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Prognostic significance of latent membrane protein 1 expression in non-Hodgkin lymphoma

A meta-analysis

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Abstract

Background: The prognostic value of latent membrane protein 1 (LMP1) in non-Hodgkin lymphoma (NHL) has been evaluated in several studies. However, the conclusions remain controversial.

Methods: We searched relevant literatures from Embase, PubMed, and China National Knowledge Infrastructure Platform databases and performed a meta-analysis to evaluate the prognostic significance of LMP1 expression in NHL. Pooled hazard ratio (HR), 95% confidence interval (CI), and *P* value were calculated. Nine relevant studies were analyzed in this meta-analysis. We performed a pooled analysis to assess the association between LMP1 expression and overall survival of NHL patients.

Results: Our results revealed that LMP1-positive NHL patients had significantly poorer outcomes than LMP1-negative patients (HR = 2.13, 95% CI = 1.31–3.46, $P_{heterogeneity} = 0.005$, $I^2 = 63.5\%$). Furthermore, in the subgroup analysis stratified by country, a statistically significant association was found among Chinese (HR = 2.80, 95% CI = 1.53–5.15, $P_{heterogeneity} = 0.342$, $I^2 = 6.9\%$); however, no statistically significant relations were found among Japanese (HR = 1.55, 95% CI = 0.74–3.24, $P_{heterogeneity} = 0.020$, $I^2 = 65.7\%$).

Conclusion: The expression of LMP1 can be considered a poor predictor of survival in patients with NHL. In addition, LMP1 expression assessment could provide more detailed information for patients with NHL and could be used to optimize therapeutic schemes.

Abbreviations: CI = confidence interval, EBV = Epstein–Barr virus, HR = hazard ratio, IHC = immunohistochemistry, LMP = latent membrane protein, LMP1 = latent membrane protein 1, NHL = non-Hodgkin lymphoma, OS = overall survival, TNF = tumor necrosis factor.

Keywords: Epstein–Barr virus, latent membrane protein 1, meta-analysis, non-Hodgkin lymphoma

1. Introduction

Non-Hodgkin lymphoma (NHL) is the most common malignancy of the blood system in the world.[1] It is more common in developed countries, and in 2014 there were 70,800 new cases in the United States. NHL, which accounts for 4.3% of all cancers in the US, is listed as the 7th most common cancer in men and the 6th most common cancer among women.[2,3] In China, NHL represents approximately 2% of new cancer cases diagnosed each year, becoming the 8th most common cancer and the 10th largest cause of cancer deaths.[4,5]

NHL is a heterogeneous group of malignant lymphoma. For the development of NHL, immune suppression is the most important risk factor. The risk of developing high-grade NHL is increased in patients with human immunodeficiency virus. Other risk is increased, including organ transplantation, stem cell transplantation in patients with high-dose chemotherapy, and those with genetic immune deficiency syndrome or autoimmune disease.[6,7] Infection does play a role in the development of certain lymphomas, either by suppressing immune function or through other mechanisms, such as chronic inflammatory induced. Epstein–Barr virus (EBV), for example, has been recognized with Burkitt and nasal NK-cell or T-cell lymphoma, and *Helicobacter pylori* as a risk factor in association with infections related to gastric mucosa-associated lymphoid tissue lymphoma.

EBV is an important paradigm for transforming viruses in several NHL subtypes.[8] The expression of EBV in NHL can be detected by immunohistochemical identification of EB virus latent membrane protein (LMP). The role of EBV as the etiological agent in the development of NHL has been supported by detecting high levels of LMP1 expression in these tumors.[9] There are several studies assessing the prognostic role of LMP1 expression in NHL, and no consistent outcomes are reported.[10–18] To provide a comprehensive assessment of the prognostic role of LMP1 expression in NHL, we performed a meta-analysis of published studies.

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2. Materials and methods

Ethical approval for this study was not unnecessary since it was a meta-analysis that collect and analysis data from the existing literatures.

2.1. Search strategy

We searched for relevant studies up to May 2015 through the PubMed, Embase, and China National Knowledge Infrastructure Platform (CNKI; http://www.cnki.net) database with the following terms and their combinations: "lymphoma/non-Hodgkin lymphoma," "Epstein–Barr virus/EB virus," "latent membrane protein 1/LMP-1," and "prognosis/survival." All scanned abstracts, studies, and citations were reviewed. Moreover, references of the retrieved manuscripts were also manually cross-searched for further relevant publications.

2.2. Selection criteria

The inclusion criteria included: be on patients with NHL; provide overall survival (OS) data to evaluate the role of LMP1 expression in the prognosis of NHL patients; and provide hazard ratios (HRs) with 95% confidence intervals (CIs) or enable calculation of these statistics from the data presented. The exclusion criteria included: the studies which used the same population or overlapping database; the studies of in vitro cell culture models.

2.3. Data extraction

Two independent investigators extracted the original data according to the inclusion criteria and exclusion criteria to ensure the accuracy of the retrieved information. The following data were collected from each study: first author name, publication year, country where the research was performed, number of patients, histology, detection method, antibody used and its dilution, cutoff value for positivity, and OS data.

2.4. Statistical analysis

Previously reported indirect methods were used to extract the log HR (logHR) and variance due to the few prognostic literature, which report these values directly.[19,20] These values were calculated either from the HR and 95% CI in the reference, the log rank *P*-value, or directly from the Kaplan–Meier curves. When an HR and 95% CI were not available in the study, estimated values were obtained indirectly by using Kaplan–Meier curves described by Tierney et al.[20] Kaplan–Meier curves were read by an Engauge Digitizer, version 4.1 (http://digitizer.sourceforge.net/), and the data from the curves were entered in the spreadsheet appended to Tierney et al's report.[20] Q-test results of $P<0.10$ suggested significant heterogeneity among studies, so the pooled HR of all studies was calculated using the random-effects model based on DerSimonian–Laird method; otherwise, the fixed-effects model based on Mantel–Haenszel method was conducted. Meta-regression was performed to detect the source of heterogeneity by country, histological type, size of study, detection method, and cutpoint. Between studies, variance Tau-squared (τ^2) value was used to evaluate the degree of heterogeneity, and the τ^2 was used to describe the extent of heterogeneity explained. We also performed sensitivity analysis by omitting an individual study each time to check whether any of these estimates can bias the overall estimate. The evaluation of potential publication bias was performed using the Begg funnel plots and Egger test ($P<0.05$ was regarded as representative of statistical significance). All the data management and analysis for this meta-analysis were performed with STATA 12.0 software (Stata corporation, College Station, TX), and all tests were 2-sided.

3. Results

3.1. Characteristics of the studies

The literature search yielded 216 articles at initial screening. After exclusion of 172 irrelevant articles, the remaining articles were systematically reviewed, and 21 articles were chosen for full-text reading. After full-text reading, 12 articles were further excluded due to the reasons indicated in Fig. 1. Therefore, 9 independent studies composed of 417 NHL patients were finally collected in this meta-analysis. The flow chart of literature search and study selection was illuminated in Fig. 1. The main characteristics of these included studies were shown in Table 1.

3.2. Quantitative synthesis

All 9 studies including 417 patients explored the prognostic significance of latent membrane protein 1 (LMP1) expression in NHL. We performed pooled analysis with available data on the correlation between LMP1 expression and OS. The main results of this meta-analysis were showed in Table 2. The pooled results showed that LMP1-positive NHL patients had significantly poorer outcomes than LMP1-negative patients (HR = 2.13, 95% CI = 1.31–3.46, $P_{\text{heterogeneity}}=0.005$, $I^2=63.5\%$) (Fig. 2). In the subgroup analysis stratified by country, a statistically significant association was found among Chinese (HR = 2.80, 95% CI = 1.53–5.15, $P_{\text{heterogeneity}}=0.342$, $I^2=6.9\%$); however, no statistically significant relations were found among Japanese (HR = 1.55, 95% CI = 0.74–3.24, $P_{\text{heterogeneity}}=0.020$, $I^2=65.7\%$) (Fig. 3). Moreover, we performed subgroup analyses according to histological type, size of study, detection method, and cutpoint. In subgroup analysis based on histological type, a statistically significant association was found in NHL (HR = 3.11, 95% CI = 1.76–5.49, $P_{\text{heterogeneity}}=0.858$, $I^2=0\%$); however, no statistically significant relations were found in ENKL (HR = 2.32, 95% CI = 0.63–8.49, $P_{\text{heterogeneity}}=0.003$, $I^2=78\%$) (Table 2). In subgroup analysis based on size of study, a statistically significant association was found in ≥50 group (HR = 2.68, 95% CI = 1.73–4.41, $P_{\text{heterogeneity}}=0.715$, $I^2=0\%$); however, no statistically significant relations were found in <50 group (HR = 1.86, 95% CI = 0.88–3.95, $P_{\text{heterogeneity}}=0.009$, $I^2=67.6\%$) (Table 2). In subgroup analysis based on detection method, a statistically significant association was found in immunohistochemistry (IHC) group (HR = 2.11, 95% CI = 1.19–3.74, $P_{\text{heterogeneity}}=0.056$, $I^2=51.1\%$); however, no statistically significant relations were found in other group (HR = 2.63, 95% CI = 0.56–12.39, $P_{\text{heterogeneity}}=0.015$, $I^2=83.1\%$) (Table 2). In subgroup analysis based on cutpoint, a statistically significant association was found in yes group (HR = 2.71, 95% CI = 1.39–5.27, $P_{\text{heterogeneity}}=0.016$, $I^2=67\%$); however, no statistically significant relations were found in no group (HR = 1.46, 95% CI = 0.56–3.76, $P_{\text{heterogeneity}}=0.026$, $I^2=67.8\%$) (Table 2).

3.3. Evaluation of heterogeneity

There was heterogeneity among studies in overall comparisons and also subgroup analyses. Meta-regression revealed that country,

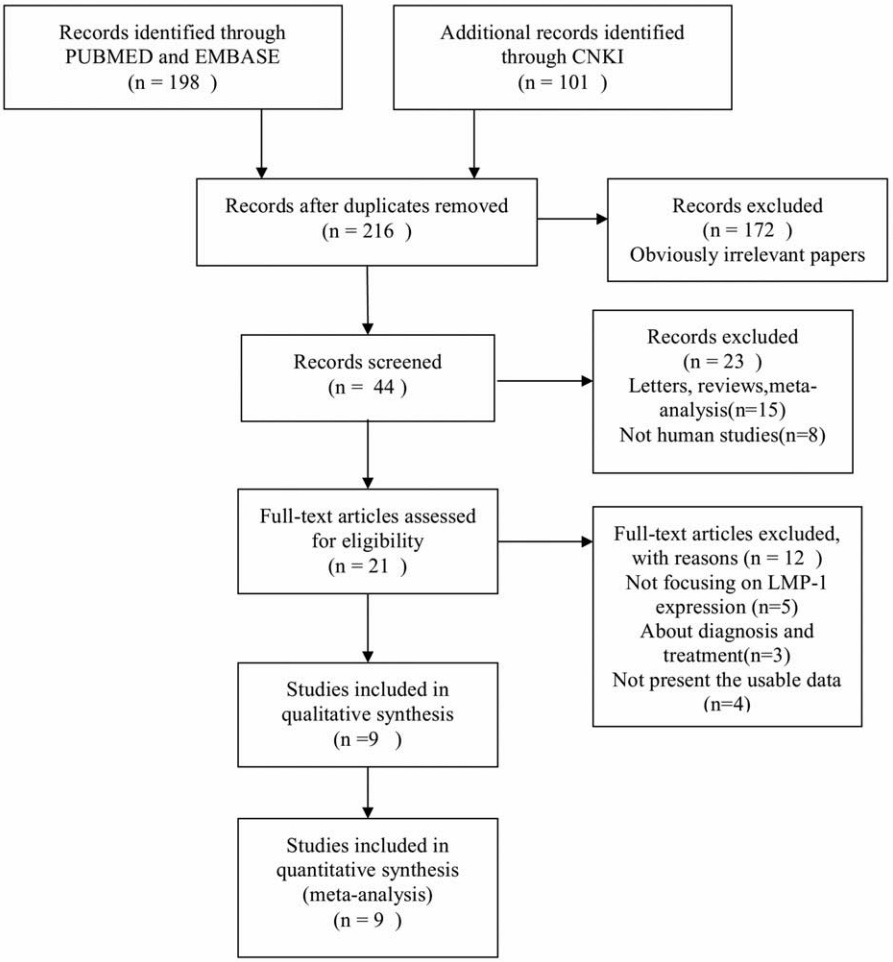

Figure 1. Flow diagram of studies identification.

histological type, size of study, detection method, and cutpoint did not contributed to the source of heterogeneity ($\tau^2 > 0.05$).

3.4. Sensitivity analysis

Sensitivity analysis was performed to investigate the influence of each study on the overall HRs, and the result showed that no individual study affected the overall HR dominantly, since the omission of any single study made no substantial difference (Fig. 4). This procedure confirmed the stability of the overall result.

3.5. Publication bias

Finally, the Egger regression test showed no evidence of asymmetrical distribution in the funnel plot in LMP1 expression in NHL (Begg test $P = 0.754$; Egger test $P = 0.221$) (Fig. 5).

Table 1

Characteristics of studies included in this meta-analysis.

Authors/year of publication	Country	Histological type	No of patients ($LMP1^+/LMP1^-$)	Method	Cutpoints	HRs
Kuze/1996[10]	Japan	BCL	6/11	IHC	NA	1.77 (0.29–10.70)
Yamamoto/1999[11]	Japan	TCL	15/10	ISH	mRNA positive	1.34 (1.02–1.75)
Cao/2003[12]	China	NHL	48/22	IHC	Percentage of positive cells, >5%	3.42 (1.03–11.41)
Hirose/2006[13]	Japan	PTCL	14/29	IHC	NA	1.91 (0.78–4.69)
Ishii/2007[14]	Japan	ENKL	13/7	Real-time PCR	≥4 copies/mL	6.63 (1.88–23.41)
Cao/2008[15]	China	ENKL	47/11	IHC	Percentage of positive cells, ≥10%	2.16 (1.01–3.96)
Paydas/2008[16]	Turkey	NHL	20/118	IHC	NA	3.02 (1.58–5.75)
Kanemitsu/2012[17]	Japan	ENKL	22/8	IHC	NA	0.28 (0.06–0.96)
Mao/2012[18]	China	ENKL	9/7	IHC	Staining intensity ≥1	8.75 (1.41–54.48)

BCL = anaplastic large cell lymphoma of B-cell type, ENKL = extranodal NK/T-cell lymphoma, HR = hazard ratio, IHC = immunohistochemistry, ISH = in situ hybridization, NA = not available, NHL = non-Hodgkin lymphoma, PCR = polymerase chain reaction, PTCL = peripheral T-cell lymphomas, TCL = T-cell lymphoma.

Table 2

Meta-analysis of prognostic significance of latent membrane protein 1 expression in NHL.

Study characteristics	No of patients ($LMP1^+/LMP1^-$)	HR (95%CI)	I^2, %	*P* for heterogeneity
Total (N=9)	194/223	2.13 (1.31–3.46)	63.5	0.005
Country Japan (N=5)	70/65	1.55 (0.74–3.24)	65.7	0.020
China (N=3)	104/40	2.80 (1.53–5.15)	6.9	0.342
Turkey (N=1)	20/118	3.02 (1.58–5.76)	–	–
Histological type ENKL (N=4)	91/33	2.32 (0.63–8.49)	78	0.003
NHL (N=2)	68/140	3.11 (1.76–5.49)	0	0.858
Other (N=3)	35/50	1.39 (1.07–1.79)	0	0.733
Size of study <50 (N=6)	79/72	1.86 (0.88–3.95)	67.6	0.009
≥50 (N=3)	115/151	2.68 (1.73–4.41)	0	0.715
Method IHC (N=7)	166/206	2.11 (1.19–3.74)	51.1	0.056
Other (N=2)	28/17	2.63 (0.56–12.39)	83.1	0.015
Cutpoints yes (N=5)	132/57	2.71 (1.39–5.27)	67	0.016
No (N=4)	62/166	1.46 (0.56–3.76)	67.8	0.026

CI=confidence interval, ENKL=extranodal NK/T-cell lymphoma, HR=hazard ratio, IHC=immunohistochemistry, LMP1=latent membrane protein 1, NHL=non-Hodgkin lymphoma.

4. Discussion

EBV, also known as human herpesvirus 4, establishes mainly latent infection based on B lymphocytes, but it can also infect other types of cells, including the NK cells, T cells, and epithelial cells. EBV infection as a causal factor has been implicated in a variety of malignant tumors, including lymphoma and virus encoded latent gene expression patterns, depending on the origin and the state of the tumor.[21] The first protein from EBV having its carcinogenic nature by experience confirmed is LMP1,[22] which is expressed on the cell surface, where it spontaneously gathered to form a constitutive activation of the receptor expression, as a member of the tumor necrosis factor (TNF) receptor family, and allows the LMP1 exert influence on cells with different intracellular signaling cascade of cellular and molecular interactions involved.[23–26] Recently, a growing number of studies have investigated the prognostic significance of LMP1 expression in NHL; however, the results are conflicting. A possible explanation is that Epstein–Barr encoding region in situ hybridization and LMP1 IHC are widely used methods for identifying EBV in tumor cells; however, some errors about these methods are relevant.[27,28] For this reason results are highly variable and the comments about the EBV and NHLs are highly different. Furthermore, certain epidemiologic factors (eg, age,

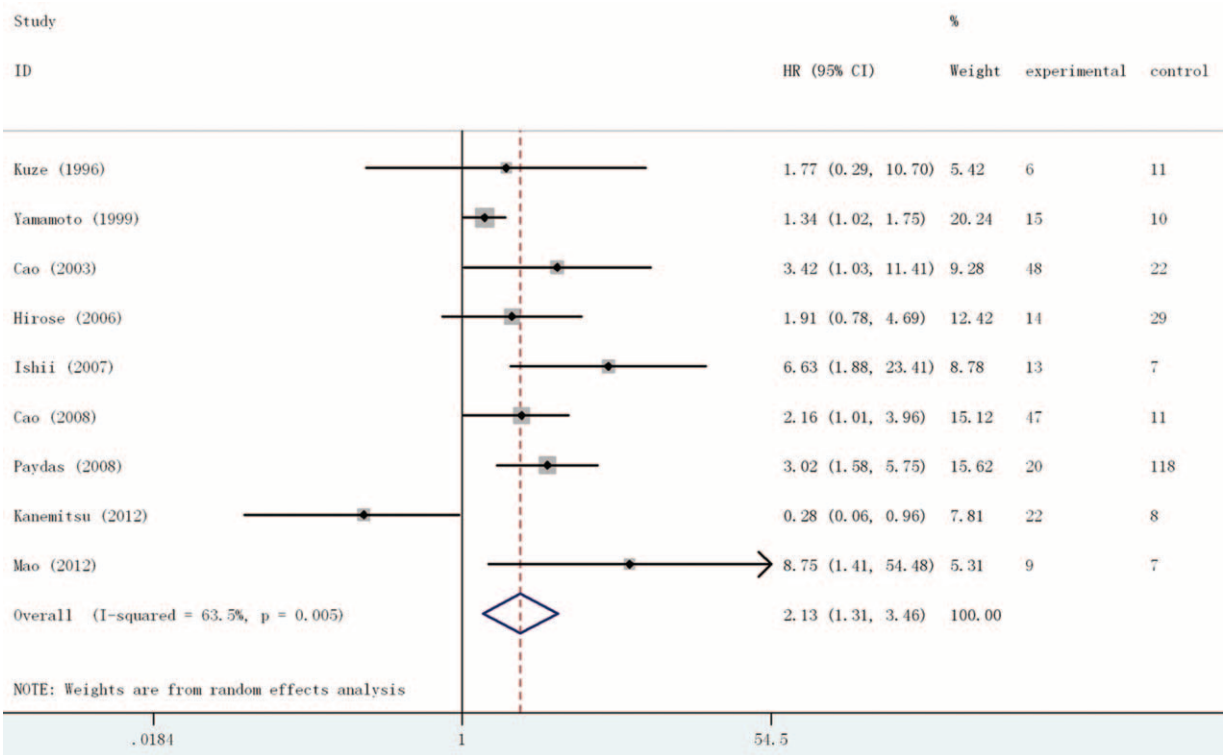

Figure 2. HRs and 95% CI of individual studies and pooled data for the association of LMP1 expression and OS in NHL patients. CI=confidence interval, HR=hazard ratio, LMP=latent membrane protein, NHL=non-Hodgkin lymphoma, OS=overall survival.

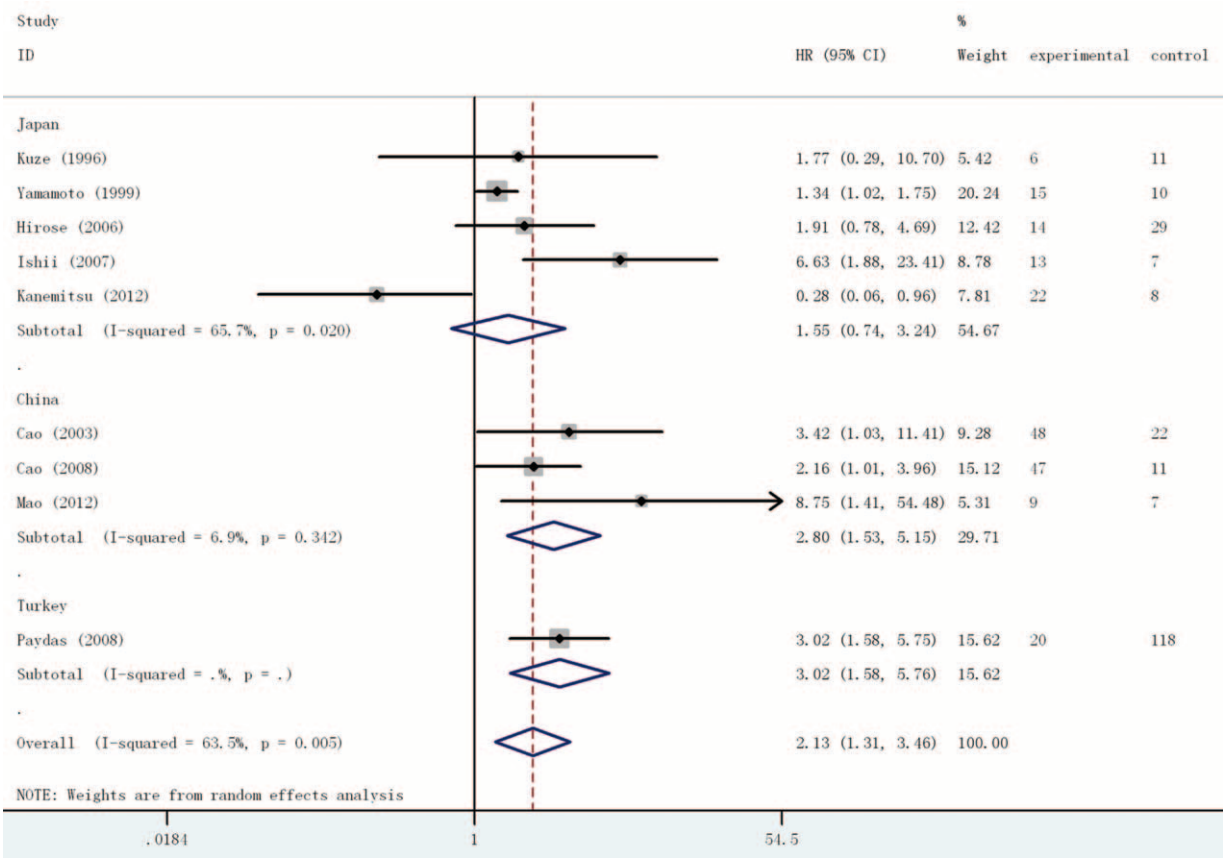

Figure 3. Forest plot of the HRs and 95% CIs of studies on the association of LMP1 expression and OS with country in NHL patients. CI = confidence interval, HR = hazard ratio, LMP1 = latent membrane protein 1, NHL = non-Hodgkin lymphoma, OS = overall survival.

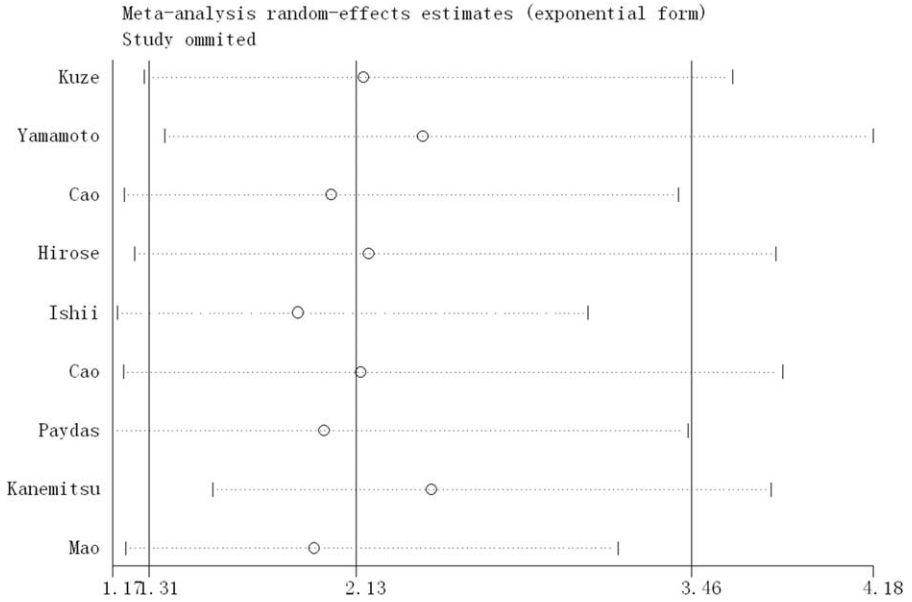

Figure 4. The influence of individual studies on the summary HRs. The middle vertical axis indicates the overall HRs and the 2 vertical axes indicate its 95% CI. Every hollow round indicates the pooled HRs when the left study was omitted in this meta-analysis. The 2 ends of every broken line represent the 95% CI. CI = confidence interval, HR = hazard ratio.

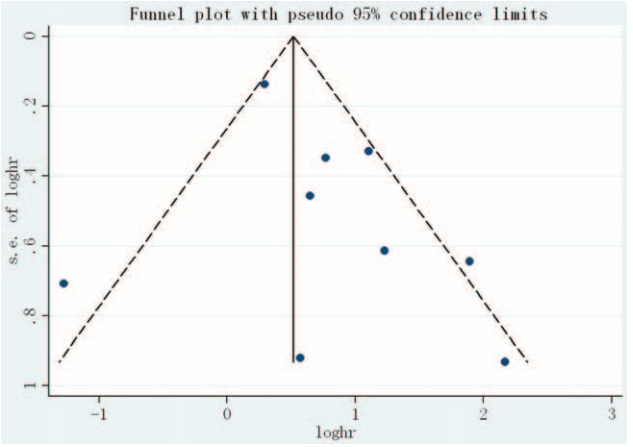

Figure 5. Begg funnel plot for publication bias test for the prognostic significance of LMP1 expression in NHL. Each point represents a separate study for the indicated association. LMP1 = latent membrane protein 1, NHL = non-Hodgkin lymphoma.

geographical factors, socioeconomic status, and so on) might influence the prognostic impact of LMP1 expression in NHLs.[29,30] In order to obtain a comprehensive conclusion, we retrieved the relevant literature and performed a meta-analysis.

Meta-analysis is a systematic review that uses quantitative methods to synthesize and summarize the results from related studies.[31,32] Most meta-analyses are based on one of 2 models, the fixed-effect statistical model or a random effects statistical model. The fixed-effects model assumes that all included studies investigate the same population and estimate the same treatment effect. That is to say, there is no between-study heterogeneity in the true intervention effect. The meaning of this pattern is that the observed changes in the therapeutic effect are only due to the difference in opportunity from sampled patients. In this study, if the *P*-value of the Q-test >0.10, we chose a fixed-effects model. The random effects meta-analysis model assumes that the observed therapeutic effects can be estimated differently depending on the actual differences in the therapeutic effect in each study, as well as the sampling variability. Therefore, even though all studies had an infinite sample size, the observed effects of the study will still vary because of the real difference in treatment outcomes. This heterogeneity of therapeutic effect is due to differences in study population, length of follow-up, interventions, and other factors. Therefore, when the *P*-value of the Q-test is <0.10, we chose a random-effects model.

The results of our meta-analysis showed significant correlations of LMP1 expression with OS in NHL (HR = 2.13, 95% CI = 1.31–3.46, $P_{\text{heterogeneity}} = 0.005$, $I^2 = 63.5\%$), implying that EBV latent infection and LMP1 expression may be an important factor for NHL development or progression. Although the physiological function of LMP1 in Hodgkin lymphoma and nasopharyngeal carcinoma are well investigated,[33,34] the pathogenesis of NHL remains largely unknown. Previous studies have shown that TNF induces LMP1 receptor signaling pathways in infected cells by recruiting TNF receptor related factors and other adaptor proteins.[33,34] LMP1 activates nuclear factor-kappa B and phosphoinositide 3-kinase/Akt signaling through the pathway signaling. These events played an important role in the immortalization of B cell and transformation of rodent fibroblasts.[33,34] Recently, Cader et al[35] reported that LMP1 can induce expression of the collagen receptor, discoidin domain receptor 1, in B cells. Discoidin domain receptor 1 expression of B cell lymphoma was protected from apoptosis by collagen exposure, suggesting that some of the oncogenic effects of LMP1 may be dependent on alterations to the microenvironment.[35] The latent 2nd pattern of NK/T cell lymphoma expression has a variable LMP1 expression, which contributes to the excessive production of proinflammatory cytokines mediated by the activation of nuclear factor-kappa B.[36]

The LMP1 expression and prognosis of lymphoma have been investigated by several meta-analyses.[37,29] Recently, Chen et al[37] conducted a comprehensive meta-analysis about effect of LMP1 expression on OS in EBV-associated cancers, and found that LMP1 expression can be used as a prognostic biomarker in nasopharyngeal carcinoma, NHL, and certain Hodgkin disease patients. Compared with Chen's work, we only focus on the association of LMP1 expression and NHL prognosis, while Chen et al analyzed a variety of EB virus-associated cancers, including nasopharyngeal carcinoma, NHL, Hodgkin disease, and gastric cancer, etc. Additionally, 2 published studies[12,18] were not included in that meta-analysis. Compared with another meta-analysis about prognostic significance of EBV LMP1 expression in lymphomas reported by Mao et al,[29] we identified more eligible studies,[10,11,13,18] while they only analyzed 5 studies about NHL.

Meanwhile, some limitations in this meta-analysis should be noticed: First, IHC method may affect the prognosis, because different detection antibody and different to determine the cut-off value for the determination of high LMP1 levels. Second, there was a significant heterogeneity. Selection criteria for different patients, treatment options, as well as for LMP1 testing methods are possible explanations for heterogeneity. Third, there may be some bias if other studies besides English and Chinese were ruled out. Fourth, although we extracted HRs and 95% CIs using the strategies reported by Tierney et al,[20] the data calculated from the Kaplan–Meier curve may not be as precise as obtaining data directly from the original article. Fifth, since more detailed individual patient data are not available, we are currently unable to conduct a more comprehensive analysis of prognostic effect. Finally, relatively small sample size in the inclusion study led to even very strong prognostic factors that may not be significant.

In conclusion, despite the limitations of this meta-analysis, our study confirmed that the expression of LMP1 can be considered a poor predictor of survival in patients with NHL. LMP1 expression assessment could provide more detailed information for patients with NHL and could be used to optimize therapeutic schemes. Further studies with larger dataset and well-designed models are required to validate our findings.

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