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RESEARCH ARTICLE

Prevalence of Epstein-Barr virus infection in individuals with nasopharyngeal carcinoma in Malaysia: The first systematic review and meta-analysis

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ABSTRACT

Epstein-Barr virus (EBV) was the first herpesvirus associated to human malignancies. Despite the well-known association between EBV and malignancies, the prevalence of EBV infection in Malaysians with malignancies is unknown. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used to conduct a systematic review and meta-analysis of published data in this study. Studies reporting the occurrence of EBV infection in Malaysian malignancy patients were searched in electronic databases like PubMed, Scopus, ScienceDirect, and Google Scholar without year or language constraints. The study protocol was filed in PROSPERO (CRD42021273769). A total of 21 studies were included, with 1,036 EBV infection cases among 2,078 malignancy patients. The random-effects model was used to produce summary estimates. The pooled prevalence of EBV infection in Malaysians with malignancy was 36.3% (95% CI, 20.3 – 56.2). When the prevalence estimates were stratified by malignancy type, nasopharyngeal carcinoma has the highest prevalence (90.5%), followed by lymphoma (23.4%), and gastric carcinoma (10.0%). Male patients had a higher cases prevalence and most patients were above the age of 40. In Malaysia, many malignancies are increasingly linked to EBV infection. Screening for EBV infection in malignancy patients is therefore important to determine disease recurrence and metastases.

Keywords: Epstein-Barr virus; EBV; prevalence; Malaysia; malignancies.

INTRODUCTION

Epstein-Barr virus (EBV) is a member of subfamily Gammaherpesvirinae of the family Herpesviridae. Burkitt's lymphoma, lymphomas associated with immuno-suppression, other non-lymphomas, Hodgkin's disease, nasopharyngeal carcinoma (NPC), gastric adenocarcinoma, lymphoepithelioma-like carcinomas, immunodeficiency-related leiomyosarcoma, possibly breast and hepatocellular carcinomas, and smooth muscle cell-derived tumours in immunodeficient individuals have all been found to carry the EBV (Hsu & Glaser, 2000; Niedobitek *et al*., 2001). EBV can reactivate in cases of immunodeficiency, such as HIV-AIDS, organ transplants, and genetic immunological abnormalities, leading to aberrant lymphocyte proliferation and the possibility for a variety of lymphomas (Thompson & Kurzrock, 2004). EBV infection can last a lifetime, even if most people show no symptoms after being exposed to the virus for a few weeks (Hjalgrim *et al*., 2007). In most people, EBV infection does not cause significant problems, and there are no medicines or other treatments available to get rid of it (CDC, 2020). In addition, there are no vaccines available to help prevent it (Cui & Snapper, 2021).

B cell lymphoproliferative disorders, often known as 'post-transplant lymphoproliferative disease' (PTLD), are EBV-related and commonly arise within the first year after transplantation in transplant recipients (Hanto *et al*., 1982; Shapiro *et al*., 1988). PTLD is more common in children than in adults, with rates ranging from 4% to 22% reported for various types of pediatric organ transplant recipients, compared with an average of 1% to 2% in adults (Hanto *et al*., 1982; Ho *et al*., 1988; Newell *et al*., 1996; Savoie *et al*., 1994). This distinction between children and adults is reasonable, given that EBV infection rates are significant in EBV-seronegative transplant

patients, reaching 100% following three months of transplant (Savoie *et al*., 1994). Since many children are EBV-seronegative prior to transplantation, they are more prone to get primary EBV infection from the donor organ or blood transfusions (Cen *et al*., 1991).

A long-term CD4+ cell drop in human immunodeficiency virus 1 (HIV-1) infected patients affects the host-EBV balance, thus increasing the incidence of EBV-related malignancies (Friis *et al*., 2013). In HIV-1 infected patients with significant immunosuppression, EBV DNA load may be useful in evaluating the effect of lymphoma treatment as well as assessing the risk of EBV-associated lymphomas (Friis *et al*., 2013; Rinaldo, 1990). According to Huo *et al.* (2012), 29.32% of patients with breast carcinoma are infected with EBV, and patients who tested positive for EBV have a much higher chance of developing breast cancer (Huo *et al*., 2012). Furthermore, a dramatic drop in antibodies to EBV-associated membrane antigens was seen in a recurrence case of Burkitt's lymphoma. The antibodies began to decline several months before the recurring tumour became clinically visible (Mukojima *et al*., 1973).

Monitoring EBV DNA levels in the blood is used as a distinguishing marker for NPC in healthy high-risk individuals and as a prognostic marker in EBV-positive NPC patients (Cao, 2017). A study of patients with loco-regionally advanced NPC in a Western country utilised plasma EBV DNA levels to determine disease recurrence and metastases (Ferrari *et al*., 2012). Despite the fact that modern chemotherapy and radiation therapy (RT) are successful, distant metastasis remains the most common cause of NPC treatment failure (Gamba *et al*., 2018). For all patients with loco-regional NPC, RT is the primary therapy option. NPC positive with EBV is extremely invasive for local and distant metastases, although it is susceptible to treatment and radiotherapy (Gamba *et al*., 2018). A study found that monitoring the changes in EBV DNA in serum was useful in monitoring the progress of NPC patients undergoing RT and treatment efficacy (Midoen *et al*., 2021).

The association between EBV infection and cancer is well understood (Hsu & Glaser, 2000). The focus of this review is on EBV infection and malignancies among Malaysians. When EBV infection is linked to cancer, particularly NPC and Burkitt's lymphoma, an unfavorable distant metastasis or relapse may occur. As a result, it is suggested that malignant patients with EBV infection be screened for potential recurrence or relapse to ensure prompt treatment for improved overall survival. Without a doubt, knowing the prevalence of EBV infection in cancer patients will help doctors make better decisions. Although there have been a few sporadic instances of EBV infection in Malaysians with malignancy, the real incidence is unknown. EBV DNA early detection and screening is now being utilised in clinical and high-risk populations. In near future, the knowledge gained about EBV can be applied to EBV based precision cancer prevention and therapy (Cao, 2017). By collecting available published data and utilising a meta-analytical technique, we give the first report of the prevalence of EBV infection among Malaysians with malignancies.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements were used to conduct and report this systematic review (Moher *et al*., 2009). The protocol for this review was registered in PROSPERO (Registration number: CRD42021273769).

Literature search and eligibility criteria

The following keywords were used to search four electronic databases (PubMed, Google Scholar, ScienceDirect and Scopus): "Epstein-Barr virus", "EBV", and "Malaysia". As a supplementary document, full details of the search strategies used for all of the databases searched are accessible (File S1). The search was thorough, with no filters for language, country, study design, or publication year. On July 8, 2021, a preliminary search was conducted. On August 5, 2021, an updated and final search was done, yielding a total of 197 articles (Figure 1). All references were exported to the EndNote X8 software, and duplicates were removed.

Studies that investigated the prevalence of EBV infection in Malaysians with malignancies were considered for inclusion. Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and other cancers linked to EBV infection are examples of malignancies. (1) Opinions, editorials, reviews and case reports were excluded; (2) studies that reported for malignancies without an EBV infection confirmation test were excluded; and (3) articles whose complete text could not be retrieved were excluded. We browsed and reviewed the references of the included studies to ensure an extensive search.

The article screening, selection and assessment criteria were participated by all authors. The publications were screened independently by two authors (ENSEAR and AAI) based on title and abstract. Following that, the whole texts were evaluated. Disagreements arose during the screening process, which were resolved by discussion with other authors.

Data extraction and quality assessment

A preset excel spreadsheet was utilised to extract the data. The study ID, year of publication, study period, types of malignancies, and number of patients involved including their age and sex, number of EBV infection cases reported, number of patients according to ethnicities, and the diagnosis method for EBV infection according to target

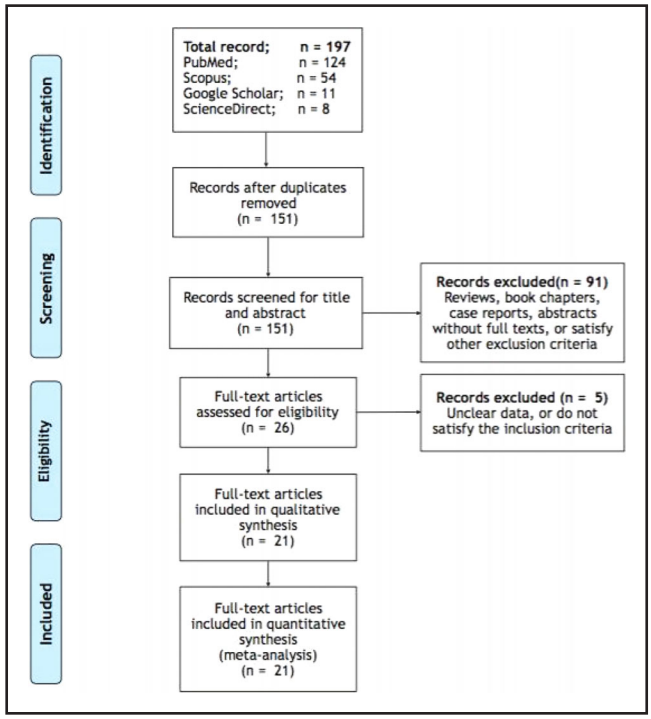

Figure 1. Summary of article identification and selection process.

antigen were all extracted independently by two authors (ENSEAR and AAI).

Three authors (RM, RHS and NML) independently assessed the methodological quality of the included studies using the Joanna Briggs Institute (JBI) critical assessment criteria for prevalence data (Munn *et al*., 2015) (File S2). To get a total quality score ranging from 0 to 9, a score of '1' for 'yes' and '0' for other characteristics were assigned. Studies having an overall score of 7 to 9 were deemed satisfactory in terms of quality.

Data synthesis and analysis

OpenMeta[Analyst] (version 10.12) and Comprehensive Meta-Analysis (CMA) (version 2.2.027) were used to analyze the data (Borenstein *et al*., 2005; Wallace *et al*., 2009). The pooled prevalence of EBV infection in Malaysians with malignancy was assessed, and sub-group analysis was performed based on the type of malignancy. The pooled estimates of reported EBV infection cases were calculated using a random-effect model and the DerSimonian-Laird technique of meta-analysis (George & Aban, 2016). A funnel plot was used to analyze potential publication bias in addition to analysing study quality. Egger's regression test was used to determine the plot's asymmetry (Egger *et al*., 1997). Cochran's *Q* test was used to assess the heterogeneity of study-level estimates, which was then quantified using I^2 statistics. Low, moderate and high heterogeneity were defined as I^2 values of 25%, 50% and 75%, respectively (Higgins & Thompson, 2002). Sources of heterogeneity were investigated using subgroup meta-analysis. The leave-one-out analysis and the exclusion of studies with few participants were used to conduct the sensitivity test. A p value of < 0.001 was considered statistically significant for all tests.

RESULTS

Study selection

Figure 1 depicts the study selection process for this study. Our search of four electronic databases yielded 197 results in total. The full texts of 26 studies were examined for eligibility after duplicate removal, and articles that did not meet our inclusion criteria were removed. Finally, 21 studies were found to be totally eligible and were analysed quantitatively.

Characteristics of the eligible studies

The studies in this meta-analysis were mostly cross-sectional studies of EBV infection in patients with malignancies in hospital settings, with study periods spanning from 1 to 34 years. The bulk of the enrolled patients were men, and several of the studies were conducted in Kuala Lumpur, Peninsular Malaysia. Table 1 lists the major characteristics of the studies that were considered.

Prevalence of EBV infection in Malaysians with malignancies

This meta-analysis includes 21 studies that contained a total of 1,036 EBV infection cases among 2,078 people with malignancy. The pooled prevalence of EBV infection in Malaysians with malignancies was estimated to be 36.3% (95% CI, 20.3 – 56.2) (Figure 2). The results revealed a significant level of heterogeneity (I^2 = 97.14%, Q = 699.682; p < 0.001).

Prevalence of EBV infection stratified by type of malignancies

A subgroup meta-analysis was performed to determine the prevalence of EBV infection in people who had different types of cancers. Data was available for three types of malignancies from the included studies, with the lymphoma group (n = 16) accounting for most of the studies. (Table 2; Figure 3). The nasopharyngeal carcinoma group had the highest pooled prevalence estimate of 90.5% (95% CI, 88.0 – 92.6), whereas the gastric carcinoma group had the lowest estimate of 10.0% (95% CI, 4.2 – 21.9) (Table 2; Figure 3). The lymphoma subgroup had the most heterogeneity (I^2 = 90.37%; p < 0.001), which could have contributed to the total heterogeneity.

Analyses of sensitivity and publication bias

The random-effects model was used to test sensitivity by omitting one study at a time (i.e., leave-one-out analysis). When the Sandvej *et al*. (1994) study was excluded, a prevalence estimate of 29.6% (95% CI, 15.3–49.5) was gotten. Following the analysis, the estimate was the lowest estimate discovered (Figure 4). However, when the study of Kim 2003 (Kim & Peh, 2003) was excluded, the highest prevalence estimate of 37.7% (95% CI, 20.6-58.6) was found. Overall, the estimates of EBV infection prevalence remained stable (Figure 4).

We would anticipate the funnel plot to be symmetric if the meta-analysis had included all relevant studies. However, using the Duval and Tweedies's Trim and Fill approach, two studies were absent from the funnel plot (Figure S1). The pooled studies' point estimate and 95% confidence interval under the random effects model was 34.1% (18.3-54.5). However, the computed point estimate using Trim and Fill was 40.2% (CI: 22.9-60.3) (Figure S1). A visual inspection of the plot revealed that it was asymmetrical, and that there were indications of publication bias (Figure 5). In addition, Egger's regression test for funnel plot asymmetry yielded p-value of 0.08763, which was not significant. The studies that were included in our analyses were of high methodological quality (Table S1).

To investigate the heterogeneity further, meta-regression was performed independently for each analysed variable. In the univariate meta-regression analysis, variables with a p-value of 0.000 were considered. A dispersed plot (Figure 6) was created using the method of moments as the computational option. Studies from lymphoma (p = < 0.001) and nasopharyngeal carcinoma (p = < 0.001) were the only ones that contributed to the study heterogeneity in the type of malignancy variable. Gastric carcinoma studies (p = 0.435) did not add to the heterogeneity found in this study (Table 3, Figure 6).

DISCUSSION

EBV is a long-lived virus that has coevolved with its various hosts over the last 90–100 million years (McGeoch *et al*., 1995). Since Epstein et al. first suggested an association between EBV infection and malignancy in 1964 (Epstein *et al*., 1964), infection with EBV has been implicated in a variety of malignancies, including NPC, B/T cell lymphoma, breast, stomach, oral, and cervical (de Lima *et al*., 2019; Aguayo *et al*., 2021). NPC is the fourth most prevalent malignancy in men in Malaysia and may explain the high prevalence of NPC cases discovered in this study (WHO, 2020). Despite the fact that gastric carcinoma is one of the most common malignancies related to EBV infection (Cohen *et al*., 2011), the true incidence of EBV infection in cancer is unknown because reported prevalence varies between studies. An attempt was made in this systematic review and meta-analysis to harmonize several studies reporting the prevalence of EBV infection in malignancy patients in order to obtain a realistic prevalence estimate.

Table 1. Major characteristics of the included studies reporting the occurrence of EBV infection in individuals with malignancies in Malaysia

Study ID	Study period	Malignancy	Participants				Ethnicity				Method	Target antigen
			Total	[1]Age	Female	EBV (+) cases	Malay	Chinese	Indian	Others		
Abdelrahim *et al.* (2018)	1981 - 2015	B-cell Non-Hodgkin's lymphoma	14	48.8 ± 23	8	0	6	5	1	2	ISH	EBER
Chai *et al.* (1999)	1981 - 1983	Hodgkin's lymphoma and Non-Hodgkin's lymphoma	107	41 ± NR	41	23	17	13	1	35 (Sarawak) 41 (Sabah) indigenous groups	ISH	EBER
Chai *et al.* (2012)	–	Nasopharyngeal carcinoma	390	50.5 (13 - 81)	–	350	86	216	2	72 (Bidayuh= 35, Kadazan= 23 and others=14)	quantitative PCR (Q-PCR) on plasma EBV DNA	BamHI-Wregion of EBV genome
Cheng *et al.* (1993)	–	Nasopharyngeal carcinoma	294	20 - 40	–	267	–	–	–	–	ELISA using EBNA1 p107 target which representing a major epitope of EBNA1	EBNA1
Hoe *et al.* (2009)	2000 - 2006	Nasopharyngeal carcinoma	53	49 ± NR	12	51	12	41	–	–	ISH	EBER
Karim & Pallesen (2003)	1994 - 2000	Gastric carcinoma	50	29 - 86	18	5	4	27	19	–	ISH	EBER
Peh *et al.* (1997)	1971 - 1992	Hodgkin's disease	100	28 ± NR	39	41	27	42	31	–	ISH	EBER
Peh *et al.* (2002)	–	Lymphomas (Hodgkin's, Burkitt's, T cell and B cell non-Hodgkin's) and NPC	64	–	–	50	21	30	11	2	ISH	EBER
Peh (2001)	1988 - 1992	Non-Hodgkin's lymphoma (B and T cell lymphomas)	173	> 15	51	20	41	107	21	4	ISH	EBER
Peh *et al.* (2008)	1996 - 2003	Non-Hodgkin's lymphoma (Diffuselarge B-cell lymphoma)	84	52 ± NR	33	5	34	38	11	1	ISH	EBER
Peh *et al.* (2000)	1993 - 1999	Hodgkin's lymphoma and Non-Hodgkin's lymphoma	92	50.5 ± NR	28	20	64	4	12	–	ISH	EBER

Peh *et al.* (2004)	1971 - 1992	Non-Hodgkin's lymphoma	69	< 15	19	21	14	46	8	1	ISH	EBER
Peh & Quen (2003)	-	T-cell non-Hodgkin's lymphoma and (NK)/T-cell lymphoma	31	46.1 ± NR	9	22	10	18	2	1	ISH	EBER
Peh *et al.* (1995)	1982 - 1991	Non-Hodgkin's lymphoma (B and T cell lymphomas)	29	5 - 72	9	13	9	18	1	2	ISH	EBER
Peh *et al.* (2003)	1997 - 1999	Hodgkin's lymphoma and Non-Hodgkin's lymphoma	125	42.1 ± NR	32	14	7	8	–	76	ISH	EBER
Teoh *et al.* (2019)	2011 - 2015	Non-Hodgkin's lymphoma (Diffuse large B-cell lymphoma)	51	56.0 (35 - 81)	15	10	–	–	–	–	ISH	EBER
Ting *et al.* (2019)	2012 - 2013	Non-Hodgkin's lymphoma (Diffuse large B-cell lymphoma)	120	54.1 ± 14.6	56	8	–	–	–	–	ISH	EBER
Yunos *et al.* (2006)	1992 - 2004	Non-Hodgkin's lymphoma	18	44.78 ± NR	7	2	–	–	–	–	ISH	EBER
Kim & Peh (2003)	-	Hodgkin's lymphoma, Burkitt's, (NK)/T- cell and diffuse large B-cell lymphomas	81	–	24	0	27	28	11	15	ISH	EBER
Sandvej *et al.* (1994)	-	Danish Hodgkin's disease (HD), Malaysian peripheral T-cell lymphomas (PTLs) and Danish infectious mononucleosis (IM)	90	–	–	90	–	–	–	–	ISH	EBER
Tai *et al.* (2004)	1979 - 2001	(NK)/T-cell lymphomas	43	4 - 77	15	24	16	22	2	3	ISH	EBER

[1]Age is presented in years [(mean ± SD/median(interquartile range(IQR)/range)]; NR, not reported. ISH = *In-situ* hybridisation for EBV-encoded RNA.

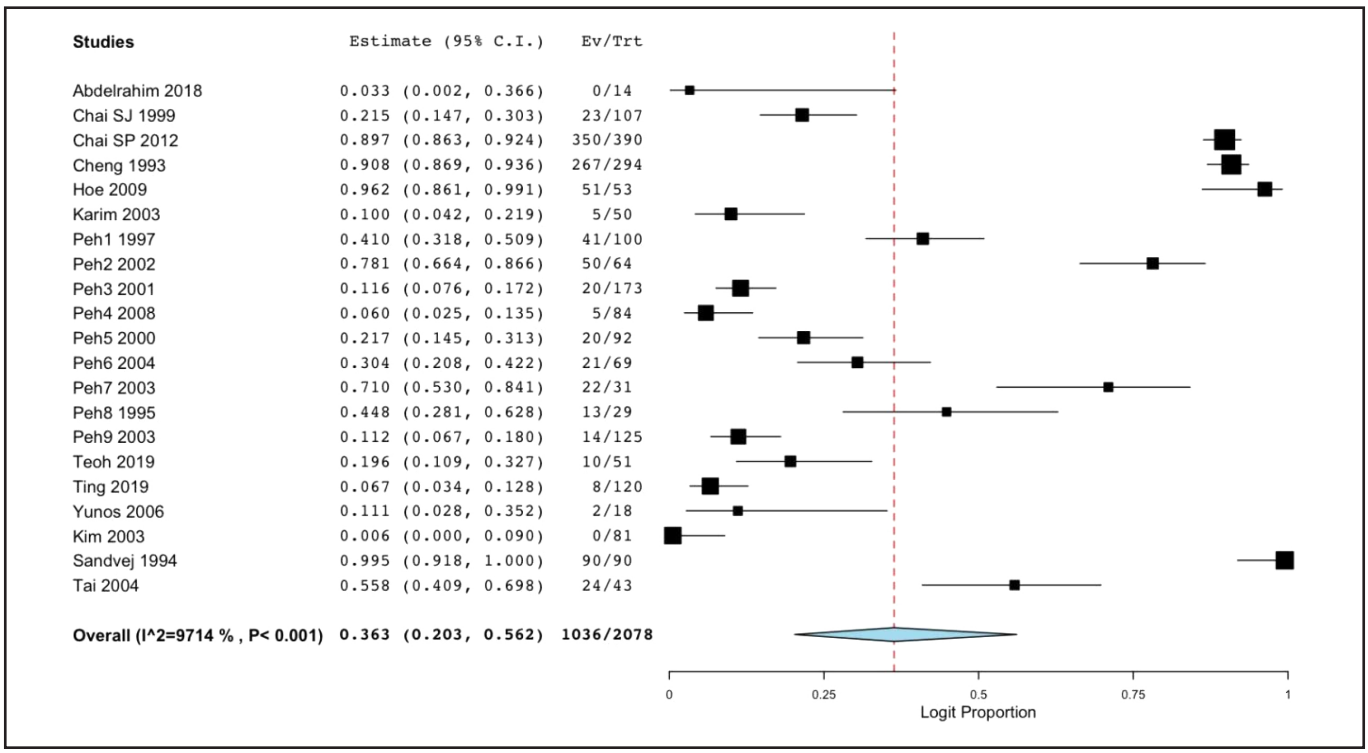

Figure 2. Forest plot of the pooled prevalence of EBV infection in individuals with malignancies in Malaysia.

Table 2. Sub-group analysis on prevalence of EBV infection in individuals with malignancies in Malaysia stratified by type of malignancy

Subgroup	No of studies	Prevalence (%)	95% CI	I^2 (%)	Q	Heterogeneity test	
						DF	*p*
Lymphoma	16	23.4	14.8 – 34.9	90.37%	155.712	15	< 0.001
Nasopharyngeal carcinoma	3	90.5	88.0 – 92.6	73.4%	2.158	2	0.340
Gastric carcinoma	1	10.0	4.2 – 21.9	NA	NA	NA	NA
Overall	20	34.1	18.3 – 54.5	97.2%	677.814	19	< 0.001

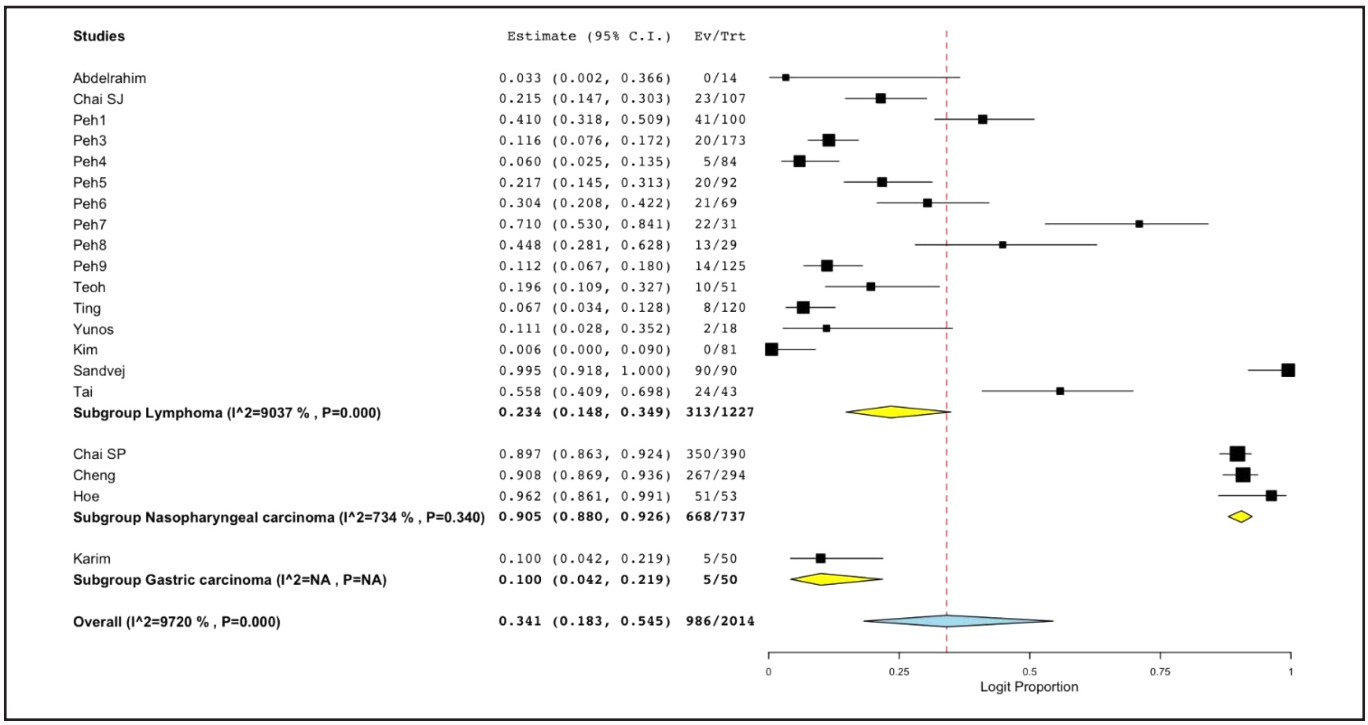

Figure 3. Forest plot of the sub-group analysis on prevalence of EBV infection in individuals with malignancies in Malaysia stratified by type of malignancy.

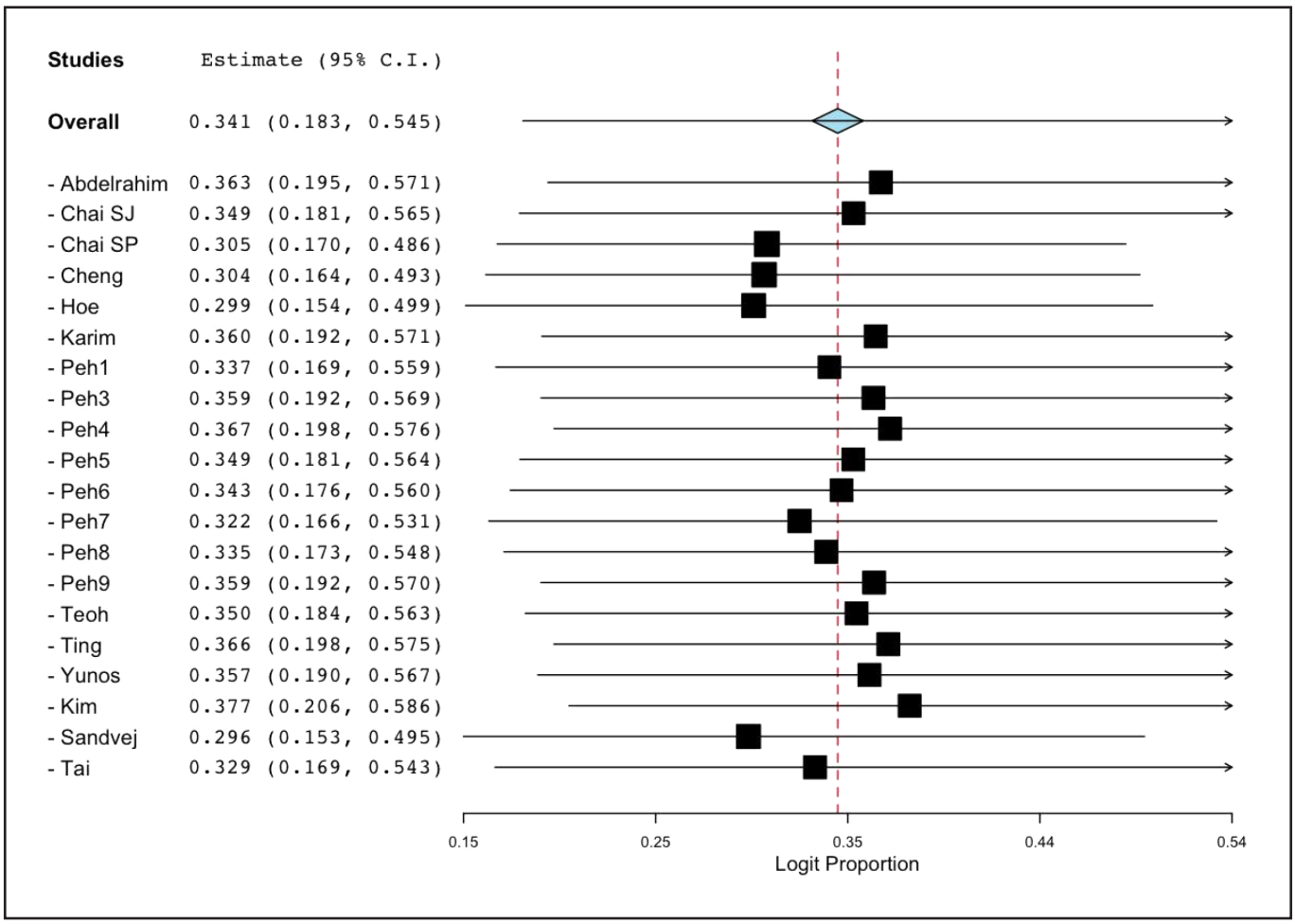

Figure 4. Forest plot of leave-one-out analysis on prevalence of EBV infection in individuals with malignancies in Malaysia stratified by type of malignancy.

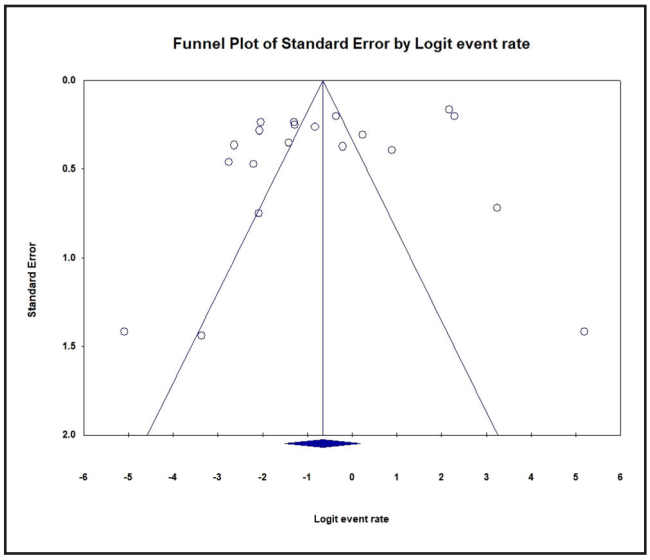

Figure 5. Funnel plot showing evidence of publication bias (Egger's test, p = 0.08763).

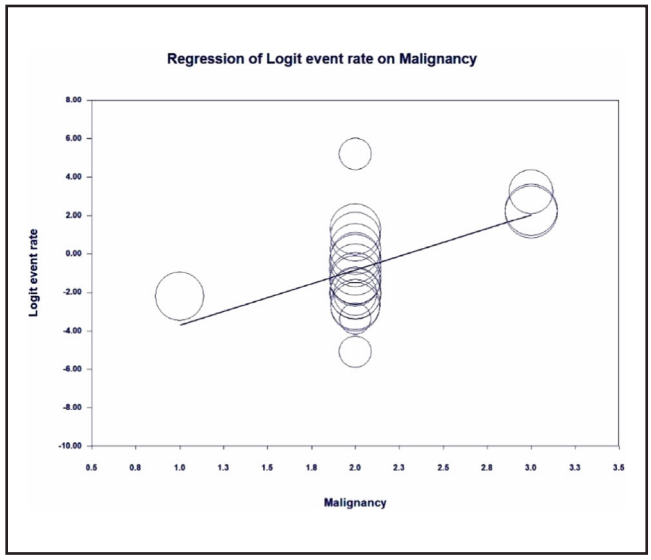

Figure 6. Scatter-plot of meta-regression analysis.

Table 3. Meta-regression on type of malignancy variable

Variable	Coefficient	95% CI	*p*-value
Type of malignancy			
Lymphoma	-1.187	-0.557 – 0.321	< 0.001
Nasopharyngeal carcinoma	3.689	2.161 – 5.217	< 0.001
Gastric carcinoma	-1.010	-3.546 – 1.525	0.435

A total of 197 relevant articles were evaluated, and 21 studies were found to be eligible. The prevalence of EBV infection in Malaysians with malignancies was found to be 36.3% in this analysis. There were three major carcinomas in the sub-group analysis; about 16 studies (23.4%) were from lymphoma cases and one study (10.0%) was from gastric carcinoma case. However, the highest pooled prevalence estimate (90.5%) were from NPC patients. This could be due to the fact that NPC is a common disease among Asians, notably in Southeast Asia and Southern China (Chang & Adami, 2006).

A close assessment of the malignancy cases investigated revealed a male predominance (Table 1). Although gender information for the majority of EBV infection with malignancies cases was not available, the high prevalence of EBV infection with malignancies among male patients in several studies suggests that gender may play a role in the disease (Peh *et al*., 1995; Karim & Pallesen, 2003; Peh & Quen, 2003; Teoh *et al*., 2019). It is due a relatively large number of people involved in many of the studies were males, the ratio of males to females in the enrolled participants across the studies reviewed (Table 1) did not appear to have an impact on the low prevalence of EBV infection with malignancies recorded in females.

The age of the participants was also taken into consideration in this study. We discovered that most of the registered participants were adults, with the most of them being over 40 years old, implying that malignancies are more common in adults. This was, however, to be expected, given older age has already been identified as a risk factor for cancer in numerous studies (Peh *et al.,* 2000; Peh *et al.,* 2003; Peh *et al.,* 2008; Peh & Quen, 2003; Yunos *et al*., 2006; Hoe *et al*., 2009; Abdelrahim *et al*., 2018; Ting *et al*., 2019).

This research is of a good merit. It is the first systematic evaluation and meta-analysis of the prevalence of EBV infection in Malaysians with malignancies. A thorough search method was used, with a large number of documents reviewed. Furthermore, sensitivity tests revealed that the prevalence estimate obtained was relatively consistent. Finally, we believe that the results obtained can be relied upon since the studies included were of good methodological quality. However, there are certain limitations, all of which are related to the state of the studies reviewed. For instance, some of the studies included in the analyses had small sample sizes. Furthermore, data on sex, age, and period of EBV infection diagnosis, all of which are important for a thorough assessment of the study population, were missing from some of the articles included in this study.

In conclusion, the prevalence of EBV infection in persons with malignancies in Malaysia was explored in this systematic review and meta-analysis, which is the first study to our knowledge. Published research from across Malaysia yielded a combined prevalence of 36.3%. According to the results of this study, screening for EBV infection in cancer patients is highly suggested since it can aid in determining disease recurrence and metastases.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Supplementary Materials

File S1: Search strategy; File S2: Joanna Briggs Institute (JBI) critical assessment criteria for prevalence data; Figure S1: Funnel plot for publication bias; Table S1: Quality assessment of included studies.

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SUPPLEMENTARY DATA

https://msptm.org/files/Vol39No1/tb-39-1-008-Engku-Abd-Rahman-E-N-S-supplementary-data.pdf