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ORIGINAL ARTICLE

Clinicohematological characteristics and treatment outcome of diffuse large B-Cell lymphoma -single center experience from Pakistan.

Ayaz Asghar[1], Rabeea Munawar Ali[2], Quratulain Rizvi[3], Aisha Jamal[4], Aisha Arshad[5], Muhammad Nizamuddin[6], Nida Anwar[7]

ABSTRACT… Objective: To assess the clinicohematological characteristics and treatment outcome in Diffuse Large B-cell Lymphoma (DLBCL) patients. **Study Design:** Cross Sectional study. **Setting:** National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD-BMT). **Period:** January 2024 to March 2025. **Methods:** This study included DLBCL patients who were treated at NIBD-BMT. The disease staging was done according to Ann Arbor staging. The IPI and Revised IPI (R-IPI) were employed for prognostic evaluation. All treatment naïve patients received 6 cycles of R-CHOP. Relapse/refractory patients were offered salvage regimen (R-ICE/R-DHAP/R-Lenalidomide/DHAP). The clinical and laboratory findings were evaluated on follow-up visits every 3 months. The statistical analysis was done by using SPSS version 25. **Results:** A total of 21 DLBCL patients were included and 57.1% were males. The median age of participants was 52 years; ranging from 32 to 58 years. Among the total, 52.4% of patients had hemoglobin levels <10.5 g/dl,81% had low TLC of <11 × 10^9/L and platelet counts >100 × 10^9/L in 71.4%.The R-IPI indicated that 82.4% of patients had a poor prognosis. The Ann Arbor staging system revealed that 52.9% had stage 4B.The 57 months overall survival (OS) was 62.5% for the entire cohort. In primary patients, the OS was 69% and in patients with relapsed lymphoma at the initial presentation OS was 50% with log rank test p-value 0.89. **Conclusion:** The study revealed the clinical characteristics, risk stratification and treatment outcomes in DLBCL in resource limited country. Furthermore, multicenter studies with large sample size are needed to validate the outcome of treatment in DLBCL patients.

Key words: Clinico-hematological, Diffuse Large B-cell Lymphoma (DLBCL), International Prognostic Index (IPI), Overall Survival, Treatment.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) and represents about 30-40% of B-cell NHL (B-NHL) with distinct molecular and clinico-pathological characteristics.[1] T6+he median age upon diagnosis is in the seventh decade, and the incidence increases with age, but it slightly predominates in men.[2-4] It may occur de novo or as a result of transformation from an underlying indolent lymphoma.

Depending on the cell of origin (COO), DLBCL can be classified into the following molecular subtypes by differences in gene expression patterns: unclassified subgroups; activated B-cell like (ABC), which has a poorer prognosis; and germinal center B-cell like (GCB), which has a better prognosis. Numerous risk factors, including genetic, viral, and environmental characteristics, contribute to the development of the disease.[5] Furthermore, patients with "double-hit" lymphoma, which is defined as a twofold rearrangement of MYC and/or BCL2 and/or BCL6, have been reclassified into a high-grade group under the World Health Organization's (WHO) classification due to their poor prognosis.[6]

In the diagnosis of DLBCL, NOS has three common morphological variants (centroblastic, immunoblastic and anaplastic) and several rare variants. Immunophenotypically, the neoplastic cells express pan-B-cell markers, such as CD19, CD20, CD22, CD79a, PAX5 and Ki-67 which is a cellular proliferation indicator.[7]

1. MBBS, Resident Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan.
2. MBBS, FCPS, Assistant Professor Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan.
3. MBBS, FCPS, Assistant Professor Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan.
4. MBBS, FCPS, Assistant Professor Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan.
5. Ph.D Hematology, Hematologist, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan/ Department of Allied Health Sciences, Ziauddin University, Karachi, Pakistan.
6. Masters in Biostatistics, Research and Development, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan.
7. MBBS, FCPS, FRCP (UK), FRCPath (UK), Professor Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan.

Correspondence Address:
Dr. Nida Anwar
Plot #Special D-3 Block 6 PECHS, Karachi, 75400, Sindh, Pakistan.
drnidairfan@yahoo.com

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The higher expression of Ki-67 has been linked with worse overall survival (OS), progression-free survival (PFS), and event-free survival (EFS). as well as a higher international prognostic index (IPI).[8]

In the majority of DLBCL patients, generalized lymphadenopathy has been observed, and about 30% of patients have extranodal involvement, which affects the gastrointestinal tract, bones, testes, spleen and central nervous system (CNS).[9] Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the currently used front-line immunochemotherapy for DLBCL, which has a 60–70% probability of curing the overall illness.[10]

An increased trend of DLBCL has been observed in third-world countries, including Pakistan, and the frequency of primary extranodal lymphoma has been almost doubled over the last 20 years compared to nodal lymphoma. Extensive data is available on DLCBL from Pakistan[11-15], but there is a lack of information on nodal and extranodal involvement in DLBCL patients residing in different areas of Pakistan due to the lack of national cancer registry, although it does have two regional cancer registries mainly in Sindh and Punjab.[16] Despite the significant incidence of DLBCL in Pakistan, challenges and outcomes of patients are still underreported due to their remote location, travel challenges, harsh weather, poverty, and low literacy rates.[17] Therefore, the aim of the present study was to assess the clinicohematological characteristics and treatment outcome in DLBCL patients presenting at a referral hematology center in Karachi, Pakistan.

METHODS

This was a cross-sectional single study comprising patients diagnosed with DLBCL as per WHO Classification including both newly diagnosed and relapse/refractory cases that presented at National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD-BMT) Karachi Pakistan from January 2024 to March 2025. The present study was approved by the Institutional Review Board of NIBD Research Ethics Committee. (NIBD/IRB-282/02-2025). A total of 21 patients (aged 12 years and above) were enrolled, including 17 treatment-naive, and 4 relapse/ refractory cases (who had received primary treatment from some other center at Pakistan). The study was approved by the hospital institutional review board. Demographic variables like age, gender, Eastern Cooperative Oncology Group [ECOG] performance status [PS], physical examination, fever [>38.6°C], weight loss [>10% of body weight in 6 months], Ann Arbor stage, and existing co morbidities were documented.

Imaging was performed using whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) preferentially or computerized tomography (CT) neck, chest, abdomen, and pelvis with contrast in cases of non-availability of PET imaging. Bone marrow (BM) biopsy or lymph node biopsy was performed to establish histological diagnosis. Baseline complete blood count (CBC), renal and hepatic profile, lactate dehydrogenase (LDH), viral markers, Echocardiography, and pulmonary function tests (PFTs) were performed as part of pretreatment evaluation.

Disease staging was done according to Ann Arbor staging. The IPI and Revised IPI (R-IPI) were employed for prognostic evaluation. CNS risk assessment was performed using the Central nervous system IPI (CNS-IPI) scoring system. All treatment naïve patients received 6 cycles of R-CHOP except for one patient who was given mini-CHOP due to frailty. Relapse/ refractory patients were offered salvage regimen (R-ICE/R-DHAP/R-Lenalidomide/ DHAP) as per availability. One patient who achieved remission was consolidated with autologous stem cell transplant (ASCT).

Response assessment was done via PET scan at two time points, interim imaging (after 2 cycles) and end of treatment. Patients were then followed up 6 monthly via CT imaging. Comprehensive physical examination and blood counts were performed on follow-up visits every 3 months.

Statistical Analysis

Qualitative variables were summarized using frequencies and percentages, whereas quantitative variables were reported as medians with interquartile ranges (IQR). The Mann–Whitney U test was used to compare differences between the dependent variable and quantitative independent variables.

Associations between categorical variables were assessed using Fisher's exact test. Survival differences were evaluated using the log-rank test, and overall survival was visualized using Kaplan–Meier curves. A p-value of <0.05 was considered indicative of statistical significance.

RESULTS

Of the twenty-one patients enrolled in this study and 57.1% were males. The median age of participants was 52 years; ranging from 32 to 58 years. Comorbid conditions were identified in 28.6% of the patients. At the time of enrollment 81% of the patients had primary disease, while 19% presented with relapsed DLBCL. Extra-nodal involvement was seen in 71% of patients, with bone marrow involvement being the most common extra-nodal site, observed in 33.3% of patients. Whereas lymphadenopathy was present in 8 (38.1%) patients and B symptoms were reported in 57.1% of the patients.

Hematological parameters revealed that 52.4% of patients had hemoglobin levels below 10.5 g/dl. However, the majority of patients had leukocyte counts below 11 × 10^9/L (81%) and platelet counts above 100 × 10^9/L (71.4%). At baseline the creatinine levels were elevated in 4.8% patients and liver function abnormalities were identified in 14.3% of cases. Serum LDH levels were elevated (>220 U/L) in 81% of patients. Performance status evaluation showed that 81% had an ECOG score below 2. Table-I

Tissue diagnosis was mostly established on bone marrow biopsy (23.8%). Histological sub typing indicated 23.8% had GCB type while 66.7% were classified as non-GCB type. Immunohistochemical staining revealed Double Expressor Lymphoma (DEL) and Triple expressor lymphoma (TEL) to be present in 23.8% and 42.9% cases, respectively. Fluorescence in situ hybridization (FISH) testing demonstrated that 4.8% had Double Hit Lymphoma (DHL).

Risk stratification based on the R-IPI indicated that 82.4% of patients had a poor prognosis. The IPI risk categorization placed 41.2% in the high-intermediate risk group, 41.2% in the low-intermediate risk group. The CNS-IPI assessment classified 64.7% as intermediate risk. The Ann Arbor staging system revealed that 52.9% had stage 4B. Table-I

TABLE-I

Clinico-hematological characteristics of DLBCL patients:

Characteristics		
Age	Median (IQR)	52 (32-58)
		N (%)
Gender	Male	12 (57.1)
	Female	9 (42.9)
Comorbidity	No	15 (71.4)
	Yes	6 (28.6)
Status at the time of 1st visit	Primary disease	17 (81)
	Relapsed	4 (19)
B symptoms	No	9 (42.9)
	Yes	12 (57.1)
Organomegaly	Unremarkable	5 (23.8)
	Splenomegaly	1 (4.8)
	Hepatomegaly	2 (9.5)
	Hepatosplenomegaly	5 (23.8)
	Lymphadenopathy	8 (38.1)
Hb (g/dl)	<10.5	11 (52.4)
	>10.5	10 (47.6)
WBC (10^9/L)	<11	17 (81)
	>11	4 (19)
PLT (10^9/L)	<100	6 (28.6)
	>100	15 (71.4)
LDH(U/L)	<220	4 (19)
	>220	17 (81)
Renal function test	Abnormal	1 (4.8)
	Normal	20 (95.2)
Urea	Normal	21 (100)
Creatinine	High	1 (4.8)
	Normal	20 (95.2)
Liver function test	Abnormal	3 (14.3)
	Normal	16 (76.2)
	Not available	2 (9.5)
Histological subtype	Non-GCB	14 (66.7)
	GCB	5 (23.8)
	not done	1 (4.8)
	Second biopsy not done	1 (4.8)

High Grade BCL Type	DEL	5 (23.8)
	NOS	6 (28.6)
	not done	1 (4.8)
	TEL	9 (42.9)
FISH	Negative	6 (28.6)
	DHL	1 (4.8)
	not done	14 (66.7)
BM Involvement	No	14 (66.7)
	Yes	7 (33.3)
ECOG	<2	17 (81)
	>2	4 (19)
Extra-nodal sites Involve (N=15/21)	Biopsy not done	1 (4.8)
	Bone Marrow	7 (33.3)
	Colon	1 (4.8)
	Gastric	2 (9.5)
	Liver	3 (14.3)
	Lung	1 (4.8)
	No	5 (23.8)
	Testicular	1 (4.8)
R-IPI Risk	Good Prognosis	3 (17.6)
	Poor prognosis	14 (82.4)
IPI risk	high risk group	3 (17.6)
	High-intermediate risk group	7 (41.2)
	Low-intermediate risk group	7 (41.2)
	Low risk group	0 (0)
CNS IPI	high risk group	3 (17.6)
	Intermediate risk	11 (64.7)
	Low risk group	3 (17.6)
Ann-Arbor Stage	2A	1 (5.9)
	2B	3 (17.6)
	4A	4 (23.5)
	4B	9 (52.9)
CHOP/R-CHOP/O	mini-chop	1 (4.8)
	Relapsed	4 (19)
	R -Chop	16 (76.2)
Type of CNS Prophylaxis	HD MTX	2 (66.7)
	Triple IT	1 (33.3)
Interim Response	Not applicable	9 (42.9)
	CR	7 (33.3)
	LTF	0 (0)
	PD	2 (9.5)
	PR	3 (14.3)
End of Treatment Response	PD	4 (19)
	CR	9 (42.9)
	LTF	3 (14.3)
	Not applicable	5 (23.8)
Relapse	No	12 (57.1)
	Yes	6 (28.6)
	LTF	3 (14.3)
Salvage Regimen	Not applicable	8 (38.1)
	DHAP D-HAP	2 (9.5)
	LTF	3 (14.3)
	No	1 (4.8)
	R- lena	1 (4.8)
	R-DHAP	2 (9.5)
	R-ICE	4 (19)
No. of Cycles of Salvage	Not applicable	9 (42.9)
	1.00	1 (4.8)
	2.00	4 (19)
	3.00	1 (4.8)
	4.00	3 (14.3)
	LTF	3 (14.3)
Response to Salvage	Not applicable	9 (42.9)
	CR	2 (9.5)
	LTF	3 (14.3)
	Expire	1 (4.8)
	No response	4 (19)
	Not done	2 (9.5)
Consolidation Auto-HSCT	No	15 (71.4)
	Yes	1 (4.8)
	Expire	1 (4.8)
	LTF	3 (14.3)
	Not applicable	1 (4.8)
ACR/AR/D/LTF/ LAMA	Alive	10 (47.6)
	Mortality	2 (9.5)
	(Mortality)Post transplant relapse	1 (4.8)
	LTF	8 (38.1)

All treatment naive patients received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) as initial chemotherapy except for one patient who was given mini-CHOP. CNS prophylaxis was administered with high dose methotrexate in two patients while one patient received intrathecal therapy.

TABLE-II

Overall survival of DLBCL patients after treatment:

		Overall Survival		Remission (n=13)				Relapse			
		OS %	Log Rank Test p-Value	No Response	Complete Response	Lost to Follow Up	P-Value	No	Yes	LTF	P- Value
N_EN	Nodal	67%	0.5	2 (50)	2 (22.2)	1 (33.3)	0.77	4 (33.3)	3 (60)	1 (33.3)	0.9
	Extra-Nodal	68%		2 (50)	7 (77.8)	2 (66.7)		8 (66.7)	2 (40)	2 (66.7)	
Histo-logical subtype	Non-GCB	59%	0.89	3 (75)	7 (77.8)	2 (66.7)	1	9 (75)	3 (50)	2 (66.7)	1
	GCB	100%		1 (25)	2 (22.2)	1 (33.3)		3 (25)	1 (16.7)	1 (33.3)	
BM Involve-ment	No	38.2%	0.18	2 (50)	6 (66.7)	1 (33.3)	0.8	7 (58.3)	6 (100)	1 (33.3)	0.06
	Yes	100%		2 (50)	3 (33.3)	2 (66.7)		5 (41.7)	0 (0)	2 (66.7)	

Fisher exact test

Treatment responses at the interim stage indicated that 33.3% of patients achieved complete remission (CRAt the conclusion of treatment, 42.9% achieved CR.

Relapse occurred in 28.6% of patients, whereas 57.1% remained in remission, and 14.3% were lost to follow-up. Salvage chemotherapy was administered to nine patients with rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) being the most commonly used regimen. Response to salvage therapy varied, with 9.5% achieving CR. Consolidation with autologous hematopoietic stem cell transplantation (Auto-HSCT) following salvage chemotherapy was done in 1 (4.8%) of cases, but unfortunately that patient also relapsed. None of these risk factors showed a significant impact on the rate of remission or relapse (Table-II).

The 57 Months overall survival was 62.5% for the entire cohort. In primary patients the overall survival was 69% and in patients with relapsed lymphoma at the initial presentation overall survival was 50%, (log rank test p-value 0.89). (Figure-1)

The impact on OS and relapse rate was compared with respect to the presence of risk factors that including histological subtype, Bone marrow involvement and the presence of nodal vs extranodal disease. In non-GCB histological sub-type patients overall survival is 59%, while 100% in GCB histological sub-type, (log rank test p-value 0.89). (Figure-2)

In Nodal and Extra-nodal category, the overall survival was 67% and 68% respectively, (log rank test p-value 0.5). (Figure-3)

OS in patients with bone marrow involvement was better than those without bone marrow involvement (100% vs. 38.2%), although not statistically significant with a log rank test p-value of 0.18. (Figure-4)

FIGURE-1

The fifty-seven months overall survival estimates

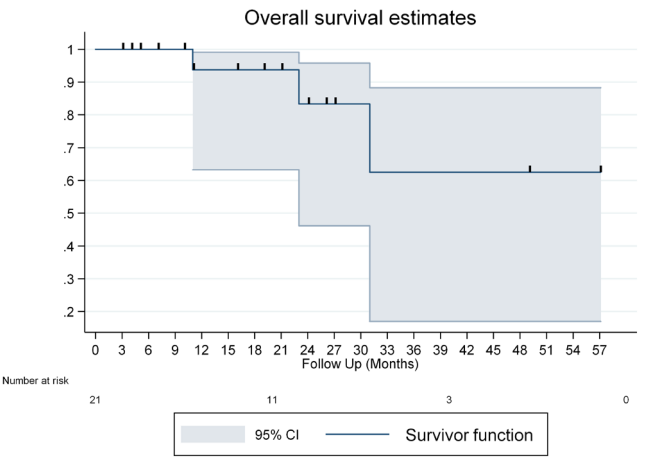


FIGURE-2

The fifty-seven months overall survival in GCB and non-GCB histological types

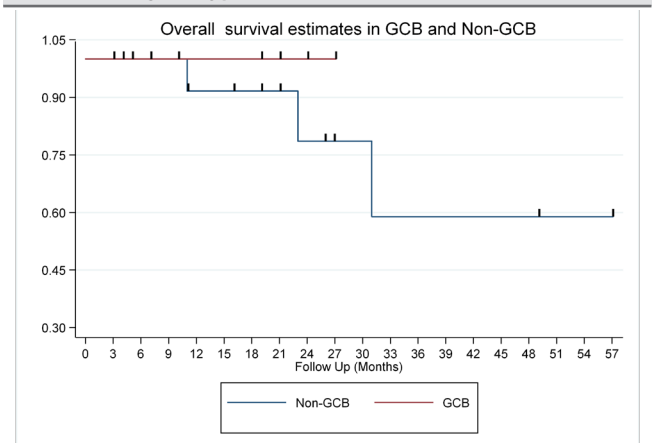


FIGURE-3

The fifty-Seven months overall survival estimates in nodal and extra-nodal disease distribution

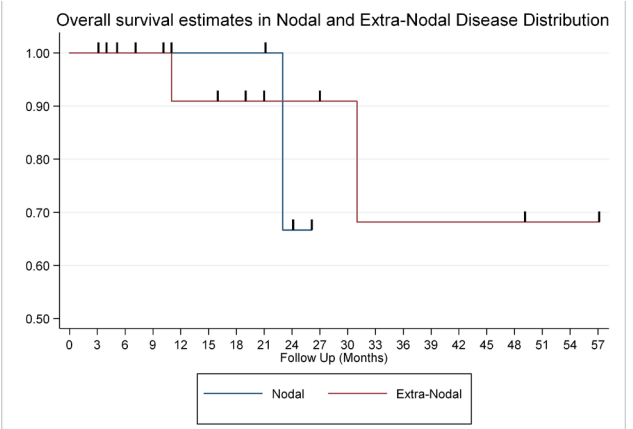
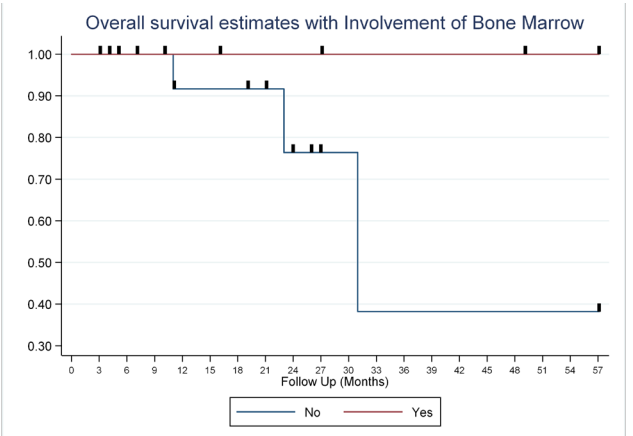


FIGURE-4

The fifty-seven months overall survival with respect to BM involvement



DISCUSSION

DLBCL is the most common NHL, accounting for 31% of adult cases of NHL.(18)DLBCL is an aggressive lymphoma with variable clinical manifestations; most commonly it presents with painless lymphadenopathy and B symptoms.[18] However, extranodal involvement is reported in up to 40% patients and is associated with a poorer prognosis compared to nodal DLBCL.[18-20] even though Waldeyer ring involvement has been reported to have a positive impact on survival.[21] I n our study, extranodal involvement was seen in 71% (n=15) of patients, with bone marrow infiltration being the most common extranodal site. Hepatosplenomegaly was also seen in a similar number of patients, although none of the patients had CNS or Waldeyer ring involvement. Similar to our study previous data suggests increased incidence of extranodal DLBCL in Asian countries including Pakistan in contrast to a higher incidence of nodal DLBCL in the west.[20,22]

The median age of presentation in our cohort was 52 years which is lower than the worldwide reported range of mid 60s to 70 years of age.[18,22] However, previously published data on DLBCL in Pakistan has shown a younger age of presentation like our study.[19,20] The younger age of presentation confers a positive impact on prognosis since advancing age has been associated with unfavorable molecular features, such as the ABC subtype and BCL2 expression, and reduced overall survival.[21,23] A predominance of male patients was seen in our study which is in accordance with previously published national and international data.[24,25]

Based on immunohistochemical stains we ascertained that more patients in our study population had non-GCB histology compared to GCB subtype. Similarly, E. Shiozawa et. al reported a higher incidence of non-GCB subtype in Japanese population and compared data from several Asian and western studies to conclude that GCB subtype is more prevalent in western population in contrast to Asian countries and proposed the higher rate of extranodal involvement in Asian population to be linked with the difference in histological subtypes.[26]

According to Ann Arbor staging, 76.4% of our patients had stage IV disease and the group mainly

comprised of intermediate to high-risk IPI and CNS-IPI score. Moreover, 66.7% patients had over expression of BCL-2, c-myc and/or BCL-6, whereas only one patient was found to have double hit lymphoma on FISH analysis. Since double or triple expressor lymphomas have been associated with worse OS and PFS our patients also comprised of a group with poor expected outcome.[27-29]

All patients presenting with primary disease were treated with R-CHOP except for one patient who received mini-CHOP due to co-morbid conditions. The R-CHOP remains the standard first line treatment for DLBCL [1] despite extensive attempts at exploring more intensive chemotherapy approaches especially for double or triple expressor lymphomas.[30] However, double, or triple hit lymphoma represent an aggressive disease entity and are treated with more intensive chemotherapy regimens such as DA-EPOCH-R, R-CODOX-M/IVAC and R-Hyper CVAD.[31,32] Recently, newer treatment options such as Polatuzumab Vedotin in combination with chemotherapy and Bruton Tyrosine Kinase inhibitors (BTKIs) have been explored for newly diagnosed DLBCL[19] but remain inaccessible for our patients due to financial constraints in this resource limited setting. Three patients who had high CNS-IPI score, received CNS prophylaxis with intrathecal triple therapy or high dose systemic methotrexate as per NCCN recommendations and none of them experienced a CNS relapse.

The relapsed and refractory cases were treated with salvage chemotherapy but only one patient received consolidation with Auto-HSCT due to low complete response rate and limited resources. Unfortunately, the only transplanted patient experienced post-transplant relapse and died.

The OS of the entire cohort was 62.5% at 57 months. Patients presenting with primary disease had an OS of 69% which did not show statistically significant difference from relapsed/refractory cases with an OS of 50%. In univariate analysis GCB histological subtype and bone marrow involvement were found to have a positive impact on OS whereas there was no difference in OS with respect to nodal or extranodal involvement (Table-II). Like our study, previous research also indicates that GCB subtype is associated with better outcome both in terms of OS and PFS.[27,33] Similarly, A. Doma et. al. demonstrated a better OS in patients with bone marrow involvement and attributed this improved outcome to treatment modification based on bone marrow involvement.[34] In our study, we did not alter treatment on the basis of bone marrow involvement, consequently, OS did not differ significantly between these two groups. Hence further research in this area with treatment escalation based on bone marrow involvement might yield better outcome. The better outcome of nodal DLBCL compared to extranodal DLBCL reported in previous studies.[20-22] was not demonstrated in our study; a finding that could either be explained by a small sample size or some genetic and ethnic characteristics affecting the outcome in this particular patient population. A larger scale, multicenter study could help us understand the effects of these variables on outcome in DLBCL in our population.

This study describes the clinical characteristics, risk stratification and treatment outcomes of DLBCL patients at a single center in Pakistan, in an attempt to elucidate the disease features observed in this particular patient cohort. However, the limited sample size was a major limitation of our study. Future studies involving a larger patient cohort and multiple centers across the country would be more informative in delineating disease characteristics specific to our population. Such studies would also enable multivariate analysis to identify factors influencing patient outcomes.

CONCLUSION

The clinical characteristics, risk stratification and treatment outcomes in DLBCL differ significantly among different geographical areas due to diverse genetic and ethnic variations. Population based studies on larger scale are warranted to describe these features and to identify actionable high-risk features.

Institutional Review Board Statement and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of NIBD Research Ethics Committee. (NIBD/IRB-282/02-2025). Informed

consent was obtained from all subjects involved in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Ayaz Asghar:** Manuscript writing.
2	**Rabeea Munawar Ali:** Manuscript writing, critical review and editing.
3	**Quratulain Rizvi:** Contributed in manuscript writing.
4	**Aisha Jamal:** Contributed in manuscript writing.
5	**Aisha Arshad:** Manuscript writing, critical review and editing.
6	**Muhammad Nizamuddin:** Statistical analysis.
7	**Nida Anwar:** Had the main concept of the study, designed, critically reviewed, editing, supervised and finalized the manuscript draft.