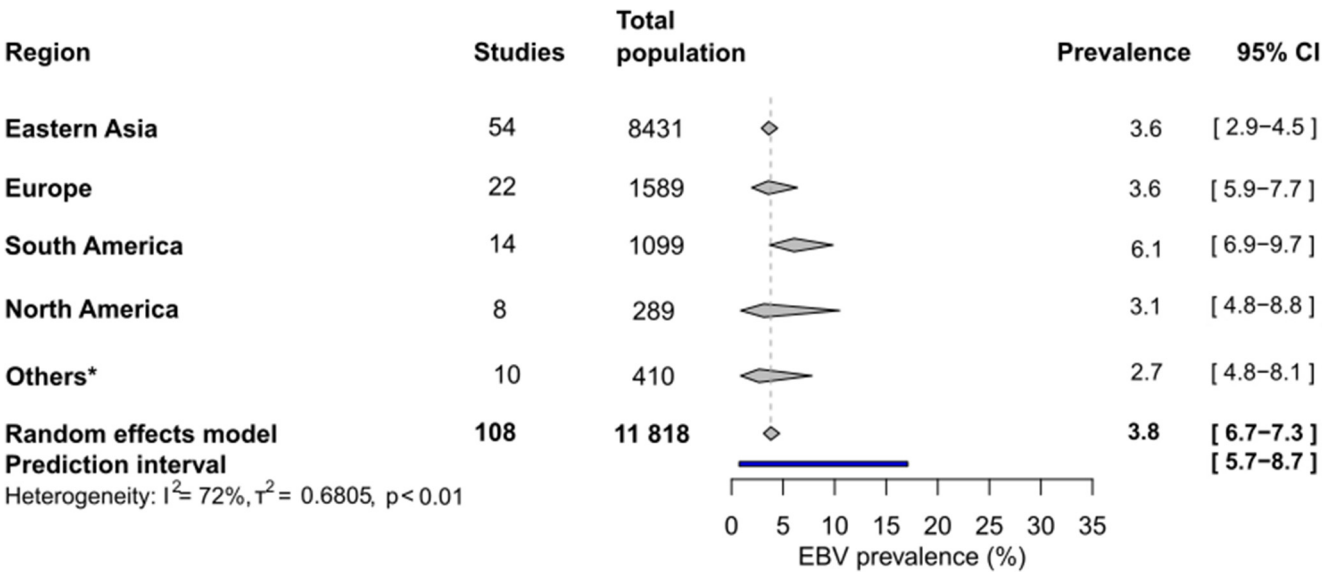
Supplementary Figure 3. Funnel plot of Egger's test result.



Supplementary Figure 4. Global Epstein-Barr virus (EBV) pooled prevalence in conventional gastric adenocarcinoma, excluding outliers. CI, confidence interval. *Includes India (n = 1); Kazakhstan (1); Malaysia (1); Pakistan (1); Singapore (2); Thailand (1);Tunisia (2); Turkey (2); and Uzbekistan (1).



Supplementary Figure 5. Global Epstein-Barr virus (EBV) pooled prevalence in conventional gastric adenocarcinoma among men. CI, confidence interval. *Includes Algeria (n = 1); India (1); Iran (1); Kazakhstan (1); Malaysia (1); Singapore (1); Tunisia (2); Turkey (1); and Uzbekistan (1).



Supplementary Figure 6. Global Epstein-Barr virus (EBV) pooled prevalence in conventional gastric adenocarcinoma among women. CI, confidence interval. *Includes Algeria (n = 1); India (1); Iran (1); Kazakhstan (1); Malaysia (1); Singapore (1); Tunisia (2); Turkey (1); and Uzbekistan (1).

Supplementary Table 1. Characteristics of Included Studies

First Author (Published Year)	Country	Region	Total Patients	EBV+	Male Patients	Male EBV+	Female Patients	Female EBV+
Shibata, D. (1992)[1]	United States	North America	138	22	99	21	39	1
Rowlads, D. (1993)[2]	United Kingdom	Europe	120	5	NA	NA	NA	NA
Rowlads, D. (1993)[2]	Japan	Eastern Asia	54	4	NA	NA	NA	NA
Tokunaga, M. (1993)[3]	Japan	Eastern Asia	1795	120	1148	100	647	20
Manivel, J. (1994)[4]	Mexico	South America	30	2	NA	NA	NA	NA
Manivel, J. (1994)[4]	United States	North America	48	2	NA	NA	NA	NA
Mori, M. (1994)[5]	Japan	Eastern Asia	31	2	NA	NA	NA	NA
Ott, G. (1994)[7]	Germany	Europe	39	7	NA	NA	NA	NA
Wang, M. (1994)[9]	China	Eastern Asia	61	1	NA	NA	NA	NA
Wang, M. (1994)[9]	China	Eastern Asia	49	3	NA	NA	NA	NA
Yamamoto, N. (1994)[10]	Japan	Eastern Asia	1806	99	NA	NA	NA	NA
Yuen, S. (1994)[11]	China	Eastern Asia	74	7	52	7	22	0
Harn, H. (1995)[12]	China	Eastern Asia	55	6	28	4	27	2
Moritani, S. (1996)[14]	Japan	Eastern Asia	132	15	87	9	45	6
Saiki, Y. (1996)[16]	Japan	Eastern Asia	114	9	NA	NA	NA	NA
Selves, J. (1996)[17]	France	Europe	59	5	43	4	16	1
Shin, W. (1996)[18]	Republic of Korea	Eastern Asia	89	12	59	8	30	4
Clark, G. (1997)[20]	Singapore	Others	137	6	81	5	56	1
Galetsky, S. (1997)[21]	Russian Federation	Europe	206	18	101	15	83	2
Ko, H. (1997)[22]	Republic of Korea	Eastern Asia	427	37	NA	NA	NA	NA
Ojima, H. (1997)[23]	Japan	Eastern Asia	347	23	NA	NA	NA	NA
Qiu, K. (1997)[24]	China	Eastern Asia	115	9	NA	NA	NA	NA
Qiu, K. (1997)[24]	Japan	Eastern Asia	210	13	NA	NA	NA	NA
Yanai, H. (1997)[25]	Japan	Eastern Asia	117	12	83	9	34	3
Baas, I. (1998)[26]	Netherlands	Europe	24	2	NA	NA	NA	NA
Wan, R. (1998)[27]	China	Eastern Asia	58	6	NA	NA	NA	NA
Ioachim, H. (1999)[28]	United States	North America	22	1	NA	NA	NA	NA
Kaizaki,I. (1999)[29]	Japan	Eastern Asia	189	17	131	14	58	3
Kume, T. (1999)[30,31]	Japan	Eastern Asia	344	40	NA	NA	NA	NA
Takano, Y. (1999)[32]	Japan	Eastern Asia	513	33	367	28	146	5
Tanaka, M. (1999)[33]	Japan	Eastern Asia	252	15	NA	NA	NA	NA
Wan, R. (1999)[35]	China	Eastern Asia	58	6	NA	NA	NA	NA
Chapel, F. (2000)[38]	France	Europe	56	7	7	7	49	24
Gurtsevich, V. (2000)[39]	Uzbekistan	Others	123	9	74	8	49	1
Gurtsevich, V. (2000)[39]	Russian Federation	Europe	80	11	61	8	19	3
Gurtsevich, V. (2000)[39]	Russian Federation	Europe	114	16	86	14	58	2
Gurtsevich, V. (2000)[39]	Russian Federation	Europe	83	13	45	10	38	3
Min, Y. (2000)[147]	China	Eastern Asia	100	1	NA	NA	NA	NA
Wu, M. (2000)[41]	China	Eastern Asia	139	19	90	13	50	6

Supplementary Table 1. Continued

First Author (Published Year)	Country	Region	Total Patients	EBV+	Male Patients	Male EBV+	Female Patients	Female EBV+
zur Hausen, A. (2000)[42]	Netherlands	Europe	132	10	NA	NA	NA	NA
Ishii, H. (2001)[45]	Japan	Eastern Asia	114	23	92	19	27	4
Koriyama, C. (2001)[46]	Japan	Eastern Asia	2966	160	NA	NA	NA	NA
Koriyama, C. (2001)[47]	Brazil	South America	300	24	201	18	99	6
Lo, Y. (2001)[48]	China	Eastern Asia	51	5	NA	NA	NA	NA
Luqmani, Y. (2001)[49]	United Kingdom	Europe	20	1	NA	NA	NA	NA
Yin, Z. (2001)[50]	China	Eastern Asia	63	7	41	5	23	2
Burgess, D. (2002)[51]	United Kingdom	Europe	534	9	NA	NA	NA	NA
Hao, Z. (2002)[53]	China	Eastern Asia	198	18	NA	NA	NA	NA
Hao, Z. (2002)[53]	China	Eastern Asia	180	11	NA	NA	NA	NA
Hoshikawa, Y. (2002)[54]	Japan	Eastern Asia	21	3	NA	NA	NA	NA
Kang, G. (2002)[55]	Republic of Korea	Eastern Asia	233	21	58	17	19	4
Kattoor, J. (2002)[56]	India	Others	215	10	161	10	54	0
Vo, Q. (2002)[57]	United States	North America	107	11	78	11	30	0
Carrascal, E. (2003)[58]	Colombia	South America	178	23	108	19	69	4
Czopek, J. (2003)[59]	Poland	Europe	40	5	30	4	10	1
Grogg, K. (2003)[52]	United States	North America	110	7	72	7	38	0
Karim, N. (2003)[60]	Malaysia	Others	50	5	32	4	18	1
Kijima, Y. (2003)[61]	Japan	Eastern Asia	417	28	298	23	122	5
Oda, K. (2003)[62]	Japan	Eastern Asia	97	5	57	5	45	0
Kerroucha, R. (2004)[64]	France	Europe	85	5	54	4	31	1
Koriyama, C. (2004)[65]	Japan	Eastern Asia	1961	100	1212	83	706	17
Lopes, L. (2004)[66]	Brazil	South America	53	6	NA	NA	NA	NA
Morewaya, J. (2004)[67]	Papua New Guinea	Others	150	2	NA	NA	NA	NA
van Beek, J. (2004)[68]	Netherlands	Europe	566	41	324	38	242	3
Wang, Y. (2004)[69]	China	Eastern Asia	185	13	134	13	51	0
Yan, L. (2004)[70]	China	Eastern Asia	185	13	NA	NA	NA	NA
Alipov, G. (2005)[71]	Kazakhstan	Others	139	14	86	12	53	2
Anwar, M. (2005)[72]	Pakistan	Others	52	1	NA	NA	NA	NA
Corvalan, A. (2005)[73]	Chile	South America	93	22	31	6	62	16
Herrera-Goepfert, R. (2005)[74]	Mexico	South America	330	24	173	13	157	11
Kim, M. (2005)[76]	Republic of Korea	Eastern Asia	564	30	NA	NA	NA	NA
Kim, M. (2005)[76]	Republic of Korea	Eastern Asia	165	22	NA	NA	NA	NA
Sakuma, K. (2005)[77]	Japan	Eastern Asia	140	24	98	20	42	4
Yoshiwara, E. (2005)[78]	Peru	South America	254	10	128	5	120	5
Begnami, M. (2006)[79]	Brazil	South America	208	25	NA	NA	NA	NA
Campos, F. (2006)[80]	Colombia	South America	326	42	230	34	138	8
Kim, H. (2006)[81]	Republic of Korea	Eastern Asia	53	7	NA	NA	NA	NA
Qian, J. (2006)[82]	China	Eastern Asia	155	10	NA	NA	NA	NA
von Rahden, B. (2006)[83]	Germany	Europe	36	3	NA	NA	NA	NA

Supplementary Table 1. Continued

First Author (Published Year)	Country	Region	Total Patients	EBV+	Male Patients	Male EBV+	Female Patients	Female EBV+
von Rahden, B. (2006)[83]	Germany	Europe	46	2	NA	NA	NA	NA
Zazula, M. (2006)[84]	Poland	Europe	84	5	NA	NA	NA	NA
Abdirad, A. (2007)[85]	Iran	Others	273	9	88	8	76	1
Enomoto, S. (2007)[86]	Japan	Eastern Asia	66	9	NA	NA	NA	NA
Jung, I. (2007)[87]	Republic of Korea	Eastern Asia	111	7	76	6	35	1
Li, S. (2007)[88]	China	Eastern Asia	217	23	165	17	52	6
Moncef, M. (2007)[89]	Tunisia	Others	68	3	NA	NA	NA	NA
Kang, J. (2008)[90]	Republic of Korea	Eastern Asia	621	31	NA	NA	NA	NA
Limaiem, F. (2008)[91]	Tunisia	Others	25	17	NA	NA	NA	NA
Nakamura, S. (2008)[92]	Japan	Eastern Asia	66	3	NA	NA	NA	NA
Liu, H. (2009)[99]	China	Eastern Asia	156	21	NA	NA	NA	NA
Park, E. (2009)[94]	Republic of Korea	Eastern Asia	457	50	NA	NA	NA	NA
Ramirez, V. (2009)[95]	Costa Rica	South America	165	14	92	12	63	1
Ryan, J. (2009)[96]	United States	North America	48	8	NA	NA	NA	NA
Ryan, J. (2009)[96]	Honduras	South America	38	3	NA	NA	NA	NA
Szkaradkiewicz, A. (2009)[97]	Poland	Europe	48	9	NA	NA	NA	NA
Truong, C. (2009)[98]	United States	North America	235	12	147	11	88	1
Carrasco, G. (2010)[100]	Chile	South America	91	5	NA	NA	NA	NA
Chen, J. (2010)[101]	China	Eastern Asia	676	45	437	37	239	8
Kim, R. (2010)[102]	Republic of Korea	Eastern Asia	247	18	178	17	69	1
Park, S. (2010)[103]	Republic of Korea	Eastern Asia	191	16	NA	NA	NA	NA
Song, H. (2010)[104]	Republic of Korea	Eastern Asia	1080	123	NA	NA	NA	NA
Wang, L. (2010)[105]	Singapore	Others	130	8	NA	NA	NA	NA
Wang, Y. (2010)[106]	China	Eastern Asia	1678	50	NA	NA	NA	NA
BenAyed-Guerfali, D. (2011)[107]	Tunisia	Others	81	12	48	6	33	6
De Lima, M. (2011)[109]	Brazil	South America	60	3	36	3	14	0
De Lima, M. (2011)[109]	Brazil	South America	100	8	67	7	33	1
Gu, X. (2011)[116]	China	Eastern Asia	96	15	67	12	29	3
Guo, Y. (2011)[115]	China	Eastern Asia	125	8	96	8	29	0
Haas, M. (2011)[110]	Germany	Europe	135	4	NA	NA	NA	NA
He, Y. (2011)[114]	China	Eastern Asia	486	18	357	16	129	2
Lee, J. (2011)[111]	Republic of Korea	Eastern Asia	30	4	NA	NA	NA	NA
Matsusaka, K. (2011)[112]	Japan	Eastern Asia	51	11	38	11	13	0
Peng, J. (2011)[113]	China	Eastern Asia	136	19	98	15	38	4
Abe, H. (2012)[117]	Japan	Eastern Asia	893	67	593	52	264	15
Chiaravalli, A. (2012)[118]	Italy	Europe	66	8	NA	NA	NA	NA
Genitsch, V. (2012)[119]	Switzerland	Europe	610	30	NA	NA	NA	NA
He, Y (2012)[120]	China	Eastern Asia	118	17	NA	NA	NA	NA
Lima, M. (2012)[121]	Brazil	South America	160	11	79	9	39	1
Park, H. (2012)[122]	Republic of Korea	Eastern Asia	141	31	115	31	26	0

Supplementary Table 1. Continued

First Author (Published Year)	Country	Region	Total Patients	EBV+	Male Patients	Male EBV+	Female Patients	Female EBV+
Sukawa, Y. (2012)[123]	Japan	Eastern Asia	222	18	152	14	70	4
Mitsuhashi, K. (2013)[124]	Japan	Eastern Asia	373	24	NA	NA	NA	NA
Warneke, V. (2013)[126]	Germany	Europe	376	15	NA	NA	NA	NA
Yang, Y. (2013)[129]	Republic of Korea	Eastern Asia	100	9	66	7	34	2
Yu, C. (2013)[127]	China	Eastern Asia	653	40	512	37	141	3
Zhang, Y. (2013)[128]	China	Eastern Asia	476	18	349	16	127	2
Ksiaa, E. (2014)[131]	Tunisia	Others	43	4	23	4	16	0
Uozaki, H. (2014)[132]	Japan	Eastern Asia	435	34	NA	NA	NA	NA
Wiegand, K. (2014)[133]	Canada	North America	253	8	NA	NA	NA	NA
Yuan, H. (2014)[134]	China	Eastern Asia	120	12	92	11	28	1
Choi, E. (2015)[135]	Republic of Korea	Eastern Asia	343	32	231	28	112	4
Genitsch, V. (2015)[136]	Germany	Europe	274	12	170	8	104	4
Genitsch, V. (2015)[136]	Germany	Europe	73	2	51	1	22	1
Ozmen, I. (2015)[137]	Turkey	Others	85	2	NA	NA	NA	NA
Aslane, M. (2016)[138]	Algeria	Others	91	18	64	15	27	3
Dai, C. (2016)[139]	China	Eastern Asia	97	10	NA	NA	NA	NA
Fu, H. (2016)[140]	China	Eastern Asia	138	6	NA	NA	NA	NA
Gonzalez, R. (2016)[141]	United States	North America	104	7	81	5	23	2
Han, N. (2016)[142]	Republic of Korea	Eastern Asia	417	30	NA	NA	NA	NA
Kim, H. (2016)[144]	Republic of Korea	Eastern Asia	438	14	300	14	138	0
Ma, C. (2016)[146]	United States	North America	44	7	25	6	19	1
Park, C. (2016)[148]	Republic of Korea	Eastern Asia	993	61	NA	NA	NA	NA
Setia, N. (2016)[149]	United States	North America	146	7	NA	NA	NA	NA
Song, Y. (2016)[150]	Republic of Korea	Eastern Asia	434	33	NA	NA	NA	NA
Zhang, Z. (2016)[151]	China	Eastern Asia	600	30	384	25	216	5
Ahn, S. (2017)[152]	Republic of Korea	Eastern Asia	349	26	225	21	124	5
Böger, C. (2017)[153]	Germany	Europe	484	22	302	20	182	2
Chen, B. (2017)[154]	China	Eastern Asia	585	41	NA	NA	NA	NA
Irkkan, C. (2017)[155]	Turkey	Others	105	8	77	8	28	0
Jenkins, T. (2017)[156]	United States	North America	52	3	NA	NA	NA	NA
Kawazoe, A. (2017)[157]	Japan	Eastern Asia	487	25	NA	NA	NA	NA
Kim, J. (2017)[158]	Republic of Korea	Eastern Asia	207	13	NA	NA	NA	NA
Kwon, M. (2017)[159]	Republic of Korea	Eastern Asia	394	26	NA	NA	NA	NA
Ma, J. (2017)[161]	China	Eastern Asia	571	32	NA	NA	NA	NA
Na, S. (2017)[162]	Republic of Korea	Eastern Asia	205	15	146	13	59	2
Narita, Y. (2017)[163]	Japan	Eastern Asia	226	13	NA	NA	NA	NA
Nogueira, C. (2017)[164]	Portugal	Europe	82	9	45	8	37	1
Ribeiro, J. (2017)[166]	Portugal	Europe	179	15	108	12	71	3
Thompson, E. (2017)[167]	United States	North America	34	2	NA	NA	NA	NA
Tsai, C. (2017)[168]	China	Eastern Asia	1039	52	619	42	420	10

Supplementary Table 1. Continued

First Author (Published Year)	Country	Region	Total Patients	EBV+	Male Patients	Male EBV+	Female Patients	Female EBV+
Wu, Y. (2017)[169]	China	Eastern Asia	340	17	NA	NA	NA	NA
Zhou, Z. (2017)[170]	China	Eastern Asia	225	6	NA	NA	NA	NA
Baek, D. (2018)[172]	Republic of Korea	Eastern Asia	276	59	201	50	75	9
Birkman, E. (2018)[173]	Finland	Europe	244	17	NA	NA	NA	NA
De Rosa, S. (2018)[174]	Italy	Europe	169	33	103	24	66	9
de Souza, C. (2018)[175]	Brazil	South America	302	62	195	43	107	19
Gullo, I. (2018)[176]	Portugal	Europe	46	15	NA	NA	NA	NA
Hewitt, L. (2018)[177]	United Kingdom	Europe	768	30	NA	NA	NA	NA
Hewitt, L. (2018)[177]	Japan	Eastern Asia	410	26	NA	NA	NA	NA
Li, H. (2018)[183]	China	Eastern Asia	86	10	62	9	24	1
Martinez-Ciarpaglini, C. (2018)[197]	Spain	Europe	209	13	137	10	72	3
Murai, K. (2018)[179]	Japan	Eastern Asia	172	8	NA	NA	NA	NA
Nakayama, I. (2018)[199]	Japan	Eastern Asia	146	2	NA	NA	NA	NA
Pereira, M. (2018)[180]	Brazil	South America	286	30	167	23	119	7
Son, B. (2018)[181]	Republic of Korea	Eastern Asia	285	38	NA	NA	NA	NA
Yun, S. (2018)[182]	Republic of Korea	Eastern Asia	502	50	NA	NA	NA	NA
Zheng, K. (2018)[184]	China	Eastern Asia	360	61	NA	NA	NA	NA
Beltrán Gárate, B. (2019)[185]	Peru	South America	111	9	63	6	48	3
Bösch, F. (2019)[186]	Germany	Europe	189	11	119	7	70	4
Cho, J. (2019)[187]	Republic of Korea	Eastern Asia	580	25	NA	NA	NA	NA
Coati, I. (2019)[188]	Italy	Europe	523	20	NA	NA	NA	NA
Cordova-Delgado, M. (2019)[189]	Chile	South America	90	12	NA	NA	NA	NA
De Castria, T. (2019)[190]	Brazil	South America	178	18	NA	NA	NA	NA
Gasenko,E. (2019)[191]	Latvia	Europe	302	26	184	22	118	4
Huang, S. (2019)[192]	China	Eastern Asia	1248	65	778	54	470	11
Kawazoe, A. (2019)[193]	Japan	Eastern Asia	225	14	136	11	89	3
Kim, T. (2019)[194]	United States	North America	43	6	24	5	19	1
Kim, Y. (2019)[195]	Republic of Korea	Eastern Asia	273	15	NA	NA	NA	NA
Kohlruss, M. (2019)[196]	Germany	Europe	617	24	NA	NA	NA	NA
Ma, Y. (2019)[210]	China	Eastern Asia	272	40	NA	NA	NA	NA
Mishima, S. (2019)[198]	Japan	Eastern Asia	68	4	NA	NA	NA	NA
Osumi, H. (2019)[200]	Japan	Eastern Asia	898	71	NA	NA	NA	NA
Osumi, H. (2019)[201]	Japan	Eastern Asia	847	96	NA	NA	NA	NA
Sun, Y. (2019)[202]	China	Eastern Asia	165	2	NA	NA	NA	NA
Valentini, A. (2019)[203]	Italy	Europe	70	2	NA	NA	NA	NA
Wanvimonsuk, S. (2019)[204]	Thailand	Others	33	4	NA	NA	NA	NA
Wei, M. (2019)[205]	China	Eastern Asia	225	70	NA	NA	NA	NA
Yanagi, A. (2019)[206]	Japan	Eastern Asia	1067	69	735	61	332	8
Yang, Y. (2019)[207]	China	Eastern Asia	3241	163	2363	137	878	26
Yoon, J. (2019)[208]	Canada	North America	107	3	NA	NA	NA	NA

Supplementary Table 1. Continued

First Author (Published Year)	Country	Region	Total Patients	EBV+	Male Patients	Male EBV+	Female Patients	Female EBV+
Zhou, H. (2019)[209]	China	Eastern Asia	300	28	NA	NA	NA	NA
Aversa, J. (2020)[211]	China	Eastern Asia	1035	19	828	19	207	3
Choi, E. (2020)[212]	Republic of Korea	Eastern Asia	514	32	347	24	167	8
Corallo, S. (2020)[213]	Italy	Europe	175	7	109	6	66	1
Dislich, B. (2020)[214]	Switzerland	Europe	415	11	257	10	158	1
Fang, W. (2020)[215]	China	Eastern Asia	430	32	306	27	124	5
Kwon, M. (2020)[216]	Republic of Korea	Eastern Asia	59	7	NA	NA	NA	NA
Lu, S. (2020)[217]	Republic of Korea	Eastern Asia	421	32	306	30	112	2
Martinson, H. (2020)[218]	United States	North America	85	19	52	13	33	6
Pinto, M. (2020)[219]	Chile	South America	91	12	60	11	31	1
Qiu, M. (2020)[220]	China	Eastern Asia	2760	140	1865	125	894	15
Tsai, J. (2020)[221]	China	Eastern Asia	329	17	196	14	133	3
Yang, B. (2020)[222]	China	Eastern Asia	356	16	272	13	84	3
Challoner, B. (2021)[223]	United Kingdom	Europe	314	8	NA	NA	NA	NA
Challoner, B. (2021)[223]	United Kingdom	Europe	153	12	NA	NA	NA	NA
Daun, T. (2021)[224]	Switzerland	Europe	115	20	74	2	41	0
Jia, X. (2021)[225]	China	Eastern Asia	1328	55	982	45	346	10
Liu, Y. (2021)[226]	Republic of Korea	Eastern Asia	871	43	NA	NA	NA	NA
Tanabe, H. (2021)[227]	Japan	Eastern Asia	54	6	44	5	10	1
Weadick, C. (2021)[228]	Ireland	Europe	103	8	67	8	36	0
Yang, N. (2021)[229]	China	Eastern Asia	236	13	NA	NA	NA	NA

EBV, Epstein-Barr Virus; NA, not available.

Supplementary Table 2. Epstein-Barr Virus Prevalence of Conventional Gastric Adenocarcinoma for HDI, ASIR, Quality Score, and Median Study Year

HDI (2019)					ASIR (2020)					Quality Score					Median Study Year				
Categories	Number of Studies	Prevalence (95% CI)	I^2 (%)	*P*	Categories	Number of Studies	Prevalence (95% CI)	I^2 (%)	*P*	Categories	Number of Studies	Prevalence (95% CI)	I^2 (%)	*P*	Categories	Number of Studies	Prevalence (95% CI)	I^2 (%)	*P*
<0.79	75	7.2 (6.6–8.0)	79		<5.7	41	7.1 (5.4–9.1)	86	0.9	<5	78	7.6 (6.5–9.0)	85		<1994	53	7.7 (6.8–8.8)	67	.8
<0.90	28	9.3 (7.3–11.8)	78	0.1	5.7–<11	39	7.6 (6.1–9.3)	82		6–8	80	7.6 (6.7–8.6)	83	0.6	1995–2007	98	7.6 (6.7–8.5)	83	
0.90+	117	7.2 (6.1–8.4)	89		11.1 +	140	7.5 (6.9–8.2)	86		9+	62	7.1 (6.2–8.0)	84		2008+	69	7.3 (6.2–8.5)	90	

ASIR, age-standardized incidence rate; CI, confidence interval; HDI, Human Development Index.