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ORIGINAL RESEARCH

Prognostic implications of circulating Epstein–Barr virus DNA for extranodal natural killer/T-cell lymphoma, nasal type: a meta-analysis

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Introduction: To evaluate the prognostic value of circulating Epstein-Barr virus DNA for extranodal natural killer/T-Cell lymphoma, nasal type (ENKTL), we performed a meta-analysis of published studies that provided survival information with pre-/post-treatment circulating EBV DNA.
Methods: Eligible studies that discussed prognostic significance of circulating EBV DNA in ENKTL were included. Random effects models were applied to obtain the estimated hazard ratios and 95% confidence intervals to evaluate prognostic significance (OS and DFS/PFS). Eleven studies covering a total of 562 subjects were included in this analysis.
Results: The summary HRs and 95% CIs of pre-treatment EBV DNA for OS and PFS/DFS were 4.43 (95% CI 2.66–7.39, $P<0.00001$) and 3.12 (95% CI 1.42–6.85, $P=0.005$), respectively. The corresponding HRs and 95% CIs of post-treatment EBV DNA for OS and PFS/DFS were 6.28 (95% CI 2.75–14.35, $P<0.0001$) and 6.57 (95% CI 2.14–20.16, $P=0.001$). Subgroup analyses indicated a strong trend of prognostic powers with pre-/post-treatment EBV DNA.
Conclusion: With the present evidence, circulating EBV DNA consistently correlated with poorer prognosis in patients with ENKTL which need further investigation in large-scale clinical studies.

Keywords: circulating EBV DNA, ENKTL, prognosis

Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL-NT) is an aggressive malignancy of putative NK-cell origin, with a minority deriving from the T-cell lineage, which presents peculiar clinicopathological features, including angioinvasion, prominent necrosis, and close association with Epstein–Barr virus (EBV).[1,2] It occurs most commonly (80%) in the nose and upper aerodigestive tract, and less commonly (20%) in the non-nasal areas (skin, gastrointestinal tract, testis, salivary gland). It generally pursues an aggressive clinical course and has a poor outcome.[3] Despite recent application of PET/CT in diagnosis,[4] concurrent chemoradiotherapy in early-stage patients,[5–7] and newly developed chemotherapy regimen containing L-asparaginase,[8,9] it still presents a poor prognosis without an established standard therapy.

Previous studies have identified several prognostic clinicopathological features of ENKTL, including age, primary sites, Ann Arbor stage,[10] International prognostic index,[11] and Korea-developed NK/T-cell prognostic index.[12] However, varying outcomes have been observed in patients with similar prognostic features and undergoing similar therapies, suggesting inherent heterogeneity of tumor and insufficiency of existing prognostication.[13] Although several biomarkers have been reported as a prognostic

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surrogate, prognostic prediction in ENKTL is still dismal. Therefore, it is of great clinical value to identify novel biomarkers, which could be utilized as effective prognostic predictors or possible therapeutic targets, in order to optimize the treatment of patients with ENKTL.

EBV is a human herpes virus that has been confirmed to be in close association with several lymphoid and epithelial malignancies.[14,15] It has been reported that inappropriate expression of EBV latent genes combined with environment and genetic cofactors may result in virus-associated malignancies.[16] In EBV-associated nasopharyngeal carcinoma (NPC), the putative tumorigenic role has been thoroughly studied and revealed in large-scale studies that circulating EBV DNA is correlated with tumor load and disease prognosis.[17–19] Circulating EBV DNA has been detected in plasma or serum in lymphomas, including ENKTL, Hodgkin's disease, AIDS-related lymphoma, and diffuse large B-cell lymphoma. Due to the rarity of ENKTL, there is only several small series of studies that reported the prognostic effect of circulating EBV DNA, with various clinical stages, primary locations and treatment regimens.

Hence, we conducted the present meta-analysis to comprehensively explore the potential prognostic impact of circulating EBV DNA in ENKTL.

Materials and methods

Search strategy

We searched systematically PubMed, Embase, the Science Citation Index, Cochrane databases, and the Ovid Database for studies discussed prognostic significance of circulating EBV DNA in ENKTL, with no restrictions on language, place of publication, or date of publication (up to June 2017). The main search terms explored were "Epstein-Barr virus", "EBV", "EBV load", "Natural killer/T-cell lymphoma", "NK/T-cell lymphoma", and "ENKTL".

Eligibility criteria

To yield potential relevant publications, we screened the titles and abstracts and author information. Full texts were considered for detailed assessment according to the following inclusion criteria: 1) containing patient cases of ENKTL, 2) measuring the titer of circulating EBV DNA in either plasma or whole blood, and 3) investigating the prognostic significance of EBV DNA titers in ENKTL patients with at least one of the outcome measures of interest. Studies excluded from our study were those that: 1) were duplicated publications, and 2) showed no survival data or insufficient data to be extracted.

Data extraction

Two investigators (CW and YZ) independently evaluated each paper and extracted data, and any discrepancy between the 2 researchers was resolved via discussion, with a third investigator if necessary. The following information was extracted: first author, publication year, type of studies, population characteristics (i.e., country, number of patients), clinicopathological characteristics (i.e., anatomical sites, tumor stage), sampling time (pre-treatment, intra-treatment, or post-treatment), detection methods (reverse transcription-polymerase chain reaction [RT-PCR]), EBV DNA positive rate, median EBV DNA copies, end points, and survival data. For 1 study using 2 different primer sets for LMP1 and Bam HI W fragment by RT-PCR, each of the cohorts was considered an independent data set.

Statistical approaches

Statistical analysis was performed using Review Manager 5.2 (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration, 2012).[22] The estimated hazard ratio (HR) and associated 95% CI were used to evaluate prognostic significance (overall survival [OS] and disease-free survival/progression-free survival [DFS/PFS]). If the HR and its variance were not reported directly in the original study, these values were calculated based on survival data or survival curves using software designed by Tierney.[20] The random-effects model was explored to perform the analyses, because this model obtained more conservative results than the fixed-effect model.[21] Heterogeneity among the studies was tested using the χ^2 test and I^2 statistic. A value of I^2<25%, within 25%–50%, or >50% was regarded as low, moderate, or significant heterogeneity, respectively. We then evaluated the potential publication bias with funnel plots. The quality of the included studies was assessed with the Newcastle–Ottawa scale (NOS) for cohort studies.[22]

Results

Baseline characteristics

The comprehensive literature search was performed till June 2017, yielding a total of 406 studies. Among these studies, 356 publications were identified as non-English publications, duplicates, or laboratory researches. The remaining 50 studies were thoroughly reviewed, of which 11 studies were appropriate for the meta-analysis (Figure 1).

Eleven studies (sample size from 15 to 120) with 562 patients, basically located in East Asia, were published between 2002 and 2016.[23–33] All the included publications provided data on the correlation between circulating EBV

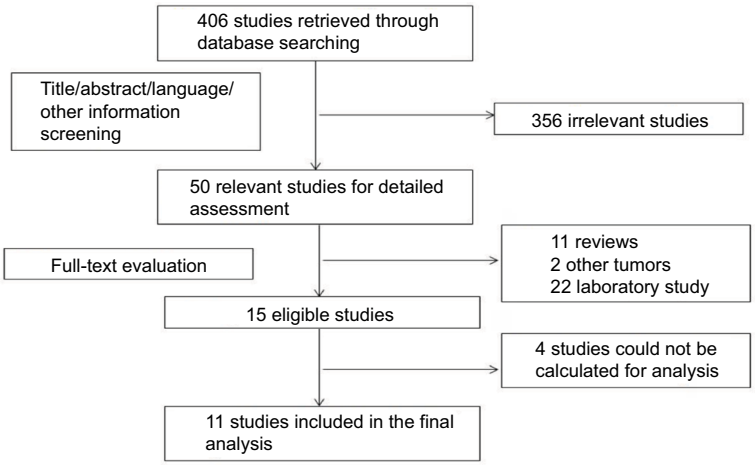

Figure 1 Selection of studies.
Note: Flow diagram showing the selection process for the enrolled studies.

DNA and prognosis in patients with ENKTL. There were 4 studies designed prospectively[25,27,29,30] and the remaining retrospectively. The most employed detection methods were RT-PCR, with 1 study from Japan[24] using 2 different primer sets for LMP1 and Bam HI W fragment, which was considered as 2 independent data sets. For the sample types of included studies, 5 studies used EBV DNA detection in plasma, 1 study used serum, 3 studies from whole blood, 1 study from plasma/MNC, and 1 study from plasma/whole blood. Positive rates of detected EBV DNA irrespective of methods and time points varied from 4.20% to 100% in extracted studies. The characteristics of the included studies are summarized in Table 1. The quality of the included studies was evaluated with NOS and summarized in Table 2.

Correlation between EBV DNA and survival outcome

Pre-treatment EBV DNA and OS

A total of 10 cohorts evaluated the relationship between pre-treatment EBV DNA and OS, with 7 cohorts giving the HRs and 95% CIs for OS directly; the HRs in the remaining studies were extracted using the survival curves with *P*-values. The χ^2 test showed low heterogeneity among the studies (P=0.34; I^2=11%). The combined pooled HR of the aforementioned studies by a random-effects model was 4.43 (95% CI: 2.66–7.39, P<0.00001), indicating that high EBV DNA load was significantly associated with a poor OS in patients with ENKTL (Figure 2A).

Pre-treatment EBV DNA and DFS/PFS

Five articles reporting the correlation between pre-treatment EBV DNA load and DFS/PFS and 6 cohorts were included for meta-analysis. HR and 95% CI for DFS/PFS were directly extracted from the study reported from 2 cohorts by Ishii et al. The χ^2 test showed moderate heterogeneity among the aforementioned studies (P=0.12; I^2=43%). The pooled HR with a random-effects model was 3.12 (95% CI: 1.42–6.85, P=0.005), suggesting lower DFS/PFS in ENKTL patients with higher circulating EBV DNA load (Figure 2B).

Post-treatment EBV DNA and OS

A total of 6 cohorts evaluated the relationship between post-treatment EBV DNA. The χ^2 test showed high heterogeneity among the studies (P=0.04; I^2=57%). The combined pooled HR of the aforementioned studies by a random-effects model was 6.28 (95% CI: 2.75–14.35, P<0.0001), indicating that high post-treatment EBV DNA load was significantly associated with a poor OS in patients with ENKTL (Figure 3A).

Post-treatment EBV DNA and DFS/PFS

Four articles reporting the correlation between post-treatment EBV DNA load and DFS/PFS were included for meta-analysis. The χ^2 test showed high heterogeneity among the aforementioned studies (P=0.007; I^2=75%). The pooled HR with a random-effects model was 6.57 (95% CI: 2.14–20.16, P=0.001), suggesting a meaningful relationship of a lower DFS/PFS in ENKTL patients with higher post-treatment circulating EBV DNA load (Figure 3B).

Subgroup analysis

To clarify the intra-study inconsistencies, we further evaluated the relationship between pre-/post-treatment EBV DNA and OS in the following subgroup analysis (Table 3).

Table 1 Baseline characteristics of the enrolled studies

References	Country	No of patients	Type of study	Clinical stage	Primary site	Detection of EBV DNA					Outcomes
						Time	Sample type	Positive rate, No (%)	Median (range) (copies/mL)	Cut-off value (copies/mL)	
Lei et al 2003[22]	HK	15	Retrospective	I–IV/recurrent	All sites	Pre/intra	Plasma	25 (96.2%)	1.67×10^3 ($307–2.25\times10^5$)	600	OS
Ishii et al 2007[24]	Japan	20	Retrospective	I–IV	UNKTL	Pre/intra/post	Serum	20/19 (100%/95%)	349.9 (74.4–1.12×10^5)/55.57 (<4–310)	700/40	OS, DFS
Suzuki et al 2011[25]	Japan	32	Prospective	I–IV	All sites	Pre/intra/post	Plasma/MNC	14 (43.75%)/6 (18.75%)	1.23×10^5 ($50–7.1\times10^5$)/0.2 (0.02–0.78)	0	OS
Wang et al 2012[26]	China	69	Retrospective	I–II	UNKTL	Pre/post	Plasma	58 (84.1%)	491 (0–4.53125×10^5)	500	OS, PFS
Ito et al 2012[27]	Japan	26	Prospective	I–IV/recurrent	ENKTL	Pre/intra/post	Plasma/whole blood	15 (59%)/22 (85%)	870 (0–1.3×10^7)/3.7×10^3 (0–1.1×10^7)	$10^4/10^5$	OS
Kwong et al 2014[28]	HK	56	Retrospective	I–IV	All sites	Pre/intra/post	Plasma	41 (73.2%)	1.9×10^2 (0–1.4×10^7)	0	OS, DFS
Kim et al 2015[29]	Korea	27	Prospective	IV	ENKTL	Pre	Whole blood	17 (63%)	60 (2–4183)	60	OS
Wang et al 2015[30]	China	68	Prospective	I, II	All sites	Pre/post	Plasma	43 (63.2%)/15 (22.1%)	NA	0	OS, PFS
Kim et al 2015[31]	Korea	102	Retrospective	I–IV	ENKTL	Pre/post	Whole blood	48 (47%)/30 (29.4%)	60 (19.3–165.5)	0	OS, PFS
Liang et al 2016[32]	China	120	Retrospective	I–IV	ENKTL	Pre	Plasma	5 (4.2%)	NR	0	OS, DFS
Lim et al 2016[33]	Korea	27	Retrospective	I–IV	ENKTL	Pre	Whole blood	12 (44.4%)	NR	0	OS, PFS

Abbreviations: DFS, disease-free survival; EBV, Epstein–Barr virus; ENKTL, extranodal NK/T-cell lymphoma; HK, Hongkong; Intra, Intra-treatment; MNC, mononuclear cells; No, number; NR, not reported; OS, overall survival; PFS, progression-free survival; post, post-treatment; pre, pre-treatment; UNKTL, upper aerodigestive tract NK/T cell lymphoma.

Table 2 Assessment of study quality using the Newcastle–Ottawa scale

References	Selection (0–4)				Comparability (0–2)		Outcome (0–3)			Total
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Lei et al 2002[23]	1	1	1	1	0	0	1	0	0	5
Ishii et al 2007[24]	0	1	1	1	0	0	1	1	1	6
Suzuki et al 2011[25]	1	1	1	1	0	0	1	1	1	7
Wang et al 2012[26]	0	1	1	1	0	0	1	1	0	5
Ito et al 2012[27]	0	1	1	1	0	0	1	1	0	5
Kwong et al 2014[28]	1	1	1	1	0	0	1	1	0	6
Kim et al 2015[29]	0	1	1	1	0	0	1	1	1	6
Wang et al 2015[30]	0	1	1	1	0	0	1	1	1	6
Kim et al 2015[31]	0	1	1	1	0	0	1	1	1	6
Liang et al 2016[32]	0	1	1	1	0	0	1	1	1	6
Lim et al 2016[33]	0	1	1	1	0	0	1	1	1	6

Notes: "1" means that the study satisfied the item, and "0" means the opposite situation.
Abbreviations: AE, ascertainment of exposure; AF, study controls for any additional factors (chemoradiotherapy, curative resection); AFU, adequacy of follow-up of cohorts; AO, assessment of outcome; DO, demonstration that outcome of interest was not present at start of study; FU, follow-up long enough for outcomes to occur; REC, representativeness of the exposed cohort; SC, study controls for age, sex; SNEC, selection of the non-exposed cohort.

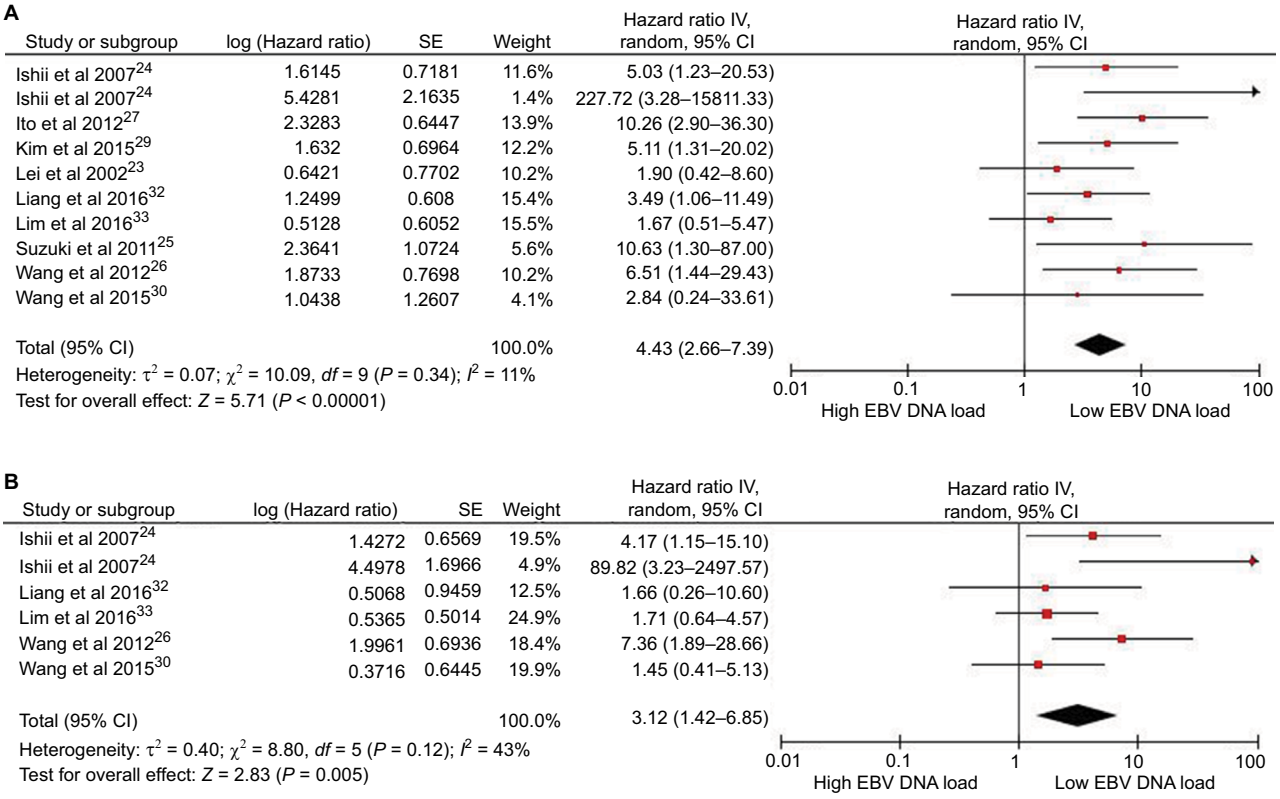

Figure 2 Estimated hazard ratios for OS and PFS/DFS in pre-treatment group.
Notes: (**A**) Forest plot of OS in pre-treatment group. (**B**) Forest plot of PFS/DFS in pre-treatment group.
Abbreviations: DFS, disease-free survival; EBV, Epstein–Barr virus; OS, overall survival; PFS, progression-free survival.

Type of samples: plasma/serum and whole blood/mononuclear cell (MNC)

Pre-treatment EBV DNA is significantly correlated with OS in both plasma/serum and whole blood/MNC subgroups. The HR and 95% CI for OS in plasma/serum and whole blood/MNC subgroups were 5.30 (95% CI: 3.01–9.33, $P<0.00001$) and 5.30 (95% CI: 1.68–16.75, $P=0.005$), respectively. The same relationship was found between post-treatment EBV DNA and OS in subgroup analysis.

Tumor sites: upper aerodigestive tract NK/T-cell lymphoma (UNKTL) and others

When considering primary tumor sites, we further evaluated combined HR and 95% CI for OS in separated subgroups.

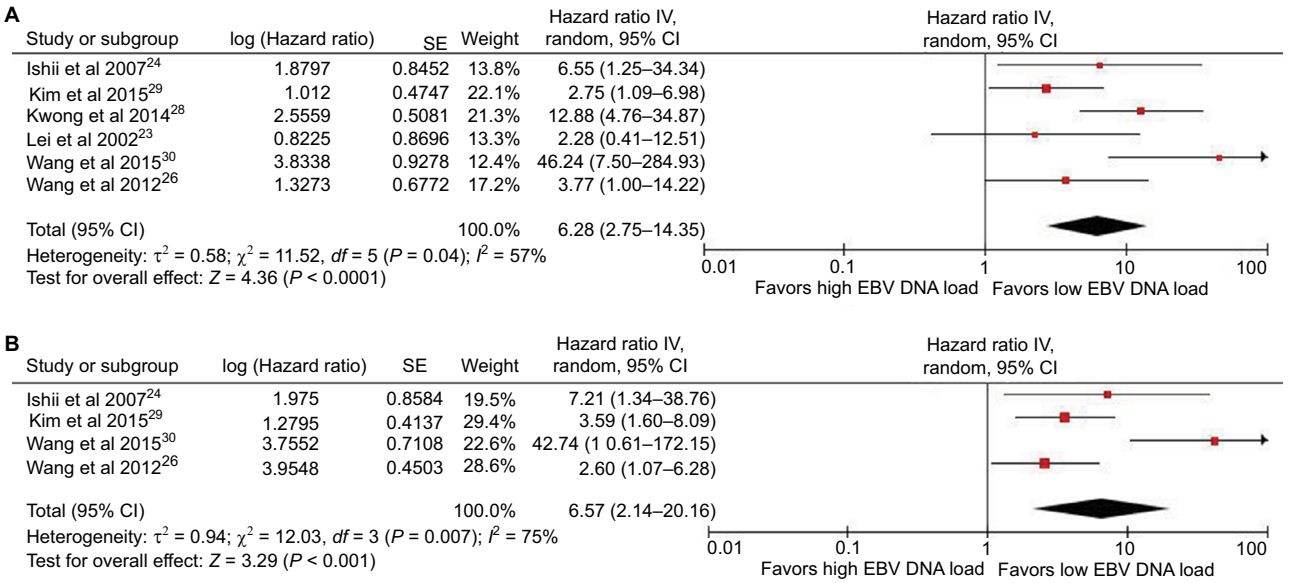

Figure 3 Estimated hazard ratios for OS and PFS/DFS in post-treatment group.
Notes: (**A**) Forest plot of OS in post-treatment group. (**B**) Forest plot of PFS/DFS in post-treatment group.
Abbreviations: DFS, disease-free survival; EBV, Epstein-Barr virus; OS, overall survival; PFS, progression-free survival.

Table 3 Results of subgroup analysis on OS

Variables	Pre-treatment				Post-treatment			
	HR (95% CI)	n	I^2 (%)	*P*-value	HR (95% CI)	n	I^2 (%)	*P*-value
Sample types								
Plasma/serum	5.30 (3.01–9.33)	8	1	0.42	8.25 (4.43–15.36)	5	49	0.10
Whole blood/MNC	5.30 (1.68–16.75)	4	58	0.07	2.75 (1.09–6.98)	1	–	–
Tumor sites								
UNKTL	7.24 (1.24–42.10)	3	38	0.20	4.68 (1.66–13.19)	2	0	0.61
Others	4.15 (2.40–7.17)	3	8	0.37	7.29 (2.13–24.91)	4	73	0.01
Type of study								
Prospective	3.05 (1.52–6.11)	6	15	0.32	46.24 (7.50–284.93)	1	–	–
Retrospective	7.53 (3.60–15.78)	4	0	0.88	4.90 (2.86–8.40)	5	35	0.19
Sample sizes								
N>30	4.81 (2.15–10.79)	4	0	0.76	7.75 (2.54–23.61)	4	71	0.02
N<30	4.43 (1.96–10.06)	6	44	0.12	3.92 (1.20–12.86)	2	0	0.38

Note: "–" = no results.
Abbreviations: HR, hazard ratio; MNC, mononuclear cells; OS, overall survival; UNKTL, upper aerodigestive tract NK/T cell lymphoma.

In UNKTL subgroup, the HR and 95% CI for OS was 7.24 (95% CI: 1.24–42.10, *P*=0.03). Meanwhile, in the subgroup in which the primary tumor was not limited to UNKTL, the HR and 95% CI for OS was 4.15 (95% CI: 2.40–7.17, *P*<0.00001). In included studies evaluating the relationship between post-treatment EBV DNA and OS, the HR and 95% CI for OS was 4.68 (95% CI: 1.66–13.19, *P*=0.003) in ENKTL subgroup, and 7.29 (95% CI: 2.13–24.91, *P*=0.002) in the subgroup in which the primary tumor was not limited to ENKTL.

Type of study: prospective and retrospective

Prospective and retrospective cohorts were both enrolled in this meta-analysis. In further subgroup analysis, the relationship between EBV DNA and OS remains statistically significant in either prospective or retrospective subgroups. The HR and 95% CI for OS in prospective and retrospective subgroups were 7.53 (95% CI: 3.60–15.78, *P*<0.00001) and 3.05 (95% CI: 1.52–6.11, *P*=0.002), respectively. Similar result was found between post-treatment EBV DNA and OS in subgroup analysis.

Sample sizes: N>30 and N<30

In subgroup with large patient number, the HR and 95% CI for OS was 4.81 (95% CI: 2.15–10.79, *P*=0.0001). Meanwhile, in the subgroup with patient number <30, the HR and 95% CI for OS was 4.43 (95% CI: 1.96–10.06, *P*=0.0004). When considering the relationship between post-treatment

EBV DNA and OS, the HR and 95% CI for OS was 7.75 (95% CI: 2.54–23.61, *P*=0.0003) in subgroup with large patient number and 3.92 (95% CI: 1.20–12.86, *P*=0.02) in subgroup with patient number <30.

Sensitivity analysis and publication bias

There was no obvious publication bias seen in this meta-analysis (Figure 4A and B)

Discussion

The standard of care for patients with ENKTL remains controversial. Concurrent chemoradiotherapy, chemotherapy regimen containing L-asparaginase, and stem cell transplantation[34] have been proposed for patients with ENKTL. However, these high-dose, aggressive therapy strategies do not always translate into survival benefits, with the cumulative probability of 5-year survival ranging from 10% to 55%.[35–37] The optimal treatment strategies and prognostic prediction have not been completely defined yet.

To our knowledge, this is the first meta-analysis to assess the prognostic value of circulating EBV DNA load in patients with ENKTL. Previous small-scale (N<60) studies have showed that high load of circulating EBV DNA is associated with a poorer survival in ENKTL patients. Hence, a quantitative meta-analysis is urgently required for individualized cancer treatment. Our meta-analysis, which

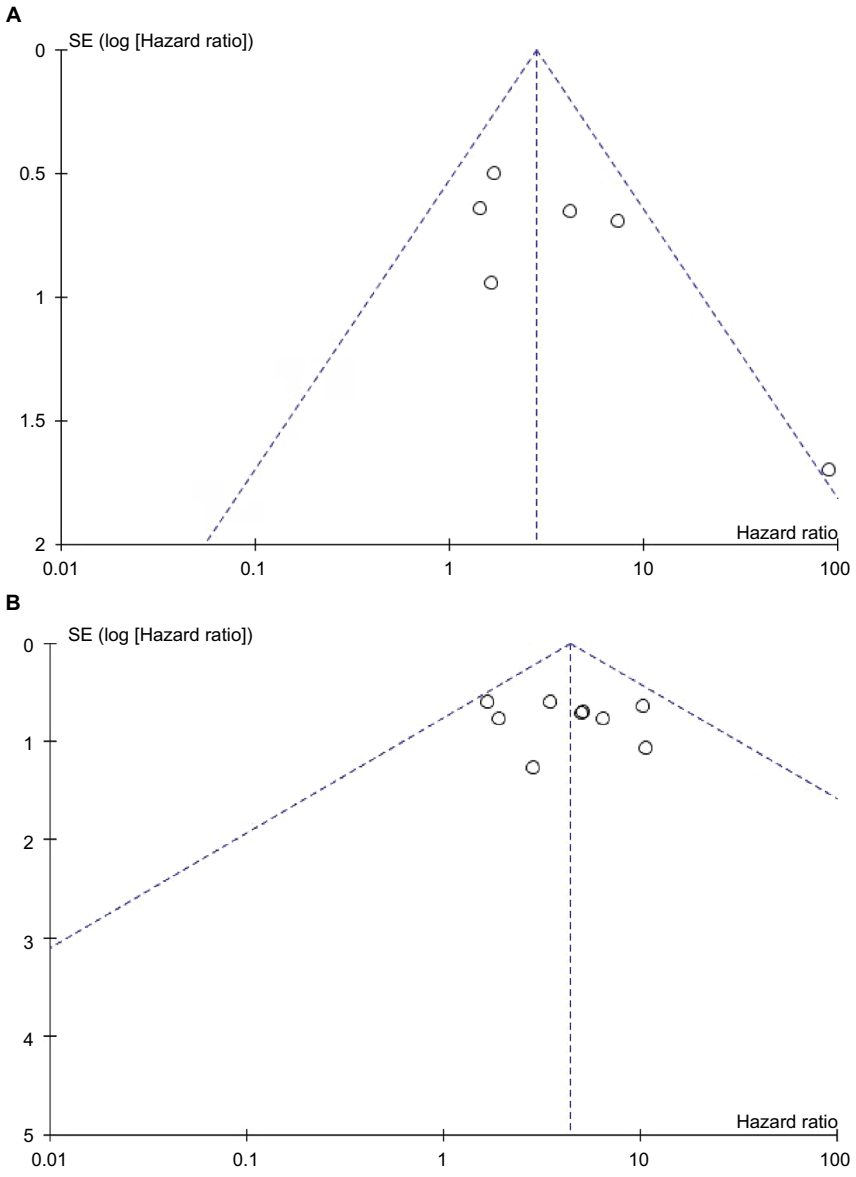

Figure 4 Funnel plots of the enrolled studies.
Notes: (**A**) OS in pre-treatment group. (**B**) OS in post-treatment group.
Abbreviation: OS, overall survival.

involved a relatively large series of patients, provided robust evidence that circulating EBV DNA load in peripheral blood is significantly associated with poor OS and PFS/DFS in patients with ENKTL.

As a well-known EBV-associated malignancy, the invariable association with episomal infection of EBV in ENKTL cells has strongly implied its tumorigenic role. Fragmented viral DNA has also been found in peripheral blood from EBV-associated malignancies, which was mostly <500 bp in length.[38,39] It is reasonable to speculate that measurement of the circulating EBV DNA level may be used as a marker for diagnosis, monitoring treatment response, and prognostication of these EBV-associated malignancies. Previous reports had shown that EBV DNA load has predictive and prognostic significance for EBV-associated malignancies, including NPC[40,41] and Hodgkin's disease.[42,43] The diagnostic and prognostic impact has also been evaluated in patients with ENKTL in relatively small-scale studies, suggesting a favorable prognosis with low EBV DNA level. Due to the rarity of the disease, the scales of these cohorts remained relatively small with heterogeneous primary locations, clinical stages, sampling time, and treatment regimens. The present meta-analyses provide stronger evidence that the quantification of EBV DNA level is effective in prognostication in patients with ENKTL.

Besides the potential prognostic impact, other clinical applications of circulating EBV DNA in ENKTL have been evaluated in previous small cohorts of publications, including its diagnostic significance,[23,44] relationship with clinicopathological features,[26] and predication of therapy response.[27,45] Due to the limited data, we did not discuss the aforementioned clinical applications in the present meta-analysis. Large-scale investigation is needed to confirm these potential correlations, which may hypothetically help for patient stratification and personalized therapy.

Circulating EBV DNA can be detected from peripheral plasma, serum, whole blood, or peripheral blood mononuclear cells (PBMNCs). There is still controversy regarding selection of the most suitable blood compartment for the detection of EBV DNA. Previous studies suggested that whole blood compartments and PBMNCs demonstrated a higher sensitivity in diagnosis and prognosis than plasma.[46,47] However, Spacek et al reported that detection of EBV DNA in plasma was better than in whole blood in predicting prognosis of Hodgkin's disease.[48] In the present studies, peripheral plasma is mostly used as samples to evaluate EBV DNA level, with 2 cohorts from Korea and Japan using whole blood and another study from Japan using PBMNC. Subgroup analysis shows that regardless of sampling type, circulating EBV DNA level constantly remains strongly correlated with patient prognosis. Comparison of sensitivity and accuracy among each blood compartments is needed for further investigation.

Multiple sampling time points were initially considered in our enrolled studies, including pre-, intra-, and post-treatment. Pre-treatment EBV DNA was mostly applied in majority of included studies, due to the relatively reliable prognostic significance regardless of different therapy regimens. On the other hand, multiple assays of EBV DNA in multiple sample times provided more information, which may be used to analyze the dynamic changes of EBV DNA levels during the treatment. Kwong et al investigated circulating EBV DNA, either baseline or post-treatment, in patients with ENKTL treated with SMILE regimen (comprising steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) and identified 3 DNA dynamic change patterns. It showed that negative EBV DNA after SMILE with pattern A change in EBV DNA (persistently undetectable) significantly correlated with lower tumor load and superior outcome.[28] The prognostic impact of EBV DNA in ENKTL is reliable and the considerations for circulating EBV DNA levels before and after treatment remains controversial, which deserves to be investigated in future studies.

It should be pointed out that limitations exist in the meta-analysis that allow us to interpret the results with caution. First, this meta-analysis was based on published data from the enrolled heterogeneous studies, and individual patient data was not available for further investigation. Second, the total number of patients from included studies was relatively small comparing with meta-analysis for other types of cancers. With regard to pediatric patients, 2 cohorts out of 11 studies included patients who were <14 years of age with no detailed information on the exact patient number, which might include rare pediatric cases. Therefore, the current meta-analysis included rare pediatric cases that were not enough for further analysis. Considering the rarity of ENKTL worldwide, it is difficult to conduct large prospective studies. High-quality meta-analysis may provide more reliable evidence to guide treatment and predict prognosis. Third, the cut-off value of EBV DNA in our enrolled publications varies from 349.9 copies/mL to 6.1×10^7 copies/mL, implying that there was not a uniform cut-off value to define the high load of circulating EBV DNA in patients with ENKTL, which might lead to heterogeneity.

Conclusion

In summary, our meta-analysis provides convincing evidence supporting the proposition that circulating EBV

DNA consistently correlated with prognosis of patients with ENKTL, regardless of primary tumor locations, sampling times, or sample types. However, to confirm this conclusion as well as derived speculations, high-quality, well designed, and large-scale clinical studies of ENKTL are urgently needed.

Novelty and impact statements

In this work, we have for the first time investigated the prognostic value of circulating EBV DNA for ENKTL by meta-analysis based on published data. Our meta-analysis provides convincing evidence supporting the proposition that circulating EBV DNA consistently correlated with prognosis of patients with ENKTL, regardless of primary tumor locations, sampling times, or sample types. To confirm this conclusion, high-quality, well-designed, and large-scale clinical studies of ENKTL are urgently needed.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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