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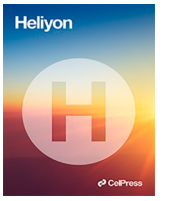

Research article

The effect of *leptin* gene polymorphisms (*LEP* rs7799039 and *LEPR* rs1137101) on febrile neutropenia

Ezgi Paslı Uysalol [a], Metin Uysalol [b], Istemi Serin [c,*], Mustafa Pehlivan [d], Yasemin Oyaci [e], Sacide Pehlivan [e], Zeynep Karakas [f]

[a] *Basaksehir Cam and Sakura City Hospital, Department of Pediatric Hematology- Oncology, Turkey*
[b] *Istanbul University, Istanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Emergency, Turkey*
[c] *Agri Training and Research Hospital, Department of Hematology, Turkey*
[d] *Basaksehir Cam and Sakura City Hospital, Department of Hematology, Turkey*
[e] *Istanbul University, Istanbul Faculty of Medicine, Department of Medical Biology and Genetics, Turkey*
[f] *Istanbul University, Istanbul Faculty of Medicine, Department of Pediatric Hematology- Oncology, Turkey*

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ABSTRACT

Background and aim: Leptin is mainly produced in adipose tissue and released into systemic circulation. Leptin and its receptor LEPR activate the Janus kinase/signal transducers and activators of transcription signaling cascade and increase cytokine discharge. In our study, we aimed to examine the role of *leptin* gene (*LEP*) rs7799039 and LEPR rs1137101 polymorphisms on the susceptibility for febrile neutropenia (FEN) attacks and their relationship with clinical findings during the course of FEN.

Methods: This study included pediatric patients with a diagnosis of malignancy who applied to the pediatric emergency department between December 2019 and June 2022 and healthy controls. The genotypes of the *LEP* rs7799039 and *LEPR* rs1137101 genes were statistically compared between patients and healthy controls. In addition, the relationship between the genotype distribution of *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms and clinical features during the course of FEN was investigated.

Results: In the statistical analysis in terms of *LEP* rs7799039 and *LEPR* rs1137101 genotype distributions between the patient and healthy groups, there was no significant difference. Patients with the AA genotype of *LEPR* rs1137101 polymorphism had significantly more commonly a body mass index (BMI) value of <25, and all the patients with the AG/GG genotype had a BMI value of 25 and above. *LEP* rs7799039 and *LEPR* rs1137101 genotype distributions were not statistically significant with other clinical features.

Conclusions: It was revealed that leptin gene polymorphisms did not have a significant effect during the course of FEN.

1. Introduction

Leptin is mainly produced in adipose tissue and released into systemic circulation. Circulating leptin levels also change in direct

* Corresponding author. Agri Training and Research Hospital, Department of Hematology, Cevre Yolu üzeri Sucatagi mevki, 04200 Merkez/Agri, Turkey.
E-mail address: serinistemi@hotmail.com (I. Serin).

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proportion to the size of adipose tissue and form a cranial positive feedback [1,2]. Leptin expression and circulating leptin levels show circadian alterations and vary with nutritional status [1,2]. The *leptin* gene (*LEP*) in humans is located on chromosome 7q31.3 and consists of three exons separated by two introns [1,2]. There are many studies conducted on the relationship between *LEP* variants and obesity. Among the variants studied, a common single nucleotide polymorphism (*LEP* rs7799039) identified in the *LEP* is the most studied [1–4].

Leptin exerts its metabolic effects through its specific receptors. Circulating leptin binds to the leptin receptor (LEPR) in the brain, which activates signaling pathways that inhibit feeding and promote calorie expenditure. The leptin receptor (*LEPR*, also known as *Ob-R*) gene is located at 1p31 [1,2].

Besides its defined functions, leptin also bridges the gap between nutritional status and the immune system. It shows structural similarity with cytokines such as interleukin (IL)-6, IL-11, IL-12 granulocyte-colony stimulating factor, which are members of the leptin cytokine family [5,6]. Because of these structural similarities, leptin can be called an "adipokine" [5]. Leptin and its receptor LEPR activate the Janus kinase/signal transducers and activators of transcription signaling cascade and increase cytokine discharge [7]. Leptin and its effects on the immune system can be examined in Table 1 [8–17]. *LEP* polymorphisms and their effect on infections is a relatively new research area.

Many studies have been conducted in recent years to reveal the role of adipokines. Leptin plays a key role in immune modulation such as activation of phagocytosis, cytokine polarization and cell-mediated immunity in infectious diseases [5]. The mechanism of leptin's effects on immune system is complex; because leptin receptor has several isoforms generated though alternative splicing. Genetic mutations in both the leptin gene and the gene for leptin receptor have been described, and these genetic variants cause similar phenotypes in terms of immune response [18]. It has been observed that systemic leptin levels exhibit significant variation during periods of cytopenia and febrile neutropenia, which occur as side effects of chemotherapy in patients with malignant diseases. It has also been noted that acute infections may lead to an increase in leptin levels, although this effect can be mitigated by the presence of underlying general diseases, which are often associated with malnutrition. Therefore, it has been concluded that acute infections do not lead to substantial changes in these patients [19].

In our study, we aimed to examine the role of *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms on the susceptibility for febrile neutropenia (FEN) attacks and their relationship with risk scores, clinical findings during the course of FEN in pediatric patients.

2. Material and methods

2.1. Subjects, inclusion and exclusion criteria and clinical data

This study included pediatric patients with a diagnosis of malignancy who applied to the pediatric emergency department between December 2019 and June 2022 and healthy controls. Inclusion criteria of 123 patients with a diagnosis of malignancy and FEN were and fever on the day of inclusion or the previous day. Thirteen patients were excluded from the study due to the inability to obtain DNA from the sample. The control group consisted of volunteers with the same ethnicity, age and gender, no active infection, and no consanguinity. A total of 110 patients with FEN and 93 healthy controls were included in this study.

The patients and healthy controls were matched in terms of age, gender, and ethnic background. In addition to demographic data such as age and gender at the time of diagnosis, body mass indexes (BMIs), the malignancy subtypes, the number of FEN attacks encountered during the treatment of malignancy, the subtypes of infections (microbiologically or clinically documented infections such as respiratory tract, soft tissue, gastrointestinal, central nervous system or fever unknown origin), subtypes of growths in the blood cultures and FEN-related mortality were recorded.

BMI was calculated by taking patients' weight, in kilograms (kg), divided by their height, in meters squared (BMI = weight (in kilogram)/height2 (in square meter)) [20].

FEN was defined based on criteria as follows: Having an absolute neutrophil count (ANC) of <500 neutrophils/mm3 or an ANC of <1000 neutrophils/mm3 and a predicted decline of ≤ 500 neutrophils/mm3 over the next 48 h as well as a temperature of ≥ 38.3 or ≥ 38 °C for longer than 1 h either prior to admission or during hospitalization [21]. The Multinational Association of Supportive Care of Cancer (MASCC) risk-index score was calculated with 7 independent factors (burden of illness, blood pressure, presence or absence of chronic obstructive pulmonary disease, solid tumor or hematological malignancy with or without a history of previous fungal

Table 1
Adipokine effects of leptin on immune system: Innate and adaptive immunity.

Innate immunity	
Neutrophils	Induction of activation, chemotaxis and phagocytosis
Monocytes/Macrophages	Induction of pro-inflammatory cytokine production, phagocytosis, antigen presentation, and inflammation
Natural Killer Cells	Induction of perforin production, IL-2 production, and cytotoxicity
Dendritic Cells	Induction of activation, IL-12 production
Adaptive immunity	
Th1-cells	Induction of stimulation, interferon-gamma and tumor necrosis-alpha production
Th2-cells and Tregs	Inhibition, induction of IL-4 and IL-10 production
Cytotoxic T-cells	Induction of activation and proliferation, granzyme production
Memory T-cells	Induction of proliferation
Th: T helper, IL: Interleukin	

infection, dehydration, inpatient or outpatient status at the time of onset of FEN, and age) recorded in the case of FEN; patients with a score of ≥21 were considered as low risk; patients with a score of <21 were considered as high risk [22,23].

The genotypes of the *LEP* rs7799039 and *LEPR* rs1137101 genes were statistically compared between patients and healthy controls. In addition, the relationship between the genotype distribution of *LEP* rs7799039 and *LEPR* rs1137101 and clinical features during the course of FEN was investigated.

2.2. DNA isolation and genotype analysis

Leukocytes were isolated from the blood collected from the individuals participating in the study, and from the obtained leukocytes, genomic DNA was isolated according to the manufacturer's instructions. (Quick-DNA Miniprep Plus Kit, Zymo Research). In this study, genotyping of *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms was performed by polymerase chain reaction (PCR)-restriction fragment length polymorphism method. For *LEP* rs7799039 polymorphism, the primary sequence was F:5′-TTTCCTGTAATTTTCCCGTGAG-3′ and R:5′-AAAGCAAAAGACAGGCATA AAAA-3′, while it was F: 5′-GCCTAATCCAGTATTTTA-TATCTG-3′, R: 5′GCCACTCTTAATACCCCCCAGTAC- 3′ for *LEPR* rs1137101 polymorphism. *Hha*I restriction enzyme was used for *LEP* rs7799039, while *Msp*I enzyme was used for *LEPR* rs1137101 [7,8]. Genotyping analyses were performed by visualizing the samples carried out in agarose gel electrophoresis under UV light. *LEP* rs7799039 genotypes were GG: 242, GA: 242, 181, 61, and AA: 181, 61 bp. *LEPR* rs1137101 genotypes were AA: 416 bp, AG: 416, 229, 187 bp, and GG: 229, 187 bp (Fig. 1(A and B)).

2.3. Statistics

IBM SPSS Statistics for Windows 21.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The descriptive statistics were expressed as the mean, standard deviation, median, minimum, and maximum for the continuous variables after assessing their normality, while frequency and percentage were used to express the nominal variables. The Pearson chi-square test or Fisher exact test was used to compare the discrete variables, and Bonferroni correction was used in the pairwise comparisons to determine which group or groups showed statistically significant results. Multivariate binary logistic regression analyses were performed to determine the association between different variants of the genes with the study parameters. The results were adjusted for age and sex. Consequently, the odds ratio (OR) and 95% confidence interval (CI) were used to express the association of the gene variants with the study parameters. The Hardy Weinberg equilibrium (HWE) was calculated using the De-Finetti program (online HWE and Association Testing - Institut für Humangenetik, Munich, Germany). Statistical significance was accepted as $p < 0.05$ in all the analyses. The effect size was determined as 0.63%. The power of the study with an alpha of 0.05 was calculated as 94%.

2.4. Results

A total of 110 patients with FEN and 93 healthy controls were included in this study. The median age of the patients was 50 months (range: 2–210). The number of patients who had severe attacks was 19 (17.3%). The most common malignancy was solid cancers with 29 patients (26.4%), while the number of patients with non-solid malignancies was 81 (73.6%). The most frequently documented subtype of infections were respiratory tract and soft tissue infections, the most frequent growths were gram-positive pathogens (Table 2).

In the statistical analysis in terms of *LEP* rs7799039 and *LEPR* rs1137101 genotype distribution between the patient and healthy groups, there was no significant difference ($p > 0.05$ for all) (Table 3). There found to be no association between *LEP* rs7799039 and *LEPR* rs1137101 genotypes and FEN susceptibility.

Statistical analyses performed to examine the relationship between clinical features and gene variant distributions were shown in Table 4 and Table 5. While there was no relationship between the *LEPR* rs1137101 genotype distribution and clinical features, it was observed that the patients with the AA genotype had significantly more commonly a BMI value of <25, and all the patients with the AG/GG genotype had a BMI value of 25 and above ($p = 0.018$, OR: 0.684, 95% CI: 0.598–0.782). *LEP* rs7799039 genotype distribution was not statistically significant with clinical features; it was also revealed that there was no significant difference in terms of BMI

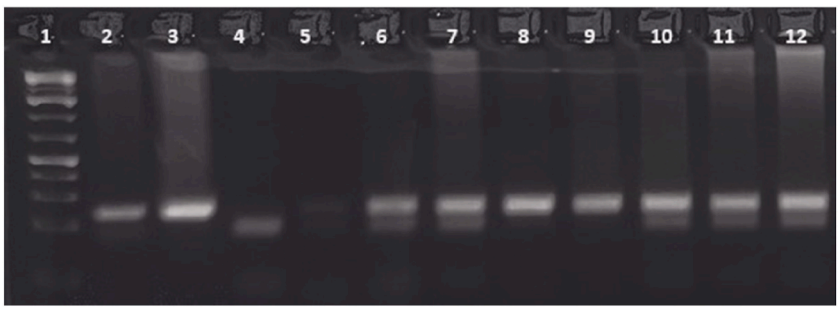

Fig. 1 (A). PCR-RFLP products of *LEP* rs7799039 polymorphism on 2.5% agarose gel (Hha1 restriction endonuclease)
Line 1: Ladder, **Line 2:** Non-digest PCR product, **Lines 3, 8, 9:** GG, **Line 4:** AA, **Lines 5, 6, 7, 10, 11, 12:** GA.

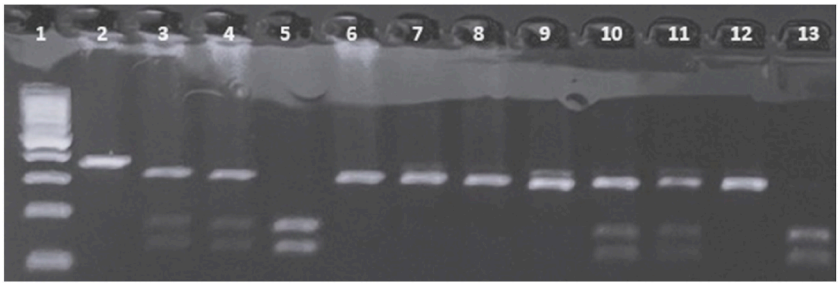

Fig. 1 (B). PCR-RFLP products *LEPR* rs1137101polymorphism on 2.5% agarose gel (Msp1 restriction endonuclease)
Line 1: Ladder**, Line 2:** Non-digest PCR product**, Lines 3, 4, 10, 11:** AG**, Lines 5, 13:** GG**, Lines 6, 7, 8, 9, 12:** AA.

Table 2
Demographic and clinical of FEN patients.

		FEN n = 110	n (%)	Healthy controls n = 93	n (%)	P
		median		median		
Age (months)		50 (2–210)		**45 (14–196)**		**0.618**[c]
Gender	Female		38 (34.5)		27 (29)	**0.452**[b]
	Male		72 (65.5)		66 (71)	
BMI	**<25**	**18 (10–31)**	**12 (10.9)**	17 (11–29) [∞]	**7 (7.5)**	**0.309**[a]
FEN						
	Number of FEN attacks	5 (3–42)				
MASCC scores	High risk		19 (17.3)			
	Low risk		91 (82.7)			
	Fever duration (days)	2 (1–14)				
Diagnosis	Solid		29 (26.4)			
	Adenocarcinoma		1			
	Neuroblastoma		12			
	Osteosarcoma		2			
	Rhabdomyosarcoma		4			
	Ewing Sarcoma		4			
	Dysgerminoma		1			
	LCH		3			
	Wilms		2			
	Non-solid		81 (73.6)			
	Lymphoma		7			
	ALL		64			
	AML		10			
Clinically documented infections			20 (18.2)			
	Respiratory		9			
	Soft tissue infections		9			
	Gastrointestinal		1			
	CNS		1			
Bloodstream			12 (10.9)			
	Gram (−)		1			
	Gram (+)		9			
	Candida		2			
Mortality			3 (2.7)			

FEN: Febrile neutropenia, BMI: Body mass index, MASCC score: The Multinational Association of Supportive Care of Cancer score, LCH: Langerhans cell histiocytosis, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, CNS: Central nervous system.
[∞] median.
[a] :OR (95%CI) was adjusted by age and sex.
[b] Fisher's Exact Test.
[c] Median Test.

distribution ($p > 0.05$, for all).

3. Discussion

In this study, we revealed the role of *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms on FEN attack susceptibility and their relationship with the clinical features of FEN in pediatric patients with malignancy. There was no significant difference between patients and healthy controls in terms of *LEP* rs7799039 and *LEPR* rs1137101 genotype distribution. The patients with the AA genotype of *LEPR* rs1137101 polymorphism had significantly more a BMI value of <25, and all the patients with the AG/GG genotype

Table 3
Comparison of the genotype distribution of ***LEP*** rs7799039 and *LEPR* rs1137101 polymorphisms between patients with FEN and healthy controls.

	Genotype	FEN	Healthy Control	OR Exp(B)	95% CI	p
		n = [a] (%)	n = 93 (%)			
***LEP* rs7799039**	AA	21 (19.1)	13 (14.0)	0.594[b]	0.257–1.373[b]	0.223[b]
	GA	53 (48.2)	44 (47.3)	0.829[b]	0.448–1.531[b]	0.548[b]
	GG	36 (32.7)	36 (38.7)	0.595[c]	0.328–1.077[c]	0.097[c]
HWEp		**0.386170**	**0.197034**			
***LEPR* rs1137101**	AA	79 (71.8)	59 (63.5)	0.704[b]	0.115–1.691[b]	0.224[b]
	AG	27 (24.5)	26 (28.0)	0.998[b]	0.151–2.463[b]	0.488[b]
	GG	4 (3.6)	6 (6.5)	0.712[c]	0.221–2.293[c]	0.564[c]
HWEp		**0.849396**	**0.939412**			

[a] n = 110.
[b] :OR (95%CI) was adjusted by age and sex.
[c] Fisher's Exact Test, HWE (Hardy Weinberg Equilibrium).

Table 4
Comparison of the genotype distribution of *LEPR* rs1137101 polymorphism between clinical features during the course of FEN.

		LEPR rs1137101		OR Exp (B)	95% CI	p[b]
		AA n = 79 (%)	AG/GG n[a] (%)			
Diagnosis	**Solid**	22 (27.8)	11 (35.5)			
	Non-solid	57 (72.2)	20 (64.5)	0.709[b]	0.290–1.731[b]	0.450[b]
MASCC score	**High risk**	27 (34.2)	12 (38.7)			
	Low risk	52 (65.8)	19 (61.3)	0.790[b]	0.328–1.900[b]	0.598[b]
Clinically documented infections	**(+)**	17 (21.5)	9 (29)			
	(−)	62 (78.5)	17 (71)	0.624[b]	0.236–1.649[b]	0.341[b]
Bloodstream infection	**(+)**	7 (8.9)	5 (16.1)			
	(−)	72 (92.1)	26 (83.9)	0.436[b]	0.120–1.586[b]	0.208[b]
BMI	**<25**	12 (15.1)	0 (0)			
	≥25	67 (84.9)	31 (100)	0.684[c]	0.598–0.782[c]	**0.018**[c]

[a] n = 31.
[b] :OR (95%CI) was adjusted by age and sex.
[c] Fisher's Exact Test.

Table 5
Comparison of the genotype distribution of ***LEP*** rs7799039 polymorphism between clinical features during the course of FEN.

		LEP rs7799039		OR Exp (B)	95% CI	p[b]
		GA/AA=74 (%)	**GG n[a] (%)**			
Diagnosis	**Solid**	26 (35.1)	10 (27.8)			
	Non-solid	51 (64.9)	26 (72.2)	0.843[b]	0.343–2.070*	0.709[b]
MASCC score	**High risk**	24 (32.4)	15 (41.7)			
	Low risk	50 (67.6)	21 (58.3)	1.310[b]	0.559–3.068[b]	0.534[b]
Clinically documented infections	**(+)**	13 (17.6)	13 (36.1)			
	(−)	61 (82.4)	23 (63.9)	2.336[b]	0.991–5.943[b]	0.075[b]
Bloodstream infection	**(+)**	8 (10.8)	4 (11.1)			
	(−)	66 (89.2)	32 (88.9)	0.754[b]	0.197–2.893[b]	0.681[b]
BMI	**<25**	9 (12.1)	3 (8.3)			
	≥25	65 (87.9)	33 (91.7)	0.618[b]	0.153–2.496[b]	0.499[b]

MASCC score: The Multinational Association of Supportive Care of Cancer score, BMI: Body mass index.
[a] n = 36.
[b] :OR (95%CI) was adjusted by age and sex.

had a BMI value of ≥25. There was no significant relationship between variant distribution and other clinical features of FEN.

GA and AA genotypes of the *LEP* rs7799039 polymorphism were associated with high serum leptin levels as well as obesity; similarly, the GG genotype of the *LEPR* rs1137101 polymorphism was found to be also associated with low receptor transcription and obesity [24–26]. In a study of Illangasekera1 et al., post hoc analysis with Bonferroni correction showed that individuals with GG genotype had significantly greater BMI values compared to the AA carriers, and also, patients with the AG/GG genotypes had significantly greater BMI values compared to patients with the AA in rural populations [27]. In another study, the *LEPR* rs1137101 polymorphism AG genotype was found to be associated with obesity [28]. In our study, the fact that all the patients with the AG/GG genotype of the *LEPR* rs1137101 polymorphism had a BMIvalue of ≥25 also supported the literature data mentioned above. *LEP* rs7799039 genotype distribution was not statistically significant with clinical features; there was also no significant difference in terms

of BMI distribution.

The relationship between leptin and obesity includes a complex set of interactions. Obese patients have been shown to have higher serum leptin levels and "leptin resistance" plays a major role in obesity. It was also revealed that leptin has many additional cytokine effects similar to acute-phase reactants. It increases the pro-inflammatory cytokines such as IL-6, IL-12, and tumor necrosis factor-a and releases inflammation [29,30,]. It has also been shown that obese individuals have more macrophages in their tissues than normal individuals and have increased inflammatory capacity [30]. In the case of obesity, adipose tissue produces high serum leptin levels into circulation; it causes leptin resistance and results in refractive T-cells response and high expression of suppressor of cytokine signaling 3, which increases susceptibility to infections [5]. Although high serum leptin levels or the presence of gene variants associated with high leptin expression are associated with high cytokine discharge; literature data show that the presence of leptin resistance leads to susceptibility to infections. In our study, however, no association of high gene expression-related variants with FEN susceptibility or clinical features was found.

Leptin deficiency has been associated with sepsis and high mortality [31]. It has been demonstrated that plasma leptin levels are lower in patients with tuberculosis compared to healthy controls [32]. T-cell dysfunction was observed in leptin-deficient mice with pulmonary tuberculosis [33]. It has been observed that the frequency of pulmonary infections was increased in mice with leptin deficiency, especially the pulmonary bacterial clearance was decreased [34]. In our study, although the most common documented infection subtypes were respiratory tract infections, no significant difference was found in terms of distribution of *LEP* and *LEPR* gene variants compared to other subtypes. Although no statistically significant results were obtained in terms of clinical parameters such as MASCC risk scores and the number of FEN attacks, there was no difference in terms of documented bloodstream infections.

A study from 2002 evaluated adult patients with acute myeloid leukemia (AML), it has been shown that serum leptin levels were decreased in untreated AML patients, and leptin levels do not change during chemotherapy-associated cytopenia or FEN attacks [35]. Our study included pediatric patients with both solid and non-solid malignancies; based on this study, it can be mentioned that the effects of leptin as adipokine in the course of FEN attacks is not significant. Cytopenia, especially in the course of FEN, could prevent leptin from revealing its effects, especially the cytokine release. Therefore, the presence of leptin resistance or gene polymorphism-related effects on leptin expression may not have had a clinical effect.

3.1. Limitations

There were also limitation points of this study. The most important limitation was the number of patients and single-center data that prevented subgroup analysis. Another limitation was that simultaneous serum leptin levels were not measured and alterations in serum leptin levels during the course of FEN attacks were not observed.

4. Conclusions

In conclusion, in our study, the effects of *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms on FEN susceptibility and FEN clinical findings were investigated in the pediatric malignancy patient group. It was revealed that *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms did not cause FEN susceptibility, all patients with *LEPR* rs1137101 AG/GG genotypes had a BMI value of $\geq$25, and there was no significant relationship between variant distribution and other clinical features. Our results will shed light on new studies in which disease subgroups can also be analysed in larger patient populations.

Availability of data and material

The data that support the findings of this study are openly available: "SERIN, Istemi (2023), "Leptin-FEN", Mendeley Data, V1, doi: 10.17632/v3zdzzsgdc.1"

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Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul University, Faculty of Medicine, approval date and number: 08.11.2019–18) and informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Ezgi Paslı Uysalol: Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Metin Uysalol:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Istemi Serin:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Mustafa Pehlivan:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Yasemin Oyaci:** Writing – review & editing, Writing – original draft, Software, Data curation, Conceptualization. **Sacide Pehlivan:** Writing – review &

editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Zeynep Karakas:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

LEPR	The leptin receptor
IL	Interleukin
FEN	Febrile neutropenia
BMI	Body mass index
ANC	Absolute neutrophil count
MASCC	The Multinational Association of Supportive Care of Cancer
PCR	Polymerase chain reaction
OR	Odds ratio
CI	Confidence interval
HWE	Hardy Weinberg equilibrium
AML	Acute myeloid leukemia

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