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EBV as a potential risk factor for hepatobiliary system cancer: A meta-analysis with 918 cases

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ABSTRACT

Objectives: Hepatobiliary system cancer, which includes hepatocellular carcinoma (HCC), cholangiocarcinoma, and gallbladder carcinoma, has an increase of incidence and mortality due to various risk factors. Epstein-Barr virus (EBV) is associated with various types of lymphomas and carcinomas, which is also acknowledged as the first-discovered human tumor virus. Despite this, there is no systematic analysis about the relationship between the infection of EBV and hepatobiliary system cancer. The aim of this meta-analysis is to explore the significance of EBV infection in the development of hepatobiliary system cancer by evaluating the EBV infection ratio.
Methods: A systematic search of PubMed, Embase, Cochrane Library, as well as China National Knowledge Infrastructure (CNKI), Chongqing VIP, Wan Fang, and China Biology Medicine databases was conducted. The EBV infection ratio and 95% confidence intervals (CIs) in hepatobiliary system cancer was evaluated. The I^2 statistic was used to represent heterogeneity. Through meta-regression, stratified analyses were applied to find out heterogeneity's sources. Odds ratios (ORs), 95% CIs of EBV infection in case-control studies were calculated.
Results: Altogether, 15 studies were included containing a total of 918 cases and 157 controls. The whole infection ratio of EBV was 23% (95% CI: 13%, 33%, $I^2 = 95.7\%$, $P < 0.001$) among all the patients. Comparable EVB infection ratios were observed in hepatobiliary system cancer as divided into different subtypes. The five case-control studies were epitomized to a pooled OR of 9.35 (95%CI: 2.95, 29.61, $I^2 = 20.1\%$, $P < 0.286$).
Conclusion: EBV may be a potentially risk factor in the process of hepatobiliary system cancer. The prospective molecular mechanism remains to be explored.

1. Introduction

Hepatobiliary system cancer, which includes hepatocellular carcinoma (HCC), cholangiocarcinoma, and gallbladder carcinoma, has an increase of incidence and mortality due to various risk factors. Liver cancer, including HCC and cholangiocarcinoma, is one of the most common malignancies worldwide, which occurs more often in male than female, and more frequent in developing countries than developed ones. Areas in the East and Southeast have the highest rates of liver cancer, with more than half of the cases and deaths occurring in China. In the United States, estimated deaths of liver cancer in men and women are 19610 and 9310 in 2017, respectively. [2–4] Separately speaking, HCC in liver cancer is the most common class of liver malignancies, accounting for 85–90% of cases, with a high morbidity and mortality [5–11].Cholangiocarcinoma is another type of liver cancer which arises from the epithelium of the bile duct and accounts for 5–10% of liver cancer cases [12–14].Besides the above two subtypes of cancer, gallbladder carcinomas is also a subtype in the hepatobiliary system cancer, which has a capacity of high invasiveness, moreover, owning to late diagnosis and early metastasis, gallbladder carcinoma becomes an aporia in clinical work [15–18].All of these three types of carcinomas can be categorized under hepatobiliary system cancer, whose incidence and mortality continue to rise because of various risk factors, including some virus.

Epstein–Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is a family member of the gamma-herpes virus family, which

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infects more than 90% of the human population. EBV is closely associated with lymphoid and epithelial malignancies and causes 1.8% of all cancer-associated deaths in the world. [19,20]. Lymphoid malignancies including Burkitt's lymphoma and Hodgkin's lymphoma are well-known to be relevant to EBV infection, as well as some other carcinomas, including nasopharyngeal and gastric carcinomas [21–24].

To date, several meta-analyses have been performed to confirm the relationship between EBV infection and carcinogenesis or prognosis of patients, including cancers of stomach, nasopharyngeal and breast, as well as Hodgkin's and non-Hodgkin's lymphomas. [25–32] Previously, only single studies were performed to explore the relationship between EBV and HCC or cholangiocarcinoma with small sample sizes, which could not reach convincing conclusions. Furthermore, there is no meta-analysis focusing on the role of EBV infection in hepatobiliary system cancer.

Hence, we performed this meta-analysis to summarize the correlation with EBV infection and hepatobiliary system cancer and, thereby, shed more light on carcinogenicity of EBV in these diseases. We hope that this study will lead us in a direction to facilitate the research of EBV-associated hepatobiliary system malignancies, which can improve the diagnosis and therapies used for hepatobiliary system cancer.

2. Materials and methods

2.1. Search strategy

A systematic literature search was conducted to screen all the applicable studies published before October 20, 2018 and the databases included PubMed, Embase, Cochrane Library, as well as China National Knowledge Infrastructure (CNKI), Chongqing VIP, Wan Fang, and China Biology Medicine databases. The following searching strategy was used: "Burkitt lymphoma virus" or "E-B virus" or "infectious mononucleosis virus" or "Epstein-Barr virus" or "human herpes virus 4″ or "HHV-4″ or "Burkitt herpes virus" or "EBV", "adenocarcinoma" or "cystadenocarcinoma" or "carcinoma" or "cancer" or "neoplasm" or "tumor" or "neoplasm*" or "malignan*", "liver" or "hepatic" or "hepatocellular" or "cholangiocellular" or "cholangiocarcinoma" or "bile duct" or "gallbladder".

2.2. Study selection and inclusion criteria

In this meta-analysis, published studies were eligible for inclusion if they conformed to all the following criteria: 1) The articles should illuminate the relationship between EBV infection and hepatobiliary system cancers and also contain sufficient information. 2) Studies were excluded if they were case reports, summaries, minutes of meetings, unpublished articles, letters, and repeated documents. 3) The studies correlated to cell strains, serum antibodies, and non-human tissue were excluded. 4) Studies published in languages except Chinese and English were excluded. 5) The methods of detecting EBV included in situ hybridization (ISH), polymerase chain reaction (PCR), and immunohistochemistry (IHC). In details, EBV-encoded RNAs (EBER) were detected by ISH with EBV Probe. For PCR, specific primers were designed for the detection of EBV. Expression levels of EBV latent membrane protein 1 (LMP1) and EBV latent membrane protein 2 (LMP2A) were examined by IHC. As a last criterion, if there were more than two papers from the same team, the one containing more samples was included. Screening of documents was operated separately by four authors (Zu-xuan Chen, Xiao-tong Peng, Tan Lin and Gao-qiang Zhai), disagreements were resolved by discussion or consulting with the other three reviewers (Gang Chen, Ting-qing Gan and Jian-jun Li).

2.3. Data extraction

The following data were extracted: name of the first author, year of publication, country, histological types of hepatobiliary system cancer, language of the paper, EBV DNA test method, materials for EBV detection, number of cases and controls, sex, mean age, pathological differentiation, clinical tumor–node–metastasis (TNM) stage of hepatobiliary system cancer, and infections of other types of viruses.

2.4. Methodological evaluation

To evaluate the quality of each study, five investigators (Zu-xuan Chen, Xiao-tong Peng, Gang Chen, Ting-qing Gan and Jian-jun Li) independently analyzed the studies with the Newcastle–Ottawa Scale (NOS) criteria. The score was composed with three aspects of the study: subject selection: 0 to 4; comparability of subject: 0 to 2; and (3) clinical outcome: 0 to 3. The NOS scores ranged from 0 to 9, and the one owning 7 or more points were scored as the high-quality ones in the scale.

2.5. Statistical analysis

The meta-analysis was performed by STATA 12.0. Among the five case-control studies, odds ratios (ORs) and 95% confidence intervals (CIs) were assessed, meanwhile, pooled EBV prevalence as shown by effect size (ES), and 95% CIs were calculated. The random-effect model was selected to evaluate statistical heterogeneity between trials. Subgroup analysis was applied to identify sources of heterogeneity. A quantified description of heterogeneity was performed based on I^2 and a P value more than 0.10; I^2 lower than 50% was defined as low heterogeneity. Funnel plots were used to assess the publication bias. The $P < 0.05$ was significant for the whole article.

3. Results

3.1. Eligible studies

The procedure of the meta-analysis was depicted in Fig. 1. A total of 1655 related publications were identified based on the primary search strategy. With the titles and abstracts being glanced over, 188 references were regarded as eligible in accordance with the above criteria. By reviewing the full text rigorously, 173 papers were eliminated, which included 62 studies with deficient information, 12 studies being conducted in non-human tissues, 29 reduplicated studies, 30 studies detecting EBV serum antibody in cancer tissues, and 41 case reports with case samples less than 5. Consequently, 15 qualified studies were included in this study, among which 10 were in English and 5 in Chinese. All 15 studies contained a total of 918 cases and 157 controls. Among the 15 studies, 5 were case-control studies, and the rest were case-only studies with 352 cases and corresponding 157 controls (Table 1).

3.2. The characteristics of the study

Within the 15 studies, 9 were performed in China. Apart from 2 unknown studies, the materials were all tissue samples being formalin-fixed and paraffin-embedded. Furthermore, the EBV DNA was detected through a PCR-based technique in 5 studies, while 9 studies used ISH, and 3 used IHC (2 of 15 studies used more than one method at the same time).The cancer type distribution was HCC = 6, intrahepatic cholangiocarcinomas (IHCC = 2), lymphoepithelioma-like cholangiocarcinomas (LELCC = 2), and other rare cancers = 5. Moreover, 10 studies provided the data about co-infection status with HBV and HCV. The detailed information was shown in Table 1.

3.3. The overall EBV prevalence in hepatobiliary system cancer

The EBV prevalence percentage was depicted by decimals in forest plots. The EBV prevalence rates with its 95% CI estimated from all 918 cases were shown in Fig. 2 calculated by a random effects model. The

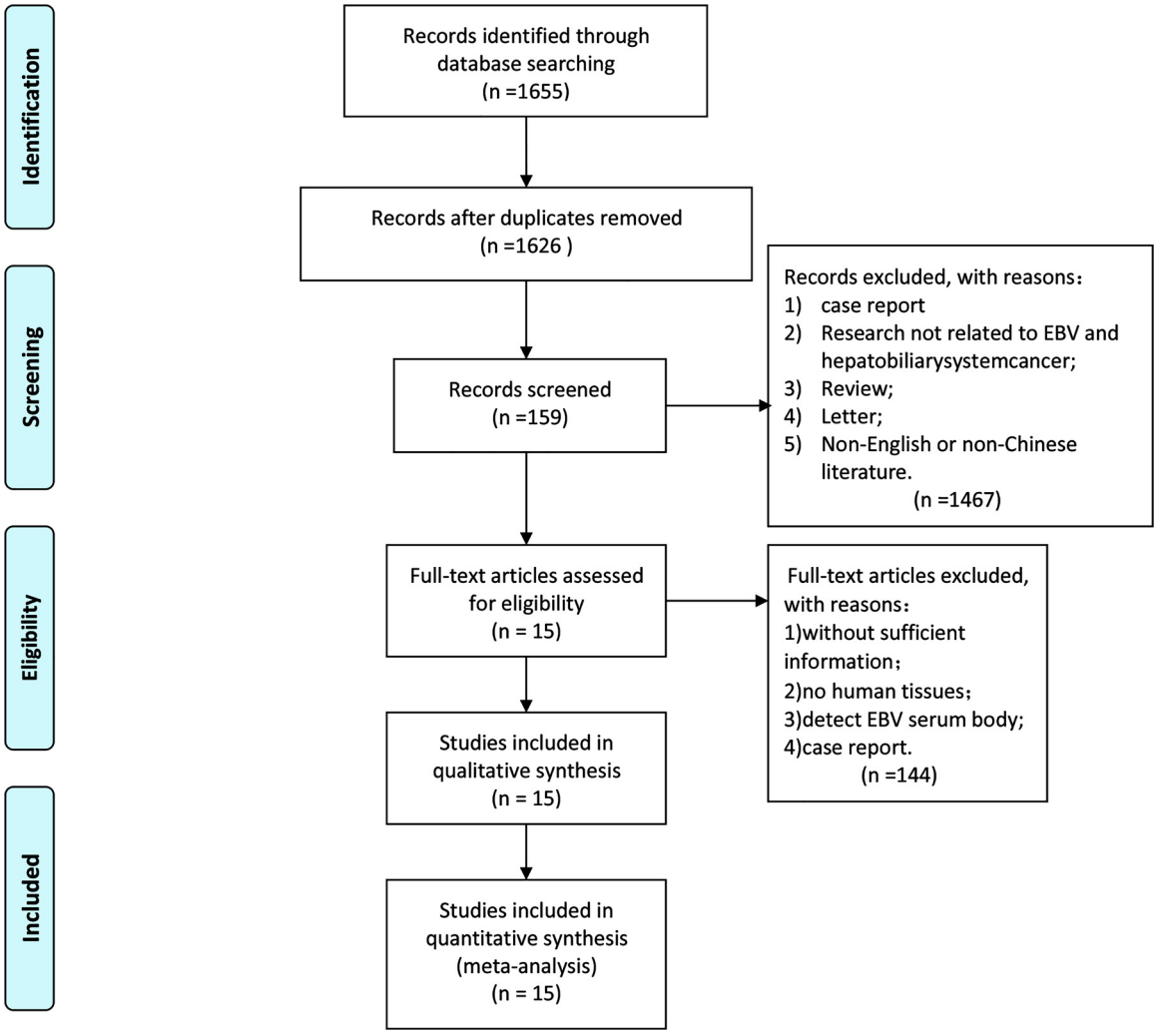

Fig. 1. The flow chart of the search process with the number of screened, excluded, and included publications.

pooled EBV prevalence was 23% (95% CI: 13%, 33%, z = 4.39, p < 0.001) and obvious heterogeneity was found between the various articles (I^2 = 95.7%, P < 0.01; Fig. 2). The five case-control studies were epitomized to a pooled OR of 9.35 (95%CI: 2.95, 29.61, Fig. 3) using the random effects model, which was statistically significant (z = 3.8, p < 0.01). The result denoted that the EBV prevalence in hepatobiliary system cancer cases was 9.35 times more than that in normal liver and duct tissues with low heterogeneity (I^2 = 20.1%, p = 0.286).

Table 1
The characteristics of all 15 eligible studies.

Author's name	Year	Country	Histological type	Sample size	Materials	Mean age	Gender	Method	Case		Control		HBV	HCV
									EBV (+)	Total	EBV (+)	Total		
Yuan FP et al	1998	Chinese	HCC	> 50	FFPE	NA	NA	ISH	14	70	0	64	NA	NA
Wu BA et al	2000	Chinese	HCC CCC	> 50	NA	48.7(22-74)	M:54F:13	PCR	26	81	2	26	60/81	1/18
Akhter S et al	2003	America	HCC	< 50	FFPE	NA	NA	PCR	0	31	0	0	12/31	10/31
Junying J et al	2003	England	HCC	> 50	FFPE	NA	NA	PCR	18	82	0	0	NA	NA
Ziarkiewicz-Wroblews et al	2005	Poland	PLL	< 50	FFPE	37.7(17-66)	M:4F:2	IHC	0	6	0	0	0	1/6
Hamed MO et al	2015	England	LMS	< 50	FFPE	58(40-71)	M:7F:1	PCR	0	20	0	0	NA	NA
Chan AW et al	2015	Chinese	LELCC	< 50	FFPE	55.7	NA	PCR	8	20	0	0	17/20	0
Wang L et al	2016	Chinese	LELCC	< 50	FFPE	61.1(41-77)	NA	IHC	8	13	0	0	6/13	0
Wang XM et al	2000	Chinese	CCC	< 50	FFPE	NA	NA	IHC	7	30	1	15	NA	NA
Zhang LH et al	2015	Chinese	DLBCL	< 50	FFPE	67.5(55-78)	M:5F:2	ISH	3	7	0	0	2/7	1/7
Xu B et al	2011	Chinese	IPT-like FDCT MFH IMT	< 50	FFPE	37 ~ 61	M:1F:2	ISH	1	3	0	7	NA	NA
Xiao P et al	2012	Chinese	LELC	< 50	NA	60, (45-76)	M:7F:7	ISH	3	14	0	0	3/14	0/14
Chu PG et al	2001	America	HCC	< 50	FFPE	58, (16-89)	M:28F:13	PCR	4	41	0	0	16/41	9/29
Sun K et al	2016	Chinese	LELC; IHCCs; LELCCs	> 50	FFPE	53.2, (30-67)	M:4F:7	IHC, ISH	11	329	0	0	5/11	0/11
Sugawara Y et al	2000	Japan	HCC	> 50	FFPE		M:138F:30	PCR	107	168	0	45	28/168	65/168

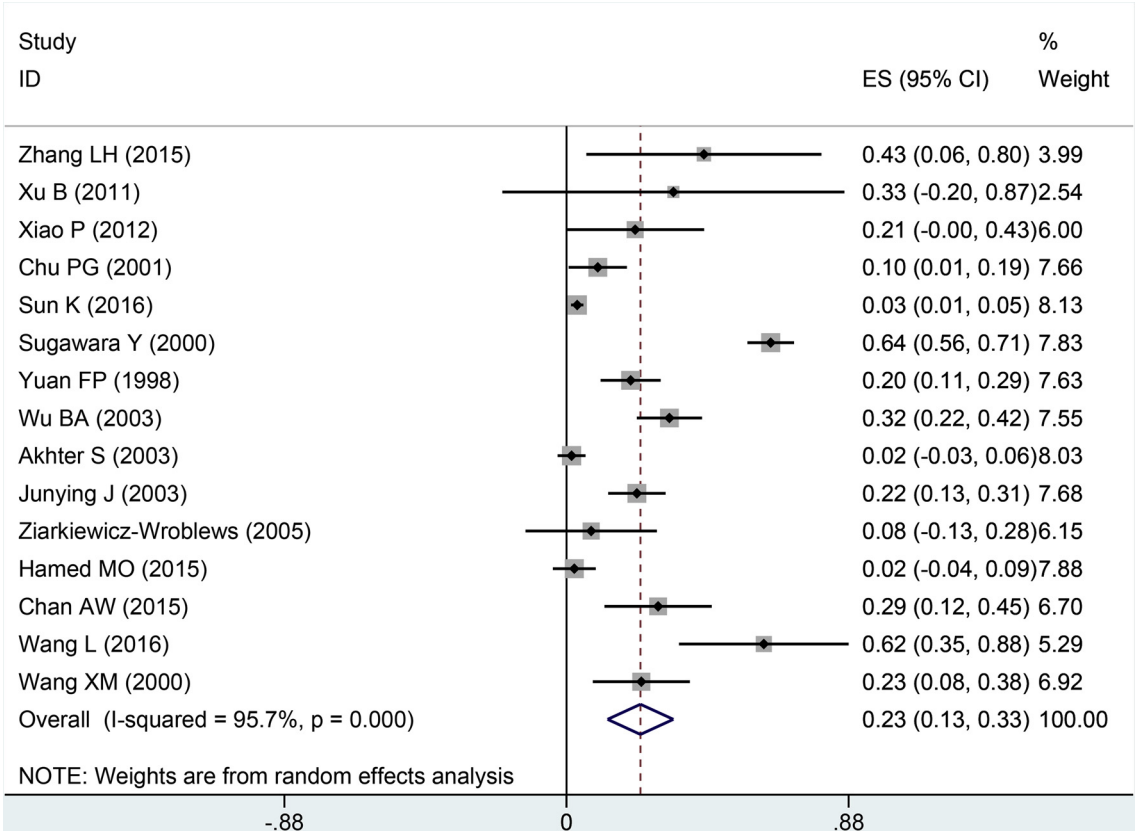

Fig. 2. Overall relations between EBV infection and hepatobiliary system cancer risk.
Abbreviations: ES, effect size.

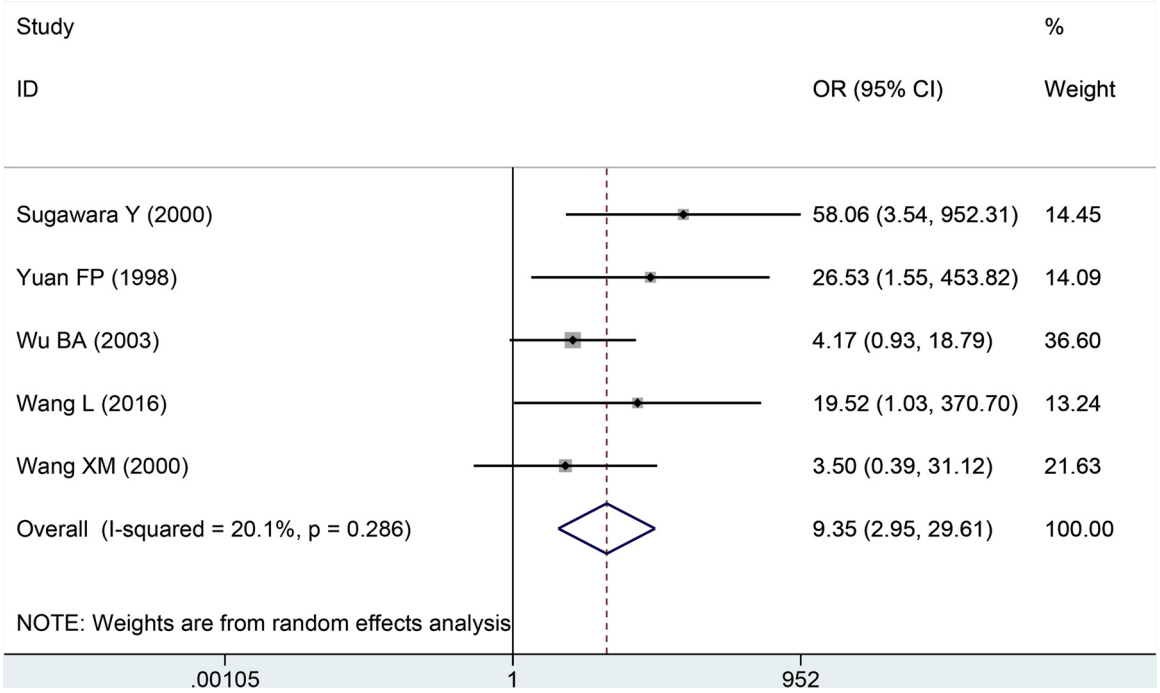

Fig. 3. The estimates of ORs with their 95% CIs were depicted in a forest plot for 5 case-control studies.
Abbreviations: CI, confidence interval; OR, odd ratio.

3.4. The EBV prevalence in subgroups analysis

All the studies could be classified into different subgroups by their EBV testing methods, cancer types, country, sample size, co-infection status, and publication year (Table 1, Fig. 4). The EBV prevalence was similar in those cases performed by ISH, PCR, and IHC methods (22% vs 13% vs 13%). The EBV prevalence in different subtypes was comparable.

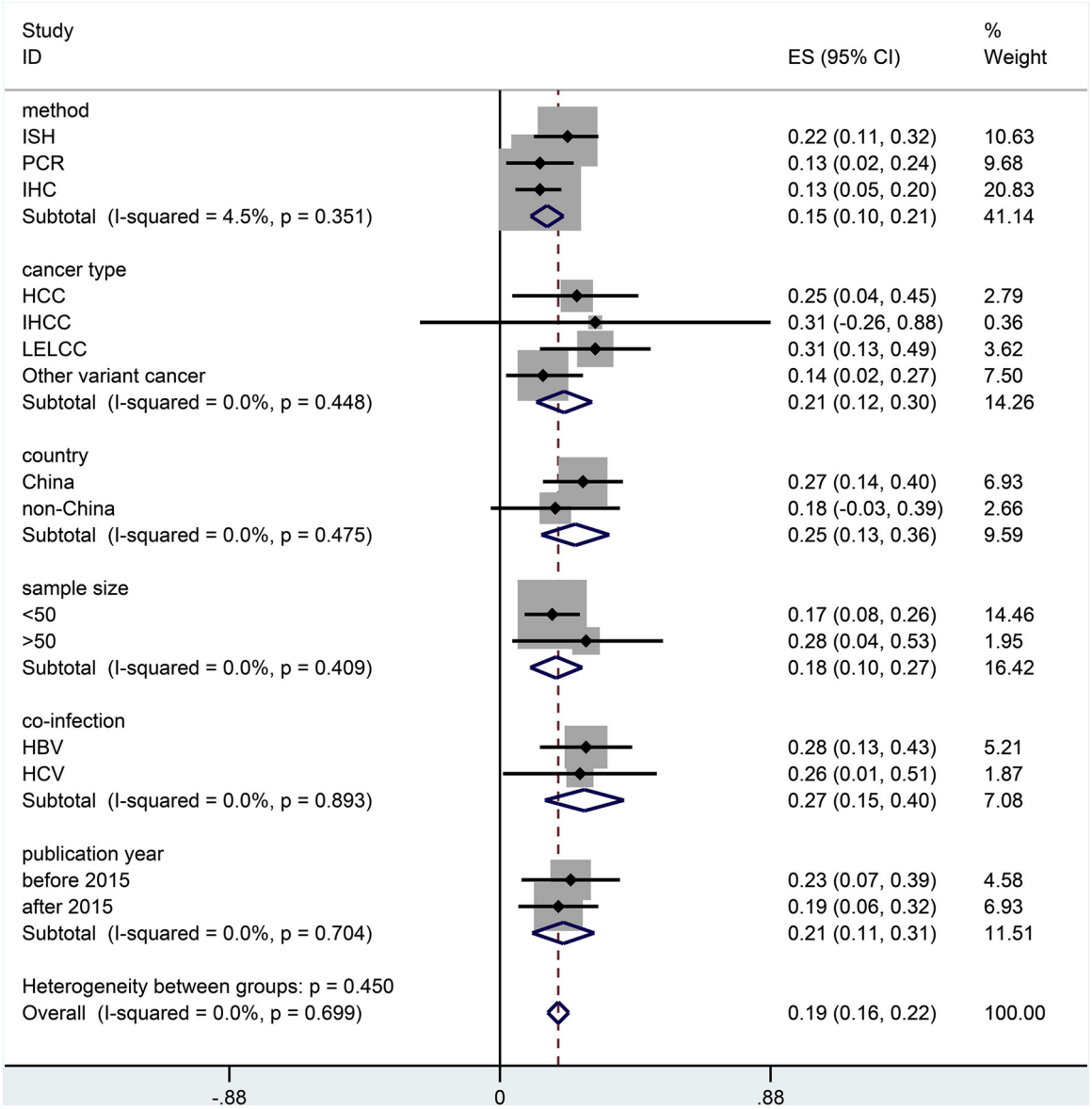

Fig. 4. The estimates of EBV prevalence with their 95% CIs were shown in decimals instead of percentages and plotted in a forest plot.
Notes: All searches were stratified by EBV test method, cancer types, country, sample size, co-infection, and publication year.
Abbreviations: CI, confidence interval; ISH, in situ hybridization; PCR, polymerase chain reaction; IHC, immunohistochemistry; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocellular carcinoma; LELCC, lymphoepithelioma like cholangiocarcinoma.

3.5. Sensitivity analysis and publication bias

Sensitivity analysis implied that each study contributed almost no significant difference on the pooled effect estimate. Begg's test and Egger's test were conducted and there were no obvious publication bias existing with P value were 0.488 and 0.158, respectively (Figs. 5 and 6).

3.6. Quality of the incorporated literature by NOS

The total score of our meta-analysis was six according to the following factors: cases we selected were of independent validation; representativeness of the cases were consecutive or obviously representative series of cases; there was no publication bias found by performing the Begg's and Egger's tests; the control cases had no hepatobiliary system cancer; the same method was used for the ascertainment of cases and controls (Table 2).

4. Discussion

Among the hepatobiliary system cancers, liver cancer is the second leading cause of malignancy-related death worldwide [[33] [34],]. China has a high incidence of liver cancer that accounts for over 55% of the cases all over the whole world. [35] The occurrence and development is caused by multiple factors and multiple gene regulation process in liver cancers [36]. According to the originating sources, liver cancer can grow from hepatic or epithelial cells of the biliary tract. As the biliary tract is anatomically connected to gallbladder, cholangiocarcinoma and gallbladder carcinoma share a consistent molecular background. Hence, the carcinoma from both hepatic cells and biliary epithelium are categorized into hepatobiliary system cancer including HCC, cholangiocarcinoma, and gallbladder carcinoma. [37–40] Even the pathogenesis of hepatobiliary system cancer has been studied for years, the role of EBV in the tumorigenesis of hepatobiliary system cancer remains unveiled.

Currently, there are several studies discovering the relationship

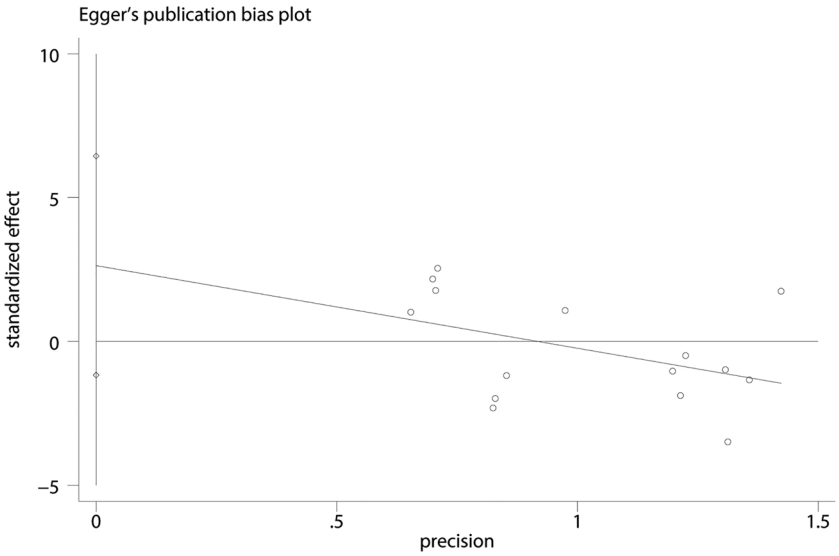

Fig. 5. No evident publication bias was demonstrated via Begg's test. (p = 0.488).

between nasopharyngeal carcinoma (NPC) or gastric cancer and EBV. [19,41–43] It could be possible that EBV also influence the risk of hepatobiliary system cancer, similar as gastric cancer, as it is also deep in the body belonged to the digestive system. Interestingly, recently, several studies have discovered possible relationships between hepatobiliary system cancer and EBV [44–46]. However, the previous studies were all based on small sample sizes and no comprehensive meta-analysis has been carried out.

Therefore, in the current study, we performed the first meta-analysis investigating the potential relationship between EBV and hepatobiliary system cancer. According to NOS, a tool used for evaluating the quality of non-randomized studies [47,48] the quality of the incorporated literature is qualified. The meta-analysis achieved a pooled EBV prevalence of 23% in 918 hepatobiliary system cancer cases among the 15 included studies. This was supported by a pooled OR of 9.35 among five case control studies, which demonstrated that EBV prevalence was a high-risk factor in hepatobiliary system cancer.

Text, we further looked into different EBV ratio in subgroups of the hepatobiliary system cancers. Six subgroups were set up based on detecting methods, cancer types, countries of the patients, sample sizes, co-infection status with HBV and HCV, also the published time. Since EBV resides in B-lymphocytes infiltrating tumor sites, in theory, these types of the EBV infected cells in a tumor sample will be challenging to be detected in PCR-based studies. However, in the current meta-analysis, the EBV ratio detected by PCR was equal with the one by IHC. More tests need to be carried out to compare the accuracy and efficiency of various detecting methods for EBV infection. In summary, no significant variation of EBV prevalence was observed in the cases of each subtype, which indicated that EBV infection is a general phenomenon in the population of all hepatobiliary system cancer.

There were some potential mechanisms contributing to the association between EBV and hepatobiliary system cancer. At the early stage of EBV infection, this virus may cause some morphology changes of the cells in the primary lesion, which will eventually lead to malignant transformation. [49] However, this hypothesis needs more experiments to confirm. It will be helpful to test the EBV infection status on the samples of pre-cancerous samples of hepatobiliary system cancers. Due to the difficulties to obtain the clinical samples, in vivo

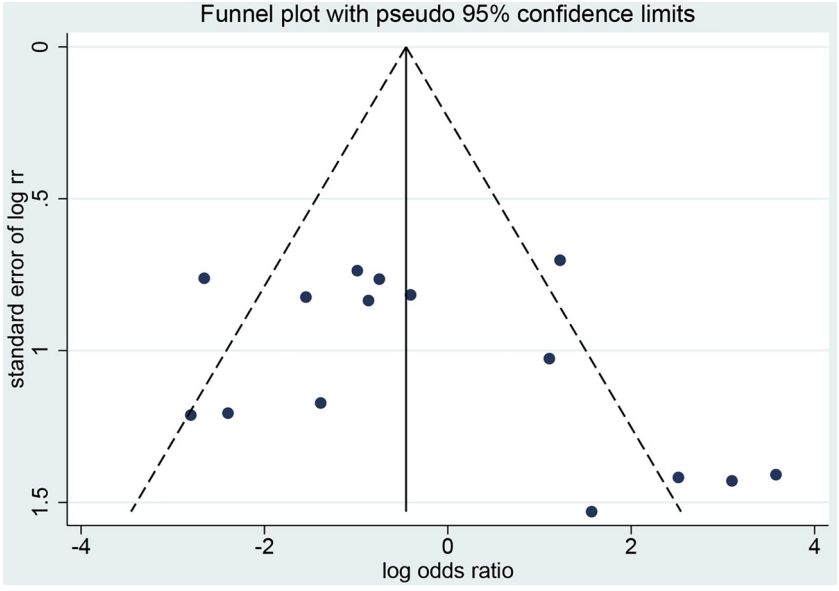

Fig. 6. No evident publication bias was demonstrated via Egger's test. (p = 0.158).

Table 2
Quality of non-randomized studies by Newcastle-Ottawa scale (NOS).

Selection				Comparability	Exposure			
Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of Controls	Control for important factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Scores
☆	☆	- ☆	☆	☆	-	☆	-	6

experimental models will be better test subjects.

Moreover, the role and mechanism of EBV infection in NPC can provide some similarities for that in hepatobiliary system cancers. [25,50–52], as NPC is the most studied disease related to EBV. EBV infection can lead to aberrant non-coding RNA levels, especially microRNAs (miRNAs) in NPC. Nineteen cellular miRNAs and nine EBV miRNAs were found to be upregulated and 31 cellular miRNAs were downregulated in NPC tissues. By using Gene Ontology and the Kyoto Encyclopedia of Genes and Genomes pathway analysis, some pathways including p53 signaling pathway, focal adhesion, Erb, MAPK, TGF-β and Wnt signaling pathways were found to be related to EBV infection in NPC. Another similar study also confirmed that 40 EBV miRNAs were highly expressed in NPC. These studies suggest that EBV miRNAs may regulate different target genes and pathways, and eventually contribute to NPC carcinogenesis. [52,53] It is also possible that EBV infection in hepatobiliary system cancer can also cause abnormal miRNA expression, and subsequently regulates multiple target genes and signaling pathways. However, this needs to be validated by further experiments. Also whether EBV promotes the development of hepatobiliary system cancer independently or cooperates with other factors remains unknown, so it is necessary to launch further studies to examine the mechanisms of EBV infection in hepatobiliary system cancer tumor genesis.

4.1. Limitations

Several limitations exist in this study and deserve attention. First, the number of primary included studies was still small and larger sample size will be needed in the future. Second, studies included in this study did not provide adequate information for estimating the hazard ratio and their corresponding confidence interval. It is noted that we could not exclude biases even though no evident publication bias was found in Begg's test. Third, more than half of the studies which we included were performed in China, which will also limit the overview of EBV infection globally.

4.2. Conclusion

In conclusion, this meta-analysis reflected a high incidence of EBV infection in 918 hepatobiliary system cancer patients. Therefore, EBV may be potentially a risk factor in the process of hepatobiliary system cancer. However, the molecular mechanism of EBV infection in hepatobiliary system cancer still needs more in-depth investigation.

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