Int J Clin Exp Pathol 2018;11(3):1281-1288
www.ijcep.com /ISSN:1936-2625/IJCEP0071322

Original Article

EBV-positive T/NK lymphoproliferative diseases: analysis of prognostic factors for patients in China

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Received December 21, 2017; Accepted January 16, 2018; Epub March 1, 2018; Published March 15, 2018

Abstract: The Epstein-Barr virus (EBV) is a ubiquitous lymphotropic herpesvirus that infects the human body through the respiratory tract. Usually, primary infection with EBV is asymptomatic and occurs early in life, however adolescents or young adults are more likely to develop a self-limited symptomatic infection, which manifests as acute infectious mononucleosis (IM). Systemic EBV-positive lymphoproliferative disease (EBV + T/NK-LPD) has been described as a disease related to chronic or persistent EBV infection after acute EBV infection, with severe IM-like symptoms. EBV + T/NK-LPD is associated with high mortality and morbidity with life-threatening complications. Information on its prognostic factors remains limited, therefore in this study, we aimed to evaluate the association between prognostic factors and mortality and complications of EBV + T/NK-LPD in China by retrospectively reviewing 173 EBV + T/NK-LPD cases. We observed that the high mortality rate of EBV + T/NK-LPD was mainly due to serious and fatal complications. Fever, lymphadenopathy, hepatosplenomegaly, EBV-encoded RNA (EBER) > 50/HPF, Ki-67 > 30%, and other visible complications were closely associated with EBV + T/NK-LPD prognosis. In addition, fever, hepatosplenomegaly, decreased WBC count, and a Ki-67 index of > 30% were risk factors for complications. Thus, disease prognosis should be based on a comprehensive analysis of pathological and clinical data. Such data will help pathologists and clinicians to pay close attention to the changes in the clinical condition of the patients as well as take precautionary measures against the occurrence of fatal complications.

Keywords: Epstein-Barr virus, proliferative disease, T/NK cell, prognostic factor

Introduction

Epstein-Barr virus (EBV) is a ubiquitous lymphotropic herpesvirus that infects the human body through the respiratory tract [1, 2]. Usually, primary infection with EBV is asymptomatic and occurs early in life. However, adolescents or young adults are more likely to develop a self-limited symptomatic infection, which manifests as acute infectious mononucleosis (IM) [3-6]. Systemic EBV-positive lymphoproliferative disease (EBV + T/NK-LPD) has been described as a disease related to chronic or persistent EBV infection lasting longer than 6 months after acute EBV infection, with severe IM-like symptoms, elevated antibody titers against EBV, and evidence of organ damage without evidence of any underlying immunodeficiency. The term EBV + T/NK-LPD encompasses a broad spectrum of diseases, including a systemic polyclonal, oligoclonal, or often monoclonal T-cell or natural killer (NK)-cell lymphoproliferative disease that exhibits varying degrees of clinical severity depending on the host immunity and EBV factor [7], as well as cutaneous manifestations, such as hydroa vacciniforme-like T/NK lymphoproliferative disease (HV-T/NK-LPD) and hypersensitivity to mosquito bites (HMB) [8-11]. Park et al. [12] reviewed the clinical and laboratory features of EBV + T/NK-LPD and showed that the disease had high mortality and high morbidity with life-threatening complications [12]. However, studies on its prognostic factors are limited. Therefore, to analyze the prognostic factors for this condition in patients in China, we retrospectively reviewed 173 cases of EBV + T/NK-LPD in this study.

Materials and methods

Case selection

A total of 173 EBV + T/NK-LPD cases were retrospectively obtained from the database of the

Table 1. Primary antibodies and conditions used for immunohistochemical staining

Antigen	Clone	Dilution	Antigen Retrieval Agent	Manufacturer
CD20	L26	1:200	HP EDTA*	Maixin Biotech
CD2	AB75	1:50	HP EDTA	Maixin Biotech
CD3	SP7	1:50	HP EDTA	Maixin Biotech
CD5	SP19	1:50	HP EDTA	Maixin Biotech
CD4	SP35	1:80	HP EDTA	Maixin Biotech
CD8	SP16	1:100	HP EDTA	Maixin Biotech
CD30	Ber-H2	1:20	HP EDTA	Maixin Biotech
CD56	56C04	1:100	HP EDTA	Maixin Biotech
Ki-67	MIB-1	1:200	HP EDTA	Maixin Biotech
Granzyme B	GZB01	1:50	HP EDTA	Maixin Biotech
TIA-1	TIA-1	1:25	HP EDTA	Maixin Biotech

*HP EDTA: EDTA (1 mM, pH 9.0) boiled under high pressure.

Department of Pathology, Beijing Friendship Hospital, Capital Medical University (at the Lymphoma Diagnosis and Research Center, Institute of Beijing Clinical Medicine). All cases were received for consultation between August 2002 and May 2016. The latest follow-up was on April 6, 2017. Of them, 135 cases with systemic EBV + T/NK-LPD, 20 cases with HV-T/NK-LPD, 10 cases with HMB, 8 cases with other types of EBV + T/NK-LPD, affecting different parts of the body different locations were included.

Clinical and pathological factors

The clinical and pathological data included sex, age, disease course, symptoms (e.g., fever, lymph node enlargement, and hepatosplenomegaly), white blood cell count (WBC) count, platelet (PLT) count, EBV-encoded RNA (EBER) count, Ki-67 index, EBV-infected cell type, types of EBV + T/NK-LPD and their associated complications, follow-up time, and whether or not death was an outcome.

Patient criteria

Diagnosis of EBV + T/NK -LPD relies on the confirmation of chronic or persistent EBV infection of T or NK cells and is defined as a severe illness lasting more than 3 or 6 months, with the following clinical and laboratory evidence: (i) primary EBV infection or markedly abnormal EBV antibody titers (e.g., anti-EBV viral capsid antigen IgG ≥ 640, anti-EBV early-antigen IgG ≥ 160, and anti-EBNA < 2); (ii) major organ involvement such as interstitial pneumonia, hypoplasia of the bone marrow, uveitis, lymphadenitis, persistent hepatitis, and splenomegaly; and (iii) increased EBV RNA or protein levels in affected tissues [7, 13].

Immunophenotypic analysis

MaxVision™ 2 kit (catalog No. KIT-5910/5931) and monoclonal antibodies, including CD20, CD3, CD2, CD5, CD4, CD8, CD56, CD30, Granzyme B, TIA-1, Ki-67, provided by Maixin Biotech (Fuzhou, China), were used for the detection of all relevant antigens. The pretreatment methods as well as primary antibodies and their working dilutions used in this study are listed in **Table 1**.

In situ hybridization of EBV

The EBV Probe In Situ Hybridization Kit (Triplex International Biosciences, China, Co. Ltd.) was used to detect EBERs according to the following steps: (1) deparaffinization and dehydration of the paraffin sections using xylene and a series of graded ethanol; (2) pretreatment with proteinase K for 5 min; (3) hybridization with digoxigenin-conjugated EBV (EBERs) probe at 37°C for 4 h; (4) signal detection using peroxidase-conjugated anti-digoxigenin antibody and 3,3'-diaminobenzidine; and (5) counterstaining of sections with hematoxylin solution. The positive signals were brownish yellow and localized within the nuclei. A known EBER-positive case of extranodal NK/T-cell lymphoma and a EBER-negative case of lymphoid hyperplasia of the tonsil were designated as positive and negative controls, respectively.

Statistical analysis

Statistical analysis was performed using SPSS for Windows Version 19.0. Either the χ^2 or the Fisher's exact test (single-sided) was used to compare categorical variables in univariate analysis. Logistic regression analysis was performed for multivariate analysis. The Kaplan-Meier estimation method and the log-rank test were used for survival analysis. A P value of < 0.05 was considered statistically significant for all analyses.

Results

Clinical findings

Systemic EBV + T/NK-LPD: Ninety-three male patients and 42 female patients (male-to-fe-

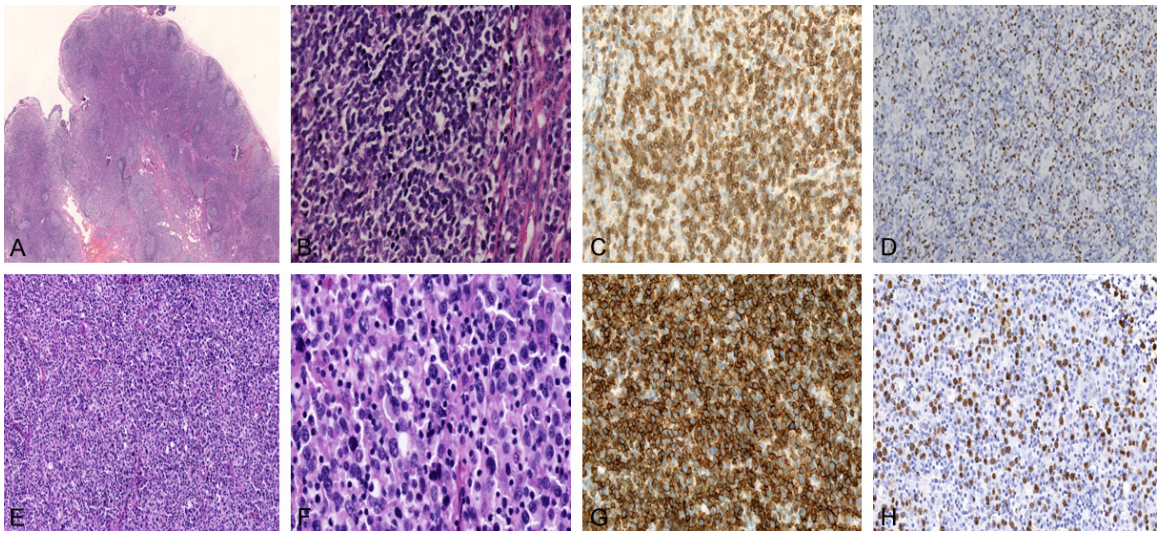

Figure 1. Histopathology of the lymph nodes. A. The lymph node architecture was normal (H&E, 40×). B. The cells were normal (H&E, 400×). C. Tissues stained positive for CD3 (H&E, 100×). D. Small cells tested positive for EBER (H&E, 100×). E. The structures were completely destroyed (H&E, 40×). F. The cellular components, including large, medium, and small cells, are mixed with eosinophilic granulocytes and plasma cells. Large cells were highly atypical (H&E, 400×). G. Large cells showed the presence of CD3 antigen (H&E, 100×). H. Large cells were positive for EBER (H&E, 100×).

male ratio of 2.2:1) were diagnosed with this disease. The patients were aged between 1 and 75 years, with a median age of 20 years. The disease course duration ranged between 1 and 84 months, with a median of 6 months. There were 108 cases of fever (80.0%), 108 cases of lymphadenopathy (80.0%), and 85 cases of hepatosplenomegaly (63.0%).

HV-T/NK-LPD: Eleven male patients and nine female patients (male-to-female ratio of 1.2:1) were diagnosed with this condition. The age of these patients ranged from 2 to 47 years, with a median age of 7.5 years. The disease course duration was 2 to 540 months, with a median of 30 months. There were 18 cases of fever (90.0%), 6 cases of lymphadenopathy (30.0%), and 9 cases of hepatosplenomegaly (45.0%).

HMB: Seven male patients and three female patients (male-to-female ratio of 2.3:1) were diagnosed with this condition. These patients were aged between 4 and 28 years, with a median age of 8 years. The duration of the disease course was between 1 and 84 months, with a median of 27 months. There were 9 cases of fever (90.0%), 5 cases of lymphadenopathy (50.0%), and 3 cases of hepatosplenomegaly (30.0%).

Other EBV + T/NK-LPD-affected locations: Six patients were men and two were women (male-to-female ratio of 3:1). These patients were aged between 6 and 52 years, with a median age of 15 years. The disease course duration was between 3 and 108 months, with a median of 17.5 months. One lesion was located in the skin, and manifested as a large skin ulcer; a solitary mass lesion was detected in the stomach, causing intermittent epigastric pain; four cases of intestinal EBV + T/NK-LPD along with abdominal pain, diarrhea, and ulcer development were detected. The gum was affected in two cases, and these patients developed a mucosal ulcer. Four cases (of eight cases) of fever (50%) were noted.

Histopathological findings of representative patients

The morphological characteristics in EBV + T/NK-LPD have a wide spectrum. The lymph node structures ranged from being normal to completely distorted, and the cells were normal to highly atypical (**Figure 1**). In different areas, the morphological characteristics were different. The cellular composition was complex, including large, medium, and small cells mixed with eosinophilic granulocytes, plasma cells, tissue cells, and immunocytoid cells. T/NK cells are often located in the liver sinus and were small, with no apparent atypia observed in cases where the liver was affected (**Figure 2**). In cases of spleen involvement, the splenic white pulp was significantly reduced, but the red pulp area

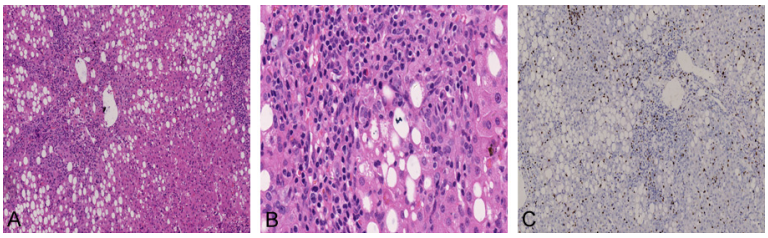

Figure 2. Histopathology of the liver. A. The structures were partially damaged (H&E, 40×). B. The atypical cells were often located in the liver sinus and are small in size and showed no apparent atypia (H&E, 400×). C. Small cells were positive for EBER (H&E, 100×).

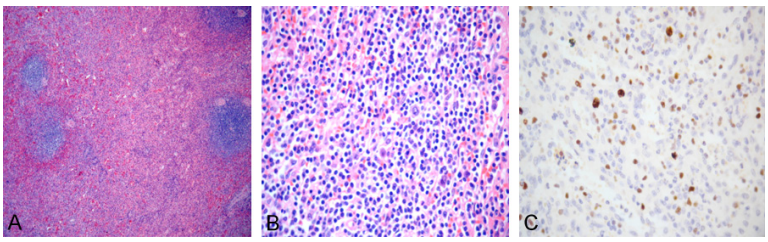

Figure 3. Histopathology of the spleen. A. White pulp was significantly reduced, but red pulp was widened (H&E, 40×). B. There were visible multifocal blue-stained nodules in the red pulp, which consisted of small lymph nodes mainly scattered in the middle of the larger atypical lymphoid cells (H&E, 400×). C. Medium and small cells were positive for EBER (H&E, 100×).

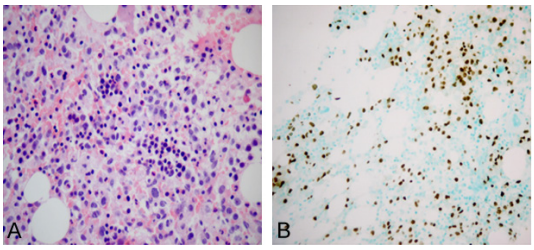

Figure 4. Histopathology of the bone marrow. A. The hematopoietic and adipose tissues were significantly reduced between the trabecular, and atypical lymphocytes were diffuse (H&E, 40×). B. Atypical cells were positive for EBER (H&E, 100×).

was wide. There were visible multifocal blue-stained nodules in the red pulp, which mainly consisted of small lymph nodes scattered in the center of large atypical lymphoid cells (**Figure 3**). In cases of bone marrow involvement, the hematopoietic and adipose tissues were significantly reduced between the trabeculae, and there was a diffused distribution of atypical lymphocytes (**Figure 4**).

Immunophenotypic analysis and in situ hybridization

All cases showed the presence of CD3 antigen, cytotoxic molecules, and EBER-positive cells in lesion areas, while 37 cases showed the presence of CD56 antigen in the same areas, indicating an NK cell phenotype. Of 49 cases, < 30% were positive for Ki-67, and of 114 cases, > 50% tested positive for this antigen. The number of EBER-positive cells was < 50/HPF in 54 cases and > 50/HPF in 119 cases.

Outcomes at follow-up

Sixty-five patients (37.6%) had complications, including hemophagocytic lymphohistiocytosis (19 cases, 11.0%), multiple organ failure (18 cases, 10.4%), lymphoma progression (18 cases, 10.4%), diffuse intravascular coagulation (4 cases, 2.3%), gastrointestinal bleeding/perforation (2 cases, 1.2%), myocarditis/arrhythmia (2 cases, 1.2%), and sepsis (1 case, 0.6%).

Forty-seven patients died from complications in this group, accounting for 27.2% (47/173) of all cases and for 72.3% of only those cases with complications (47/65). The cause of death involved one of the following complications: multiple organ failure (18 cases, 10.4%), hemophagocytic lymphohistiocytosis (14 cases, 8.1%), lymphoma progression (6 cases, 3.5%), diffuse intravascular coagulation (4 cases, 2.3%), gastrointestinal bleeding/perforation (2 cases, 1.2%), arrhythmia/myocarditis (2 cases, 1.2%), and severe infection (1 case, 0.6%).

Factors associated with mortality

Univariate analysis of factors related with EBV + T/NK-LPD-associated mortality are presented in **Table 2**. We observed that fever, lymphadenopathy, hepatosplenomegaly, EBER > 50/HPF, Ki-67 > 30%, and disease-associated complications demonstrated a statistically significant association with mortality ($P < 0.05$). There was no statistically significant difference between sex, age, WBC count, PLT count, and NK cell infection ($P > 0.05$) (**Figure 5**).

Factors associated with complications

Univariate analysis (**Table 3**) demonstrated that fever, lymphadenopathy, hepatospleno-

Table 2. Univariate analysis of factors related with EBV + T/NK-LPD-associated mortality

	OR (95% CI)	*P* value
Sex	1.18 (0.57-2.44)	NS
Age at onset	1.04 (0.53-2.04)	NS
Fever	4.79 (1.39-16.50)	**0.004**
Lymphadenopathy	2.96 (1.22-7.16)	**0.013**
Hepatosplenomegaly	3.17 (1.48-6.78)	**0.002**
Decreased WBC	3.77 (0.89-15.85)	NS
Decreased PLT	1.37 (0.43-4.36)	NS
NK cell infection	0.991 (0.44-2.25)	NS
EBER > 50/HPF	2.80 (1.21-6.51)	**0.014**
Ki-67 > 30%	1.96 (0.87-4.45)	**< 0.001**
Complications	3.61 (2.44-5.35)	**< 0.001**

NS indicates not significant. $P < 0.1$ is shown; $P < 0.05$ (shown in bold) is statistically significant.

megaly, decreased WBC count, EBER > 50/HPF, and Ki-67 > 30% were correlated with complications of EBV infection ($P < 0.05$). Multivariate analysis showed that fever, hepatosplenomegaly, decreased WBC count, and Ki-67 > 30% were associated with the occurrence of complications, and thus, were statistically significant risk factors ($P < 0.05$).

Discussion

To the best of our knowledge, this is the first study investigating the prognostic factors of EBV + T/NK-LPD for patients in China. A few studies have described the clinical and laboratory features of EBV + T/NK-LPD and demonstrated that the disease has high mortality and high morbidity with life-threatening complications [12, 14-16]. Compared with what is reported in the foreign literature, in China, it has been known that the prognostic factors of EBV infection, such as age at disease onset, WBC and PLT counts, NK cell infection, do not have any statistically significant correlation with mortality. However, other factors including fever, lymphadenopathy, hepatosplenomegaly, EBER > 50/HPF, Ki-67 > 30%, and disease-associated complications show a statistically significant correlation.

In the present study, we evaluated prognostic factors among patients with EBV + T/NK-LPDs. Multivariate analysis showed that fever, hepatosplenomegaly, decreased WBC count, and Ki-67 > 30% were independent risk factors for complications. Previously, two studies revealed that a later onset age (patients aged 8 years) was associated with mortality in patients with EBV + T/NK-LPD [14, 17]. Furthermore, a report demonstrated that adult-onset chronic active Epstein-Barr virus infection (CAEBV) patients had more progressive and aggressive courses than childhood-onset cases [18]. However, the present study did not reveal such risk factors.

In previous research, patients with CD4+ T-cell infection had shorter survival rates than those with NK cell infection, whereas clinical categories were not correlated with survival rates [14]. Moreover, the onset age of patients with CD4+ T-cell infection was high (median, 14.5 years). These results suggest that adult patients with CD4 T-cell infection may have more aggressive features and are likely to develop multiple organ failure. Although the underlying reason is unclear, we should be cautious about rapid progression in patients with CD4+ T-cell infection. For patients in the present study, we did not have enough data to analyze whether they have CD4+ T-cell infection or not. This is an interesting aspect that will be addressed in a follow-up study.

The high mortality rate of EBV + T/NK-LPD was mainly due to serious and fatal complications, which has been demonstrated in previous reports and studies by other research groups [10, 16]. In the present study, we determined the risk factors, and through a multivariate analysis, we show that fever, hepatic splenomegaly, low WBC count, and Ki-67 index are independent risk factors for complications associated with the aforementioned disease.

In the present study, there were 8 cases with other types of EBV + T/NK-LPD, including HV and HMB, one of which has been reported previously [19]. In addition, some of these cases developed systemic disease in a few months or years after diagnosis. Although some clinical symptoms did not appear serious, the auxiliary examination revealed a malignant tumor. On performing morphological analysis, we noted that there was no obvious damage of architecture. Therefore, we thought the localized EBV + T/NK-LPD represents a local or an organ-restricted lesion that can transform into a systemic disease after a certain time period. Regardless of transformation or chemotherapeutic intervention, localized EBV + T/NK-LPD could lead to serious life-threatening complica-

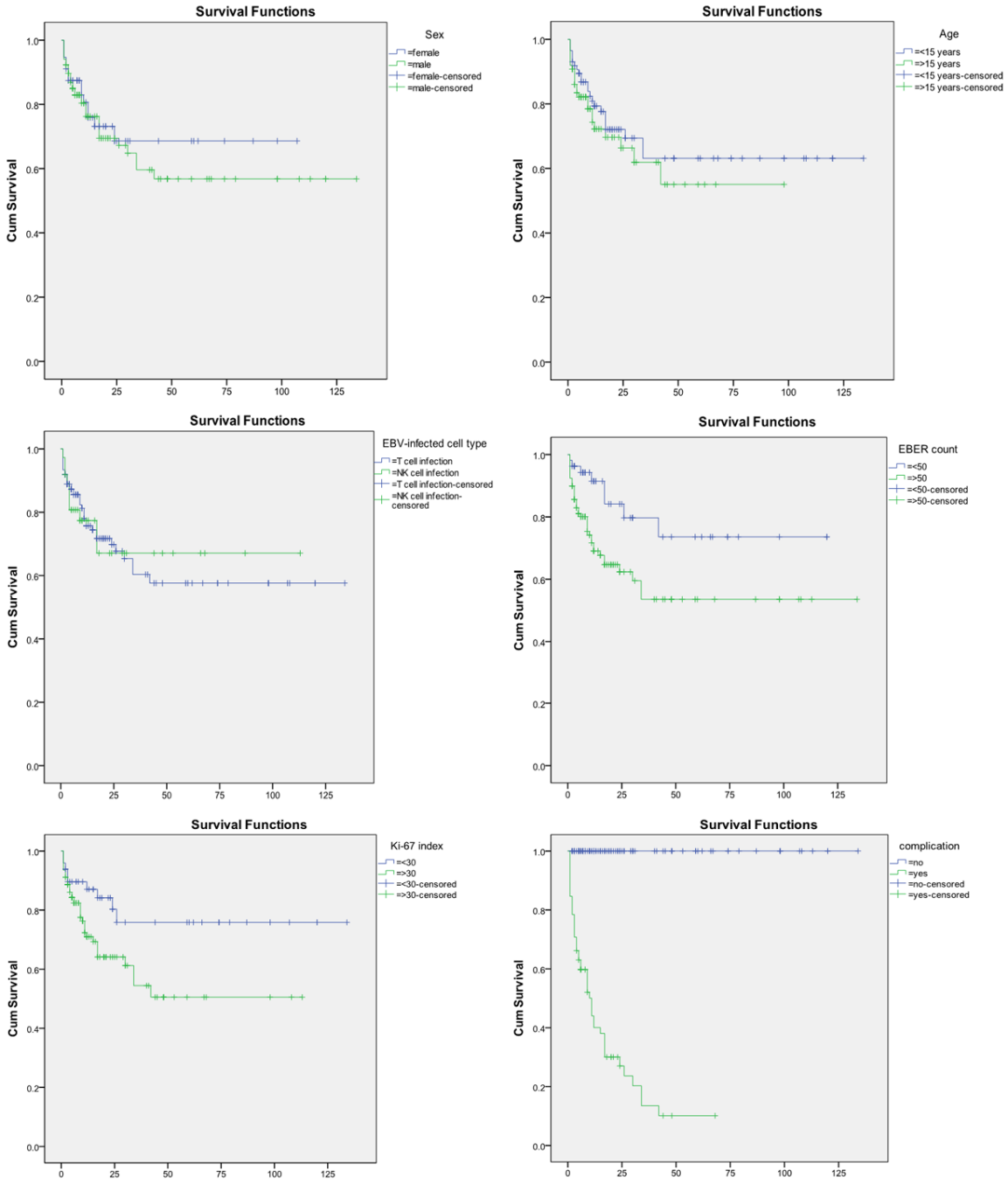

Figure 5. Probability of survival rates from the time of disease onset. Overall survival rates from the time of disease onset were calculated between each subgroup (sex, onset age, presence or absence of complications, EBV-infected cell types, Ki-67 index, and EBER count) by the Kaplan-Meier estimation method.

tions similar to systemic EBV + T/NK-LPD, which is consistent with previous case reports [20, 21].

In the present study, we performed a preliminary statistical analysis on risk factors for complication occurrence and found some significant associations. Besides immunohistochemistry, we were unable to perform polymerase chain reaction for clonality of cell gene rearrangement and other molecular biology examinations using adequate samples, and this should be evaluated in future studies to find more potential risk factors. Furthermore, data

Table 3. Univariate and multivariate analyses of factors associated with complications in 173 patients with EBV + T/NK-LPD

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex	1.00 (0.52-1.94)	NS		
Age	1.70 (0.91-3.16)	0.095	1.92 (0.97-3.80)	0.060
Fever	4.41 (1.61-12.05)	**0.002**	3.33 (1.13-9.81)	**0.029**
Lymphadenopathy	3.24 (1.49-7.05)	**0.002**	1.76 (0.74-4.15)	NS
Hepatosplenomegaly	3.42 (1.74-6.75)	**< 0.001**	2.74 (1.32-5.71)	**0.007**
Decreased WBC	3.73 (0.98-14.20)	**0.036**	3.07 (1.09-10.39)	**0.049**
Decreased PLT	1.95 (0.62-6.15)	NS		
NK cell infection	0.86 (0.41-1.87)	NS		
EBER > 50/HPF	2.81 (1.35-5.87)	**0.005**	1.91 (0.86-4.22)	NS
Ki-67 > 30%	2.67 (1.25-5.70)	**0.01**	2.42 (1.09-5.37)	**0.030**

NS indicates not significant. $P < 0.1$ is shown; $P < 0.05$ (shown in bold) is statistically significant.

on other related clinical aspects, such as liver function, bone marrow examination, blood smear analysis, detection of serum ferritin levels, and other post-treatment conditions remain limited. Thus, the determination and investigation of risk factors warrant the support of information on related clinical aspects of EBV + T/NK-LPD. Therefore, clinicians and pathologists should pay close attention to changes in the clinical information of patients as well as take precautionary measures against the occurrence of fatal complications.

Disclosure of conflict of interest

None.

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