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Clinical features and survival impact of EBV-positive diffuse large B-cell lymphoma with different age cutoffs

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Abstract. – OBJECTIVE: In 2016 WHO classification, EBV +DLBCL of the elderly was replaced by EBV+ DLBCL NOS. This is due to the fact that many young patients of EBV+ DLBCL were found in recent years.

PATIENTS AND METHODS: In this study, we retrospectively analyzed clinical features and survival outcomes of EBV positive DLBCL patients in different age groups. All the patients treated at a single center.

RESULTS: When we use different ages (40, 50 and 60 years old) as cutoffs, the prevalence of EBV positive DLBCL was 12.0%, 12.3% and 13.0% in younger patients and 19.0%, 15.4% and 13.8% in elder patients respectively. Whatever the age cutoff was, EBV positive associated with unfavorable clinical prognosis in elder groups. When we use 40 and 50 years old as age cutoffs, poor impacts of EBV positive on overall survival and progression-free survival were observed only in elder patients, but not in younger patients. It should be noted that when we use 60 years old as age cutoff, the results were the opposite.

CONCLUSIONS: EBV+ DLBCL patients with age of 40 to 60 years old showed poorer prognostic features than EBV- DLBCL patients; however, patients in other age groups did not show evident differences in prognosis between EBV+ DLBCL patients and EBV- DLBCL patients. This finding was not reported before.

Key Words:
DLBCL, EBV, Lymphoma, Prognosis, Age.

Abbreviations

EBV: Epstein-Barr virus; DLBCL: diffuse large B-cell lymphoma; EBER: EBV-encoded RNA; ISH: *in situ* hybridization; IHC: immunohistochemical; GCB: germinal center B-cell-like; PFS: progression-free survival; OS: overall survival; CR: complete response; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: lactic dehydrogenase..

Introduction

Epstein-Barr virus (EBV) positive diffuse large B-cell lymphoma (DLBCL) of the elderly is defined in the 2008 World Health Organization (WHO) classification by age at diagnosis over 50 years, with detectable EBV infection in the tumor cells and without secondary immune deficiencies[1]. However, this entity was changed to EBV+ DLBCL, NOS, in 2016 WHO classification, because younger patients were found with EBV+ DLBCL. EBV positive DLBCL of the elderly was initially described by Oyama et al[2,3] in a report of 22 immunocompetent elderly patients who had poor responses and short survival with standard combination chemotherapy. There were many other reports showed that patients with EBV+ DLBCL had worse prognosis compared with patients with EBV- DLBCL when treated with CHOP[4-7]. The introduction of this entity was based mostly on data from Asians, especially Japan and Korean. But reports from western countries had different conclusions that the prognosis showed no significant differences between EBV positive and negative patients, and all the patients in these reports were Caucasian. Differences between these reports might be related to ethnic background and geographic variation of EBV strains. However, little has been demonstrated regarding the clinical characteristics and prognosis of EBV positive and negative DLBCL patients in China.

Age cutoff of EBV+ DLBCL of the elderly was set as >50 years previously. With more research found that EBV+ DLBCL could occur in young adults[8-10] and there were no significant differences in survival between elderly and young patients with EBV positive[10-12], the conception of EBV+ DLBCL has changed. We consider the above conclusions were based on the age cutoff of 50 years old. But as

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people live longer, 50 is not a suitable age definition for elderly people in modern times. The definition of elderly people has changed to 60 or older.

In this study, we retrospectively evaluated the different effects of EBV status on clinical features and overall survival in DLBCL patients according to different age groups with 3 age cutoffs in Chinese patients.

Patients and Methods

Patients

A total of 104 patients diagnosed as *de novo* DLBCL in the First Affiliated Hospital of Zhengzhou University between 2015.01-2019.6 were evaluated in this study. All the patients met the following criteria: 1) pathologically confirmed diagnosis of DLBCL according to the WHO classification; 2) adequate amount and quality of paraffin-embedded biopsy specimens for EBV-encoded RNA (EBER) in situ hybridization; 3) no previous malignancy or second malignancy; 4) clinical data and follow-up information available. Patients with post-transplant lymphoproliferative disorder, primary mediastinal B-cell lymphoma, primary cutaneous DLBCLs and DLBCL transformation from a low-grade B-cell lymphoma, primary central nervous system lymphoma, association of immunodeficiency (e.g., HIV infection or common variable immunodeficiency) were excluded. This investigation was conducted in accordance with the Declaration of Helsinki and approved by the Zhengzhou University Ethics Committee.

In Situ Hybridization and Immunohistochemistry

In situ hybridization (ISH) for EBV-encoded RNA (EBER) was carried out using a fluorescein-conjugated EBER oligonucleotide probe and the purified IgG fraction of a mouse monoclonal anti-fluorescein antibody. According to Wada et al[13], we adopted the criterion of >50% EBV-positive. Immunohistochemical (IHC) staining and analysis were carried out using the following antigens: CD20, CD3, CD10, BCL-6, MUM-1, Ki-67, CD30. Germinal center B-cell-like (GCB) and non-GCB groups were subclassified according to the algorithm of Hans.

Statistical Analysis

Progression-free survival (PFS) was defined as the duration from the date of diagnosis to the date of relapse, progression, death, or last follow-up. Overall survival (OS) was defined as the duration from the date of diagnosis to the date of death or last follow-up. OS and PFS were calculated by the Kaplan-Meier method, and comparisons between groups were analyzed by the log-rank test and Bonferroni correction. Differences of clinical features between the two groups were analyzed using Pearson's χ^2-test. A two-tailed p-value<0.05 by log-rank test was considered statistically significant. Statistical analysis was performed using the SPSS 20.0 (IBM, Armonk, NY, USA) statistical software package.

Results

Clinical Features of Patients

There were 104 cases included in the analysis as the whole cohort. Of these 104 cases, 14 (13.5%) showed EBER positive. Using 40 years old as cut-off, the prevalence of EBER positive was 19.0% (4/21) and 12.0% (10/83) in elder and younger group respectively (p=0.401). Using 50 as cut-off, the prevalence of EBER positive was 15.4% (6/39) and 12.3% (8/65) in elder and younger groups respectively (p=0.656). And using 60 as cut-off, 13.8% (8/58) and 13.0% (6/46) were positive for EBER in elder and younger groups respectively (p=0.911). No significant differences of prevalence for EBER positive were observed between younger and elder groups no matter the age cut-off was.

The median age of EBER positive patients was 51.5 (range, 23-80 years). In the whole cohort, EBER positive was significantly associated with advanced clinical stage (stage III/IV), poor performance status (ECOG PS status 2-4), decreased Lymphocyte number of peripheral blood, and elevated LDH (Table I). Using 40 and 50 years old as cut-off respectively, compared with EBER negative, EBER positive was associated with advanced clinical stage (stage III/IV), poor performance status (ECOG PS status 2-4), extranodal involvement, high-intermediate IPI, decreased Lymphocyte number of peripheral blood, and elevated LDH in elder groups (Tables I and II). In younger groups, EBER positive did not associate with any clinical features (Tables I and II). Using 60 years old as cut-off, EBER positive associated with high-intermediate IPI, elevated LDH and decreased Lymphocyte number of peripheral blood in elder group. In younger group, EBER positive associated with advanced clinical stages (stage III/IV), poor performance status (ECOG PS status 2-4), and decreased Lymphocyte number of peripheral blood (Table II).

Table I. Clinical features of all patients and patients in different groups (40 years old as age cutoff).

Variable	Number (%)	All patients (N=162)		*p*-value	Young group (≤40)		*p*-value	Elderly group (>40)		*p*-value
		EBV +	EBV-		EBV+	EBV-		EBV+	EBV-	
		Number (%)			Number (%)			Number (%)		
Sex										
Male	51 (49.0)	7 (50.0)	44 (48.9)	0.938	2 (50.0)	8 (47.1)	1	5 (50.0)	36 (49.3)	0.968
Female	53 (51.0)	7 (50.0)	46 (51.1)		2 (50.0)	9 (52.9)		5 (50.0)	37 (50.7)	
Performance status										
ECOG 0-1	45 (43.3)	1 (7.1)	44 (48.9)	0.003	1 (25.0)	10 (58.8)	0.508	0 (0)	34 (46.6)	0.005
ECOG 2-4	59 (56.7)	13 (92.9)	46 (51.1)		3 (75.0)	7 (41.2)		10 (100)	39 (53.4)	
Ann Arbor stage										
I-II	33 (31.7)	0 (0)	33 (36.7)	0.006	0 (0)	5 (29.4)	0.555	0 (0)	28 (38.4)	0.016
III-IV	71 (68.3)	14 (100)	57 (63.3)		4 (100)	12 (70.6)		10 (100)	45 (61.6)	
Site										
Extranodal	50 (48.1)	9 (64.3)	41 (45.6)	0.192	1 (25.0)	9 (52.9)	0.652	8 (80.0)	32 (43.8)	0.032
Lymph node	54 (51.9)	5 (35.7)	49 (54.4)		3 (75.0)	8 (47.1)		2 (20.0)	41 (56.2)	
IPI										
Low/low intermediate	53 (51.0)	4 (28.6)	49 (54.4)	0.072	3 (75.0)	11 (64.7)	1	1 (10.0)	38 (52.1)	0.012
High intermediate	51 (49.0)	10 (71.4)	41 (45.6)		1 (25.0)	6 (35.3)		9 (90.0)	35 (47.9)	
B symptom										
Positive	29 (27.9)	6 (42.9)	23 (25.6)	0.179	2 (50.0)	3 (17.6)	0.475	4 (40.0)	20 (27.4)	0.651
Negative	75 (72.1)	8 (57.1)	67 (74.4)		2 (50.0)	14 (82.4)		6 (60.0)	53 (72.6)	
Treatment										
R-CHOP	31 (29.8)	5 (35.7)	26 (28.9)	0.603	2 (50.0)	7 (41.2)	1	3 (30.0)	19 (26.0)	0.79
CHOP	73 (70.2)	9 (64.3)	64 (71.1)		2 (50.0)	10 (58.8)		7 (70.0)	54 (74.0)	
Response to frontline treatment										
CR	42	4 (28.6)	38 (42.2)	0.333	1 (25.0)	9 (52.9)	0.652	3 (30.0)	29 (39.7)	0.553
non-CR	62	10 (71.4)	52 (57.8)		3 (75.0)	8 (47.1)		7 (70.0)	44 (60.3)	
LDH										
Over ULN	46 (44.2)	9 (64.3)	32 (35.6)	0.041	2 (50.0)	11 (57.9)	1	7 (70.0)	21 (29.6)	0.012
Normal	58 (55.8)	5 (35.7)	58 (64.4)		2 (50.0)	8 (42.1)		3 (30.0)	50 (70.4)	
Lymphocyte number of peripheral blood										
Under ULN	20 (19.2)	8 (57.1)	12 (13.3)	0	3 (75.0)	3 (17.6)	0.095	5 (50.0)	9 (12.3)	0.003
Normal	84 (78.5)	6 (42.9)	78 (86.7)		1 (25.0)	14 (82.4)		5 (50.0)	64 (87.7)	
Ki-67										
≥70	85 (81.7)	9 (64.3)	76 (84.4)	0.069	0 (0)	16 (94.1)	0.001	9 (90.0)	60 (82.2)	0.536
<70	19 (18.3)	5 (35.7)	14 (15.6)		4 (100)	1 (5.9)		1 (10.0)	13 (17.8)	
Histological subtype										
GCB	40 (38.5)	5 (35.7)	35 (38.9)	0.82	2 (50.0)	10 (58.8)	1	2 (20.0)	25 (34.2)	0.367
non-GCB	64 (61.5)	9 (64.3)	55 (61.1)		2 (50.0)	7 (41.2)		8 (80.0)	48 (65.8)	

EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; CR, complete remission; LDH, lactic dehydrogenase; GCB, germinal center B-cell.

Table II. Clinical features of patients in different age groups (50 and 60 years old as age cutoff respectively)

Variable	Young group (≤50)		*p*-value	Elderly group (>50)		*p*-value	Young group (≤60)		*p*-value	Elderly group (>60)		*p*-value
	EBV+	EBV-		EBV+	EBV-		EBV+	EBV-		EBV+	EBV-	
	Number (%)			Number (%)			Number (%)			Number (%)		
Sex												
Male	4 (66.7)	14 (42.4)	0.273	3 (37.5)	30 (52.6)	0.423	4 (50.0)	23 (46.0)	0.833	3 (50.0)	21 (52.5)	0.909
Female	2 (33.3)	19 (57.6)		5 (62.5)	27 (47.4)		4 (50.0)	27 (54.0)		3 (50.0)	19 (47.5)	
Performance status												
ECOG 0-1	1 (16.7)	19 (57.6)	0.161	0 (0)	25 (43.9)	0.017	1 (12.5)	29 (58.0)	0.017	0 (0)	15 (37.5)	0.068
ECOG 2-4	5 (83.3)	14 (42.4)		8 (100)	32 (56.1)		7 (87.5)	21 (42.0)		6 (100)	25 (62.5)	
Ann Arbor stage												
I-II	0 (0)	10 (30.3)	0.291	0 (0)	23 (40.4)	0.025	0 (0)	18 (36.0)	0.041	0 (0)	15 (37.5)	0.068
III-IV	6 (100)	23 (69.7)		8 (100)	34 (59.6)		8 (100)	32 (64.0)		6 (100)	25 (62.5)	
Site												
Extranodal	2 (33.3)	17 (51.5)	0.707	7 (87.5)	24 (42.1)	0.016	4 (50.0)	24 (48.0)	0.916	5 (83.3)	17 (42.5)	0.062
Lymph node	4 (66.7)	16 (48.5)		1 (12.5)	33 (57.9)		4 (50.0)	26 (52.0)		1 (16.7)	23 (57.5)	
IPI												
Low/low intermediate	4 (66.7)	21 (63.6)	1	0 (0)	28 (49.1)	0.009	4 (50.0)	32 (64.0)	0.449	0 (0)	17 (42.5)	0.044
High intermediate	2 (33.3)	12 (36.4)		8 (100)	29 (50.9)		4 (50.0)	18 (36.0)		6 (100)	23 (57.5)	
B symptom												
Positive	2 (33.3)	8 (24.2)	1	4 (50.0)	15 (26.3)	0.168	4 (50.0)	13 (26.0)	0.166	2 (33.3)	10 (25.0)	0.665
Negative	4 (66.7)	25 (75.8)		4 (50.0)	42 (73.7)		4 (50.0)	37 (74.0)		4 (66.7)	30 (75.0)	
Treatment												
R-CHOP	3 (50.0)	14 (42.4)	1	2 (25.0)	12 (21.1)	0.799	3 (37.5)	17 (34.0)	0.847	2 (33.3)	9 (22.5)	0.562
CHOP	3 (50.0)	19 (57.6)		6 (75.0)	45 (78.9)		5 (62.5)	33 (66.0)		4 (66.7)	31 (77.5)	
Response to frontline treatment												
CR	2 (33.3)	17 (51.5)	0.707	2 (25.0)	21 (36.8)	0.512	3 (37.5)	27 (54.0)	0.386	1 (16.7)	11 (27.5)	0.573
non-CR	4 (66.7)	16 (48.5)		6 (75.0)	36 (63.2)		5 (62.5)	23 (46.0)		5 (83.3)	29 (72.5)	
LDH												
Over ULN	3 (50.0)	17 (51.5)	1	6 (75.0)	15 (26.3)	0.006	5 (62.5)	23 (46.0)	0.386	4 (66.7)	9 (22.5)	0.025
Normal	3 (50.0)	16 (48.5)		2 (25.0)	42 (73.7)		3 (37.5)	27 (54.0)		2 (33.3)	31 (77.5)	
Lymphocyte number of peripheral blood												
Under ULN	3 (50.0)	6 (18.2)	0.24	5 (62.5)	6 (10.5)	0	5 (62.5)	8 (16.0)	0.003	3 (50.0)	4 (10.0)	0.011
Normal	3 (50.0)	27 (81.8)		3 (37.5)	51 (89.5)		3 (37.5)	42 (84.0)		3 (50.0)	36 (90.0)	
Ki-67												
≥70	2 (33.3)	29 (87.9)	0.013	7 (87.5)	47 (82.5)	0.722	4 (50.0)	42 (84.0)	0.028	5 (83.3)	34 (85.0)	0.916
<70	4 (66.7)	4 (12.1)		1 (12.5)	10 (17.5)		4 (50.0)	8 (16.0)		1 (16.7)	6 (15.0)	
Histological subtype												
GCB	2 (33.3)	17 (51.5)	0.707	2 (25.0)	18 (31.6)	0.706	2 (25.0)	23 (46.0)	0.265	2 (33.3)	12 (30.0)	0.869
non-GCB	4 (66.7)	16 (48.5)		6 (75.0)	39 (68.4)		6 (75.0)	27 (54.0)		4 (66.7)	28 (70.0)	

EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; CR, complete remission; LDH, lactic dehydrogenase; GCB, germinal center B-cell.

Immunohistochemical Studies

Based on Hans algorithm, EBER positive patients were classified into two groups: 9 cases (64.3%) were categorized as non-GCB type, and 5 cases (35.7%) were categorized as GCB-type. Compared with EBER negative patients, the proportion of non-GCB and GCB (p=0.82) (Table I) in EBV positive patients showed no significant differences. Using different ages as cutoff, significant differences of subtypes proportions were not seen between any older and younger groups (Tables I and II). In the whole cohort, Ki-67 expression (≥70%) showed no association with EBER positive. Regardless of the age cutoff, Ki-67 expression (≥70%) showed no association with EBER positive in elder and younger group (Tables I and II).

Treatment Response and Survival Analysis

The CHOP or R-CHOP regimens were given to these patients. There were no apparent disparities in the distribution of primary treatment between EBER positive and negative groups (Table I) (p=0.603). In the whole cohort, 28.6% of EBER positive and 42.2% of EBER negative patients achieved CR. Although patients who achieved CR in EBER positive group were less than patients in EBER negative group, the difference did not show statistical significance (p=0.333).

In patients older than 50 years old, the CR rate was 25.0% and 36.8% for EBV positive and negative patients respectively (p=0.512). In patients younger than 50 years old, the CR rate was 33.3% and 51.5% for EBV positive and negative patients (p=0.707). The differences did not show statistical significance. Furthermore, using 40 and 60 years old as cutoff, the CR rates did not show significant differences between EBV positive and negative patients in elder and younger patients respectively (Tables I and II).

The median follow-up duration was 15 months (range, 1- 52 months) for all the 104 patients. In the whole cohort, EBV positive patients showed significantly worse OS (median OS, 11 months *vs.* 19 months, p=0.039) and PFS (median PFS, 5 months *vs.* 14 months, p=0.027) than EBV negative patients (Figure 1A and B). Using 50 years old as cutoff, we analyzed EBV positive and negative groups in younger and elder patients, respectively. In elder patients, EBV positive group showed significantly worse OS (median OS, 4 months *vs.* 14 months, p=0.023) and PFS (median PFS, 3 months *vs.* 11 months, p=0.024) than EBV negative group (Figure 1E and F). However, the same tendency was not seen in younger patients (Figure 1K and L). To verify whether the age cutoff of 50 years old was appropriate, we chose 40 and 60 years old as cutoff. When we carried out 40 years old as cutoff, EBV positive group showed significantly worse OS (median OS, 6 months *vs.* 15 months, p=0.030) and PFS (median PFS, 4 months *vs.* 13 months, p=0.013) than negative group in elder patients (Figure 1C and D). But in younger patients, differences were not seen between the two groups (Figure 1I and J). When we use 60 years old as cutoff, differences of OS and PFS between EBV positive and negative groups were not seen in elder patients (Figure 1G and H), but in younger patients EBV positive group showed significantly worse OS (median OS, 12 months *vs.* 52 months, p=0.032) and PFS (median PFS, 5 months *vs.* 29 months, p=0.033) than EBER negative group (Figure 1M and N).

Discussion

EBV is one of the earliest viruses and plays an important role in carcinogenesis of many malignant tumors, including several types of leukemia, lymphoma and solid tumors. EBV infection usually targets B cell proliferation[14] and takes part in the promotion of B cell lymphoma, such as Burkitt lymphoma and Hodgkin lymphoma. EBV positive DLBCL is another malignant disease which associated with EBV infection. EBV positive DLBCL of the elderly was initially described by a Japanese group[2]. This tumor is defined as an EBV positive monoclonal large B-cell lymphoproliferative disorder arising in immunocompetent patients older than 50 years[15]. But the age cutoff of 50 years seems too young to be designated as "elderly" and appears somewhat arbitrary. In some studies, young patients with EBV positive DLBCL were also reported and these young patients showed worse survival just like elder patients. So they suggested that age cutoff for EBV positive DLBCL was unnecessary or needed to be modified[8,12]. In present study, we use 40, 50 and 60 years old as cutoff respectively to separate these patients and compare younger and elder patients in several aspects for a forward to find an appropriate age cutoff for this disease.

There were 14 (13.5%) patients in the whole cohort showed EBV positive. The prevalence of EBV positive DLBCL was higher than many reports. Such as in Japan and Korea, the prevalence was 8.7%-11.4%[3,5,16] and in some western countries it is less than 5%[13,17]. But it was comparable with results from China, Peru and Poland[6,18,19].

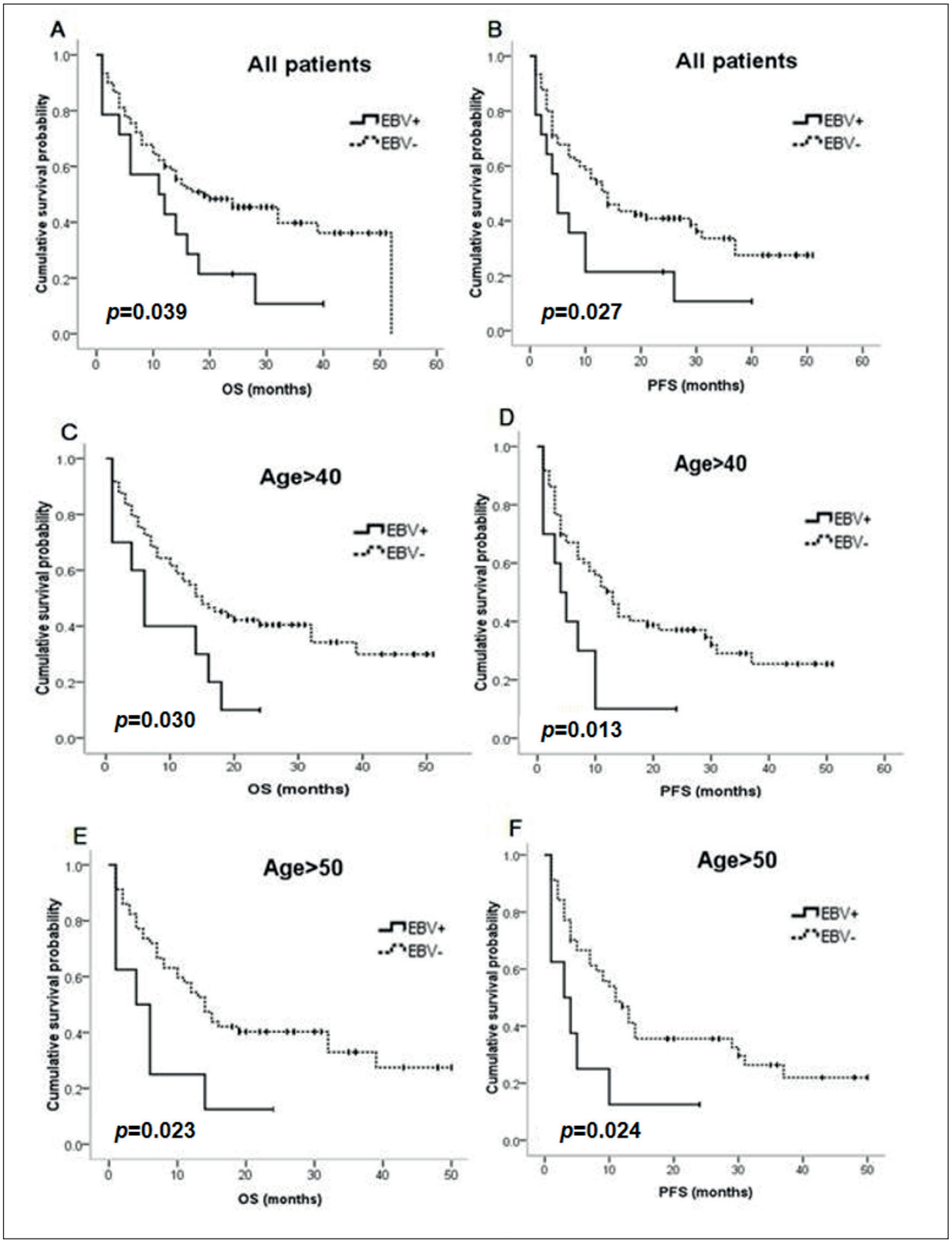

Figure 1. Overall survival (OS) and progression-free survival (PFS) of all patients, and patients grouped with different age-cutoffs. **A-B**, OS and PFS for all patients; **C-D**, OS and PFS for patients older than 40 years old; **E-F**, OS and PFS for patients older than 50 years old.

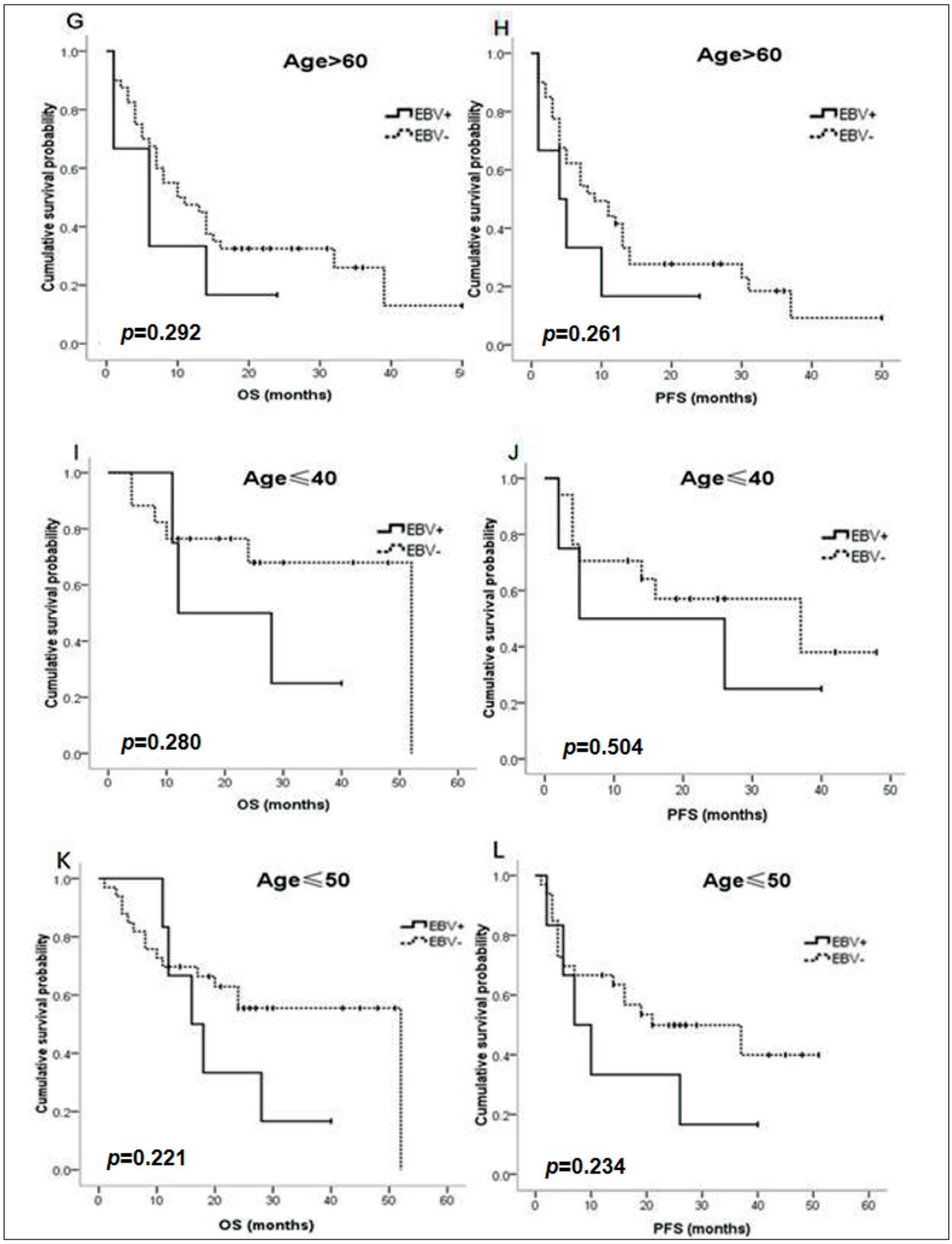

Figure 1 (Continued). **G**-**H**, OS and PFS for patients older than 60 years old; **I**-**J**, OS and PFS for patients younger than 40 years old. **K**-**L**, OS and PFS for patients younger than 50 years old.

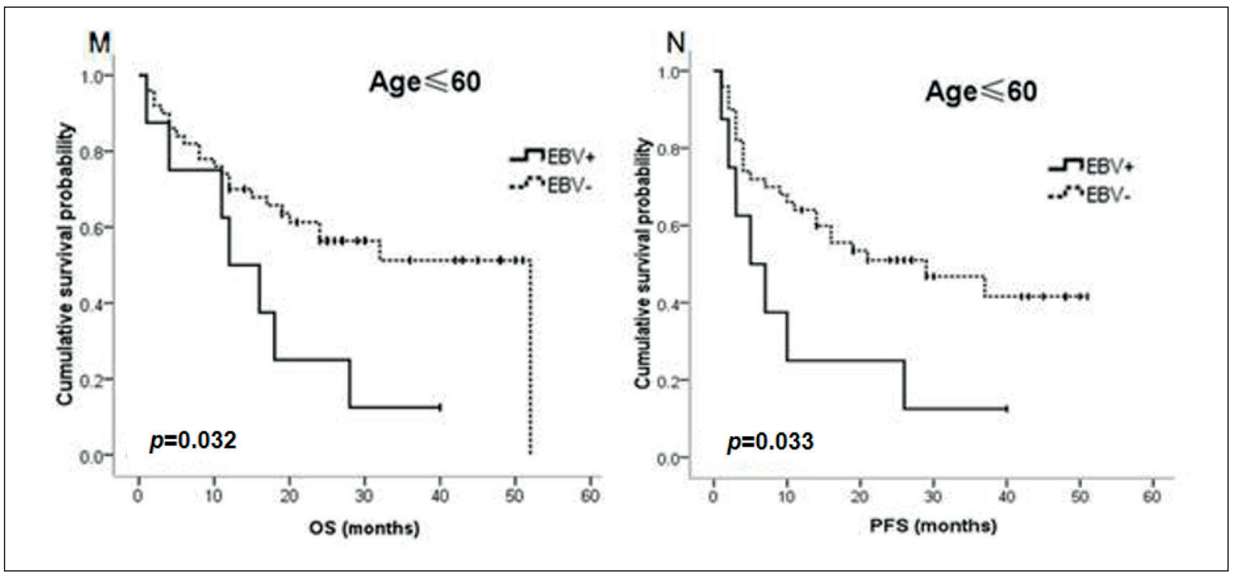

Figure 1 (Continued). M-N, OS and PFS for patients younger than 60 years old.

When we used different ages (40, 50 and 60 years old) as cutoffs, the prevalence of EBV positive DLBCL is 12.0%, 12.3% and 13.0% in younger patients and 19.0%, 15.4% and 13.8% in elder patients, respectively. Hong et al[8] reported that the prevalence of EBV positive was 6.7% and 9.3% in younger group (<50) and elder group (>50). Our results were comparable with a report from China. Lu et al[18] found that the prevalence of EBV positive was 11.9% (10/84) and 15.1% (25/166) in younger and elder group respectively. These reports had the same tendency that the proportions of EBV positive DLBCL in elder patients were higher than younger patients.

In present study, EBV positive had a close association with advanced clinical stages (stage III/IV), poor performance status (ECOG PS status 2-4), extranodal involvement, high-intermediate IPI, decreased Lymphocyte number of peripheral blood, and elevated LDH in elder group when we use 40 or 50 years old as cutoffs, but did not in younger group. It was comparable with reports from Asian and Western countries[8,17,18]. But Lu et al[20] suggested that these clinical features were not different between EBV positive and negative DLBCL patients. This report retrospectively investigated 89 patients with newly diagnosed DLBCL in Taiwan. However, when we use 60 years old as cutoff, there were a few differences in elder group. EBV positive DLBCL associated with high-intermediate IPI, decreased Lymphocyte number of peripheral blood, and elevated LDH, but was not associated with poor performance status and extranodal involvement.

The impacts of EBV on survival outcomes of DLBCL were different in previous studies. In Asian and some European countries EBV positive DLBCL showed inferior clinical outcomes[8,10,18,20-23]. But reports from America showed that EBV infection did not predict a worse outcome[8,16]. Hong et al[8] reported that EBV positive DLBCL had worse OS (median OS, 17.3 months *vs.* 192.6 months, $p < 0.001$) and PFS (median PFS, 8.6 *vs.* 149.9 months, $p < 0.001$) compared with EBV negative DLBCL in Korea. When performed sub group analysis based on age (50 years old as cut-off), in the younger patients, there was no significant difference in median OS and PFS between two groups. Lu et al[18] found that EBV positive DLBCL had worse OS and PFS than EBV negative ones not only in the older group but also in the younger group in China. Sato et al[21] revealed that even in the rituximab era, EBV negative DLBCL patients showed better OS (median OS, 8.7 months *vs.* not reached, p=0.0002) and PFS (median PFS, 6.8 *vs.* not reached, p<0.0001) than positive patients in Japan. In Taiwan, patients with EBV positive DLBCL appeared to have a shorter OS (median, 17.7 months *vs.* not reached in EBV negative DLBCL), but the differences were not statistically significant. Contrary to previous reports from Asian country, reports from American, all the patients were Caucasians, showed that EBV infection did not predict inferi-

or outcomes and co-expression with CD30 harbor extremely poor survival[17,18]. But another study with Caucasians from Poland, a central European country, showed an opposite result that EBV positive DLBCL of elder patients had worse OS than EBV negative ones. In recent years the introduction of rituximab, the outcome of DLBCL patients was improved with R-CHOP. But the impact on the prognosis of EBV positive DLBCL patients remained controversial. In a multicenter study, patients were treated with R-CHOP. The survival rates and clinical presentation showed no statistical differences between the two groups[8]. Another study[10] in Korea with 18 EBV positive and 204 EBV negative DLBCL patients showed no differences in the OS rates between the two groups. Conversely, in a Spanish study EBV positive DLBCL elderly who received R-CHOP-like regimens, the 2-year OS rate was 40%, which appeared lower than patients with EBV negative DLBCL[9]. In our study, there were no significant differences of the use of rituximab between EBV negative and positive groups (Table I). Patients with EBV positive showed significantly worse OS and PFS compared with the EBV negative patients. The data was consistent with the results of earlier studies from Asian[18,20,22]. To find the optimal cutoff value for age criterion, we use different age cutoffs to analyze the impact of EBV. When we use 50 years old as cutoff, which used most commonly in previous studies, EBV positive DLBCL had worse OS than EBV negative ones only in elder group. In younger patients EBV positive of DLBCL did not predict worse outcomes. It was consistent with the results of a Korean study[8] but was different with the report of southern China[18]. When we use 40 years old as cutoff, the clinical outcome showed the same trend between EBV positive patients and negative patients in elder group and younger group with the clinical outcome when using 50 years old as cutoff. Of note, when we use 60 years as age cutoff, the trend reversed. In patients younger than 60, EBV positive patients showed inferior outcome compared with negative patients. But in elder patients, there were no differences between the two groups. Similar results were not seen in any previous studies and needed to be noted. We think the reason for this phenomenon is that patients older than 60 years old are more sensitive to external factors and in the course of aging there are more opportunities for various pathogens, not only EBV, that weaken human's immune system and result in immnosenescence. Our report is a retrospective study in a single center and the follow-up was not very long for more precise prediction of prognosis in EBV positive DLBCL patients. A prospective and randomized clinical trial is needed for better understanding of this disease.

In summary, EBV positive DLBCL patients showed poor prognostic features. When using 40 and 50 years old as age cutoffs respectively, EBV positive DLBCL patients showed unfavorable clinical features and worse outcomes only in elder groups but not in younger groups. When use 60 years old as age cutoff, EBV positive did not associated with worse clinical features and outcomes in elder group but associated with worse outcomes in younger patients. Based on these results, we suggest EBV positive is an independent prognostic factor for DLBCL, regardless of age.

Conclusions

In summary, EBV positive is an independent prognostic factor for DLBCL, especially in patients with age of 40 to 60 years old. So, we think more attention should be paid on these patients.

Conflict of Interests

The authors declared there is no conflict of interest.

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