

Original Article

Clinicopathological characteristics and prognostic analysis of Epstein-Barr virus-positive lymphoma: a meta-analysis

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Received December 31, 2015; Accepted March 22, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: This meta-analysis is to clarify that EBV infection is an independent prognostic factor in patients with lymphoma. Literatures were searched via electronic databases of PubMed, MEDLINE and Chinese Biomedical Literature Database (CBM), using the following key words: EBV associated lymphoma, EBV positive lymphoma, EBV related lymphoma and therapy. A meta-analysis was conducted to assess association between EBV infection and overall survival of lymphoma patients by hazard ratios (HRs) with 95% confidence intervals (95% CIs). The heterogeneity was also evaluated in all studies. By following inclusion and exclusion criteria, a total 13 studies containing 784 lymphoma patients were collected for the meta-analysis. We observed that the incidence of lymphoma is higher in males than in females. Compared with diffuse large B-cell lymphoma (DLBCL), the median age was significantly younger in patients with NK/T cell lymphoma which also displayed earlier clinical stages, higher international prognostic index (IPI) and more striking B symptoms. The pooled HR for all studies on EBV-positive lymphoma patients was 2.17 (95% CI: 1.82-2.59), suggesting that EBV infection was significantly associated with a worse overall survival in lymphoma patients. When stratified by ethnicity, tissue types, assays and histological types, HR values on EBV-positive lymphoma patients were greater than 1 in all groups. By using HR as a prognostic value, our meta-analysis confirmed that EBV infection was significantly associated with adverse overall survival in lymphoma patients.

Keywords: Epstein-Barr virus, lymphoma, prognosis, overall survival, hazard ratio

Introduction

Lymphoma, a group of hematologic malignancies in lymph node or extranodal lymphoid tissue, is one of the leading causes of death worldwide. Each year the incidence and mortality of lymphoma show an increasing tendency. Mounting evidence indicates that Epstein-Barr virus (EBV) plays an important role in the pathogenesis of several tumor types, including lymphoma and lymphoproliferative diseases [1-4]. EBV, a member of the human herpesvirus family, is a double stranded DNA virus which was first isolated from Burkitt lymphoma cell culture in 1964 [5]. Epidemiological studies indicate that more than 90% of the world's population is asymptotically or latently infected with EBV [6, 7], although only very few of them undergo malignant transformation. The World Health Organization (WHO) classifies EBV-associated

lymphomas into three groups: EBV-associated Hodgkin lymphoma (HL), EBV-associated B-cell lymphomas and EBV-associated NK/T cell lymphomas [8].

To date, the underlying mechanism by which EBV promotes oncogenesis remains unclear. Previous studies have demonstrated that the latent virus infection does not lead to malignant transformation due to immune surveillance and elimination. To evade the host cell immune surveillance, EBV expresses a small subset of genes, including six nuclear antigens (EBNA-1, -2, -3A, -3B, -3C, and -LP), three latent membrane proteins (LMP-1, -2A and -2B), two small noncoding RNAs (EBER-1 and -2), and BamHI-A rightward transcriptions (BART) [9-13]. Based on the genomic expression pattern, three types of latent gene expression of the EBV genome have been identified: latent I, II, III [14]. Type I

shows the expression of only EBNA1, which is generally associated with EBV-positive B cell lymphomas [15]. Type II latency expresses EBNA1 and the LMPs [10], which is associated with EBV-positive HL, peripheral NK/T cell lymphomas and diffuse large B-cell lymphoma (DLBCL) in the elderly [16]. In type III latency, all EBNA1s and LMPs are expressed, which are associated with EBV-positive posttransplantation lymphoproliferative disorders, AIDS-associated lymphoproliferative disorders, and lymphoblastoid cell lines [17]. The complex formed by EBV encoding proteins contributes to the spread of EBV infection, B lymphocyte proliferation, and evasion of the host's immune system [18].

EBV infection has been implicated in the pathogenesis of a variety of types of tumors, especially in patients with nasopharyngeal carcinoma, Burkitt's lymphoma, NK/T cell lymphoma, Hodgkin lymphoma, and lymphomas in immune incompetent condition [19-23]. In addition, certain epithelial cell tumors, such as gastric carcinoma and breast carcinoma, have also been found to be associated with EBV infection [24, 25]. EBV usually infects B cells, but rarely T- or NK-cells [26, 27]. Most primary EBV infections in normal individuals are asymptomatic. Following primary infection, EBV then persists latently in host memory B lymphocytes [28]. It has been shown that the interplay among virus latency, replication and immune control contributes to the proliferation of EBV-infected lymphocytes and malignant transformation [29, 30]. EBV-positive lymphomas display various clinical features and outcomes in different histologic types. In this meta-analysis review, we summarized the findings of clinicopathological characteristics and outcomes in patients with EBV-positive lymphomas from all selected studies and attempted to clarify the prognostic value of EBV infection in lymphomas.

Methods

Literature search strategy

Studies were retrieved via electronic databases of PubMed, MEDLINE and Chinese Biomedical Literature Database (CBM) using the following key words: EBV associated lymphoma, EBV positive lymphoma, EBV related lymphoma and therapy. All databases were searched up to April 12, 2015 with the earliest

study on January 1, 1995. The abstracts of articles and reviews were initially screened to select relevant articles. After the screening, a meticulous reading was conducted to narrow our search according to inclusion and exclusion criteria.

Inclusion and exclusion criteria

To be eligible for inclusions, studies have to meet the following criteria: (1) Virus infection in lymphoma patients was measured by multiple assays with the availability of data of EBV-DNA in peripheral blood and EBER, LMP1, LMP2A in tumor tissues. The common assays to quantify virus contents are polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). (2) Overall survival (OS) in patients between EBV-positive and EBV-negative lymphoma was compared. (3) Hazard ratio (HR) and 95% confidence interval (CI) for OS were reported or could be calculated from the data presented.

The exclusion criteria were as follows: (1) Letters, reviews, case reports, conference abstracts, editorials, and expert opinion were excluded. (2) Articles in which OS was not given, or HR could not be calculated were excluded. (3) Immunodeficient patients, such as HIV infection or transplantation, were excluded. Secondary lymphomas such as connective tissue diseases or drug related lymphomas were also excluded. Studies published in both English and Chinese were searched.

Statistical analyses

We reviewed all studies that met the inclusion and exclusion criteria. Data from selected articles were extracted and stratified by first author's name, year of publication, source of patients, language of publications, numbers of patients, location of expression, assays, HR estimate, HR and 95% confidence interval (**Table 1**). HR and 95% confidence interval were used to estimate the impact of EBV infection on overall survival of lymphoma patients. A combined $HR > 1$ indicated a worse prognosis. Moreover, the impact of EBV infection was considered statistically significant of 95% confidence interval when the combined HR did not overlap 1. The value of HR and 95% confidence was calculated from Kaplan-Meier curves in some studies that did not provide

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Table 1. Characteristics of included studies

First Author	Year	Source	Language	N. of P EBV(+)	N. of P EBV(-)	Sample	Method	HR Estimate	95% CI
Oyama T [35]	2007	Japan	English	96	107	Tissue	FISH	HR	3.5 (2.3-5.5)
Wang ZY [36]	2012	China	English	34	35	Peripheral blood	PCR	Sur. Curve	1.39 (0.07-27.92)
Ahn JS [37]	2013	Korea	English	18	204	Tissue	FISH	Sur. Curve	1.82 (0.99-3.35)
Jung CK [38]	2011	Korea	English	35	16	Tissue	FISH	Sur. Curve	0.38 (0.18-0.81)
Jarrett RF [39] (16-34 y)	2005	United Kingdom	English	53	175	Tissue	FISH	Sur. Curve	0.71 (0.20-2.54)
Jarrett RF [39] (>50 y)	2005	United Kingdom	English	64	62	Tissue	FISH	Sur. Curve	1.70 (1.02-2.84)
Claviez A [40]	2005	Germany	English	263	579	Tissue	IHC	Sur. Curve	1.13 (0.77-1.65)
Koh YW [41]	2012	Korea	English	55	104	Tissue	FISH	Sur. Curve	3.26 (1.462-7.226)
Mao Y [42] (LPM1)	2012	China	English	9	7	Tissue	IHC	Sur. Curve	1.85 (0.28-12.48)
Mao Y [42] (LMP2A)	2012	China	English	7	9	Tissue	IHC	Sur. Curve	1.56 (0.26-9.25)
Ito Y [43]	2012	Japan	English	26	100	Peripheral blood	PCR	HR	4.0 (1.2-13.7)
Paydas S [44]	2008	Turkey	English	25	152	Tissue	IHC	Sur. Curve	3.40 (1.95-5.91)
Dupuis J [45] (<60 y)	2006	France	English	22	33	Tissue	FISH	Sur. Curve	1.13 (0.48-2.69)
Dupuis J [45] (>60 y)	2006	France	English	23	32	Tissue	FISH	Sur. Curve	4.48 (1.99-10.08)
Kwong YL [46]	2013	China	English	21	33	Peripheral blood	PCR	HR	19.887 (5.331-74.104)
Park S [47]	2007	America	English	34	346	Tissue	FISH	Sur. Curve	2.9 (1.1-8.1)
Hahn JS [48]	2002	Korea	English	20	34	Tissue	FISH	Sur. Curve	1.88 (0.57-6.20)
Zhan HQ [49]	2014	China	Chinese	35	46	Tissue	FISH	Sur. Curve	1.65 (0.83-3.27)

N. of P: Number of Patients, HR: Hazard ratio, 95% CI: 95% confidence interval, FISH: Fluorescence in situ hybridization, PCR: Polymerase chain reaction, IHC: Immunohistochemistry.

Table 2. Clinical Characteristics of included studies

First Author	Pathological types	Age	Male/Female	Ann Arbor (III/IV)	ECOG 2-4	IPI (HI/H)	B symptom	LDH elevated	Extranodal infiltration ≥2	CR
Oyama T	DLBCL	71 (45-92)	56/40	48	36	43	38	47	28	38.5%
Wang ZY	NK/T	39 (15-71)	20/14	0	0	0	34	34	6	NA
Ahn JS	DLBCL	66 (51-82)	14/4	10	5	7	6	10	4	50%
Jung CK	NK/T	42 (30-78)	10/3	8	0	1	NA	5	NA	40%
Jarrett RF	HL	NA	NA	NA	NA	NA	NA	NA	NA	NA
Claviez A	HL	11 (2.7-19.1)	180/83	85	NA	NA	87	NA	NA	NA
Koh YW	HL	NA	40/15	41	NA	25	29	35	NA	AN
Mao Y	NK/T	51 (25-71)	13/3	2	NA	5	8	5	NA	43.75%
Ito Y	NK/T	46.5 (17-67)	14/12	12	0	NA	11	7	NA	46.15%
Paydas S	NA	NA	14/11	11	9	NA	18	22	NA	NA
Dupuis J	PTCL	NA	36/9	38	13	18	NA	29	13	NA
Kwong YL	NK/T	52.5 (16-83)	NA	21	NA	18	NA	16	NA	23.81%
Park S	DLBCL	65 (20-95)	18/16	19	10	12	13	13	11	72%
Hahn JS	NK/T	39 (20-73)	11/9	2	3	NA	7	NA	NA	65%
Zhan HQ	PTCL	NA	24/11	18	NA	NA	8	NA	NA	NA

HI/H: High-intermediate/high, LDH: Lactate dehydrogenase, CR: Complete remission, DLBCL: Diffuse large B cell lymphoma, HL: Hodgkin's lymphoma, PTCL: Peipheral T-cell lymphoma, NA: Not applicable.

these results [31]. Kaplan-Meier curves were analyzed by Engauge Digitizer version 4.1. To assess heterogeneity among the studies, we used the Cochran Q and I^2 statistics. For the Q statistic, P value <0.05 was considered statistically significant for heterogeneity [32]. The random effects model was calculated according to the DerSimonian-Laird method, otherwise, the fix-effects model (Mantel-Haenszel method) was used [33]. For I^2 , a value $>50\%$ was considered a measure of severe heterogeneity [34]. The statistical analyses were performed by Review Manager 5.0. Forest plot of HR for survival of EBV-positive lymphoma patients and funnel plots for assessment of publication bias were analyzed by Review Manager 5.0.

Results

Literature selection

A total of 1575 potentially relevant articles were collected after the initial search of databases, including 1025 articles in English and 550 articles in Chinese. Among them, 1446 articles were excluded from analysis after the screening through titles and abstracts, leaving 119 articles for further full-text reading. After full-text reading, 46 studies were then excluded due to irrelevant lymphomas to the present review (23 transplantation-caused, 16 HIV-related and 7 secondary lymphomas), leaving

63 articles for further reading. These 63 articles studied the correlation between EBV infection and clinicopathological features as well as prognostic significance of lymphomas. After the exclusion due to insufficient data, 15 studies fulfilled the inclusion criteria and were eligible for our meta-analysis.

Characteristics of included studies

The basic feature descriptions were summarized in **Tables 1** and **2**. This systemic review included 15 clinical retrospective studies from 2002 to 2014. The study population came from 8 countries, including China, Japan, Korea, United Kingdom, Germany, Turkey, France and United States of America with 840 patients included. All articles were published in English but one in Chinese. The numbers of EBV-positive lymphoma patients and control group in included studies ranged from 7 to 263 and 7 to 579, respectively. Twelve studies investigated EBV levels using lymphoma tissues and three studies using peripheral blood. Different assays were applied in these studies. FISH and IHC were used to detect EBV infection in lymphoma tissues in nine and three studies respectively and PCR was applied to quantify EBV DNA contents in peripheral blood samples in three studies. These studies used HR and 95% confidence interval to estimate OS with this data directly provided in five studies. For remaining ten studies without providing the data, OS was calculated from survival curves.

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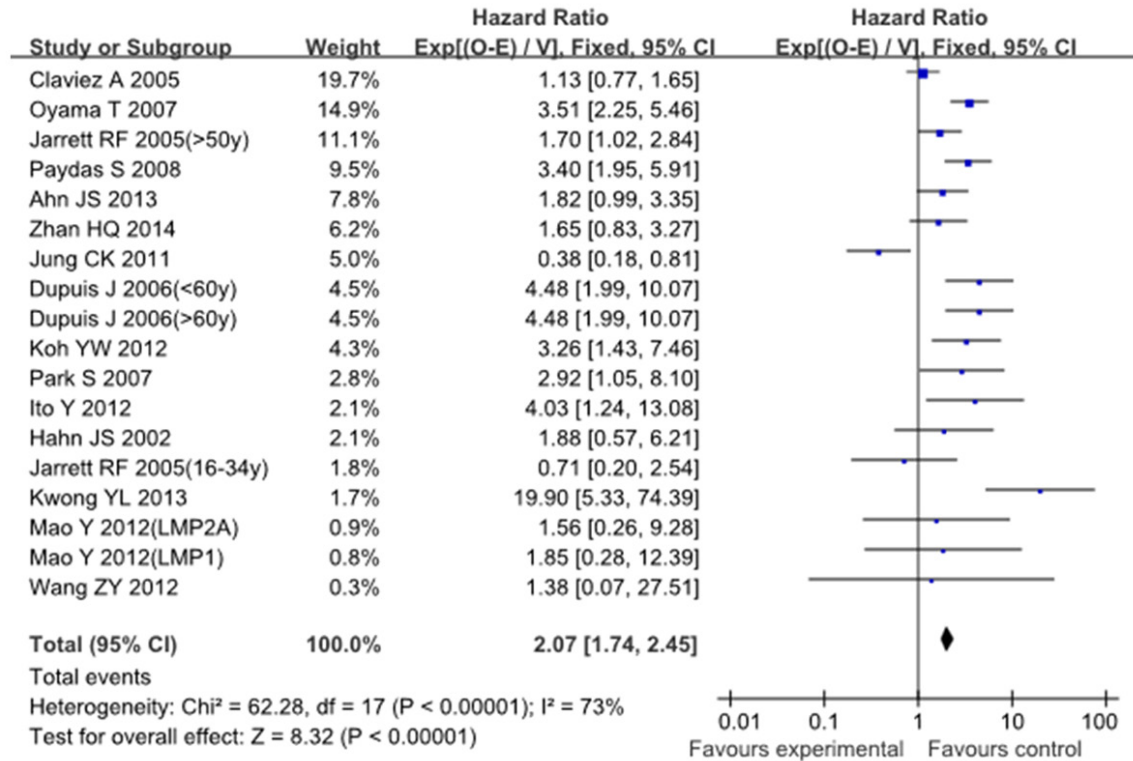


Figure 1. Forest plot of hazard ratio(HR) for survival of EBV-positive lymphoma patients.

Regarding histological types, Hodgkin and non-Hodgkin lymphomas were investigated in three and twelve studies, respectively. Among the 12 studies of non-Hodgkin lymphoma, there were three diffuse large B cell lymphoma (DLBCL), six NK/T cell lymphoma, two peripheral T cell lymphoma (PTCL) and one non-classified NHL. In context of sex, there were more male patients than females, suggesting a higher incidence in male. The median age was significantly younger in patients with NK/T cell lymphoma than DLBCL, with earlier clinical stages (according to Ann Arbor stage and ECOG), higher international prognostic index and more striking B symptoms.

Assessment of heterogeneity

To assess the study heterogeneity in this review, we performed Cochran Q and I^2 analysis. As shown in **Figure 1**, there was a significant heterogeneity when all studies were pooled (Chi-squared: 62.28, I^2 : 73%, $P < 0.00001$). From the forest plot (**Figure 1**), we found that two studies of Jung CK and Kwong YF especially contributed to this statistical heterogeneity. To minimize the heterogeneity in our analysis, we excluded these two studies based on the fol-

lowing reasons: (1) In Jung CK's study, other pathological types besides NK/T cell lymphoma were included, such as T lymphoblastic lymphoma, angioimmunoblastic T-cell lymphoma, PTCL and anaplastic large cell lymphoma, all of which are non-EBV-associated lymphomas. Furthermore, the curve of overall survival was plotted according to those T cell lymphomas. (2) Kwong YL demonstrated the diagnostic and prognostic value of circulating EBV level in NK/T cell lymphoma with SMILE chemotherapy. However, the EBV level was measured during and after chemotherapy courses, in which the impact of drugs cannot be distinguished. (3) The sample size of these two studies was small ($n=56$) and the total weight was slight (6.7%), so the impact of the combined HR from two studies was negligible. After excluding these two studies, a final analysis of 784 patients from 13 studies was performed. Heterogeneity still existed, but it dropped to a lower level (Chi-squared: 31.71, I^2 : 53%, $P=0.007$).

Results of meta-analysis

The meta-analysis was performed and results were summarized in **Table 3**. Overall, the pooled

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Table 3. Summarized HRs of overall and subgroup analysis for the EBV(+) patients survival

	N. of studies	N. of P.	HR (95% CI)	Heterogeneity test		
				Chi-squared	I ²	P value
Overall	13	784	2.17 (1.82, 2.59)	31.71	53%	0.007
Ethnicity						
Asian	8	300	2.54 (1.94, 3.34)	6.46	0%	0.60
European	5	484	1.94 (1.54, 2.45)	23.06	74%	0.008
Sample						
Tissue	11	724	2.15 (1.79, 2.57)	30.55	57%	0.004
Peripheral blood	2	60	3.49 (1.17, 10.44)	0.42	0%	0.51
Method						
FISH	8	420	2.48 (1.99, 3.10)	15.29	41%	0.08
PCR	2	60	3.49 (1.17, 10.44)	0.42	0%	0.51
IHC	3	304	1.62 (1.19, 2.20)	10.34	71%	0.02
HR estimated						
HR	4	211	3.43 (2.42, 4.86)	0.19	0%	0.98
Sur. Curve	9	573	1.85 (1.51, 2.28)	22.63	51%	0.02
Pathogenic types						
NHL	10	349	2.88 (2.30, 3.62)	9.80	0%	0.55
HL	3	435	1.41 (1.06, 1.87)	6.88	56%	0.08
Pathogenic types*						
HL	3	435	1.41 (1.06, 1.87)	6.88	56%	0.08
DLBCL	3	148	2.81 (2.00, 3.94)	2.92	31%	0.23
NK/T	4	96	2.33 (1.17, 4.62)	1.32	0%	0.86
PTCL	2	80	2.97 (1.91, 4.60)	4.82	58%	0.09

*: One study without definite pathological type was excluded from calculating HR.

HR of all evaluable studies on EBV-positive patients was 2.17 (95% CI: 1.82-2.59), suggesting that EBV positivity was significantly associated with a worse overall survival in lymphoma patients. In the subgroup of ethnicity, a similar finding was observed that the combined HR of both Asian and European studies was greater than 1 (Asian: HR: 2.23; 95% CI: 1.94-3.34 and European: HR: 1.94; 95% CI: 1.54-2.45), although the heterogeneity of European studies was significantly higher (Chi-squared: 23.06, I²: 74%, P=0.008). In terms of sample types, the combined HR was 2.15 (95% CI: 1.79-2.57) and 3.49 (95% CI: 1.17-10.44) for lymphoma tissue, and peripheral blood, respectively. Regarding assay types, the combined HR was 2.48 (95% CI: 1.99-3.10) for FISH, 3.49 (95% CI: 1.17-10.44) for PCR, and 1.62 (95% CI: 1.19-2.20) for IHC. When HR could be detected directly in the studies with OS result provided, the combined HR was 3.43 (95% CI: 2.42-4.86) while the HR was 1.85 (95% CI: 1.15-2.28) in studies in that OS must be calculated from survival curve. The combined HR

was 2.88 (95% CI: 2.20-3.62) for NHL and 1.41 (95% CI: 1.06-1.87) for HL. After further stratification, the combined HR was 2.81 (95% CI: 2.00-3.94) for DLBCL, 2.33 (95% CI: 1.17-4.62) for NK/T cell lymphoma and 2.97 (95% CI: 1.91-4.60) for PTCL. One study without definite pathological type was excluded from calculating HR. Taken together, these results suggest that EBV infection might be an independent prognostic factor in patients with Hodgkin or non-Hodgkin lymphoma.

Publication bias

Publication bias was examined by using funnel plots. As shown in **Figure 2**, no obvious funnel plot asymmetry was found in all included studies. Thus, no evidence of publication bias was detected.

Discussion

Lymphoma is a malignancy of immune system in lymph node or extranodal lymphoid tissue with an increased incidence and mortality each

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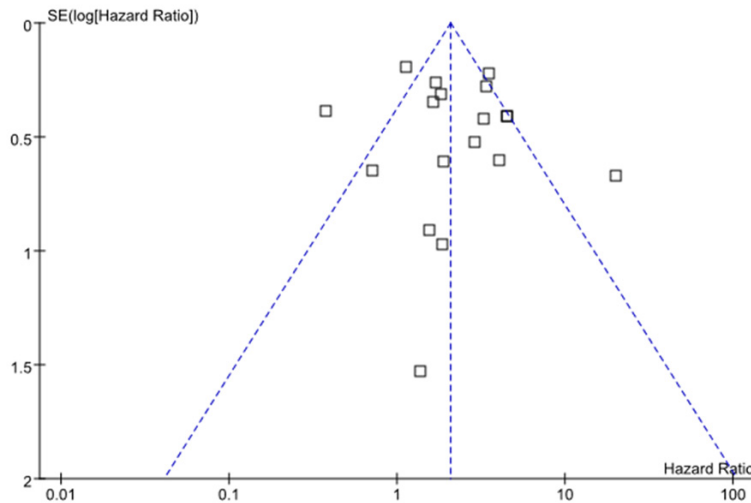


Figure 2. Funnel plots were used to estimate publication bias.

year. Lymphoma is classified into B-, T-, NK-derived lymphoma with high heterogeneity in clinical characteristics. EBV infection is closely associated with the occurrence, progression and prognosis of lymphomas. However, the underlying mechanism by which EBV promotes oncogenesis remains unclear. EBV has been demonstrated to transform B cells into lymphoblastoid cell lines in vitro. Many human cancers, including Burkitt lymphoma, Hodgkin lymphoma, immunodeficiency-associated lymphoproliferative diseases, and diffuse large B cell lymphoma, are associated with EBV infection [50-53]. In addition, it is widely accepted that EBV is a B-lymphotropic and epitheliotropic virus and rarely infects T cells and NK cells. Actually, T cells play a crucial role in the suppression of EBV-associated oncogenesis. The life cycle of EBV is composed of a lytic state and a latency state, the latter allowing lifelong persistence of the virus in the host cells. The replication cycle of EBV consists of three phases: (1) entry into either epithelial cells or naive B cells after oropharyngeal transmission; (2) lytic replication, and (3) latency. Once a cell has become infected, the viral capsid dissolves and the DNA is transported into the cell nucleus. EBV persists in B cells throughout the differentiation from naive B cells to germinal center cells to long-lived memory B cells [50, 54]. In memory B cells, no infectious virus is produced in the latency state. Depending on the expression of specific EBV-associated proteins and RNAs, three different viral latency types have been described, which promote the development of lymphoma in the patients.

Given that EBV infection is related to the development of lymphoma, a number of studies have investigated the prognostic value of EBV in lymphoma. However, the findings from these reports are somewhat controversial possibly due to limited sample size in each study. We therefore performed a meta-analysis to amplify the sample size and evaluate the prognostic value of EBV infection in patients with lymphoma.

In this review, 15 articles were included according to the inclusion criteria with a highly

significant heterogeneity. To reduce the heterogeneity, we excluded two studies. In one study, the OS curve was plotted based on data from T cell lymphomas which are EBV-irrelevant lymphomas. Another study tested EBV level after SMILE chemotherapy without distinguishing the impact of drugs. Ultimately, 13 articles were included in our meta-analysis to assess the prognostic value of EBV in lymphoma. In all studies, EBV infection was confirmed by FISH, PCR and IHC using either lymphoma tissue or peripheral blood. These studies included the common pathological types, such as DLBCL, NK/T cell lymphoma, PTCL, and HL. Overall, male has a higher incidence than female. Although the median age in NK/T cell lymphoma was significantly younger than DLBCL, the patients with this histological type usually were under earlier clinical stages (Ann Arbor stages and ECOG) with higher IPI and more striking B symptoms. In this meta-analysis, we observed that the pooled HR for all studies on EBV-positive lymphoma patients was greater than 1. This holds true when stratified by ethnicity, tissue types, assays and histological types, confirming that EBV positivity was significantly associated with a worse overall survival in lymphoma patients.

In this meta-analysis, the heterogeneity exists, which can be contributed by patient characteristics such as age, sex, region, ethnicity, pathologic types. We minimized the heterogeneity by excluding two studies whose results were not in line with the focus of this review. Regarding

publication bias, our analysis showed that there was no evidence of publication bias in this meta-analysis review.

In summary, this meta-analysis confirmed that EBV infection is significantly associated with adverse overall survival in patients with Hodgkin or non-Hodgkin lymphoma, suggesting that EBV infection might be an independent prognostic factor in lymphoma.

Acknowledgements

This review article was supported by: National Natural Science Foundation (No. 81270598, and No. 81473486), National Public Health Grand Research Foundation (No. 201202017), Natural Science Foundations of Shandong Province (No. 2009ZRB14176 and No. ZR2012-HZ003), Technology Development Projects of Shandong Province (No. 2008GG2NS02018, No. 2010GSF10250, and No. 2014GSF118-021), Promotive Research Fund for Excellent Young and Middle-aged Scientists of Shandong Province (No. BS2013YY003 and No. BS2013-YY009), Program of Shandong Medical Leading Talent, and Taishan Scholar Foundation of Shandong Province.

Disclosure of conflict of interest

None.

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