A retrospective analysis of EBV-DNA status with the prognosis of lymphoma

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INTRODUCTION

Epstein–Barr virus (EBV), a ubiquitous human herpes virus characterized by an asymptomatic latency after primary infection,1 is implicated in the development of various haematological diseases, including Hodgkin lymphoma (HL),2 non-Hodgkin lymphoma (NHL),3 and post transplantation lymphoproliferative disorder (PTLD).4 EBV-associated lymphomas can be divided into those occurring in...
immunodeficient individuals, which are true virally driven lymphomas, such as PTLD and HIV-associated immunoblastic lymphoma, and those occurring in immunocompetent individuals. The latter group includes Burkitt lymphoma, Hodgkin’s lymphoma, diffuse large B-cell lymphoma, extranodal NK/T cell lymphoma nasal type, and so on and EBV infection is a cofactor rather than the driving influence.

Epstein-Barr virus spreads through oral cavity, proliferates in the throat, and then lurks in B lymphocytes, usually presenting as a latent infection without clinical symptoms. Given the long-term latent infection, EBV antibody detection is insufficient to diagnose EBV-associated lymphomas. Epstein Barr encoded RNA (EBER) and EBV-DNA are used to define reactivation of EBV. EBER in situ hybridization (FISH) assay is considered to be the gold standard for the detection and diagnosis of EBV active infection. However, biopsies are usually not performed when tumour biopsy tissue is difficult to obtain or when the patient is refractory or relapsed lymphoma. Detection and quantification of EBV nucleic acids in peripheral blood by polymerase chain reaction (PCR) has also been widely used in the diagnosis and monitoring of EBV-associated lymphomas. However, whether EBV-DNA conversion to negative after treatment and qualitative results of EBV-DNA level before treatment could affect prognosis are unclear. To elucidate these questions, we analysed the clinical characteristics and prognosis of immunocompetent patients with EBV associated lymphoma.

HLH is a rapidly progressive disease with a high fatality rate, which can occur secondary to lymphoma or severe pathogen infection, and its main clinical manifestations are persistent fever, hepatosplenomegaly, and pancytopenia. Previous studies showed that EBV-associated HLH was the most prevalent subtype. In order to study the relationship between EBV active infection and the development of HLH in lymphoma patients, we also analysed the clinical characteristics and prognosis of EBV-associated lymphoma patients with HLH.

2 | MATERIALS AND METHODS

2.1 | Patients

The positivity rates of EBV-DNA in peripheral blood of 26,527 patients who were definitively diagnosed as lymphoma between May 1, 2010 and May 1, 2021 in Department of Lymphoma at Tianjin Medical University Cancer Institute and Hospital were calculated. And the clinical characteristics and prognosis of 202 patients were retrospectively analysed, including 100 EBV-DNA-positive patients and 102 randomly selected EBV-DNA-negative patients. Equidistant random sampling was used to number the patients according to the time of admission. Since the total number of patients is more than 26,000 and there are 100 EBV-positive patients, the sampling interval is set at 260. Select a random number as the sampling unit in the first sampling interval and conduct equidistant sampling according to the sampling interval. A total of 102 negative patients were sampled and statistically analysed. This study and all experiment protocols were approved by the Research Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and performed in accordance with relevant guidelines and regulations. Informed consent of all patients was obtained.

2.2 | Treatment

The first-line chemotherapy regimen was based on cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The second-line regimens include: DHAP (dexamethasone, cisplatin and cytarabine), DA-EPOCH (cyclophosphamide, etoposide, vincristine, doxorubicin and prednisone), GDP (gemcitabine, cisplatin, dexamethasone), Gemox (gemcitabine, Oxaliplatin), and ICE (Ifosfamide, carboplatin, etoposide). All patients were followed up to the date of death or May 1, 2021 (median follow-up: 23.92 months), with 37 patients (29 EBV-DNA-positive patients and 8 EBV-DNA-negative patients) lost follow-up.

2.3 | Clinical evaluation index

The response evaluation was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the 2007 Revised International Working Group Response Criteria for Malignant Lymphoma. OS was measured from the time of diagnosis to the date of death or the final follow-up. PFS was measured from the time of diagnosis to the date of disease progression, death, or the final follow-up.

2.4 | EBV-DNA quantification

Real-time polymerase chain reaction (PCR) was used to detect EBV-DNA in peripheral blood. DNA was extracted from 150 μl plasma
using Kit Ribo Virus. Amplification was performed with EBV Real-TM Quant following the standard manufacturer’s instructions in reaction volumes of 25 μl and using the Quant Studio Dx Real-Time PCR Instrument. The primers of the latent membrane protein (LMP2) region of EBV-DNA were as follows: forward: 5‘-AGC TGT AAC TGT GGT TTC CAT GAC-3‘; reserve: 5‘-GCC CCC TGG CGA AGA G-3‘. 5 × 10^5 copy/ml was defined to be the critical value. Higher than 5 × 10^5 copy/ml was considered to be EBV-DNA positive. EBV-DNA load in peripheral blood was measured before initial treatment and after four cycles of chemotherapy.

2.5 Statistical analysis

Univariate analysis was performed using the Kaplan–Meier model. Multivariate analysis was performed using the Cox regression model, and the differences were assessed using the log-rank test. The qualitative data were compared using the χ^2 test. p < 0.05 was considered to be statistically significant different. All statistical analyses were performed using SPSS 26.0 software.

3 RESULTS

3.1 Proportion of EBV-DNA positivity in each subtype

Among all lymphoma cases, 100 patients were EBV-DNA positive, with a total EBV active infection rate of 0.376%. The active infection rate of EBV in HL was 0.196%. Among aggressive B-cell lymphoma, EBV active infection rate of B-cell lymphoblastic lymphoma (B-LBL) was higher than that of DLBCL (0.358% vs. 0.264%). For indolent B-cell lymphoma, chronic lymphocytic leukaemia (CLL) was the most common subtype infected with EBV. The active infection rate of EBV in T/NK cell lymphoma was higher compared to B-cell lymphoma, among which angioimmunoblastic T-cell lymphoma (AITL) is the highest (3.56%), followed by peripheral T cell lymphoma (PTCL). Taken together, T/NK cell lymphomas were more commonly associated with EBV-DNA active infection (Table 1).

| Subtype               | Total (n) | EBV positive (n) | Infection rate (%) |
|-----------------------|-----------|------------------|--------------------|
| **Aggressive B-cell lymphoma** |           |                  |                    |
| DLBCL                 | 10,976    | 29               | 0.264              |
| B-LBL                 | 279       | 1                | 0.358              |
| **Indolent B-cell lymphoma** |           |                  |                    |
| FL                    | 5031      | 3                | 0.059              |
| MZL                   | 641       | 1                | 0.156              |
| SLL/CLL               | 314       | 1                | 0.318              |
| **T or NK/T cell lymphoma** |           |                  |                    |
| NK/T                  | 2744      | 30               | 1.093              |
| ALCCL                 | 942       | 2                | 0.212              |
| AITL                  | 337       | 12               | 3.56               |
| PTCL                  | 497       | 11               | 2.21               |
| T-LBL                 | 192       | 1                | 0.521              |
| **HL**                | 4574      | 9                | 0.196              |
| **Total**             | 26,527    | 100              | 0.376              |

3.2 Clinical characteristics between EBV-DNA-positive and -negative patients

The patients’ characteristics are listed in Table 2. The total number of EBV-DNA-positive patients in our large sample over 1 years is 100. One hundred and two patients with negative EBV-DNA were randomly sampled as controls. Of the 202 patients, 130 (64.4%) were male and 72 (35.6%) were female. The average age was 52.56 ± 15.77 years old, and the median age was 51 years old (range 18–83 years). Seventy-six patients (37.6%) were older than 60 years, 139 patients (68.8%) presented with Ann Arbor stage III-IV, and 99 patients (50%) had elevated LDH levels (>250U/L). Nearly half of the patients (48.8%) had normal β2-MG level (≤2.6 mg/L), 74.0% patients were categorized into the low to intermediate risk group (IPI ≤ 2) according to the International Prognostic Index (IPI). B symptoms (57.0% vs. 26.5%, p < 0.001) and hemophagocytic syndrome (13.0 vs. 0.0%, p < 0.001) were more common in EBV-DNA-positive patients. EBV-DNA-positive patients obtained higher LDH level (66.7% vs. 34.3%, p < 0.001), more advanced Ann Arbor stage (78.0% vs. 59.8%, p = 0.005), higher β2-MG (67.7% vs. 35.3%, p < 0.001), and higher IPI score (32.3% vs. 19.8%, p = 0.044) compared to EBV-DNA-negative patients. However, the involvement of liver, spleen, bone, and the lymph node size between these two groups showed no significant difference. EBV-DNA-negative patients had a significantly higher ORR (74.5% vs. 57.0%, p = 0.009) compared to positive patients.

In order to investigate whether the level of EBV-DNA before treatment affect the prognosis of EBV-positive patients, the survival time of patients with EBV-DNA levels of 1 × 10^3, 1 × 10^5, 1 × 10^6 and 1 × 10^9 was compared. The results showed that EBV-DNA level before treatment could affect PFS of patients with T/NK cell lymphoma (Figure 2B, p = 0.009), but had no effect on OS and PFS of patients with B cell lymphoma (Figure 1) nor the OS of patients with T/NK cell lymphoma (Figure 2A).

3.3 Different EBV-DNA status after treatment

EBV-DNA status in patients’ peripheral blood was re-detected after four cycles of chemotherapy. The negative conversion rates of different subtypes of lymphomas were shown in Figure 3, in which indolent B-cell lymphoma is higher than other subtypes. Kaplan–Meier analysis revealed that EBV-DNA converting negative after treatment was correlated with improved PFS of T/NK cell lymphoma (Table 3, p = 0.001) but had no effect on OS (Table 3, p = 0.226). For B-cell lymphoma, there was no significant difference in EBV-DNA-negative conversion rate between first-line CHOP regimen
TABLE 2 Baseline characteristics of EBV-DNA-positive and -negative patients

| Factors                        | EBV-DNA positive | EBV-DNA negative | Total n (%) | \( \chi^2 \) | p value |
|--------------------------------|------------------|------------------|-------------|-------------|---------|
| Sex                            | Male             | 68               | 62          | 130 (64.4)  | 1.146   | 0.284  |
|                                | Female           | 32               | 40          | 72 (35.6)   |         |        |
| Age                            | \( \geq 60 \)    | 41               | 35          | 76 (37.6)   | 0.962   | 0.327  |
|                                | \(< 60 \)        | 59               | 67          | 126 (62.4)  |         |        |
| Ann Arbor stage                | I-II             | 22               | 41          | 63 (31.2)   | 7.790   | 0.005  |
|                                | III-IV           | 78               | 61          | 139 (68.8)  |         |        |
| Disease status after treatment | PR/CR            | 57               | 76          | 133 (65.8)  | 6.884   | 0.009  |
|                                | PD/SD            | 43               | 26          | 69 (34.2)   |         |        |
| B symptom                      | Yes              | 57               | 27          | 84 (41.6)   | 19.347  | <0.001 |
|                                | No               | 43               | 75          | 118 (58.4)  |         |        |
| LDH level                      | \( > 250 \)      | 64               | 35          | 99 (50)     | 20.706  | <0.001 |
|                                | \( \leq 250 \)   | 32               | 67          | 99 (50)     |         |        |
| \( \beta_2\)-MG                | \( \leq 2.6 \)   | 32               | 66          | 98 (48.8)   | 21.086  | <0.001 |
|                                | \( > 2.6 \)      | 67               | 36          | 103 (51.2)  |         |        |
| IPI                            | \( \leq 2 \)     | 67               | 81          | 148 (74)    | 4.074   | 0.044  |
|                                | \( > 2 \)        | 32               | 20          | 52 (26)     |         |        |
| Liver involvement              | Yes              | 2                | 7           | 9 (4.5)     | 2.754   | 0.097  |
|                                | No               | 97               | 95          | 192 (95.5)  |         |        |
| Spleen involvement             | Yes              | 43               | 42          | 85 (42.3)   | 0.105   | 0.746  |
|                                | No               | 56               | 60          | 116 (57.7)  |         |        |
| Lymph node                     | \( \geq 7 \) cm  | 6                | 6           | 12 (5.9)    | 0.001   | 0.972  |
|                                | \( < 7 \) cm     | 94               | 96          | 190 (94.1)  |         |        |
| Bone marrow involvement        | Yes              | 17               | 10          | 27 (13.4)   | 3.470   | 0.176  |
|                                | No               | 81               | 92          | 173 (86.1)  |         |        |
| Hemophagocytic syndrome        | Yes              | 13               | 0           | 13 (6.4)    | 14.172  | <0.001 |
|                                | No               | 87               | 102         | 189 (93.6)  |         |        |

FIGURE 1 The EBV-DNA level in peripheral blood to the prognosis of B cell lymphoma. (A) EBV-DNA level before treatment showed no relationship with the OS of B cell lymphoma. (B) EBV-DNA level before treatment was not related to PFS of B-cell lymphoma

and second-line therapy (\( p = 0.226 \), Table 3). However, for T/NK cell lymphoma, second-line therapy appeared to result in higher EBV-DNA-negative conversion rate compared to CHOP-based therapy (\( p = 0.009 \), Table 3).

### 3.4 Prognostic analysis

The univariate analysis showed that EBV-DNA, age, response status, \( \beta_2\)-MG level, LDH level, and hemophagocytic lymphohistiocytosis
QIU et al. (HLH) were prognostic factors relating to OS and PFS \((p<0.05)\), while patients with IPI score \(>2\) were associated with poor OS \((p=0.013)\) and patients with B symptoms had worse PFS \((p=0.026)\). Multivariate analysis found that age, EBV-DNA, response status, and HLH were significantly independent prognostic factors for both poor PFS and OS \((p<0.05, \text{Table 4})\).

3.5 | EBV active infection was related to secondary HLH

Among the 26,527 recruited lymphoma patients, a total of thirteen patients were accompanied with HLH. EBV-DNA was positive in all HLH patients, indicating that EBV active infection was related to the occurrence of HLH \((p<0.001, \text{Table 2})\). Univariate and multivariate analyses indicated that HLH was an independent factor affecting the prognosis (Table 4). In addition, we found that the HLH patients had higher levels of LDH \((p=0.045)\), \(\beta_2\) MG \((p<0.001)\), and EBV-DNA \((p<0.001)\) compared to those without HLH. The average value of EBV-DNA in patients with HLH \((36 \times 10^5 \text{copy/ml})\) was significantly higher than that in EBV-positive patients without HLH \((6 \times 10^5 \text{copy/ml})\) \((p<0.001)\).

4 | DISCUSSION

Epstein–Barr virus, a member of the human herpesvirus family, is widespread in world's population\(^{11}\) and is carried as a latent asymptomatic infection in individuals.\(^{12}\) Persistent EBV active infection is considered a high-risk factor for nasopharyngeal carcinoma and malignant lymphomas, including Hodgkin and non-Hodgkin lymphomas.\(^{5}\) B cells are known to be the primary lymphoid target of EBV infection. EBV-associated NK and T cell lymphoproliferative diseases are more common in Asia.\(^{13}\) A study in China indicated that EBV-DNA was more frequently detected in T/NK cell lymphomas than in B cell lymphomas.\(^{14}\) A similar result was observed in our study, and EBV-DNA positivity rate was higher in T/NK cell lymphomas than that in B-cell lymphomas.

Some studies revealed that EBV-DNA positivity before treatment could reflect the tumour burden.\(^{15-19}\) We found that EBV-DNA-positive patients generally presented more risk factors such as elevated LDH level, higher \(\beta_2\)-MG level, and B symptoms compared to EBV-DNA-negative patients. In addition, patients with positive EBV-DNA are more likely to develop HLH. These data suggest that the EBV-DNA positivity may be used as a surrogate biomarker for assessing tumour burden.

Clinically, EBV-DNA positivity is a useful prognostic biomarker in EBV-associated lymphomas. Liang et al.\(^7\) showed that the pretherapy EBV-DNA positivity is a better biomarker for poor OS than EBER. Our multivariate analysis also revealed that EBV-DNA positivity was an independent prognostic factor. However, no reports on EBV-DNA level to the prognosis of lymphoma patients were published as we known. We found that EBV-DNA level before treatment could affect PFS of patients with T/NK cell lymphoma, but had no effect.
on OS and PFS of patients with B cell lymphoma nor the OS of patients with T/NK cell lymphoma.

Previous studies reported that EBV-DNA status after treatment was correlated with the treatment response and survival of T/NK cell lymphoma patients.20,21 Similar results were observed in our study. We divided lymphomas into B-, T/NK- lineages and HL to investigate whether the change of EBV-DNA status after treatment could affect the survival. In T/NK cell lymphomas, patients with negative EBV-DNA conversion showed a better PFS than patients who remained positive. However, negative EBV-DNA conversion did not significantly affect the OS and PFS of B-cell lymphoma and HL patients. We also found that in patients with EBV-DNA-positive T/NK lymphoma, second-line treatment seems to lead to a high EBV-DNA-negative conversion rate. In addition, we found that the change of LDH level after treatment was positively correlated with EBV-DNA, suggesting that the change of EBV-DNA status could affect LDH level.

HLH is a rapidly progressive, highly fatal disease that may occur either as a result of the lymphoma disease itself or pathogen infection during immunosuppression.22 Secondary HLH is often associated with a variety of underlying diseases, such as infection, tumour, and rheumatic diseases. Among the infectious factors, EBV infection is the most important one. We found that HLH patients in the study were all EBV-DNA positive, indicating that EBV active infection increased the risk of HLH in lymphoma patients. Our study also showed that the prognosis of HLH patients was significantly worse, which may be related to the high copy number of EBV-DNA in lymphoma patients.

In our study, we found that EBV active infection rate in T/NK cell lymphoma was significantly higher than that in B cell lymphoma,

| TABLE 3 Analysis of different EBV-DNA status after treatment |
|--------------------------------------------------------------|
| Factors                       | EBV-DNA turn negative | EBV-DNA still positive | Total n (%) | χ² | p value |
|-------------------------------|-----------------------|------------------------|-------------|----|---------|
| OS B-cell lymphoma            | 8                     | 3                       | 11 (28.2)   | 0.279 | 0.598   |
| T or NK/T cell lymphoma       | 16                    | 12                      | 28 (71.8)   | 1.004 | 0.316   |
| PFS B-cell lymphoma           | 8                     | 3                       | 11 (28.2)   | 0.596 | 0.440   |
| T or NK/T cell lymphoma       | 16                    | 12                      | 28 (71.8)   | 7.094 | 0.008   |
| LDH High                      | 29                    | 16                      | 45 (70.3)   | 0.245 | 0.621   |
| Normal                        | 11                    | 8                       | 19 (29.7)   |      |         |
| Therapy B-cell lymphoma       | CHOP-based            | 12                      | 3           | 15 (26.7) | 1.466 | 0.226   |
| Second-line                   | 2                     | 2                       | 4 (7.2)     |      |         |
| T or NK/T cell lymphoma       | CHOP-based            | 3                       | 8           | 11 (19.7) | 6.782 | 0.009   |
| Second-line                   | 19                    | 7                       | 25 (46.4)   |      |         |

| TABLE 4 Univariate analysis and multivariate analysis of factors potentially associated with survivals |
|-----------------------------------------------------------------------------------------------|
| Factors                                  | OS Univariate analysis | Multivariate analysis | PFS Univariate analysis | Multivariate analysis |
|------------------------------------------|------------------------|-----------------------|------------------------|-----------------------|
|                                          | HR (95% CI)            | p value               | HR (95% CI)            | p value               |
| initial EBV-DNA                          | p < 0.001              | 0.542 (0.326–0.902)   | 0.018                  | 0.461 (0.237–0.897)   | 0.022                 |
| Age                                      | p < 0.001              | 2.131 (1.280–3.548)   | 0.004                  | 2.318 (1.214–4.425)   | 0.011                 |
| Sex                                      | 0.615                  |                       |                        |                       |                       |
| Ann Arbor stage                          | 0.100                  | 0.866 (0.477–1.570)   | 0.635                  | 1.131 (0.543–2.393)   | 0.748                 |
| Disease status after treatment           | p < 0.001              | 2.595 (1.640–4.140)   | <0.001                 | 4.571 (2.466–8.473)   | <0.001                |
| B symptom                                | 0.070                  | 0.805 (0.505–1.284)   | 0.363                  | 0.663 (0.362–1.216)   | 0.184                 |
| β2-MG                                    | 0.001                  | 1.160 (0.682–1.970)   | 0.584                  | 1.001 (0.510–1.964)   | 0.998                 |
| IPI                                       | 0.013                  | 0.980 (0.550–1.747)   | 0.947                  | 0.831 (0.408–1.694)   | 0.611                 |
| LDH level                                 | 0.001                  | 0.709 (0.426–1.182)   | 0.188                  | 0.957 (0.497–1.845)   | 0.896                 |
| Liver involvement                        | 0.796                  |                       |                        | 0.213                 |                       |
| Spleen involvement                       | 0.894                  |                       |                        | 0.852                 |                       |
| Bone marrow involvement                  | 0.724                  |                       |                        | 0.698                 |                       |
| Lymph node                               | 0.616                  |                       |                        | 0.841                 |                       |
| Hemophagocytic syndrome                  | p < 0.001              | 0.906 (0.437–1.878)   | 0.791                  | 0.633 (0.278–1.440)   | 0.275                 |
suggesting that EBV may play an important effect in the pathogenesis of T/NK cell lymphoma. Our results also revealed that EBV-DNA positivity before treatment could be a surrogate biomarker representing the tumour burden and was correlated to poor prognosis of lymphoma patients. EBV-DNA level before treatment was an independent prognostic factor for T/NK cell lymphoma. EBV-DNA turning negative after treatment was related to improved PFS of T/NK cell lymphoma, and second-line therapy resulted in increased EBV-DNA-negative conversion.

AUTHOR CONTRIBUTIONS

Lihua Qiu: Data curation (equal); writing – original draft (equal).
Junqi Si: Data curation (equal); writing – original draft (equal). Junnan Kang: Data curation (equal); writing – original draft (equal). Zehui Chen: Writing – review and editing (equal). Rixinan Nuermaimaiti: Methodology (equal); resources (equal). Zhengzi Qian: Data curation (equal). Lanfang Li: Data curation (equal). Shiyong Zhou: Data curation (equal). Mingjian James You: Methodology (equal). Huilai Zhang: Resources (equal); writing – review and editing (equal). Chen Tian: Formal analysis (equal); funding acquisition (equal); methodology (equal); validation (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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