

Leukemia – Lymphoma and Myeloma

Therapeutic Outcomes in High-Grade B-Cell Lymphoma, NOS: Retrospective Analysis

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South Asian J Cancer 2022;11(1):68–72.

Abstract



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Keywords

- ▶ aggressive B cell lymphoma
- ▶ DLBCL
- ▶ HGBL
- ▶ HGBL NOS
- ▶ high-grade B cell Lymphoma

The nomenclature high-grade non-Hodgkin's lymphoma was repurposed in the World Health Organization (WHO) 2016 update as high-grade B cell lymphoma (HGBL). However, among the HGBL entities HGBL, not otherwise specified (NOS) remains a poorly described entity with a lack of literature regarding its treatment and prognosis. The baseline characteristics, treatment, and outcome of HGBL, NOS cases were analyzed. Thirty HGBL, NOS patients were diagnosed between January 2017 and December 2019. Their median age was 49.3 years, and 30% had advanced IPI. The majority received R-CHOP chemotherapy, while five patients received dose-adjusted R-EPOCH. At a median follow-up of 15 months, nine patients had disease progression or relapse. EFS and OS were 22 months (12.1–31.9 months) and 37 months (29.4–44.0 months) respectively. Only NCCN-IPI ≤ 2 showed significant influence on the outcome. The results were similar to the outcomes previously reported.

This study highlights the importance of NCCN-IPI in ascertaining the prognosis of HGBL, NOS. The literature review suggests that more intensive chemotherapy is ideal for HGBL, NOS. However, prospective trials are needed to prove whether the treatment of HGBL, NOS can be tailored based on NCCN-IPI.

Introduction

High-grade B cell lymphoma (HGBL) is a new disease entity as per the World Health Organization (WHO) 2016 update. The name resulted from the re-purposing of an existing lymphoma entity—high-grade B cell non-Hodgkin's lymphoma. High-grade lymphoma was traditionally used to describe morphologically aggressive lymphoma with many mitotic figures, a

starry-sky pattern, and a high proliferation rate. The newly defined HGBL consisted of two entities—HGBL with a double hit (DH) or triple hit (TH) and HGBL, not otherwise specified (NOS).¹ HGBL DH is defined based on the rearrangement of *MYC* and *BCL2* or *BCL6*. HGBL TH is defined as the rearrangement of all the above three genes. The other entity in this category—HGBL, NOS was defined solely based on the morphology in the absence of the above genetic rearrangements.²

DOI <https://doi.org/10.1055/s-0041-1739365> ISSN 2278-330X

How to cite this article: Karunakaran P, Selvarajan G, Kalaiyarasi JP, et al. Therapeutic Outcomes in High-Grade B-Cell Lymphoma, NOS: Retrospective Analysis South Asian J Cancer 2022;11(1): 68–72.

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HGBL with DH/TH has shown to have a poor prognosis compared with diffuse large B cell lymphoma (DLBCL). These DH/TH lymphomas require more aggressive therapy than the standard R-CHOP regimen. In contrast, HGBL, NOS remains a poorly described entity. Four years after the WHO introduced the entity, there is a conspicuous lack of literature on this entity, with no definite guidelines for treating this entity. We performed this retrospective analysis to analyze the clinical characteristics and therapeutic outcomes of HGBL, NOS cases at our institute.

Methods

This study was a single-center, retrospective analysis of all patients diagnosed with HGBL, NOS from January 2017 to December 2019. We obtained ethical clearance from the Institutional Ethics Committee. Data were retrieved from the electronic records of patients diagnosed with HGBL, NOS. All patients aged over 18 years who received at least more than three planned chemotherapy cycles were included. High-grade transformations from indolent lymphomas were excluded.

The Eastern Cooperative Oncology Group performance status (ECOG-PS), baseline serum LDH, histopathology reports, FISH report for rearrangement of *MYC*, *BCL2*, and *BCL6*, staging investigations, treatment details, response assessment, and outcomes were collected from the case records.

Diagnosis of HGBL, NOS was made based on the morphology and immunophenotypic features as described in the literature.³ Patients with gene rearrangement by FISH for *MYC* with *BCL2* and/or *BCL6* were excluded from the analysis. The choice of chemotherapy regimen was at the discretion of the individual physician. The chemotherapy regimen of R-CHOP or dose-adjusted R-EPOCH was given as previously described in the literature.^{4,5} The response to therapy was evaluated upon completion of planned treatment based on the Lugano criteria.⁶

Non-achievement of complete response (CR) at the end of planned chemotherapy, relapse of the disease after achieving CR, or death from any cause were defined as events. Event-free survival (EFS) was calculated from the date of diagnosis to the occurrence of the event. Overall survival (OS) was calculated from the date of diagnosis to the death due to any cause or until the last follow-up. The data were censored in August 2020.

Baseline characteristics were reported as descriptive analysis. EFS and OS were plotted as Kaplan–Meier curves. Age, stage, LDH, International Prognostic Index (IPI), NCCN-IPI, and type of chemotherapy were analyzed for prognostic significance by Cox regression. Univariate analysis was performed for each factor by log-rank test. Achieving a *p*-value of less than or equal to 0.05 was considered significant. The statistical analysis was performed with SPSS software version 21.

Results

Thirty patients were diagnosed with HGBL, NOS during the 3-year study period. The median age was 49.3 years (range:

20–72 years). Sixteen patients (53.3%) presented with advanced-stage disease (Stage III/IV). A high IPI score (3–5) was observed in nine patients (30%) with a score > 1 in 73.3%. Among 30 patients, 20 (66.6%) had an NCCN-IPI score of more than 2. The majority were with ECOG-PS 1 (22 patients, 73.3%). Extra-nodal involvement was observed in 18 patients (60%), while bone marrow and CNS involvement were observed in 4 patients and 1 patient, respectively. Twelve patients (40%) presented with bulky disease, defined as any lymph node measuring > 7.5 cm. The median LDH value was 632.0 U/L (range: 466.18–823.0), and the median K_i -67 value was 90% (range: 60–95%). Among the 30 cases, 2 had isolated *MYC* positivity on FISH (negative for *BCL2* and *BCL6* rearrangement). Out of 30 patients, 25 received R-CHOP chemotherapy, while 5 patients received dose-adjusted R-EPOCH. The median number of chemotherapy cycles was 6 (range: 3–8 cycles). Seven out of 30 patients (23.3%) received consolidation radiotherapy to the initial site of bulky disease after attaining metabolic response. The baseline characteristics of the patients are presented in [Table 1](#).

The median follow-up of study subjects was 15 months (12.3–17.6 months). The median EFS was 22 months (12.1–31.9 months), and the median OS was 37 months (29.4–44.0 months). The Kaplan–Meier curves for overall EFS and OS are as shown in [Fig. 1](#). Among the 30 cases of HGBL, 9 had disease progression. One patient received DA R-EPOCH, while the other eight received R-CHOP. Among these 8 cases, four had primary progressive disease while undergoing chemotherapy. The remaining four had an early relapse, with a median event-free interval of only 6.5 months (range: 4–11 months). Out of nine patients, five received only metronomic therapy as they were not fit for further chemotherapy. Only four cases received salvage therapy with R-gemcitabine/oxaliplatin (R-GemOx) with or without radiotherapy. None of them could complete the planned six cycles of salvage therapy due to disease progression. None of the nine cases received an autologous stem cell transplant.

The univariate and multivariate analyses of variables affecting EFS and OS are as described in [Table 2](#). In univariate analysis, the NCCN-IPI score of ≤ 2 demonstrated a statistically significant influence on EFS and OS ($p = 0.013$ and $p = 0.031$, respectively). Similarly, IPI score of ≤ 1 influenced EFS ($p = 0.03$). However, with multivariate analysis, none of the factors influenced survival. [Fig. 2](#) shows the Kaplan–Meier curve analysis for OS and EFS for those with IPI score ≤ 1 and > 1 , respectively, as well as for those with NCCN-IPI score ≤ 2 and > 2 .

Discussion

The clinical profile and optimal therapy for HGBL, NOS have not been established. In general, clinical correlations from studies on HGBL, NOS are hampered by overlap with other lymphoma types and their retrospective nature. Numerous reports are available in the literature on B cell lymphoma, unclassifiable from which HGBL, NOS was derived. However, these reports were enriched with HGBL-DH and cannot be compared with HGBL, NOS. Since the WHO update in 2016,

Table 1 Comparison of baseline characteristics of this study with published studies on HGBL, NOS

	Present study	Li et al ⁸	Rush et al ⁷
No. of cases	30	41	50
Men	73.3%	63.4%	
Age > 60 y	26.6%	26.8%	
ECOG PS > 2	03.3%	31.7%	
Stage III/IV	53.3%	56.1%	
Extra nodal site > 1	20.0%	56.1%	
LDH > ULN	76.66%	61%	
LDH > 2ULN	33.3%		
IPI score > 2	30.0%	58.5%	
IPI > 1	73.3%		
NCCN-IPI > 2	66.6%		
Ki67 > 90%	80.0%	78%	
FISH-Myc rearrangement only	06.6%	39%	
Chemotherapy R-CHOP DA R-EPOCH	83.3% 16.6%	41.5% 58.5% ^a	63% 37% ^a
Outcome • CR • PR • SD • PD	76.6% 06.6% 03.3% 13.3%	31.7% 26.8% 02.4% 39.0%	
Median OS	37months	18 months	
2-year OS (%)	68%		76%

^aIncluded other intensive regimens.

Abbreviations: ULN, upper limit of normal; 2ULN, twice the ULN.

there have been only two retrospective studies on HGBL, NOS. Among the two, the report by Rush et al is available only as an abstract.⁷ Hence, we compared our data to 41 cases of HGBL, NOS from China by Li et al.⁸

The comparison of the clinical profiles along with baseline characters of these studies with the present study is shown in Table 1. The overall outcome reported in our study was similar to that reported by Rush et al (2-year OS: 68% vs. 76%). However, in comparison to Li et al's study, a higher fraction of cases attained CR in this study (83.3% vs. 58.5%). This disparity could be explained by the higher percentage of patients presenting with poor PS (31.7% vs. 3.3%) and higher IPI (58.5% vs. 30%) in their study.

The higher proportion of single-hit HGBL (only *MYC* positive) in Li et al's study (39% vs. 6.6%) may also have contributed to the lower CR rate. Interestingly, HGBL, NOS with *MYC* rearrangement alone (without *BCL2* or *BCL6*) was classified as Burkitt's lymphoma in the WHO 2016 update, reaffirming the fact that they had a poor prognosis.² However, this is not universally accepted, with some authors suggesting that these cases can still be classified as HGBL, NOS if *BCL2* is positive.⁹ Furthermore, data from the MD Anderson Cancer Centre suggests that this subset of HGBL benefits the most from intensive chemotherapy.¹⁰ Similarly, Li et al also demonstrated that isolated *MYC* positivity was associated with more inferior PFS and OS.

To summarize, HGBL covers three disease entities with varied prognoses. HGBL with isolated *MYC* positivity has the worst prognosis, followed by HGBL with DH/TH.¹¹⁻¹⁴ HGBL, NOS (excluding *MYC* isolated positivity) has a relatively better prognosis although they still perform poorly in comparison to DLBCL, NOS.^{3,9,11,12}

The therapy of HGBL with DH/TH is well defined now with multiple studies showing benefits for more intensive

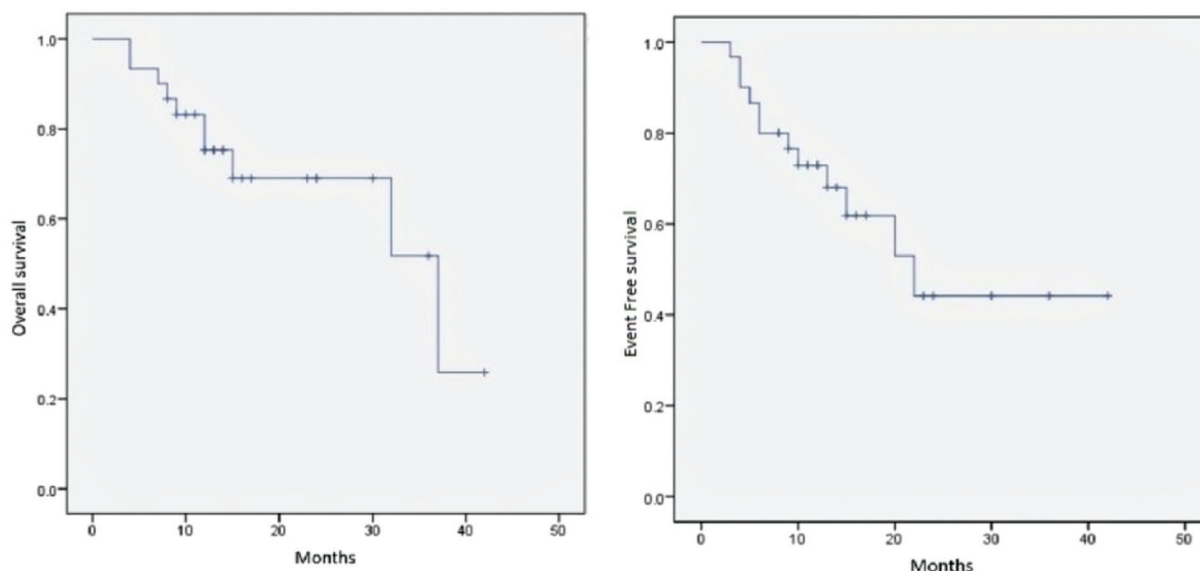
**Fig. 1** Overall survival and event-free survival curves of all 30 patients.

Table 2 Univariate and multivariate analyses of various factors for EFS and OS

Variable	Univariate analysis (by log-rank) <i>p</i> -value		Multivariate analysis (by Cox-regression) <i>p</i> -value	
	EFS	OS	EFS	OS
Age (y)	0.09	0.12	0.919	0.609
Stage ≤ 2 vs. > 2	0.445	0.083	0.119	0.81
LDH ≤ 2 ULN vs. > 2 ULN	0.06	0.1	0.903	0.929
IPI ≤ 1 vs. > 1	0.03	0.057	0.994	0.990
NCCN-IPI ≤ 2 vs. > 2	0.013	0.031	0.973	0.980
Type of chemotherapy	0.128	0.736	0.241	0.776

Abbreviations: EFS, event-free survival; OS, overall survival.

protocols.⁷ Similarly, the NCCN guidelines have endorsed the need for more intensive protocols for HGBL NOS.¹⁵ In Li et al's study, nearly 60% of the patients received more intensive chemotherapy regimens. In our study, the patients who

received dose-adjusted R-EPOCH fared better than those who received R-CHOP although the difference in outcomes was not statistically significant. However, our data support using IPI or NCCN-IPI to determine the intensity of therapy, as

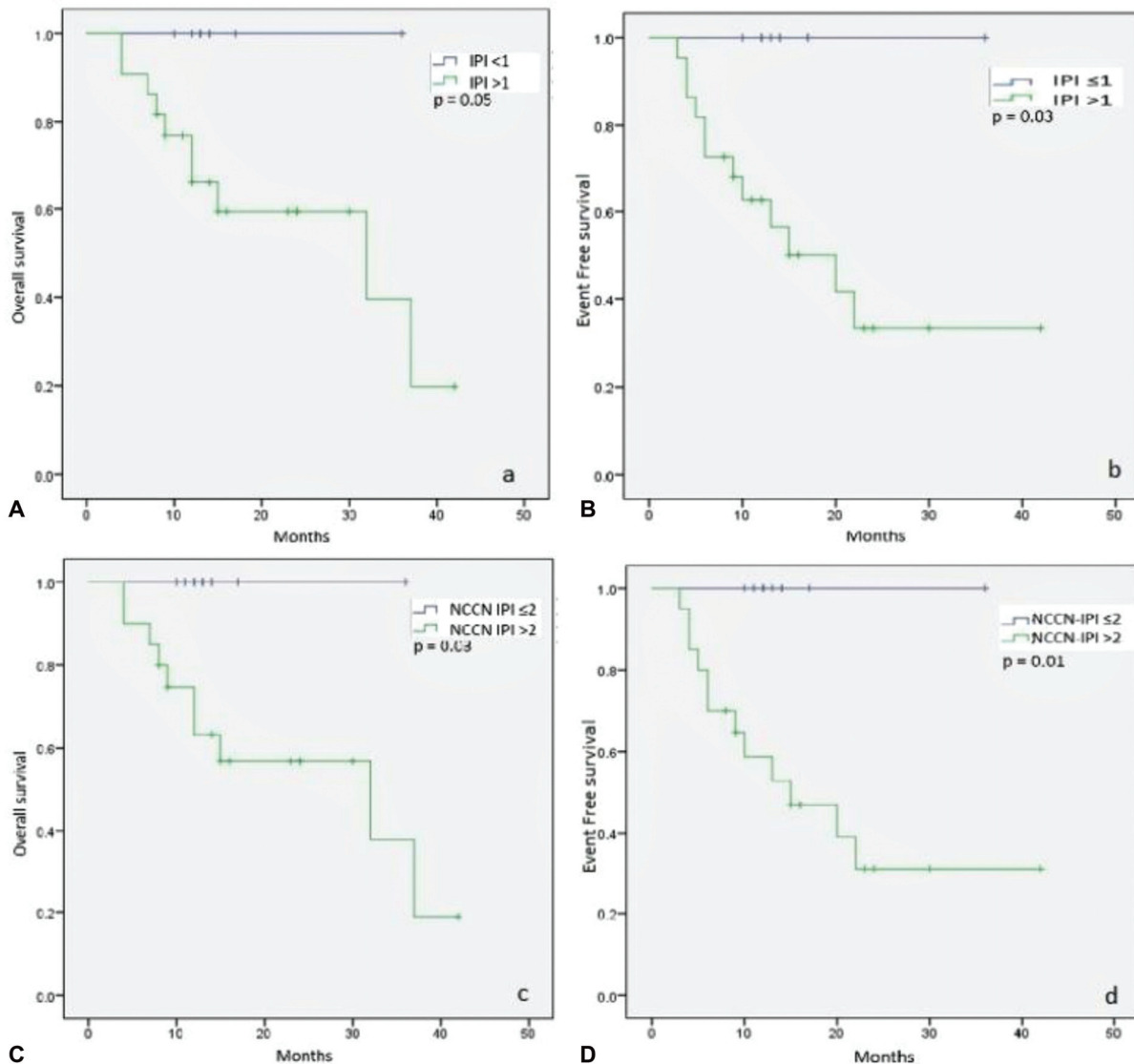


Fig. 2 (A and B) show overall survival and event-free survival curves for those with IPI score ≤ 1 and > 1 , respectively. (C and D) show OS and EFS survival curves for those with NCCN-IPI score ≤ 2 and > 2 , respectively.

those with IPI ≤ 1 or NCCN-IPI ≤ 2 had an excellent outcome with R-CHOP alone.

None of the patients who relapsed in our study attained a second CR. The lack of response to salvage therapy with R-GemOx seen in this study is similar to the poor real-world outcome reported in the literature.¹⁶ The lack of access to newer immunotherapy and chemotherapeutic modalities is reflected in the poor outcome among the cases with disease progression. This serves to underline that ideal upfront chemotherapy offers the best chance to cure a lymphoma patient in low- and middle-income countries.

In addition to the retrospective nature of this study, the other potential limitations of our study include the small sample size and the lack of a consistent chemotherapy regimen with dose-adjusted R-EPOCH given in only five patients. Nevertheless, collectively, the data are hypothesis-generating and suggest a possible role for more intensive therapy such as R-EPOCH in HGBL, NOS in high IPI/NCCN-IPI or those with isolated MYC positivity.

Conclusion

HGBL, NOS is a heterogeneous subgroup of high-grade B cell lymphoma. There is an unmet need to characterize HGBL, NOS without a high-risk MYC single hit. The intensive chemotherapy approach appears to be the ideal choice of therapy upfront. Prospective trials are needed to prove this hypothesis.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We would like to thank Dr. Swaminathan (Department of Epidemiology and Tumour Registry) and his staff for assisting in data retrieval.

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