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# Early Characteristics of Patients with Systemic Juvenile Idiopathic Arthritis and Differences with Adult-Onset Still's Disease

## Sistemik Juvenil İdiyopatik Artritli Hastaların Erken Dönem Özellikleri ve Erişkin Başlangıçlı Still Hastalığı ile Farklılıkları

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## Abstract

**Aim**: The purpose of this study was to evaluate the demographic characteristics, early clinical and laboratory findings and treatment approaches in patients with systemic juvenile idiopathic arthritis (sJIA). In addition, it was aimed to discuss the differences of patients with sJIA from adult-onset Still's disease (AOSD).

**Material and Method**: Patient data were collected from two tertiary hospital rheumatology centers. Pediatric patients diagnosed with sJIA according to ILAR criteria between 2015 and 2022 and adult patients diagnosed with AOSD according to Yamaguchi criteria between 2016 and 2022 were included in the study. Demographic, clinical and laboratory findings were recorded from patient files.

**Results**: The median age at diagnosis of 63 sJIA patients included in the study was 6.4 years. Fever (n=63, 100%), arthritis (n=53, 84.1%), skin rash (n=50, 79.4%), hepatosplenomegaly (n=42, 66.7%), and lymphadenopathy (n=24, 38.1%) were commonly observed. The monocyclic pattern was the most frequently observed disease pattern (n=39, 61.9%). The mean leukocyte count was 15830±6604/mm3, while the mean erythrocyte sedimentation rate was 75.9±27.3 mm/hour. Methotrexate (n=21, 33.3%) and cyclosporine (n=9, 14.3%) were the most frequently preferred immunosuppressive agent in combination with corticosteroids. Among biological agents, canakinumab was used in 16 patients, etanercept in 11, infliximab in 10, tocilizumab in 9 and anakinra in 9 patients. Remission was achieved in 59 (98.3%) patients within the study group. To compare with sJIA patients, 39 AOSD patients were included in the study. Arthritis and hepatosplenomegaly were more common in sJIA (p<0.001). Duration of fever, frequency of lymphadenopathy, skin rash and serositis were similar in both groups. Ferritin and CRP levels were significantly higher in AOSD (p=0.021 and p<0.001, respectively). Monocyclic pattern was more common in sJIA and chronic pattern was more common in AOSD (p=0.005). The duration of oral steroid and synthetic DMARD treatment was significantly longer in AOSD (p<0.001 and p=0.017, respectively).

**Conclusion**: sJIA is a complex and multifaceted autoinflammatory disease characterized by a range of symptoms including fever, rash, and arthritis. Although it has similar characteristics to AOSD, AOSD patients have longer treatment durations.

**Keywords**: Biological drugs, fever, juvenile idiopathic arthritis, Adult onset Still disease

## Öz

**Amaç**: Bu çalışmanın amacı sistemik juvenil idiyopatik artrit (sJIA) hastalarının demografik özelliklerini, erken dönem klinik ve laboratuvar bulgularını ve tedavi yaklaşımlarını değerlendirmektir. Ayrıca hastalarımızın erişkin başlangıçlı Still hastalığından (EBSH) farklılıklarının tartışılması amaçlandı.

**Gereç ve Yöntem**: Hasta verileri iki üçüncü basamak hastane romatoloji merkezinden toplandı. Çalışmaya 2015-2022 yılları arasında ILAR kriterlerine göre sJIA tanısı alan çocuk hastalar ve 2016-2022 yılları arasında Yamaguchi kriterlerine göre erişkin başlangıçlı Still hastalığı tanısı alan erişkin hastalar dahil edildi. Demografik, klinik ve laboratuvar bulguları hasta dosyalarından kaydedildi.

**Bulgular**: Çalışmaya dahil edilen 63 sJIA hastasının tanı anındaki ortanca yaşı 6,4 yıldı. Ateş (n=63, %100), artrit (n=53, %84,1), deri döküntüsü (n=50, %79,4), hepatosplenomegali (n=42, %66,7) ve lenfadenopati (n=24, %38,1) yaygın olarak gözlendi. Monosiklik patern en sık gözlenen hastalık paterniydi (n=39, %61,9). Ortalama lökosit sayısı 15830±6604/mm3, ortalama eritrosit sedimentasyon hızı ise 75,9±27,3 mm/saat idi. Metotreksat (n=21, %33,3) ve siklosporin (n=9, %14,3) kortikosteroidlerle birlikte en sık tercih edilen immünsüpresif ilaçlardı. Biyolojik tedavi kapsamında hastaların 16'sında canakinumab, 11'inde etanersept, 10'unda infliximab, 9'unda tocilizumab ve 9'unda anakinra kullanıldı. Çalışma grubundaki 59 (%98,3) hastada remisyon sağlandı. sJIA hastaları ile karşılaştırmak amacıyla 39 EBSH hastası çalışmaya dahil edildi. Artrit ve hepatosplenomegali sJİA'da daha sık görüldü (p<0,001). Ateşin süresi, lenfadenopati sıklığı, deri döküntüsü ve serozit her iki grupta da benzerdi. EBSH'da ferritin ve CRP düzeyleri anlamlı derecede yüksekti (sırasıyla p=0,021 ve p<0,001). Monosiklik patern sJIA'da, kronik patern ise AOSD'da daha sıktı (p=0,005). AOSD'de oral steroid ve sentetik DMARD tedavisinin süresi anlamlı olarak daha uzundu (sırasıyla p<0,001 ve p=0,017).

**Sonuç**: sJIA, ateş, döküntü ve artrit gibi bir dizi semptomla karakterize karmaşık ve çok yönlü bir otoinflamatuar hastalıktır. EBSH ile benzer özelliklere sahip olsa da EBSH hastalarının daha uzun süreli tedaviye ihtiyacı vardır.

**Anahtar Kelimeler**: Biyolojik ilaçlar, ateş, jüvenil idiyopatik artrit, erişkin başlangıçlı Still hastalığı

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## INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a rare childhood autoinflammatory disease. It differs from other juvenile arthritis subtypes with extraarticular systemic findings. Symptoms of the disease can mimic bacterial or viral infection, malignancy and other inflammatory disease. The unique combination of quotidian fevers, arthritis and salmon-colored rash serves as a defining triad (1). Additional clinical observations comprise hepatomegaly, splenomegaly, generalized lymphadenopathy, and serositis (1, 2).

All of the classic features may not be present at the onset of the disease, symptoms and signs are non-specific, overlapping with other inflammatory and non-inflammatory conditions.

Adult-onset Still's disease (AOSD) is similarly a systemic inflammatory disease, characterized by a clinical triad of high fever, arthralgia and/or arthritis and skin rash. It is proposed that AOSD and sJIA represent a continuum of the same disease (3, 4).

The purpose of this study was to evaluate the demographic characteristics, early clinical and laboratory findings and treatment approaches of sJIA patients admitted to a rheumatology referral center. It was also aimed to present the early findings of our patients and to discuss the differences from AOSD.

## MATERIAL AND METHOD

This study was approved by the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 02/06/2021, Decision No: E2-21-557). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Study Design and Participants

The study was designed as a medical record review. Patient data were collected from two tertiary hospital rheumatology centers. Pediatric patients diagnosed with sJIA according to International League of Associations for Rheumatology (ILAR) criteria between 2015-2022 and adult patients diagnosed with AOSD according to the to the Yamaguchi criteria between 2016-2022 were included in the study (5). SJIA and AOSD patients with missing data were excluded.

### Data Collection

Data were collected from the files of patients. Age, gender, presenting features (joint involvement, rash, fever, serositis, hepatosplenomegaly, lymphadenopathy), and all initial laboratory findings such as complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase were recorded. Treatments, the course, frequency and number of disease attacks, treatment response, complication of disease were noted.

### Definitions

The clinical course of the disease was divided into three different groups: monocyclic, polycyclic and persistent course. Monocyclic sJIA course is characterized with a single episode of systemic symptoms and arthritis, resolving within 24 months. Polycyclic course has multiple recurrences of active disease alternating with periods of remission. The persistent sJIA is characterized by ongoing active systemic features and arthritis, possibly leading to severe joint deformities (2).

Wallace criteria were used to define inactive disease. According to these criteria, there must be an absence of fever, rash, serositis, splenomegaly, lymphadenopathy, and arthritis, as well as normal levels of ESR and CRP (6).

### Statistical Analyses

Data analysis was performed in IBM SPSS (Statistical Package for Social Sciences) version 25 package program. The conformity of the variables to normal distribution was examined visually and analytically. Descriptive analyses were presented as mean and standard deviation, median and interquartile range for numerical variables and frequency tables for ordinal and categorical variables. For intergroup comparisons, Student's T-Test was used for normally distributed numerical variables, Mann Whitney U test was used for non-normally distributed numerical variables, and Chi-square or Fisher's test was used for categorical variables. Results were considered statistically significant for $p<0.05$.

## RESULTS

### Demographic Characteristics, Clinical and Laboratory Findings and Treatments of sJIA Patients

Sixty-three sJIA patients were included in the study. The mean age at diagnosis was 6.4 years. All patients had fever at presentation. The median duration of the fever was 20 days. The most common musculoskeletal manifestation was arthritis in 53 (84.1%) patients. The other symptoms were skin rash in 50 (79.4%) patients, hepatosplenomegaly in 42 patients (66.7%), and lymphadenopathy in 24 (38.1%) patients. Sore throat, pericarditis, and pleuritis were less commonly reported symptoms (**Table 1**). The mean leukocyte

count was 158306604/mm3, while the mean ESR was 75.9±27.3 mm/hour. The median CRP and ferritin levels were 28.7 mg/dL and 1279.5 ng/ml, respectively. Disease pattern was monocyclic in 39 (61.9%) patients, polycyclic in 17 (27%) patients and chronic in 7 (11.1%) patients (**Table 1**).

**Table 1. Demographic and Clinical Characteristics of sJIA Patients**

| | sJIA (n=63) |
|---|---|
| Age of diagnosis (years), median (IQR) | 6.4 (7.7) |
| Fevera, n(%) | 63 (100.0) |
| Duration of fevera (day), median (IQR) | 20 (13) |
| Musculoskeletal features | |
| Artritis, n(%) | 53 (84.1) |
| Number of the involved joints, median (IQR) | 2 (3) |
| Arthralgia, n(%) | 5 (7.9) |
| Organ involvementa | |
| Skin rash, n(%) | 50 (79.4) |
| Hepatosplenomegaly, n(%) | 42 (66.7) |
| Lymphadenopathy, n(%) | 24 (38.1) |
| Sore throat, n(%) | 17 (27.0) |
| Pericarditis, n(%) | 9 (14.3) |
| Pleuritis, n(%) | 12 (19) |
| Laboratory abnormalities | |
| Leukocyte count,±SD | 15830±6604 |
| ESR (mm/h), ±SD | 75.9±27.3 |
| CRP (mg/dl), median (IQR) | 28.7 (118.4) |
| Ferritin (ng/ml), median (IQR) | 1279.5 (4847) |
| ALT (U/L), median (IQR) | 17.5 (30) |
| Disease patternsb | |
| Monocyclic, n(%) | 39 (61.9) |
| Polycyclic, n(%) | 17 (27.0) |
| Chronic, n(%) | 7 (11.1) |

aCollected at the time of diagnosis, bCollected at the end of the follow-up, IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis

Corticosteroids were the most commonly used immunosuppressive agent. Thirty-eight (60.3%) of the patients had required pulse corticosteroid treatment. Among conventional immunosuppressive drugs, methotrexate (n=21, 33.3%) and cyclosporine (n=9, 14.3%) were the most frequently preferred agents. Fifty-five (87.3%) patients received biological drugs, 16 canakinumab, 11 etanercept, 10 infliximab, 9 tocilizumab and 9 anakinra. The median duration of the biological disease modifying antirheumatic drugs (DMARD) was 6 month (**Table 2**). The majority of patients (98.3%) achieved remission, and among them, 29 (49.2%) achieved drug-free remission. The median time of remission was 9 months. One (1.7%) patient died from active disease (**Table 2**).

## Comparison of sJIA and AOSD patients

To compare with sJIA patients, 39 AOSD patients were included in the study. **Table 3** summarizes the demographic characteristics, clinical and laboratory findings and course of AOSD patients in comparison with sJIA patients. Arthritis and hepatosplenomegaly were more common in sJIA (p<0.001), while sore throat was more common in AOSD (p=0.041). Duration of fever, frequency of lymphadenopathy, skin rash and serositis were similar in both cases. Ferritin and CRP levels were significantly higher in AOSD (p=0.021 and p<0.001, respectively). Monocyclic pattern was more common in sJIA and chronic pattern was more common in AOSD (p=0.005). MAS developed more in sJIA patients (p=0.002) (**Table 3**). **Table 4** shows the treatments used in AOSD patients in comparison with sJIA patients. The duration of oral steroid and synthetic DMARD treatment was significantly longer in AOSD (p<0.001 and p=0.017, respectively).

**Table 2. Treatment Details of sJIA Patients**

| | sJIA (n=63) |
|---|---|
| Pulse corticosteroid, n(%) | 38 (60.3) |
| Duration of oral corticosteroid (month), median (IQR) | 6 (5) |
| Synthetic DMARDs treatment | |
| Methetrexate, n(%) | 21 (33.3) |
| Cyclosporine, n(%) | 9 (14.3) |
| Biological DMARDs treatment | |
| Infliximab, n(%) | 10 (15.9) |
| Etanercept, n(%) | 11 (17.5) |
| Tocilizumab, n(%) | 9 (14.3) |
| Anakınra, n(%) | 9 (14.3) |
| Canakınumab, n(%) | 16 (25.4) |
| Duration of treatment (month), median (IQR) | 6 (15) |
| Complications | |
| Macrophage activation syndrome, n(%) | 14 (22.2) |
| Last status | |
| Remission (drug-free) , n(%) | 29 (49.2) |
| Remission (on medication) , n(%) | 30 (50.8) |
| Remission, n(%) | 59 (98.3) |
| Non-remission, n(%) | 1 (1.7) |
| Mortality, n(%) | 1 (1.7) |

IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis, DMARD: disease modifying drugs,

**Table 3. Comparison of Demographic Characteristics, Clinical and Laboratory Findings and Prognosis of SJIA and AOSD Patients**

| | sJIA (n=63) | AOSD (n=39) | P-value |
|---|---|---|---|
| Age of diagnosis (years), median (IQR) | 6.4 (7.7) | 41 (32) | <0.001*** |
| Fevera, n(%) | 63 (100.0) | 37 (94.9) | 0.144* |
| Duration of fevera (day), median (IQR) | 20 (13) | 30 (58.3) | 0.198*** |
| Musculoskeletal features | | | |
| Artritis, n(%) | 53 (84.1) | 20 (51.3) | <0.001** |
| Number of the involved joints, median (IQR) | 2 (3) | 0 (2) | <0.001*** |
| Arthralgia, n(%) | 5 (7.9) | 0 (0) | 0.151* |
| Organ involvementa | | | |
| Skin rash, n(%) | 50 (79.4) | 26 (66.7) | 0.166** |
| Hepatosplenomegaly, n(%) | 42 (66.7) | 18 (46.2) | 0.041** |
| Lymphadenopathy, n(%) | 24 (38.1) | 18 (46.2) | 0.422** |
| Sore throat, n(%) | 17 (27.0) | 18 (46.2) | 0.024** |
| Pericarditis, n(%) | 9 (14.3) | 5 (12.8) | 0.834** |
| Pleuritis, n(%) | 12 (19) | 8 (20.5) | 0.856** |
| Laboratory abnormalities | | | |
| Leucocyte count, ±SD | 15830±6604 | 16883±9208 | 0.507**** |
| ESR (mm/h), ±SD | 75.9±27.3 | 83.2±21.7 | 0.170**** |
| CRP (mg/dl), median (IQR) | 28.7 (118.4) | 150 (182) | <0.001*** |
| Ferritin (ng/ml), median (IQR) | 1279.5 (4847) | 3425.5 (9472.8) | 0.021*** |
| ALT (U/L), median (IQR) | 17.5 (30) | 40 (90) | <0.001*** |
| Complications | | | |
| Macrophage activation syndrome, n(%) | 14 (22.2) | 0 (0) | 0.002** |
| Disease patternsb | | | |
| Monocyclic, n(%) | 39 (61.9) | 16 (41.0) | 0.005** |
| Polycyclic, n(%) | 17 (27.0) | 8 (20.5) | |
| Chronic, n(%) | 7 (11.1) | 15 (38.5) | |
| Last status | | | |
| Remission (drug-free) , n(%) | 29 (49.2) | 13 (39.4) | 0.367** |
| Remission (on medication), n(%) | 30 (50.8) | 20 (60.6) | |
| Remission, n(%) | 59 (98.3) | 33 (91.7) | 0.147* |
| Non-remission, n(%) | 1 (1.7) | 3 (8.3) | |
| Mortality, n(%) | 1 (1.7) | 3 (8.3) | |
| Comorbidities | 1 (1.6) | 15 (38.5) | <0.001** |

aCollected at the time of diagnosis, bCollected at the end of the follow-up, *Fisher's Exact Test, **Chi-square, ***Mann-Whitney U test, ****Independent samples T test, IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis, AOSD: adult onset still disease

**Table 4. Comparison of Treatments of SJIA and AOSD Patients**

| | sJIA (n=63) | AOSD (n=39) | P-value |
|---|---|---|---|
| Pulse corticosteroid, n(%) | 38 (60.3) | 28 (71.8) | 0.238** |
| Duration of oral corticosteroid (month), median (IQR) | 6 (5) | 24 (40.5) | <0.001*** |
| Synthetic DMARDs treatment | | | |
| Methetrexate, n(%) | 21 (33.3) | 29 (74.4) | <0.001** |
| Cyclosporine, n(%) | 9 (14.3) | 10 (25.6) | 0.152** |
| Leflunomide, n(%) | 0 (0) | 2 (5.1) | 0.144* |
| Biological DMARDs treatment | | | |
| Infliximab, n(%) | 10 (15.9) | 0 (0) | 0.009** |
| Etanercept, n(%) | 11 (17.5) | 1 (2.6) | 0.023** |
| Adalimumab, n(%) | 0 (0) | 1 (2.6) | 0.382* |
| Tocilizumab, n(%) | 9 (14.3) | 6 (15.4) | 0.879** |
| Anakınra, n(%) | 9 (14.3) | 17 (43.6) | 0.001** |
| Canakınumab, n(%) | 16 (25.4) | 0 (0) | 0.001** |
| Duration of treatment (month), median (IQR) | 6 (15) | 5.5 (35.75) | 0.521*** |

*Fisher's Exact Test, **Chi-square, ***Mann-Whitney U test, IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis, AOSD: adult onset still disease, DMARD: disease modifying drugs,

## DISCUSSION

Systemic juvenile idiopathic arthritis is a rare cause of fever with unknown origin in childhood and can lead to life-threatening complications if not treated. It requires high suspicion due to the nonspecific and incomplete nature of its clinical manifestations. In this study, it was shown that although fever was the most common feature in sJIA, arthritis, skin rash, hepatosplenomegaly and lymphadenopathy were also commonly observed. Acute phase reactants were shown to be elevated, reflecting systemic inflammation. Remission was achieved in 98.3% of patients with intensive treatment.

Adult-onset Still's disease is a systemic inflammatory disease that usually affects young adults (3, 4). Clinical and laboratory manifestations, complications and treatment approaches emphasize the similarities between sJIA and AOSD. Therefore, sJIA and AOSD represent a continuum of a single disease entity. We aimed to compare sJIA patients with AOSD patients. While arthritis and hepatosplenomegaly were more frequent in sJIA, duration of fever, frequency of lymphadenopathy, skin rash and serositis were similar. Monocyclic pattern was more common in sJIA and chronic pattern was more common in AOSD. Duration of oral steroid and synthetic DMARD treatment was significantly longer in AOSD.

Although sJIA can develop at any age, it tends to peak between 1 and 5 years. In our study, the age of onset was 6.4 years (7, 8). AOSD usually affects young adults; the mean age at diagnosis is approximately 38 years (3). As with sJIA, delayed diagnosis is common due to non-specific symptoms. Considering that fever is the main symptom, it is possible to make the diagnosis after excluding diseases such as infection and malignancy that cause prolonged fever. Because of the devastating complications of the disease in the early period and due to increased awareness, the delay in diagnosis is decreasing over the years. While fever was observed in all patients, other clinical findings were not present at the disease onset in all patients. Arthritis (84.1%), rash (79.1%) and hepatosplenomegaly (66.7%), the most common clinical findings. Clinical findings which specialized the diagnosis such as generalized lymphadenopathy, pericarditis, and pleuritis were lower.

The fact that fever is the only clinical finding in some patients and infections are common in early childhood, diagnosing the condition becomes challenging. In patients without accompanying arthritis, the pattern of fever (1 or 2 times a day and returning to normal) and the character of the rash (usually accompanied by fever and no residuals) may be suggestive. Kishida et al. showed that the percentage of AOSD patients with fever, arthralgia, skin rash, lymphadenopathy, splenomegaly, pericarditis, interstitial pneumonia, abdominal pain and myalgia was not different from sJIA patients (4). They also found that the incidence of disseminated intravascular coagulation and macrophage activation syndrome (MAS) in elderly-onset AOSD patients was significantly higher than in the younger-onset group (4). Although MAS did not develop in 39 AOSD patients in our study, it should be kept in mind that MAS may develop in AOSD. MAS is also a critical and life-threatening complication in sJIA and AOSD. Elevated ferritin levels are typically observed in patients with clinically established MAS. Nevertheless, elevated ferritin levels might also use as an early indicator of subclinical MAS in some cases. Early diagnosis and timely intervention have the potential to be life-saving. We found percentage of MAS 22.2% in our study. Previous studies reported MAS frequency in sJIA patients between 5-17% (9). Sağ et al reported a higher frequency of MAS (33%) (10). The high rate of MAS requires even more caution in patients with fever of unknown origin. sJIA patients are predisposed to develop MAS and this life-threatening complication can result in death due to the difficulty in diagnosis.

The cornerstone of sJIA treatment involves the use of corticosteroids and NSAIDs (1-3). These medications help control inflammation and manage symptoms, but their prolonged use can come with potential side effects. In our study median duration of corticosteroids was 6 months. We preferred MTX and cyclosporin as a NSAID. In a recent adult study, methotrexate was shown to be effective in disease control, especially in 40-70% of steroid-dependent AOSD patients (11). As the field of rheumatology has progressed, targeted therapies, such as biologic agents that inhibit specific cytokines, such as interleukin-1 and interleukin-6 inhibitors, have provided more targeted and effective treatment options for sJIA (12). In our study, biological agents were used in 87.3% of the patients and remission was achieved in 98% of the patients. Until the last few decades, the predominant treatment for patients with AOSD was corticosteroids. However, it is known that the frequency of comorbidity is high in patients with AOSD depending on the increase in age. These comorbidities caused the patient's condition to worsen easily when corticosteroids were used. Therefore, it is inevitable that elderly patients with AOSD need treatment with drugs other than corticosteroids. Methotrexate and/or biological agents are commonly used in AOSD, just as in sJIA (13). In our study, it was observed that immunosuppressive drugs other than corticosteroids and biological agents were commonly used in both sJIA and AOSD patients. However, it is noteworthy that the duration of use of oral steroids and synthetic DMARDs was also longer in AOSD.

The major limitations of our study were the retrospective design with small sample size. However, the interpretation of the data of sJIA patients with the data of AOSD patients is the strength of this study.

## CONCLUSION

Early recognition, careful monitoring, and tailored treatment strategies are essential to provide the best possible outcomes for children affected by sJIA. Similar clinical findings, laboratory findings and treatment approaches of sJIA and AOSD seem to reflect the continuity of the same disease.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** This study was approved by the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 02/06/2021, Decision No: E2-21-557).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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