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REVIEW

The Presence of Human Papillomavirus and Epstein-Barr Virus Infection in Gastric Cancer: A Systematic Study

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ABSTRACT

Background and Aim: Gastric cancer (GC) is one of the most common infection-related malignancies worldwide. Human Papillomavirus (HPV) and Epstein-Barr virus (EBV) are among the most important viruses affecting many people worldwide. The potential role of these viruses in gastric tissue may explain the possibility of GC, as seen in *Helicobacter pylori* (*H. pylori*). This study aimed to systematically investigate the presence of HPV and EBV in GC. **Methods:** According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, this study is a systematic review based on reported cases. The keywords HPV, EBV and GC, were searched in PubMed, Web of Science, Scopus, EMBASE and Google scholar databases from 2012 to 2022. Articles were selected and evaluated by five researchers independently. The odds ratio of HPV and EBV viruses in GC was estimated. Data analysis was performed by SPSS (Version 20) software. **Results:** Sixty studies with 14949 patients were included in the study after obtaining the inclusion criteria. The mean prevalence of HPV and EBV viruses in GC was 10.58% and 8.58%, respectively. The highest prevalence of HPV and EBV were 37.74% and 44.44% in Turkey and Iraq, respectively. The highest odds of HPV and EBV in GC were observed in Asia (17.54%) and Africa (19.02%), respectively. **Conclusion:** The findings indicate the presence of HPV and EBV in GC in the study areas. However, the present study's results are insufficient for a more accurate conclusion. Therefore, further studies are necessary for the conclusion in this regard.

KEYWORDS

Human Papillomavirus; Epstein-Barr virus; gastric cancer; systematic study

1 Background

Cancer is the leading cause of death in most developing and developed countries. Gastric cancer (GC) is the second leading cause of death and the most common malignant tumor globally [1]. GC is one of the multifactorial diseases whose main reason is the presence of infectious, genetic and environmental factors in individuals [2]. The prevalence of GC varies from the resulting mortality rate because the second phenomenon is more due to the late diagnosis of GC in the advanced phase of the disease [3]. Viruses

cause many cancers, with about 15%–20% of human cancers associated with viruses [4]. Human Papillomavirus (HPV) is a DNA virus found in all human populations, and sometimes the infection it causes can lead to cancer [5,6]. The virus is divided into high-risk and low-risk types in terms of its potential to cause cancer [7]. HPV16 and HPV18 are among the most common subtypes involved in carcinogenesis [8]. Various studies have indicated the oncogenic properties of HPV, suggesting a role for the virus in the pathogenesis of cancer [9]. Integration of HPV DNA in the host genome is the main cause of carcinogenesis that causes the regulation of cellular oncogenes (mainly E6 and E7). The virus disrupts HPV E2 expression and causes overexpression of E6 and E7 oncoproteins [10]. Epstein-Barr virus (EBV) is a DNA virus in the herpes virus family. EBV is the first human virus responsible for approximately 1.8% of all human cancers, including Hodgkin's lymphoma, Burkitt's lymphoma, NK/T cell lymphoma, and Nasopharyngeal [11]. The first association between EBV and gastric epithelial lymphatic carcinoma was identified in 1990, indicating the first association between GC and EBV [12]. Subsequent studies have also shown an association between gastric adenocarcinoma and EBV, which may indicate an important role for EBV in pathogenesis [13]. Thus, these findings suggest that 10% of GCs worldwide are associated with EBV [13–15]. Considering that EBV can continuously infect a cell with monoclonal proliferation, EBV infection is effective in the early stages of GC [16–18]. Although various studies have investigated the mechanism of occurrence and development of GC and positive EBV, they found no association between EBV titer and GC risk [19]. Studies show that latent EBV infection and the expression of latent EBV genes as a co-factor increase carcinogenicity, which causes abnormalities in the host genome (such as aberrant DNA methylation), disruption of cell pathways, and immune cell function [20]. Nowadays, extensive research has reported the prevalence of HPV and EBV in GC. Therefore, the present study aimed to gain new insight into the prevalence of HPV and EBV in GC for a better understanding of carcinogenesis.

2 Methods

The present study was conducted by the indicators of preferred reporting items for systematic reviews and meta-analyses (PRISMA) [21].

2.1 Search Strategy

This study examined PubMed, Web of Science, Scopus, EMBASE and Google scholar databases to find studies on HPV, EBV and GC. Databases were searched from 2012 to 2022 with the keywords HPV, EBV and GC.

2.2 Study Selection

All findings from appropriate databases regarding subject matter, quality, and method were entered into the X9 version of EndNote (Thomson Reuters) software, and duplicate inputs were removed. Two researchers (AJS and BJ) performed screening of the obtained data independently. The full text of the remaining articles was then reviewed, and any disagreements were resolved through discussion by the third and fourth researchers (ASH and HBB).

2.3 Inclusion and Exclusion Criteria

The following eligible studies were included: (1) All research studies that report the prevalence of HPV and EBV infection in patients with GC; (2) Articles with free access; (3) Articles published in ten years in English in reputable journals. Studies with the following characteristics were excluded from the study: (1) Studies at intervals other than ten years, (2) Studies published in languages other than English, (3) Articles in the review process, letters to the editor and case report.

2.4 Extracting the Data

The following data were extracted from eligible studies: country, year, authors' names, virus type, the total number of samples, positive samples, percentage of positive samples to total samples and source. The

data obtained in this section were entered into a checklist and, after evaluation by the fifth researcher (BB), were entered in Table 1.

2.5 Statistical Analysis

The prevalence of HPV and EBV in the GC and the odds ratio of positive samples (ORs) with a 95% confidence interval (CIs) were used to assess the relationship between HPV and EBV and the occurrence of GC. In this study, SPSS software (version 16) was used for the statistical analysis of data.

3 Results

A total of 327 articles were searched. After screening, 60 articles were selected (Fig. 1) with the necessary standards to enter the study. A comparison of the prevalence of HPV and EBV viruses in GC is given in Table 1. The prevalence of HPV and EBV in 2249 GC samples was studied in 24 countries, and according to the results, the prevalence varied from 0% to 44.44%. The mean prevalence of HPV and EBV viruses in GC was 10.58% and 8.58%, respectively. Then, after classification based on the research area and calculating the average data of each country, it was found that the highest prevalence of HPV and EBV were 37.74% and 44.44% in Turkey and Iraq, respectively. However, the lowest prevalence of HPV and EBV were 0% and 0.69% in China and Japan, respectively. The total number of HPV and EBV samples in GC was analyzed based on continental segmentation (Table 2 and Fig. 2). By comparing the odds ratios for each continent, it was found that HPV in Asia, Europe, Africa and America was 17.54%, 14.6%, 6.67% and 3.51%, respectively. For the EBV in Africa, America, Europe and Asia, this ratio was 19.02%, 18.08%, 8.71% and 6.07%, respectively.

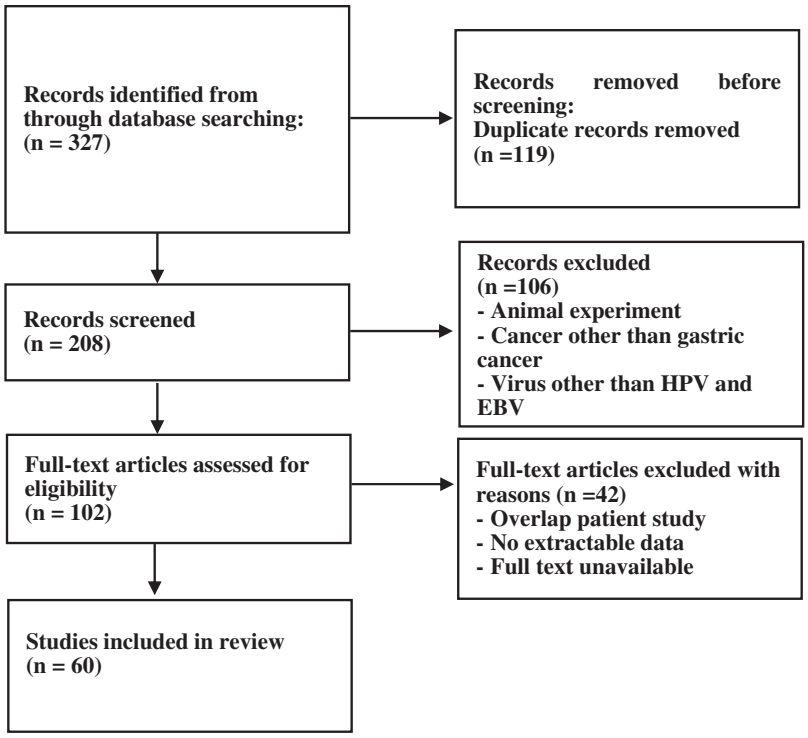

Figure 1: Flow-chart of the literature search and selection

Table 1: Comparison of HPV and EBV infection in GC classified based on the publication calendar period, region, Virus type, and odds ratio

Country	Year	Author	Method	Virus type	Number of case	Positive case	P/N %	Ref.
Brazil	2012	Lima et al.	*In situ* hybridization and PCR	EBV	160	11	6.88	[22]
China	2013	Wang et al.	PCR	HPV	92	20	21.73	[23]
China	2013	Yuan et al.	PCR	HPV	24	0	0	[24]
Brazil	2013	Cândido et al.	PCR	HPV	40	4	10	[25]
Tunisia	2014	Ksiaa et al.	*In situ* hybridization and PCR	EBV	43	4	9.3	[26]
Poland	2015	Snietura et al.	Real-time PCR	HPV	84	0	0	[9]
China	2015	Su et al.	PCR	HPV	15	1	6.67	[27]
Sudan	2016	Elemam et al.	Immunohistochemistry	HPV	30	2	6.67	[28]
Iran	2016	Fakhraei et al.	PCR	HPV	100	5	5	[29]
Algeria	2016	Aslane et al.	*In situ* hybridization and Immunohistochemistry	EBV	97	22	22.68	[30]
China	2016	Zhang et al.	*In situ* hybridization and Immunohistochemistry	EBV	600	30	5	[31]
China	2016	Liu et al.	*In situ* hybridization and PCR	EBV	206	15	7.28	[32]
Germany	2016	Böger et al.	Immunohistochemistry	EBV	451	20	4.43	[33]
China	2016	Dong et al.	Immunohistochemistry	EBV	855	59	6.9	[34]
China	2016	Li et al.	*In situ* hybridization and Immunohistochemistry	EBV	137	30	21.9	[35]
USA	2016	Ma et al.	Immunohistochemistry	EBV	44	7	15.91	[36]
Iran	2016	Leila et al.	PCR	EBV	90	10	11.11	[37]
Taiwan	2016	Tsai et al.	*In situ* hybridization and qPCR	EBV	1039	52	5	[38]
South Korea	2017	Na et al.	*In situ* hybridization	EBV	205	15	7.32	[39]
Germany	2017	Boger et al.	*In situ* hybridization	EBV	484	22	4.55	[40]
South Korea	2017	Kim et al.	Immunohistochemistry	EBV	207	13	6.28	[41]
Japan	2017	Kawazoe et al.	*In situ* hybridization	EBV	487	25	5.13	[42]
Korea	2017	Kwon et al.	*In situ* hybridization and Immunohistochemistry	EBV	394	26	6.6	[43]
Japan	2017	Saito et al.	*In situ* hybridization and Immunohistochemistry	EBV	232	96	41.38	[44]
USA	2017	Thompson et al.	*In situ* hybridization and Immunohistochemistry	EBV	34	2	5.88	[45]

(Continued)

Table 1 (continued)

Country	Year	Author	Method	Virus type	Number of case	Positive case	P/N %	Ref.
Portugal	2017	Nogueira et al.	*In situ* hybridization and PCR	EBV	82	9	10.98	[46]
Portugal	2017	Ribeiro et al.	*In situ* hybridization and Immunohistochemistry	EBV	179	15	8.38	[11]
Brazil	2018	de Souza et al.	PCR	HPV	302	8	2.65	[47]
Brazil	2018	de Souza et al.	PCR	EBV	302	62	20.53	[47]
Korea	2018	Chang et al.	Quantitative image analysis	EBV	241	40	16.6	[48]
Italy	2018	de Rosa et al.	Immunohistochemistry	EBV	169	33	19.53	[49]
USA	2018	Hissong et al.	*In situ* hybridization and Immunohistochemistry	EBV	31	7	22.58	[50]
Brazil	2018	Pereira et al.	*In situ* hybridization and Immunohistochemistry	EBV	287	30	10.45	[51]
Thailand	2019	Wanvimonsuk et al.	*In situ* hybridization and PCR	EBV	33	4	12.12	[52]
Turkey	2019	Bozdayi et al.	PCR	HPV	53	20	37.74	[53]
Spain	2019	Martinez-Ciarpaglini et al.	*In situ* hybridization	EBV	209	13	6.22	[54]
Portugal	2019	Gullo et al.	*In situ* hybridization	EBV	78	19	24.36	[55]
Italy	2019	Valentini et al.	Immunohistochemistry	EBV	70	2	2.86	[56]
Japan	2019	Kawazoe et al.	*In situ* hybridization	EBV	2025	14	0.69	[57]
China	2019	Sun et al.	*In situ* hybridization and Immunohistochemistry	EBV	165	2	1.21	[58]
Japan	2019	Mishima et al.	*In situ* hybridization	EBV	80	4	5	[59]
Germany	2020	Moore et al.	qPCR	EBV	74	17	22.97	[60]
Taiwan	2020	Fang et al.	*In situ* hybridization	EBV	460	43	9.35	[61]
Korea	2020	Choi et al.	*In situ* hybridization	EBV	514	32	6.23	[62]
Korea	2020	Kim et al.	*In situ* hybridization and Immunohistochemistry	EBV	286	17	5.94	[63]
USA	2020	Martinson et al.	*In situ* hybridization and Immunohistochemistry	EBV	85	19	22.35	[64]
Italy	2020	di Pinto et al.	*In situ* hybridization and Immunohistochemistry	EBV	70	2	2.86	[65]
Korea	2020	Liu et al.	*In situ* hybridization	EBV	300	18	6	[66]
Irish	2021	Weadick et al.	*In situ* hybridization	EBV	103	8	7.77	[67]

(Continued)

Table 1 (continued)

Country	Year	Author	Method	Virus type	Number of case	Positive case	P/N %	Ref.
Brazil	2021	Moreira-Nunes et al.	*In situ* hybridization	EBV	1000	190	19	[68]
Morocco	2021	Nshizirungu et al.	*In situ* hybridization	EBV	97	6	6.19	[69]
Congo	2021	Mambouene et al.	PCR	EBV	52	2	3.85	[70]
Turkey	2021	Gareayaghi et al.	ELISA and qPCR	EBV	34	12	35.29	[71]
China	2021	Yang et al.	*In situ* hybridization	EBV	226	11	4.87	[72]
Morocco	2021	Rihane et al.	PCR	EBV	100	40	40	[73]
Japan	2021	Suzuki et al.	*In situ* hybridization	EBV	618	12	1.94	[74]
Iraq	2022	Mallakh et al.	*In situ* hybridization and Immunohistochemistry	HPV	54	24	44.44	[75]
Peru	2022	Castañeda et al.	*In situ* hybridization and qPCR	EBV	98	41	41.84	[76]
Russia	2022	Danilova et al.	*In situ* hybridization	EBV	282	27	9.57	[77]
China	2022	Ye et al.	PCR	EBV	40	5	12.5	[78]
Total				HPV	794	84	10.58%	
				EBV	14155	1215	8.58%	

Table 2: Comparison of HPV and EBV infection in GC classified by continental type

Continent	Virus type	Total number of cases	Positive cases
America	HPV	342	12
	EBV	2041	369
Europe	HPV	137	20
	EBV	2285	199
Africa	HPV	30	2
	EBV	389	74
Asia	HPV	285	50
	EBV	9440	573

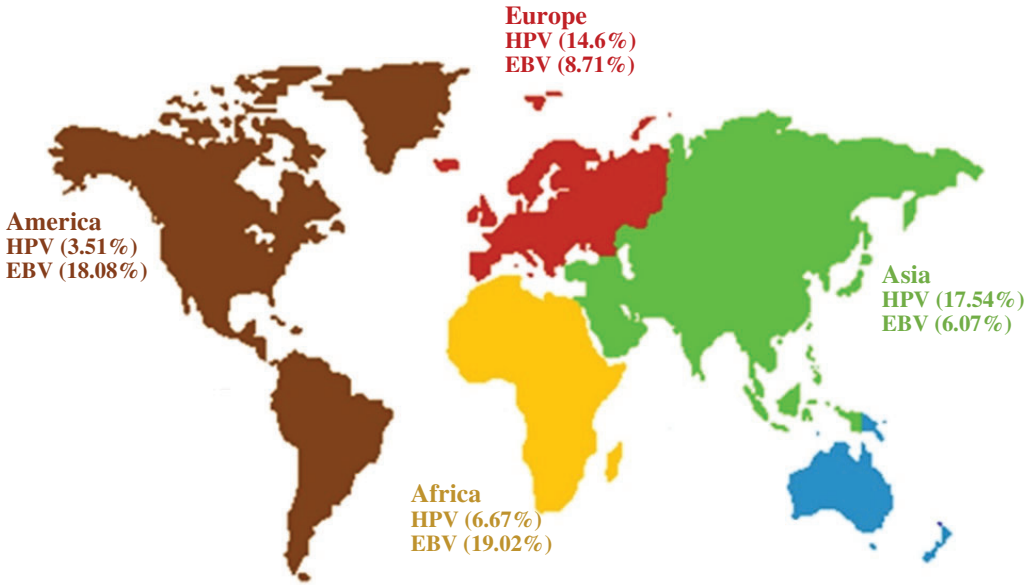

Figure 2: Odds ratios for HPV and EBV positive GC on different continents

4 Discussion

GC is one of the most common malignancies associated with infection worldwide. Various studies have proven the carcinogenic mechanisms of *Helicobacter pylori (H. pylori)* and EBV virus [79–82]. However, comprehensive information on other carcinogenic viruses has not been obtained. Therefore, this systematic study was performed to determine this. The researchers' findings indicate that HPV is one of the main infectious agents involved in prostate, cervical, anal, and colorectal cancer [83–87]. Most studies suggest that HPV can lead to cancer if it co-occurs with *H. pylori*, while other studies indicate that the prevalence of HPV is not associated with *H. pylori* [25,88]. HPV infection enters the esophagus through the mouth and eventually into the stomach, and the integration of HPV DNA into the host genome plays a key role in carcinogenesis [89]. Various studies in HPV-infected cells show that overexpression of E6 and E7 oncoprotein (caused by the integration of HPV in the host genome) in addition to tumorigenesis, can regulate the expression of multiple genes involved in cellular processes (such as proliferation, differentiation, apoptosis, adhesion, angiogenesis, transcription and protein translation), and induce genomic instability in normal human cells [90–96]. Yamato et al. and Jabbar et al. [97,98] have shown that the activity of E6 and E7 is necessary for the persistence of cancer caused by HPV because in the absence of the activity of these oncoproteins, cancer cells to senesce or undergo apoptosis. Our systematic study showed that the prevalence of HPV among GC patients from 24 countries was 10.58%. During a meta-analysis study, Zeng et al. concluded that out of the 1917 patients studied, 28% were HPV positive, which was more than the present study's findings [89]. In their study, Bae showed that the proportion of HPV-positive cases in Chinese studies was 1.43 times higher than in non-Chinese studies [99]. In 2020, Wang et al. examined the presence of HPV in 901 patients with GC and found that 23.6% of the samples were HPV positive. Therefore, there is a significant relationship between HPV infection and the risk of gastric malignancy [100]. EBV is found in approximately 9% of GC [12,101]. Various studies have revealed the role of EBV infection in the progression of GC, which can be caused by EBV entering B lymphocytes in the oropharyngeal lymphoid tissues and then entering gastric epithelial cells, which can occur through cell-to-cell contact between B lymphocytes and gastric epithelial cells or direct entry into the gastric epithelium. This entry can be facilitated by mucosal damage [102,103]. The prevalence of EBV in the present study was 8.58%. Our findings are consistent with previous meta-

analysis studies that reported the presence of EBV in GC from 6.9% to 8.8% [101,104–108]. Pyo et al. [109] estimated the presence of EBV in GC at 0.113%. Tavakoli et al. [110] reported an EBV prevalence of 8.77% in 20361 patients with GC. In addition, for the presence of EBV in GC, genome atlas research showed repeated PIK3CA mutations, severe DNA hypermethylation, amplification of JAK2, CD274, and PDCD1LG2 [111], which can enhance our understanding of the carcinogenic mechanism of EBV. This study contained the following limitations due to the data sources used in the systematic study. Age, sex, and *H. pylori* infection are important factors in the development of GC. However, the studies used were not mainly classified by age or sex, and there were no reports of an association between *H. pylori* infection and GC, so information on age, sex, and co-infection was not considered. There was also significant heterogeneity due to differences in sample size and geographical areas.

5 Conclusion

Overall, the present study's findings indicated that the prevalence of HPV and EBV infections in GC was 10.58% and 8.58%, respectively. These findings suggest an association between HPV, EBV and GC infections. However, the evidence inferred in the present study is insufficient to conclude that HPV and EBV infection are associated with GC risk. In addition, the prevalence of HPV and EBV was found in 24 countries worldwide. Therefore, extensive studies in other countries are strongly recommended to obtain more reliable results.

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Authors' Contributions: All authors contributed to the conception and the main idea of the work. AJS wrote the manuscript. ASH, HBB, BB, and BJ analyzed the data and edited the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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