Research Article / Araştırma Makalesi

The Effects of Body Mass Index and Blood Group on Immune Thrombocytopenia Therapy

Vücut Kitle İndeksi ve Kan Gruplarının İmmün Trombositopeni Tedavisine Etkisi

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Abstract

Background: The effects of body mass index (BMI) and blood groups on immune thrombocytopenia (ITP) are not clearly known. This study aims to investigate the effect of BMI and blood groups on the treatment of ITP.
Materials and Methods: All cases included in this study were primary ITP patients. Body measurements, treatment history, demographic, and laboratory data were recorded. The data obtained were analyzed after the patients were divided into groups based on BMI and blood groups.
Results: The study included 68 (100%) cases, 53 of which were female (77.9%). The median age of the cases was 44 years (min: 18, max: 87). The median BMI was 28.05 (min: 17.6, max: 51.4), and patients with normal weight, overweight, and obesity were found in 24 (35.3%), 20 (29.4%), and 24 (35.3%) cases, respectively. According to blood groups, 29 (42.6%), 20 (29.4%), 11 (16.2%), and 8 (11.8%) cases had blood groups A, O, B, and AB, respectively. The analysis of BMI and blood groups together with demographic and laboratory variables revealed that patients with obesity had a higher mean age (p=0.049) and lactate dehydrogenase levels (p<0.001) than other BMI groups. In the analysis of treatment responses, it was found that using eltrombopag in the second-line treatment in the patients with normal weight group was associated with a better response than other BMI groups (p=0.025).
Conclusions: This is the first study to look investigate the relationship between BMI and ITP therapy. According to the results of our study, we believe that BMI should be considered in the selection of second-line therapy for ITP.

Key Words: Blood Group Antigens, eltrombopag, Obesity, Overweight.

Öz

Amaç: Vücut kitle indeksi (VKİ) ve kan gruplarının immün trombositopeni (ITP) üzerindeki etkileri net olarak bilinmemektedir. Bu çalışmada VKİ ve kan gruplarının ITP tedavisindeki etkisinin araştırılması amaçlanmaktadır.
Materyal ve Metod: Bu çalışmaya dahil edilen tüm vakalar primer ITP hastalarından oluşmaktadır. Vücut ölçütleri, tedavi geçmişleri, demografik ve laboratuvar verileri kayıt altına alınmıştır. Hastalar VKİ ve kan gruplarına göre gruplara ayrıldıktan sonra elde edilen veriler analiz edilmiştir.
Bulgular: Çalışmaya 53'ü kadın (%77,9) toplamda 68 (%100) vaka dahil edilmiştir. Vakaların ortanca yaşı 44 yıl (min:18, max:87) saptanmıştır. Ortanca VKİ 28,05 (min:17,6, max:51,4) olup sırasıyla 24 (%35,3), 20 (%29,4) ve 24 (%35.3) vaka normal kilolu, aşırı kilolu ve obeziteli olarak saptandı. Kan gruplarına göre sırasıyla 29 (%42,6), 20 (%29,4), 11 (%16,2) ve 8 (%11,8) vaka A, O, B ve AB kan grubuna sahipti. VKİ ve kan gruplarının demografik ve laboratuvar değişkenleri ile analizinde obeziteli hastaların diğer VKİ gruplarına göre yaş ortalamalarının (p=0.049) ve laktat dehidrogenaz düzeylerinin daha yüksek olduğu (p<0.001) saptanmıştır. Tedavi yanıtlarının analizinde ise normal kilolu grupta ikinci sıra tedavide eltrombopag kullanımının diğer VKİ gruplarına göre daha iyi yanıtla ilişkisi saptanmıştır (p=0.025).
Sonuç: Bu çalışma VKİ ve kan gruplarının ITP tedavisindeki etkisini araştıran ilk çalışmadır. Çalışma sonuçlarımıza göre ITP'nin ikinci basamak tedavi seçiminde VKİ'ninde göz önünde bulundurulması gerektiği görüşündeyiz.

Anahtar Kelimeler: Kan grubu antijenleri, Eltrombopag, Obesite, Aşırı kilo

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Introduction

Immune thrombocytopenia (ITP) is a condition characterized by a decrease in platelet production and increased destruction of platelets due to the presence of antiplatelet autoantibodies. The clinical presentation of ITP can vary, with some patients asymptomatic while others may experience different bleeding patterns, ranging from mild to severe (1). The decision to initiate treatment in ITP can be controversial, and the threshold platelet values that require treatment initiation may vary among physicians. However, the clinical findings and the presence of bleeding symptoms are the main determinants for starting treatment. A commonly held view is that treatment should be considered in patients with a platelet count below $30x10^9$/L or in those with a platelet count above $30x10^9$/L who exhibit signs and have a high risk of bleeding (1-3).

The increasing prevalence of obesity has been a concern worldwide, not only in adults but also in children and adolescents. In recent years, there has been a growing interest in studying the impact of changes in body mass index (BMI) on various medical conditions, including hematological diseases such as hematological malignancies. Multiple studies have shown a correlation between higher BMI and an increased risk of developing and dying from certain hematological malignancies. For example, a meta-analysis indicated that both the incidence and mortality risk of multiple myeloma (MM) were higher in overweight and obese patients (4). Similarly, research has demonstrated that BMI can influence the development and survival outcomes of acute leukemias (5-10). Beyond hematological malignancies, the impact of BMI on thrombocytes has also been investigated. One study observed a significant increase in platelet count in populations with overweight, obesity, and morbid obesity compared to populations with normal weight, particularly among women (11). Furthermore, weight loss following bariatric surgery in patients with obesity was associated with a decrease in platelet count (12). However, there is limited literature available on the incidence of ITP and its relationship with BMI, as well as the effect of BMI on treatment outcomes in ITP.

It appears that recent studies have been investigating the potential relationship between blood groups and hematological malignancies, such as lymphoma and MM (13-16). Two separate studies have reported associations between specific blood groups and poor survival outcomes in lymphoma and MM patients, with blood groups B and O being implicated, respectively (14, 15). Additionally, the effects of blood groups on thrombocyte counts have also been examined. One study found that individuals with Rh (-) blood group had lower thrombocyte counts, while another study reported that individuals with blood group O had lower thrombocyte counts compared to those with blood group A (17, 18). While there is some emerging knowledge about the importance of blood groups in various hematological diseases, it is worth noting that the available literature on the effects of blood groups on ITP is limited. In this study, we aimed to evaluate the influence of BMI and blood groups on the therapy of ITP to address a knowledge gap.

Materials and Methods

Study design and group selection

This study was designed as a retrospective, cross-sectional observational study conducted at the Hatay Mustafa Kemal University hematology clinic between July 2022 and December 2022. The inclusion criteria for the study were adult patients (aged 18 years and older) with primary ITP of both genders. Patients with secondary ITP were excluded from the study. In the study, the co-morbidities of the patients were recorded. Diseases affecting multiple organ systems such as diabetes mellitus, congestive heart failure, chronic renal failure, chronic obstructive pulmonary disease and hypertension have been noted as co-morbid diseases. The treatment history, demographic data, and laboratory parameters of the patients included in the study were all recorded. Based on the height and weight measurements at the time of diagnosis, the patients were categorized into three groups: normal weight, overweight, and obesity, using the BMI formula: BMI = Weight (kg)/Height (m^2). The BMI ranges used for categorization were as follows: normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30 kg/m^2) (19). Additionally, the patients were divided into groups based on their blood types (A, B, AB, and O). After the data was obtained, the treatment characteristics of the cases were analyzed in terms of BMI and blood groups. This study protocol adhered to the ethical principles outlined in the Declaration of Helsinki. It received approval from the Hatay Mustafa Kemal University local ethics committee, with the approval number 20-12/01/2023.

Treatment management and response criteria

Corticosteroids constitute the standard first-line treatment for newly diagnosed primary ITP. Corticosteroid options are methylprednisolone or dexamethasone. In our center, methylprednisolone is preferred in first-line treatment. Therefore, methylprednisolone was used in first-line treatment in all cases included in the study. In corticosteroid refractory and relapsing patients, eltrombopag, splenectomy, rituximab, and romiplostim are used in the second-line treatment according to patient characteristics and preference in our center, although there is currently no standardized treatment recommendation. Furthermore, for patients who are refractory to multiple lines of treatment, alternative immunosuppressive therapies such as azathioprine and cyclosporine are also considered as options.

The response evaluation criteria for the treated cases were categorized into three groups: complete response (CR), partial response (PR), and no response. CR was considered as a platelet count >$100x10^9$/L. PR platelet count between 30-$100x10^9$/L or reaching at least 2 times the initial platelet count. Patients with a platelet count <$30x10^9$/L and those whose initial platelet count did not reach double the initial platelet count were considered non-responders (20).

Statistical Analysis

The statistical analyses for this study were performed using IBM SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were reported as mean±SD, while categorical variables were presented as numbers (n) and percentages (%). To assess the normality assumptions of the data, Kolmogorov-Smirnov values were computed, and a significance level of $p<0.05$ was used. Based on these results, parametric tests were employed to examine the significant differences between continuous variables and the demographic and various data of the participants. For variables with two groups, the Independent Samples t-test was used. On the other hand, variables with three or more groups were analyzed using the One-Way ANOVA test. Categorical variables were compared using the chi-square test. A significance level of $p<0.05$ was considered statistically significant for all tests.

Results

The study comprised 68 (100%) primary ITP cases, 53 of whom were women (77.9%). The median age was 44 years (min:18, max:87), and 29 (42.6%), 20 (29.4%), 11 (16.2%), and 8 (11.8%) cases had blood type A, O, B, and AB, respectively. The median BMI was 28.05 (min:17.6, max:51.4), and 24 (35.3%), 20 (29.4%), and 24 (35.3%) cases were patients with normal weight, overweight, and obesity, respectively. Table 1 contains demographic and laboratory data.

According to BMI data, there is a statistically significant difference between patients with obesity and age (years) (p=0.049). The median age of patients with obesity was found to be higher than that of the other BMI groups. Also, a statistically significant difference was identified between patients with obesity and LDH levels at diagnosis ($p<0.001$). Patients with obesity showed greater LDH levels than the other BMI groups. No statistically significant difference was found between BMI groups and gender (p=0.095), comorbidity (p=0.560), white blood cell count (p=0.085), neutrophils (p=0.209), lymphocytes (p=0.801), thrombocytes (p=0.082) and mean platelet volume (p=0.169). Table 2 summarizes the results of the analysis comparing BMI groups and variables.

In the comparison of cases according to blood groups, there was no statistically significant difference between; age (years) (p=0.879), gender (p=0.227), BMI (p=0.201), BMI groups (p=0.487), comorbidity (p=0.515), white blood cell count (p=0.310), neutrophils (p=0.523), lymphocytes (p=0.302), thrombocytes (p=0.875), mean platelet volume (p=0.405) and LDH (p=0.681). Table 3 summarizes the findings of the analysis comparing the variables according to blood groups.

When the effects of BMI and blood groups on treatment response were compared, no significant difference was found between blood groups and treatment responses ($p>0.05$), whereas the use of eltrombopag in the second-line treatment in the patients with normal weight group was associated with better response compared to other BMI groups (p=0.025). Tables 4 and 5 show the effect of BMI and blood groups on treatment respons.

Table 1. Demographic data of the participants (n=68)

Variables	n or median (min-max)	% or mean±SD
Age (years)	44 (18-87)	47.3±18.1
Gender		
Female	53	77.9
Male	15	22.1
Blood group		
A	29	42.6
B	11	16.2
AB	8	11.8
O	20	29.4
BMI (kg/m²)	28.0 (17,6-51.4)	27.5±6.4
BMI group		
Patients with normal weight	24	35.3
Patients with overweight	20	29.4
Patients with obesity	24	35.3
Comorbidity		
Available	15	22.1
None	53	77.9
WBC (10^9/L)	7.0 (4.0-25.0)	8.33±3.89
NEUT (10^9/L)	4.0 (2.0-20.0)	5.53±3.60
LYM (10^9/L)	2.0 (0.9-4.0)	1.93±0.73
PLT (10^9/L)	17.0 (1.0-79.0)	20.1±17.9
MPV (fL)	11.0 (5.0-16.0)	11.2±1.7
LDH (U/L)	232.5 (105-455)	235.3±67.8

Abbreviations: BMI, body mass index; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; PLT, thrombocyte; MPV, mean platelet volume; LDH, lactate dehydrogenase.

Table 2. Comparison of Variables According to BMI Groups

Variables	BMI groups			p
	Patients with normal weight (n=24)	Patients with overweight (n=20)	Patients with obesity (n=24)	
Age (Years), mean±SD	40.3±17.9	49.6±17.5	52.6±17.2	**0.049[a]**
Gender, n (%)				
Female	22 (91.7)	13 (65)	18 (75)	0.09[b]
Male	2 (8.3)	7 (35)	6 (25)	
Comorbidity, n (%)				
Available	4 (16.7)	4 (20)	7 (29.2)	0.56[b]
None	20 (83.3)	16 (80)	17 (70.8)	
WBC (10^9/L), mean±SD	7.13±2.51	8.25±3.80	9.61±4.77	0.08[a]
NEUT (10^9/L), mean±SD	4.67±2.44	5.40±3.66	6.50±4.36	0.2[a]
LYM (10^9/L), mean±SD	1.96±0.62	1.85±0.88	2.00±0.73	0.8[a]
PLT (10^9/L), mean±SD	18.5±17.1	19.4±13.8	22.2±21.9	0.08[a]
MPV (fL), mean±SD	11.7±1.9	11.2±1.9	10.8±1.4	0.16[a]
LDH (U/L), mean±SD	210.5±51.7	248.6±64.9	249.1±79.2	**<0.001[a]**

[a]: One Way ANOVA test, [b]: Pearson Chi-Square test, [c]: Fisher's Exact Chi-Square test, p<0.05

Abbreviations: BMI, body mass index; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; PLT, thrombocyte; MPV, mean platelet volume; LDH, lactate dehydrogenase.

Table 3. Comparison of Variables According to Blood Groups

Variables	Blood groups				p
	Type A (n=29)	Type B (n=11)	Type AB (n=8)	Type O (n=20)	
Age (Years), mean±SD	47.8±16.7	47.7±18.5	51.1±19.9	45.0±20.1	0.8[a]
Gender, n (%)					
Female	23 (79.3)	9 (81.8)	8 (100)	13 (65)	0.2[c]
Male	6 (20.7)	2 (18.2)	0 (0)	7 (35)	
BMI (kg/m²), mean±SD	26.5±4.0	26.8±4.2	31.9±11.2	27.6±7.2	0.2[a]
BMI Group, n (%)					
Patients with normal weight	9 (31)	5 (45.5)	3 (37.5)	7 (35)	0.4[c]
Patients with overweight	10 (34.5)	3 (27.3)	0 (0)	7 (35)	
Patients with obesity	10 (34.5)	3 (27.3)	5 (62.5)	6 (30)	
Comorbidity, n (%)					
Available	7 (24.1)	1 (9.1)	3 (37.5)	4 (20)	0.5[c]
None	22 (75.9)	10 (90.9)	5 (62.5)	16 (80)	
WBC ($10^9/L$), mean±SD	9.07±4.41	9.09±5.72	7.63±1.69	7.13±1.93	0.3[a]
NEUT ($10^9/L$), mean±SD	6.17±4.23	5.82±5.08	4.75±1.98	4.76±1.71	0.5[a]
LYM ($10^9/L$), mean±SD	2±0.80	2.18±0.75	2.00±0.76	1.7±0.58	0.3[a]
PLT ($10^9/L$), mean±SD	20.5±19.4	19.8±21.5	24.2±20.2	18±13.1	0.8[a]
MPV (fL), mean±SD	11.6±1.7	11.4±1.1	10.6±1.6	10.9±2.1	0.4[a]
LDH (U/L), mean±SD	243.9±66.3	243±58.8	229.6±100.3	221.0±62.0	0.6[a]

[a]: One Way ANOVA test, [b]: Pearson Chi-Square test, [c]: Fisher's Exact Chi-Square test, p<0.05

Abbreviations: BMI, body mass index; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; PLT, thrombocyte; MPV, mean platelet volume; LDH, lactate dehydrogenase.

Table 4. Comparison of Treatment Responses According to BMI Groups

Variables	BMI groups			p
	Patients with normal weight (n=21)	Patients with overweight (n=19)	Patients with obesity (n=24)	
Methylprednisolone in 1st line treatment, n (%)				
No response	11 (52.4)	13 (68.4)	18 (75)	0.3[c]
CR	8 (38.1)	6 (31.6)	6 (25)	
PR	2 (9.5)	0 (0)	0 (0)	
Eltrombopag in 2nd line treatment, n (%)				
No response	0 (0)	2 (28.6)	4 (50)	0.025[c]
CR	8 (100)	3 (42.9)	4 (50)	
PR	0 (0)	2 (28.6)	0 (0)	
Rituximab in 2nd line treatment, n (%)				
No response	1 (100)	1 (50)	2 (66.7)	1.0[c]
CR	0 (0)	1 (50)	1 (33.3)	
Splenectomy in 2nd line treatment, n (%)				
No response	0 (0)	2 (66.7)	0 (0)	0.6[c]
CR	1 (100)	1 (33.3)	2 (100)	
Eltrombopag in 3rd line treatment, n (%)				
No response	1 (33.3)	0 (0)	1 (20)	0.8[c]
CR	2 (66.7)	3 (75)	4 (80)	
PR	0 (0)	1 (25)	0 (0)	
Rituximab in 3rd line treatment, n (%)				
No response	-	1 (50)	2 (40)	1.0[c]
CR	-	1 (50)	2 (40)	
PR	-	0 (0)	1 (20)	
Splenectomy in 3rd line treatment, n (%)				
No response	-	0 (0)	2 (100)	0.3[c]
CR	-	1 (100)	0 (0)	
Romiplostim in 3rd line treatment, n (%)				
No response	0 (0)	0 (0)	1 (33.3)	1.0[c]
CR	0 (0)	0 (0)	1 (33.3)	
PR	1 (100)	1 (100)	1 (33.3)	

[c]: Fisher's Exact Chi-Square test, p<0.05

Abbreviations: BMI, body mass index; CR, complete response; PR, partial response.

Table 5. Comparison of treatment responses according to blood groups

Variables	Blood groups				p
	Type A (n=28)	Type B (n=11)	Type AB (n=8)	Type O (n=17)	
Methylprednisolone in 1st line treatment, n (%)					
No response	20 (71.4)	5 (45.5)	4 (50)	13 (76.5)	0.2[c]
CR	8 (28.6)	5 (45.5)	4 (50)	3 (17.6)	
PR	0 (0)	1 (9.1)	0 (0)	1 (5.9)	
Eltrombopag in 2nd line treatment, n (%)					
No response	3 (33.3)	1 (33.3)	0 (0)	2 (25)	0.9[c]
CR	5 (55.6)	2 (66.7)	3 (100)	5 (62.5)	
PR	1 (11.1)	0 (0)	0 (0)	1 (12.5)	
Rituximab in 2nd line treatment, n (%)					
No response	1 (50)	1 (100)	2 (66.7)	2 (25)	1.0[c]
CR	1 (50)	0 (0)	1 (33.3)	5 (62.5)	
Splenectomy in 2nd line treatment, n (%)					
No response	2 (50)	-	-	0 (0)	0.4[c]
CR	2 (50)	-	-	2 (100)	
Eltrombopag in 3rd line treatment, n (%)					
No response	2 (33.3)	0 (0)	0 (0)	0 (0)	0.8[c]
CR	3 (50)	2 (100)	1 (100)	3 (100)	
PR	1 (16.7)	0 (0)	0 (0)	0 (0)	
Rituximab in 3rd line treatment, n (%)					
No response	1 (33.3)	-	-	1 (50)	1.0[c]
CR	1 (33.3)	-	-	1 (50)	
PR	1 (33.3)	-	-	0 (0)	
Splenectomy in 3rd line treatment, n (%)					
No response	2 (100)	0 (0)	-	-	0.3[c]
CR	0 (0)	1 (100)	-	-	
Romiplostim in 3rd line treatment, n (%)					
No response	1 (25)	-	-	0 (0)	1.0[c]
CR	1 (25)	-	-	0 (0)	
PR	2 (50)	-	-	1 (100)	

[c]***: Fisher's Exact Chi-Square test, p<0.05***

Abbreviations: CR, complete response; PR, partial response.

Discussion

In this study, which investigated the effect of BMI and blood groups on ITP treatment responses, no effect of blood groups on treatment outcomes was found, but the use of eltrombopag in second-line treatment in the patients with normal weight group was associated with better treatment outcomes compared to other BMI groups (p=0.025).

Currently, corticosteroids are the standard first-line treatment for primary ITP, while thrombopoietin receptor agonists, splenectomy, rituximab, and various immunosuppressive therapies are among the options for second-line treatment (1, 2). There are few studies on which option to use in second-line treatment. Since the choice of treatment in these studies is usually influenced by patient preferences, patient characteristics, cost, and geographical variables, there is no standard second-line treatment recommendation for the time being (21-23). In recent years, studies on the effect of BMI on hematological diseases have gained momentum. In particular, many studies have reported that BMI plays a role in both the development and survival of malignant hematological diseases (5-10). Apart from this, research in the literature addressing the impact of BMI on thrombocytes are mostly based on studies investigating the effect of BMI on hematological parameters (24-27). In these studies, it was reported that obesity increased the number of thrombocytes and it was stated that the increase in thrombocytes played a role in the risk of obesity-related thrombosis (26, 27). Although there are many studies in the literature on the effect of BMI on thrombocyte increase and outcomes, there are very few studies on its relationship with thrombocytopenia. In a report consisting of 3 cases from these few studies, it was stated that obesity caused refractory ITP (28). In another study by Bloom et al. investigating the relationship between BMI and thrombocytopenia in patients in intensive care units, a strong relationship between BMI increase and heparin-associated thrombocytopenia was found (29) . In our study, no relationship was found between the BMI groups and the incidence of ITP. However, when we looked at treatment responses, we found that there was no difference between BMI groups in first-line treatment, whereas treatment responses with eltrombopag were better in the normal weight group compared to other BMI groups who needed second-line treatment (p=0.025). The efficacy and safety profile of eltrombopag were investigated in clinical trials conducted in 2011 (RAISE) and 2017 (EXTEND) (30, 31). When the details of these trials were examined, we could not find any information on the effect of BMI on eltrombopag response. Therefore, we think that the better eltrombopag response in patients with normal weight patients observed in our study is an important finding.

In recent years, the role of blood groups, like BMI, in both benign and malignant hematological diseases has become a subject of interest (13-15, 32, 33). In the study of Osada et al. investigating the relationship between blood groups and lymphoma survival, it was reported that the survival of patients with B blood group was shorter (14). In another study investigating the relationship between MM blood groups, it was reported that MM developed less frequently in individuals with blood group O, but their prognosis in terms of extramedullary disease and survival was poorer (15). Looking at the studies investigating the relationship between thrombocyte diseases and blood groups, Karnes et al. reported that blood group O increased the risk of heparin-induced thrombocytopenia (32). In another study, it was reported that thrombotic thrombocytopenic purpura developed more frequently in the A blood group, while the need for plasma exchange was higher and recurrence was observed more frequently in the O blood group (33). Although there are studies in the literature investigating the relationship between blood groups and thrombocyte diseases, we could not find any study investigating the clinical effect of blood groups in patients with ITP. In our study, we could not find any difference between blood groups and age, gender, and laboratory characteristics in patients with ITP. In addition, we could not find any significant difference between blood groups in terms of treatment outcomes.

Our study has some limitations. The retrospective design of the study constitutes the main limitation. Another limitation is the number of patients in our study. While the total number of patients was sufficient, the decrease in the number of patients in need of second-line and subsequent treatment in subgroups constitutes an important limitation of our study. As the last limitation, the lack of information on response times under treatment can be considered. However, this study was planned to evaluate the response to treatment rather than evaluating the duration of response to treatment.

In conclusion, in this study the use of eltrombopag as a second-line treatment in patients with ITP who have a normal weight according to their BMI has shown to yield better treatment outcomes. This is the first study to look investigate the relationship between BMI and ITP therapy. We believe that the important information obtained in this study should be investigated with further studies in the future in order to be recommended in clinical practice.

Ethical Approval: *The study protocol was approved by Hatay Mustafa Kemal University local ethics committee (Approval No: 2023/12/01-20).*

Author Contributions:
Concept: M.K.
Literature Review: M.K., Y.K.
Design : M.K.
Data acquisition: Y.K.
Analysis and interpretation: M.K.
Writing manuscript: M.K.
Critical revision of manuscript: M.K., Y.K.

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