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Determination of Serum Interleukin-36 Alpha, Beta, Gamma, and Interleukin-17 Levels in Patients with Non-Hodgkin Lymphoma

Non-Hodgkin Lenfoma'lı Hastaların Serum İnterlökin-36 Alfa, Beta, Gamma ve İnterlökin-17 Düzeylerinin Belirlenmesi

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ABSTRACT

Aim: Non-Hodgkin lymphoma (NHL) is a diverse group of hematologic cancers characterized by uncontrolled proliferation of lymphoid cells. This study aimed to evaluate the relationship between serum concentrations of interleukin-36 alpha (IL-36α), interleukin-36 beta (IL-36β), interleukin-36 gamma (IL-36γ), and interleukin-17 (IL-17), which play an important role in the immune system, in NHL patients and whether these cytokines can serve as potential biomarkers or therapeutic targets for NHL.

Material and Methods: A total of 88 individuals, including 55 NHL patients diagnosed and followed up in the Department of Hematology, Sivas Cumhuriyet University Medical Faculty, and 33 healthy controls, were included in the study. Blood samples were collected from patients at the time of diagnosis and from individuals in the control group for hemogram and biochemistry tests and serum IL-17, IL-36α, IL-36β, and IL-36γ levels. Patients were divided into three groups, complete remission (CR), partial remission (PR), and progression according to interim positron emission tomography/computed tomography (PET/CT) results.

Results: Serum IL-36α ($p<0.001$), IL-36β ($p=0.022$), IL-36γ ($p<0.001$), and IL-17 ($p<0.001$) concentrations were statistically significantly higher in NHL patients compared to healthy controls. Although IL-17, IL-36α, IL-36β, and IL-36γ levels were lower in patients with progression compared to the CR and PR groups, these differences were not statistically significant ($p=0.065$, $p=0.186$, $p=0.151$, and $p=0.065$, respectively).

Conclusion: These cytokines may influence the etiopathogenesis and even the progression of NHL. However, since NHL constitutes a highly heterogeneous disease group, more extensive in-vivo and in-vitro studies are needed.

Keywords: Interleukin; non-Hodgkin lymphoma; therapeutic targets.

ÖZ

Amaç: Non-Hodgkin lenfoma (NHL), lenfoid hücrelerin kontrolsüz çoğalmasıyla tanımlanan çeşitli bir hematolojik kanser grubudur. Bu çalışmanın amacı, NHL hastalarında immün sistemde önemli bir rol oynayan interlökin-36 alfa (IL-36α), interlökin-36 beta (IL-36β), interlökin-36 gama (IL-36γ) ve interlökin-17 (IL-17) serum konsantrasyonları arasındaki ilişkiyi ve bu sitokinlerin NHL için potansiyel biyobelirteçler veya tedavi hedefleri olarak hizmet edip edemeyeceğini değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Hematoloji bölümünde tanı almış ve takip edilmiş 55 NHL hastası ve 33 sağlıklı kontrol olmak üzere toplam 88 birey dahil edildi. Hastaların tanı anındaki ve kontrol grubundaki bireylerin hemogram ve biyokimya tetkikleri ile serum IL-17, IL-36α, IL-36β ve IL-36γ düzeylerinin çalışılması için kan örnekleri alındı. Hastalar interim pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) sonuçlarına göre komplet remisyon (CR), parsiyel remisyon (PR) ve progresyon olmak üzere üç gruba ayrıldı.

Bulgular: Serum IL-36α ($p<0,001$), IL-36β ($p=0,022$), IL-36γ ($p<0,001$) ve IL-17 ($p<0,001$) konsantrasyonları NHL hastalarında sağlıklı kontrollere kıyasla istatistiksel olarak anlamlı derecede daha yüksekti. Progresyon gösteren hastalarda IL-17, IL-36α, IL-36β ve IL-36γ düzeyleri CR ve PR gruplarına göre daha düşük olmasına rağmen bu farklar istatistiksel olarak anlamlı değildi (sırasıyla $p=0,065$; $p=0,186$; $p=0,151$ ve $p=0,065$).

Sonuç: Bu sitokinler NHL'nin etyopatogenezi ve hatta progresyonu üzerinde etkili olabilir. Ancak, NHL oldukça heterojen bir hastalık grubunu oluşturduğundan, daha geniş kapsamlı in-vivo ve in-vitro çalışmalara ihtiyaç vardır.

Anahtar kelimeler: İnterlökin; non-Hodgkin lenfoma; terapötik hedefler.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) encompasses diverse malignancies originating from lymphoid tissues. NHL are among the most prevalent cancers worldwide and represent a broad spectrum of malignancies derived from lymphoid tissue. This category encompasses around 60 subtypes with clinical and biological profiles (1). While precise classification of NHL subtypes is essential for accurate diagnosis and effective treatment, conducting risk assessments specific to each subtype poses significant difficulties. These challenges arise from the limited number of cases and the relative rarity of each subtype (2). Interleukin-36 (IL-36) is a pro-inflammatory cytokine that is part of the interleukin-1 (IL-1) superfamily, consisting of three agonists (IL-36α, IL-36β, IL-36γ) and one antagonist (IL-36Ra) (3). IL-36 activates the MAPK and NF-kB pathways, essential in innate and adaptive immunity. It is primarily expressed at barrier sites such as the bronchial, intestinal, and dermal epithelium, linking innate and adaptive immune responses. IL-36 is associated with various inflammatory conditions and cancer (4). Interleukin-17 (IL-17), mainly produced by Th17 cells, has a multifaceted role in cancer progression. It supports tumor growth by enhancing angiogenesis, cell proliferation, and metastasis and inhibiting apoptosis (5). The network of cytokines plays a crucial role in the development and progression of these lymphomas by affecting both tumor growth and the immune response (6). Cytokines such as IL-36α, IL-36β, IL-36γ, and IL-17 are known to be involved in various inflammatory and autoimmune disorders (7). Despite their significant roles in these conditions, their specific contributions to NHL are poorly understood. This study sought to evaluate the serum levels of IL-36α, IL-36β, IL-36γ, and IL-17 in patients with NHL and to investigate their potential associations with disease features and outcomes.

MATERIAL AND METHODS

The single-center, multidisciplinary, and cross-sectional study project was conducted by the Department of Internal Medicine, Hematology Division, and the Department of Medical Biochemistry at Sivas Cumhuriyet University Medical Faculty Hospital, and commenced following the approval from Sivas Cumhuriyet University Clinical Research Ethics Committee, dated September 12, 2023, with decision number 2023-09/03.

Study Groups

Patients diagnosed with NHL according to the 2016/2022 lymphoma classification of the World Health Organization (WHO), and histopathologically confirmed, not receiving any NHL treatment, aged 18 years and over and admitted to the Hematology Department of the Sivas Cumhuriyet University, Faculty of Medicine Hospital between February 6, 2022, and February 6, 2023, were included in the study as the patient group. As the control group, healthy individuals had a similar mean age to the patient group were included. Patients with known additional hematological malignancies and healthy individuals with any hematological or rheumatological diseases were excluded from the study. Also, the presence of any known acute and/or chronic disease, having a solid and/or hematological malignancy, regular medication use, pregnancy, breastfeeding, or smoking were additional exclusion criteria for healthy individuals. Based on this framework, adjustments to the number of patients and healthy individuals included in the study were deemed necessary. For the sample calculation, it was decided to include 56 patients in the NHL group and 34 people in the control group by taking $\alpha=0.05$, $\beta=0.10$, $(1-\beta)=0.90$, and $R=1.62$ with the Epi Info 7.2.6.0 program. One person in each patient and control group was excluded from the study due to insufficient data. The study finally involved 88 participants, comprising 55 individuals with NHL and 33 healthy controls. These participants' comprehensive clinical, laboratory, and imaging data were retrieved from patient records. For NHL patients, venous blood samples were collected at the time of diagnosis before initiating any treatment. Serum levels of IL-36α, IL-36β, IL-36γ, and IL-17 were quantified in both NHL patient and healthy control groups. The clinical data and performance status of the patients at the time of diagnosis were recorded during their first admission, and the routine biochemical test results were accessed through the automation system.

Patients diagnosed with NHL were grouped according to histologic subtypes. Patients were classified according to the Ann-Arbor staging system based on positron emission tomography/computed tomography (PET/CT) imaging at the time of diagnosis. According to the treatment response evaluation based on the Lugano revised response criteria, patients were categorized into three groups, complete response (CR), partial response (PR), and progression at the interim PET evaluation.

Sample Collection and Cytokine Measurement

Peripheral blood was collected from new patients diagnosed with NHL and healthy controls. Blood samples were drawn into appropriate tubes for measuring IL-36α, IL-36β, IL-36γ, IL-17 levels, and other laboratory parameters. The collected blood samples were centrifuged at 4000 G for 10 minutes and stored at -80°C in Eppendorf tubes for the measurement of IL-36α, IL-36β, IL-36γ, and IL-17, SunRed brand enzyme-linked immunosorbent assay (ELISA) kits were used.

Statistical Analysis

Data analysis was conducted using IBM SPSS v.26.0, with a confidence level set at 95%. The Kolmogorov-Smirnov test assessed whether the data followed a normal distribution. Since the data were not normally distributed, the Mann-Whitney U test was used for two-group comparisons, and the Kruskal-Wallis H test was used for more than two-group comparisons. Descriptive statistics of the median, 25^{th}-75^{th} percentiles, minimum, and maximum were calculated for the measurements and frequency and percentages for the categorical variables.

RESULTS

Demographic and Clinical Characteristics

Out of 55 NHL patients, 22 (40%) were female, 33 (60%) were male. There were 33 individuals in the control group, of whom 20 (60.6%) were female and 13 (39.4%) were male. The median age of individuals in the patient group was 65 (range, 34-88) years, while the median age in the control group was 53 (range, 37-63) years. While the gender was homogeneously distributed between the two groups ($p=0.052$), the patient group with NHL had a higher median age ($p=0.001$).

Out of 55 patients histologically diagnosed with NHL, except for one with NK/T-cell lymphoma, the rest were classified as B-cell lymphomas according to cell origin. Among these, diffuse large B-cell lymphoma (DLBCL) was the most common histopathologic subtype with a frequency of 65.5% (n=36). The other histological subtypes were follicular lymphoma (FL) with 16.4% (n=9), mantle cell lymphoma (MCL) with 12.7% (n=7), and marginal zone lymphoma (MZL) with 3.6% (n=2). The distribution of histopathological subtypes and the treatment protocols applied to the patients were presented in Table 1.

Comparison of Cytokine Levels and Laboratory Parameters

Serum levels of the IL-36α ($p<0.001$), IL-36β ($p=0.022$), IL-36γ ($p<0.001$), and IL-17 ($p<0.001$) were significantly elevated in NHL patients compared to healthy controls. In comparing laboratory data between the patient and control groups, statistically significant differences were observed in white blood cells ($p=0.005$), neutrophils ($p=0.001$), lymphocytes ($p=0.002$), monocytes ($p=0.001$), and hemoglobin ($p=0.015$) values. The comparison results of the hemogram parameters and IL-17, IL-36α, IL-36β, and IL-36γ levels between the patient and control groups were presented in Table 2. In the patient group, when laboratory parameters and IL-17, IL-36α, IL-36β, and IL-36γ levels were compared by gender, statistically significant differences were found between the two groups for hemoglobin and creatinine values. Hemoglobin ($p=0.001$), and creatinine ($p=0.009$) levels were significantly higher in males compared to females (Table 3).

Comparison Based on Clinical Parameters

Patients were classified into three groups (CR, PR, and progression) based on the interim PET results during the first-line treatment. There were 40 patients in the CR group, 10 in the PR group, and 5 in the progression group. When IL-17, IL-36α, IL-36β, and IL-36γ levels were compared according to the interim PET/CT responses, no statistically significant differences were observed. The comparison of interleukin levels according to interim PET/CT results was presented in Table 4. The levels of IL-17 and IL-36γ were found to be considerably lower in the progression group compared to the other groups, however, this difference was not statistically significant.

Table 1. Histopathologic subtypes of patients and treatments

	n=55
Subtype, n (%)	
DLBCL	36 (65.5)
FL	9 (16.4)
MCL	7 (12.7)
MZL	2 (3.6)
TL	1 (1.8)
First-Line Treatment, n (%)	
CHOP	1 (1.8)
R-Bendamustine	3 (5.5)
R-Bendamustine + Rituximab Maintenance	5 (9.1)
R-CHOP	22 (40.0)
R-CHOP + Intrathecal Methotrexate	9 (16.4)
R-CHOP/R-DHAP Protocol	6 (10.9)
R-CNOP	2 (3.6)
R-CVP + Rituximab Maintenance Therapy	1 (1.8)
R-EPOCH	1 (1.8)
R-EPOCH + Intrathecal Methotrexate	1 (1.8)
R-MiniCHOP	3 (5.5)
No Therapy	1 (1.8)
Second-Line Treatment, n (%)	
DeAngelis protocol (8)	1 (1.8)
R-DHAP	4 (7.3)
R-ICE	2 (3.6)
Rituximab-Ibrutinib	2 (3.6)
R-VCD	1 (1.8)
Radiotherapy	1 (1.8)
Third-Line Treatment, n (%)	
Autologous Stem Cell Transplant	7 (12.7)
Lenalidomide + Obinutuzumab	1 (1.8)
Fourth-Line and Beyond Treatment, n (%)	
R-GemOx	1 (1.8)

DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, MCL: mantle cell lymphoma, MZL: marginal zone lymphoma, TL: T-cell lymphoma, R: rituximab, CHOP: cyclophosphamide- doxorubicin- vincristine- prednisone, DHAP: dexamethasone- cytarabine- cisplatin, CNOP: cyclophosphamide- mitoxantrone- vincristine- prednisone, CVP: cyclophosphamide- vincristine- prednisone, EPOCH: etoposide- prednisone- vincristine- cyclophosphamide- doxorubicin, ICE: ifosfamide- carboplatin- etoposide, VCD: bortezomib- cyclophosphamide- dexamethasone, GemOx: gemcitabine- oxaliplatin

Table 2. Comparison of hemogram and interleukin values between patient and healthy groups

	Patient (n=55)	**Control (n=33)**	**p**
WBC (10^9/L)	7.78 (6.29-10.30) [1.87-34.65]	6.45 (5.43-7.41) [3.81-10.59]	**0.005**
Neu (10^9/L)	5.39 (3.50-6.84) [0.04-13.11]	3.46 (2.69-4.60) [2.02-6.82]	**0.001**
Lymp (10^9/L)	1.48 (0.99-2.25) [0.31-20.44]	2.16 (1.73-2.58) [1.15-3.08]	**0.002**
Mono (10^9/L)	0.57 (0.46-0.92) [0.10-1.77]	0.47 (0.36-0.56) [0.30-0.83]	**0.001**
Hgb (g/dL)	13.2 (11.5-14.6) [7.2-17.0]	13.9 (13.1-15.4) [10.4-16.7]	**0.015**
Plt (10^9/L)	255 (200-327) [34-829]	291 (245-342) [188-409]	0.115
Cre (mg/dL)	0.83 (0.67-1.03) [0.31-6.88]	0.76 (0.64-0.88) [0.50-1.16]	0.063
LDH (U/L)	240 (185-343) [128-1340]	167 (153-181) [124-242]	**<0.001**
IL-17 (pg/ml)	111.5 (90.4-138.4) [15.0-819.1]	298.3 (136.6-607.7) [70.9-1000.0]	**<0.001**
IL-36α (ng/L)	11.99 (9.18-15.77) [0.27-57.77]	23.44 (12.57-41.31) [5.36-73.97]	**<0.001**
IL-36β (ng/L)	6.27 (4.94-8.22) [0.17-39.32]	14.57 (5.42-27.33) [1.92-55.50]	**0.022**
IL-36γ (ng/L)	5.57 (4.63-6.80) [0.23-34.51]	12.97 (7.31-36.77) [4.30-59.94]	**<0.001**
Age (year)	65 (52-73) [34-88]	53 (51-57) [37-63]	**0.001**

WBC: white blood cell, Neu: neutrophil, Lymp: lymphocyte, Mono: monocyte, Hgb: hemoglobin, Plt: platelet, Cre: creatinine, LDH: lactate dehydrogenase, IL: interleukin, IL-17: interleukin-17, IL-36α: interleukin-36 alpha, IL-36β: interleukin-36 beta, IL-36γ: interleukin-36 gamma

Table 3. Comparison of hemogram and interleukin values between genders in the patient group

	Female (n=22)	Male (n=33)	p
WBC (10^9/L)	8.30 (6.23-11.20) [1.87-16.64]	7.58 (6.22-9.36) [3.22-34.65]	0.437
Neu (10^9/L)	5.56 (3.22-8.01) [0.04-10.31]	5.30 (3.69-6.35) [2.38-13.11]	0.618
Lymp (10^9/L)	1.47 (0.66-2.99) [0.31-7.90]	1.51 (1.07-2.09) [0.53-20.44]	0.979
Mono (10^9/L)	0.52 (0.45-0.74) [0.10-1.77]	0.63 (0.50-0.95) [0.28-1.72]	0.120
Hgb (g/dL)	11.7 (10.0-13.8) [7.2-15.2]	13.8 (12.5-15.3) [8.0-17.0]	**0.001**
Plt (10^9/L)	274 (201-430) [34-543]	245 (192-293) [48-829]	0.213
Cre (mg/dL)	0.64 (0.55-0.96) [0.31-6.88]	0.92 (0.78-1.10) [0.54-1.44]	**0.009**
LDH (U/L)	259 (183-478) [128-926]	240 (191-326) [143-1340]	0.594
IL-17 (pg/ml)	114.5 (93.2-267.3) [57.4-819.1]	106.5 (84.3-130.4) [15.0-794.1]	0.192
IL-36α (ng/L)	11.87 (10.16-27.95) [6.84-57.77]	12.16 (8.97-15.27) [0.27-53.24]	0.303
IL-36β (ng/L)	6.12 (4.92-13.89) [3.13-37.98]	6.27 (4.74-8.03) [0.17-39.32]	0.718
IL-36γ (ng/L)	5.85 (4.57-11.89) [3.05-34.51]	5.37 (4.47-6.57) [0.23-32.57]	0.405
Age (year)	57 (47-71) [34-86]	63 (56-73) [34-88]	0.191

WBC: white blood cell, Neu: neutrophil, Lymp: lymphocyte, Mono: monocyte, Hgb: hemoglobin, Plt: platelet, Cre: creatinine, LDH: lactate dehydrogenase, IL: interleukin, IL-17: interleukin-17, IL-36α: interleukin-36 alpha, IL-36β: interleukin-36 beta, IL-36γ: interleukin-36 gamma

Table 4. Comparison of hemogram and interleukin values according to the interim PET results in the patient group

	CR (n=40)	PR (n=10)	Progression (n=5)	p
WBC (10^9/L)	7.82 (6.34-9.51) [1.87-16.55]	7.45 (4.98-11.02) [3.22-34.65]	7.53 (6.97-13.37) [6.94-16.64]	0.812
Neu (10^9/L)	5.55 (3.63-6.82) [0.04-10.31]	3.77 (1.92-6.65) [1.38-13.11]	5.42 (4.97-9.39) [4.55-9.71]	0.305
Lymp (10^9/L)	1.44 (0.97-2.19) [0.50-7.35]	1.94 (1.26-4.86) [0.83-20.44]	1.07 (0.36-3.91) [0.31-5.66]	0.203
Mono (10^9/L)	0.56 (0.46-0.81) [0.25-1.72]	0.61 (0.45-0.97) [0.31-1.51]	0.56 (0.29-1.39) [0.10-1.77]	0.909
Hgb (g/dL)	12.8 (11.2-14.6) [7.2-17.0)	13.5 (11.7-14.3) [8.0-15.7]	12.4 (10.8-15.5) [9.9-16.6]	0.940
Plt (10^9/L)	264 (224-341) [34-650]	174 (128-204) [49-829]	279 (221-369) [173-411]	**0.010**
Cre (mg/dL)	0.82 (0.67-1.02) [0.31-6.88]	0.90 (0.74-1.08) [0.55-1.17]	0.84 (0.69-2.55) [0.59-4.18]	0.842
LDH (U/L)	230 (186-337) [128-1340]	263 (177-330) [143-380]	455 (197-692) [180-926]	0.495
IL-17 (pg/ml)	109.8 (90.4-145.8) [15.0-819.1]	120.7 (103.3-201.9) [86.9-521.7]	77.7 (60.6-107.1) [57.4-111.5]	0.065
IL-36α (ng/L)	12.07 (9.17-16.01) [0.27-57.77]	14.37 (10.19-19.71) [9.08-34.25]	10.33 (6.71-11.85) [6.58-12.76]	0.186
IL-36β (ng/L)	6.13 (4.96-8.67) [0.17-39.32]	7.01 (5.71-11.87) [4.55-22.05]	4.33 (3.02-6.55) [1.80-7.28]	0.151
IL-36γ (ng/L)	5.73 (4.32-7.14) [0.23-34.51]	6.27 (5.16-12.14) [4.94-15.24]	4.67 (2.62-5.30) [2.20-5.72]	0.065

PET: positron emission tomography, CR: complete remission, PR: partial remission, WBC: white blood cell, Neu: neutrophil, Lymp: lymphocyte, Mono: monocyte, Hgb: hemoglobin, Plt: platelet, Cre: creatinine, LDH: lactate dehydrogenase, IL: interleukin, IL-17: interleukin-17, IL-36α: interleukin-36 alpha, IL-36β: interleukin-36 beta, IL-36γ: interleukin-36 gamma

A total of 14 patients received second-line treatment, including 5 patients who progressed according to interim PET/CT results and 9 patients who experienced treatment failure based on PET/CT evaluation at the end of first-line therapy. Following second-line treatment, 7 (12.7%) patients underwent autologous stem cell transplantation (Table 1).

Survival Status

When evaluating NHL patients' survival status, 34 (61.8%) were alive, while 21 (38.2%) had exitus. As of July 2024, a reassessment of the patients revealed that out of 55 patients, 21 had deceased, while 34 were alive. It was determined that all 34 surviving patients were in remission. Among the deceased, 6 patients had achieved a CR response in the interim PET evaluation. However, 1 patient died due to pulmonary thromboembolism, 1 due to liver failure, and 4 due to febrile neutropenia and sepsis. The remaining 15 deceased patients were found to have died from non-treatment-related causes such as cerebrovascular disease, respiratory failure, myocardial infarction, and traffic accidents.

DISCUSSION

Non-Hodgkin lymphomas (NHLs) represent a diverse collection of malignancies that arise from lymphoid tissue, consisting of around 60 distinct subtypes, each exhibiting different clinical and biological characteristics (9). NHL is a heterogeneous group of tumors caused by the malignant transformation of mature and immature cells of the lymphoid system, primarily originating from B lymphocytes (in 85-90% of cases) and, to a lesser extent, from T lymphocytes and natural killer (NK) cells. NHL is an extremely heterogeneous group of diseases, with the clinical courses and treatment responses of different subtypes varying significantly (10).

Recent studies have explored the role of interleukins in lymphomas and other cancers. IL-36, comprising three subforms (α, β, γ), has been implicated in chronic inflammation and cancer, activating various immune and non-immune cells (11). IL-36 cytokines belong to the IL-1 family and have various roles in inflammatory diseases and cancer. A meta-analysis indicated that elevated IL-36α expression correlates with improved overall survival in

cancer patients, while the effect of IL-36γ differs depending on the type of cancer. IL-36 signaling promotes pro-tumorigenic characteristics in colon cancer cells, and the administration of IL-36R antagonists has been shown to reduce tumor burden in vivo (12,13). In multiple myeloma, serum levels of the IL-36α, IL-36β, IL-36γ, and IL-17 were significantly lower in patients than in healthy controls, suggesting a potential role in the disease's etiopathogenesis (14). In non-small cell lung cancer, IL-36γ expression was higher in tumor tissues than adjacent normal tissues, with elevated protein levels associated with higher tumor grade in lung adenocarcinoma (15). IL-17 plays a crucial role in cancer progression, especially in lung, colorectal, and breast cancers. IL-17 facilitates tumor angiogenesis, cell proliferation, and metastasis while suppressing apoptosis through inflammatory signaling pathways (5,16). The role of IL-17 in cancer is multifaceted, with some evidence indicating possible antitumor effects during cancer therapies (17).

Among NHL patients included in the present study, significant differences were observed in hemoglobin levels and monocyte counts between those who survived and those who did not. Based on existing literature, we believe these hematological parameters may impact the prognosis of the disease (18,19).

These findings highlight the complex roles of interleukins in various cancers and their potential as prognostic markers or therapeutic targets. In the present study, IL-17 and IL-36α, IL-36β, and IL-36γ levels were found higher in NHL patients compared to the control group, suggesting that these interleukins may play a role in the etiopathogenesis of NHL. However, during interim evaluations of patients undergoing treatment, it was noted that IL-17 and IL-36γ levels were markedly lower in the progression group compared to those who achieved CR or PR. Although this difference was not statistically significant, it is considered a noteworthy finding.

NHL represents a heterogeneous group of diseases with various subtypes characterized by distinct clinical courses and biological features. This heterogeneity can lead to different responses to treatment and varying prognoses across subtypes (1,2). Therefore, future studies involving larger cohorts of NHL patients with more homogenous distribution are needed to clarify the potential prognostic impact of IL-17 and IL-36 levels on disease progression.

Previous studies have shown that IL-17 and IL-36 have diverse roles in different types of cancer, influencing tumor development, progression, and response to therapy with both tumor-promoting and anti-tumor effects. Based on the findings of the present study, it can be suggested that IL-17 and IL-36α, IL-36β, and IL-36γ may play a role in the etiopathogenesis and prognosis of NHL. However, it is important to acknowledge that the heterogeneity of the NHL and the limited sample size may have influenced the results.

CONCLUSION

Further comprehensive in vivo and in vitro studies are necessary to better understand the roles of IL-17 and IL-36 in the pathogenesis and prognosis of NHL. These interleukins hold promise as potential therapeutic targets, and future research should focus on investigating their utility as biomarkers for cancer diagnosis, prognosis, and treatment strategies.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Cumhuriyet University (12.09.2023, 09/03).

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