



Pediatric Acute Liver Failure: Etiologies, Intensive Care Management, and Prognostic Trends in a Tertiary Center

Üçüncü Basamak Bir Merkezde Pediyatrik Akut Karaciğer Yetmezliği: Etiyoloji, Yoğun Bakım Yaklaşımı ve Prognoz

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Abstract

Introduction: Pediatric acute liver failure (PALF) is a life-threatening multisystem disorder characterized by rapid hepatic dysfunction. This study aimed to describe the etiologies, intensive care management, and outcomes of children with PALF admitted to a tertiary pediatric intensive care unit.

Methods: We retrospectively reviewed 53 children with PALF admitted to our pediatric intensive care unit between January 2014 and December 2019. Demographic characteristics, etiology, intensive care interventions, and clinical outcomes were analyzed.

Results: Toxic or drug-induced causes (43.4%) and indeterminate etiologies (32.1%) were most frequent. Twenty patients (37.7%) required invasive mechanical ventilation, 22 (41.5%) underwent plasma exchange, 11 (20.8%) received continuous renal replacement therapy, and 7 (13.2%) underwent liver transplantation. The mean pediatric intensive care unit stay was 7.4±9.0 days. Patients with toxic/drug-induced PALF required fewer interventions and had lower sepsis rates than those with other etiologies ($p<0.01$).

Conclusion: Early recognition and comprehensive supportive care improve outcomes in children with PALF. Toxic or drug-induced PALF is associated with a milder clinical course. Continuous assessment of prognostic indicators is essential to guide management and decisions regarding liver transplantation.

Öz

Giriş: Pediyatrik akut karaciğer yetmezliği (PAKY), karaciğer fonksiyonlarının kısa sürede yerine getirilememesi sonucu gelişen, birden fazla organ sistemini etkileyebilen ve yaşamı ciddi biçimde tehdit eden bir hastalık tablosudur. Bu çalışmada, üçüncü basamak bir çocuk yoğun bakım ünitesine yatırılan PAKY tanılı çocukların etiyolojik dağılımları, yoğun bakım sürecindeki tedavileri ve klinik sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntemler: Ocak 2014 ile Aralık 2019 tarihleri arasında çocuk yoğun bakım ünitesine kabul edilen 53 PAKY tanılı çocuk geriye dönük olarak incelendi. Hastaların demografik özellikleri, hastalığa yol açan nedenler, uygulanan yoğun bakım tedavileri ve klinik sonuçları değerlendirildi.

Bulgular: En sık saptanan nedenler zehirlenme veya ilaca bağlı etiyolojiler (%43,4) ile nedeni belirlenemeyen olgular (%32,1) idi. Hastaların 20'sinde (%37,7) invaziv mekanik ventilasyon gereksinimi gelişti, 22'sine (%41,5) plazma değişimi uygulandı, 11'i (%20,8) sürekli böbrek destek tedavisi aldı ve 7 hastaya (%13,2) karaciğer nakli yapıldı. Çocuk yoğun bakım ünitesinde ortalama yatış süresi 7,4±9,0 gün olarak saptandı. Zehirlenme veya ilaca bağlı PAKY olgularında, diğer nedenlere bağlı olgulara kıyasla daha az yoğun bakım girişimi uygulandığı ve enfeksiyon gelişme oranlarının daha düşük olduğu görüldü ($p<0,01$).

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Received/Geliş Tarihi: 24.07.2025 **Accepted/Kabul Tarihi:** 30.12.2025 **Pub: 25.02.2026** **Publication Date/Yayınlanma Tarihi:** 01.04.2026

Cite this article as: Aycan F, Kendirli T, Gün E, Botan E, Kuloğlu Z, et al. Pediatric acute liver failure: etiologies, intensive care management, and prognostic trends in a tertiary center. J Pediatr Emerg Intensive Care Med. 2026;13(1):39-46



Abstract

Keywords: Pediatric acute liver failure, intensive care, prognosis, liver transplantation, plasma exchange

Öz

Sonuç: PAKY tanılı çocuklarda erken tanı ve etkin destekleyici tedavi, klinik sonuçların iyileştirilmesinde belirleyici rol oynamaktadır. Zehirlenme veya ilaca bağlı PAKY olguları genellikle daha hafif bir klinik seyir göstermektedir. İzlem sürecinde hastalığın gidişatını gösteren bulguların düzenli olarak değerlendirilmesi, karaciğer nakli gereksiniminin zamanında belirlenmesi açısından büyük önem taşımaktadır.

Anahtar Kelimeler: Pediyatrik akut karaciğer yetmezliği, çocuk yoğun bakım, hastalık gidişatı, karaciğer nakli, plazma değişimi

Introduction

Pediatric acute liver failure (PALF) is a potentially life-threatening condition in previously healthy children due to its rapidly progressive course. The PALF study group defines ALF by the following criteria: no prior evidence of chronic liver disease; biochemical markers of acute liver injury or coagulopathy; and encephalopathy with a prothrombin time (PT) >15 seconds or international normalized ratio (INR) >1.5 not correctable by vitamin K, or PT >20 seconds or INR >2 regardless of encephalopathy.¹ PALF represents one of the most challenging critical illnesses in pediatric patients, owing to its association with severe multisystem organ failure, unpredictable complications, and the need for urgent decisions about emergent liver transplantation (LT).²

The clinical course of PALF may be influenced by age, geographic location, underlying etiology, and genetic background. PALF is most frequently observed in neonates and infants, followed by teenagers.^{1,3,4} In neonates, liver failure is commonly caused by immunological, viral, or hematological etiologies, whereas in teenagers it is most commonly due to drug-induced injury.^{1,3} However, in a significant proportion of cases, the underlying cause remains unidentified.^{1,5-8} Currently, no standardized method exists to grade the severity of PALF in children for either research or clinical practice.⁹

Several clinical and laboratory variables have been associated with worse outcomes, including younger age; cerebral edema; neurological status; multisystem organ failure; prolonged PT; elevated levels of ammonia (NH₃), bilirubin, and creatinine; hepatic encephalopathy (HE) grade at onset and peak; and pediatric end-stage liver disease (PELD) score.^{7,9-15} Despite advances in critical care and LT, PALF outcomes remain suboptimal.^{13,16-19} For eligible patients, LT can be lifesaving, with reported survival rates of 62-83% when modern supportive care is combined with transplantation.^{1,6,20}

This study retrospectively analyzed, over a six-year period, children diagnosed with ALF in our pediatric intensive care unit (PICU). We aimed to describe etiologies, clinical course,

and outcomes and to explore associations between commonly used prognostic markers, such as PELD and pediatric risk of mortality (PRISM) scores, and survival outcomes.

Materials and Methods

We retrospectively reviewed the medical records of 53 patients with PALF who were admitted to our PICU between January 2014 and December 2019 (a six-year period). Patients from the neonatal period up to 18 years of age were eligible. Children diagnosed with ALF who required PICU care were included. The study was approved by the Ankara University Institutional Review Board (approval no: İ5-215-19, date: 14.11.2019). As this was a retrospective chart review, informed consent was waived by the institutional review board. The data were collected through medical record review; therefore, individual patient consent was not required.

Demographic data, including age and sex, were collected, along with PALF etiology, HE grades, and PRISM scores at admission. For patients under 12 years of age, PELD was calculated; for patients aged 12 years or older, the model for end-stage liver disease (MELD) score was calculated using the online calculator.²¹ Patient information, including presenting complaints, symptom duration, parental consanguinity, growth failure, and prior drug exposures, was recorded. Physical examination findings at admission, including ascites, jaundice, hepatomegaly, splenomegaly, edema, and encephalopathy, were also documented.

Etiologies were classified into six categories: metabolic, autoimmune, infectious, drug- or toxin-related, indeterminate, and other or unclassified. The term "indeterminate" was defined as cases in which no viral markers, drug or toxin exposure, or metabolic causes were identified. "Other" included rare or unclassified causes that did not fit into the main categories.

To explore potential prognostic differences by etiology, patients were divided into two groups: group 1 comprised patients with toxic ALF, and group 2 comprised patients with ALF from other causes. This classification was based on the

hypothesis that the underlying etiology may influence the severity of organ dysfunction, the response to supportive therapy, and the clinical course. Clinical and laboratory parameters, including PELD or MELD scores, alanine aminotransferase (ALT), aspartate aminotransferase, NH_3 , PT, INR, and the need for invasive or non-invasive respiratory support, plasma exchange (PEX), and continuous renal replacement therapy (CRRT), were compared between groups to evaluate etiology-specific differences in disease progression and outcomes.

Supportive therapies were administered according to each patient's clinical status and etiology, including electrolyte and glucose replacement, N-acetylcysteine, antibiotics, laxatives, H₂-receptor blockers, PEX, CRRT, respiratory support, and LT. Indications for LT included progressive coagulopathy or worsening HE despite maximal supportive care. Radiological assessments (abdominal ultrasound, hepatobiliary Doppler, abdominal computed tomography), electroencephalography, and liver biopsy were performed when clinically indicated. Complications, including sepsis, gastrointestinal bleeding, cerebral edema, seizures, spontaneous bacterial peritonitis, acute kidney injury, and adrenal failure, were recorded. Neurological outcomes at discharge were assessed using the pediatric cerebral performance category scale (PCPC).²²

Definitions

PALF was defined according to the criteria established by the PALF study group.²³ The severity of HE was graded clinically as follows: grade 1, slowness of mentation; grade 2, drowsiness and confusion; grade 3, very sleepy but arousable, combative, and hyperreflexic; and grade 4, unconsciousness with decerebrate or decorticate posturing.²⁴ PRISM scores were calculated using 14 physiological variables,²⁵ while PELD and MELD scores were determined as previously described for patients aged 12 years or older and for those younger than 12 years, respectively.^{26,27} Pediatric malnutrition was defined using weight-for-height z-score (WHz) or body mass index for age, with WHz considered a sensitive early indicator of growth faltering.²⁸

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 11.0 (IBM Corp., Armonk, NY, USA). Continuous variables were first evaluated for normality using the Shapiro-Wilk test. Variables with approximately normal distributions were presented as mean \pm standard deviation, whereas non-normally distributed variables were reported as median (interquartile range). Median values were primarily used for variables with skewed distributions, such as PICU length of stay, ALT, blood ammonium level, INR, PELD and MELD scores.

Comparisons between groups were performed using Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate.

To identify potential prognostic factors associated with poor outcomes (death or LT), logistic regression analysis was performed, including key clinical and laboratory parameters such as ALT, INR, PELD, and NH_3 levels.

A p-value <0.05 was considered statistically significant; and significant values are highlighted in bold. This approach ensures that the selection of descriptive statistics and inferential tests is consistent with the data distribution and aligned with the study's objective of identifying prognostic indicators in PALF.

Results

Over a 6-year period, 53 children diagnosed with PALF were evaluated; 29 (54.7%) were male. At presentation, the median age was 42 months, and parental consanguinity was present in 18 patients (34%). The etiology was identified in 36 patients, while in 17 (32.1%) it remained indeterminate. Toxic hepatitis was the most frequent cause, accounting for 23 cases (43.4%), followed by metabolic disorders (7 cases, 13.2%), infectious diseases (1 case, 1.9%), and other or unclassified causes (5 cases, 9.4%) (Table 1). Age distribution, presenting complaints, and clinical findings are summarized in Table 1.

Neurological assessment at admission revealed normal function in 19 patients (35.8%), HE grade I-II in 16 (30.2%), grade III in 14 (26.4%), and grade IV in 4 (7.5%). Laboratory results and treatment details are summarized in Table 1.

Respiratory support was not required in 28 patients (52.8%), whereas 20 patients (37.7%) required invasive mechanical ventilation, 4 patients (7.5%) required non-invasive ventilation, and 1 patient (1.8%) required high-flow nasal cannula oxygen. PEX was performed in 22 patients (41.5%), predominantly among patients in the indeterminate-etiology group. CRRT was required in 11 patients (20.8%), including continuous venovenous hemodialysis (n=5), continuous venovenous hemodiafiltration (n=5), and peritoneal dialysis (n=1). The majority of patients requiring CRRT had metabolic ALF. LT was performed in 7 patients (13.2%), all from living donors, with the most frequent indications being indeterminate and toxic- or drug-related ALF.

During the PICU stay, complications included suspected or proven sepsis in 20 patients (37.7%), gastrointestinal bleeding in 5 patients (9.4%), cerebral edema in 5 patients (9.4%), acute kidney injury in 10 patients (18.9%), and adrenal failure

Table 1. Demographic, clinical, laboratory characteristics, and treatments of children with pediatric acute liver failure

Variable	n/median (IQR)	% (fraction)	Unit/notes
Age group			
>1 month	2	4% (2/53)	
1-12 months	14	26% (14/53)	
1-5 years	17	32% (17/53)	
>5 years	20	38% (20/53)	
PALF etiology			
Toxic	23	43% (23/53)	Mushroom 8, drug overdose 15
Indeterminate	17	32% (17/53)	
Metabolic	7	13% (7/53)	Urea cycle 3, MMA 1, tyrosinemia type 1 1, mitochondrial 1, orotic aciduria 1
Other	5	9% (5/53)	
Infectious	1	2% (1/53)	
Complaints			
Nausea and vomiting	33	62% (33/53)	
Confusion	28	52% (28/53)	
Weakness	17	32% (17/53)	
Jaundice	10	18% (10/53)	
Diarrhea	5	9% (5/53)	
Weight loss	4	8% (4/53)	
Abdominal pain	2	4% (2/53)	
Fever	1	2% (1/53)	
Bloody stool	1	2% (1/53)	
Cough	1	2% (1/53)	
Clinical findings			
Hepatomegaly	17	33% (17/53)	
Jaundice	16	30% (16/53)	
Splenomegaly	8	16% (8/53)	
Edema	3	5% (3/53)	
Ascites	1	2% (1/53)	
Rash	1	2% (1/53)	
Laboratory results			
Hemoglobin	10.8 (9.1-12.3)		g/dL
WBC	8.928 (5.100-12.400)		cells/mm ³
Platelet count	199.000 (85.000-325.000)		cells/mm ³
PT	31.2 (14-49)		Second
APTT	61.4 (36-86)		Second
INR	2.51 (1.7-3.3)		-
ALT	168.7 (90-280)		U/L
AST	1.423 (450-2.600)		U/L
GGT	123 (55-190)		U/L
Total bilirubin	5.8 (2.2-9.0)		mg/dL
Direct bilirubin	2.6 (1.0-4.5)		mg/dL
Total protein	5.6 (4.9-6.2)		g/dL
Albumin	3.4 (2.9-3.9)		g/dL
BUN	12.4 (6-18)		mg/dL
Creatinine	0.53 (0.3-0.7)		mg/dL
Glucose	92 (72-110)		mg/dL
Alpha-fetoprotein	4.746 (1.200-8.100)		U/L
Alpha-1 antitrypsin	1.5 (1.0-2.0)		mg/dL
Blood ammonium	24.1 (12-35)		µmol/L

Table 1. Continued

Variable	n/median (IQR)	% (fraction)	Unit/notes
Required treatments			
Fluid, electrolyte, and glucose replacement	53	100% (53/53)	
N-acetyl cysteine	51	96% (51/53)	
H2 blocker	46	87% (46/53)	
Oral/IV antibiotics	38	71% (38/53)	
Laxative	37	70% (37/53)	
Antifungal therapy	30	57% (30/53)	
L-ornithine/L-aspartate	29	55% (29/53)	
Total parenteral nutrition	28	53% (28/53)	
Anticonvulsants	9	17% (9/53)	
Hypertonic saline infusion	8	15% (8/53)	

IQR: Interquartile range, PALF: Pediatric acute liver failure, MMA: Methylmalonic acidemia, WBC: White blood cell, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, BUN: Blood urea nitrogen, IV: Intravenous

Table 2. Clinical and laboratory differences between toxic/drug-induced and other pediatric acute liver failure groups

Parameter	Group 1 Median ± SD	Group 2 Median ± SD	p-value (test used)
PICU length of stay (days)	3.9±4.02	10.03±10.71	0.07 (Mann-Whitney U)
ALT (U/L)	65±32	514±259	0.021 (Mann-Whitney U)
Ammonium (µmol/L)	107±63.8	286.7±467.5	0.548 (Mann-Whitney U)
INR	2±1.07	2.85±1.32	0.003 (Mann-Whitney U)
PELD score	6±4.16	27±9.05	0.0001 (Mann-Whitney U)
MELD score	14±7.97	33±16.8	0.456 (Mann-Whitney U)

CRRT and PEX were initiated based on clinical criteria, including severe encephalopathy, worsening renal function, fluid overload, or laboratory indicators of liver failure. Significance was initially evaluated at p<0.05. After Bonferroni correction for multiple comparisons, the adjusted significance threshold is 0.005; therefore, differences in CRRT and PEX usage should be interpreted cautiously.
SD: Standard deviation, PICU: Pediatric intensive care unit, ALT: Alanine aminotransferase, INR: International normalized ratio, PELD: Pediatric end-stage liver disease, MELD: Model for end-stage liver disease

in 1 patient (1.8%). At discharge, PCPC scores were 1 in 32 patients (60.4%), 2 in 8 patients (15.1%), 3 in 3 patients (5.7%), and 6 in 10 patients (18.9%). The mean PICU length of stay was 7.38±9 days (median 4 days). Overall survival was 81.1% (43 patients); there were 10 deaths (18.9%), which occurred most commonly in patients with metabolic disease

Table 2 summarizes disease severity scores and key laboratory parameters in patients with toxic- or drug-induced ALF (group 1) compared with patients with ALF from other causes (group 2). Group 1 exhibited lower PELD scores, ALT levels, and INR values, indicating milder liver injury. Although MELD and PRISM scores were higher in group 2, these differences did not reach statistical significance. Use of CRRT and PEX was more common in group 2; however, after applying the Bonferroni correction for multiple comparisons (adjusted significance threshold of 0.005), these differences were not statistically significant. Both CRRT and PEX were initiated based on established clinical criteria, including severe encephalopathy, worsening renal function, fluid overload, or abnormal laboratory markers indicative of liver failure.

Notably, five patients initially classified as having indeterminate PALF underwent whole-genome sequencing during long-term follow-up, resulting in definitive diagnoses in all cases. These included mitochondrial depletion syndrome and 3-beta-hydroxy-delta-5-C-27-steroid dehydrogenase deficiency, both established causes of PALF; biotinidase deficiency, a rare metabolic contributor to liver dysfunction; and spinocerebellar ataxia type 21 coexisting with Ehlers-Danlos syndrome type 3, which are unlikely to cause liver failure directly but may reflect broader multisystem involvement.

Discussion

ALF, although rare, can be fatal. While survival rates have improved due to advances in intensive care and timely LT, no specific medical therapy has been established.¹ This study aimed to evaluate the etiological characteristics and prognostic outcomes of children admitted to our PICU between January 2014 and December 2019.

Consanguinity is reported in up to 10% of the global population²⁹ and 25.1% of the population in Türkiye;³⁰

in our cohort it was observed in 34% of patients. A one-sample proportion Z-test comparing our cohort to the national rate yielded a Z-score of 1.49 ($p=0.135$), indicating that this difference was not statistically significant. Therefore, although numerically higher, consanguinity in our cohort cannot be considered significantly more frequent than the national average.

In our series, toxic drug-related (43.3%) and indeterminate (32.1%) etiologies were the most common causes of ALF. International studies have reported an indeterminate-etiology as the predominant finding.^{1,31,32} In developed countries, ALF secondary to viral hepatitis accounts for less than 10% of cases.^{6,33} A prior Turkish study conducted between 1997 and 2003 reported infectious causes in 35% of cases.³⁴ In contrast, none of our patients had hepatitis-related ALF, likely reflecting improved sanitation, rising socioeconomic standards, and the introduction of the hepatitis A vaccination program in Türkiye in October 2012.

Wild mushroom ingestion is a recognized cause of toxic ALF. Globally, more than 5,000 species of mushrooms exist, approximately 3% of which are poisonous.^{35,36} In Türkiye, mushroom poisoning is primarily due to cyclopeptide toxins,^{37,38} and the specific species ingested are unknown in over 90% of cases.^{38,39} In our cohort, most cases of toxic ALF were caused by mushroom poisoning. Particular attention should be paid to children with a family history of poisoning, especially in regions with seasonal agricultural workers engaged in mushroom cultivation. Public education and healthcare-provider awareness are essential, as clinical presentations vary depending on the species ingested and children are at high risk for exposure to wild or improperly cooked mushrooms.³⁷

Although intoxications with colchicine and metformin were classified as toxic ALF, these agents do not primarily target hepatocytes, and management is guided by systemic toxicity rather than by liver-specific failure. These patients were included because their hospital courses were severe and prolonged, requiring PICU admission and management of liver dysfunction as part of multisystem involvement. Colchicine intoxication was particularly relevant to Familial Mediterranean Fever, an autosomal recessive autoinflammatory disease prevalent in the Turkish population (1 in 400-1,000).⁴⁰⁻⁴² Children treated with colchicine may be at increased risk of toxicity, highlighting the need to limit inappropriate or excessive exposure to colchicine.

The most common presenting symptoms and physical findings were nausea, vomiting, confusion, jaundice, and hepatomegaly, consistent with previous studies from Türkiye.^{34,43} Notably, no cases of Wilson's disease were identified. One patient developed ALF secondary to varicella-zoster virus (VZV) infection despite the absence of underlying immunosuppression, which contrasts with prior reports

linking VZV-induced ALF to immunocompromised states.⁴⁴ Liver ultrasound was the most frequently used radiological modality, in line with previous studies.⁴⁵

In our cohort, survival without LT was 67.9%, which is higher than previously reported rates of 28-33%.^{6,7,44} Early referral and timely supportive intensive care likely contributed to improved spontaneous survival.⁴⁶ LT was performed in seven patients, all of whom survived and were discharged from the PICU, thereby highlighting its critical role in improving prognosis.⁴⁷ CRRT, PEX, and LT were performed in 21.8%, 41.5%, and 13.2% of patients, respectively, compared with 18%, 14%, and 50% of patients reported by Di Giorgio et al.⁴⁸

Evaluation of prognostic factors revealed that patients with toxic drug-related ALF required fewer interventions-including IMV, PEX, and CRRT-than did patients with ALF from other etiologies. In our cohort, toxic or drug-related ALF was associated with a relatively more favorable clinical course, consistent with previous reports.¹

Study Limitations

This study has several limitations. Its retrospective design and relatively small, single-center sample limit the generalizability of the findings. A substantial proportion of patients remained without a definitive diagnosis, highlighting gaps in current knowledge of PALF etiology and the limitations of available diagnostic tools. The absence of a standardized severity grading system for PALF complicates comparisons across studies and hinders the development of universally accepted clinical guidelines. Although prognostic indicators, such as PELD and PRISM scores, were assessed, the lack of validated PALF-specific models limits the accuracy of outcome prediction. Future multicenter prospective studies employing standardized criteria and advanced molecular diagnostics are warranted to address these challenges.

Conclusion

PALF is a life-threatening condition that requires prompt recognition and intensive management. Early referral to a PICU and, when indicated, to an LT center markedly improves spontaneous survival. Identifying patients who require LT is critical, as timely transplantation can be life-saving. Children with PALF should be closely monitored, with careful attention to relevant clinical and laboratory parameters. Supportive therapies-including all forms of PEX and CRRT-play a vital role in survival and may serve as a bridge to LT. Promoting organ donation is particularly important in regions with limited cadaveric transplant availability, as LT remains the definitive life-saving intervention.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Institutional Review Board (approval no: İ5-215-19, date: 14.11.2019).

Informed Consent: As this was a retrospective chart review, informed consent was waived by the institutional review board. The data were collected through medical record review; therefore, individual patient consent was not required.

Footnotes

This manuscript was presented at the 17th Turkish International Pediatric Intensive Care and Emergency Congress, Antalya, Türkiye, October 16, 2021.

Authorship Contributions

Surgical and Medical Practises: F.A., T.K., E.G., E.B., Z.K., C.T.K., M.K., S.F., E.İ., D.B., A.K., Concept: F.A., T.K., Z.K., C.T.K., E.İ., Design: F.A., T.K., Z.K., Data Collection or Processing: F.A., T.K., B.D.E., E.İ., Analysis or Interpretation: F.A., T.K., Z.K., B.D.E., E.İ., Literature Search: F.A., Writing: F.A., T.K., E.İ.

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

One of the authors of this article (T.K.) is a member of the Editorial Board of this journal. He was completely blinded to the peer review process of the article.

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

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