RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2023.2023.0295
Turk J Hematol 2023;40:251-257

Immune Thrombotic Thrombocytopenic Purpura in Elderly Patients: The Roles of PLASMIC and French Scores

İleri Yaştaki İmmün Trombotik Trombositopenik Purpura Hastalarında; PLASMIC ve French Skorlamalarının Rolü

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Abstract

Objective: In recent years, new developments have been incorporated into daily practice in the management of immune thrombotic thrombocytopenic purpura (iTTP). In particular, clinical scoring systems could help clinicians with clinical decision-making and early recognition. However, older patients frequently present with more organ involvement and in unusual ways. The ways in which age could affect these clinical prediction scoring systems remain unclear. We evaluated the use of PLASMIC and French scores in patients over 60 years of age.

Materials and Methods: We performed a retrospective cross-sectional analysis of patients over 60 years of age with a presumptive diagnosis of iTTP between 2014 and 2022 at 10 centers. We calculated PLASMIC and French scores and compared our data with a single-center analysis of younger patients presenting with thrombotic microangiopathy.

Results: Our study included 30 patients over 60 years of age and a control group of 28 patients younger than 60 years. The diagnostic sensitivity and specificity of a French score of ≥1 were lower in older patients compared to the control group (78.9% vs. 100% and 18.2% vs. 57.1%, respectively). The diagnostic sensitivity and specificity of a PLASMIC score of ≥5 were 100% vs. 95% and 27.3% vs. 100% for the study group and control group, respectively. Our study showed a

Öz

Amaç: Son yıllarda, immün trombotik trombositopenik purpura (iTTP) yönetiminde günlük uygulamalara yeni gelişmeler eklenmiştir. Özellikle klinik skorlama sistemleri klinisyenlere klinik karar verme ve erken tanıda yardımcı olabilir. Ancak, yaşlı hastalar genellikle daha fazla organ tutulumu ve alışılmadık şekillerde başvurabilmektedir. İleri yaşın bu klinik tahmin skorlama sistemleri üzerindeki etkisi belirsizdir. Bu bağlamda, PLASMIC ve French skorlarının 60 yaş ve üzeri hastalarda kullanılabilirliğini değerlendirdik.

Gereç ve Yöntemler: 2014 ile 2022 yılları arasında on merkezde iTTP olası tanısı alan 60 yaş üstü hastalar retrospektif olarak değerlendirildi. PLASMIC ve French skorlarını hesapladık ve verilerimizi trombotik mikroanjiyopati ile başvuran genç hastaların tek merkezli analiziyle karşılaştırdık.

Bulgular: Çalışmamız 60 yaş üstü 30 hasta ve 60 yaş altı 28 hastadan oluşan kontrol grubunu içeriyordu. French skoru ≥1'in tanısal duyarlılığı ve özgüllüğü yaşlı hastalarda kontrol grubuyla karşılaştırıldığında daha düşüktü (sırasıyla %78,9'a karşı %100 ve %18,2'ye karşı %57,1). PLASMIC skoru ≥5'in tanısal duyarlılığı ve özgüllüğü, çalışma grubu ve kontrol grubu için sırasıyla %100'e karşı %95 ve %27,3 ve %100 idi. Çalışmamızda yaşlı hastalarda kontrol grubuyla karşılaştırıldığında daha yüksek ölüm oranı saptandı (%30 vs %7,1 p-değeri =0,043).

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Received/Geliş tarihi: July 24, 2023
Accepted/Kabul tarihi: October 4, 2023

higher mortality rate in older patients compared to the control group (30% vs. 7.1%, p=0.043).

Conclusion: For a limited number of patients (n=6), our results showed that rituximab can reduce mortality. Given that the reliability of clinical prediction scores for iTTP in older patients may be lower, more caution must be undertaken in interpreting their results.

Keywords: Thrombotic thrombocytopenic purpura, PLASMIC score, French score, Elderly, Age, Thrombotic microangiopathy

Sonuç: Sınırlı sayıda hastada (n=6) sonuçlarımız ritüksimabın mortaliteyi azaltabildiğini göstermektedir. Yaşlı hastalarda iTTP için klinik öngörme skorlamalarının güvenilirliğinin daha az olabileceği göz önüne alındığında, sonuçların yorumlanmasında daha dikkatli olunmalıdır.

Anahtar Sözcükler: Trombotik trombositopenik purpura, PLAZMIC, French skoru, Yaşlı, Yaş, Trombotik mikroanjiyopati

Introduction

Immune thrombotic thrombocytopenic purpura (iTTP) is a rare life-threatening disease characterized by microangiopathic hemolytic anemia and thrombocytopenia, presenting with microvascular thrombosis and organ injury [1]. iTTP is caused by a deficiency in the von Willebrand factor (VWF) cleaving protease denoted as ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [2]. Therapeutic plasma exchange (TPE) has resulted in significant improvement in mortality [2]. iTTP is usually diagnosed on the basis of clinical suspicion and confirmed by ADAMTS13 activity results [3,4]. Since ADAMTS13 activity tests can take a long time, various clinical prediction scoring systems have been developed to start treatment quickly [5,6,7,8,9,10,11,12]. To avoid delays in treatment, the guidelines of the International Society of Thrombosis and Hemostasis (ISTH) suggest that the PLASMIC and French clinical prediction scoring systems be used in the management of iTTP [3].

The median age of onset for iTTP is 40 years [8,13]. It has been reported that elderly iTTP patients may present with a higher frequency of renal and neurological manifestations and show higher mortality rates compared to younger patients [14,15,16]. These findings may be attributed to the comorbid conditions of elderly patients [15]. Previous studies reported that the sensitivity of clinical prediction scoring systems such as the PLASMIC and French scores were lower and that their clinical value decreased in elderly patients [17]. In the present study, we evaluated patients over 60 years of age for whom TPE was initiated with a presumptive diagnosis of iTTP and samples were sent for ADAMTS13 analysis. We also aimed to study the impact of rituximab on mortality and relapse in iTTP patients over 60 years of age.

Materials and Methods

We retrospectively evaluated patients over 60 years of age who were prediagnosed with iTTP and treated by TPE in 10 centers in Türkiye between 2014 and 2022. All patients presented with microangiopathic hemolytic anemia and thrombocytopenia and the final diagnosis was confirmed by ADAMTS13 activity levels of <10%. All samples were centrifuged and kept at -80 °C prior to analysis. The activity of ADAMTS13 was assessed by enzyme-linked immunosorbent assays [18]. Data at the time of presentation relevant to the PLASMIC score (platelet count of $<30x10^9$/L; hemolysis variables including reticulocyte count of >2.5%, undetectable haptoglobin, or indirect bilirubin of >2 mg/dL; cancer status; solid organ or stem cell transplant status; mean corpuscular volume of <90 fL; international normalized ratio of <1.5; and serum creatinine of <2.0 mg/dL) and the French score (platelet count of $<30x10^9$/L; creatinine of <2.26 mg/dL) were collected. The PLASMIC score was stratified into three risk categories of 0 to 4 (low risk), 5 (intermediate risk), and 6 to 7 (high risk), and the French score was divided into three categories of 0 = low risk, 1= intermediate risk, and 2= high risk [6,19]. The interpretation of the clinical prediction scores is detailed in Table 1.

We used our previous recent study as a control group to compare sensitivity and specificity analysis in patients older and younger than 60 years old [20]. In our previous study, a total of 35 patients with a diagnosis of thrombotic microangiopathy

Table 1. Interpretation of PLASMIC scores and French scores for the prediction of severe ADAMTS13 deficiency.

	PLASMIC score	French score
Platelet count	$<30x10^9$/L: 1 point	$\leq 30x10^9$/L: 1 point
Creatinine level	<2 mg/dL: 1 point	≤2.26 mg/dL: 1 point
Parameters of hemolysis	Reticulocyte count >2.5%: 1 point Haptoglobin undetectable: 1 point Indirect bilirubin >2 mg/dL: 1 point	N/A
Associated conditions	No active cancer: 1 point No history of solid-organ or hematopoietic stem cell transplantation: 1 point	N/A
MCV	<90 fL: 1 point	N/A
INR	<1.5: 1 point	N/A
Interpretation of risk category, total score		
Low	0-4	0
Intermediate	5	1
High	6-7	2

(TMA) were evaluated. Seven of those patients were over 60 years of age and the remaining 28 patients were under 60 years old [20]. The data of those 28 patients were used as a control group in the present study. This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (2011-KAEK-25 2023/02-029).

TPE with 1 to 1.5 volumes of fresh-frozen plasma was initiated as well as oral or intravenous methylprednisolone at 1 mg/kg. We collected data about complementary therapies and treatment responses evaluated according to a consensus report on the definitions and revised outcomes of iTTP [21]. Clinical response was defined as a maintainable platelet count of 150x10^9/L, lactate dehydrogenase (LDH) <1.5 times the upper normal limit, and no signs of developing or new ischemic organ impairment. Clinical remission was defined as sustained clinical response with either no TPE or no anti-VWF therapy for 30 days with attainment of ADAMTS13 remission (partial or complete), whichever occurred first. Clinical exacerbation was defined as thrombocyte count drops to 150x10^9/L within 30 days of ceasing TPE or anti-VWF medication with or without clinical indications of new or progressing ischemic organ damage after achievement of clinical response but before clinical remission. Clinical relapse after clinical remission was defined as a platelet count decrease to 150x10^9/L with other causes of thrombocytopenia ruled out with or without clinical evidence of new ischemic organ injury [21]. Mortality was defined as death from the time of the iTTP diagnosis to 1 year afterward.

Statistical Analysis

Descriptive statistics were reported as percentage, number, and median (minimum-maximum) values. To compare categorical variables, chi-square or Fisher exact tests were used. The sensitivity and specificity of the screening tools were calculated as true positives (true positives + false negatives) and true negatives (true negatives + false positives), respectively. Patients diagnosed with confirmed iTTP were considered true positives, while those with unconfirmed disease were classified as false positives. Statistical calculations were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

Results

Thirty patients were included in this study. The median age of the study population was 65.5 years. Twenty patients were female and 10 patients were male. The median thrombocyte count, median hemoglobin, and median LDH of the cohort were 29.5x10^9/L, 729 U/L, and 8.3 g/dL, respectively. Demographic and baseline laboratory features of the patients are summarized in Table 2. According to the PLASMIC score, 3 patients (10%) scored 4 points and were regarded as being of low risk, 12 patients (40%) scored 5 points and were regarded as being of intermediate risk, and 15 (50%) patients scored 6 or 7 points and were regarded as being of high risk for severe ADAMTS13 deficiency. Based on the French score, 6 patients (20%) scored 0 points and were evaluated as being of low risk, 11 patients scored 1 point and were evaluated as being of intermediate risk (36.7%), and 13 patients (43.3%) scored 2 points and were evaluated as being of high risk for severe ADAMTS13 deficiency. The risk classification according to the scoring systems is summarized in Table 3.

Of the 30 patients included in our study, 19 patients (63.3%) had ADAMTS13 activity levels below 10% and were diagnosed with high test-probability iTTP. Regarding the definite diagnosis, 3 patients (10%) had cancer-associated TMA, 2 patients (6.7%) had hemolytic uremic syndrome (HUS), 2 patients (6.7%) had atypical HUS, 2 patients (6.7%) had systemic lupus erythematosus (SLE)/connective tissue disorder, 1 patient (3.3%) had drug-associated TMA, and 1 patient (3.3%) had unclassified or undiagnosed TMA. Briefly, in the control group, 20 of the 28 patients were diagnosed with iTTP with ADAMTS13 levels below

Table 2. Demographic, clinical, and laboratory features of patients aged over 60 years and the control group.

	Patients aged over 60 (n=30)	Control group of patients aged under 60 (n=28)
Age, years, median (range)	65.5 (60-85)	38 (20-59)
Sex, number (percentage) Male Female	 10 (33.3%) 20 (66.6%)	 10 (35.7%) 18 (64.3%)
Hemoglobin, g/dL, median (range)	8.3 (3.4-11.8)	7.8 (4.1-10.4)
Thrombocyte count, x10^9/L, median (range)	29.5 (7-162)	25 (4-106)
White blood cell count, x10^9/L, median (range)	8.1 (1.1-24.5)	6.6 (3.2-17.8)
LDH, U/L, median (range)	729 (271-5599)	866 (366-2086)
Creatinine, mg/dL, median (range)	1.1 (0.4-5.6)	1.5 (0.8-3.8)
ADAMTS13 activity level, %, median (range)	1.4 (0.002-72)	5 (0.2- 80.2)

LDH: Lactate dehydrogenase, MCV: mean corpuscular volume; INR: international normalized ratio; N/A: not applicable.

Table 3. Distribution of patients over 60 years of age according to PLASMIC and French risk scores.

PLASMIC score, number (percentage) Low risk (≤4 points) Intermediate risk (5 points) High risk (6-7 points)	 3 (10%) 12 (40%) 15 (50%)
French score, number (percentage) Low risk (0 points) Intermediate risk (1 point) High risk (2 points)	 6 (20%) 11 (36.7%) 13 (43.%)

10%. Six patients were diagnosed with HUS and 2 patients were diagnosed with SLE/connective tissue disorder associated with TMA.

Patients received a median of 12 TPE procedures with a range of 3 to 31. Nine patients received additional treatments, with 6 patients receiving rituximab and 3 patients receiving eculizumab. Response was achieved by 26 patients (86.7%) receiving TPE treatment. In 2 patients (6.7%) with cancer-associated TMA, a response could not be achieved, and 2 patients (6.7%) were refractory to TPE and deteriorated rapidly. Clinical exacerbation occurred in 5 patients (16.7%) and clinical relapse occurred in 6 patients. The definite diagnoses and treatment outcomes are given in Table 4.

We analyzed the sensitivity and specificity of the PLASMIC and French scores for detecting severe ADAMTS13 deficiency in patients over 60 years old. PLASMIC scores of ≥5 showed 100% sensitivity and 27.3% specificity. PLASMIC scores of ≥6 showed 63.2% sensitivity and 72.7% specificity. French scores of ≥1 showed 78.9% sensitivity and 18.2% specificity. French scores of ≥2 showed 47.4% sensitivity and 63.6% specificity. In our control group, which included patients below 60 years of age, the same sensitivity and specificity analysis for detecting severe ADAMTS13 deficiency was performed. PLASMIC scores of ≥5 showed 95% sensitivity and 100% specificity. PLASMIC scores of ≥6 showed 50% sensitivity and 100% specificity. French scores of ≥1 showed 100% sensitivity and 57.1% specificity. French scores of ≥2 showed 70% sensitivity and 85.7% specificity. The sensitivity and specificity analyses are presented in Table 5. In our study, the 1-year mortality rate was higher in patients over 60 compared to the control group (30% vs. 7.1%, p=0.043). We examined the effect of rituximab treatment on mortality in patients over 60 years old. There was 1 death among the 6 rituximab-treated patients compared to 8 deaths among 24 patients who did not receive rituximab (p=0.67). There was also 1 relapse among the rituximab-treated patients (n=6) compared to 5 relapses among patients who did not receive rituximab (n=24) (p=0.656).

We also analyzed clinical parameters including hemoglobin levels, thrombocyte counts, LDH levels, creatinine levels, ADAMTS13 activity, and PLASMIC and French scores of the 19 patients over the age of 60 and compared them with the control group of 20 patients under the age of 60 (Table 6). We also kept in mind and acknowledged the potential limitations in drawing comparisons between two age groups considering the differences in the numbers of centers involved.

Table 4. Definitive diagnosis, treatment, and mortality data of the patients aged over 60.

Definite diagnosis, number (percentage)	
TTP	19 (63.3%)
HUS	2 (6.7%)
aHUS	2 (6.7%)
SLE/mixed connective tissue disease	2 (6.7%)
Cancer-associated TMA	3 (10%)
Drug-associated TMA	1 (3.3%)
Other	1 (3.3%)
Patients with ADAMTS13 activity level of <10%, number (percentage)	19 (63.3%)
Number of therapeutic plasma exchanges, median (range)	12 (3-31)
Clinical exacerbations, number (percentage)	5 (16.7%)
Clinical relapses, number (percentage)	6 (20%)
Mortality, number (percentage)	9 (30%)
Additional treatments, number (percentage)	
Rituximab	6 (20%)
Eculizumab	3 (10%)
None	21 (70%)
Clinical response with therapeutic plasma exchange, number (percentage)	
Yes	26 (86.7 %)
No	4 (13.3 %)

TTP: Thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome; aHUS: atypical hemolytic uremic syndrome; SLE: systemic lupus erythematosus; TMA: thrombotic microangiopathy

Discussion

Several clinical prediction scores have been introduced to daily clinical routines to predict severe ADAMTS13 deficiency. There are many studies on the effectiveness and validation of these scoring systems conducted in many parts of the world [11,12,22,23,24,25]. However, older patients could present in more complicated ways than younger thrombotic thrombocytopenic purpura (TTP) patients, undermining the presumptions of clinical prediction scoring systems [16,23]. Not only do older TTP patients show higher mortality rates compared to younger patients, but the sensitivity and specificity of clinical scoring systems also tend to decrease in older patients [15,26]. Moreover, older patients are underrepresented in these scoring systems. We aimed to evaluate the utility of the PLASMIC and

Table 5. Sensitivity and specificity of the PLASMIC and French scores for thrombotic thrombocytopenic purpura.

Patients over 60 years of age (n=30)	Sensitivity	Specificity
PLASMIC score		
≥5	100%	27.3%
≥6	63.2%	72.7%
French score		
≥1	78.9%	18.2%
≥2	47.4%	63.6%
Control group of patients under 60 years of age (n=28)		
PLASMIC score		
≥5	95%	100%
≥6	50%	100%
French score		
≥1	100%	57.1%
≥2	70%	85.7%

Table 6. Comparison of clinical presentation and laboratory values of patients diagnosed with thrombotic thrombocytopenic purpura between those aged over 60 and control group of patients under 60 years of age.

	Patients over 60 (n=19)	Control group of patients under 60 (n=20)
Age, years, median (range)	66.6 (60-82)	36 (20-59)
Sex, number (percentage) Male Female	 6 (33.3%) 13 (66.6%)	 7 (35.7%) 13 (64.3%)
Hemoglobin, g/dL, median (range)	8.2 (5.6-10.8)	7.8 (5.1-10.4)
Thrombocyte count, x109/L, median (range)	32.6 (7-79)	35 (9-106)
White blood cell count, x109/L, median (range)	9.4 (2.6-24.5)	7.8 (3.8-17.8)
LDH, U/L, median (range)	881 (288-3153)	960 (562-1680)
Creatinine, mg/dL, median (range)	1.2 (0.4-2.8)	1.5 (0.8-2.8)
ADAMTS13 activity level, %, median (range)	1.2 (0.002-8.4)	3.1 (0.2-9.8)
Number of therapeutic plasma exchanges, median (range)	8 (3-31)	7 (4-21)
PLASMIC score, number (percentage) Low risk Intermediate risk High risk	 0 7 (36.8%) 12 (63.2%)	 1 (5%) 10 (50%) 9 (45%)
French score, number (percentage) Low risk (0 point) Intermediate risk (1 point) High risk (2 points)	 3 (15.8%) 7 (36.8%) 9 (47.4%)	 1 (5%) 8 (40%) 11 (55%)

LDH: Lactate dehydrogenase.

French scores to detect severe ADAMTS13 deficiency in patients over 60 years of age. Our results demonstrated that a PLASMIC score of ≥5 showed 100% sensitivity and a French score of ≥1 showed 78.9% sensitivity for detecting severe ADAMTS13 deficiency. However, specificity rates were lower (27.3% for PLASMIC scores of ≥5 and 18.2% for French scores of ≥1). In comparison, our control group, which included patients below 60 years of age with a presumptive diagnosis of TMA, showed higher sensitivity and specificity (PLASMIC score of ≥5: 95% sensitivity and 100% specificity; French score of ≥1: 100% sensitivity and 57.1% specificity). With this analysis, we have shown that the specificity of the PLASMIC and French scores for diagnosing TTP were lower compared to rates reported in previous derivation and validation studies. In a cohort of 75 TTP patients, 13 of whom were above 60 years of age, Liu et al. [17] reported that the sensitivities of PLASMIC scores of ≥5 and ≥6 were 76.9% and 61.5%, respectively. The same study reported that the sensitivities of French scores of ≥1 and ≥2 were 76.9% and 46.2%, respectively, while the reported specificities of PLASMIC scores of ≥5, PLASMIC scores of ≥6, French scores of ≥1, and French scores of ≥2 were 50%, 85.7%, 40%, and 73.3%, respectively [17]. In the original study that led to the development of the PLASMIC score, the sensitivity and specificity of PLASMIC scores of ≥6 were 90% and 92%, respectively [6]. However, the median ages of the study population in the derivation cohort and the external validation cohort were 51 and 44 years, respectively.

Older patients have more comorbidities, and it is possible that this may account for the lower predictive value of these scoring systems. In one study from Japan, patients aged over 60 presented with higher creatinine levels, higher rates of central venous system involvement, and higher short-term mortality compared to younger patients [26]. Short- and long-term mortality rates were found to be higher in older patients compared to patients aged below 60. The authors of this study stated that older individuals frequently appear with an unusual form of iTTP, the diagnosis of which may be delayed, resulting in a greater extent of organ involvement [26]. The authors further suggested that organ damage resulting from microthrombus formation might be more severe in elderly patients and that organs might be more prone to microthrombi and ischemia, which could partly account for higher mortality rates in patients aged over 60 years [26]. Similarly, in the original study that led to the development of the French score, it was suggested that more prevelant cardiovascular risk factors, preexisting comorbidities, and predominance of organ injury resulted in higher mortality rates in older patients [6]. As a result of these confounding factors, the scoring systems seem to be less accurate in patients over 60 years of age.

Efforts are being made to boost the utility and diagnostic accuracy of the PLASMIC score, including the addition of LDH levels to the original PLASMIC score [27]. In another study, the authors chose to incorporate an LDH level of more than twice the normal upper limit and generated the PLASMIC-LDH score. However, these studies included fewer cases compared to the original scoring system studies and also smaller numbers of

patients aged over 60 years. Thus, they require confirmation in cohorts with larger numbers of patients [28]. One practical solution is adding age as a variable in the scoring systems. This could involve assigning additional points for patients over a certain age threshold (e.g., 60 years) based on empirical evidence from our research.

Exacerbations and relapses are major challenges in the management of iTTP with limited options to prevent or delay relapse. Rituximab has been shown to prevent and extend the time to relapse in iTTP [29,30,31]. Whether rituximab is effective in preventing relapses in older patients has yet to be determined. Compared to younger patients, older iTTP patients could be more prone to lymphodepletion caused by the consecutive administration of the anti-CD20 antibody rituximab. Rituximab has been shown to induce closed ADAMTS13 conformation, which is associated with higher remission and lower relapse rates [29,32]. However, it is not known how the ADAMTS13 conformation changes in older patients and whether the effect of rituximab on this conformation in elderly patients differs from that of younger patients.

Study Limitations

Our study has certain limitations, including its retrospective design and the relatively small sample size. However, taking into account that the estimated incidence of acquired TTP in adults is 2.9 cases per 1 million per year [33,34], it is challenging to conduct studies with larger sample sizes for rare disorders like TTP. Another limitation of our study is the use of another retrospective analysis as the control group.

Conclusion

The PLASMIC and French scores are the most used and adapted clinical prediction scoring systems for assisting in iTTP diagnosis. However, older patients often have complicated presentations and more comorbidities, which could reduce the accuracy of clinical prediction scoring systems. Moreover, since older patients are more likely to experience morbidity and mortality from iTTP, there should be greater suspicion and lower diagnostic thresholds to improve the prognosis for older iTTP patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Boards of Trakya University and was performed in compliance with the guidelines of the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: Consent to participate/for publication was obtained from all individual participants included in the study.

Authorship Contributions

Surgical and Medical Practices: G.S., R.Ç., C.Ö.; Concept: M.B., F.K.K., V.Ö.; Design: M.B., F.K.K., B.T., C.Ö., S.D., Y.İ.; Data Collection or Processing: F.H., A.M.D., G.S., S.A., B.T., R.Ç., S.D., Y.İ.; Analysis or Interpretation: F.H., A.M.D., F.Ö., R.Ç., Y.İ., R.D.K.; Literature Search: E.G.Ü., V.Ö.; Writing: M.B., F.H., E.G.Ü., F.Ö., R.D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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