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Factors Associated with Unresponsiveness to Treatment in Patients with Non-Hodgkin Lymphoma: 10 Years of Experience From A Single Center

Non-Hodgkin Lenfoma Hastalarında Tedaviye Yanıtsızlık ile İlişkili Faktörler: Tek Merkezden 10 Yıllık Deneyim

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ABSTRACT

Aim: To investigate factors associated with response to treatment in non-Hodgkin lymphoma (NHL) patients receiving chemo(radio)therapy, and secondarily, to identify parameters influencing mortality.

Methods: This was a retrospective single center study carried out between January 2013 and December 2022. A total of 245 patients newly diagnosed with NHL who were treated in our department were included. Clinicodemographic features, NHL characteristics, treatments and follow-up data were retrieved from the hospital database and charts. Patients were grouped as responders (RT) and non-responders (NRT) to treatment, as well as deceased (DP) and survivors (SP). Factors associated with response to treatment and mortality were determined by univariate and multivariable analysis.

Results: Age was similar in the RT (56.2 ± 14.5) and NRT (59.5 ± 13.7) groups; however, male sex was significantly more frequent in the RT group (58.1% vs. 35.71%; p = 0.042). Multiple logistic regression revealed that female sex, low performance status, frailty, high lymphocyte level, extranodal involvement, mantle cell lymphoma, thrombocytopenia during treatment, and cardiac complications during treatment were independently associated with no response to treatment. With respect to groups based on mortality, the DP group was significantly younger compared to the SP group (50.8 ± 11.7 vs. 57.1 ± 14.6; p = 0.048), while sex distribution was similar (males comprised 54.7% of the DP and 63.6% of SP group). Multiple regression showed that extranodal involvement, thrombosis during treatment, and secondary malignancy were independently associated with mortality.

Conclusion: Considering these characteristics when making treatment decisions and throughout the follow-up period may improve survival and reduce mortality in NHL.

Key Words: Non-Hodgkin lymphoma, Response to treatment, Mortality, Extranodal involvement

ÖZET

Amaç: Kemo(radyo)terapi alan non-Hodgkin lenfoma (NHL) hastalarında tedaviye yanıtla ilişkili faktörleri araştırmak ve ikincil olarak mortaliteyi etkileyen parametreleri belirlemek.

Yöntemler: Bu çalışma Ocak 2013-Aralık 2022 tarihleri arasında retrospektif tek merkezli olarak gerçekleştirilmiştir. Bölümümüzde tedavi gören yeni NHL tanısı almış toplam 245 hasta çalışmaya dahil edilmiştir. Klinikodemografik özellikler, NHL özellikleri, tedavi ve takip verileri hastane veri tabanından ve kayıtlarından elde edilmiştir. Hastalar tedaviye yanıt verenler (RT) ve yanıt vermeyenler (NRT) ile ölenler (DP) ve hayatta kalanlar (SP) olarak gruplandırılmıştır. Tedaviye yanıt ve mortalite ile ilişkili faktörler, tek değişkenli ve çok değişkenli analizlerle belirlenmiştir.

Bulgular: RT (56,2 ± 14,5) ve NRT (59,5 ± 13,7) gruplarında yaş benzerdi; ancak erkek cinsiyet RT grubunda anlamlı olarak daha sıktı (%58.1'e karşı %35.71; p = 0.042). Çoklu lojistik regresyon, kadın cinsiyet, düşük performans durumu, kırılganlık, yüksek lenfosit düzeyi, ekstranodal tutulum, mantle hücreli lenfoma, tedavi sırasında trombositopeni ve tedavi sırasında kardiyak komplikasyonların tedaviye yanıtsızlıkla bağımsız olarak ilişkili olduğunu ortaya koydu. Mortaliteye dayalı gruplara göre, DP grubu SP grubuna kıyasla anlamlı düzeyde daha gençti (50,8 ± 11,7'ye karşı 57,1 ± 14,6; p = 0,048), cinsiyet dağılımı benzerdi (erkekler DP'nin %54,7'sini ve SP'nin %63,6'sını oluşturuyordu). Çoklu regresyon, ekstranodal tutulum, tedavi sırasında tromboz ve sekonder malignitenin mortalite ile bağımsız olarak ilişkili olduğunu gösterdi.

Sonuç: NHL'de tedavi kararı verilirken ve takip süresince bu özelliklerin göz önünde bulundurulması sağkalımı artırabilir ve mortaliteyi azaltabilir.

Anahtar Kelimeler: Non-Hodgkin lenfoma, Tedaviye yanıt, Mortalite, Ekstranodal tutulum

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Introduction

Non-Hodgkin lymphoma (NHL) accounts for about 90% of all lymphomas [1]. It is the 11th most widely diagnosed cancer and 11th most common cause of cancer-related deaths in the world [2]. It is a neoplasm of the lymphoid tissues originating from B and T cell precursors and their mature forms [3]. Approximately 85-90% of NHLs are derived from B cells, while the remaining lymphomas are derived from T cells or natural killer cells [1].

NHLs demonstrate a wide spectrum of pathological characteristics, ranging from the most indolent to the most aggressive malignancies [1]. Various scoring systems have been developed to predict prognosis and make management-related decisions in patients with NHL, such as the International Prognostic Index (IPI) [4], revised-IPI (R-IPI) [5], biological marker-adjusted IPI (B-IPI) [6], the National Comprehensive Cancer Network IPI (NCCN-IPI) [7], and several specialized IPI scores for different NHL subtypes [8,9]. In addition, many independent risk factors have been identified to predict high-risk patients [10-12].

Despite advances in therapies, chemotherapy- and/or radiotherapy-resistant cases and subjects with relapse still represent a considerable proportion of the population with NHL [1]. Similar to all cancers, there is a direct relationship between survival in NHL and appropriate treatment decisions. Response to administered treatment is established as one of the most important prognostic markers associated with NHL-related survival times and mortality rates [1,13]. Therefore, for the optimal management of the disease, it is very important to define high-risk patients not responding to the treatment, before starting treatment. However, there are shortcomings in the availability of prognostic systems with sufficient accuracy to predict treatment-refractory patients. New studies and prognostic markers are needed to identify high-risk patients who are unlikely to respond to treatment [11]. While there are plenty of studies investigating prognostic factors associated with mortality and survival in NHL patients, the number of studies investigating prognostic factors in the context of treatment response is rather low [14,15]. Moreover, existing studies have investigated a limited number of factors [14,15].

Therefore, we aimed to investigate factors related to treatment response in NHL patients receiving chemo(radio) therapy and, as a secondary aim, to identify factors associated with mortality.

Material And Methods

Study design, setting and ethical issues

This was a retrospective single center study carried out at the Hematology Department of Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Turkey. The protocol for this study was approved by the local ethics committee (date: 22.02.2023, no: 2023/514/244/2). All procedures were performed according to the ethical standards laid down in the Declaration of Helsinki in its latest revision. The requirement for informed consent was waived because of the retrospective study design.

Study participants, inclusion and exclusion criteria

A total of 245 patients newly diagnosed with NHL who received treatment in our department between January 2013 and December 2022 were included in the study. Patients younger than 18 years of age, those whose treatment had not been completed, patients who did not receive treatment for NHL at our center, those undergoing surgical treatment, patients who dropped out of follow-up, those with missing relevant data, and patients who died of causes unrelated to NHL were excluded from the study.

Data collection

Patients' information at initial diagnosis, including age, sex, comorbidity status, smoking status, performance status, presence of B symptoms, blood group, tumor stage and pathology information (NHL type, extranodal involvement, lymph node involvement), R-IPI scores, laboratory results [lactate dehydrogenase (LDH), white blood cell (WBC), lymphocyte and platelet count, hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and C- reactive protein (CRP) levels)] and frailty status were recorded. Also, treatment information and data concerning the period during or after treatment, including interim controls, response to treatment, infection and febrile neutropenia status, anemia, thrombocytopenia and neutropenia status, treatment- or disease-related complications (respiratory, liver, cardiac, renal, gastrointestinal tract, neurologic, psychiatric, dermatologic, musculoskeletal, endocrinologic complications and side effects and thrombosis and severe bleeding), secondary malignancy information, follow-up information, and survival-death information were retrieved from the hospital database and patient charts.

Biochemical and pathological analyses

The blood results studied during the diagnosis process were included in the study. All measurements were made in the Clinical Chemistry Department of Kartal Dr. Lütfi Kırdar City Hospital via use of routine calibrated standard measuring devices according to the manufacturer's recommendations and international standards. Pathological analyses were performed in the Pathology Department of our hospital in accordance with the up-to-date guidelines.

Radiologic imaging

All imaging methods required for cancer diagnosis, nodal and extranodal involvement, response to treatment, secondary tumor diagnosis and complications were performed in our hospital's Radiology and Nuclear Medicine Departments in accordance with international standards using calibrated devices. Imaging with [18F] fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET) / computed tomography (CT) was performed according to the method described previously [11].

Non-Hodgkin lymphoma diagnosis and management

The diagnosis, treatment and follow-up of NHL patients throughout the 10-year study period were performed according to the most up-to-date guidelines from the European Society for Medical Oncology (ESMO) (http://www.esmo.org), National Comprehensive Cancer Network (NCCN), USA, Clinical Practice Guidelines (https://www.nccn.org), and The National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk). Clinical staging was made according to the Ann Arbor classification system [16].

Instruments and definitions

Performance status (PS) was evaluated by the Eastern Cooperative Oncology Group (ECOG) criteria [17].

The presence of B symptoms was defined as the presence of at least one of the following symptoms; unexplained fever, night sweats, and weight loss (10% in the last six months) [18].

Frailty was assessed using the FRAIL scale, a frailty tool based on 5 components (Fatigue, Resistance (inability to climb stairs), Ambulation (inability to walk a certain distance), Illnesses, and Loss of weight) recommended by The International Association of Nutrition and Aging Task Force. FRAIL scale scores range from 0–5 (i.e., 1 point for each component; 0=best to 5=worst) and the presence of frailty was defined as having 3–5 point [19].

The presence and localization of conglomerate lymph node mass (LNM) and extranodal involvement were detected by PET-CT or CT. An LNM of 7 cm or larger in radiological imaging was defined as conglomerate LNM.

The R-IPI classification was applied as previously described [5]. Briefly, the presence of 5 risk factors (age 60 years, stage III/IV disease, high LDH level, ECOG-PS ≥ 2, more than one extranodal site of disease) was investigated. The absence of any of these factors was classified as "very good", presence of 1 or 2 of them as "good", and presence of more than 2 as "poor" [5]. High LDH was defined as an LDH value of >214 U/L [20].

Responses to treatment were evaluated both in the middle (interim response) and at the end (final response) of the treatment according to the International Workshop Criteria [21] using PET/CT scans. In the interim response, grouping was done as follows: patients with stable disease or progressive disease were defined as "no response", while the other two groups were defined as "complete response" or "partial response" as appropriate, based on the definitions by the International Workshop Criteria. In the final response, the grouping was done as follows: patients with stable disease or progressive disease were defined as "non-responders (NRT)", and patients with complete or partial response were defined as "responders (RT)", again based on the International Workshop Criteria definitions [1]. Patients were also grouped according to their final status as deceased (DP) and survivors (SP).

According to the infection status during or after the treatment, the patients were grouped as no infection (no), infection not requiring treatment (mild), presence of infection requiring treatment but not requiring hospitalization (moderate), and infection requiring hospitalization (severe).

The patients were divided into 5 groups according to their anemia status during or after the treatment as absence of anemia [defined as hemoglobin levels (Hb) ≥12 g/dL [22]], 9.5 ≤ Hb <12, 8.0 ≤ Hb <9.5, 7.0 ≤ Hb <8.0, Hb <7.

Thrombocytopenia status was examined in five groups, during or after the treatment as follows: absence of thrombocytopenia [defined as absolute platelet count (APC) of ≥150000 /μL [23]], 100000 ≤ APC <150000, 50000 ≤ APC < 100000, 30000 ≤ APC < 50000, APC < 30000. Thrombocytopenia management was performed according to the recommendations by the American Society of Clinical Oncology (ASCO) [24,25].

The patients were divided into 5 groups according to their neutropenia status during or after the treatment: absence of neutropenia [defined as the absolute neutrophil count (ANC) of ≥2000 /μL], 1500 ≤ ANC <2000, 1000 ≤ ANC <1500 , 500 ≤ ANC < 1000, ANC < 500 [26]. Febrile neutropenia was defined as the combination of chemotherapy-induced neutropenia (defined as absolute neutrophil count <500 cells/μL or <1000 cells/μL with predicted decrease to <500 cells/μL) and fever (defined as single oral temperature ≥38.3 °C or ≥38.0 °C sustained over a one-hour period) [27]. Management was carried out in accordance with the recommendations of the ASCO and Infectious Diseases Society of America clinical practice guidelines [28,29].

Follow-up time (months) was calculated as the time between the date of diagnosis and the current date or date of death.

Acta Medica Alanya 2023;7(1): 66-80
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Statistical analysis

The statistical analysis of the data was performed using IBM SPSS for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The normality of variables was determined by assessing Histogram and Q-Q plots. Continuous variables were reported as either mean ± standard deviation or median (1st quartile - 3rd quartile) based on their normality, and categorical variables were presented as frequency (percentage). Depending on the normality of the distribution, Student's t-test or Mann Whitney U test was used to compare continuous variables, while categorical variables were compared using the chi-square test, Fisher's exact test, or Fisher-Freeman-Halton test. Logistic regression analysis using the forward conditional method was used to identify significant factors associated with treatment response and mortality, with the initial model including variables that were statistically significant in univariate analyses. The level of statistical significance was set at $p<0.05$.

Results

The rate of non-response to first line treatment was 11.4%. The mean age of the RT group was 56.19 ± 14.49 years, while the NRT group had a mean age of 59.50 ± 13.70 years (p = 0.254). Males represented 58.06% of the RT and 35.71% of the NRT group, and the difference in sex distribution significant (p = 0.042). The percentage of patients with diabetes (p = 0.036), an ECOG-PS of 3 (p = 0.003) and stage IV NHL (p = 0.005) was significantly higher in the NRT group. Hemoglobin level (p<0.001) and follow-up time (p<0.001) of the NRT group were significantly lower than RT. The percentages of patients with frailty (p<0.001), high LDH (p<0.001), extranodal involvement (p = 0.001), conglomerate LNM (p = 0.026), 'poor' R-IPI (p = 0.001), mantle cell lymphoma (p = 0.026), non-response at interim control (p<0.001), severe infection (p<0.001), febrile neutropenia (p<0.001), Hb <8 g/dL (p<0.001) were significantly higher in the NRT group compared to the RT group. Additionally, respiratory (p = 0.034) and cardiac (p = 0.026) complications were more common in NRT, and LDH (p<0.001) and lymphocyte (p = 0.001) levels were significantly higher in NRT (Table 1, Table 2).

The secondary malignancies that occurred were as follows: 1 lung cancer along with stomach cancer, 1 ureter cancer, 1 colon cancer along with bladder cancer and renal cell cancer, 2 malignant melanomas, 1 papillary thyroid cancer, 1 multiple myeloma, 1 colon cancer, 1 bladder cancer, 1 lung cancer, and 1 acute lymphocytic leukemia.

Multiple logistic regression analysis revealed that female sex (OR: 3.388, 95% CI: 1.060 - 10.827, p=0.039), low ECOG-PS score at diagnosis (OR: 1.898, 95% CI: 1.127 - 3.196, p=0.016), frailty at diagnosis (OR: 52.269, 95% CI: 4.096 - 667.070, p=0.002), high lymphocyte level at diagnosis (OR: 3.714, 95% CI: 1.736 - 7.948, p=0.001), extranodal involvement at diagnosis (OR: 5.010, 95% CI: 1.274 - 19.703, p=0.021), mantle cell lymphoma (OR: 7.391, 95% CI: 1.685 - 32.431, p=0.008), thrombocytopenia during treatment (OR: 1.682, 95% CI: 1.104 - 2.564, p=0.016) and cardiac complications during treatment (OR: 13.166, 95% CI: 1.348 - 128.597, p=0.027) were independently associated with non-response to treatment. Other variables included in the analysis, diabetes mellitus at diagnosis (p=0.094), stage at diagnosis (p=0.092), LDH level at diagnosis (p=0.314), hemoglobin level at diagnosis (p=0.179), conglomerate LNM (≥7 cm) at diagnosis (p=0.446), R-IPI at diagnosis (p=0.145), infection during treatment (p=0.880), febrile neutropenia during treatment (p=0.267), anemia during treatment (p=0.898) and respiratory complications during treatment (p=0.985) were found to be non-significant (Table 3).

Analyses concerning mortality showed an overall mortality rate of 8.97%. The mean age of the DP group was 50.77 ± 11.71 years, while it was 57.14 ± 14.55 years in the SP group (p = 0.048). Males represented 54.71% of the DP and 63.64% of the SP group (p = 0.563). Percentage of patients with B symptoms (p = 0.040), extranodal involvement (p = 0.005), thrombosis (p = 0.049) and secondary malignancy (p = 0.001) were significantly higher in DP compared to SP. As expected, median follow-up time of DP was significantly shorter compared to the SP group (p<0.001) (Table 4, Table 5).

Multiple logistic regression analysis revealed that extranodal involvement at diagnosis (OR: 5.534, 95% CI: 1.853 - 16.528, p=0.002), thrombosis during treatment (OR: 6.037, 95% CI: 1.291 - 28.228, p=0.022) and secondary malignancy (OR: 15.322, 95% CI: 3.915 - 59.969, p<0.001) were independently associated with mortality. Other variables included in the analysis age (p=0.058) and B symptoms at diagnosis (p=0.056) were found to be non-significant (Table 6).

Discussion

The main findings of this study demonstrate that female sex and initial findings of ECOG-PS, frailty and lymphocyte count, and the presence of extranodal involvement, mantle cell lymphoma, thrombocytopenia and cardiac complications during treatment were independent risk factors associated with non-response to treatment. Also, extranodal involvement, thrombosis during treatment and secondary malignancy were identified as independent risk factors for mortality.

Response to treatment is one of the most important prognostic markers associated with NHL-related survival times

Table 1. Summary of basic variables with regard to response to treatment

		Response to treatment		
	Total (n=245)	Yes (n=217)	No (n=28)	p
Age	56.57 ± 14.41	56.19 ± 14.49	59.50 ± 13.70	0.254
Sex				
Male	136 (55.51%)	126 (58.06%)	10 (35.71%)	**0.042**
Female	109 (44.49%)	91 (41.94%)	18 (64.29%)	
Smoking	79 (32.24%)	71 (32.72%)	8 (28.57%)	0.820
Comorbidities				
Diabetes mellitus	54 (22.04%)	43 (19.82%)	11 (39.29%)	**0.036**
Hypertension	72 (29.39%)	64 (29.49%)	8 (28.57%)	1.000
Coronary artery disease	33 (13.47%)	30 (13.82%)	3 (10.71%)	1.000
Respiratory diseases	24 (9.80%)	21 (9.68%)	3 (10.71%)	0.744
Chronic renal failure	6 (2.45%)	5 (2.30%)	1 (3.57%)	0.521
Other	15 (6.12%)	15 (6.91%)	0 (0.00%)	0.230
B symptoms	100 (40.82%)	92 (42.40%)	8 (28.57%)	0.232
ECOG performance score				
0	129 (52.65%)	120 (55.30%)	9 (32.14%)	
1	70 (28.57%)	63 (29.03%)	7 (25.00%)	
2	20 (8.16%)	17 (7.83%)	3 (10.71%)	**0.003**
3	24 (9.80%)	16 (7.37%)	8 (28.57%)	
4	2 (0.82%)	1 (0.46%)	1 (3.57%)	
Stage				
Stage I	11 (4.49%)	11 (5.07%)	0 (0.00%)	
Stage II	36 (14.69%)	36 (16.59%)	0 (0.00%)	**0.005**
Stage III	41 (16.73%)	39 (17.97%)	2 (7.14%)	
Stage IV	157 (64.08%)	131 (60.37%)	26 (92.86%)	
Blood group, ABO				
A	155 (63.27%)	138 (63.59%)	17 (60.71%)	
B	12 (4.90%)	11 (5.07%)	1 (3.57%)	0.939
AB	15 (6.12%)	13 (5.99%)	2 (7.14%)	
O	63 (25.71%)	55 (25.35%)	8 (28.57%)	
Blood group, Rh				
Rh(-)	20 (8.16%)	15 (6.91%)	5 (17.86%)	0.062
Rh(+)	225 (91.84%)	202 (93.09%)	23 (82.14%)	
Frailty	156 (63.67%)	129 (59.45%)	27 (96.43%)	**<0.001**
LDH, U/L	245 (190 - 298)	220 (187 - 285)	296.5 (266.5 - 322)	**<0.001**
High LDH (>214)	140 (57.14%)	112 (51.61%)	28 (100.00%)	**<0.001**
WBC, 10^3/uL	5.90 (4.41 - 7.32)	5.96 (4.45 - 7.33)	5.25 (4.15 - 6.78)	0.082
Lymphocyte, 10^3/µL	2.80 (2.43 - 3.30)	2.80 (2.24 - 3.20)	3.17 (2.85 - 3.68)	**0.001**
Hemoglobin, g/dL	13.0 (12.0 - 14.1)	13.2 (12.2 - 14.2)	12 (10.7 - 12.7)	**<0.001**
Platelet, 10^3/µL	209 (162 - 250)	206 (158 - 248)	209.5 (181 - 259)	0.194
AST, U/L	22 (17 - 26)	22 (17 - 26)	18 (12 - 26)	0.094
ALT, U/L	17 (14 - 24)	17 (14 - 25)	15.5 (11 - 21.5)	0.053

Acta Medica Alanya 2023;7(1): 66-80
Doi: 10.30565/medalanya.1269949

Table 1. Summary of basic variables with regard to response to treatment *(continued)*

CRP, mg/L	10.46 (5.82 - 13.74)	10.14 (4.86 - 13.98)	11.27 (9.77 - 12.56)	0.136
Extranodal involvement	27 (11.02%)	18 (8.29%)	9 (32.14%)	**0.001**
Gastric	10 (4.08%)	7 (3.23%)	3 (10.71%)	
Liver	4 (1.63%)	3 (1.38%)	1 (3.57%)	
Spleen	11 (4.49%)	6 (2.76%)	5 (17.86%)	
Esophagus	1 (0.41%)	1 (0.46%)	0 (0.00%)	
Breast	1 (0.41%)	1 (0.46%)	0 (0.00%)	
Conglomerate LNM (≥7 cm)	22 (8.98%)	16 (7.37%)	6 (21.43%)	**0.026**
R-IPI				
Very good	61 (24.90%)	61 (28.11%)	0 (0.00%)	
Good	135 (55.10%)	118 (54.38%)	17 (60.71%)	**0.001**
Poor	49 (20.00%)	38 (17.51%)	11 (39.29%)	
Diagnosis				
Diffuse large B-cell lymphoma	174 (71.02%)	157 (72.35%)	17 (60.71%)	
Mantle cell lymphoma	27 (11.02%)	18 (8.29%)	9 (32.14%)	
Follicular lymphoma	35 (14.29%)	33 (15.21%)	2 (7.14%)	
Burkitt lymphoma	1 (0.41%)	1 (0.46%)	0 (0.00%)	**0.026**
Double-hit/triple-hit lymphoma	3 (1.22%)	3 (1.38%)	0 (0.00%)	
T-cell lymphoma	5 (2.04%)	5 (2.30%)	0 (0.00%)	
Treatment				
CHOP +/- R	213 (86.94%)	188 (86.64%)	25 (89.29%)	
R-BENDA	1 (0.41%)	1 (0.46%)	0 (0.00%)	
R-PRED	0 (0.00%)	0 (0.00%)	0 (0.00%)	
DA-EPOCH +/- R	25 (10.20%)	23 (10.60%)	2 (7.14%)	0.559
R-LEN	1 (0.41%)	1 (0.46%)	0 (0.00%)	
CHOEP	2 (0.82%)	2 (0.92%)	0 (0.00%)	
CHOP +/- R & DA-EPOCH +/- R	2 (0.82%)	1 (0.46%)	1 (3.57%)	
R-PRED & DA-EPOCH +/- R	1 (0.41%)	1 (0.46%)	0 (0.00%)	

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
Abbreviations; ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CHOP +/- R: Cyclophosphamide, doxorubicin, vincristine, and prednisone +/- radiotherapy, CHOEP: Cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone, CRP: C-reactive protein, DA-EPOCH +/- R: Dose-adjusted EPOCH +/- radiotherapy, ECOG: The Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, LNM: Lymph node mass, R-BENDA: Bendamustine plus rituximab, R-IPI: Revised International Prognostic Index, R-LEN: Lenalidomide plus rituximab, R-PRED: Prednisone plus rituximab, WBC: White blood cell

Table 2. Summary of follow-up characteristics with regard to response to treatment

		Response to treatment		
	Total (n=245)	Yes (n=217)	No (n=28)	p
Interim control				
No response	13 (5.31%)	4 (1.84%)	9 (32.14%)	
Partial response	84 (34.29%)	65 (29.95%)	19 (67.86%)	**<0.001**
Complete response	148 (60.41%)	148 (68.20%)	0 (0.00%)	
Infection				
No	114 (46.53%)	107 (49.31%)	7 (25.00%)	
Mild	60 (24.49%)	56 (25.81%)	4 (14.29%)	**<0.001**
Moderate (Outpatient)	44 (17.96%)	39 (17.97%)	5 (17.86%)	
Severe (Inpatient)	27 (11.02%)	15 (6.91%)	12 (42.86%)	
Febrile neutropenia	62 (25.31%)	46 (21.20%)	16 (57.14%)	**<0.001**
Anemia				
No	68 (27.76%)	64 (29.49%)	4 (14.29%)	
9.5 < Hb <12 g/dL	116 (47.35%)	108 (49.77%)	8 (28.57%)	
8.0 ≤ Hb ≤ 9.5 g/dL	39 (15.92%)	34 (15.67%)	5 (17.86%)	**<0.001**
7.0 ≤ Hb < 8.0 g/dL	15 (6.12%)	9 (4.15%)	6 (21.43%)	
Hb <7 g/dL	7 (2.86%)	2 (0.92%)	5 (17.86%)	
Thrombocytopenia				
No	186 (75.92%)	176 (81.11%)	10 (35.71%)	
APC > 100000 /µL	29 (11.84%)	24 (11.06%)	5 (17.86%)	
50000 ≤ APC < 100000 /µL	14 (5.71%)	10 (4.61%)	4 (14.29%)	**<0.001**
30000 ≤ APC < 50000 /µL	10 (4.08%)	5 (2.30%)	5 (17.86%)	
APC < 30000 /µL	6 (2.45%)	2 (0.92%)	4 (14.29%)	
Neutropenia				
No	87 (35.51%)	81 (37.33%)	6 (21.43%)	
1500 ≤ ANC < 2000 /µL	28 (11.43%)	27 (12.44%)	1 (3.57%)	
1000 ≤ ANC < 1500 /µL	22 (8.98%)	19 (8.76%)	3 (10.71%)	0.108
500 ≤ ANC < 1000 /µL	34 (13.88%)	30 (13.82%)	4 (14.29%)	
ANC <500 /µL	74 (30.20%)	60 (27.65%)	14 (50.00%)	
Respiratory complications	68 (27.76%)	55 (25.35%)	13 (46.43%)	**0.034**
Liver complications	13 (5.31%)	11 (5.07%)	2 (7.14%)	0.649
Cardiac complications	11 (4.49%)	7 (3.23%)	4 (14.29%)	**0.026**
Renal complications	8 (3.27%)	5 (2.3%)	3 (10.71%)	0.051
Thrombosis	10 (4.08%)	9 (4.15%)	1 (3.57%)	1.000
Severe bleeding	8 (3.27%)	8 (3.69%)	0 (0.00%)	0.602
Gingiva	5 (2.04%)	5 (2.30%)	0 (0.00%)	
Epistaxis	2 (0.82%)	2 (0.92%)	0 (0.00%)	
Hemorrhoid	1 (0.41%)	1 (0.46%)	0 (0.00%)	
GIS side effect[1]	79 (32.24%)	71 (32.72%)	8 (28.57%)	0.820
Nausea/Vomiting	38 (15.51%)	32 (14.75%)	6 (21.43%)	

Acta Medica Alanya 2023;7(1): 66-80
Doi: 10.30565/medalanya.1269949

Table 2. Summary of follow-up characteristics with regard to response to treatment *(continued)*

Constipation	30 (12.24%)	29 (13.36%)	1 (3.57%)	
Diarrhea	11 (4.49%)	8 (3.69%)	3 (10.71%)	
Oral aphthae/Mucositis	10 (4.08%)	10 (4.61%)	0 (0.00%)	
Gastritis/Dyspepsia	6 (2.45%)	6 (2.76%)	0 (0.00%)	
Dysphagia/Odynophagia	4 (1.63%)	4 (1.84%)	0 (0.00%)	
Neurologic side effect(1)	65 (26.53%)	62 (28.57%)	3 (10.71%)	0.074
Neuropathy/Paresthesia	60 (24.49%)	57 (26.27%)	3 (10.71%)	
Vertigo	6 (2.45%)	6 (2.76%)	0 (0.00%)	
Headache	3 (1.22%)	3 (1.38%)	0 (0.00%)	
Psychiatric side effect(1)	10 (4.08%)	9 (4.15%)	1 (3.57%)	1.000
Insomnia	7 (2.86%)	6 (2.76%)	1 (3.57%)	
Anxiety	3 (1.22%)	3 (1.38%)	0 (0.00%)	
Amnesia	1 (0.41%)	1 (0.46%)	0 (0.00%)	
Dermatologic side effect(1)	27 (11.02%)	25 (11.52%)	2 (7.14%)	0.749
Dermatitis/Urticaria	12 (4.90%)	12 (5.53%)	0 (0.00%)	
Acne	2 (0.82%)	2 (0.92%)	0 (0.00%)	
Zoster	8 (3.27%)	6 (2.76%)	2 (7.14%)	
Cellulitis	3 (1.22%)	3 (1.38%)	0 (0.00%)	
Nail pathology	4 (1.63%)	4 (1.84%)	0 (0.00%)	
Musculoskeletal side effect	3 (1.22%)	3 (1.38%)	0 (0.00%)	1.000
Endocrinologic side effect	3 (1.22%)	3 (1.38%)	0 (0.00%)	1.000
Hypertension	1 (0.41%)	1 (0.46%)	0 (0.00%)	
Diabetes mellitus	1 (0.41%)	1 (0.46%)	0 (0.00%)	
Osteoporosis	1 (0.41%)	1 (0.46%)	0 (0.00%)	
Seconder malignancy	11 (4.49%)	10 (4.61%)	1 (3.57%)	1.000
Follow-up time, months	51 (25 - 82)	60 (31 - 87)	15 (9.5 - 37)	**<0.001**
Final status				
Alive	223 (91.02%)	200 (92.17%)	23 (82.14%)	0.149
Deceased	22 (8.98%)	17 (7.83%)	5 (17.86%)	

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
(1) Patients may have more than one of the followings.
Abbreviations; ANC: Absolute neutrophil count, APC: Absolute platelet count, GIS: Gastrointestinal system, Hb: Hemoglobin

Table 3. Significant factors independently associated with non-response to treatment, multiple logistic regression analysis

	β coefficient	Standard error	p	Exp(β)	95% CI for Exp(β)	
Sex, Female	1.220	0.593	0.039	3.388	1.060	10.827
ECOG performance score	0.641	0.266	0.016	1.898	1.127	3.196
Frailty	3.956	1.299	0.002	52.269	4.096	667.070
Lymphocyte, 10^3/uL	1.312	0.388	0.001	3.714	1.736	7.948
Extranodal involvement	1.611	0.699	0.021	5.010	1.274	19.703
Diagnosis, Mantle cell lymphoma	2.000	0.754	0.008	7.391	1.685	32.431
Thrombocytopenia	0.520	0.215	0.016	1.682	1.104	2.564
Cardiac complications	2.578	1.163	0.027	13.166	1.348	128.597
Constant	-12.080	2.289	<0.001			

Nagelkerke R^2=0.574
Abbreviations; CI: Confidence Interval, ECOG: The Eastern Cooperative Oncology Group

Table 4. Summary of basic variables with regard to mortality

	Final status		
	Alive (n=223)	Deceased (n=22)	p
Age, years	57.14 ± 14.55	50.77 ± 11.71	**0.048**
Sex			
Male	122 (54.71%)	14 (63.64%)	0.563
Female	101 (45.29%)	8 (36.36%)	
Smoking	72 (32.29%)	7 (31.82%)	1.000
Comorbidities			
Diabetes mellitus	48 (21.52%)	6 (27.27%)	0.590
Hypertension	69 (30.94%)	3 (13.64%)	0.146
Coronary artery disease	32 (14.35%)	1 (4.55%)	0.326
Respiratory diseases	22 (9.87%)	2 (9.09%)	1.000
Chronic renal failure	6 (2.69%)	0 (0.00%)	1.000
Other	15 (6.73%)	0 (0.00%)	0.374
B symptoms	86 (38.57%)	14 (63.64%)	**0.040**
ECOG performance score			
0	117 (52.47%)	12 (54.55%)	0.908
1	64 (28.70%)	6 (27.27%)	
2	19 (8.52%)	1 (4.55%)	
3	21 (9.42%)	3 (13.64%)	
4	2 (0.90%)	0 (0.00%)	
Stage			
Stage I	11 (4.93%)	0 (0.00%)	0.190
Stage II	34 (15.25%)	2 (9.09%)	
Stage III	40 (17.94%)	1 (4.55%)	
Stage IV	138 (61.88%)	19 (86.36%)	
Blood group, ABO			

Acta Medica Alanya 2023;7(1): 66-80
Doi: 10.30565/medalanya.1269949

Table 4. Summary of basic variables with regard to mortality *(continued)*

A	142 (63.68%)	13 (59.09%)	0.620
B	12 (5.38%)	0 (0.00%)	
AB	14 (6.28%)	1 (4.55%)	
O	55 (24.66%)	8 (36.36%)	
Blood group, Rh			
Rh(-)	18 (8.07%)	2 (9.09%)	0.697
Rh(+)	205 (91.93%)	20 (90.91%)	
Frailty	142 (63.68%)	14 (63.64%)	1.000
LDH, U/L	245 (190 - 298)	236.5 (187 - 308)	0.981
High LDH (>214)	127 (56.95%)	13 (59.09%)	1.000
WBC, 10^3/uL	5.90 (4.39 - 7.32)	6.14 (5.33 - 7.33)	0.516
Lymphocyte, 10^3/ µL	2.80 (2.41 - 3.25)	2.86 (2.65 - 3.46)	0.149
Hemoglobin, g/dL	13.0 (12.0 - 14.1)	13.05 (10.8 - 14.1)	0.490
Platelet, 10^3/ µL	206 (158 - 248)	236 (175 - 299)	0.184
AST, U/L	22 (17 - 26)	18.5 (16 - 25)	0.082
ALT, U/L	17 (14 - 24)	16.5 (14 - 25)	0.727
CRP, mg/L	10.62 (5.82 - 13.90)	9.59 (5.74 - 12.18)	0.281
Extranodal involvement	20 (8.97%)	7 (31.82%)	**0.005**
Gastric	7 (3.14%)	3 (13.64%)	
Liver	3 (1.35%)	1 (4.55%)	
Spleen	8 (3.59%)	3 (13.64%)	
Esophagus	1 (0.45%)	0 (0.00%)	
Breast	1 (0.45%)	0 (0.00%)	
Conglomerate LNM (≥7 cm)	21 (9.42%)	1 (4.55%)	0.703
R-IPI			
Very good	59 (26.46%)	2 (9.09%)	0.155
Good	119 (53.36%)	16 (72.73%)	
Poor	45 (20.18%)	4 (18.18%)	
Diagnosis			
Diffuse large B-cell lymphoma	158 (70.85%)	16 (72.73%)	0.526
Mantle cell lymphoma	24 (10.76%)	3 (13.64%)	
Follicular lymphoma	33 (14.8%)	2 (9.09%)	
Burkitt lymphoma	1 (0.45%)	0 (0.00%)	
Double-hit/triple-hit lymphoma	2 (0.90%)	1 (4.55%)	
T-cell lymphoma	5 (2.24%)	0 (0.00%)	
Treatment			
CHOP +/- R	196 (87.89%)	17 (77.27%)	0.410
R-BENDA	1 (0.45%)	0 (0.00%)	
R-PRED	0 (0.00%)	0 (0.00%)	
DA-EPOCH +/- R	20 (8.97%)	5 (22.73%)	
R-LEN	1 (0.45%)	0 (0.00%)	
CHOEP	2 (0.90%)	0 (0.00%)	
CHOP +/- R & DA-EPOCH +/- R	2 (0.90%)	0 (0.00%)	
R-PRED & DA-EPOCH +/- R	1 (0.45%)	0 (0.00%)	

Table 4. Summary of basic variables with regard to mortality *(continued)*

Interim control			
No response	11 (4.93%)	2 (9.09%)	
Partial response	75 (33.63%)	9 (40.91%)	0.334
Complete response	137 (61.43%)	11 (50.00%)	

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Abbreviations; ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CHOP +/- R: Cyclophosphamide, doxorubicin, vincristine, and prednisone +/- radiotherapy, CHOEP: Cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone, CRP: C-reactive protein, DA-EPOCH +/- R: Dose-adjusted EPOCH +/- radiotherapy, ECOG: The Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, LNM: Lymph node mass, R-BENDA: Bendamustine plus rituximab, R-IPI: Revised International Prognostic Index, R-LEN: Lenalidomide plus rituximab, R-PRED: Prednisone plus rituximab, WBC: White blood cell

Table 5. Summary of follow-up characteristics with regard to mortality

	Final status		
	Alive (n=223)	Deceased (n=22)	p
Infection			
No	101 (45.29%)	13 (59.09%)	
Mild	57 (25.56%)	3 (13.64%)	0.110
Moderate (Outpatient)	38 (17.04%)	6 (27.27%)	
Severe (Inpatient)	27 (12.11%)	0 (0.00%)	
Febrile neutropenia	58 (26.01%)	4 (18.18%)	0.583
Anemia			
No	65 (29.15%)	3 (13.64%)	
9.5 < Hb <12 g/dL	105 (47.09%)	11 (50.00%)	
8.0 ≤ Hb ≤ 9.5 g/dL	34 (15.25%)	5 (22.73%)	0.166
7.0 ≤ Hb < 8.0 g/dL	14 (6.28%)	1 (4.55%)	
Hb <7 g/dL	5 (2.24%)	2 (9.09%)	
Thrombocytopenia			
No	171 (76.68%)	15 (68.18%)	
APC > 100000 /µL	25 (11.21%)	4 (18.18%)	
50000 ≤ APC < 100000 /µL	13 (5.83%)	1 (4.55%)	0.532
30000 ≤ APC < 50000 /µL	9 (4.04%)	1 (4.55%)	
APC < 30000 /µL	5 (2.24%)	1 (4.55%)	
Neutropenia			
No	79 (35.43%)	8 (36.36%)	
1500 ≤ ANC < 2000 /µL	24 (10.76%)	4 (18.18%)	
1000 ≤ ANC < 1500 /µL	20 (8.97%)	2 (9.09%)	0.832
500 ≤ ANC < 1000 /µL	32 (14.35%)	2 (9.09%)	
ANC <500 /µL	68 (30.49%)	6 (27.27%)	
Respiratory complications	63 (28.25%)	5 (22.73%)	0.762
Liver complications	13 (5.83%)	0 (0.00%)	0.614
Cardiac complications	10 (4.48%)	1 (4.55%)	1.000
Renal complications	8 (3.59%)	0 (0.00%)	1.000
Thrombosis	7 (3.14%)	3 (13.64%)	**0.049**
Severe bleeding	7 (3.14%)	1 (4.55%)	0.534

Acta Medica Alanya 2023;7(1): 66-80
Doi: 10.30565/medalanya.1269949

Table 5. Summary of follow-up characteristics with regard to mortality *(continued)*

Gingiva	4 (1.79%)	1 (4.55%)	
Epistaxis	2 (0.90%)	0 (0.00%)	
Hemorrhoid	1 (0.45%)	0 (0.00%)	
GIS side effect(1)	71 (31.84%)	8 (36.36%)	0.846
Nausea/Vomiting	35 (15.70%)	3 (13.64%)	
Constipation	27 (12.11%)	3 (13.64%)	
Diarrhea	10 (4.48%)	1 (4.55%)	
Oral aphthae/Mucositis	8 (3.59%)	2 (9.09%)	
Gastritis/Dyspepsia	6 (2.69%)	0 (0.00%)	
Dysphagia/Odynophagia	2 (0.90%)	2 (9.09%)	
Neurologic side effect(1)	58 (26.01%)	7 (31.82%)	0.737
Neuropathy/Paresthesia	55 (24.66%)	5 (22.73%)	
Vertigo	4 (1.79%)	2 (9.09%)	
Headache	2 (0.90%)	1 (4.55%)	
Psychiatric side effect(1)	8 (3.59%)	2 (9.09%)	0.223
Insomnia	6 (2.69%)	1 (4.55%)	
Anxiety	2 (0.90%)	1 (4.55%)	
Amnesia	1 (0.45%)	0 (0.00%)	
Dermatologic side effect(1)	26 (11.66%)	1 (4.55%)	0.483
Dermatitis/Urticaria	11 (4.93%)	1 (4.55%)	
Acne	2 (0.90%)	0 (0.00%)	
Zoster	8 (3.59%)	0 (0.00%)	
Cellulitis	3 (1.35%)	0 (0.00%)	
Nail pathology	4 (1.79%)	0 (0.00%)	
Musculoskeletal side effect	3 (1.35%)	0 (0.00%)	1.000
Endocrinologic side effect	2 (0.9%)	1 (4.55%)	0.247
Hypertension	1 (0.45%)	0 (0.00%)	
Diabetes mellitus	0 (0.00%)	1 (4.55%)	
Osteoporosis	1 (0.45%)	0 (0.00%)	
Seconder malignancy	6 (2.69%)	5 (22.73%)	**0.001**
Follow-up time, months	60 (29 - 88)	16.5 (11 - 37)	**<0.001**
Response to treatment			
Yes	200 (89.69%)	17 (77.27%)	0.149
No	23 (10.31%)	5 (22.73%)	

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
(1) Patients may have more than one of the following.
Abbreviations; ANC: Absolute neutrophil count, APC: Absolute platelet count, GIS: Gastrointestinal system, Hb: Hemoglobin

Table 6. Significant factors independently associated with mortality, multiple logistic regression analysis

	β coefficient	Standard error	p	Exp(β)	95% CI for Exp(β)	
Extranodal involvement	1.711	0.558	**0.002**	5.534	1.853	16.528
Thrombosis	1.798	0.787	**0.022**	6.037	1.291	28.228
Seconder malignancy	2.729	0.696	**<0.001**	15.322	3.915	59.969
Constant	-3.052	0.332	<0.001			

Nagelkerke R^2=0.207
Abbreviations; CI: Confidence Interval.

and mortality rates [1]. Patients with primary resistant or recurrent aggressive lymphomas have poor prognosis. Over 50% of patients with diffuse large B-cell lymphoma relapse within two years of diagnosis [15]. Therefore, predicting patients who will not respond to chemo(radio) therapy will allow the application of different or additional treatment strategies for these patients, and thus, will make significant contributions to the improvement of mortality rates and survival times in NHL. Our results showed that female sex, low ECOG-PS score, presence of frailty and high lymphocyte count (at baseline), and the presence of extranodal involvement, mantle cell lymphoma, thrombocytopenia and cardiac complications (during treatment) were poor prognostic factors independently associated with unresponsiveness to treatment. In one study, advanced disease was shown to be a risk factor for recurrent or resistant disease in patients with gastrointestinal NHL (GISNHL) [14]. Provencio et al. reported that C-MYC mRNA positivity in pretreatment samples was a significant predictor of poor progression-free survival and absence of complete response to first-line treatment [15]. In another study, patients with relapsed or refractory NHL with low or low-intermediate IPI score had higher overall response rate to the salvage chemotherapy than patients with high or high-intermediate IPI score –although the difference was not significant. Also, older patients (over 60 years) had significantly lower overall response rate than younger patients [30]. A significant relationship between pretreatment albumin level and survival has been suggested, but such a relationship was not found between pretreatment albumin level and response to treatment [31]. Another important issue is when to start treatment after diagnosis and to determine the patients who need urgent treatment. Drawing attention to this issue, Olszewski et al., in their comprehensive retrospective study of patients with aggressive lymphoma, reported that the time elapsing between diagnosis and treatment may be a significant factor which cannot be identified by standard prognostic assessments [32]. We believe that the risk factors identified in this study should be considered in future studies in order to assess their validity. Also, it may be possible to suggest that patients with these risk factors should be followed more carefully in terms of response to treatment.

NHL-related mortality has an important share in cancer-related deaths. Death from NHL itself, from NHL treatment, and from second primary tumors are all relevant problems today, and the assessment of these features is a major challenge. Conventional factors, such as Ann Arbor stages and extranodal involvement, as well as other factors in IPI scores are still important predictors of clinical outcome [33]. Considering the length of the study period, we also aimed to investigate risk factors associated with NHL-related mortality as a secondary analysis. The only factors independently associated with mortality were extranodal involvement, thrombosis development during treatment, and secondary malignancies. In a study involving patients with primary pulmonary lymphoma (PPL), 78.9% of whom were NHL, it was found that older age (>60 years), elevated LDH and β2-microglobulin levels, clinical stage (II2E disease or higher), and nonsurgical treatment were associated with poor prognosis, but age was the only independent prognostic factor for PPL [10]. Multivariable analysis from one study revealed that bone marrow involvement (defined on ^{18}F-FDG PET/CT), IPI, metabolic tumor volume and elevated LDH were independent predictors for progression free survival. Furthermore, the same study reported that bone marrow involvement, SUVmax value and metabolic tumor volume were independent predictors of overall survival [11]. In another study, it was shown that high LDH levels, poor PS, advanced staging, and malignant pathological type were independent predictors of survival outcomes [12]. Shannon et al. showed that female sex, gastric localization, follicular or mantle cell histology, and radiation therapy were associated with improved survival in patients with primary GISNHL [34]. Wang and colleagues reported that increased pretreatment CRP and higher NCCN-IPI scores were independent predictors for overall survival and progression-free survival. In this study, age (>60 years), extranodal involvement ≥2, higher LDH concentration or higher IPI scores were not associated with survival in multivariable analysis [33]. In a review, the following were identified as clinically significant prognostic markers for pediatric B-cell NHL: central nervous system involvement at diagnosis, elevated LDH, cytogenetic factors, stage, and poor response after pre-phase chemotherapy [35]. Jiang and colleagues reported that age (>60

Acta Medica Alanya 2023;7(1): 66-80
Doi: 10.30565/medalanya.1269949

years), male sex, and ≥3 involved nodal sites were independent prognostic factors associated with survival in NHL patients with multiple primary malignant tumors [36]. The most important reason for this diversity of risk factors in the literature is probably the differences in patient characteristics. Additionally, the majority of studies investigated risk factors in a specific region or specific type of NHL. In this context, the inclusion of patients with all NHL subtypes and regions in our study may make the results more comprehensive. Nonetheless, considering the results of this study and the large variations in the literature, it is evident that there is a need for new comprehensive studies that include patients with all NHL subtypes.

Although NHL usually involves lymph nodes, it also may occur in any tissue [11]. About half of the patients develop extranodal lymphoma (secondary extranodal disease); whereas, between 10 and 35% of patients have primary extranodal lymphoma at the time of diagnosis [3]. It is very important to demonstrate the presence of extra-lymphatic involvement which can affect therapeutic decision-making [37]. One of the most striking results in the present study is possibly the identification of extranodal involvement as an independent risk factor for both treatment response and mortality. In the present study, extranodal involvement was determined in 11.02% of patients. Given this high rate and its established negative impact on NHL prognosis, the importance of developing treatment protocols specific to the management of patients with extranodal involvement becomes apparent. On the other hand, the most common location of primary extranodal disease is reported as the gastrointestinal tract [3]. In our study, the most common extranodal disease was found in the spleen (4.49%), followed by the gastrointestinal system (4.08%). The reason for this difference may be that many researchers consider spleen as nodal disease [3].

Some limitations of the study should be noted. Firstly, this is a retrospective and single-center study spanning 10 years, throughout which definitions, classifications, management and options for treatment have evolved. This not only limits the assessment of newer data / markers of interest, but also leads to potential bias. Despite being a limitation in and of itself, it is important to mention that the most current guidelines were used for the treatment each patient; thus, this was an unavoidable limitation. Consequently, in relation with aforementioned concerns and the low number of cases with mortality, we did not perform detailed survival analyses. Secondly, due to the difficulties in accessing data and insufficient data, the distinction between treatment-related mortality and NHL-related mortality could not be made, and therefore, these results could not be presented. Thirdly, prognostic factors associated with response to treatment and/or mortality may vary depending on the localization of the tumor, its type, and the treatment protocol applied (both initial and salvage therapy). However, these were not analyzed due to the difficulties in obtaining reliable data. Finally, the short follow-up period of some patients may have affected mortality rates, thereby impacting mortality-related findings.

In conclusion, in patients with NHL, we found that female sex, low performance status, frailty, high lymphocyte count (all analyzed at baseline) and extranodal involvement, mantle cell lymphoma, thrombocytopenia and cardiac complications (at follow-up) were independently associated with non-response to treatment. Extranodal involvement, thrombosis at follow-up, and secondary malignancy were independent risk factors for mortality. Considering these characteristics when making treatment decisions and throughout the follow-up period may have a positive impact on survival and mortality in patients with NHL.

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Ethics Committee Approval: The protocol for this study was approved by the local ethics committee (Kartal Dr. Lütfi Kırdar City Hospital, Clinical Research Ethics Committee; date: 22.02.2023, no: 2023/514/244/2). All procedures were performed according to the ethical standards laid down in the Declaration of Helsinki in its latest revision.

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