

# High-Grade B-Cell Lymphomas, Not Otherwise Specified: A Study of 41 Cases

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**Purpose:** To analyze the clinical and pathological characteristics, treatment, and prognosis of high-grade B-cell lymphomas, not otherwise specified (HGBL, NOS), and to increase awareness of this type of lymphoma.

**Patients and Methods:** We collected clinical and pathological data of 41 cases of newly diagnosed HGBL, NOS, and analyzed diagnosis, prognosis and treatment to examine progression-free survival (PFS) and overall survival (OS).

**Results:** Among the 41 cases studied, the median PFS was 6.0 months and the median OS was 18.0 months. Compared with patients treated with the R-CHOP regimen, patients treated with a high-intensity chemotherapy (DA-EPOCH-R, R-CODOX-M/IVAC, or R-Hyper-CVAD) had superior PFS and OS (PFS:  $\chi^2=4.173$ ,  $P=0.041$ ; OS:  $\chi^2=5.200$ ,  $P=0.023$ ). A subgroup analysis showed that the OS for the double-expressor lymphoma (DEL) was inferior to that for the non-DEL ( $\chi^2=4.563$ ,  $P=0.033$ ), and this trend was also seen for the single-hit lymphoma with *MYC* rearrangement (SHL) and the non-SHL ( $\chi^2=4.955$ ,  $P=0.026$ ). Patients with low International Prognostic Index (IPI) scores ( $\leq 2$ ) had better survival rates than those with high scores ( $> 2$ ) (PFS:  $\chi^2=6.482$ ,  $P=0.011$ ; OS:  $\chi^2=10.156$ ,  $P=0.001$ ).

**Conclusion:** HGBL, NOS is associated with a high degree of malignancy, short survival period, and substantial extranodal involvement. High-intensity chemotherapy may improve patient prognosis. While IPI scores statistically correlated with the prognosis, SHL and DEL correlated with an inferior survival rate. New and improved treatments will be needed for HGBL, NOS.

**Keywords:** HGBL, NOS, clinical and pathological, treatment, prognosis

## Introduction

High-grade B-cell lymphoma (HGBL) is a newly introduced category in the updated 2016 revision of the World Health Organization (WHO) classification, which primarily replaces “B-cell lymphoma, unclassifiable, with features intermediate between a diffuse large B cell lymphoma (DLBCL) and the Burkitt lymphoma (BL) (BCLU, DLBCL/BL).” Currently, HGBL comprises 2 types of lymphomas: HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL, R) and high-grade B-cell lymphomas, not otherwise specified (HGBL, NOS).<sup>1–5</sup> HGBL, R is also called a double/triple-hit lymphoma (HGBL, DH/TH).<sup>6</sup> HGBL, NOS do not contain *MYC* and *BCL2* or *BCL6* gene rearrangements, but present morphologies between DLBCL and BL.

HGBL, NOS belong to a type of gray zone lymphomas, as they are rarely encountered in the clinic, and their etiology and pathogenesis remain unclear.<sup>7</sup> Therefore, these gray zone lymphomas have been listed separately, to facilitate

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better study of the pathological and clinical features of the tumors. While a standard treatment has not been established for HGBL, NOS,<sup>8</sup> the following regimens have been used at the National Comprehensive Cancer Network member institutions: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine), DA-EPOCH-R (rituximab, dose-adjusted doxorubicin, cyclophosphamide, vincristine, etoposide, prednisone), R-Hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin and methotrexate alternating with ifosfamide, etoposide, and cytarabine), in consolidation with a high-dose therapy with an autologous hematopoietic stem cell transplantation (ASCT).

Although the pathological features and clinical characteristics of patients with HGBL, DH/TH have been well characterized in the literature,<sup>5,6</sup> few studies have focused on patients with HGBL, NOS. We retrospectively analyzed a group of patients with HGBL, NOS and summarized the clinical and the pathological features, and explored the patient diagnosis, treatment, and prognosis. We hope to improve the medical community's understanding of this type of tumor.

## Methods

### Clinical Characteristics

We collected data from 1802 patients with a newly diagnosed aggressive mature B-cell lymphomas, from January 01, 2013 to June 01, 2019, in The First Affiliated Hospital of Zhengzhou University, People's hospital of Zhengzhou University, and The Affiliated cancer Hospital of Zhengzhou University (Henan Cancer Hospital). Of the included patients, 67 were diagnosed with HGBL. While 26 met the criteria of HGBL, DH/TH, 41 met the diagnostic criteria of HGBL, NOS. Pathological sections of the 41 HGBL, NOS patients were reread by 2 senior lymphoma pathologists, who referred to the WHO lymphohematopoietic system tumor classification (2016)<sup>3</sup> to identify the morphological, immunophenotypic, and cytogenetic characteristics. If the opinions of the two experts differed, then the pathological sections were consulted in the superior hospital. The expression of *MYC/BCL2/BCL6* was detected by immunohistochemistry (IHC), while *MYC/BCL2/BCL6* rearrangement was detected by fluorescence in situ hybridization (FISH). For IHC, the positivity cutoff values

were 40% for *MYC* and 50% for *BCL2*.<sup>6,9</sup> Lymphomas that do not harbor *MYC* and *BCL2* and/or *BCL6* rearrangements but exhibit the *MYC* and *BCL2/BCL6* protein expression are known as double-expressor lymphoma (DEL).<sup>10,11</sup> HGBL, NOS with *MYC* rearrangement have been defined as single-hit lymphomas (SHL) in this study. The Hans classification<sup>12</sup> was used to analyze the cell of the origin subtype. Patient baseline clinical characteristics included sex of the individual, age, the eastern cooperative oncology group score (ECOG), the Ann Arbor stage, the international prognostic index (IPI) score, B symptoms, the serum lactate dehydrogenase (LDH) level, the  $\beta 2$  microglobulin, extranodal sites, the Ki-67 level, and the bone marrow involvement.

### Regimens

All patients with HGBL, NOS received therapy after the results of FISH were available. For first-line therapy, 17 of the 41 (41.5%) patients were treated with R-CHOP and 24 of the 41 (58.5%) were treated with a high-intensity chemotherapy (DA-EPOCH-R, R-CODOX-M/IVAC, and R-Hyper-CVAD). Out of the 41 patients, 15 (36.6%) patients who were at a higher risk for CNS involvement<sup>13</sup> received a CNS prophylaxis. Six (19.5%) patients received an ASCT after complete remission and 2 (4.9%) received the chimeric antigen receptor T-cell immunotherapy after relapse.

### Observation of Efficacy and Follow-Up

According to the International Working Group's efficacy evaluation criteria,<sup>14,15</sup> efficacy is divided into complete remission (CR), partial remission (PR), disease stabilization (SD), and progressive disease (PD). The objective response rate (ORR) is calculated according to the percentage of CR+ PR patients among all patients. Progression-free survival (PFS) was defined as the period of time from HGBL, NOS diagnosis to PD or death of any cause. Overall survival (OS) was defined as the time from HGBL, NOS diagnosis to death from any cause or to the last follow-up. The follow-up deadline was October 01, 2019.

### Statistical Analysis

All data were analyzed using the SPSS 24.0. The survival rates (PFS and OS) of each group were estimated using the Kaplan–Meier method, and the survival rates were compared between two groups by a Log rank test. All *P* values <0.05 were considered statistically significant.

## Results

### Morphological, Immunophenotypic, and Cytogenetic Features

The included 41 patient samples presented medium-sized cell characteristics, with thin, scattered nuclei or the BL-like nuclei, some with a “starry sky” phenomenon. These morphological changes were uncertain but overall, cell sizes and shapes of the HGBL, NOS samples were larger than those of the BL samples. Since most specimens were obtained from medium-sized tumor cells with a diffuse hyperplasia and a partial large cell infiltration, small lymphocytes were rare (Figure 1A and B). All cases showed similar morphological markers, which included the expression of mature B-cell markers (such as CD19, CD20, and CD22) that were detected by IHC. Thirty-one (75.6%) cases expressed CD10, twenty-six (63.4%) expressed MUM-1, and thirty-four (82.9%) expressed *BCL6*. Variable proliferation indices (Ki-67 rates) were observed: 32 (78.0%) cases had high Ki-67 (> 90%), and the median Ki-67 was 90%. According to the Hans classifier,<sup>12</sup> the phenotype of 33 (80.5%) cases was germinal center B-cell (GCB); and that of 8 (19.5%) cases was non-GCB. *MYC* and *BCL2* or *BCL6* were positively detected by IHC in 24 (58.5%) of the 41 cases that were diagnosed with DEL. Of all cases, 70.7% strongly expressed the *MYC* protein. Sixteen (39.0%) of the cases were diagnosed with SHL by FISH. The full list of cytogenetic results detected by FISH has been tabulated in Table 1 (n=41). Overall, 13 (31.7%) patients had a *MYC* rearrangement only, 2 (4.9%) had a *BCL2* rearrangement only, 3 (7.3%) had a *BCL6* rearrangement only, and none of the patients had both *BCL2* and *BCL6* rearrangements. Three

**Table 1** Cytogenetic Findings of 41 Patients with HGBL, NOS (n=41)

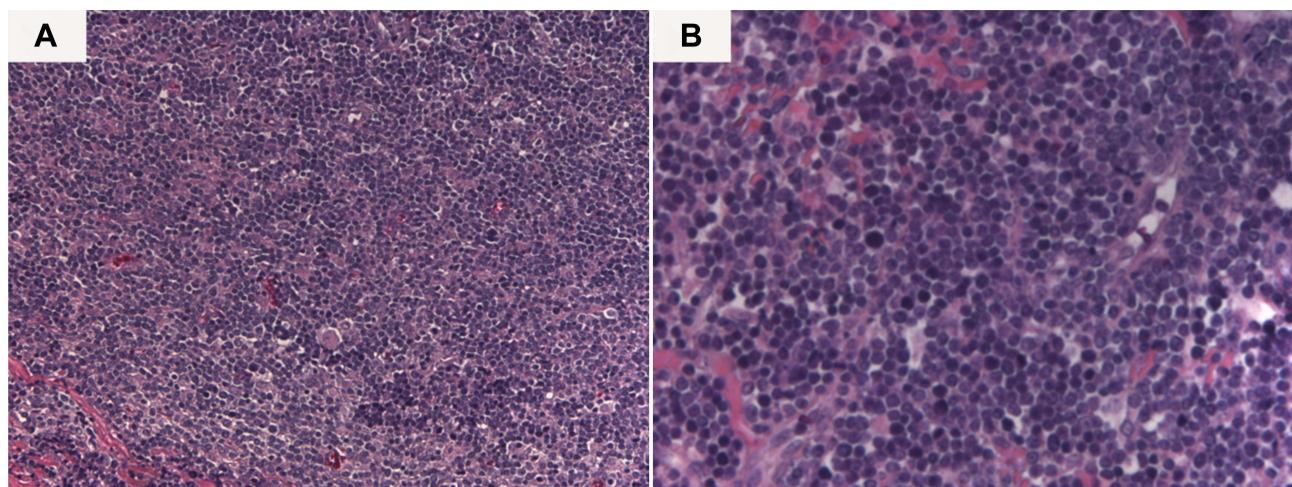
Cytogenetic Abnormalities	n	Percent
IHC (protein express)		
<i>MYC</i> and <i>BCL-2</i>	3	7.3%
<i>MYC</i> and <i>BCL-6</i>	8	19.5%
<i>MYC</i> , <i>BCL-2</i> , and <i>BCL-6</i>	13	31.7%
FISH		
Gene rearrangement		
<i>MYC</i> only	16	39.0%
<i>BCL-2</i> only	2	4.8%
<i>BCL-6</i> only	3	7.3%
<i>BCL-2</i> and <i>BCL-6</i>	1	2.4%
Copy number changes without rearrangement		
<i>MYC</i>	3	7.3%
<i>BCL-2</i> or <i>BCL-6</i>	4	9.8%
<i>MYC</i> and <i>BCL-2</i> or <i>BCL-6</i>	2	4.9%
Abnormalities not detected	11	26.8%

**Abbreviations:** IHC, immunohistochemistry; FISH, fluorescence in situ hybridization.

(7.3%) cases had both the copy number changes and gene rearrangements, which included 1 case with a *MYC* gene rearrangement and the copy number change of *BCL2*, 1 case with a *BCL2* rearrangement and the *MYC* copy number change, and 1 case with both *BCL2* copy number changes and rearrangements. Five (12.5%) cases had copy number changes without gene rearrangement, and the remaining cases had no cytogenetic abnormalities.

### Clinical Features

The characteristics of 41 cases of HGBL, NOS patients have been listed in Table 2. Twenty-six (63.4%) patients



**Figure 1** The morphological features of one case of HGBL, NOS. (A) hematoxylin-eosin, original magnification ×200. (B) hematoxylin-eosin, original magnification ×400.



**Table 2** Patients Characteristics (n=41)

Factor	HGBL, NOS	
	Values of n	Percent
Sex		
Male	26	63.4%
Female	15	36.6%
Age		
≤60	30	73.2%
>60	11	26.8%
ECOG		
0-2	28	68.3%
3-4	13	31.7%
Stage		
I/II	18	43.9%
III/IV	23	56.1%
IPI score		
≤2	17	41.5%
>2	24	58.5%
B symptoms		
Yes	14	34.1%
No	27	65.9%
Extranodal sites		
0/1	18	43.9%
≥2	23	56.1%
LDH		
Elevated	25	61.0%
Normal	16	39.0%
β2 microglobulin		
Elevated	14	34.1%
Normal	27	65.9%
COO subtype		
GCB	31	75.6%
Non-GCB	10	24.4%
First-line therapy		
R-CHOP	17	41.5%
R-Hyper-CVAD	8	19.5%
R-CODOX-M/IVAC	8	19.5%
DA-EPOCH-R	8	19.5%
Response to initial therapy		
CR	13	31.7%
PR	11	26.8%
SD	1	2.4%
PD	16	39.0%

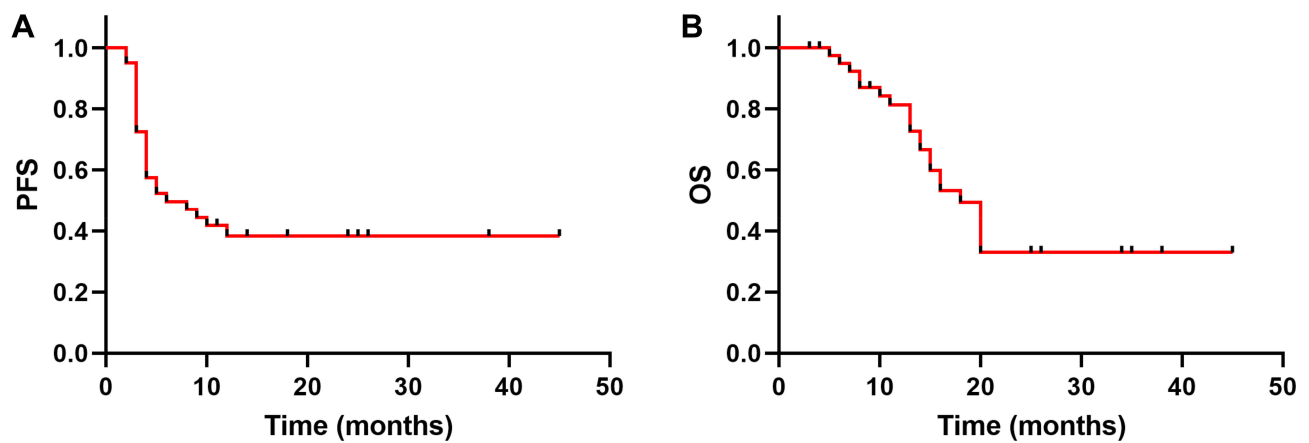
**Abbreviations:** ECOG, Eastern Cooperative Oncology Group performance status; IPI, international prognostic index; LDH, lactate dehydrogenase; COO subtype, cell of origin subtype; GCB, germinal center; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine; R-Hyper-CVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; R-CODOX-M/IVAC, rituximab, cyclophosphamide, vincristine, doxorubicin and methotrexate alternating with ifosfamide, etoposide, and cytarabine; DA-EPOCH-R, rituximab, dose-adjusted doxorubicin, cyclophosphamide, vincristine, etoposide, prednisone; CR, complete remission; PR, partial remission; SD, disease stabilization; PD, progressive disease.

were male and 15 (36.6%) were female. The median patient age was 41 years (range 12–79 years). The first reported symptoms were: unexplained fever, lymph node swelling, night sweats, decreased body mass, abdominal pain, and abdominal distension. Twenty-three (56.1%) patients had the Ann Arbor stage grade III/IV, while 24 (58.5%) patients had an IPI score of >2. B symptoms were observed in 14 (34.1%) patients, an elevated LDH in 25 (61.0%), and an elevated β2 microglobulin in 14 (34.1%).

The median follow-up duration was 28.0 months and from the beginning of the study to the end of the follow-up period, there were a total of 20 deaths. The median PFS was 6.0 months (95% CI: 0.035–11.965 months) and the median OS was 18.0 months (95% CI: 14.772–21.228 months) (Figure 2A and B). Over a 2-year follow-up, the PFS rate was 41.5% and the OS rate was 36.7%.

All 41 patients received therapy which included R-CHOP regimen (n=17), DA-EPOCH-R regimen (n=8), R-CODOX-M/IVAC regimen (n=8), and R-Hyper-CVAD regimen (n=8). Fifteen (36.6%) patients, including 5 cases that received R-CHOP regimen, and 10 of other regimens, were treated with a CNS prophylaxis via an intrathecal injection. Six of the 41 (14.6%) patients received consolidation with an ASCT and 2 (4.9%) received a CAR-T therapy after disease relapse. The median number of chemotherapy cycles was 4 (range: 4 cycles–6 cycles). All 41 patients who were enrolled were evaluated for efficacy. Efficacy measures included CR (13 cases, 31.7%), PR (11 cases, 26.8%), SD (1 case, 2.4%), and PD (16 cases, 39.0%), and the ORR was 58.5%. The 41 patients were divided into 2 groups based on the therapeutic regimens (R-CHOP or high-intensity chemotherapy). Their baseline characteristics have been listed in Table 3. Compared to patients treated with the R-CHOP regimen, those treated with a high-intensity chemotherapy (DA-EPOCH-R, R-Hyper-CVAD, or R-CODOX-M/IVAC) had superior PFS and OS (PFS:  $\chi^2=4.173$ ,  $P=0.041$ ; OS:  $\chi^2=5.200$ ,  $P=0.023$ ) (Figure 3A and B).

We performed subgroup analyses on DEL and non-DEL of HGBL, NOS. The PFS and OS of the patients who were non-DEL were superior to those of the DEL group ( $\chi^2=7.785$ ,  $P=0.005$  for PFS;  $\chi^2=4.563$ ,  $P=0.033$  for OS) (Figure 4A and B). The patients were then divided into 2 groups, based on whether they were diagnosed with SHL. Analyses showed a significant tendency toward better PFS and OS for patients who were non-SHL than those who were diagnosed with SHL ( $\chi^2=4.247$ ,  $P=0.039$  for



**Figure 2** PFS (A) and OS (B) of patients with HGBL-NOS (n=41).  
**Abbreviations:** PFS, progression-free survival; OS, overall survival.

PFS,  $\chi^2=4.955$ ,  $P=0.026$  for OS) (Figure 5A and B). We also analyzed the association of PFS and OS with patient clinical features (such as sex of the individual, age, the ECOG, stage, the IPI score, the B symptoms, the LDH level, the  $\beta 2$  microglobulin level, and the extranodal sites), with results showing that patients with a high IPI scores ( $>2$ ) had inferior PFS ( $\chi^2=6.482$ ,  $P=0.011$ ) and OS ( $\chi^2=10.156$ ,  $P=0.001$ ) (Figure 6A and B). The other factors were not independent prognostic factors (Table 4).

## Discussion

HGBL, NOS belong to a heterogeneous category of rare, invasively mature B-cell lymphomas that are often difficult to classify during pathological diagnosis.<sup>16,17</sup> In 2001, the WHO classified HGBL, NOS as the “atypical Burkitt’s lymphoma” BL subtype.<sup>18</sup> In 2008, the WHO revised the classification of non-Hodgkin’s lymphoma, which was classified separately as BCLU, DLBCL/BL. This new classification included lymphomas that were morphologically between BL and DLBCL but presented immunophenotypes that were close to those of the BL and the lymphomas that were morphologically similar to the BL, but were *BCL2* positive and with or without *MYC* and *BCL2* and/or *BCL6* rearrangements.<sup>19</sup> In 2016, the WHO reclassified lymphomas that did not contain *MYC* and *BCL2* or *BCL6* gene rearrangements, but presented morphologies between DLBCL and BL as HGBL, NOS.<sup>3</sup> A few researchers investigated BCLU before the revised WHO lymphoma classification of 2016, and their studies mostly included HGBL, DH/TH and HGBL, NOS. No study has investigated the features and prognosis of HGBL, NOS after the 2016 WHO revision for tumor

classification. To address the lack of evidence for this type lymphoma and to improve the understanding of this type of tumor, we hereby report a study summarizing the clinical and pathologic features, and exploring the diagnosis, treatment, and prognosis of HGBL, NOS.

The morphology of tumor cells is diverse. Some cases of HGBL, NOS present cells that are similar to the BL, but the immunophenotype and genetic characteristics are inconsistent with the BL. In other cases, the immunophenotype is consistent with the BL, but the size of the nuclei range between that in the BL and in the DLBCL.<sup>7,8</sup> HGBL, NOS often shows a complex karyotype, with Ki-67 scores mostly  $>90\%$  and no genetic rearrangement of *MYC*, *BCL-2*, or *BCL-6*. *MYC* plays an important role in the pathogenesis of cancer and its expression is elevated in up to 70% of all malignancies.<sup>20</sup> *MYC* rearrangement usually results in a sustained expression of the *MYC* protein, which affects cell proliferation, migration, differentiation, and metabolism. Although *MYC* gene rearrangement is a characteristic of BL, it can also be found in the DLBCL and the BCLU.<sup>21</sup> HGBL, DH/TH usually progresses more rapidly, is resistant to R-CHOP chemoimmunotherapy,<sup>6</sup> and the mean OS fluctuates between 5 months and 2 years.<sup>22,23</sup> In our study the median OS of HGBL, NOS was 18.0 months. Baryakh et al<sup>24</sup> investigated 25 patients with BCLU and found that the 3-year OS was 62% and was lower in the DHL group than that in the non-DHL group (HGBL, NOS) (43% vs 75%,  $P<0.05$ ). It seems, therefore, that HGBL, NOS has a better prognosis than HGBL, DH/TH.

HGBL, NOS appears as a blastoid or with a DLBCL/BL morphology (eventually more closely resembling BL than DLBCL), and in up to half of the DLBCL/BL cases,

**Table 3** Patients Characteristics (n=41) Based on Therapeutic Regimens

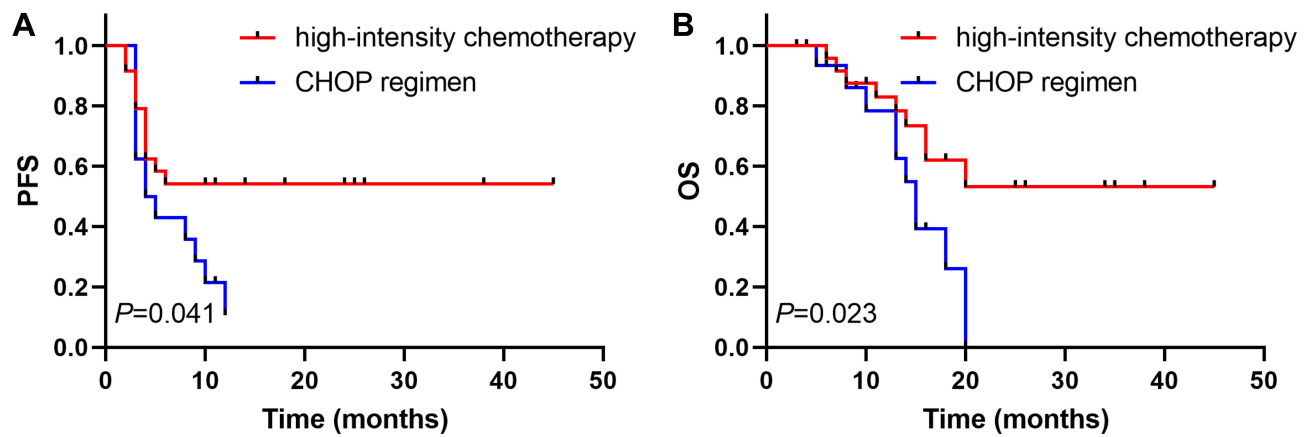
	R-CHOP (n=17)	High-Intensity Therapy (n=24)	P-value
Sex			0.885
Male	11(64.7%)	15(62.5%)	
Female	6(35.3%)	9(37.5%)	
Age			0.753
≤60	12(70.6%)	18(75.0%)	
>60	5(29.4%)	6(25.0%)	
ECOG			0.732
0-2	12(70.6%)	16(66.7%)	
3-4	5(29.4%)	8(33.3%)	
Stage			0.732
I/II	8(47.1%)	10(58.3%)	
III/IV	9(52.9%)	14(58.3%)	
IPI score			0.975
≤2	7(41.2%)	10(41.7%)	
>2	10(58.8%)	14(58.3%)	
B symptoms			0.326
Yes	5(29.4%)	9(37.5%)	
No	12(70.6%)	15(62.5%)	
Extranodal sites			0.326
0/1	9(52.9%)	9(37.5%)	
≥2	8(47.1%)	15(62.5%)	
LDH			0.124
Elevated	8(47.1%)	17(70.8%)	
Normal	9(52.9%)	7(29.2%)	
β2 microglobulin			0.896
Elevated	6(35.3%)	8(33.3%)	
Normal	11(64.7%)	16(66.7%)	
IHC			0.975
DEL	10(58.8%)	14(58.3%)	
Non-DEL	7(41.2%)	10(41.7%)	
FISH			0.288
SHL	5(29.4%)	11(45.8%)	
non-SHL	12(70.6%)	13(54.2%)	

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group performance status; IPI, international prognostic index; LDH, lactate dehydrogenase; COO subtype, cell of origin subtype; GCB, germinal center; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; DEL, double-expressor lymphoma; SHL, single-hit lymphoma.

*MYC* rearrangements as one separate hit have been found.<sup>2</sup> A retrospective study by Li et al<sup>25</sup> found that over a median follow-up of 25 months, the OS of 61 patients with a single-hit lymphoma was poor and similar to that of patients with DHL (2-year OS: 41% vs 48%;  $P=0.35$ ) and significantly worse than that of patients with DLBCL/BL

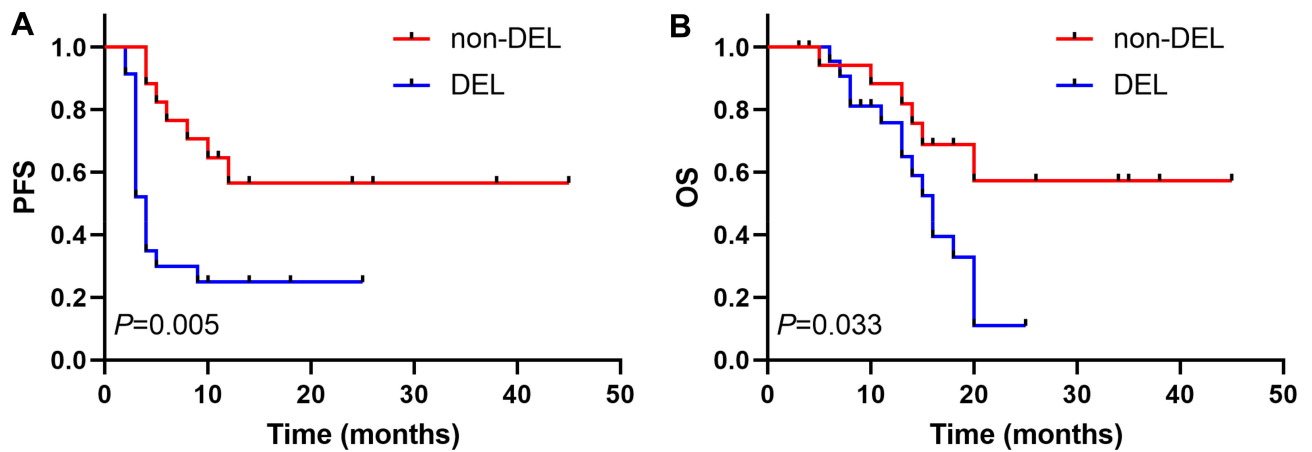
without *MYC* rearrangements ( $P<0.05$ ). Pedersen et al<sup>26</sup> investigated an independent validation cohort of 28 patients with a *MYC* translocation-positive DLBCL in a retrospective analysis and found that *MYC* expression of >75% was associated with both reduced PFS ( $P=0.004$ ) and OS ( $P=0.05$ ). However, DH did not confer a worse outcome than *MYC* single-hit (SH). A prospective study by Landsburg et al<sup>27</sup> found that patients with SHL appeared to have a poor prognosis ( $P<0.001$  for PFS and OS) compared with to patients with DLBCL and BCLU with normal *MYC*. In our study, 16 cases of *MYC* rearrangements were detected by FISH, results which showed that patients with non-SHL of HGBL, NOS had a superior PFS ( $P=0.039$ ) and OS ( $P=0.026$ ) compared with that in the SHL. The expression of *MYC* and *BCL2/BCL6* proteins by IHC is known as DEL. The retrospective study by Herrera et al<sup>5</sup> reported that the 4-year PFS in patients with DEL, compared with those with non-DEL, was 48% vs 59% ( $P=0.049$ ), and the 4-year OS was 56% vs 67% ( $P=0.10$ ), respectively. DEL was independently associated with an inferior PFS in DLBCL. Teoh et al<sup>28</sup> investigated 104 patients with DLBCL in a retrospective study and found that co-expression of *MYC/BCL2* proteins was associated with a significantly inferior OS and an event-free survival (EFS) ( $P<0.05$ ). In our study of HGBL, NOS, the results were similar to those of DLBCL. DEL has also been associated with an inferior survival, compared to that in the non-DEL.<sup>28</sup> DEL and SHL of HGBL, NOS had poor clinical outcomes in the general population of our study.

Although the incidence of HGBL, NOS is low, accounting for 3% of the adult invasive B-cell lymphomas, and has a median age of onset of 55 (18–80) years.<sup>7</sup> Incidences are higher in males than in females. Patients with HGBL, NOS often present with an elevated LDH, bone marrow and CNS involvement, and a high IPI. In our study, the median age of onset was 41 (12 to 79) years, and the ratio of males to females was 1.7:1. Extranodal involvement occurred in 29 (70.7%) patients, which included 4 cases of a gastrointestinal tract invasion, 13 (34.1%) of the involvement of bone marrow, and 5 (12.2%) of involvement of the central nervous system. These findings are consistent with those reported in the literature. Perry et al<sup>29</sup> found that patients with BCLU with low IPI scores (0–2) and normal serum LDH levels had better survival rates. In agreement, our univariate analysis showed that for patients with HGBL, NOS, IPI score was an independent prognostic factor, while the other factors we investigated were not independent predictors of patient prognosis.



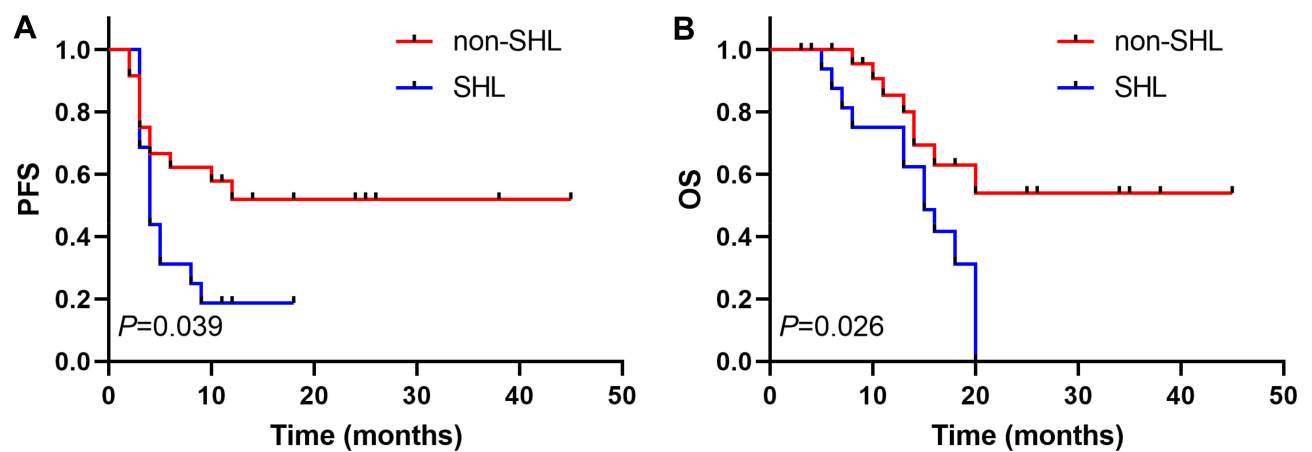
**Figure 3** PFS (A) and OS (B) of patients based on the treatment regimens (CHOP regimen vs high-intensity chemotherapy).

**Abbreviations:** high-intensity chemotherapy, DA-EPOCH-R, R-Hyper-CVAD, or R-CODOX-M/IVAC; PFS, progression-free survival; OS, overall survival.



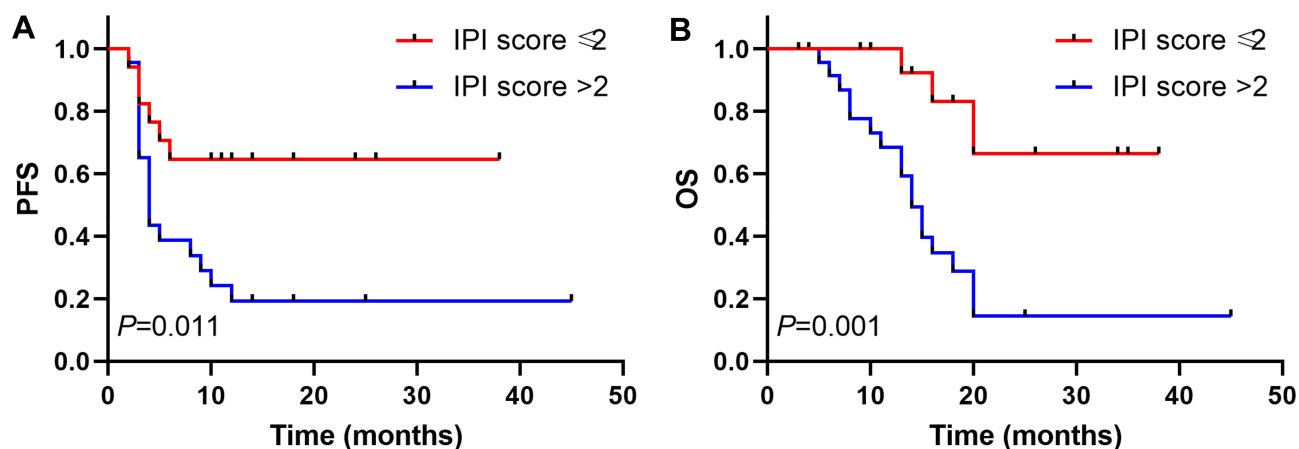
**Figure 4** PFS (A) and OS (B) of patients divided into two groups according to *MYC* and *BCL-2* or *BCL-6* protein express (DEL vs non-DEL).

**Abbreviations:** DEL, double-expressor lymphoma; PFS, progression-free survival; OS, overall survival.



**Figure 5** PFS (A) and OS (B) of patients divided into two groups according to *MYC* rearrangement (SHL vs non-SHL).

**Abbreviations:** SHL, single-hit lymphoma with *MYC*; PFS, progression-free survival; OS, overall survival.



**Figure 6** PFS (A) and OS (B) of patients based on the International Prognostic Index (IPI) scores (IPI score  $\leq 2$  vs IPI score  $> 2$ ).

**Abbreviations:** IPI, international prognostic index; PFS, progression-free survival; OS, overall survival.

Due to the limited knowledge and research on HGBL, NOS, there is no international consensus on a standard therapeutic approach for this lymphoma.<sup>8</sup> Lin et al<sup>17</sup> investigated 52 cases of DLBCL/BL in a retrospective analysis, and showed that in cases with *MYC* rearrangement, the CODOX-M/IVAC or the Hyper-CVAD group had a better OS than that in the R-CHOP group. However, among patients without *MYC* gene rearrangements, there was no statistically significant difference between the different chemotherapy regimens. Corazzelli et al<sup>30</sup> investigated 30

patients in a prospective analysis and found that the application of the CODOX-M/IVAC with the addition of rituximab and the liposome-encapsulated cytarabine had a better PFS outcome than that in the CODOX-M/IVAC (65% vs 37%;  $P=0.05$ ). In another study, McPhail et al<sup>4</sup> investigated 100 patients diagnosed with HGBL, R in a retrospective analysis, and showed that, compared to patients treated with other therapies, those treated with R-CODOX-M/IVAC had superior EFS12 (72% vs 39%,  $P=0.04$ ), and although there was an improved OS ( $P=0.10$ ), this was not significant. Taken together, these studies suggest that stronger chemotherapy regimens may improve the survival of patients with HGBL. In agreement, our study found that patients treated with intensive regimens (DA-EPOCH-R, R-CODOX-M/IVAC, or R-Hyper-CVAD) had superior PFS and OS.

Of all the patients examined in this study, 6 received transplantation after chemotherapy, resulting in a complete remission in 5 patients, and a relapse half-a-year after transplant in one patient. Of the 2 patients who received CAR-T after the disease relapsed, 1 patient received regular follow-up and 1 patient died. Herrera et al<sup>5</sup> found that a relapsed or refractory DEL and DHL had inferior PFS after ASCT ( $P<0.05$ ). For HGBL, NOS, intensive chemotherapy combined with ASCT seemed to improve the prognosis, but a larger sample size will be needed to verify this observation. CAR-T therapy is emerging as a novel treatment modality for lymphoma,<sup>31</sup> and further investigations on applicability of CAR-T therapy in HGBL, NOS will be needed.

**Table 4** Univariate Analysis Results of the Clinical and Pathological Characteristics of Patients with HGBL, NOS

Factor	PFS	OS
	P-value	P-value
Sex	0.590	0.610
Age	0.460	0.464
Ann Arbor stage	0.391	0.305
IPI	0.011	0.001
LDH	0.864	0.858
$\beta 2$ microglobulin	0.984	0.379
ECOG PS	0.499	0.070
Ki-67(%)	0.095	0.434
B symptoms	0.550	0.058
Bone marrow involvement	0.636	0.139
Extranodal involvement	0.082	0.064
CNS prophylaxis	0.244	0.479
Therapeutic regimen	0.041	0.023
DEL	0.005	0.033
SHL	0.039	0.026

**Abbreviations:** PFS, Progression-free survival; OS, Overall survival; IPI, international prognostic index; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; DEL, double-expressor lymphoma; SHL, single-hit lymphoma.

## Conclusion

In summary, our retrospective study showed that HGBL, NOS were highly malignant tumors that were associated



with short survival. We suggest that a high-intensity chemotherapy combined with ASCT may prolong the survival of patients and that DEL and SHL appear to be associated with poor prognoses. Moreover, we suggest that an IPI score  $>2$  may be a poor prognostic factor. However, due to the limitations inherent in our small sample size and retrospective analysis, we propose further prospective and large-scale studies to clarify the clinical outcomes, effective treatments, and survival durations of patients with HGBL, NOS.

## Ethics

This study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University, People's hospital of Zhengzhou University, and The Affiliated cancer Hospital of Zhengzhou University (Henan Cancer Hospital). Informed consent for the collection of medical information was obtained from all patients. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee. The patient consent was written informed consent, and that this study was conducted in accordance with the Declaration of Helsinki.

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## Disclosure

The authors report no conflicts of interest in this work.

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