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Epstein–Barr virus as a prognostic factor in *de novo* nodal diffuse large B-cell lymphoma

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Abstract
Although the International Prognostic Index (IPI) score is a valuable prognostic tool in diffuse large B-cell lymphoma (DLBCL), other risk-stratifying factors may be of value. The aim of this study was to define the prognostic value of EBV expression in *de novo* nodal DLBCL. Seventy-four cases were selected between January 2002 and December 2007. Clinical data were reviewed and tissue samples were evaluated for expression of CD20, CD10, bcl-6, MUM1, and EBV-encoded RNA (EBER). Of 74 evaluated cases, 53 cases (72%) were of non-germinal center-like subtype and 11 cases (15%) were positive for EBER. In a univariate analysis of the 57 patients who received chemotherapy, factors associated with survival were EBV status, performance status, LDH level, and IPI score. Using a multivariate analysis, a prognostic model was developed using IPI score and EBV status, which showed statistical significance. Our study supports EBV status as a powerful prognostic factor in *de novo* nodal DLBCL. Prospective studies should be carried to validate this hypothesis.

Keywords: *Diffuse large B-cell lymphoma, EBV, prognostic factors, CHOP*

Introduction

Lymphoproliferative disorders (LPDs) are neoplastic processes that originate from central and/or peripheral lymphoid tissue. LPD comprise of diverse morphological, immunological, genetic and clinical entities, which is a clear reflection of the functional diversity of lymphoid cells. The incidence of LPD has experienced a sustained increase worldwide for the last several decades [1], especially in older patients. This phenomenon can only be partly explained by the HIV epidemics and the increased risk of lymphoma seen in patients with autoimmune processes [2]. Other risk factors which have also been implicated in lymphomagenesis are exposure to herbicides, solvents, chemotherapy, or radiotherapy [1]. Infectious agents have also been associated with the development of lymphoma, such as *Helicobacter pylori* [3], Epstein–Barr virus (EBV) [4], human T-lymphotropic virus (HTLV)-1 [5], human herpesvirus (HHV)-8 [6] and, recently, Simian virus (SV)-40 [7]. Weaker but potentially significant associations have been described with type 2 diabetes mellitus [8], tobacco smoking [9], and allogeneic blood transfusions [10].

The current World Health Organization (WHO) classification of lymphoid disorders establishes more than 30 distinct anatomoclinical entities grouped by morphological, immunophenotypical, cytogenetical, and clinical criteria [11]. The most common NHL subtype is diffuse large B-cell lymphoma (DLBCL), representing 31% of the total cases of lymphoma in the US [12]. In order to prognosticate survival in patients with DLBCL, clinicians have used different

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parameters, such as age, clinical stage, presence of B symptoms, β2-microglobulin, and lactate dehydrogenase (LDH) levels besides other biological and genetic markers. Since 1993, the International Prognostic Index (IPI) has served as the most widely used prognostic tool in DLBCL and includes five clinical variables (i.e. age, performance status, number of extranodal sites, serum LDH level, and clinical stage) allowing to risk-stratify patients in four categories [13]. However, patients in each risk category may present great variability in terms of response to therapy and outcome.

DLBCL has more recently been recognized as a heterogeneous entity from clinical and morphological viewpoints. DNA microarray techniques [14] and immunohistochemical studies using CD10, bcl-6, and MUM1 [15] have rendered at least two phenotypically distinct subgroups, germinal center (GC)-like and non-germinal center (non-GC)-like DLBCL. Even in the post-rituximab era, these two distinct subgroups are associated with different clinical features and prognosis [16]. Thus, the present risk-stratification of patients with DLBCL may need further refinement.

EBV infection has been associated with the development of multiple LPD, such as Burkitt lymphoma [17], extranodal natural killer (NK)/T-cell lymphoma [18], aggressive NK-cell leukemia/lymphoma [19], plasmablastic lymphoma [20], lymphomatoid granulomatosis [21], Hodgkin lymphoma [22] and T-cell hydroa-like lymphoma [23]. Although some studies have investigated the prognostic role of EBV in Hodgkin [24] and T-cell lymphoma [25], the value of EBV status in DLBCL prognosis has not yet been firmly established.

The main objective of the current study is to define the association of EBV status with survival in patients with *de novo* nodal DLBCL. Secondary objectives of the study are to evaluate the effect of immunohistochemical profile (GC *vs.* non-GC) and identify potential prognostic indicators in EBV-positive *de novo* nodal DLBCL.

Patients and methods

The authors gathered clinical data on cases diagnosed with DLBCL between January 2002 and December 2007 at the Edgardo Rebagliati Martins Hospital in Lima, Peru. From a total of 1248 cases of malignant lymphoma, 466 cases were diagnosed with DLBCL. The present study included patients older than 18 years, with untreated, pathologically confirmed CD20-positive nodal DLBCL. Cases with transformed lymphoma, HIV-positivity, or cases without adequate sample to run the proper studies were excluded. Seventy-four cases met the inclusion criteria. Clinical parameters identified included age, sex, performance status, Ann Arbor clinical stage, serum LDH levels, number of extranodal sites, IPI score, type of therapy received, and overall survival (OS).

Samples of each of the 74 cases were stained using antibodies against CD3 (Dako, Carpinteria, CA; dilution 1:25), CD20 (Dako; dilution 1:100), CD10 (Novocastra, Newcastle upon Tyne; UK; dilution 1:100), bcl-6 (Dako; dilution 1:10), and MUM1 (Santa Cruz Biotechnology, Santa Cruz, CA; dilution 1:200); 30% expression in tumoral cells was considered positive. Cases were then subcategorized as GC or non-GC according to the algorithm presented by Hans et al. [15]. Chromogenic *in situ* hybridization was used to detect the presence of EBV-encoded RNA (EBER; Dako). The reaction was considered positive if there was nuclear expression of EBER by tumoral cells. Manufacturer's instructions were followed scrupulously to avoid contamination.

An unpaired *t*-test and the chi-square method were used for the comparison of the clinical characteristics between groups, when appropriate. For the univariate survival analyses, the Kaplan–Meier method for incomplete observations was used. Survival curves between groups were compared using the log-rank test. OS was defined as the time elapsed from diagnosis to death or last contact. Cox proportion-hazard regression method was used to perform multivariate survival analyses. All reported *p*-values are two-sided and were considered significant if < 0.05.

Results

General characteristics

General characteristics are shown in Table I. From 74 selected cases, median age at diagnosis was 66 years (range 24–87 years), and 73% of the cases were 60 years or older. There was a slight male predominance (53%). Performance status of 2 and higher was observed in 53% of the cases. Advanced stages (III and IV) were seen in 66% of cases. Fourteen percent of cases had two or more extranodal sites involved and 57% had serum LDH levels above the upper limit of normal. An IPI score of 3 or higher was seen in 57% of the cases. In regard to therapy, 55 cases (74%) received some form of chemotherapy; 44 cases (80%) received cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), 8 cases received cyclophosphamide, mitoxantrone vincristine and prednisone (CNOP), and 3 cases received cyclophosphamide, vincristine and prednisone (CVP). Two cases received radiation

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Table I. General characteristics of 74 patients with *de novo* diffuse large B-cell lymphoma according to immunohistochemical profile and EBV status.

	All patients	GC	Non-GC	*p*	EBER+	EBER−	*p*
Total	74 (100.0%)	21 (28.4%)	53 (71.6%)		11 (14.9%)	63 (85.1%)	
Median age (range)	66 (23–87)	69 (45–85)	70 (23–87)	NS	71 (34–85)	65 (23–87)	NS
Age							
60 years or less	20 (27.0%)	7 (33.3%)	13 (24.5%)	NS	1 (9.1%)	19 (30.2%)	NS
Older than 60 years	54 (73.0%)	14 (66.7%)	40 (75.5%)		10 (90.9%)	44 (69.8%)	
Sex							
Male	39 (52.7%)	13 (61.9%)	26 (49.1%)	NS	7 (63.6%)	32 (50.8%)	NS
Female	35 (47.3%)	8 (38.1%)	27 (50.9%)		4 (36.4%)	31 (49.2%)	
Performance status							
ECOG 0–1	33 (47.1%)	14 (70.0%)	19 (38.0%)	0.015	4 (44.4%)	29 (47.5%)	NS
ECOG 2–5	37 (52.9%)	6 (30.0%)	31 (62.0%)		5 (55.6%)	32 (52.5%)	
Clinical stage							
I–II	24 (34.3%)	6 (30.0%)	18 (36.0%)	NS	2 (22.2%)	22 (36.1%)	NS
III–IV	46 (65.7%)	14 (70.0%)	32 (64.0%)		7 (77.8%)	39 (63.9%)	
Extranodal sites							
0–1	60 (85.7%)	17 (85.0%)	43 (86.0%)	NS	8 (88.9%)	52 (85.2%)	NS
≥2	10 (14.3%)	3 (15.0%)	7 (14.0%)		1 (11.1%)	9 (14.8%)	
LDH level							
Normal	22 (43.1%)	8 (53.3%)	14 (38.9%)	NS	3 (37.5%)	19 (44.2%)	NS
Above normal	29 (56.9%)	7 (46.7%)	22 (61.1%)		5 (62.5%)	24 (55.8%)	
IPI score							
0–2	28 (43.1%)	9 (52.9%)	19 (39.6%)	NS	3 (33.3%)	25 (44.6%)	NS
3–5	37 (56.9%)	8 (47.1%)	29 (60.4%)		6 (66.7%)	31 (55.4%)	
Treatment							
Chemotherapy	57 (77.0%)	16 (76.2%)	41 (77.4%)	NS	6 (54.5%)	51 (81.0%)	0.112
Supportive	17 (23.0%)	5 (23.8%)	12 (22.6%)		5 (45.5%)	12 (19.0%)	
Immunohistochemical profile							
GC	21 (28.4%)	–	–	–	2 (18.2%)	19 (30.2%)	NS
Non-GC	53 (71.6%)	–	–	–	9 (81.8%)	44 (69.8%)	

GC, Germinal center; EBV, Epstein–Barr virus; EBER, EBV-encoded RNA; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; NS, Not significant.

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therapy in both cases to treat early stages. Finally, 17 cases (36%) received only supportive therapy, mostly due to poor performance status (i.e. ECOG > 2), advanced age and/or comorbidities.

Germinal center vs. *non-germinal center subtypes*

From the 74 cases, 17 cases (23%) were positive for CD10, 42 cases (57%) for bcl-6, and 57 cases (77%) for MUM1. All cases were negative for CD3 expression. Based on Hans' immunohistochemical classification, 21 cases (28%) were considered GC, and 53 cases (72%) were considered non-GC subtype. When comparing GC and non-GC subgroups, the latter was observed more frequently in association with female sex (38% *vs.* 51%), age older than 60 years (67% *vs*. 76%), elevated LDH levels (47% *vs*. 61%), and elevated IPI scores (47% *vs*. 60%). However, these differences did not reach statistical significance. Similarly, there was no statistical difference when comparing clinical stage or number of extranodal sites of involvement. However, the non-GC subgroup showed a significantly higher proportion of cases with poor performance status than the GC subgroup (62% *vs*. 30%; $p = 0.015$).

Epstein–Barr virus-positive vs. *Epstein–Barr virus-negative cases*

EBER was detected in 11 (15%) of the 74 evaluated cases. EBV-positivity was more frequently associated with male sex (64% *vs*. 51%), age older than 60 years (91% *vs*. 70%), advanced stages (78% *vs*. 64%), higher IPI scores (67% *vs*. 56%), and non-GC subtype (82% *vs*. 70%). However, these differences did not reach statistical significance. EBV-positive cases had a median age of 71 years (range 35–85 years) while EBV-negative cases had a median age of 65 years (range 24–87 years). There was no difference when comparing performance status or number of extranodal sites. EBV-positive cases were less likely to receive chemotherapy (55% *vs*. 81%; $p = 0.112$). When treatment was given, CHOP was used as therapy in 76% of the EBV-negative and 83% of the EBV-positive cases; this was not a statistically significant difference ($p = 0.7$; data not shown).

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Survival analysis

Median OS for all 74 patients was 15 months and the estimated 5-year OS was 29% [Figure 1(A)]. As expected, patients who received chemotherapy ($n = 57$) had longer survival than patients who did not receive any treatment ($n = 17$), with a median OS of 42 months *versus* 1 month ($p < 0.0001$; data not shown).

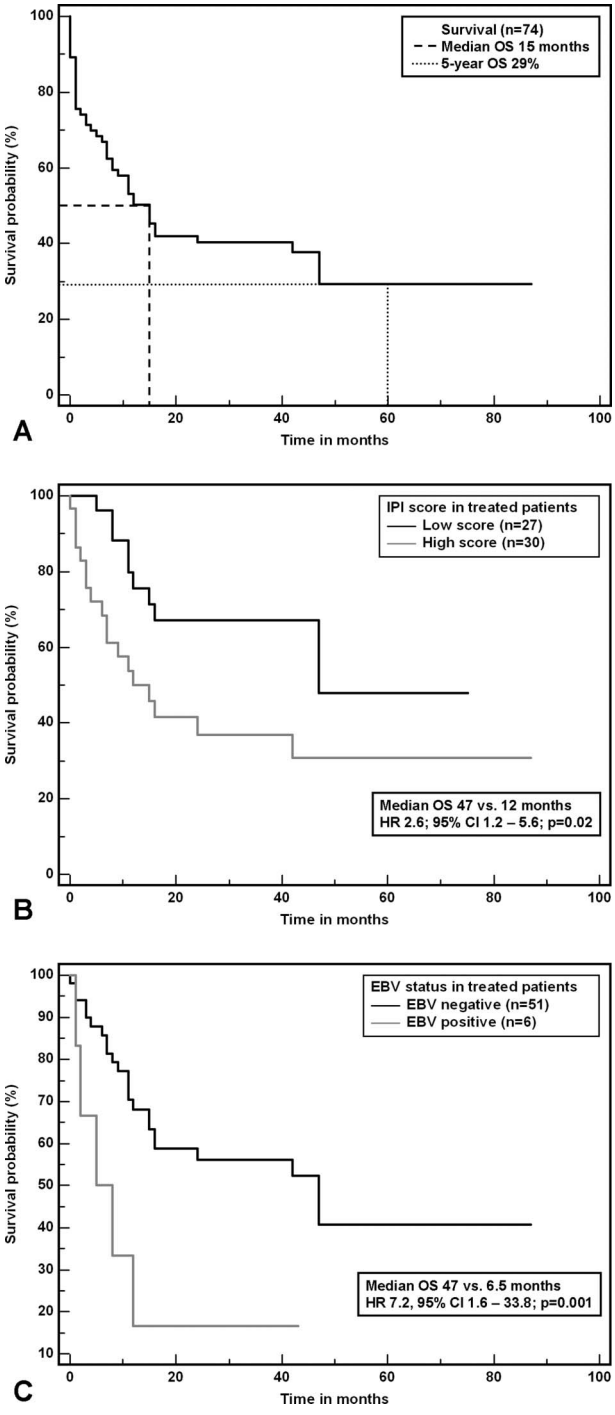

Figure 1. Survival analyses in patients with *de novo* diffuse large B-cell lymphoma. (A) Median and 5-year overall survival of the entire group ($n = 74$); (B) Overall survival by International Prognostic Index score in 57 patients who received chemotherapy; (C) Overall survival by EBV status in 57 patients who received chemotherapy.

Univariate and multivariate survival analyses were performed including only the 57 patients with *de novo* DLBCL who received chemotherapy. In the univariate analysis, factors associated with worse survival in *de novo* DLBCL were high IPI scores [Figure 1(B)], EBV-positivity [Figure 1(C)], LDH levels, and performance status (Table II). The immunohistochemical profile and the use of anthracyclines showed a trend toward statistical significance (Table II). In the multivariate analysis, EBV status, IPI score, immunohistochemical profile, and use of anthracyclines were evaluated; EBV status and IPI scores showed to be independent prognostic indicators in patients with *de novo* DLBCL (Table III).

Since both variables (i.e. EBV status and IPI score) had a similar hazard ratio in the multivariate analysis, a prognostic score using these two risk factors was developed. The proposed score assigned 1 point per

Table II. Univariate analysis of prognostic factors for survival in 57 patients with *de novo* diffuse large B-cell lymphoma who received chemotherapy.

Variables	Median OS	Hazard ratio (95% CI)	*p*
Age			
60 years or younger	NR	1.0	
Older than 60 years	16	1.8 (0.8–3.9)	0.15
Performance status			
ECOG 0–1	47	1.0	
ECOG 2–5	15	2.4 (1.1–5.3)	0.03
LDH level			
Normal	NR	1.0	
Above normal	12	3.5 (1.6–7.8)	0.001
Extranodal sites			
0–1	47	1.0	
≥2	42	1.7 (0.5–5.5)	0.34
Clinical stage			
I–II	47	1.0	
III–IV	16	1.4 (0.7–3.1)	0.37
IPI score			
Low (0–2)	47	1.0	
High (3–5)	12	2.6 (1.2–5.6)	0.02
Immunohistochemical profile			
Germinal center	NR	1.0	
Non-germinal center	16	2.1 (1.0–4.6)	0.06
EBV status			
EBER negative	47	1.0	
EBER positive	7	7.2 (1.6–33.8)	0.001
B symptoms			
No	47	1.0	
Yes	42	1.0 (0.4–2.1)	0.9

OS, overall survival (in months); CI, confidence interval; NR, not reached; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; EBV, Epstein–Barr virus; EBER, EBV-encoded RNA.

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risk factor, hence 0 for no risk factors ($n = 24$), 1 for the presence of a single risk factor ($n = 30$), and 2 for both risk factors ($n = 3$). This proposed prognostic score showed a statistically significant survival trend (Figure 2).

Discussion

The present study adds to the growing body of literature of EBV-positive DLBCL, and is the first report demonstrating the prognostic value of EBV expression in the survival of patients with *de novo* nodal DLBCL in a Latin American population.

The occurrence rate of EBV-positive DLBCL in the current study was 15%. This percentage is slightly higher than what is reported by other studies. Park et al. reported 9% [26] and Kuze et al. reported 11% EBV-positivity in DLBCL [27]. EBV-positive DLBCL has also shown associations with older age, advanced stages, and high IPI scores. The present study confirmed these previous findings. In our series, the median age of EBV-positive cases was 71 years with the majority being older than 60 years. The only case younger than 60 years was a 34-year-old man who presented with advanced stage, an IPI score of 4, and a non-GC phenotype. Despite an extensive review, we were unable to identify an underlying immunodeficiency in this patient, who was HIV-negative, had normal levels of immunoglobulins and denied a history of recurrent infections.

Table III. Multivariate analysis of prognostic factors for risk of death in 57 patients with *de novo* diffuse large B-cell lymphoma that received chemotherapy.

Variables	Hazard ratio (95% CI)	*p*
EBV status		
EBER negative	1.0	
EBER positive	3.1 (1.2–8.3)	0.02
IPI score		
Low (0–2)	1.0	
High (3–5)	2.4 (1.1–5.3)	0.02

CI, Confidence interval; EBV, Epstein–Barr virus; EBER, EBV-encoded RNA; IPI, International Prognostic Index.
Using the Cox proportional-hazards regression test in a stepwise method, EBV status and IPI score were retained in the model.

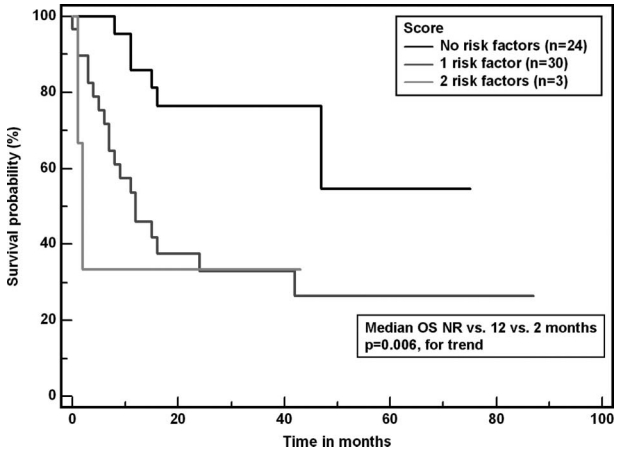

Figure 2. Overall survival according to the proposed score developed using EBV status and IPI score as prognostic factors.

The presence of EBV has been associated with poor response to chemotherapy and higher rates of relapse. A small Japanese study evaluating the predictive role of EBV status in primary gastric DLBCL showed that 50% of the EBV-positive cases presented with chemotherapy-refractory disease [28]. Additionally, Park et al. reported that cases of EBV-positive DLBCL showed poorer response to first-line therapy than EBV-negative cases (72% *vs.* 92%) [26]. In the same study, EBV-positive DLBCL cases showed a worse OS and progression-free survival than EBV-negative cases. Recently, Oyama et al. have described 96 cases of EBV-positive DLBCL, confirming that the presence of EBV confers a worse prognosis [29]. The authors defined this entity as an age-related EBV-associated B-cell LPD and showed that it more commonly affects older individuals, has an aggressive clinical course and frequent extranodal involvement. The authors established a two-variable score (age older than 70 and presence B symptoms) in order to risk-stratify these patients. In the present study, EBV-positive patients showed an association with worse survival in both the univariate and multivariate analyses. This finding further confirms the importance of the tumoral expression of EBER in the clinical course of DLBCL.

The IPI score has been defined as the most important prognostic tool in aggressive subtypes of NHL, particularly, but not exclusively, in DLBCL. This scoring system was defined based on a series of 3273 previously untreated cases of aggressive NHL and separates patients with DLBCL in four prognostic categories [13]. However, patients in each risk category may present a great variability in terms of response to therapy and outcome. In the present study, a prognostic scale using both IPI score and EBV status could be developed to predict survival in our population with nodal DLBCL. Ultimately, this may serve to identify patients with higher risk who perhaps may benefit from more intensive therapies.

Our study, however, has several limitations. First, the sample size is small, with only 11 cases of EBV-positive DLBCL. Second, not all cases received standard CHOP chemotherapy, since some cases (20%) received CNOP, CVP, or radiotherapy alone. Third, rituximab was not administered to cases in this cohort given understandable economical restrictions within the Peruvian healthcare system, limiting

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our conclusions to DLBCL cases treated without the anti-CD20 monoclonal antibody. Finally, the retrospective nature of this study also limits the generalization of the conclusions.

Despite these shortcomings, it is clear that the role of EBV in the pathogenesis of DLBCL needs further clarification. Recent studies have shown that EBV-selective immunodeficiency would favor chronic infection and subsequent lymphoma development [30]. EBV attaches the B-cell CD21 antigen increasing the production of IL-6 and mRNA allowing for blastic transformation to occur. EBV genome is then inserted into the cellular nucleus generating EBV nuclear antigens (EBNA), which are essential for immortalization. Production of latent membrane proteins (LMP) ensues increasing the expression of bcl-2 driving the cell into a latent phase, which is maintained by EBER molecules. In this way, EBV-infected B-cells are resting, avoiding immunosurveillance, but are also activated and, thus, more prone to suffer oncogenic changes [31]. In conjunction, bcl-2, which belongs to the tumor necrosis factor receptor superfamily, activates several transcriptional pathways, such as nuclear factor-kappa B (NF-κB) [32], MAP kinase [33], and AKT/phosphatidylinositol 3-kinase [34]. Further research is necessary to evaluate EBV and its key proteins in the pathogenesis of lymphoma in order to potentially find newer treatments and possibly improve therapy in patients with EBV-positive DLBCL.

The present study supports EBV-positive DLBCL as a distinct subtype of DLBCL. The impact of newer treatments for EBV-positive DLBCL should be validated prospectively including the use of anti-CD20 monoclonal antibodies (i.e. rituximab, ofatumumab and others) as well as proteasome inhibitors (i.e. bortezomib), given their effects on the NF-κB pathway, which may be important in the presumed pathogenesis of EBV-induced lymphomagenesis. Additional therapeutic strategies could include EBV-directed therapy. A recent study utilizing ganciclovir in combination with arginine butyrate showed efficacy in EBV-associated lymphoid malignancies [35]. EBV-directed cytotoxic T lymphocyte (CTL) therapy has been tried with limited success in post-transplant LPDs [36] and Hodgkin lymphoma [37]. Few studies are ongoing using CTL therapy alone (NCT00002663, NCT00671164, NCT00675571) or in combination with anti-CD45 antibodies (NCT00608478) in patients with EBV-positive DLBCL.

Conclusion

Based on the results of the present study and supported by previous evidence, the presence of EBV is an independent prognostic factor associated with worse survival in cases with *de novo* DLBCL. Further research is necessary to validate prospectively the prognostic value of EBV in DLBCL and to evaluate the role of immunochemotherapy and other novel agents, including EBV-directed therapy, in the treatment of EBV-positive DLBCL.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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