RETROSPECTIVE ANALYSIS OF CLINICO-EPIDEMIOLOGICAL FEATURES AND OUTCOMES OF DIFFUSE LARGE B CELL LYMPHOMA IN ADULT PATIENTS TREATED AT CLINICAL ONCOLOGY DEPARTMENT, AIN SHAMS UNIVERSITY HOSPITALS

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Received: 19/3/2023
Accepted: 14/4/2023

Online ISSN: 2735-3540

ABSTRACT:

Background: *Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-hodgkin's lymphoma (NHL) comprising 25-30% of all NHLs worldwide. The primary site of DLBCL is important in determining the clinical features and the disease outcomes.*

Aim Of The Work: *Analyzing the clinical, epidemiological features and outcomes including response, toxicity, and survival rates (DFS, PFS &OS) in DLBCL adult patients treated at Ain Shams University hospitals.*

Patient And Methods: *This retrospective study included 78 DLBCL adult patients treated at Ain shams clinical oncology department from January 2016 to December 2019. Patients' clinical characteristics and outcomes were analyzed and categorized according to the disease primary site to nodal-only, extra-nodal-only, and both nodal & extra-nodal disease.*

Results: *The mean age at presentation was 45.54 ±15.38 years, 48.7% were 40-60 years with female predominance (57.7%). Half of the patients had early stages (I – II). The most common extra-nodal sites were bone (35.6%) and GIT (26.7%). The median IPI score was 2, with 38.5% were of low-risk. Nodal-only DLBCL (n=33) was significantly more common in males, performance 0-1, negative B-symptoms, and low risk. Extra-nodal-only DLBCL (n=11) significantly presented in females, performance (2-4), negative B-symptoms, and equally with low, high-intermediate, and high risk. Both nodal & extra-nodal DLBCL was significantly more common in females, performance 0-1, positive B-symptoms, equally bulky and non-bulky disease, and high-risk. Complete response was achieved in 56.4% and was significantly correlated with performance (0-1), negative B-symptoms, DLBCL NOS subtype, early stages (I – II), low-risk, and received R-CHOP. The 5-year DFS, PFS, and OS were 75.2%, 83.7%, and 93.8% respectively. Higher mean PFS was observed in early stages (I – II) while OS was higher in nodal-only disease.*

Conclusion: *Nodal-only DLBCL had a characteristic clinical presentation with better prognosis and outcomes compared to extra-nodal-only DLBCL and both nodal & extranodal DLBCL.*

Keywords: *Nodal, extra-nodal, DLBCL*

INTRODUCTION:

Lymphoma is one of the most common hematopoietic cancers worldwide. It may be broadly divided into non-Hodgkin (90%) and Hodgkin (10%) subtypes[(1)].

Non-Hodgkin lymphoma (NHL) ranks as the seventh most common cancer in both males and females worldwide. In 2020, an estimated 544 000 new cases of NHL were diagnosed worldwide, and approximately 260 000 people died from the disease[(2)].

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL accounting for about 25% to 30% of all the NHLs worldwide. It results from the malignant proliferation of B cells during their different stages of development. Depending on the morphology, the genetics and the immune phenotype of the neoplastic cells, a cell of origin can be proposed and upon which DLBCL can be divided into either germinal centre B cell (GCB)-like or activated B cell (ABC)-like subtypes. Each subtype has its unique genomic profile and is associated with variable clinical outcomes[(3)].

The etiology of most cases of DLBCL is still poorly understood. It was recognized that certain clinical and epidemiological factors have a strong role in the development of the disease, such as: age, sex, ethnicity, and geographic differences[(4)].

Increased risk of DLBCL was observed also in association with diseases or treatments that suppress the immune system including organ transplantation, autoimmune diseases, and primary or acquired immune deficiencies (e.g human immune deficiency virus (HIV)). In addition, several infectious organisms have been linked to the increased risk of DLBCL incidence, including Epstein-Barr virus (EBV), human herpes virus 8 (HHV 8), Helicobacter pylori and hepatitis C virus (HCV)[(5)].

Diffuse large B cell lymphoma usually presents with enlarged lymph nodes or rapidly growing mass in addition to presence of B symptoms (fever, night sweats, and weight loss). A full physical examination should be done along with the laboratory and imaging studies upon the results of which an excisional biopsy of an abnormally enlarged, suspicious lymph node should be done with immunohistochemistry (IHC) to confirm the diagnosis. Also, DLBCL can involve extra-nodal sites, including the brain, kidney, adrenal gland, bones, and other soft tissues. Positron emission tomography-computed tomography (PET/CT) can be used to detect the sites of disease with the highest standardized uptake value (SUV) to determine the preferred site of biopsy[(6)].

Over the last decade, advances in DLBCL treatment strategies have led to excellent outcomes for many patients through the combination of chemotherapy as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and the immunotherapy (rituximab) to form the standard treatment regimen R-CHOP for most cases of DLBCL and in spite of improvement of DLBCL outcomes after approval of R-CHOP regimen as the standard of care, 30% to 40% of cases will relapse during the first 2 years[(7)]. Hence, the salvage therapy and consolidation with autologous stem cell transplantation (ASCT) have been considered as the standard approach for these cases[(8)].

AIM OF THE WORK:

This study aims at analyzing the clinical, epidemiological factors and treatment outcomes including response, survival rates (PFS, DFS & OS) as well as toxicity patterns in DLBCL adult patients who were treated at the clinical oncology department, Ain Shams University hospitals.

PATIENTS AND METHODS:

Study design:

After obtaining the approval of Ain shams university research ethics committee, we performed a retrospective cohort study on 78 DLBCL adult patients who were treated at Ain Shams Clinical Oncology department in the period from January 2016 to December 2019.

Both males and females were included, patients ≥ 18 years old with pathologically proven large B cell lymphoma biopsy at the time of diagnosis, Pre-treatment assessments by CT neck, chest, abdomen, pelvis with contrast +/-PET/CT scan were done and patients from all Stages (I-IV) were included. Uncertain cases due to inadequate biopsy were excluded.

Patients' demographic and clinical characteristics were collected. Patients were categorized into three groups; nodal-only group, extra-nodal-only group, and both nodal & extra-nodal group according to the site of the disease involvement. Received treatment (chemotherapy; CHOP, R-CHOP, irregular R-CHOP i.e some cycles were without rituximab, CEOP, CVP or radiotherapy), reported treatment toxicity according to CTC version 4[(9)], treatment response according to RECIST 1.1 criteria[(10)] and follow up data including DFS (refers to the time from the date of diagnosis to the first evidence of disease recurrence or death)[(11)], PFS (refers to the duration from the date of diagnosis until the evidence of disease progression or death)[(12)] and OS (refers to the duration from the date of diagnosis to death or last follow-up)[(13)].

Statistical analysis:

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. The comparisons between groups with qualitative data were done by using ***Chi-square test***, the comparisons between more than two groups with quantitative data and parametric distribution were done by ***One Way ANOVA*** while the comparison between more than two groups with quantitative data and non-parametric distribution was done by using ***Kruskall Wallis test***. In addition, ***Kaplan-Meier Analysis*** was carried out for PFS, DFS and OS.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value <0.05 was considered significant.

Ethical Consideration:

The study was commenced after obtaining the approval of Ain Shams university research ethics committee and data confidentiality was maintained.

RESULTS:

I. Demographic characteristics of the study population:

This study collected data from 78 patients who were presented to Ain shams hospital, clinical oncology department from January 2016 till December 2019. The mean age of the patients (n=78) at diagnosis was 45.54 ± 15.38 years ranging from 20 to 77 years and 48.7% of them were in the range of 40-60 years. More than half of the patients were females representing 57.7% and 71.8% (n=56) of the patients were married. More than half of the patients (62.8%) were non-smokers. The patients' residence was classified into two groups; inside greater Cairo (76.9%) and outside greater Cairo (23.1%). Only 16.7% of the patients (n=13) had a family history of cancer.

Patient characteristics:

The ECOG performance score was ≤1 in 74.4% of the patients (n=58) and the most commonly reported viral infection was HCV (21.8%). The most common reported comorbidity was hypertension (24.4%).

II. Disease characteristics:

The most commonly presented symptom was swelling comprising 42.3%. DLBCL not otherwise specified (DLBCL NOS) was the most commonly reported subtype comprising 64.1% of all cases. B-symptoms were +ve in 29.5% of the patients and LDH serum level was high in the majority of the patients comprising 73.1%. Half of the patients were presented in advanced stages (III – IV).

Both nodal & extra-nodal involvement was reported in 43.6% of cases (n=34) while 42.3% of cases (n=33) had nodal-only DLBCL, and only 14.1% of cases (n=11) had an extra-nodal-only disease. The most common site of extra-nodal involvement was the bone (35.6%) followed by the GIT (26.7%). The median IPI score was 2 and the majority of the patients (38.5%) were of IPI low-risk.

Nodal-only DLBCL was significantly correlated with males (51.5%), ECOG performance 0-1(87.9%), negative B-symptoms (87.9%), and IPI low-risk (57.6%). Extra-nodal-only DLBCL significantly presented in females (90.9%), performance (2-4) (54.5%), negative B-symptoms (90.9%), and equally with IPI low, high-intermediate and high-risk (27.3% for each). Both nodal & extra-nodal DLBCL was significantly correlated with females (55.9%), performance 0-1(70.6%), positive B-symptoms (52.9%), and IPI high-risk (29.4%) (Table 1).

Table (1): Correlation between the site of the disease and different variables

		Nodal-only	**Extra-nodal only**	**Both nodal & extranodal**	**Test value**	**P-value**
		N. = 33	**N. = 11**	**N. = 34**		
Age	Mean±SD	44.88 ± 16.07	47.36 ± 17.64	45.59 ± 14.35	0.105•	0.900
	Range	20 – 76	20 – 77	20 – 70		
Age group	< 40 yrs	13 (39.4%)	3 (27.3%)	10 (29.4%)	3.420*	0.490
	40-60 yrs	13 (39.4%)	5 (45.5%)	20 (58.8%)		
	> 60 yrs	7 (21.2%)	3 (27.3%)	4 (11.8%)		
Sex	Females	16 (48.5%)	10 (90.9%)	19 (55.9%)	6.164*	**0.046**
	Males	17 (51.5%)	1 (9.1%)	15 (44.1%)		
Performance	PS 0-1	29 (87.9%)	5 (45.5%)	24 (70.6%)	8.237*	**0.016**
	PS 2-4	4 (12.1%)	6 (54.5%)	10 (29.4%)		
Viral infection	No	24 (72.7%)	9 (81.8%)	25 (73.5%)	1.900*	0.929
	HCV	8 (24.2%)	2 (18.2%)	7 (20.7%)		
	HBV	0 (0.0%)	0 (0.0%)	1 (2.9%)		
	CMV	1 (3.1%)	0 (0.0%)	0 (0.0%)		
	EBV	0 (0.0%)	0 (0.0%)	1 (2.9%)		
LDH level	Normal	13 (39.4%)	2 (18.2%)	6 (17.6%)	4.523*	0.104
	High	20 (60.6%)	9 (81.8%)	28 (82.4%)		
B-symptoms	No	29 (87.9%)	10 (90.9%)	16 (47.1%)	15.982*	**0.000**
	Yes	4 (12.1%)	1 (9.1%)	18 (52.9%)		
Bulky	No	23 (69.7%)	8 (72.7%)	17 (50.0%)	3.422*	0.181
	Yes	10 (30.3%)	3 (27.3%)	17 (50.0%)		
DLBCL subtype	NOS	22 (66.7%)	7 (63.6%)	21 (61.8%)	1.533*	0.957
	T-cell rich B cell	9 (27.3%)	3 (27.3%)	10 (29.4%)		
	Mediastinal	2 (6.1%)	1 (9.1%)	2 (5.9%)		

	EBV +ve	0 (0.0%)	0 (0.0%)	1 (2.9%)		
IPI interpretation	IPI low	19 (57.6%)	3 (27.3%)	8 (23.5%)	14.439*	**0.025**
	IPI low intermediate	9 (27.3%)	2 (18.2%)	8 (23.5%)		
	IPI high intermediate	4 (12.1%)	3 (27.3%)	8 (23.5%)		
	IPI high	1 (3.0%)	3 (27.3%)	10 (29.4%)		

•: One Way ANOVA test; *: Chi-square test; N: number; SD: standard deviation; PS: performance status; HCV: hepatitis C virus; CMV: Cytomegalovirus; HBV: hepatitis B virus; EBV: Epstein-Barr virus; LDH: lactate dehydrogenase; NOS: not otherwise specified, EBV: Epstein-Barr virus; IPI: international prognostic index.

III. Treatment:

The whole cohort (n=78) received first-line chemotherapy with a median number of 6 cycles ranging between 3 to 8 cycles. Complete response was achieved in 56.4% of the patients and was significantly reported in patients with performance (0-1) (79.5%), negative B-symptoms (81.8%), DLBCL NOS subtype (61.4%), early stages (I – II) (63.6%), IPI low-risk (52.3%) and received R-CHOP regimen (52.3%) (Table 2). Irregular R-CHOP regimen (i.e some cycles were without rituximab) was received by 42.3% of the patients (n=33) with an average of 4 rituximab cycles ranging between 1 to 7 cycles and 34.1% of them achieved CR Vs 11.4% in patients who received CHOP-only regimen without any cycle of rituximab (Table 2).

Table (2): Correlation between the treatment response after 1st line chemotherapy and different variables

		CR	RD	SD	PD	Test value	P-value
		N.%	N.%	N.%	N.%		
Age (years)	Mean±SD	45.20 ± 15.32	47.89 ± 14.77	42.80 ± 18.35	43.90 ± 17.27	0.239 •	0.869
	Range	20 – 76	20 – 77	20 – 63	23 – 70		
Age group	< 40 yrs	15 (34.1%)	5 (26.3%)	2 (40.0%)	4 (40.0%)	2.404 *	0.879
	40-60 yrs	20 (45.5%)	12 (63.2%)	2 (40.0%)	4 (40.0%)		
	> 60 yrs	9 (20.5%)	2 (10.5%)	1 (20.0%)	2 (20.0%)		
Sex	Females	24 (54.5%)	9 (47.4%)	5 (100.0%)	7 (70.0%)	5.295 *	0.151
	Males	20 (45.5%)	10 (52.6%)	0 (0.0%)	3 (30.0%)		
Performance	PS 0-1	35 (79.5%)	3 (60.0%)	16 (84.2%)	4 (40.0%)	8.320 *	0.040
	PS 2-4	9 (20.5%)	2 (40.0%)	3 (15.8%)	6 (60.0%)		
B-symptoms	No	36 (81.8%)	3 (60.0%)	12 (63.2%)	4 (40.0%)	7.943 *	0.047
	Yes	8 (18.2%)	2 (40.0%)	7 (36.8%)	6 (60.0%)		
LDH level	Normal	16 (36.4%)	0 (0.0%)	3 (15.8%)	2 (20.0%)	5.276 *	0.153
	High	28 (63.6%)	5 (100.0%)	16 (84.2%)	8 (80.0%)		
DLBCL subtype	NOS	27 (61.4%)	13 (68.4%)	3 (60.0%)	7 (70.0%)	22.448	0.008
	T-cell rich B cell	17 (38.6%)	4 (21.1%)	0 (0.0%)	1 (10.0%)		
	Mediastinal	0 (0.0%)	1 (5.3%)	2 (40.0%)	2 (20.0%)		
	EBV +ve	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)		
Bulky	No	30 (68.2%)	11 (57.9%)	3 (60.0%)	4 (40.0%)	2.892 *	0.409
	Yes	14 (31.8%)	8 (42.1%)	2 (40.0%)	6 (60.0%)		
Site of the disease	Nodal-only	21 (47.7%)	8 (42.1%)	0 (0.0%)	4 (40.0%)	5.823 *	0.443
	Extra-nodal-only	6 (13.6%)	2 (10.5%)	2 (40.0%)	1 (10.0%)		
	Both nodal & extra-nodal	17 (38.6%)	9 (47.4%)	3 (60.0%)	5 (50.0%)		
Stage	Early (I – II)	28 (63.6%)	1 (20.0%)	8 (42.1%)	2 (20.0%)	9.146 *	0.027
	Advanced (III – IV)	16 (36.4%)	4 (80.0%)	11 (57.9%)	8 (80.0%)		
IPI	IPI low	23 (52.3%)	0 (0.0%)	4 (21.1%)	3 (30.0%)	26.71	0.002

interpretation	IPI low intermediate	9 (20.5%)	0 (0.0%)	9 (47.4%)	1 (10.0%)	7*	
	IPI high intermediate	5 (11.4%)	4 (80.0%)	4 (21.1%)	2 (20.0%)		
	IPI high	7 (15.9%)	1 (20.0%)	2 (10.5%)	4 (40.0%)		
Type of chemotherapy	CHOP	5 (11.4%)	2 (40.0%)	4 (21.1%)	1 (10.0%)	24.530*	0.017
	R-CHOP	23 (52.3%)	1 (20.0%)	1 (5.3%)	2 (20.0%)		
	Irregular R-CHOP	15 (34.1%)	2 (40.0%)	12 (63.2%)	4 (40.0%)		
	CVP	1 (2.3%)	0 (0.0%)	1 (5.3%)	2 (20.0%)		
	CEOP	0 (0.0%)	0 (0.0%)	1 (5.3%)	1 (10.0%)		

N-DLBCL: nodal-diffuse large B cell lymphoma; EN-DLBCL: extra-nodal-diffuse large B cell lymphoma; BNEN-DLBCLS: both noda & extra-nodal-diffuse large B cell lymphoma; •: One Way ANOVA test *: Chi-square test; N: number; SD: standard deviation; PS: performance status ; LDH: lactate dehydrogenase; NOS: not otherwise specified,; IPI: international prognostic index; , CR: complete response, PR: partial response, PR: partial response, PD: progressive disease; CHOP: cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone; R-CHOP: rituximab-cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone; CVP: cyclophosphamide-vincristin-predisone; CEOP: cyclophosphamide- etoposide-vincristine- prednisone

On the other hand, 66.7% of the patients had treatment toxicity after first-line chemotherapy. The most commonly reported toxicity was neutropenia (55.1%). In addition, 15 patients (19.2%) received second-line chemotherapy with a median number of 6 cycles. Toxicity after second-line chemotherapy was reported in 66.7% of the patients (n=10) and the most commonly reported toxicity was vomiting (100%). Only 10.3% of the total cohort received third-line chemotherapy (n=8) and toxicity after third-line chemotherapy was reported in 50% of the patients (n=4). The most commonly reported toxicity after third-line chemotherapy was vomiting (50%). Also, 38.5% of patients (n=30) received radiotherapy, 50% of them received radiotherapy for consolidation, 33.3% received radiotherapy on bulky disease and 16.7% received palliative radiotherapy. The most common site of radiotherapy was dorsal spine (20%) followed by mediastinal mass (16%) and neck (13.3%).

IV. Survival analysis:

Overall, of the 78 patients in the present study, only 2 patients (2.6 %) died, and 76 patients (97.4 %) were alive till the end of our follow-up. The mean OS was 67.388±1.797 months. Only 10 patients had PD with mean PFS of 60.324± 2.840 months. Twelve patients had disease recurrence after achieving CR and the mean DFS was 56.618 ± 3.464 months (Table 3).

Table (3): Mean OS, PFS & DFS among the study population

	N of evaluable patients	months		95% CI		Survival (%)		
		Mean	SE	Lower	Upper	1 year	3 years	5 years
OS	78	67.388	1.797	63.865	70.910	100.00%	93.8%	93.8%
PFS	10	60.324	2.840	54.758	65.890	86.6%	83.7%	83.7%
DFS	12	56.618	3.464	49.829	63.407	88.8%	75.2%	75.2%

N: number; CI: Confidence interval; OS: overall survival; PFS: progression free survival; DFS: disease free survival

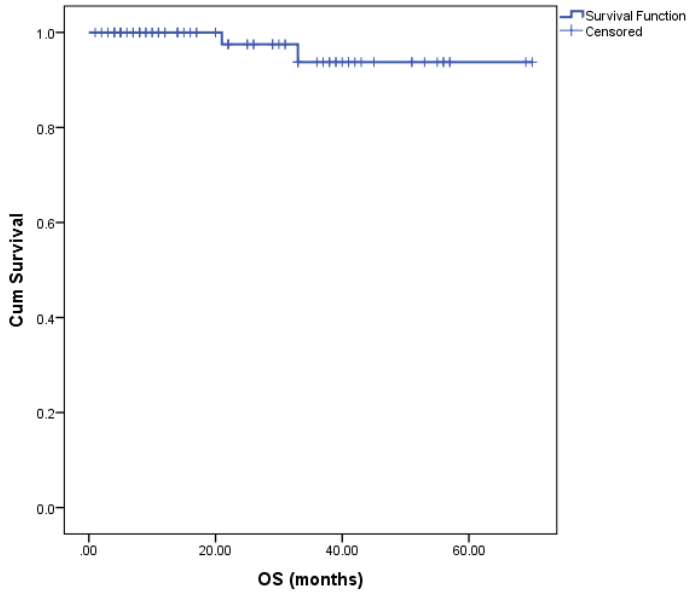

Figure (1): Overall survival analysis (Kaplan –Meier estimation)

The correlation of survival rates with the site of the disease significantly denoted the highest OS among the nodal-only group with a mean OS of 29±17.44 months vs 25.73±18.69 months in the extra-nodal-only group and 19±17.33 in the both nodal & extra-nodal group (P =0.043). (Table 4).

Table (4) Correlation between overall survival (OS) with site of the disease

		Nodal	Extranodal	Both	Test value	P-value
		N. = 33	N. = 11	N. = 34		
OS (months)	Median (IQR)	29 (14 – 39)	26 (9 – 37)	12 (5 – 31)	6.303≠	0.043
	Mean ± SD	29.09 ± 17.44	25.73 ± 18.69	19 ± 17.33		
	Range	1 – 69	2 – 56	3 – 70		

OS: overall survival; N: number; SD: standard deviation; IQR: interquartile range; ≠: Kruskall Wallis test

Additionally, the highest PFS was significantly observed in early stages (I – II) with a mean of 66.3±2.5 months vs 35±3 months in advanced stages (III – IV). Furthermore, a highly significant association was proven between PFS and the number of received chemotherapy cycles. (P value= 0.000) (Table 5)

Table (5) correlation between mean PFS and different variables

		Total N	N of Events	PFS		95% CI		Log Rank test	
				Mean	SE	Lower	Upper	X^2	P-value
Age group	< 40 yrs	26	4	57.077	5.397	46.498	67.655	0.462	0.794
	40-60 yrs	38	4	62.528	3.521	55.627	69.430		
	> 60 yrs	14	2	36.182	4.335	27.686	44.678		
Sex	Females	45	7	56.88	4.503	48.053	65.706	1.257	0.262
	Males	33	3	63.119	3.233	56.783	69.455		
Site of the disease	Nodal	33	4	60.593	3.911	52.928	68.257	0.589	0.745
	Extranodal	11	1	50.667	5.028	40.811	60.522		

	Both nodal/extranodal	34	5	58.537	4.677	49.369	67.704		
Stage	I – II	39	2	66.317	2.527	61.364	71.27	5.493	0.019
	III – IV	39	8	35.027	3.093	28.965	41.089		
IPI risk groups	IPI low	30	3	51.326	3.089	45.272	57.380	5.874	0.118
	IPI low intermediate	19	1	65.000	3.795	57.562	72.438		
	IPI high intermediate	15	2	58.583	7.530	43.824	73.343		
	IPI high	14	4	30.138	5.202	19.942	40.335		
N of cycles	3 cycles	9	3	5.063	0.7	3.69	6.435	36.805	0.000
	4-6 cycles	52	6	60.89	3.092	54.829	66.951		
	7-8 cycles	17	1	65.462	4.36	56.915	74.008		

CI: Confidence interval; PFS: progression free survival; IPI: international prognostic index; N: number

DISCUSSION:

Our retrospective study assessed 78 DLBCL patients. The mean age at diagnosis was 45.54 (± 15.38) years, which is younger than the mean age of 51.6 years found in the Chinese study by Sun et al [14]. On the other side, it was higher than the mean age of 42 (±12) years reported in the Chinese study by Yao et al [15].

In contrast to the majority of other studies, which showed a higher disease incidence in males [16, 17], the gender distribution in the entire DLBCL cohort in our study revealed a slight female predominance comprising 57.7%. This may be explained by the fact that working men in our nation have slightly higher access to health insurance in Egypt than females (50.3% males vs 44.5% for females in the whole of Egypt) according to the Central Agency for Public Mobilization and Statistics [18], whereas housewives do not and therefore rely on state-funded healthcare, as is the case at our hospital.

Furthermore, our data revealed that the majority of patients (76.9%) came from urban areas. This is similar to data found by Tao et al [19]. which analyzed the impact of socioeconomic disparities on mortality after DLBCL in the modern treatment era. They reported that the majority of the patients were from urban areas. This can be explained by the fact that our hospital is located in the nation's capital and that other rural areas have neighboring facilities to serve.

Most of the patients in our study (62.8%) (n=49) were non-smokers in contrast to Geyer et al [20] in which most of the patients (75.4%) were smokers and proved to have more comorbidities that can also impact survival. On the other side, the most frequently observed co-morbidities in our study were hypertension (24.4%) followed by diabetes mellitus (20.5%).

Furthermore, the most common presenting symptom in our study was swelling comprising 42.3% of all presented symptoms consistent with the Brazilian study by Rodrigues et al.[21].

According to the histological subtypes of DLBCL, the most common pathology in our study was DLBCL NOS which is consistent with findings from some studies [22,23].

In this study, lymphomas arising in nodal and extra-nodal sites showed different clinical features at diagnosis. Extra-nodal involvement presented in 57.7% in this study (14.1% in the extra-nodal-only group

+ 43.6% in the both nodal & extra-nodal group). Extra-nodal involvement was more than 50% in several studies [15,17]. However, many other studies had an extra-nodal involvement less than 50% ranging from 22-48.3% [24,25].

In our present study, patients with extranodal-only DLBCL were most commonly from the age group (40-60 years old) in contrast with a study conducted in Pakistan [16] in which extra-nodal disease was most frequently present in patients less than 40 years.

Furthermore, compared to a large Chinese analysis comprising over one thousand DLBCL cases [24], an agreement was noted for a significant male predominance in the nodal-only group whilst the female predominance in the extranodal group conflicted their reported findings.

The most common involved extra-nodal site in our study was the bone, followed by the GIT conflicting with several studies and with the SEER database were the GI tract and the head/neck were the most common involved extranodal sites [14, 24,26].

Patients in the nodal-only group in our study presented with significantly better performance status compared with the extranodal-only group (P=0.016). This concurs with the results shown in the Chinese study [14] that evaluated the impact of extra-nodal involvement on the clinical characteristics of DLBCL patients and their treatment outcomes. They found that better ECOG performance (0-1) was most commonly reported in nodal disease (100%) vs 82% in the extra-nodal arm (P <0.001). This can be explained by the fact that extra-nodal tissues and organs primarily perform unique physiological functions and when major organs are involved, the performance status would be more seriously affected.

In our study, no significant difference was observed between nodal and extra-nodal DLBCL in correlation with HCV infection conflicting with Park et al [27] that showed statistical significance when comparing nodal and extranodal groups regarding HCV infection. They revealed that HCV-positive cases were less likely than HCV-negative cases to have extra-nodal involvement (53.1% vs. 71.1%, respectively, P = 0.044). The lack of this association may be due to the low number of HCV patients in our study (n=17).

Elevated serum LDH levels were reported in the majority of our cases (73.1%) in contrast to a retrospective Korean study in which the majority of cases (56.6%) had normal LDH serum levels [28]. In addition, our study demonstrated no significant difference between the nodal-only group, the extra-nodal-only group, and the both nodal & extra-nodal group regarding the serum LDH level. This was in contrast with Lopez-Guillermo et al that included 382 DLBCL patients consecutively to analyze their clinical and biological characterization and outcome according to the nodal or extra-nodal primary origin and reported a significantly high serum LDH level in the nodal group (P = 0.05) [29].

Compared to the Chines study [24] that analyzed the clinical features and outcomes of DLBCL patients based on nodal or extra-nodal primary sites of origin, B-symptoms in our study were highly significantly present in both nodal & extranodal group (p =0.000) conflicting with their findings in which B-symptoms were significantly present in the nodal arm (P =0.021). Additionally, in our study, bulky disease was non-significantly predominant in the both nodal & extranodal group conflicting with their data that showed a significant predominance of the bulky disease in the nodal arm (p = 0.001). This may be due to our classification of patients into 3 groups (nodal-only, extranodal-only & both nodal and extranodal involvement) not only two groups (nodal & extranodal) as in Shi et al study which decreased the number of our patients in the extranodal group.

The correlation between the site of the disease with the IPI risk groups was significant (P = 0.025). The both nodal and extranodal group was most frequently of IPI high-risk (29.4%) while the nodal-only group was most commonly of IPI low-risk (57.6%). This contrasts Møller et al data [30] in which high-risk was found most commonly in the nodal group and low-risk most commonly presented in the extranodal group (P = 0.879).

In terms of the received treatment, our results demonstrated that the addition of rituximab to CHOP (R-CHOP) significantly increased CR reaching 86.4% (52.3% for R-CHOP + 34.1% for irregular R-CHOP) vs only 11.4% for CHOP-only regimen (P = 0.017). This increase is found in several studies highlighting the effect of rituximab [17, 31]. Furthermore, 38.5% of our patients received radiotherapy vs 49.2% of patients in a Mexican study [32] in which an improvement in PFS and OS was reported with minimal toxicity through the addition of radiotherapy to the treatment plan and recommended that adjuvant RT should be considered as a part of the initial treatment even in the rituximab era.

On the other hand, the most commonly reported treatment toxicity in our study was hematological toxicity (neutropenia) with 55.1% in consistency with a study conducted by Ines et al [33] in which the hematological toxicities were also the most commonly reported toxicities comprising 92%.

The correlation of the treatment response with patients' age showed no statistical significance in contrast to an Italian study [34] which showed a better treatment response in patients < 60 years old (P= 0.004). In addition, in our analysis, the correlation of the treatment response with patients' gender showed no significant difference between males and females in line with Riihijärvi et al [35].

On the other hand, our study was in agreement with Colomo et al [34] showing a better treatment response with CR of 79.5% in patients with good ECOG performance status (0-1) (P = 0.04) and in patients with negative B-symptoms with CR of 81.8% (P=0.047).

Furthermore, our study showed non-significant results regarding the correlation between the treatment response and the level of serum LDH in contrast with an Asian study [36] which correlated worse treatment response (PR and PD) with high LDH serum level (p =0.001).

In consistency with the GELA study [37] and several studies conducted in Europe & Asia[38,39], our study showed no statistical significance regarding the correlation between the bulky disease and the treatment outcomes. This can be explained by the weakened impact of bulky disease on the clinical outcome of DLBCL in the R-CHOP setting than in conventional chemotherapy. This is supported by the recent extrapolatory analysis of MabThera International Trial Group (MInT) which showed a stronger effect of bulky disease on the outcome of patients who were not assigned to rituximab (n=410 comprising 49.8%)[40].

On the other hand, comparing the nodal group with the extra-nodal one regarding response to chemotherapy showed no statistical significance in agreement with Lopez et al [29] that found no difference between nodal and extranodal arms regarding the treatment response and contrasting the Danish study[30] which related the better response to the extra-nodal disease after the rituximab era.

Our study revealed that early disease stages (I - II) showed a significantly better response (63.6% of patients who achieved CR) in line with a study conducted in Spain [34]. In addition, IPI low-risk group in our study showed better treatment response (P = 0.002) with 52.3% of patients achieved CR Vs 83% in this Spanish study [34].

Furthermore, the correlation between treatment response and DLBCL subtype was highly statistically significant as DLBCL NOS had the better treatment response comprising 61.4% of the patients who had achieved CR in contrast to a study conducted in the USA (P = 0.008 vs 0.49 in the American study)[41].

A retrospective study conducted in Slovenia[42] showed a significant correlation between IPI different risk groups (low-risk, low-intermediate risk, high-intermediate risk & high-risk group) and the treatment response correlating the better treatment response to the IPI low-risk group with CR comprising 59% (P-value < 0.0001) in agreement with our study that showed a highly significant difference between the 4 IPI risk-groups concerning the better treatment response to the IPI low-risk group with CR comprising 52.3% (P =0.002).

In terms of survival, our results show that the 5-year OS among all patients was 93.8%. Our findings are better than those obtained from the international statistics. The 5-year relative survival rate was reported as 56.1% in EUROCARE west, 47.1% in EUROCARE east [43], and 56.3% in SEER [4&,45]**.** This is owed to the advances in understanding the disease biology & genetics and the availability of new diagnostic methods and therapies which have improved since the last review of NHL in the Lancet in 2012[46]**.**

As regards the PFS, our results showed a 5-years PFS of 83.7% which was better than Shi et al that showed a 5-years PFS of 54.2%[24]**.** In addition, Rajasooriyar et al.[11] showed a 5-years DFS of 73% which was slightly less than our study that demonstrated a 5-year DFS of 75.2%.

Regarding the comparison between the nodal-only group, the extra-nodal-only group and the both nodal & extra-nodal group, our results were in agreement with the Chinese study[24] in which the best OS was significantly higher in the nodal arm (P =0.043)**.**

On the other hand, there was no statistical significance in comparison between the nodal-only group, the extra-nodal-only group and the both nodal & extra-nodal group regarding the PFS. There were also no significant results found in Yao et al study[15].

A retrospective Swedish study[47] comprising 535 patients with de novo DLBCL showed that there were non-significant results regarding the correlations of PFS with patients' age in agreement with our study. While conflicting with our study in the correlation of PFS with patients' sex, as in that study, male patients were found to have a significantly lower PFS than females while no significant correlation was found in our study.

A study conducted in Slovenia in central Europe[48] evaluated the correlation between survival rates and the different IPI risk groups. In this study, the difference between the 4 risk groups was statistically significant regarding PFS (P= 0.000) correlating the highest PFS to the IPI low-risk group which was non-consistent with our study that showed insignificant correlation between IPI-risk groups and PFS.

Furthermore, our results significantly correlate the advanced disease stages (III – IV) with worse PFS (P =0.019) in consistency with the German study conducted by Lehners et al.[49]**.**

A randomized, phase 3, non-inferiority trial conducted in Germany[50] showed a non-significant difference in PFS in patients received more chemotherapy cycles (4 cycles vs 6 cycles) conflicting with our study that revealed higher PFS in patients who received more chemotherapy cycles (6-8 cycles) (P= 0.000).

Amongst the strengths of the current work is it being an updated analysis of demographic data and clinical outcomes of adult DLBCL

patients who attended the clinical oncology department, Ain shams University hospitals in the period from January 2016 to December 2019. We were targeting a specific sub-group of NHL with a particular pathology in which multiple risk factors were explored that significantly impacted the prognosis of DLBCL and played a substantial role in survival rates. We can speculate these results as a representative of our population as our hospital is a tertiary center treating patients from all over the country.

Limitations of this study include:

The main limitation of this study is that we conducted a retrospective, not a prospective study that proves only association, not causation. Additionally, a considerable number of patients were referred from other centers, particularly National Health Insurance after having been started on treatment or completed part of it with no option for ASUCOD to change the treatment plans, so this study does not reflect accurately ASUCOD's preference of treatment. Furthermore, in spite of the current process of transitioning to electronic data systems, still some of the files were in paper form and some patients' files could not be easily retrieved. Also, there was a lack of standardization of laboratory tests and imaging studies due to the diversity of laboratory evaluations and requested imaging based on availability or cost concerns (PET/CT vs CTs).

Conclusion:

In the present series of DLBCL patients from a single institution, the primary site of the disease was associated with particular clinico-pathological features and with the outcome, although the latter largely depended on other prognostic variables such as IPI score. Nodal-only-DLBCL showed a better presentation, treatment response, and survival outcomes compared to the extra-nodal-only group and the both nodal & extra-nodal group.

Conflicts of Interest:

The authors state that the publishing of this paper is free of any conflicts of interest.

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دراسة بأثر رجعى لتحليل العوامل الاكلينيكية والوبائية ونتائج علاج ورم الغدد الليمفاوية (ذو الخلايا ب الكبيرة المنتشرة) فى المرضى البالغين فى قسم علاج الأورام بمستشفيات جامعة عين شمس

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قسم علاج الأورام والطب النووي -كلية الطب جامعة عين شمس**

خلفية: سرطان الغدد الليمفاوية ذو الخلايا ب الكبيرة المنتشرة (DLBCL) هو النوع الفرعي الأكثر شيوعا من سرطان الغدد الليمفاوية اللاهودجكين (NHL) الذي يضم ٢٥-٣٠٪ من جميع NHLs في جميع أنحاء العالم. الموقع الرئيسي ل DLBCL مهم في تحديد السمات السريرية ونتائج المرض.

الأهداف: تحليل السمات والنتائج السريرية والوبائية بما في ذلك الاستجابة والسمية ومعدلات البقاء على قيد الحياة (DFS، PFS OS) في مرضى DLBCL البالغين الذين عولجوا في مستشفيات جامعة عين شمس.

المريض والأساليب: شملت هذه الدراسة الاسترجاعية ٧٨ مريضا بالغا من مرضى DLBCL الذين عولجوا في قسم الأورام في مستشفيات جامعة عين شمس من يناير ٢٠١٦ إلى ديسمبر ٢٠١٩. تم تحليل الخصائص والنتائج السريرية للمرضى وتصنيفها وفقا للموقع الأساسي للمرض إلى مرض عقدي فقط ، وخارج عقدي فقط ، وكلاهما مرض عقدي وخارج العقدة معا.

النتائج: كان متوسط عمر المرضى ٤٥,٥٤ ±١٥,٣٨ سنة، و ٤٨,٧ % تتراوح اعمارهم بين ٤٠-٦٠ سنة مع غلبة الإناث (٥٧,٧ %). كانت المواقع خارج العقدة الأكثر شيوعا هي العظام (٣٥,٦٪) والجهاز الهضمي (٢٦,٧٪). كان نصف المرضى في مراحل مبكرة (١ - ٢). كان متوسط درجة IPI يساوي ٢ ، مع ٣٨,٥٪ من المرضى ذو مخاطر منخفضة.كان DLBCL العقدي فقط (العدد = ٣٣) أكثر شيوعا بشكل ملحوظ في الذكور ، وفى الأداء ٠-١ ، وأعراض B السلبية ، والمخاطر المنخفضة. كان DLBCL خارج العقد فقط (العدد = ١١) موجود بشكل ملحوظ في الإناث ، والأداء (٢-٤) ، وأعراض B السلبية ، وعلى قدم المساواة مع مخاطر منخفضة وعالية متوسطة وعالية. كان كل من DLBCL العقدي و خارج العقدة معا أكثر شيوعا بشكل ملحوظ في الإناث ، والأداء ٠-١ ، وأعراض B الإيجابية ، والمرض الضخم وغير الضخم على حد سواء ، والمخاطر العالية. تم تحقيق استجابة كاملة في ٥٦,٤٪ وكانت مرتبطة بشكل كبير بالأداء (٠-١) ، وأعراض B السلبية ، والنوع الفرعي DLBCL NOS ، والمراحل المبكرة (I - II) ، والمخاطر المنخفضة ، وتلقي R-CHOP. كانت DFS و PFS و OS لمدة ٥ سنوات ٧٥,٢٪ و ٨٣,٧٪ و ٩٣,٨٪ على التوالي. لوحظ ارتفاع متوسط PFS في المراحل المبكرة (I - II) بينما كان OS أعلى في مرض العقد فقط.

الخلاصة: كان ل DLBCL العقدي فقط عرض سريري مميز مع تشخيص ونتائج أفضل مقارنة ب DLBCL خارج العقد فقط و DLBCL العقدي وخارج العقدة معا.