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SHORT REPORT

Haematological Malignancy – Clinical

Outcome of malignant lymphoma in Ukraine. Analysis of 563 cases registered in the Ukrainian Lymphoma Registry in 2019–2021

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Summary

We report the outcome of 563 cases of newly diagnosed lymphoma registered in 2019–2021, including 176 cases (31.2%) of Hodgkin lymphoma (HL), 130 (23.1%) of diffuse large B-cell lymphoma (DLBCL), 28 (5%) of follicular lymphoma (FL), 16 (2.9%) of mantle cell lymphoma (MCL) and 20 (3.5%) of peripheral T-cell lymphoma (PTCL). After a median follow-up of 30.1 months (95% CI: 28.8–31.3), the 3-year overall survival rates were 95%, 83%, 86%, 100%, 61% and 42% for HL, DLBCL, CLL, FL, MCL and PTCL respectively. These data offer valuable information on the curability of lymphoma patients in Ukraine, in a real-world setting.

KEYWORDS
lymphoma registry, malignant lymphoma, survival outcomes

INTRODUCTION

Lymphomas are a heterogeneous group of diseases, with more than 100 different subtypes in the most recent revision of the World Health Organization (WHO) classification of haematopoietic and lymphoid tumours.[1] According to SEER, 89 380 new cases 8830 of HL and 80 550 of non-Hodgkin lymphoma (NHL) and 29 180 deaths (900 HL and 20 180 NHL) are expected in the USA in 2023. For cases diagnosed in the years 2013–2019, the 5-year relative survival rate is 88.9% and 74.3% for HL and NHL respectively.[2] According to the Ukrainian National Cancer Registry (UNCR), 2890 patients

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were diagnosed with lymphoma (770 cases of HL and 2120 of NHL) in 2021.[3] Few data are available on lymphoma treatments and outcomes outside the setting of clinical trials. The Ukrainian Lymphoma Registry (ULR) was established in 2019 to collect and analyse real-world data in order to verify the quality of lymphoma diagnosis and to better understand the epidemiology, treatment and outcomes of lymphoma in Ukraine. Here, we describe the clinical characteristics, therapeutic approach and survival outcomes of the first 563 cases registered in 2019–2021.

PATIENTS AND METHODS

The ULR is located at the National Cancer Institute (NCI) in Kyiv, Ukraine. The ULR prospectively collects information on baseline clinical and disease characteristics, first-line treatment and response evaluation of all new cases of lymphoma classified according to the 2016 WHO classification.[1] All cases initially diagnosed outside the Pathology Department of the NCI are revised by two national expert haematopathologists. The disease stage was defined according to the Ann Arbor staging system and the 2014 Lugano Classification.[4] All initial data are entered into the electronic case report forms (eCRFs) as real-time registration, with data on treatment and effectiveness entered subsequently. Registration was performed on a secured dedicated database. ECRFs were reviewed and verified by the ULR team. This registry operates in compliance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the NCI of Kyiv. The ULR required each patient to provide written consent before data registration.

The primary end-point of the analysis was OS measured from the date of diagnosis until the date of death from any cause or censoring at the last follow-up.

Data were analysed using Fisher's exact test to identify associations between categorical variables. OS was calculated using the Kaplan–Meier method. Statistical analyses were performed using Stata version 14.2 and SPSS version 28.

RESULTS

Overall, 563 patients with newly diagnosed lymphoma were registered as follows: 176 cases (31.2%) of HL, 130 cases (24%) of DLBCL, 237 (42%) of other B-cell lymphomas and 20 cases (3%) of T-NHL. The ULR registered 36 of the 91 lymphoma subtypes in the 2016 WHO classification; of the 55 other entities, however, including 37 'old' and 18 'new' entities, not even one case was recorded. Notably absent were mature T-cell non-Hodgkin lymphomas (T-NHL), specifically follicular helper T-cell-related lymphomas (TFH). The male-to-female ratio (M/F) for the whole population was 0.7, and the overall median age at diagnosis was 46.5 years (18–100), with 82% ($n = 454$) under age 65. Two hundred and eighty-three (46.5%) had pure nodal disease, and extranodal involvement was observed in 280 cases (50.9%), with 90 cases classified as primary extranodal lymphoma (16.5%). Advanced stage (III and IV) was diagnosed in 316 cases (56%): 82 (46.6%) HL, 64 (56%) DLBCL, 158 (67%) other B-NHL and 12 (60%) T-NHL. Table 1 reports patients' characteristics by histological subtype, and Table S1 reports the frequency of different subtypes.

Information on therapy was available for 516 (92%) cases (162 HL, 122 DLBCL, 214 other B-NHL and 18 T-NHL). The most frequently adopted treatment strategy for patients

TABLE 1 Patients' characteristics overall and by histological category ($N = 563$).

Parameters	Patients evaluable total $N = 563$	HL $N = 176$	DLBCL $N = 130$	Other B-NHL $N = 237$	T-NHL $N = 20$
		N (%)	*N* (%)	*N* (%)	*N* (%)
Median age, years (range)	562	30 (18–77)	52.5 (18–81)	52.7 (18–81)	51 (19–67)
Age >65	562	6 (3.4)	37 (29)	64 (27)	2 (10)
Male	536	51 (29)	57 (43)	107 (45)	10 (50)
B symptoms	563	77 (43.8)	78 (60)	161 (68)	11 (55)
Extranodal involvement	550	55 (31.2)	92/127 (72)	124/232 (53.4)	9 (45)
STAGE					
I–II	562	94 (53.4)	56 (44)	79 (33)	8 (40)
III–IV		82 (46.6)	64 (56)	158 (67)	12 (60)
ECOG PS >1	563	11 (6.3)	34 (26%)	43 (19%)	2 (10)
LDH > ULN	495	78 (44.3)	58.5 (45)	97(41)	9 (45)
Albumin <3.5 g/L	499	13 (7.4)	11 (8.5)	22 (9)	2 (10)
Haemoglobin <12 g/dL	529	71 (40.3)	62.5 (48)	118 (51)	11 (55)
Platelet count $<150 \times 10^9$	534	9 (5.1)	11 (8.5)	21 (9)	2 (10)
ANC $>6.5 \times 10^3/mm^3$	492	59 (33.5)	37.7 (28)	71 (31)	5 (25)

Abbreviations: ANC, absolute neutrophil count; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; LDH, lactate dehydrogenase; T-NHL, T-cell non-Hodgkin lymphoma.

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with a diagnosis of HL was ABVD/ABVD-like in 146 cases (90.1%), followed by BEACOPP in 12 cases (7.4%). Sixty-four patients received radiation therapy, including 57 (61%) with localized stages and 7 (8.5%) with advanced stages. In patients diagnosed with DLBCL, the most frequently used regimens were R-CHOP/R-CHOP-like in 98 cases (80%), while rituximab plus bendamustine was prescribed for 85 cases (40%) with other B lymphomas. R-da-EPOCH was the most adopted regimen in PMBCL (80% of cases; Table S2). Finally, CHOP/CHOP-like was the main treatment approach for patients with T-NHL (14 cases, 77.7%).

After the administration of front-line therapy, the overall response rate (ORR) of the 480 patients for whom this information was available was 85%, with 320 patients (66.7%) in complete response (CR) and 88 (18.3%) in partial response (PR); instead, 72 patients (15%) were in stable disease or progressive disease at response assessment. The ORR by histological category was 83% in HL, 74% in DLBCL, 82% in other B-NHL and 40% in T-NHL.

Overall, radiotherapy was administered to 101 patients (19.2%) of the 527 for whom this information was available: 67 (66%) in HL, 18 (18%) in DLBCL, 12 (12%) in other B-NHL and 4 (4%) in T-NHL. Stem cell transplant as first-line consolidation was performed in only nine cases (6 MCL and 3 PCNSL).

After a median follow-up of 30.1 months (95% CI: 28.8–31.3), the 3-year OS of the whole cohort was 86% (Figure 1A). The 3-year OS by subtype was 95% for HL, 83% for DLBCL, 78% for primary mediastinal (thymic) large B-cell lymphoma (PMBCL), 86% for chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), 80% for primary diffuse large B-cell lymphoma of the CNS (CNS-DLBCL), 100% for follicular lymphoma (FL), 82% for marginal zone lymphoma (MZL), 61% for mantle cell lymphoma (MCL) and 42% for T-NHL, (Figure 1B,D). Among patients with DLBCL, the 3-year OS was 92% for those with germinal centre B-cell subtype and 81% for those with activated B cell; the difference was statistically significant ($p = 0.02$; Figure 1C).

Regarding HL, we also analysed the most frequent histologies (cHL, NSCHL, MCCHL) ($N = 164$, 93.2%); the 3-year OS for cHL, NSCHL and MCCHL was 95%, 97% and 100% respectively. Finally, due to the rarity of T-NHLs, the

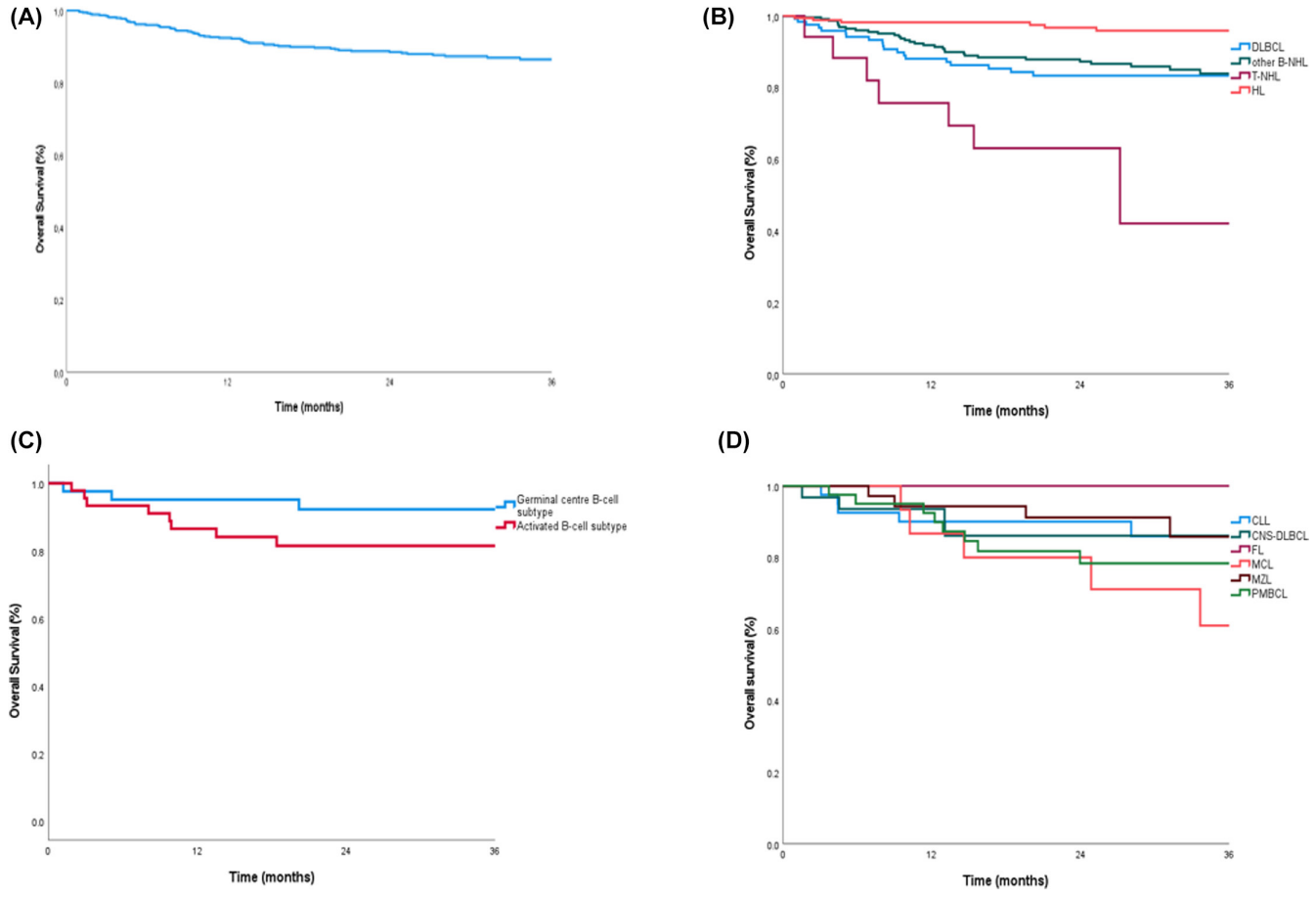

FIGURE 1 (A) OS for 563 cases; (B) OS for DLBCL, HL, T-NHL and other B-NHL; (C) OS and for DLBCL NOS, GCB and ABC; (D) OS for CLL/SLL, PMBCL, CNS-DLBCL, FL, MCL, MZL. ABC, activated B cell; B-NHL, B-cell non-Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; CNS-DLBCL, primary diffuse large B-cell lymphoma of the CNS; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; GCB, germinal centre B cell; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; OS, overall survival; PMBCL, primary mediastinal (thymic) large B-cell lymphoma; T-NHL, T-cell non-Hodgkin lymphoma.

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frequency of individual T-NHL histologies was too low to permit survival comparisons among different subtypes.

DISCUSSION

Our study provides a comprehensive analysis of the clinical characteristics and outcome of unselected, prospectively registered cases of lymphomas in Ukraine classified according to the 2016 WHO classification. Our study aimed to offer comprehensive and clinically relevant information on lymphomas in Ukraine; we achieved this by collecting and analysing histological and clinical features within a well-described patient series. Unlike most epidemiological studies, we incorporated clinical entities based on the 2016 WHO classification system criteria.[1] Hence, we opted to categorize both SLL and CLL as a single histological group. This approach enhances the practical relevance of our results for clinicians. Nevertheless, our results may indicate substantial differences in frequency compared to previously published data.[5,6]

In the years 2019–2021, 176 cases of HL were registered in the ULR, representing 31.3% of all lymphomas. These data compare with those of the UNCR, where 770 (25.8%) cases of HL were reported in the year 2021.[3] However, although the high number of cases seems to us mainly dependent on the young median age of the Ukrainian population[7,8] (Figure S1), other genetic or environmental causes cannot be excluded: a Canadian study found that a greater risk of HL was found in people of Eastern European descent when compared with people of North American descent; and in those with exposure to phenoxy herbicides.[9]

DLBCL was found to be the second most frequent lymphoma subtype, accounting for 23.6%. Notably, PMBCL and PCNSL were more frequent in the ULR (7.2% and 5.6%, respectively) compared to other sources. The incidence of PMBCL and PCNSL reported in the literature is far lower: approximately 2–3% and 1% of NHLs respectively.[10,11] This could partially be explained by NCI's being a referral centre, offering up-to-date treatments to patients with these rare disorders. The proportion of CLL/SLL and FL in the ULR (6.7% and 5% of B-NHL, respectively) were lower than that reported in Western countries.[12] Potential explanations include the younger study population, reduced hospital admissions and the exclusion of patients not requiring active therapy.

The lack of any diagnosis of TFH and T-NHL in the ULR is intriguing, given their diagnosis can be potentially misinterpreted as reactive follicular hyperplasia.[13] Despite the fact that the 2016 WHO classification of Hodgkin lymphomas (HLs) remains consistent with the 2008 edition, some notable updates are offered, particularly pertaining to nodular lymphocyte-predominant HL (NLPHL). In the Ukrainian Lymphoma Registry, only 5 out of 176 HL cases (2.7%) have been identified as NLPHL.

Our study also aimed to contribute to better assessing the quality of care of patients in Ukraine. Notable findings include the widespread use of bendamustine-based regimens in B-cell malignancies, adoption of DA-EPOCH-R for aggressive large B-cell lymphomas and a consistent preference for ABVD in HL. The findings indicate that while the 2016 WHO classification had a limited impact on treatment decisions, it contributed to understanding the biology of various lymphomas.

The results of this study emphasize the need to account for regional and centre-specific factors in interpreting epidemiological data on lymphoma. Despite this, our data maintain high accuracy due to prospective data collection and meticulous record reviews. In conclusion, we believe that by providing a comprehensive description of all lymphoma cases collected by the ULR, we have contributed to an increased understanding of this disease in terms of both clinical features and patient outcomes.

AUTHOR CONTRIBUTIONS

MF and IK designed the present analysis. YS, MM, MC, TS and GG analysed the data; YS, AB, NS, KM, IT, OA, YP, HG, TK, TR, KF, AM and ON made a significant contribution to the data acquisition; all authors performed the research and wrote the paper. All authors approved the submitted version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to disclose.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study may be released upon reasonable request, approved by the National Cancer Institute advisory board.

ETHICS STATEMENT

The study was approved by the Institutional Ethics Committee of the National Cancer Institute on 21 May 2019; No 138.

PATIENT CONSENT STATEMENT

The ULR required each patient to provide written consent before data registration.

PERMISSION TO PRODUCE MATERIAL

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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