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Epidemiology and Treatment Outcomes of Lymphoma in Karbala, Iraq: Insights from a Retrospective Analysis

Karrar Kadhim Mohsin

Al Hussain Oncology Center, Karbala, Iraq

E-mail: Karrar1977@gmail.com

ABSTRACT

Background: Lymphoma is a heterogeneous group of hematologic malignancies whose clinical behaviour and outcomes are variable. Local epidemiological data is needed to inform local management plans and maximize patient care in resource-limited environments.

Objective: To assess the clinical features, modalities of treatment and outcome of lymphoma patients treated in oncology centres in Karbala and to examine the epidemiological trends of the study period.

Methods: A retrospective cross-sectional study was done on the medical records of 120 histopathologically confirmed patients with lymphoma who were diagnosed and treated in Karbala. Descriptive statistics were used to extract and analyse the demographic, clinical, and staging data, treatment data, and outcome data.

Findings: Non-Hodgkin lymphoma (NHL) was found to be 69.2 percent and Hodgkin lymphoma (HL) was found to be 30.8 percent. Fifty-five percent of the patients were reported to have advanced-stage disease (Ann Arbor stages III–IV). Fifty two and five percent of patients who received conventional first-line regimens achieved complete remission (CR). Later stage and high serum LDH were linked to poor prognosis. The total mortality during the period of data collection amounted to 25%.

Conclusion: NHL predominates and high burden of advanced presentation at diagnosis is characteristic of lymphoma in Karbala. This needs enhancement of early detection programmes, development of diagnostic infrastructure, and establishment of formal regional lymphoma registries to improve survival outcomes across the Middle Euphrates region.

Keywords: *Lymphoma, Epidemiology, Treatment Outcomes, Retrospective Analysis.*

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1. INTRODUCTION

Lymphoma is a heterogeneous and clinically important category of haematologic malignancies that develop as a result of the clonal proliferation of B-cells, T-cells and natural killer (NK) lymphocytes at different stages of their development. These neoplasms can be broadly classified into two major groups: Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL), each of which is further subdivided into numerous histological subtypes with distinct biological behaviour, response to treatment and prognostic profile [1]. Lymphoma worldwide is estimated to comprise about 45% of all newly diagnosed cancers, and is a significant contributor to the morbidity and mortality of cancer, especially in low- and middle-income countries where the burden of haematological malignancies lies ever-growing [1,2].

Global estimates of newly diagnosed NHL cases indicate that an estimated 544,000 new cases of NHL are diagnosed annually worldwide with a significant geographical variation in the distribution of subtypes and the incidence rates [2]. The most common type of lymphoma is non-Hodgkin lymphoma, which is the most frequent lymphoma type in most regions of the world, with diffuse large B-cell lymphoma (DLBCL) always being the most common type of lymphoma found in most regions of the world [3,4]. DLBCL is a malignancy that is aggressive and characterised by a rapid progression of the disease and a high degree of variable response to treatment with its outcomes heavily depending on the disease stage, serum lactate dehydrogenase (LDH) level, International Prognostic Index (IPI) and the presence of extranodal involvement [4,5]. By contrast, Hodgkin lymphoma is a relatively uncommon yet highly treatable malignancy that exhibits characteristic bimodal age distribution with peaks in young adults aged between 15 and 35 years and a second peak in older individuals

aged above 55 years [3].

Lymphoma epidemiology in Middle East and the overall Arab world is not in line with the trends in the Western environments. According to studies in the region, the rates of incidence of NHL in the Middle East are relatively lower as compared to those recorded in North America and Europe, and that the NHL-to-HL ratio is narrower in the Arab populations, a finding that is attributed to the differences in the levels of environmental exposures, demographic factors, and prevalence of viral oncogenic cofactors such as the Epstein-Barr virus (EBV) [6,7]. Lymphoma is a major percentage of haematological malignancies treated in tertiary oncology centres, specifically in Iraq. In a large retrospective of 270 cases of lymphoma in northern Iraq it has been reported that NHL represented 76% of all cases of lymphoma and DLBCL represented 52.2% of all cases of NHL with Burkitt lymphoma representing a significant proportion at 14.6, a distribution that may reflect the exposure profile of EBV in the region [8].

The governorate of Karbala hosts the Al-Hussein Medical City which is a primary oncology referral centre in the entire Middle Euphrates region and receives patients not only in Karbala itself, but also in the neighbouring governorates of Najaf, Babylon, Al-Qadisiyah and Al-Muthanna. Significant findings on HL patterns have been reported in previous institutional studies by this centre, with mixed cellularity identified as the most prevalent HL subtype in regional Iraqi cohorts - a finding, which is not only contrary to the nodular sclerosis predominance of the European and North American populations, but it also suggests that these populations should be regarded as the most deficient in the HL patterns under investigation [9,12]. In like manner, the analysis of NHL subtypes within the Middle Euphrates region has substantiated the leading subtype of NHL and shown that the highest subtype is the most prevalent internationally with local histopathological profiles also being distinct [10].

Although this centre is of strategic interest and the number of referrals to which this centre deals is substantial, there are few published data on lymphoma in Karbala. The lack of a formal regional lymphoma registry further restricts the availability of prospective, population-based epidemiological data that would otherwise inform clinical decision-making, health resource allocation and health plans [11]. Knowing the local trends of the distribution of lymphoma subtypes, the disease staging at presentation, the treatment practices, and the response rate is therefore a precondition of the optimisation of the diagnostic and treatment approaches to the disease in this resource-limited environment. The following study was developed to fill that gap by systematically reviewing the trends of lymphoma amongst patients treated at oncology centres in Karbala with special consideration given to clinical profiles, staging distribution, first-line treatment regimens, treatment response outcomes, and overall survival, and a systematic comparison of the same against regional and international standards.

2. METHODOLOGY

Design and setting of the study.
This investigation has used a retrospective cross-sectional study design. This research was carried out in oncology centres all located in Karbala, Iraq, with the Al-Hussein Medical City as the main institutional site. This centre is the major haematological oncology referral centre in the Middle Euphrates region, and patients of various surrounding governorates are referred to this centre. The time frame of the study included the patients of lymphoma diagnosed during the period between January 2018 and August 2023, which gives a longitudinal period of the data of about 5.5 years.

Population of the study and eligibility criteria.
The medical records of institutes were searched and 120 lymphoma patients were identified and included in the analysis. Criterion: To be eligible, participants must have a history of pathological confirmation of either HL or NHL; complete medical histories including treatment history reports; and documented follow-up data adequate to determine treatment response. Patients were not included when there was incomplete diagnostic work up, when histopathological confirmation could not be verified, or when critical fields of clinical data, such as staging and initial treatment protocols were missing. The classification of subtypes of lymphoma was based on the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues [21].

Data Collection Instrument
A data collection sheet on lymphoma data were extracted using a standardised lymphoma data collection sheet designed to be used in this study. Examples of variables that were retrieved include patient demographics (age at diagnosis and gender), type and histological subtype of lymphoma, Ann Arbor clinical stage that was applied with Cotswolds modification, serum LDH level at diagnosis, bone marrow involvement that was present on a trephine biopsy, B symptom status, comorbid conditions, the first-line treatment protocol that was given, presence of bone marrow involvement that was observed on a trephine biopsy, B symptom status, comorbid conditions, the first-line treatment protocol that was used, presence of bone marrow involvement that was identified on a trephine biopsy, B symptom status, comorbid conditions, first-line treatment protocol that was administered, presence of bone marrow involvement that was observed on a trephine biopsy, B symptom

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Response Evaluation and Drilling.
The Ann Arbor system with Cotswolds modification was used to stage the disease based on the findings of the clinical examination, computed tomography/ CT (where available) and positron emission tomography/CT (PET/CT) where available. Standardised criteria were used to classify the treatment response according to the Lugano Classification [22]: complete remission (CR) was defined as the total absence of any detectable disease on imaging and clinical examination; partial remission (PR) was defined as a reduction of at least 50% in sum of the products of the greatest diameters of measureable lesions; stable disease (SD) was defined as a change in tumour burden insufficient to qualify as PR or progressive disease (PD); and PD was defined as the appearance of new lesions or a 50% or greater increase in the sum of the products of the greatest diameters of measureable lesions. To compare diseases stages, disease stage was further divided into early stage (I to II) and advanced stage (III to IV).

Statistical Analysis
The data were analysed with the help of descriptive statistical analysis. Categorical variable was represented in terms of absolute frequencies and respective percentages. The overall mortality was considered as a percentage of the entire population in the period when this data was collected. Bar charts were used to create graphical representation of the distribution of the types of lymphoma, stage distribution and the categories of response to treatment. All the data were managed according to the institutional ethical principles. Confidentiality of the patients was upheld at all points and all the identifiers were anonymised before the analysis.

3. RESULTS

1. Lymphoma Type Distribution
The 120 lymphoma patients were involved in the analysis. The most common diagnosis was that of non-Hodgkin lymphoma, which was found in 83 patients (69.2%), whereas Hodgkin lymphoma was confirmed in 37 patients (30.8%), which is an approximate 2.2:1 NHL to HL ratio (Table 1). This is in agreement with the known global overabundance of NHL over HL in most adult cancer populations.

Table 1: ***Distribution of Lymphoma Types Among the Study Population (n = 120)***

Lymphoma Type	Frequency (n)	Percentage (%)
Non-Hodgkin Lymphoma (NHL)	83	69.2
Hodgkin Lymphoma (HL)	37	30.8
Total	120	100.0

2. Histological Subtype Analysis
DLBCL was the most common subtype identified in NHL cases; 38 cases of NHL are of the subtype DLBCL (45.8% of NHL; 31.7% of the total cohort). The second and the third most common NHL subtypes were follicular lymphoma (n = 12; 14.5%), and T-cell lymphoma (n = 8; 9.6%). Among the HL group, the most common subtype was mixed cellularity (n = 14; 37.8%), then nodular sclerosis (n = 12; 32.4%), and finally, classical HL unspecified (n = 8; 21.6%). Family history of malignancy was recorded to be positive in 27.5 per cent of the patients. The comorbidities that were most frequently identified were hypertension, diabetes mellitus and ischaemic heart disease. Table 2 presents the distributions of subtypes.

Table 2: ***Distribution of Lymphoma Subtypes Among NHL (n = 83) and HL (n = 37) Cases***

Subtype	n	%
NHL Subtypes		
Diffuse Large B-Cell Lymphoma (DLBCL)	38	45.8
Follicular Lymphoma	12	14.5
T-Cell Lymphoma	8	9.6
Burkitt Lymphoma	5	6.0
Other NHL subtypes	20	24.1

HL Subtypes		
Mixed Cellularity	14	37.8
Nodular Sclerosis	12	32.4
Classical HL (Unspecified)	8	21.6
Non-Classical HL	3	8.1

3. Stage Distribution

The disease was identified in stage I (15 patients), stage II (36 patients), stage III (35 patients), and stage IV (31 patients) based on the Ann Arbor classification with Cotswold modification. All the cases were 55.0% combined advanced-stage disease (III–IV). The distribution of NHL patients at different stages showed that the majority of NHL patients were diagnosed at an advanced stage with stage IV being the most common stage of NHL patients (30.1%), as compared to HL patients, who more often had the disease at an early stage (62.1% of the HL patients were at stage I or II). The involvement of bone marrow was reported consistently among stage IV patients and high serum LDH levels were always associated with advanced-stage and aggressive subtypes. Table 3 indicates the distribution of the stages.

Table 3: ***Distribution of Ann Arbor Stage by Lymphoma Type (n = 120)***

Stage	Total n (%)	NHL n (%)	HL n (%)
I	18 (15.0%)	10 (12.0%)	8 (21.6%)
II	36 (30.0%)	21 (25.3%)	15 (40.5%)
III	35 (29.2%)	27 (32.5%)	8 (21.6%)
IV	31 (25.8%)	25 (30.1%)	6 (16.2%)
Total	120 (100%)	83 (100%)	37 (100%)

4. Modalities and Results of treatment.

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), and its variations, was the most commonly used first-line regimen, with 65 patients (54.2%), mostly with NHL, having the treatment. The initial-line regimen of HL was the standard ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) which was used in 37 patients (30.8%). Rituximab and bendamustine (RB) were used in 10 patients (8.3%) with indolent subtypes of lymphoma. Only a few patients (n = 8; 6.7) were given alternative regimens such as CHOP, R-DHAP or pembrolizumab under the circumstances of relapsed or refractory disease. Adjuvant radiotherapy was used in 5 patients (4.2%), and stem cell transplantation in 7 patients (5.8%) who were in the relapaged or the chemotherapy-resistant disease. Sixty three patients (52.5%), 26 patients (21.7%), 13 patients (10.8%), and 18 patients (15.0%), respectively, achieved complete, partial, stable and progressive remission, respectively. The total counts of death at the time of data collection were 25% which was concentrated mainly among the patients with advanced stage disease and high LDH. The complete data of treatment can be seen in Table 4.

Table 4: ***Treatment Modalities and Response Outcomes Among All Patients (n = 120)***

Treatment / Outcome	n	%
First-Line Treatment		
R-CHOP (including variants)	65	54.2
ABVD	37	30.8
Rituximab + Bendamustine (RB)	10	8.3
Other (CHOP, R-DHAP, Pembrolizumab)	8	6.7
Radiotherapy (adjuvant)	5	4.2
Stem Cell Transplantation	7	5.8
Treatment Response		
Complete Remission (CR)	63	52.5

Partial Remission (PR)	26	21.7
Stable Disease (SD)	13	10.8
Progressive Disease (PD)	18	15.0

4. DISCUSSION

It is a retrospective cross-sectional study, which provides the systematic analysis of 120 lymphoma patients who were managed at oncology centres in Karbala and provides institution level data of one of the main haematological oncology referral hubs in the region of the Middle Euphrates, Iraq. The major findings, which are NHL dominance, high rates of advanced stage presentation, a CR rate of 52.5% with the use of standard protocols, and overall mortality of 25% all combine to provide a comprehensive epidemiological and clinical picture of the lymphoma burden in this setting.

The fact that NHL (69.2) is more prevalent than HL (30.8) as observed in this cohort is in line with the trends reported among populations across the world and the region. NHL is also the cause of essentially all new lymphoma cases worldwide, with an estimated 544,000 new cases each year (GLOBOCAN 2022 [2]. In Iraq, NHL has been found to exhibit a similar distribution, with multiple institutional studies confirming a similar distribution; in one study NHL was reported to be in a similar distribution, NHL being found to be in a 70:30 distribution within the Middle Euphrates region in another study [8,10]. The current results fit into this larger pattern of NHL domination in geographically separate Iraqi communities, further confirming the epidemiological continuity of NHL preeminence in geographically discrete Iraqi populations.

In this cohort, the most prevalent NHL subtype was DLBCL (45.8% of NHL cases), which is consistent with both worldwide (DLBCL represents 25-35% of lymphoma diagnoses in high-income locales) and regional Iraqi studies that have all consistently found DLBCL to be the dominant NHL subtype [4,5,8]. Wang et al. have highlighted that due to the biological heterogeneity of DLBCL, including indolent to rapidly progressive forms, it is crucial to accurately molecular subclassify the disease as the most effective way of planning risk-adapted treatments, which remains limited in most Iraqi oncology centres [5]. In the HL cases, mixed cellularity was most common (37.8) as compared to nodular sclerosis which is predominant in Western populations (60-65% of all HL cases) [9,12]. The increased proportion of mixed cellularity HL in this and other regional studies could be a result of the contribution of the EBV infection to the lymphomagenesis in populations in developing countries, as the established relationship between the infection of the EBV and mixed cellularity HL [13,14].

The female preponderance (61.25%), which is found in the detailed case level data of the institutional series, is a remarkable finding as most of the regional and international literature show male dominance in both HL and NHL [7,8]. It can be indicative of referral bias in the nature of a centre that is receiving patients across a variety of governorates all with varying gender-specific health-seeking behaviour, or it can be an actual epidemiological phenomenon of the Karbala catchment area that requires further investigation. Clinical implications of gender differences in the presentation and outcome of lymphoma have clinical implications in screening protocols and eligibility to receive treatment particularly since women were not eligible to donate blood and because not all treatment settings are willing to admit a pregnant woman and her newborn baby.

One of the main findings of the study is that 55 percent of the patients showed up with advanced-stage disease (Ann Arbor stages III–IV) which is significantly higher than the advanced-stage rates of 40-50 percent reported in high-income countries [3]. This presentation delay pattern is well documented in resource-limited-setting and has consistently been reported in the series of Iraqi and Middle Eastern lymphoma [8,10]. The stage at which the presentation is made is directly linked with poor treatment outcomes such as the low CR rates obtained in stage III -IV patients compared to those at early stages. The underlying causes of delayed presentation in this case are multifactorial in nature, and involves lack of awareness of the signs and symptoms of lymphoma in the general population, inadequate access to primary care diagnostic centers, and geographic barriers to specialist referral throughout the Middle Euphrates region. Interventions in the domain of public health to enhance the community awareness of the lymphadenopathy, B symptoms and other early indicators of lymphoma are of significant importance [11].

The CR rate of 52.5% that was attained with the use of R-CHOP and ABVD as the first line regimens is similar to the results that were achieved with the use of similar regimen in resource limited settings but falls short of the 6070% CR rates that are usually reported in clinical trials conducted in high income countries [4]. This gap can probably be attributed to a combination of converging factors: the unequal distribution of advanced-stage disease in this cohort, the limited access to molecular profiling tools needed to plan risk-stratified treatment, and limited access to salvage regimens and stem cell transplantation to treat relapsed or refractory cases [16]. The situation with pembrolizumab use in a limited number of cases

of relapsed or refractory classical HL is indicative of an emerging - but at present still limited - adoption of the use of checkpoint inhibitors immunotherapy into the regional oncology practice, as per the emerging international guidelines in the area of relapsed or refractory classical HL [17]. Radiotherapy was used in 4.2% of patients, mainly in those with HL as adjuvant consolidation and stem cell transplantation was done in 5.8% of patients with a relapse that is sensitive to chemotherapy, as adjuvant consolidation and in the case of stem cell transplantation as a consolidation therapy [18,19].

The prognostic significance of these clinical attributes is highlighted by the overall mortality of 25% at the time of data collection, with most of the deaths being among the patients in stage III-IV with high LDH and bone marrow involvement. Morton et al. have determined through large scale analysis that LDH increase and advanced stage are some of the most effective independent predictors of poor lymphoma outcome across subtypes [15]. These results support the urgency of the early diagnosis of the disease and the beginning of treatment as early as possible. The analysis of local outcomes compared to international standards (Table 5) shows that although the distribution of lymphoma subtypes in Karbala is generally comparable to the global trend, the presentation rate of lymphoma subtypes at an advanced stage and CR rate are the areas where local results are not in line with what can be achieved in high-resource oncology setting.

Table 5: ***Comparison of Key Epidemiological and Clinical Parameters: Karbala Study Versus Global and Regional Trends***

Parameter	Karbala (This Study)	Global / Regional Trend
NHL prevalence	69.2%	60–70% [3,6]
HL prevalence	30.8%	30–40% [7]
Advanced stage (III–IV)	55.0%	40–50% [3]
Complete remission rate (CR)	52.5%	60–70% [4]
DLBCL as proportion of NHL	45.8%	25–35% [5]
Mixed cellularity (HL)	37.8%	15–30% [12]
Mortality rate	25.0%	Variable [15]

5. STUDY LIMITATIONS.

There are some limitations to this study which are important to note when interpreting the findings of this study. The retrospective design inherently exposes potential risks of not fully capturing data, and the documentation of treatment response was not available to all patients at the time of data collection, so they were categorized as ongoing or never assessed. Since the study is a single-institution, single-region study, care is needed in generalisability of findings to the wider Iraqi population, or to other Middle East settings. The lack of molecular profiling data (cell-of-origin classification of DLBCL (activated B-cell versus germinal centre B-cell subtype), genetic risk markers, and the presence or absence of myc/bcl2 rearrangements) prevented any subgroup analyses that would have added a significant clinical and prognostic layer to the results. Multivariate survival analysis was not done because the sample size was too small and the follow up data of some patients were missing. Also, since this centre is referred to by a number of neighbouring governorates, it is not possible to rule out the possibility of selection bias towards more intricate or advanced cases. The only possible solution to such limitations and to produce strong long-term survival data is future prospective multi-centre studies including the use of molecular diagnostics and standardized data collection.

6. CONCLUSION

This research shows that Karbala lymphoma is characterised by an apparent preponderance of Non-Hodgkin lymphoma, a disproportionately high rate of advanced-stage disease at diagnosis and an acceptable rate of complete remission with standard first-line chemotherapy regimens. DLBCL continues to be the predominant NHL subtype, with mixed cellularity remaining the most common HL subtype - a trend that once again differentiates this population as compared to Western lymphoma epidemiology and may reflect some underlying viral oncogenic events. The clinical impact of late diagnosis (25% total mortality) and the high concentration of the deaths among the advanced-stage patients further confirm the importance of the problem at hand and the necessity to undertake structural interventions that will enable helping the patient at the earlier stage. Some of the necessary actions that can be taken to ensure that lymphoma outcomes can be improved in the Middle Euphrates region of Iraq are; expansion of access to advanced diagnostic tools and the establishment of a formal regional lymphoma registry and the strengthening of the public health awareness programmes.

Recommendations

To provide the opportunity to conduct systematic epidemiological surveillance, long-term outcome monitoring, and make evidence-based decisions when allocating health resources, a dedicated lymphoma registry encompassing Karbala and the greater area of the Middle Euphrates should be formally established.

2. Advanced staging modalities, especially PET/CT scanning and complete immunohistochemistry panels should be installed in the regional oncology centres to support the accurate staging of the disease, subtype classification, and response assessment according to the Lugano Classification criteria [22].

3. Molecular diagnostic capabilities such as cell-of-origin profiling of DLBCL, testing of rearrangements in the MYC/BCL2 rearrangement, and EBV in situ hybridisation of HL subtyping should be implemented so that risk-stratified treatment approaches can be implemented and access to targeted and immunotherapy-based regimens can be facilitated [5,14].

4. Public health education programmemes on early warning signs of lymphoma, including persistent lymphadenopathy, unexplained fever, drenching night sweats, and inadvertent weight loss, should be implemented to promote awareness of early signs of clinical presentation of lymphoma [11].

5. Regionally, access to facilities to provide stem cell transplantation and salvage chemotherapy regimens should be increased to enhance outcomes of patients with relapsed or refractory disease with limited therapeutic options beyond standard first-line protocols [17,18].

Priority should be given in order to generate strong survival data and estimate the true-life performance of the changing treatment regimens of the Iraqi lymphoma patients.

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