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RETROSPECTIVE EVALUATION OF PATIENTS FOLLOWED-UP AND TREATED FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA: A 21-YEAR SINGLE-CENTER EXPERIENCE

İDİYOPATİK TROMBOSİTOPENİK PURPURA NEDENİYLE TAKİP VE TEDAVİ EDİLEN HASTALARIN RETROSPEKTİF DEĞERLENDİRİLMESİ: 21 YILLIK TEK MERKEZ DENEYİMİ

Gözde DOYMUŞ [1]
Zühal KESKİN SARILAR[2]

[1] Pediatrics Clinic, Erzurum City Hospital, Erzurum, TURKEY
[2] Department of Pediatric Hematology-Oncology, Samsun University School of Medicine, Samsun, TURKEY

ORCID: 0000-0002-8284-8456, 0000-0001-8689-4014

e-mail: gozdedoymus@hotmail.com

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Abstract / Özet

Objectives: Primary immune thrombocytopenia (ITP) is an autoimmune disorder that is distinguished by a low platelet count (<100×109/L) without any other underlying causes. The aim of this study is to determine the factors affecting chronicity by retrospectively evaluating the demographic characteristics, examination findings, laboratory results, treatment regimens and treatment responses of patients followed-up for idiopathic thrombocytopenic purpura in our clinic. **Materials and methods:** This study retrospectively reviewed the medical records of patients diagnosed with idiopathic thrombocytopenic purpura and admitted to the Department of Paediatrics at the Faculty of Medicine from January 1, 1997, to December 31, 2018. **Results:** A total of 447 patients diagnosed with idiopathic thrombocytopenic purpura (ITP) between January 1997-December 2018 were identified. Four hundred twenty-eight patients were included in the study. The mean age of diagnosis in chronic ITP was higher than that of acute ITP (p=0.000). Platelet count at admission was lower in acute ITP patients than that of chronic patients (p=0.035). ANA positivity was much higher among chronic patients than in other groups (p=0.014). The difference between the platelet count at the time of diagnosis and on the 3rd day was much higher in patients on steroid and IVIG therapy than that of the patients under combined therapy (p<0.001). The 3rd and 7th-day platelet counts of patients with remission was higher than that of the patients without remission (p<0.001). Age of diagnosis, mean follow-up period, and platelet count at day 7 were identified as the risk factors for chronicity. **Conclusion:** It was found that older age of diagnosis, absence of upper respiratory tract infections (URTI) history, high platelet count were the factors affecting chronicity in children with ITP. **Keywords:** Thrombocytopenia, childood, purpura, chronic

Giriş: Primer immün trombositopeni (ITP), altta yatan başka bir neden olmaksızın düşük trombosit sayısı (<100×109/L) ile ayırt edilen otoimmün bir hastalıktır. Bu çalışmanın amacı kliniğimizde idiyopatik trombositopenik purpura nedeniyle takip edilen hastaların demografik özelliklerini, muayene bulgularını, laboratuvar sonuçlarını, tedavi rejimlerini ve tedaviye yanıtlarını retrospektif olarak değerlendirerek kronikleşmeyi etkileyen faktörleri belirlemektir. **Materyal ve metot:** Bu çalışmada, 1 Ocak 1997 ile 31 Aralık 2018 tarihleri arasında Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı'na başvuran ve idiyopatik trombositopenik purpura tanısı alan hastaların tıbbi kayıtları retrospektif olarak incelendi. **Bulgular:** Ocak 1997-Aralık 2018 tarihleri arasında idiyopatik trombositopenik purpura (İTP) tanısı alan toplam 447 hasta belirlendi. Dört yüz yirmi sekiz hasta çalışmaya dahil edildi. Kronik İTP'de ortalama tanı yaşı akut İTP'ye göre daha yüksekti (p=0.000). Başvuru sırasındaki trombosit sayısı akut İTP hastalarında kronik İTP hastalarına göre daha düşüktü (p=0,035). ANA pozitifliği kronik hastalarda diğer gruplara göre çok daha yüksekti (p=0.014). Tanı anındaki ve 3. gündeki trombosit sayısı arasındaki fark, steroid ve IVIG tedavisi gören hastalarda kombine tedavi gören hastalara göre çok daha yüksekti (p<0.001). Remisyona giren hastaların 3. ve 7. gün trombosit sayıları remisyona girmeyen hastalarınkinden daha yüksekti (p<0.001). Tanı yaşı, ortalama takip süresi ve 7. gün trombosit sayısı kronikleşme için risk faktörleri olarak belirlendi. **Sonuç:** İleri tanı yaşı, üst solunum yolu enfeksiyonu öyküsünün olmaması ve yüksek trombosit sayısının İTP'li çocuklarda kronikleşmeyi etkileyen faktörler olduğu bulunmuştur. **Anahtar Kelimeler:** Trombositopenik, çocukluk çağı, purpura, kronik

1. INTRODUCTION

Primary immune thrombocytopenia (ITP) is an autoimmune disorder that is distinguished by a low platelet count (<100×109/L) without any other underlying causes (1). ITP is a frequently occurring condition in children, with a prevalence rate ranging from 1.9 to 6.5 cases per 100,000 individuals (2). The disease is caused by the increased breakdown of platelets and suboptimal platelet production in the bone marrow due to humoral or cellular immunity mechanisms. In children, it is essentially common between ages 2-7 and usually there is a history of respiratory or gastrointestinal system infection 2-4 weeks prior. ITP is a disease that is generally characterized by petechiae, purpura, gingival bleeding, mucosal bleeding, thrombocytopenia, plasma anti-platelet antibodies and increased megakaryocytes (3). The classification of ITP duration has been revised based on the duration of platelet count below the threshold level of 100×109/L after the initial diagnosis. It is now categorised as acute (0-3 months), persistent (3-12 months), and chronic (>12 months) (4). Around 20-40% of newly diagnosed ITPs may progress to chronic ITP. Primary therapies for paediatric ITP encompass patient surveillance, corticosteroids, intravenous immunoglobulin (IVIG), and intravenous anti-D. Secondary therapy options including rituximab, thrombopoietin receptor agonists, other immunosuppressive medications, and splenectomy (5).

This study aimed to retrospectively analyse the demographic features, examination findings, laboratory data, treatment regimens, and treatment responses of patients with ITP in our clinic in order to discover the factors that contribute to chronicity.

2. MATERIALS AND METHODS

For this study, the files of patients younger than 18 years of age who were diagnosed with idiopathic thrombocytopenic purpura and admitted to Faculty of Medicine, Department of Pediatrics, Department of Pediatric Hematology-Oncology, between January 1, 1997 and December 31, 2018 were evaluated retrospectively. In the diagnosis of ITP, normal physical examination findings other than bleeding findings, absence of organomegaly and lymphadenopathy, normal erythrocyte and white blood cell counts in the complete blood count, peripheral smear, and complete blood count being compatible with thrombocytopenia (platelet count <100000/mm3), absence of a disease that causes thrombocytopenia, increased or normal megakaryocytes in bone marrow examination, were used. Patients who had lymphadenopathy or organomegaly, a history of splenectomy or thrombocytopenia due to other diseases, with no available data, ongoing treatment in another center, and did not give their consent to treatment were excluded from the study.

Demographic data, admission times (seasonal), admission complaints (skin findings, mucosal bleeding, other systemic bleeding findings) of all subjects included in the study were recorded from their files. In order to find the etiological causes in all subjects, the infections they had in the last month, their vaccination history, and the drugs they used were identified. In our clinic, complete blood count, peripheral smear, biochemical workup, viral serology, hepatic markers, direct Coombs test, Antinuclear antibody (ANA), Anti dsDNA, Helicobacter Pylori (H. Pylori) serological test data and treatments applied to the patients were obtained from the patient files. If the platelet count was below the threshold level of 100×109/L for 0-3 months after the initial diagnosis, this was defined as acute ITP; if it was below the threshold level for 3-12 months this was defined as persistent ITP; if it was below the threshold level for 12 months or longer this was defined as chronic ITP. Remission was defined as platelet count above 100,000/mm3 at the end of follow-up.

2.1 Statistical Analysis

Analyses were conducted with IBM SPSS 20 software for statistical analysis. The data were presented using descriptive statistics, including the mean, standard deviation, median, minimum, maximum, percentage, and quantity. For the comparison of continuous variables among several independent groups, the ANOVA test was employed when the normal distribution assumption was satisfied, while the Kruskal-Wallis test was utilised when this assumption was not met. The Backward Stepwise (Likelihood Ratio) method of logistic regression analysis was employed to analyse predictive risk factors between groups in multivariate analysis. The probable risk factors identified in earlier analyses were used in this research. A p value less than 0.05 was deemed to be statistically significant.

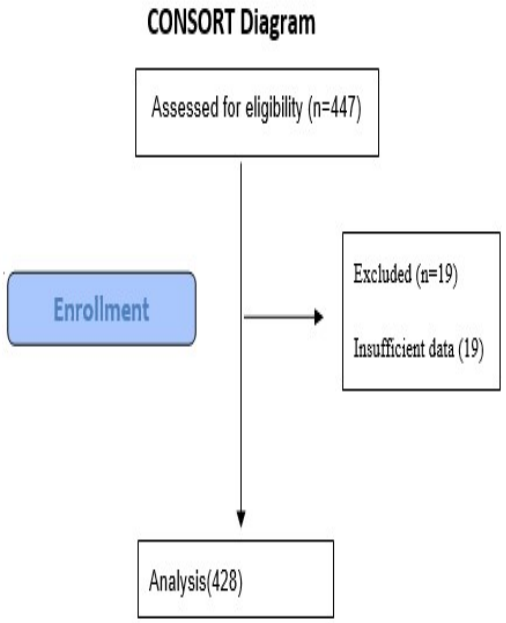
3. RESULTS

A total of 447 patients diagnosed with ITP between January 1997-December 2018 were identified. A total of nineteen patients were eliminated from the study due to the unavailability of their patient data, receiving ongoing therapy at another medical facility, being lost to follow-up, or withholding consent for treatment.

Of 428 patients, 208 (48.6%) were female and 220 (51.4%) was male. The age of the patients at the time of diagnosis was 73.6±47.9 months. The most common complaints at admission were bruising, epistaxis, gingival bleeding, and hypermenorrhea. The most common examination findings were petechiae and ecchymosis.

Of our patients, 291 (68%) were diagnosed with acute ITP, 29 (6.8%) with persistent ITP, and 108 (25.2%) with chronic ITP. The characteristics of the cases by ITP types are given in Table 1.

Figure 1: Consort Flow Diagram



The mean age at diagnosis in chronic ITP patients was found to be significantly higher than in acute ITP patients (p=0.000). Of the 428 patients included in the study, 166 (38.7%) had a history of infection 1-4 weeks before the admission date. It was found that patients with a history of infection became less chronic (p=0.04) (Table 2). Anti-nuclear antibody (ANA) was tested in 283 patients, and 42 (14.8%) patients were found to be ANA-positive. ANA positivity was statistically higher in chronic patients than in other groups (p=0.014). H. pylori seropositivity was found to have no effect on disease course.

There was no difference in terms of gender between the patients who entered remission. The rate of remission was significantly higher in ANA-negative patients (p=0.009). Remission was observed in 350 of the 428 patients included in the study. The remission rate was found to be significantly higher in patients with acute ITP compared to persistent and chronic ITP (p<0.001). When the platelet counts of the patients were examined based on their remission status, the 3rd and 7th-day platelet counts of the patients with remission were significantly higher than the platelet counts of the patients without remission (p<0.001). Table 3 presents the characteristics of the patients who went into remission.

A model was established with the variables that we consider as clinical risk factors between the groups in acute and chronic ITP. According to the results of the model, age at diagnosis, mean follow-up period, and 7th-day platelet count were found to be risk factors for chronicity (Table 4).

Table 1: Comparison of Cases by ITP Types

	Acute ITP(n=291)	Persistent ITP(n=29)	Chronic ITP(n=108)	p
Gender	**n(%)**	**n(%)**	**n(%)**	
Male	154 (%70)	14 (%6,4)	52 (%23,6)	0,615[a]
Female	137 (%65,9)	15 (%7,2)	56 (%26,9)	
Mean age at diagnosis (months) mean±SD Median(min-max)	65,3±45,4 56(1.5-204)	79,9±48,9 84(5-158)	94,1±48,1 84(3-199)	**0,000[b]**
Platelet count (mm3) mean±SD Median(min-max)	10606±11115 7000(400-68000)	13878±14706 10000(1300-72000)	13408±12433 9000(1000-75000)	**0,035[b]**
Infection	n(%)	n(%)	n(%)	
Positive	111(%78,2)	8 (%5,6)	23 (%16,2)	**0.040[a]**
Negative	179 (%62,8)	21 (%7,4)	85 (%29,8)	
ANA	n(%)	n(%)	n(%)	
Positive	20 (%47,6)	3 (%7,1)	19 (%45,2)	**0,014[a]**
Negative	163 (%67,6)	23 (%9,5)	55 (%22,8)	
H.pylori	n(%)	n(%)	n(%)	
Positive	58 (%58,0)	8 (%8,0)	34 (%34,0)	0,150[a]
Negative	119 (%68,0)	16 (%9,10)	40 (%22,9)	
Treatment	n(%)	n(%)	n(%)	
Steroid	156 (%68,4)	18 (%7,9)	54 (%23,7)	0,229[a]
IVIG	76 (%73,8)	4 (%3,9)	23 (%22,3)	
Combined	26 (%56,5)	4 (%8,7)	16 (%34,8)	

Values are mean ± standard deviation (SD), n(%)

[a] Pearson's *chi-squared* test

[b] Kruskal-Wallis Test

Table 2. The Effect of Upper Respiratory Tract Infection History on the Course of the Disease

	URTI		p
	Yes	No	
Acute	111(%78,2)	179 (%62,8)	**0.040**[a]
Persistent	8 (%5,6)	21 (%7,4)	
Chronic	23 (%16,2)	85 (%29,8)	

Table 3. Characteristics of the Patients In Remission

		Remission		
		Positivie n(%)	Negative n(%)	p
Gender	**Male**	183 (%52,3)	39 (%50,0)	0,715[a]
	Female	167 (%47,7)	39 (%50,0)	
ANA	**Positive**	27 (%12,2)	15 (%25,9)	**0,009**[a]
	Negative	195 (%87,8)	43 (%74,1)	
Disease Process	**Acute ITP**	276 (%94,8)	15 (%5,2)	**<0,001**[a]
	Persistent ITP	24 (%82,8)	5 (%17,2)	
	Chronic ITP	50 (%46,3)	58 (%53,7)	
Platelet count at diagnosis mean±SD Median(min-max)		11678±12187 7000(400-75000)	11004±9750 7500(1000-41000)	0,586[b]
3rd day platelet count mean±SD Median(min-max)		78500±71202 64000(2000-531000)	54095±60312 37000(1000-313000)	**<0,001**[b]
7th day platelet count mean±SD Median(min-max)		190361±146454 150500(2000-934000)	86296±80646 62000(2000-376000)	**<0,001**[b]

[a] Pearson's chi-squared test
[b] Mann Whitney U Test

Table 4. Analysis of Factors Affecting Chronicity

	p	OR	OR for %95 GA
Diagnosis Age	,001	1,015	1,006-1,023*
Tracking Time	,000	1,080	1,051-1,110*
7th day platelet count	,012	1,000	1,000-1,000*

*Logistic regression (Method=Bacward Stepwise (Likelihood Ratio))

4. DISCUSSION

ITP is a haematological disorder marked by a reduced number of platelets caused by the destruction of platelets due to the immune system and inadequate platelet synthesis.

In the study by Güngör et al., (6) which covered a 4-year follow-up period; 49.3% of the patients were male and 50.7% female. In a retrospective study of 409 patients (7), the mean age of the patients was found to be 4.72 years. ITP occurs with equal frequency in both sexes and is most common in children aged 2-6 years (8). In this study, 212 patients presented with purpuric rash and ecchymosis; mucosal bleeding was observed in 78 patients, epistaxis in 37 patients, GIS bleeding in 11 patients, and menorrhagia with hematuria in 5 patients. Our findings were in accordance with many studies evaluating the demographic characteristics, age, and first admission complaints of the patients. Factors such as an early age upon diagnosis, a recent viral infection or immunisation, a lower platelet count, the appearance of wet purpura, and being male are associated with a higher probability of a more severe disease progression. (9).

In the multicenter study by Zeller et al. (10), it was found that 25.1% of the patients became chronic. In another study, (11) it was found that the incidence of chronic ITP was higher in girls than boys. In addition, the median age of patients with chronic ITP was found to be higher than patients with persistent ITP. In a study in which the natural course and remission rates of ITP were screened retrospectively (12), no difference was found between patients diagnosed with persistent ITP and patients with chronic ITP in terms of sex and platelet counts at the time of diagnosis, however, patients with chronic ITP found to be older at the time of diagnosis than the patients with acute ITP. In our study, chronicity was detected in 108 (25.2%) patients. While 51.8% of our chronic patients were female, 48.2% were male. The mean age at diagnosis was found to be higher in chronic patients than in acute patients. These findings were found to be in accordance with the literature. Platelet count at the time of diagnosis

was found to be lower in acute ITP patients than in chronic ones.

In the study of Roganovic et al. (13), a history of prior infection was found in 73% of patients diagnosed with acute ITP and 16% of the patients diagnosed with chronic ITP, and it was shown that the absence of a prior viral infection was associated with the development of chronic ITP. In another study (14), history of prior infection and vaccination were found to be predictive factors for acute ITP. Viral infections are thought to cause thrombocytopenia by triggering the formation of autoantibodies against platelets (15). Our study confirmed the findings of previous research, showing a significant decrease in chronicity among those with a prior infection. Factors such as early onset of diagnosis, recent viral infection or immunisation, decreased platelet count, presence of wet purpura, and male gender contribute to a higher probability of a more severe illness progression.

Immune thrombocytopenia in children is more common in winter and autumn when viral infections and infectious and environmental agents such as vaccination can trigger the immune system to produce autoantibodies against platelets. It is assumed that the seasonal differences in the distribution of ITP result from the difference in the incidence of viral infections according to the climate in different countries (16, 17). In a study by Hafiz et al. (18), the incidence was found to be high in summer months, but low in winter. In the study by Zeller et al. (10), the highest incidence was observed in the winter months, while an increased incidence was found in the summer months in another study (19). It was found that our patients were admitted mostly in the summer season, but this was not statistically significant. The harsh winter season in our region causes disruptions in transportation; this situation leads to less hospital admissions in winter. We think that due to school holidays and easier transportation in the summer, the number of admissions increase and more patients are diagnosed.

In their study, Altıntaş et al.(20) discovered a statistically significant disparity in ANA positivity between paediatric acute and chronic ITP patients. The study involved 365 children and 108 adult patients. In another study (21), no statistically significant difference was found between ANA-positive and ANA-negative groups in terms of chronic ITP development. In the study by Bensouda et al. (22), no relationship was found between ANA positivity and disease chronicity.

The decision to treat patients is contingent upon the extent of thrombocytopenia, the gravity of bleeding, and the existence of additional bleeding risk factors. The American Society of Hematology's evidence-based treatment guidelines advise that children who do not have bleeding or only have minimal bleeding (such as bruises or petechiae) should be managed with observation alone, irrespective of their platelet count. Therapeutic intervention should be administered to promptly elevate the number of platelets, sustain a consistent platelet count, or attain prolonged remission of the condition. (23, 24). In their study, Glanz et al. (25) found that 80% of patients diagnosed with ITP received at least one treatment. Of the patients who received treatment, 67% were treated with intravenous immunoglobulin, 42% with corticosteroids, and 15% with both drugs. In another study (14), the rate of patients receiving intravenous immunoglobulin (IVIG) and/or steroids were found to be more common in chronic ITP. Tamminga et al. (26) discovered that administering IVIG as the first treatment resulted in a slight yet significant enhancement in the long-term increase of platelet count after 6 months. This effect was observed regardless of other established risk factors. A meta-analysis (27) compared the efficacy of glucocorticoids and IVIG in pediatric acute ITP and showed that IVIG was more effective in raising the platelet count above 20000/mm3 in 48 hours. It was found that 25% of patients treated with corticosteroids and 18% of patients treated with IVIG progressed to chronic ITP. Bruin et al. (28) found that the risk of progression to chronic ITP in patients treated with IVIG was lower than in patients receiving corticosteroids.

The unresolved topic is whether IVIG treatment provides protection against chronic disease, or if corticosteroid treatment raises the likelihood of chronic disease. The rapid recovery of platelets in ITP patients may be attributed to two well-documented therapeutic effects of IVIG: the inhibition of FcɣR-dependent reticuloendothelial system (RES) function and the neutralisation of anti-idiotypic interactions. Therapeutic intervention should be administered to promptly elevate the number of platelets, sustain a consistent platelet count, or attain prolonged remission of the condition. (28). In their study in which they compared IVIG, steroid and Anti-D Ig treatments, Çelik et al. found that the 3rd and 7th-day platelet counts in the IVIG group were higher than the patients who were given steroids, and they found a significant difference in terms of the 7th-day platelet counts. As side effects of steroids they just observed weight gain, facial fat accumulation, and increased appetite (29). In our clinic, the majority of patients received steroids, others received IVIG or combined therapy. About 11% of these patients recovered without treatment. A relationship could not be determined between these treatments and the course of the disease (acute-chronic). In our study, the difference between the platelet count on the 3rd day and at the time of diagnosis was found to be higher in the IVIG group compared to the steroid group ($p<0.001$).

In the study by Kim et al. (12), IVIG, steroid, Rho (D) immunoglobulin, and observation were provided to the patients as the first treatment. No significant

difference was found between the patients who received treatment in terms of their treatment response rates. Glanz et al. (25) showed that the provided treatments protected from the complications of ITP, but no evidence was found that indicates they prevented the chronicity of ITP. Tamminga et al. (26) found that the rate of chronic ITP was 18% after IVIG treatment and 25% after steroid treatment, and it was found that children who were initially treated with IVIG had a higher chance of having normal platelet count 6 months after diagnosis compared to children who did not receive IVIG. In our study, when the disease course of the patients was evaluated by the type of treatment they received, it was observed that the treatments were not superior to each other and no statistically significant difference was found. Again, it was found that the treatment option had no predictive value in chronicity.

In a prospective study to further investigate the factors predicting remission in children, Bennet et al. (30) evaluated the remission rates at 12 and 24 months in a total of 1088 patients. Data such as demographic information, platelet count at diagnosis, initial treatment, bleeding sites, and bleeding severity were collected using the Bolton-Maggs and Moon scale. The predominant pharmacological interventions included the administration of intravenous immunoglobulin (IVIG) as a standalone treatment (25%), the use of corticosteroids as a standalone treatment (26%), and the combination therapy of IVIG and corticosteroids (13%). The utilisation of Anti-D immune globulin was infrequent, accounting for only 3% of cases. Remission was attained in 419 (59%) patients during a span of 12 months, and in 211 (55%) patients within a span of 24 months. Remission at both 12 months and 24 months was positively correlated with a younger age. The study revealed a substantial correlation between the initial pharmacological treatment administered at the time of diagnosis and remission rates at both the 12 and 24-month marks. The IVIG and corticosteroid treatment group exhibited the most elevated rates of remission, with percentages of 76% and 77% respectively. There was no discernible correlation between gender and platelet count at diagnosis, as well as the rates of remission from ITP after 12 or 24 months.

In our study, remission was observed in 350 out of 428 patients. Of the patients with remission, 52.3% were male and 47.7% were female. ANA-negative patients had high remission rates and this was statistically significant. In patients with acute ITP, the remission rate was higher than in persistent and chronic ITP, and the difference was statistically significant. While no relationship was found between the platelet count at the time of diagnosis and remission, the 3rd and 7th-day platelet counts of the patients who entered remission were higher than the platelet counts of the patients who did not enter remission and the difference was statistically significant. In addition, the relapse rates of patients who received IVIG treatment alone were found to be significantly lower than those who received steroids or steroid + IVIG.

Thrombocytopenia is a frequently seen issue during the perioperative period. Although numerous patient and procedure-related factors affect global haemostasis, accurately predicting the impact of thrombocytopenia on bleeding risk is challenging due to the lack of a linear correlation between platelet count and the probability of bleeding. The likelihood of bleeding is also influenced by the cause of thrombocytopenia. Patients with immune thrombocytopenia (ITP) experience bleeding less frequently compared to other patients with similarly low platelet counts. This is likely due to the larger size and enhanced functionality of their platelets (31).

Since the patient files were analyzed retrospectively, the lack of access to some data was our limitation.

In conclusion, our study demonstrated that low platelet count, younger patient age, the presence of a recent history of infection, and ANA negativity increased the likelihood of an acute disease course. In addition, in our study; age at diagnosis, mean follow-up period, and platelet count at day 7 were found to be risk factors for chronicity.

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Author Contributions: The study's design, sample collection, data collecting and/or processing, and preparation of the original manuscript were conducted by GD and ZKS.

Ethical Approval: The ethical approval for our study was obtained in the Atatürk University Clinical Research Ethics Evaluation Committee's Clinical Research Meeting No:5, Resolution No:10, dated 27.06.2019.

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