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SURVIVORSHIP IN MALIGNANT NON-HODGKIN LYMPHOMA PATIENTS IN ALBANIA

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ABSTRACT

Background: Malignant Non-Hodgkin Lymphoma (NHL) represents serious health conditions that eventually affect patient survival. **Objective:** To assess the general profile of NHL patients and the factors associated with survival and death from NHLs in Albania. **Materials and methods:** This is a case-series study of patients newly diagnosed with NHLs in the Hematology Service at the University Hospital Center (UHC) "Mother Teresa" in Tirana and followed-up during 2011-2015. The present study included 107 patients newly diagnosed with NHLs during this time period. All patients with previously known NHLs were excluded from the survey. Basic demographic and other data relevant to the disease were collected. Survival analyses were performed with Kaplan-Meier test and Cox proportional hazard models. **Results:** Mean age of patients was 57.7 years and 61.7% were males. Most NHL patients had intermediate-high or high grade and Ann Arbor stage 3-4 NHL and presence of B symptoms at the moment of diagnosis. More than one-third of patients had level 3-4 performance status. The overall 50 months survival was 57.2%. The risk of death from NHL was significantly higher among patients with high level performance status, higher NHL grade and stage, higher levels of LDH, B symptoms and bone marrow involvement at the time of diagnosis. **Conclusion:** Survivorship and its related factors among Albanian NHL patients resemble those reported by international literature. The present findings could support awareness raising activities towards early detection and treatment of NHLs in Albania.

KEYWORDS: *Albania, Non-Hodgkin Lymphoma, prognosis, survival.*

1. INTRODUCTION

Malignant Non-Hodgkin Lymphoma (NHL) represents a heterogeneous group of malignant diseases that originate from B and T lymphocytes, in different stages of differentiation, usually affecting the lymphoid tissue (lymph nodes, spleen, bone marrow, etc.) even though any other body tissue could be involved, and ranging from indolent follicular lymphoma (FL) to more aggressive diffuse lymphoma such as diffuse large B cell lymphoma (DLBCL).[1,2] NHLs are classified according to the fourth edition of 2008 World Health Organization classification of lymphoid tissues, a classification recently being revised that introduces small and fine changes compared to 2008 classification.[3] B-cell NHLs comprise the vast majority of NHL (up to 90%) whereas T-cell and natural-killer cell NHLs account for the remaining proportion, with DLBCL and FL being the most common NHLs.[4,5]

According to scientific information, the incidence of NHL has almost doubled between 1970-1990 and then the disease rates in the general population were somehow stable, with highest increases among Caucasians, males, older people and patients diagnosed with extranodal NHL.[1] A recent study suggested that, in US, the incidence of lymphoma declined in recent years (except for plasma cell neoplasms and mycosis fungoides), with considerable variations by lymphoma subtypes.[4]

The survival of NHL patients also varies by disease subtype.[4] For example, among T-cell NHLs, mycosis fungoides had the best 5-year survival (ranging between 79%-92%) and peripheral T-cell lymphomas the worst survival (36%-56%) whereas for B-cell NHLs the 5 year survival rate ranged between 83%-91% for marginal zone lymphoma and dropping to 44%-48% for Burkitt lymphoma.[4] NHL survival is dependent on several factors, including race and sex, with blacks and males showing worst survival for the majority of NHLs.[4] Unfavorable International Prognostic Index (IPI), a predictive model based on age, tumor stage, serum concentration of lactate dehydrogenase (LDH), performance status and extranodal involvement[6] is also associated with worst NHL survival.[7] Other risk factors

might include bone marrow involvement, advanced age,[8] performance status, Ann Arbor stage of the tumor, increased level of LDH, reduced hemoglobin level, involvement of two or more extranodal sites, tumor size more than 10 cm in one site, etc.[9] Smoking, alcohol and obesity[10] as well as other factors related to the host tumor reaction, host immune response and tumor invasive potential are also associated with NHL survival.[9]

In Albania there is little information about NHL patients, their characteristics and survival measures. In this context, the aim of this study was to determine the factors associated with the overall survival of NHL patients in this South-East European country.

2. MATERIALS AND METHODS

Study population

This is a case-series study of a group of patients followed up prospectively in time. The study population comprises of patients that showed up at the Hematology Service in the premises of the University Hospital Center (UHC) "Mother Teresa" in Tirana, Albania, and being diagnosed with Malignant Non-Hodgkin Lymphoma, during 2011-2015 and dynamically followed up during this period of time. Therefore, the inclusion criteria was: NHL diagnosis set at the Hematology Service of UHC, implying that all cases represent new cases (recently diagnosed), and thus excluding all patient previously known to suffer from NHL (exclusion criteria). For this reason, the recruitment of subjects lasted about 5 years (from 2011 to 2015).

During this period of time a total of 107 patients satisfied the inclusion criteria, representing the final study population.

Data collection

After the diagnosis of NHL was established, the respective patient was asked to become part of the survey. Each patient was asked to give the informed consent after the aim and objectives of the study were explained to them. Data collection process comprised of two main components: basic demographic (sex and age) data and other data regarding the disease (NHL), different examinations and accompanying data such as concomitant diseases (diabetes, hypertension, liver cirrhosis).

NHL data included information on histologic type, disease grade and stage at the moment of diagnosis. The stage of NHL at the moment of diagnosis was based on the Ann Arbor criteria whereas NHL grade was determined based on the microscopy of the affected lymph node or other involved tissues. Based on the differences between normal and tumor cells the NHL grade was determined as low-grade (low cell growth rate), low-intermediate, intermediate, intermediate-high and high grade (high cell growth rate). Also, whenever possible, the mass of the biggest tumor and mass of lien was measured.

At the moment of diagnosis (denoting the moment of treatment initiation), and by the end of treatment we assessed the following parameters: performance status (ranging from 0 (fully active) to 5 (dead), presence of B symptoms, extranodal and other tissues involvement (such as liver, pulmonary, lymph nodes, bone marrow, central nervous system, lactate dehydrogenase and albumin. Based on relevant parameters, the International Prognostic Index (IPI) was calculated for each patient.[11]

After the diagnosis, the appropriate treatment was initiated. The life status (dead/alive) of the participant was measured at the moment of diagnosis and at the end of the follow-up period. This is the main variable for assessing the survival of participants under survey.

This study was approved by the Board of Medical Bio-Ethics in the premises of the Faculty of Medicine.

Statistical analysis

Various statistical methods were used to analyze the available data. Categorical variables were compared using the chi square test. Because of the relatively small number of study subjects, the non-parametric Wilcoxon test was used to compare mean values of numeric variables across categories of independent variables.

To determine overall survival the Kaplan-Meier test was used. For the assessment of the respective p-value we were based on Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware tests, with a p-value less than 0.1 considered as statistically significant.

To assess the risk of dying from NHL we used the Cox Regression test. This test reports the hazard ratios (HR). Two models of this test were run: initially the crude analysis (not adjusted for any factor) was carried out and then, the second model was run, taking into account the potential confounding effects of age and sex.

The Statistical Package for Social Sciences software (SPSS), version 17 was used for all the statistical analysis.

3. RESULTS

In total 107 patients newly diagnosed with malignant Non-Hodgkin Lymphoma in the Hematology Service of University Hospital Center "Mother Teresa" participated in the survey. Table 1 presents baseline characteristics of study participants at the moment of diagnosis.

More than half of participants were males (61.7%), the average age was 57.7 years ± 12.7 years and ranging between 16 and 78 years. Low, low-intermediate or intermediate grade NHL was detected in 29.9% of patients, whereas more than two thirds of participants

(70.1%) had intermediate-high or high grade NHL at the time of diagnosis (Table 1). In addition, about three-quarters of study participants (74.7%) were at the stage 3 or stage 4 of the disease and more than one-third of them had performance status level of 3 or 4 (36.4%) at the time of diagnosis (Table 1).

Table 1. Baseline characteristics of study subjects at the moment of NHL diagnosis

Study variable		**Absolute number**	**Percentage**
Total		*107*	*100.0*
Gender	**Male**	66	61.7
	Female	41	38.3
Age (years) - mean ± SD		57.7 ± 12.7	
Age-group	16-54 years	35	32.7
	55-63 years	35	32.7
	64-78 years	37	34.6
NHL grade	Low	12	11.2
	Low-intermediate	17	15.9
	Intermediate	3	2.8
	Intermediate-high	41	38.3
	High	34	31.8
NHL stage	Stage 1	12	11.2
	Stage 2	15	14.0
	Stage 3	33	30.8
	Stage 4	47	43.9
Performance status	1	11	10.3
	2	57	53.3
	3	32	29.9
	4	7	6.5
Biggest tumor (cm)		4.39±4.35	
Lien mass (cm)		16.22±3.69	
LDH level (U/l)		459±1080	
Extranodal involvement	No	51	47.7
	Yes	56	52.3
B symptoms	No	40	37.4
	Yes	67	62.6
Bone marrow involvement	No	78	72.9
	Yes	29	27.1
Liver involvement	No	99	92.5
	Yes	8	7.5

The average dimensions of lien and of biggest tumor were 16.22 cm and 4.39 cm, respectively, whereas the average LDH level was 459 U/l (Table 1). B symptoms were present in 62.6% of cases; extranodular areas, bone marrow and liver were affected in 52.3%, 27.1% and 7.5% of cases, respectively.

The most common histologic type of NHL was DLBCL (29.9% of all cases), followed by other B-cell lymphomas (14% of all cases), follicular lymphoma (13% of cases) and T-cell lymphomas (13% of cases). The main histologic types are then specified into a large number of different sub-types. The most common treatment scheme was R-CHOP (applied in about 62% of cases), followed up by CHOP (18% of cases) and R-CVP (8% of cases) [data not shown in tables].

Figures 1-8 show the survival of NHL patients. Figure 1 shows the overall survival during the entire follow-up period; about 50 months after the diagnosis the overall survival rate was 57.2%. Figures 2-7 show that the survival of NHL patients is poorer among those with high grade lymphoma, high performance status (ECOG 4), presence of B symptoms, extranodal, bone marrow and liver involvement, and those with high levels of LDH (tertile 3) at the moment of NHL diagnosis.

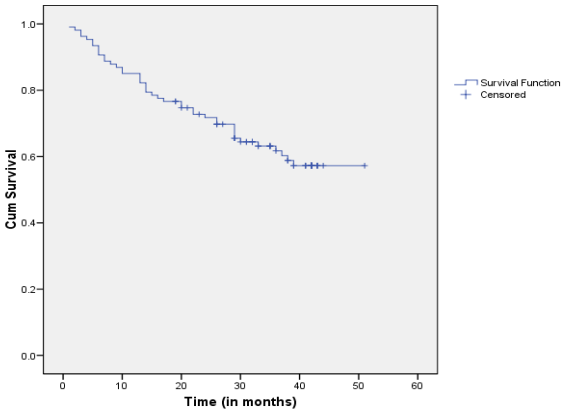

Figure 1: NHL overall survival.

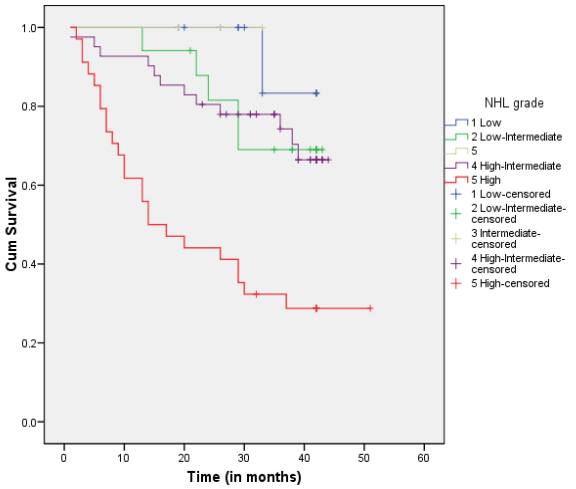

Figure 2: NHL survival by NHL grade at the moment of diagnosis.

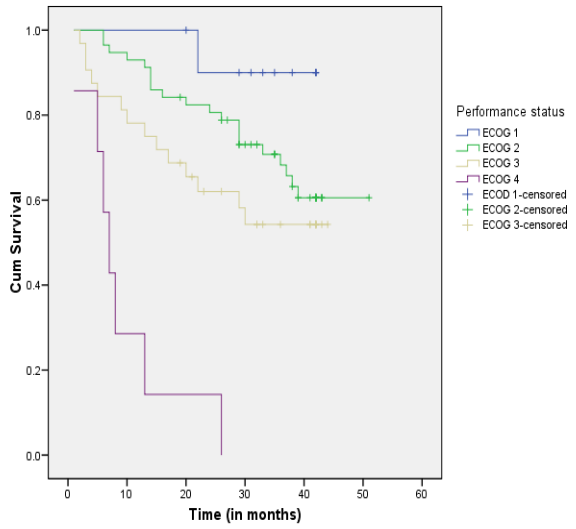

Figure 3: NHL survival by performance status at the moment of diagnosis.

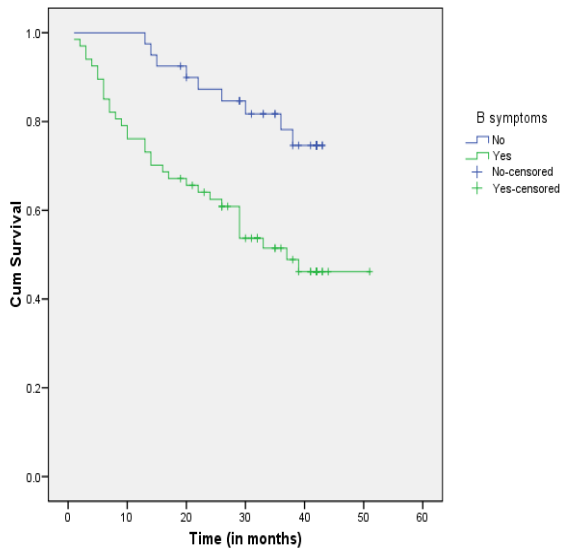

Figure 4: NHL survival by status of B symptoms at the moment of diagnosis.

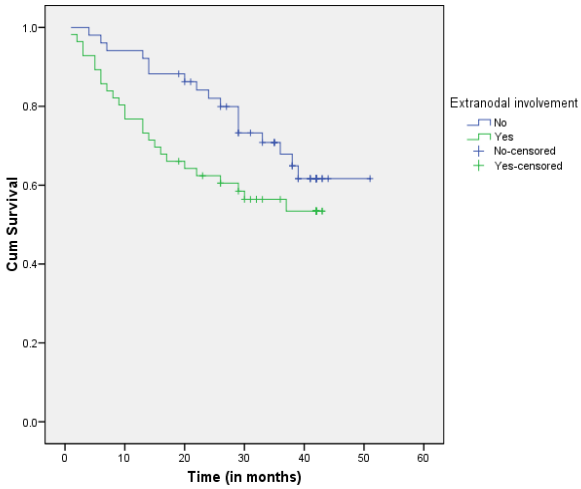

Figure 5: NHL survival by status of extranodal involvement at the moment of diagnosis.

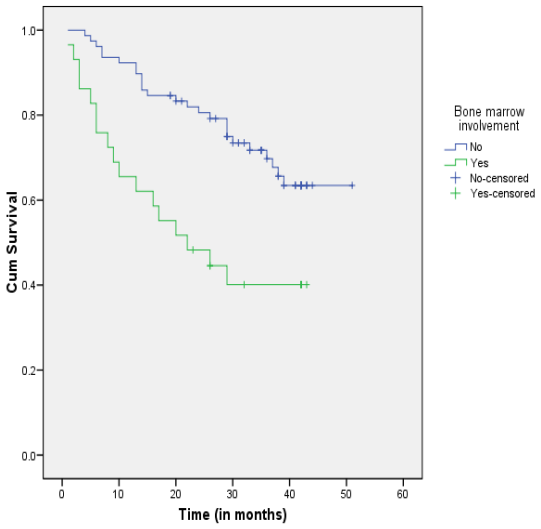

Figure 6: NHL survival by status of bone marrow involvement at the moment of diagnosis.

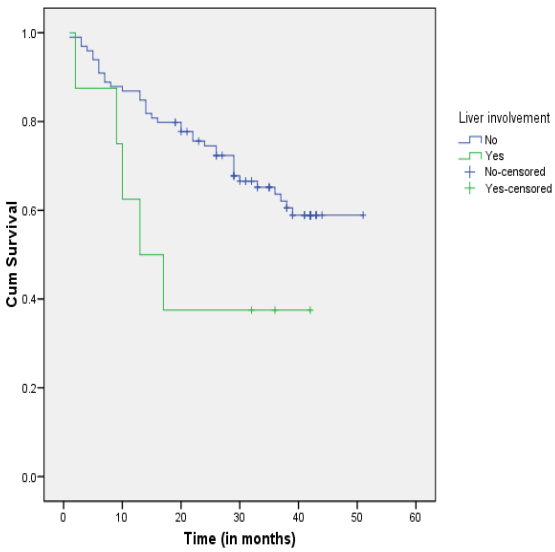

Figure 7: NHL survival by status of liver involvement at the moment of diagnosis.

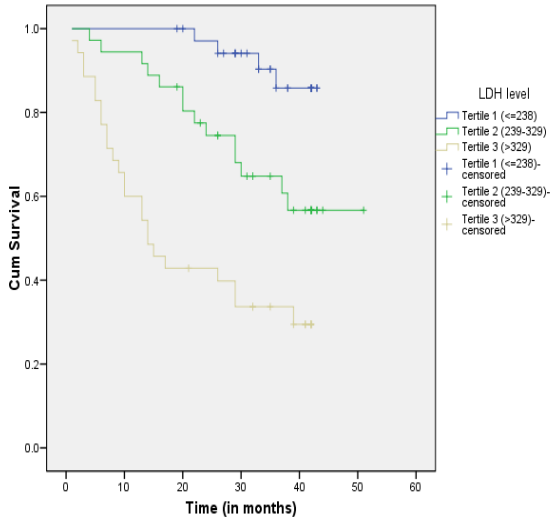

Figure 8: NHL survival by LDH level at the moment of diagnosis.

Table 2 presents information about the risk of death from NHL according to selected independent variables assessed at the time of diagnosis (initiation of treatment). The adjustment for age and sex (Model 2 in Table 2) resulted only in small changes from crude analysis (Model 1 in Table 2). The risk of dying from NHL was significantly higher among patients with performance status 4 at the time of diagnosis (HR=46.4; P<0.001), those with high grade NHL (HR=15.9; P=0.007), stage 4 NHL (HR=5.7; P=0.018), high levels of LDH (HR=11.0; P<0.001), presence of B symptoms (HR=2.9; P=0.005), and patients presenting with bone marrow involvement at the time of diagnosis (HR=2.8; P=0.001). Involvement of extranodal sites and liver at the moment of diagnosis did not increase significantly the risk of dying from NHL among our patients (Table 2).

Table 2. Risk of death from NHL according to selected independent variables; hazard ratios (OR) from Cox Regression

Variable	Unadjusted models		Multivariable-adjusted models[†]	
	HR (95% CI)[*]	P	HR (95% CI)	P
Performance status		<0.001 (3) [‡]		<0.001 (3)
ECOG 1	1.00 (reference)	-	1.00 (reference)	-
ECOG 2	4.1 (0.6-30.7)	0.167	4.2 (0.6-31.3)	0.163
ECOG 3	6.5 (0.9-49.4)	0.071	6.7 (0.9-51.5)	0.066
ECOG 4	43.2 (5.2-360.5)	**0.001**	46.4 (5.5-391.6)	**<0.001**
NHL grade		<0.001 (4)		<0.001 (4)
Low	1.00 (reference)	-	1.00 (reference)	-
Low-intermediate	3.4 (0.4-28.7)	0.269	3.7 (0.4-31.8)	0.269
Intermediate	- [¶]	-	-	-
Intermediate-high	3.6 (0.5-27.4)	0.222	3.9 (0.5-30.2)	0.222
High	12.9 (1.7-95.2)	**0.012**	15.9 (2.1-118.9)	**0.007**
NHL stage		<0.001 (3)		<0.001 (3)
Stage 1	1.00 (reference)	-	1.00 (reference)	-
Stage 2	1.8 (0.3-9.8)	0.501	1.9 (0.4-10.9)	0.429
Stage 3	1.8 (03-8.0)	0.486	1.9 (0.4-8.6)	0.429
Stage 4	5.3 (1.3-22.2)	**0.024**	5.7 (1.3-24.2)	**0.018**
LDH level		<0.001 (2)		<0.001 (2)
Tertile 1	1.00 (reference)	-	1.00 (reference)	-
Tertile 2	4.0 (1.3-12.2)	0.014	4.0 (1.3-12.2)	0.014
Tertile 3	10.8 (3.7-31.3)	**<0.001**	11.0 (3.8-32.0)	**<0.001**
B symptoms				
No	1.00 (reference)	**0.004**	1.00 (reference)	**0.005**
Yes	2.9 (1.4-6.2)		2.9 (1.4-6.1)	
Extranodal involvement				
No	1.00 (reference)	0.122	1.00 (reference)	0.119
Yes	1.6 (0.9-3.0)		1.6 (0.9-3.0)	
Liver involvement				
No	1.00 (reference)	0.065	1.00 (reference)	0.073
Yes	2.4 (0.9-6.2)		2.4 (0.9-6.1)	
Bone marrow involvement				
No	1.00 (reference)	**0.002**	1.00 (reference)	**0.001**
Yes	2.6 (1.4-4.8)		2.8 (1.5-5.1)	

[*] *HR: Risk of dying vs. being alive.*

† *This model was simultaneously adjusted for age and sex.*
‡ *Overall p-values and degrees of freedom (in parentheses).*
¶ *Insufficient number of subjects to run the analysis.*
Note: Multivariable-adjusted model is based on 2774 subjects (816 cases and 1958 controls) for whom information on all included variables was available.

4. DISCUSSION

In this work we assessed the factors associated with survival and risk of dying from NHL in a group of patients newly diagnosed in the premises of the Hematology Service at the University Hospital Center "Mother Teresa" in Tirana and followed up during 2011-2015. Our results suggest that the approximately 50 months overall survival of NHL patients was 57.2% and it reduced significantly by the presence of generally known risk factors. Conversely, we determined that the factors significantly increasing the risk of death from NHL were higher performance status, high grade and stage NHL, high LDH levels, presence of B symptoms and bone marrow involvement at the moment of diagnosis. To our knowledge, this is the first study evaluating the general profile of malignant NHL patients and exploring the factors associated with NHL survival and risk of death in Albania.

In general our findings mimic those reported by the international literature. The male dominance among NHL patients and the relatively high average of patients diagnosed with NHL mimics the results of international literature.[12,13]

In our study we noted that over two-thirds of NHL patients had intermediate-high or high grade NHL and about three-quarters had stage 3-4 NHL at the moment of diagnosis. Probably these data indicate that patients in Albania often overlook their health and contact health services when the disease has progresses considerably. We determined that both these are major prognostic and risk factors of death from NHL. The late contact of NHL patients with medical services is an issue not only in Albania because a similar situation is observed in other countries, in general. For example, a study among 168 peripheral T-cell NHL reported that about 64% of them had the disease at stage 3-4 in the moment of diagnosis,[14] and this disease stage was present in 78% of malignant NHL patients in another survey[15] and in about 80% of lymphoma patients in Europe.[16] Similarly, about 50% of NHL patients have intermediate-high or high grade disease at the moment of diagnosis or contacts with health services.[7]

In our study, about 36% of patients had a performance status of 3-4, implying the gravity of their situation as they were forced to lay down for more than 50% of the daytime or confined to bed due to the inability to take care about themselves. International literature reports various prevalence of ECOG 3-4, depending on the study population.[16,17] However, in our study all patients (100%) had a performance status of ≥1, meaning that no patient was fully active at the moment of diagnsosis, whereas 897% of patients had performance status of ≥2. Despite the variability of performance status estimations, it is clear that in Albania NHL patients are heavily neglected and they turn to medical services only when the disease has become partly or fully disabling.

The average level of LDH was very high among our patients (459.3 U/l), thus being in line with literature that suggests the increasing of LDH in malignant disease patients.[18] Also, increasing of lien dimensions is reported by the literature.[19]

Presence of B symptoms, extranodal and bone marrow involvement in a good proportion of NHL patients is supported by the literature as well, even though the variations are considerable.[7,16,17,20-22]

Factors associated with an increased risk of death from NHL and poorer NHL survival evidence in our study are in accordance with literature reports as well. For example, a study among 560 patients (68 patients with PTCL lymphoma and 492 with DLBCL lymphoma) reported that the overall 5-year survival was 39% among PTCL patients and 62% among DLBCL patients.[15] Another survey suggested an overall 5-year survival of 49% among PTCL patients, 58% among classic ALCL patients after aggressive combined therapy, 57% among small cell ALCL patients and 26% among T-cell angioimmunoblastic lymphoma patients[7] and yet another survey among 5796 patients with different types of lymphomas at the moment of diagnosis during 2004-2012 reported that 85.6% of lymphomas were NHLs and the overall 5-year survival among NHL patients was 53.7%.[12]

The association between overall survival and risk of death from NHL and disease grade has also been reported in literature.[20,23] For example, a study among T-cell NHL patients reported that patient with intermediate-high and high grade NHL had a significantly higher risk (6.7 folds and 20.2 fold higher, respectively) of dying from their lymphoma compared to low grade NHL patients.[7] We detected a very strong association between NHL grade and risk of death from NHL with high grade NHL patients having a 16 times higher risk of dying compared to low grade NHL patients.

The information about the association of risk of death from NHL and LDH level, NHL stage, extranodal involvement and performance status, evidenced in our study, is supported by the international literature as well.[8,13,17,20] A study among NHL patients reported that intermediate and high LDH level was associated with a

2.1 folds and 3.3 folds increased risk of death from NHL, respectively, compared to normal LDH level patients,[17] a finding which is similar to our results. A recent study suggested that increased LDH level is associated with a 2.52 times higher risk of death from NHL compared to normal LDH level patients.[8]

Similarly to our findings, different studies suggest that a high level of performance status (2-4) is associated with 1.9-4.36 times increased risk of death from NHL compared to patients with 0-1 level of performance status.[8,17]

Furthermore, the presence of B symptoms as a risk factor for dying from NHL is also supported by international literature; it suggests that presence of B symptoms at the moment of diagnoses increases the risk of death from NHL by 3.2 to 3.38 times compared to patient without presence of B symptoms.[24,25] High stage NHL is also a significant risk factor for dying from these diseases. International literature suggests that patients with a high stage NHL, according to Ann Arbor criteria, and extranodal involvement at the moment of diagnosis have a significantly higher risk (1.5 times higher) of death from LJH compared to low stage NHL patients and those without extranodal involvement[17] and other studies report that patients with stage 3-4 NHL have a 3.4-4.7 times higher risk of dying from NHL compared to stage 1-2 NHL patients.[8,20]

Finally, bone marrow involvement at the moment of diagnosis is associated with a 2.02 times higher risk of death from NHL compared to patients without bone marrow involvement,[8] a finding very similar to our results (bone marrow involvement is significantly associated with a 2.8 times higher risk of dying from NHL compared to patients where the bone marrow is not affected).

Limitations and strength of study

The present study has several limitations. Firstly, it might be prone to selection bias because we recruited all patients showing up at the premises of Hematology Service of Mother Teresa Hospital in Tirana and being diagnosed with NHL. However, not all patients with NHL have showed up to this health institution during the study period as some of them might not know they are already affected by the disease. Therefore, our study population might not be representative of all NHL patients in the population. Secondly, because this is a case-series study we cannot establish definitively the temporal relationships between exposure and disease. Nevertheless, the present survey has some strong points as well. To the best of our knowledge, it is the first study scientifically assessing and reporting the profile of NHL patients in Albania, their survivorship and the factors associated with survival and risk of death from NHLs in Albania. Another strong point is the very high response rate as no patient refused to participate in the study.

CONCLUSIONS

The present study has offered some novel and interesting information about NHL patients in Albania, a small country in South East Europe. The general characteristics of Albanian NHL patients and the factors associated with NHL survival and risk of death from NHL among Albanian patients are rather similar to the NHL patients in other countries and mimic those reported by the international literature, even though certain findings could indicate that Albanian patients more often overlook their disease and contact health services relatively late, when the disease has progressed considerably compromising this way its prognosis. The findings could enhance efforts to educate the public about these diseases aiming to early detection and treatment.

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Competing Interests: The authors declare that they have no competing interests.

Author’s Contributions: **AH** and **AI** designed and preformed the study; they were involved in data collection and also prepared the initial draft of the manuscript in cooperation with **ET**; **AH** and **AI** were also involved in data collection and coordination of clinical, laboratory and other patient data; **ET** was responsible for statistical analysis. All authors have contributed to the discussion and preparation of manuscript draft and have read and approved the final version of it.

REFERENCES

1. Chiu BC-H, Hou N. Epidemiology and etiology of Non-Hodgkin Lymphoma. In: Evens AM, Blum K. (eds). Non-Hodgkin Lymphoma. Pathology, imaging, and Current Therapy. Springer, 2015.
2. What Is Non-Hodgkin Lymphoma? Available at: https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/what-is-non-hodgkin-lymphoma.html. Last accessed: April 2017.
3. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016; 127(20): 2375-90.
4. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. Ca Cancer J Clin, 2016; 66(6): 443-59.
5. Evens AM, Winter JS, Gordon LI, CHI BC-H, Tsang R. Rosen ST. Non-Hodgkin Lymphoma. Available from: http://www.cancernetwork.com/cancer-

management/non-hodgkin-lymphoma. Last accessed: April 2017.
6. Zhang Y, Dai Y, Zheng T, Ma S. Risk factors of Non-Hodgkin Lymphoma. Expert Opin Med Diagn, 2011; 5(6): 539-550; Hermans J, Krol AD, van Groningen K, Kluin PM, Kluin-Nelemans JC, Kramer MH, Noordijk EM, Ong F, Wijermans PW. International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. Blood, 1995; 86(4): 1460-3.
7. Arrowsmith ER, Macon WR, Kinney MC, Stein RS, Goodman SA, Morgan DS, *et al*. Peripheral T-cell lymphomas: clinical features and prognostic factors of 92 cases defined by the revised European American lymphoma classification. Leuk Lymphoma, 2003; 44(2): 241-9.
8. Cho SF, Liu YC, Hsiao HH, Huang CT, Tsai YF, Wang HC, *et al*. Investigation on treatment strategy, prognostic factors, and risk factors for early death in elderly Taiwanese patients with diffuse large B-cell lymphoma. Sci Rep, 2017; 7: 44282.
9. Nicolaides C, Dimou S, Pavlidisa N. Prognostic Factors in Aggressive Non-Hodgkin's Lymphomas. Oncologist, 1998; 3(3): 189-97.
10. Zhang Y, Dai Y, Zheng T, Ma S. Risk factors of Non-Hodgkin Lymphoma. Expert Opin Med Diagn, 2011; 5(6):5 39-50.
11. Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, *et al*. Standard International Prognostic Index Remains a Valid Predictor of Outcome for Patients With Aggressive CD20+ B-Cell Lymphoma in the Rituximab Era. J Clin Oncol, 2010; 28(4): 2373-90.
12. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, *et al*. Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. Br J Cancer, 2015; 112(9): 1575-84.
13. Vose J, Armitage J, Weisenburger D. International T-Cell Lymphoma Project International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol, 2008; 26(25): 4124-30.
14. Ascani S, Zinzani PL,Gherlinzoni F, Sabattini E, Briskomatis A, de Vivo A, *et al*. Peripheral T-cell lymphomas. Clinico-pathologic study of 168 cases diagnosed according to the R.E.A.L. Classification. Ann Oncol, 1997; 8(6): 583-92.
15. Melnyk A, Rodriguez A, Pugh WC, Cabannillas F. Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. Blood, 1997; 89(12): 4514-20.
16. Bellei M, Chiattone CS, Luminari S, Pesce EA, Cabrera ME, de Souza CA, *et al*. T-cell lymphomas in South America and Europe. Rev Bras Hematol Hemoter, 2012; 34(1): 42-7.
17. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, *et al*. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood, 2014; 123(6): 837-42.
18. Strijk SP, Theo Wagener DJ, Bogman MJ. The spleen in Hodgkin's disease: diagnostic value of CT. Radiology, 1985; 154(3): 753–7.
19. Saboo SS, Krajewski KM, O'Regan KN, Giardino A, Brown JR, Ramaiya N, *et al*. Spleen in haematological malignancies: spectrum of imaging findings. Br J Radiol, 2012; 85(1009): 81-92.
20. Abdelhamid T, Samraa M, Ramadana H, Mehessinb M, Mokhtarc N. Clinical prognostic factors of diffuse large B cell non-Hodgkin lymhoma: A retrospective study. J Egypt Natl Canc Inst, 2011; 23(1): 17-24.
21. Das J, Ray S, Sen S, Chandy M. Extranodal involvement in lymphoma - A Pictorial Essay and Retrospective Analysis of 281 PET/CT studies. Asia Ocean J Nucl Med Biol, 2014; 2(1): 42-56.
22. Conlan MG, Bast M, Armitage JO, Weisenburger DD. Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska Lymphoma Study Group. J Clin Oncol, 1990; 8(7): 1163-72.
23. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. Br J Haematol, 2005; 129(5): 597-606.
24. Gómez H, Hidalgo M, Casanova L, Colomer R, Pen DL, Otero J, *et al*. Risk factors for treatment-related death in elderly patients with aggressive non-Hodgkin's lymphoma: results of a multivariate analysis. J Clin Oncol, 1998; 16(6): 2065-9.
25. d'Amore F, Brincker H, Grønbaek K, Thorling K, Pedersen M, Jensen MK, *et al*. Non-Hodgkin's lymphoma of the gastrointestinal tract: a population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. Danish Lymphoma Study Group. J Clin Oncol, 1994; 12(8): 1673-84.