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# Demographics and outcome of diffuse large B-cell lymphoma patients in Hiwa Hospital - Iraq-Kurdistan-Sulaimani

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## Abstract:

**BACKGROUND:** Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous form of hematological malignancy which comprises about 30% of lymphomas with variable outcome. Onset is usually in the sixth decade of life with male predominance. Morphological, clinical, and biological variation of DLBCL confirms the coexistence of several subtypes of the disease with distinct behavior of each type.

**OBJECTIVE:** The aims of this study were to determine the demographics and outcome of patients with DLBCL and compare these parameters with regional and international data.

**PATIENTS AND METHODS:** A retrospective study was conducted on 61 patients with confirmed diagnosis of DLBCL. The diagnosis was based on histopathological and immunohistochemistry which was done in the Department of Pathology, Shorsh General Hospital in Sulaimani. The cases were randomly selected according to the availability of data since March 2013–March 2017.

**RESULTS:** Median age at diagnosis was about 51 years with peak age of incidence between 50 and 64 years, with female predominance. The most common site of the primary tumor was nodal in which cervical lymph node is the most common site, and majority of the patients were in Stage III with predominance of B-symptoms. Vast majority of the patients have normal chest X-ray, and majority of the patients were in remission over a period of 19 months of follow-up.

**CONCLUSION:** We found that there is a significant relationship between age, stage, and performance of the patients, while no significant relation between other parameters and the outcome of the patients is near to their Peers internationally.

## Keywords:

Demographics, diffuse large B-cell lymphoma, outcome

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 30% of all newly diagnosed cases and >80% of aggressive lymphomas.<sup>[1]</sup> Onset is usually in the sixth decade of life with male predominance. Morphological, clinical, and biological variation of DLBCL confirms the coexistence of several subtypes of the disease with distinct behavior of each type. Based on gene expression profile, three

basic subgroups of DLBCL were defined: (i) germinal center B-cell characterized by expression of genes typically expressed in germinal center centroblasts, (ii) activated B-cell (ABC) derived from postgerminal B-cell-expressing genes characteristic of *in vitro* ABCs, and (iii) primary mediastinal B-cell lymphoma with gene expression completely different from those in the previous two subtypes.<sup>[2,3]</sup> MYC oncogene rearrangement is a hallmark of Burkitt lymphoma and can be identified in 10% of patients with DLBCL. Increased expression of MYC protein promotes cellular growth

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and proliferation. Numerous studies have correlated the presence of a MYC rearrangement with a poorer outcome in DLBCL patients treated with rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone (R-CHOP).<sup>[4,5]</sup> However, more recent studies have revealed that the impact of MYC is strongly influenced by BCL2. Concurrent MYC and BCL2 translocation, “double-hit” lymphoma, occurs in 5% of cases of DLBCL and represents a treatment-refractory subgroup with a median survival of 8 months.<sup>[6,7]</sup>

The International prognostic index (IPI), developed before the availability of rituximab, is the primary clinical tool used to predict outcome in patients with DLBCL.<sup>[8]</sup> Using five negative prognostic features present at the time of diagnosis (age >60 years, Stage III/IV disease, elevated serum lactate dehydrogenase [LDH] level, Eastern Cooperative Oncology Group [ECOG] performance status  $\geq 2$ , and >1 extranodal site of disease), the IPI segregated patients into four outcome groups with a 5-year overall survival (OS) ranging from 26% to 73%. IPI has been reevaluated in patients treated with rituximab-based therapy and has been shown to retain its prognostic utility.<sup>[9,10]</sup>

The revised IPI (R-IPI) identifies three distinct prognostic groups with a very good (4-year progression-free survival [PFS]: 94%, OS: 94%), good (4-year PFS: 80%, OS: 79%), and poor (4-year PFS: 53%, OS: 55%) outcome, respectively ( $P < 0.001$ ). IPI (or R-IPI) no longer identifies a risk group with less than a 50% chance of survival. In the era of R-CHOP treatment, R-IPI is a clinically useful prognostic index that may help guide treatment planning and interpretation of clinical trials.<sup>[9]</sup> The aims of this study were to determine the demographics and outcome of patients with DLBCL and compare these with regional and international data.

## Patients and Methods

A retrospective study was conducted on 61 patients with confirmed diagnosis of DLBCL. The diagnosis was based on histopathological and immunohistochemistry which was done in the Department of Pathology, Shorsh General Hospital in Sulaimani. The cases were randomly selected according to the availability of data since March 2013–March 2017.

The inclusion criteria for this study included new adult patients, their age >18 years, and both sexes with confirmed diagnosis of DLBCL, while our exclusion criteria were age <18 years and other types of lymphoma with cases with incomplete data. All the patients were admitted to Hiwa hospital, and the histopathology with immunohistochemistry was confirmed in Sulaimani Reference Laboratory of Shorsh

General Hospital. All included patients have full hematological and biochemical panel, with chest X-ray and echocardiography with sonography; some of them had computed tomography (CT) scan for staging with viral screen before starting chemotherapy. The study was approved by the Review Ethical Committee of Hiwa Hospital. Data were entered into Excel sheet and then transferred to SPSS-21 (IBM company-USA). Descriptive analysis (numbers, percentages, median, means, and standard deviation [SD]) was performed for all variables. Analytic analysis was conducted to find any association or differences between compared variables using *t*-test, Chi-square test, and Fisher’s exact test.  $P < 0.05$  was regarded as a significant.

## Results

Among 61 patients with DLBCL, the predominant age group was in 50–64 years with 32.8%, while the least was in the age group of  $\geq 80$  years (9.8%) [Table 1]. The minimum age for them was 23 years, while maximum was 90 years with the median age of 51 years; 29 cases are male and 32 patients are female, and male:female ratio is 1:1.1 [Table 1]. The majority of patients at presentation were Stage III (29 cases, 47.5%), while minimum number of them had Stage IV lymphoma at presentation (4 cases, 6.6%). About 33 patients comprising 55% of patients had B-symptoms while 28 patients comprising 45% of patients had no B-symptoms. The least hemoglobin level for those patients during admission was 6.1 g/l while the upper level was 15.9 g/l with mean of  $12.3 \pm 2.31$  SD, and also, the mean white blood cell counts was  $7383.86 \pm 3672.2$  SD, while the minimum erythrocyte sedimentation rate was 4 and the largest was 115 with mean of  $30.97 \pm 26.81$  SD, but the mean LDH was  $496.33 \pm 329.09$  with minimum value of 179 and maximum of 1590. There were 21 patients (34.4%) with performance Grade 0 and just 8 patients (13.1%) with performance status 4, as shown in Table 2.

Imaging of patients at presentation showed that 36 patients (59%) had nodal presentation, with

**Table 1: Age and gender distribution of the patients**

Variables	Frequencies (%)
Age groups	
20-34	10 (16.4)
35-49	18 (29.5)
50-64	20 (32.8)
65-79	7 (11.5)
$\geq 80$	6 (9.8)
Total	61 (100.0)
Gender	
Male	29 (47.5)
Female	32 (52.5)
Total	61 (100.0)

**Table 2: Demographic characteristics of 61 patients with diffuse large B-cell lymphoma**

Variables	Minimum	Maximum	Median	Mean±SD
Age (years)	23	90	51	53.26±16.57
Hb (g/dl)	6.3	15.9	12.1	12.13±2.31
WBC (×10 <sup>9</sup> /L)	15.8	21,700.0	6700	7383.86±3672.26
Platelet (×10 <sup>9</sup> /L)	127,000.0	418,000.0	258,000	18,206.18±72,604.06
ESR	4	115	25	30.97±26.81
Follow-up/ months	10	51	19	22.22±12.12
LDH (u/L)	179	1590	410	496.33±329.09
Variables	n (%)			
Stage of disease				
I	14 (23.0)			
II	14 (23.0)			
III	29 (47.5)			
IV	4 (6.6)			
B symptom				
B symptom	33 (55.0)			
No B symptom	28 (45.0)			
Performance status				
0	21 (34.4)			
1.0	12 (19.7)			
2.0	7 (11.5)			
3.0	13 (21.3)			
4.0	8 (13.1)			

Hb=Hemoglobin, WBC=White blood cell, ESR=Erythrocyte sedimentation rate, LDH=Lactate dehydrogenase, SD=Standard deviation

neck being the common site of nodal presentation in 21 patients (58.3%), while 25 patients (41%) had extranodal presentation, with stomach being the most common extranodal site in 10 patients comprising 40% of extranodal cases as shown in Table 3.

All of the patients before starting chemotherapy had chest X-ray in which 53 patients (93.4%) showed normal images, while 3 of them (4.9%) had mediastinal widening and 1 patient (1.7%) had pleural effusion. What is interesting about viral screen for hepatitis B and C and HIV serology testing is that only 40 patients (65.6%) had the test of which 2 patients (3.3%) had positive hepatitis B surface antigen test while the rest had no viral screen. Regarding bone marrow biopsy, only 11 patients out of 61 patients did bone marrow examination of which 2 patients had bone marrow involvement, while only 5 patients (8.2%) had cerebrospinal fluid (CSF) test and the rest 56 cases (91.8%) had no CSF test. Reasonable mentioning the blood group of the patients, about 19 patients (31.1%) are blood Group O positive while none of the patients is blood Group O negative, and 10 patient (16.4%) blood group was not done. One-third of the patients after finishing their chemotherapy underwent positron emission tomography (PET)-CT

**Table 3: Nodal and extranodal involvement of 61 patients**

Variables	Frequencies (%)
Nodal	
Neck	21 (58.3)
Waldyersring	4 (11.2)
Axillary	3 (8.4)
Paraaortic	1 (2.7)
Medistinum	5 (14.0)
Retroperitoneal	1 (2.7)
Inguinal	1 (2.7)
Total	36 (100.0)
Extranodal	
Stomach	10 (40.0)
Head	4 (16.0)
Testicular	1 (4.0)
Colon	2 (8.0)
Bone marrow	2 (8.0)
CNS	2 (8.0)
Thyroid	1 (4.0)
Small intestine	2 (8.0)
Breast	1 (4.0)
Total	25 (100)

CNS=Central nervous system

scan; about 14 patients (23%) had negative scan, while 4 patients (6.6%) had positive scan with residual disease, as shown in Table 4.

Duration of admission of the cases to Hiwa Hemato-Oncology Hospital varies between 10 and 51 months with a median of 19 months [Table 3], and about 58 patients (95.1%) received only chemotherapy while only 3 patients (4.9%) received chemotherapy + radiotherapy.

All of the patients were started on R-CHOP chemotherapy; 54 cases (88.5%) received 4–8 courses, while 7 patients (11.5%) received ≤4 courses of chemotherapy.

Although all patients, i.e. 61 cases (100%), received R-CHOP chemotherapy, some patients in addition, i.e., 4 cases (6.6%), received other chemotherapies.

For the 61 treated patients with a median follow-up of 19 months, 51 of them (83.6%) attained full remission with complete response, while 3 patients (4.9%) had progressive disease and 7 patients (11.5%) died due to disease and complications of therapy [Figure 1].

Regarding the relation of the same age grouping to the stage of the lymphoma, more of 20- to 34-year patients had Stage III disease, more patients in the age group of 35–49 years had Stage II disease, no patients in the age group of 50–64 years had Stage IV disease, more patients in the age group of 65–79 years had Stage III disease, and more cases in the age group of ≥80 years

**Table 4: Laboratory findings in 61 cases with diffuse large B-cell lymphoma**

Variables	Frequencies (%)
CXR	
Normal	57 (93.4)
Mediastinal widening	3 (4.9)
Pleural effusion	1 (1.7)
Total	61 (100.0)
Viral screen	
N/A	21 (34.4)
Negative	38 (62.3)
HBsAg positive	2 (3.3)
Total	61 (100.0)
Bone marrow	
Active	9 (14.8)
N/A	50 (82.0)
Involved	2 (3.3)
Total	61 (100.0)
CSF	
N/A	56 (91.8)
Negative	5 (8.2)
Total	61 (100.0)
PET scan	
N/A	43 (70.5)
Negative	14 (23.0)
Positive	4 (6.6)
Total	61 (100.0)

CXR=Chest X-ray, HBsAg=Hepatitis B surface antigen, CSF=Cerebrospinal fluid, PET=Positron emission tomography, N/A=Not available

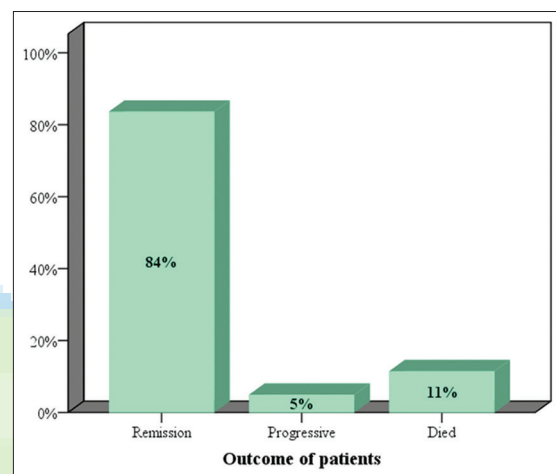
had Stage III disease. Again, the relation between different age groups and lymphoma stages is statistically not significant ( $P = 0.331$ ). We also want to find any relation between gender of patients and lymphoma stage; we found that more female patients have Stage III, while more male patients have again Stage III disease, but again, this relation is also statistically not significant ( $P = 0.514$ ) [Table 5].

It was obvious that there was a highly significant correlation between B-symptom and stage of presentation, with majority of patients of Stage III having B-symptoms with  $P = 0.001$ .

We tried to elaborate any relation between nodal and extranodal lymphoma in both genders; most of male patients have nodal disease while female patients have again slightly more nodal involvement in comparison to extranodal type, but again, the relation is not significant with  $P = 0.326$  [Table 6]. However, interestingly, the relation between nodal lymphomas with both gender is statistically significant ( $P = 0.026$ ), with more male and female patients having cervical lymph node involvement in comparison to other nodes. On the other hand, the relation of both sexes with the extranodal sites is statistically nonsignificant ( $P = 0.286$ ), although gastric lymphoma patients are mostly female [Tables 5 and 6].

**Table 5: Relation between gender and stages of lymphoma and involvement**

Variables	Stage				P
	Stage I, n (%)	Stage II, n (%)	Stage III, n (%)	Stage IV, n (%)	
Gender					
Male	8 (27.6)	8 (27.6)	12 (41.4)	1 (3.4)	0.514
Female	6 (18.8)	6 (18.8)	17 (53.1)	3 (9.4)	
Total	14 (23.0)	14 (23.0)	29 (47.5)	4 (6.6)	
Variables	Involvement type				P
	Nodal, n (%)		Extranodal, n (%)		
Gender					
Male	19 (65.5)		10 (34.5)		0.326
Female	17 (53.1)		15 (46.9)		
Total	36 (59.0)		25 (41.0)		

**Figure 1: Outcome of patients**

Whereas the relation between different age groups with performance status is statistically significant ( $P = 0.005$ ), more patients in the age group of 50–64 years had 0 performance status of ECOG scale, while majority of patients in the age group of 65–79 years had a performance of 3. Regarding the association between the disease stage and performance status of the patients, we found that more Stage III patients had performance 3 status, while no patients of Stage IV had 0 performance with highly significant  $P < 0.001$  [Table 7]. Finally, association between age and gender with the outcome of patients – whether they are in remission and progressive disease or died – is statistically not significant, as shown in Table 8 and Figure 2, although majority of patients in the age group of 35–49 and 50–64 years were in remission and more female patients died.

## Discussion

DLBCL is the most common type of NHL. Treatment paradigm has changed since the addition of rituximab to historic standard of care CHOP.<sup>[11]</sup> We randomly and retrospectively collect 61 patients, and the median age of



**Table 6: Relation between gender and location of lymphoma**

Subtype	Location	Gender		P
		Male, n (%)	Female, n (%)	
Nodal	Neck	12 (57.1)	9 (42.9)	0.026
	Waldyersring	4 (100.0)	0	
	Axillary	0	3 (100.0)	
	Paraaortic	0	1 (100.0)	
	Medistinum	2 (40.0)	3 (60.0)	
	Retroperitoneal LN	0	1 (100.0)	
	Inguinal	1 (100.0)	0	
	Total	19 (52.8)	17 (47.2)	
	Stomach	2 (20.0)	8 (80.0)	
	Head	2 (50.0)	2 (50.0)	
Extra nodal	Testicular	1 (100.0)	0	0.286
	Colon	1 (50.0)	1 (50.0)	
	Bone marrow	1 (50.0)	1 (50.0)	
	CNS	2 (100.0)	0	
	Thyroid	0	1 (100.0)	
	Small intestine	1 (50.0)	1 (50.0)	
	Breast	0	1 (100.0)	
	Total	10 (40.0)	15 (60.0)	

CNS=Central nervous system, LN=Lymph node

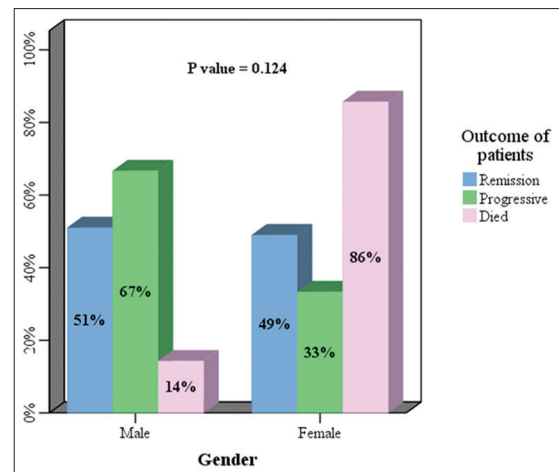
**Table 7: Relation between stage and performance status**

Variables	Performance status					P
	0, n (%)	1.0, n (%)	2.0, n (%)	3.0, n (%)	4.0, n (%)	
Stage						
I	6 (46.2)	3 (23.1)	3 (23.1)	1 (7.7)	0	<0.001
II	9 (69.2)	2 (15.4)	2 (15.4)	0	0	
III	4 (13.8)	7 (24.1)	2 (6.9)	9 (31.0)	7 (24.1)	
IV	0	0	0	3 (75.0)	1 (25.0)	
Total	19 (32.2)	12 (20.3)	7 (11.9)	13 (22.0)	8 (13.6)	

**Table 8: Relation between age and outcome of patients**

Variables	Outcome of patients			P
	Remission, n (%)	Progressive, n (%)	Died, n (%)	
Age groups				
20-34	8 (80.0)	1 (10.0)	1 (10.0)	0.577
35-49	17 (94.4)	0	1 (5.6)	
50-64	17 (85.0)	1 (5.0)	2 (10.0)	
65-79	4 (57.1)	1 (14.3)	2 (28.6)	
≥80	5 (83.3)	0	1 (16.7)	
Total	51 (83.6)	3 (4.9)	7 (11.5)	

their presentation is about 51 years with more females; this is in contrary to what is common in the western world as the onset is usually in the sixth decade of life with male predominance.<sup>[2,3]</sup> In the previous study in Northern part of Iraq, DLBCL comprised about 52.2% of NHL cases with median age of 53 years which is near to our figure, with male:female ratio of 1.8:1,<sup>[12]</sup> which is contrary to our finding (male:female ratio of 1:1.1 which could be due to small number of patients). We tried to find any

**Figure 2: Relation between gender and outcome**

relation between age of the patients and their gender but statistically it was not significant. Furthermore, the relation of age and stages of lymphoma presentation was statistically not significant, although we have more patients with advanced stages of lymphoma above 50 years of age. Again, the relation between sex and stages of lymphoma was statistically not significant although slightly more female patients have advanced stages of disease. While topographical presentation of nodal type of disease showed that majority of male and female patients have cervical lymph node disease which is statistically significant, this is parallel to what was found in Pakistan with 37.2% of cases having DLBCL of cervical lymph nodes.<sup>[13]</sup> While the most common site for extranodal DLBCL was the stomach and found in 10 out of 25 cases although the relation between extranodal sites and both genders statistically is not significant, as found in other papers in which majority of extranodal DLBCL are from gastrointestinal tract.<sup>[1,14]</sup> Regarding the relation between B-symptoms and stages of DLBCL, we found this comparison which is highly significant as vast majority of advanced stages of disease have B-symptoms, and generally, less than two-thirds of our patients have B-symptoms, while in western patients, only one-third have B-symptoms. This is probably due to the delay in consultation and also to the disseminated character of the disease.<sup>[15-17]</sup>

We observed that more than two-thirds of those patients who are above 65 years have performance status of 3 and 4; on the other hand, there is highly significant proximity between advanced stages of lymphoma and worst performance status as all Stage IV patients have a score 4 of the ECOG scale.

What is interesting is that we found that about one-third of our patients have O-positive blood group while just one patient had A negative and B negative without any one of them having Group O negative; actually, we do not know if there is any relation between blood group distribution

and its prognostic significance in our patients, and this may need further researches as we could not find any research about ABO blood grouping in DLBCL except one paper talking about the prognostic role of ABO blood type in patients with extra nodal natural killer/T-cell lymphoma, nasal type, which shows that the distribution of blood groups is near to the general population with better survival in blood Group O patients.<sup>[18]</sup>

We studied these patients retrospectively with a median follow-up of 19 months from the first diagnosis, and the outcome of the patients was 84% of patients in complete remission, 5% had progressive disease, while 11% died due to disease progression or complications of therapy; this is near to what was observed in nearly 200 patients treated with R-CHOP.<sup>[19]</sup>

We tried to find a relation between age and gender with the outcome, but this was not significant, as we found that about 51% of remission cases were male while 49% of them were female; 67% of progressive cases were male while 33% of them were female; and 86% of cases who died were female and 14% were male.

In our study, we faced a lot of obstacles regarding the availability of data, and we could get data with a median of 19 months of follow-up only, which is relatively a short period of time to know the exact outcome of the patients; this may affect the results that we got about the work-up for the patients in our locality and actually we do not have cytogenetic and molecular study, but we have the best pathology laboratory with immunohistochemistry.

In the region, PET-CT scan is not available, and among those patients that did PET, about 18 patients were sent outside Iraq to Turkey, Jordan, and Lebanon with the support from the Kurdistan Regional Government, and nearly, all of them did their PET after finishing their planned course of chemotherapy, while two-thirds of them did not have the scan; this is because of economic and political crises in our region.

We observed despite availability of some tests for workup, for example, viral screen which is an important baseline test for lymphomas before starting R-CHOP chemotherapy, but still about one-third of the patients have no documented viral screen, this especially important for the patients with viral hepatitis as positive cases should receive antiviral treatment with the R-CHOP chemotherapy. About the practice of doing bone marrow examinations with CSF test, we think that again a little number of patients have these workups, and all these should encourage our hematologists in adult hemato-oncology department to improve their workup and staging tools before starting chemotherapy to cancer patients in their future practice.

## Conclusion

We found that there is a significant relationship between age, stage, and performance of the patients, while there was no significant relation between other parameters and the outcome of the patients is near to their Peers internationally. Furthermore, we discover that we have problems in arranging for a thorough workup and staging tests before starting chemotherapy for the patients, and a short period of availability of patients' data should encourage all of us to document them in our hospital's electronic database so as it can be used for future works.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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