RESEARCH ARTICLE

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# Arterial Thrombosis in Patients with Primary Immune Thrombocytopenia: A Nationwide Study

## Primer İmmün Trombositopenisi Olan Hastalarda Arteriyel Tromboz: Ülke Genelinde Yapılan Bir Çalışma

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## Abstract

**Objective:** Primary immune thrombocytopenia (pITP) is an acquired bleeding disorder involving decreased numbers of platelets due to platelet destruction or impaired production. The clinical presentation of pITP can be multifaceted and thrombotic events may rarely manifest. Thrombosis can develop with treatment or during the untreated period. The primary objective of this study was to examine the frequency of arterial thromboembolic events (ATEs) in patients with pITP. We also aimed to evaluate the risk factors in these patients and the effect of ITP treatments on ATEs.

**Materials and Methods:** The study was designed as a retrospective multicenter study conducted under the guidance of the Turkish Society of Hematology's Scientific Subcommittee on Hemostasis-Thrombosis. Patients over the age of 18 with pITP who subsequently developed ATE while undergoing follow-up for pITP were evaluated.

## Öz

**Amaç:** Primer immün trombositopeni (pITP), trombosit yıkımı veya trombosit üretiminin bozulması nedeniyle trombosit sayısının azalmasıyla ilişkili edinilmiş bir kanama bozukluğudur. pITP'nin klinik sunumu çok yönlü olabilir ve trombotik olaylar nadiren ortaya çıkabilir. Tromboz, tedavi ile veya tedavi edilmeyen dönemde gelişebilir. Çalışmanın birincil amacı, pITP'li hastalarda arteriyel tromboembolizm (ATE) sıklığını incelemekti. Ayrıca bu hastalardaki risk faktörlerini ve ITP tedavilerinin ATE üzerindeki etkisini değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** Çalışma, Türk Hematoloji Derneği Hemostaz-Tromboz Bilimsel Alt Komitesi altında yürütülen retrospektif, çok merkezli bir çalışma olarak tasarlandı. pITP tanısı almış ve daha sonra pITP takibi sırasında ATE geliştiren 18 yaş üstü hastalar çalışmaya dahil edildi.

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## Abstract

**Results:** A total of 2,178 patients with pITP were screened and 37 patients (1.7%) were observed to have developed ATE. The mean age was 62 years. Fifteen (40.5%) of the patients who developed ATEs were not receiving pITP treatment at the time of thromboembolism. Among the patients receiving pITP treatment at the time of the ATE, 9 (24.3%) were receiving eltrombopag and 10 (27%) were receiving corticosteroids. Compared to patients who did not develop ATEs, multivariate analysis revealed that the presence of hypertension, comorbidity, and history of venous thromboembolism statistically significantly increased the risk of developing ATEs (p=0.008, p=0.018, and p=0.038, respectively).

**Conclusion:** The risk of ATEs may increase in pITP patients both during and without treatment. It is important to inquire thoroughly about the presence of comorbidities, atherosclerotic risk factors, hypertension, and history of thrombosis in these patients at the initiation of treatment. Correctable risk factors should be addressed to minimize the number of risk factors present. The treatment of pITP must be individualized, including consideration of age-related disorders.


**Keywords:** Arterial thrombosis, Immune thrombocytopenia, Atherosclerosis


## Öz

**Bulgular:** pITP'li toplam 2.178 hasta tarandı ve 37 hastada (%1,7) ATE olduğu görüldü. Ortalama yaş 62 idi. ATE gelişen hastaların 15'i (%40,5) tromboembolizm sırasında pITP tedavisi almıyordu. ATE sırasında pITP tedavisi alan hastalardan 9'u (%24,3) eltrombopag, 10'u (%27) ise kortikosteroid alıyordu. ATE gelişmeyen hastalar ile karşılaştırıldığında, çoklu risk faktörleri birlikte değerlendirildiğinde, hipertansiyon, komorbidite ve venöz tromboz öyküsünün ATE gelişme riskini istatistiksel olarak belirgin artırdığı saptandı (p=0,008, 0,018, 0,038).

**Sonuç:** pITP hastalarında ATE riskinin hem tedavi sırasında hem de tedavi olmadan artabileceği unutulmamalıdır. Tedavi başlangıcında hastalarda komorbiditelerin, aterosklerotik risk faktörlerinin, hipertansiyon varlığının ve potansiyel trombotik risk faktörlerinin varlığının kapsamlı bir şekilde değerlendirilmesi önemlidir. Mevcut risk faktörlerinin sayısını en aza indirmek için düzeltilebilir risk faktörleri ele alınmalıdır. pITP tedavisi, morbidite ve mortaliteyi önlemek için kişiye özel olmalı ve yaşa bağlı bozuklukları kapsamalıdır.


**Anahtar Sözcükler:** Arteriyel tromboz, İmmün trombositopeni, Ateroskleroz

## Introduction

Primary immune thrombocytopenia (pITP) is an acquired bleeding disorder involving decreased numbers of platelets due to platelet destruction or impaired production. While it may develop in all age groups, population-based studies have revealed two age peaks of 1-5 years and over 60 years [1,2]. A majority of the symptoms are related to bleeding due to thrombocytopenia, although recently both venous and arterial thrombosis have been recognized and reported. From this perspective, a paradoxical tendency toward thrombosis has been implicated and clinical trials on the treatment of pITP have included the survey of thromboembolic events as secondary endpoints [3,4,5].

Thrombotic events in pITP are multifactorial and depend mainly on factors related to the patient and his or her comorbidities, the treatment offered to the patient, and factors related to the specific case of ITP. The universally accepted triad of Virchow, entailing vessel walls, blood components, and blood flow as the three pillars of coagulation, may be compromised, and many hypotheses have been proposed, including increased von Willebrand factor levels as a result of endothelial damage induced with autoimmune activity or increased amounts of microparticles of phosphatidylserine and tissue factor released from the damaged tissue on surface membranes. Large, young, and reactive platelets in circulation may play a role in the pathophysiology of thrombosis [5,6]. Furthermore, there are studies in the literature showing that platelet microparticles formed by the platelet membrane, which cannot be detected in the platelet count, increase the risk of inflammation, atherosclerosis, and thrombosis in ITP [7]. In addition to disease-related factors, pITP treatments and patient-related factors have been suggested as probable contributing risk factors. Arterial thrombosis can be a significant cause of mortality and morbidity in these patients. The management of ITP patients due to thrombocytopenia is also difficult. In this study, we retrospectively screened arterial thromboembolic events (ATEs) including myocardial infarcts, ischemic stroke, and peripheral arterial disease (PAD) in adult patients who were diagnosed with pITP, aiming to determine contributing risk factors such as known atherosclerotic risks as well as pITP treatments.

## Materials and Methods

This study was planned as a retrospective multicenter study under the guidance of the Turkish Society of Hematology's Hemostasis-Thrombosis Scientific Subcommittee and 14 centers participated. Patients diagnosed with pITP aged 18 years and older were screened and those who developed arterial thrombosis during follow-up were included in the study (Group 1). The patients' demographic data, diagnosis time, follow-up period, atherosclerotic risk factors, thrombosis history, cardiovascular disease history, ITP treatments, comorbidities, laboratory findings, and splenectomy history were reviewed. Additionally, a control group was formed from a single center, consisting of patients diagnosed with pITP without a history of arterial thrombosis, and their cases were retrospectively reviewed in a similar manner (Group 2). This study was approved by Trakya University Faculty of Medicine's Ethics Committee (protocol

code: TÜTF-GOBAEK 2023/503, decision no: 01/32, date: 08.01.2024) with consent letters from the participants' own centers.

ATEs were based on documentation of a confirmed diagnosis of cerebrovascular events (CVEs), acute coronary events (ACEs), or PAD. Details of thrombosis were characterized with attention to demographic features, time since diagnosis, previous ITP therapies, current ITP therapies, cardiac risk factors, thrombotic risk factors, platelet count, maximum platelet count before thrombosis, and the subsequent management of the event. Type 2 diabetes, smoking, hypertension, hypercholesterolemia, family history, and prior acute myocardial infarction/CVE were evaluated as cardiac risk factors [8].

### Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality assumption. The continuous variables that did not comply with normal distribution were expressed as median (minimum-maximum) values. Categorical variables were summarized as counts (percentages). For continuous variables, the Mann-Whitney U test was used to compare independent groups. Categorical variables were examined using the Pearson/Fisher exact test.

Univariate logistic regression analysis was used to analyze ATE risk factors. A two-sided p value of <0.05 was considered statistically significant. Multivariate logistic regression analysis was then used to predict the potential risk factors for ATE. The variables that had a significance level of p<0.25 according to univariate analysis were identified as candidate variables for the multivariate model.

## Results

A total of 2178 pITP patients were screened. During the follow-up of these patients, ATEs were observed in 37 patients (1.7%). The incidence rate was 1.95 cases per 1000 person-years. The mean age was 62 (26-84) years and 21 patients were male (57%). Most patients (83.7%) had at least one comorbidity (Table 1).

Twelve of the 37 patients had a history of thrombosis (ATE in 8 patients and venous thromboembolism in 4 patients). It was observed that 22 patients had ACEs, 10 patients had CVEs, and 5 patients had PAD (Table 2). Twenty-one patients were aged 65 years or older (57%). Of these patients, 16 had ACEs, 4 had CVEs, and 1 had PAD (Figure 1). At the time of the ATE, it was determined that 3 patients were already using acetylsalicylic acid, 1 patient was using a direct oral anticoagulant, 1 patient was using warfarin, 1 patient was using clopidogrel, and 1 patient was using low-molecular-weight heparin.

Fifteen (40.5%) patients who developed ATEs were not receiving treatment for pITP at the time of thromboembolism. Nine (24.3%) patients were receiving eltrombopag, 10 (27%) patients were receiving corticosteroids, and 2 patients were receiving combined treatment. An ATE was detected in 1 patient at the time of diagnosis (Table 3).

**Table 1. Characteristic features of pITP patients with and without arterial thromboembolism.**

| | | pITP with arterial thromboembolism, Group 1 | pITP without arterial thromboembolism, Group 2 | p |
|---|---|---|---|---|
| Number of patients | | 37 | 128 | |
| Age, years | **Mean** | 62 (26-84) | 52 (20-85) | 0.002 |
| Age at diagnosis | **Mean** | 53 (18-82) | 44 (19-79) | 0.017 |
| Sex | **Number, %** | Male, n=21, 57%<br>Female, n=16, 43% | Male, n=51, 40%<br>Female, n=77, 60% | 0.068 |
| Comorbidities (≥1) | | n=31, 83.7% | n=53, 41.4% | <0.001 |
| Coronary arterial disease | | n=12, 32.4% | n=0 | - |
| Family history of coronary artery disease | | n=10, 27% | n=31, 24.4% | 0.539 |
| Risk factor of coronary artery disease | | n=27, 73% | n=44, 34.3% | <0.001 |
| Atrial fibrillation | | n=3, 8.3% | n=6, 4.7% | 0.421 |
| Smoking | | n=13, 35% | n=43, 33.5% | 0.847 |
| Hyperlipidemia | | n=10, 27% | n=37, 29% | 0.823 |
| Type 2 diabetes | | n=9, 24% | n=20, 15.6% | 0.227 |
| Hypertension | | n=21, 57% | n=22, 17.1% | <0.001 |
| BMI | | Overweight or obese n=26, 70.2% | Overweight or obese n=70, 54.6% | 0.129 |
| Splenectomy | | n=7, 18.9% | n=18, 14% | 0.468 |
| History of thrombosis | | Venous: n=4, 10.8%<br>Arterial: n=8, 21.6% | Venous: n=4, 3.1%<br>Arterial: n=0 | 0.076<br>- |

pITP: Primary immune thrombocytopenia; BMI: body mass index.

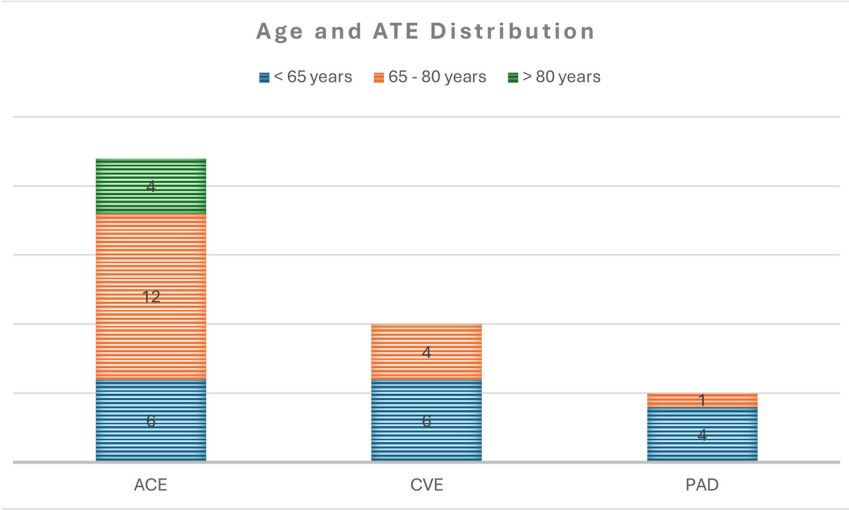


**Figure 1.** Distribution of arterial thromboembolic events in older patients.
ACE: Acute coronary event; PAD: peripheral arterial disease; CVE: cerebrovascular event; ATE: arterial thromboembolic event.

The average period between diagnosis and manifestation of the ATE was 65.07 (0-486) months. In patients receiving eltrombopag, the ATE occurred after an average of 30.13 (1-108) months of treatment. Furthermore, in patients undergoing corticosteroid treatment, the ATE was observed in an average of 2.05 months (8 days to 6 months) after the commencement of corticosteroid therapy. In all splenectomized patients, the ATE was observed to develop at least 2 years after splenectomy.

At the time of the ATE, the mean platelet count was $142x10^9$/L, mean platelet volume was 10.3 fL, and mean leukocyte count was $12x10^9$/L. Twenty patients had platelet counts above $100x10^9$/L and 5 patients had platelet counts below $30x10^9$/L (Table 4). The average maximum platelet count before the arterial event was $252x10^9$/L. Lupus anticoagulant and anticardiolipin antibodies were found to be positive in 1 patient, and no tests were performed for 7 patients. Titers were low in the positive patient and not clinically significant.

In Group 2, the complete data of 128 pITP patients with no history of arterial thrombosis were evaluated. The mean age was 52 (20-85) years and 51 patients (40%) were male. Almost half of the patients (41.4%) had at least one comorbidity. Coronary artery risk factors and hypertension history were observed at lower rates compared to Group 1. The mean follow-up period in Group 2 was 62.9 (2-297) months and 65.6% of the patients were followed without treatment (Table 5).

In pITP patients with ATEs, the distribution of male patients (p=0.068) and the mean age (p=0.002) were higher. Again in patients who developed ATEs, rates of the presence of hypertension and the presence of at least one comorbidity and one cardiovascular risk factor were higher, and these differences were statistically significant (p<0.01) (Table 1). Multivariate analysis showed that the presence of hypertension, comorbidities, and history of venous thrombosis increased the risk of an ATE (p=0.008, p=0.018, and p=0.038, respectively, with adjusted odds ratios of 3.6, 2.8, and 5.4) (Table 6).

## Discussion

In patients with pITP, comorbidities, ITP-related factors, and treatments may increase the risk of thrombosis. In our study, male patients were more prevalent and mean age was higher in patients with ATEs (p=0.07 and p=0.03, respectively). The literature consistently highlights both age and male sex as significant risk factors for atherosclerotic endpoints. In our study, an analysis of Group 1 revealed that 56.7% of the patients were of geriatric age. In the study by Zhang et al. [9], most ITP patients developing ATEs were of advanced age and 80% had one or more thrombosis risk factors. Population-based Scandinavian and Danish studies also highlighted the importance of advanced age and the presence of comorbidities for the risk of ATEs in ITP [5,10]. Consistent with the findings in the literature, our multivariate analysis revealed that hypertension and comorbidities were significantly associated with an elevated risk of ATEs. Accompanying comorbidities, ITP-related thromboembolic risks, and the treatments given to the patients due to ITP may all increase the risk of thrombosis. Furthermore, patient-related arterial thromboembolic risk factors should not be forgotten. The development of ATEs in half of our patients during periods in which they were not receiving treatment suggests that comorbidities and the multi-hit hypothesis are important in the development of thromboembolism. Ongoing and untreated pITP processes may also be assumed to be risk factors.

In a population-based study, the cumulative incidence of venous and arterial thromboembolism in patients with pITP was reported

**Table 2. pITP treatments and cardiovascular risk factors in patients with arterial thromboembolic events.**

| ATE | Number/% | Treatment, number/% | CVrf of ≥1, number/% | CVrf of ≥3, number/% |
|---|---|---|---|---|
| Acute coronary events | 22/59% | **Eltrombopag** 7/19% **No treatment*** 7/19% **Corticosteroids** 7/19% **Combined treatment** 1/2% | 10/27% | 11/30% |
| Cerebrovascular events | 10/27% | **Eltrombopag** 0/0% **No treatment** 6/17% **Corticosteroids** 3/9% **Combined treatment** 1/2% | 3/8% | 4/11% |
| Peripheral arterial disease | 5/14% | **Eltrombopag** 4/11% **No treatment** 1/2% **Corticosteroids** 0/0% | 3/8% | 1/2% |

*: One patient was in the diagnosis stage; pITP: primary immune thrombocytopenia; ATE: arterial thromboembolic event; CVrf: cardiovascular risk factors.

to be increased compared to the healthy population at respective rates of 2.9% versus 1.9% and 4.1% versus 3%. This finding was regarded as being independent of comorbidities and treatments [11]. The risk of developing an ATE in pITP may be considered as mildly or moderately increased with annual incidence of 0.96-1.15 per 100 person-years [12]. In our study, similar to the literature, the incidence of arterial thromboembolism as an endpoint of atherosclerotic events was determined to be 1.7% in pITP with an incidence rate of 1.95 cases per 1000 person-years. Additionally, the incidence of stroke in Türkiye has been reported as 1.54 cases per 1,000 person-years and the mean age of ACE patients is 62 years [13,14]. In our cohort, we observed a slightly higher rate of atherosclerotic events among patients of comparable age, which may be attributable to pITP, including both the disease itself and its treatments, as a potential risk factor for atherosclerotic endpoints.

The increase in the risk of thromboembolism after the global use of thrombopoietin receptor agonists (TPO-RAs) is also a controversial issue. There are studies demonstrating a minimal increase in risk for both eltrombopag and romiplostim, especially in the first year of treatment, as well as studies with significant numbers of patients reporting no increased risk in long-term follow-up after these treatments. Individual risk factors have been emphasized as the major factors that lead to thromboembolic events and they should be recognized and addressed accordingly [10,15,16]. It was observed that ATEs developed in 9 (24.3%) of our patients while receiving eltrombopag. However, all of these patients had at least one additional cardiovascular risk factor. The mean time to development of ATE in patients receiving eltrombopag was 30.13 months, while this period was considerably shorter for corticosteroids. The negative effects of corticosteroids on endothelial damage and vascular remodeling may be the main mechanism involved in the development of ATEs in the early period [17]. Likewise, the use of corticosteroids as a rescue treatment in ITP and during the active disease period may accelerate the development of atherosclerotic plaques and contribute to the development of thromboembolic events. Rapid platelet increase after steroids and the release of active and reactive young platelets may also increase the risk. In such cases, novel treatment models may prove crucial in ensuring the safety of patients, particularly regarding the potential for adverse effects, including the risk of thromboembolism associated with the use of corticosteroids and TPO-RAs. In the follow-up of patients receiving fostamatinib, a spleen tyrosine kinase inhibitor, a mild transient ischemic attack was detected in only one of 146 patients (87% of whom had at least one thrombosis risk factor), and that case was not considered treatment-related. Consequently, access to novel treatment modalities that mitigate thrombosis risk is emerging as a pivotal consideration for patients of advanced age and/or those possessing multiple thrombosis risk factors [18]. The unavailability of fostamatinib in Türkiye constitutes a notable deficit in the therapeutic options available to the Turkish population.

The impact of splenectomy on the risk of ATE in patients with pITP remains to be clarified. The study by Ruggeri et al. showed that ATE rates were increased after splenectomy in pITP patients [19]. However, in population-based studies, rates of myocardial infarction and stroke were similar in comparison to patients

**Table 3. Characteristics of pITP patients with the complication of thrombosis.**

| No. | Sex | Age | Thrombotic event | PLT count at the time of ATE (x$10^9$/L) | ITP treatment at the time of ATE | Splenectomy history | Time between ITP treatment and ATE development (months) |
|---|---|---|---|---|---|---|---|
| 1 | F | 51 | ACE | 240 | Eltrombopag | - | 40 |
| 2 | F | 59 | ACE | 92 | No treatment | - | |
| 3 | F | 52 | PAD | 175 | Eltrombopag | + | 1 |
| 4 | F | 74 | ACE | 72 | GC | - | 2 |
| 5 | F | 67 | ACE | 191 | Eltrombopag | - | 1 |
| 6 | M | 84 | ACE | 154 | No treatment | - | |
| 7 | M | 74 | ACE | 278 | GC | - | 3 |
| 8 | F | 58 | CVE | 148 | No treatment | - | |
| 9 | M | 51 | ACE | 19 | Diagnosis stage | - | |
| 10 | M | 74 | ACE | 134 | No treatment | - | |
| 11 | F | 72 | ACE | 313 | Eltrombopag | - | 108 |
| 12 | F | 30 | CVE | 225 | GC | - | 5 |
| 13 | M | 80 | ACE | 191 | Eltrombopag | - | 72 |
| 14 | F | 38 | CVE | 220 | GC | + | 6 |
| 15 | M | 70 | ACE | 93 | Eltrombopag | - | 6 |
| 16 | M | 34 | PAD | 105 | No treatment | - | |
| 17 | F | 34 | CVE | 77 | No treatment | - | |
| 18 | M | 59 | PAD | 96 | No treatment | - | |
| 19 | M | 73 | ACE | 97 | Eltrombopag | | 9 |
| 20 | M | 80 | ACE | 36 | Combined treatment | - | 8 |
| 21 | M | 59 | ACE | 19 | GC | + | 0.3 |
| 22 | F | 75 | CVE | 141 | GC | - | 0.5 |
| 23 | M | 84 | ACE | 34 | No treatment | - | |
| 24 | M | 75 | CVE | 14 | No treatment | - | |
| 25 | M | 69 | ACE | 26 | No treatment | - | |
| 26 | M | 64 | PAD | 31 | No treatment | - | |
| 27 | M | 26 | CVE | 20 | Combined treatment | + | 0.5 |
| 28 | F | 27 | CVE | 249 | No treatment | - | |
| 29 | M | 75 | CVE | 222 | No treatment | + | |
| 30 | F | 68 | CVE | 278 | No treatment | - | |
| 31 | M | 61 | ACE | 194 | No treatment | - | |
| 32 | F | 59 | ACE | 530 | Eltrombopag | + | 5 |
| 33 | M | 69 | ACE | 82 | GC | - | 0.5 |
| 34 | F | 66 | ACE | 58 | GC | - | 1 |
| 35 | M | 67 | ACE | 40 | GC | - | 1 |
| 36 | M | 76 | ACE | 225 | GC | - | 1 |
| 37 | F | 65 | PAD | 690 | Eltrombopag | + | 30 |

PLT: Platelet; ATE: arterial thromboembolic event; ITP: immune thrombocytopenia; F: female; M: male; ACE: acute coronary event; PAD: peripheral arterial disease; CVE: cerebrovascular event; GC: glucocorticoids.

**Table 4. Platelet counts at the time of arterial thromboembolic events.**

| | Platelet counts | Number/% |
|---|---|---|
| **At the time of arterial thromboembolic event** | >100x$10^9$/L | 20/54% |
| | 50-100x$10^9$/L | 8/22% |
| | 30-50x$10^9$/L | 4/11% |
| | <30x$10^9$/L | 5/13% |

**Table 5. Treatment history of patients in Group 2 (pITP without arterial thromboembolism).**

| | No. | % |
|---|---|---|
| **Follow-up without treatment** | 84 | 65.6 |
| **TPO-RAs**<br>**Eltrombopag**<br>**Romiplostim** | 41<br>39<br>2 | 32.1<br>30.5<br>1.6 |
| **Combined treatment**<br>(TPO-RAs, azathioprine, mycophenolate mofetil, corticosteroids) | 3 | 2.3 |
| **Immunosuppressive treatment history**<br>(rituximab, azathioprine, mycophenolate mofetil, vincristine) | 18 | 14 |
| **Splenectomy history** | 18 | 14 |

pITP: Primary immune thrombocytopenia; TPO-RAs: thrombopoietin receptor agonists.

**Table 6. Results of regression analysis for risk factors of arterial thromboembolic events.**

| Risk factors for ATEs | Univariate logistic regression analysis | | | Multivariate logistic regression analysis | | |
|---|---|---|---|---|---|---|
| | Crude OR | 95% CI | p | Adjusted OR | 95% CI | p |
| **Sex (reference: female)** | 1.982 | 0.945-4.155 | 0.070 | - | - | - |
| **Mean age** | 1.035 | 1.012-1.059 | 0.003 | - | - | - |
| **Mean age at diagnosis** | 1.026 | 1.005-1.047 | 0.016 | - | - | - |
| **Hyperlipidemia** | 0.911 | 0.401-2.068 | 0.824 | - | - | - |
| **AF** | 1.794 | 0.426-7.550 | 0.425 | - | - | - |
| **Smoking** | 1.071 | 0.497-2.308 | 0.862 | - | - | - |
| **Type 2 diabetes mellitus** | 1.736 | 0.713-4.226 | 0.224 | - | - | - |
| **Hypertension** | 6.324 | 2.852-14.020 | <0.001 | 3.640 | 1.403-9.444 | 0.008 |
| **Overweight or obese** | 1.958 | 0.892-4.299 | 0.094 | | | |
| **Comorbidities** | 7.311 | 2.850-18.759 | <0.001 | 3.770 | 1.259-11.289 | 0.018 |
| **Family history of coronary artery disease (reference: no)**<br>**Yes**<br>**Unknown** | <br>1.223<br>1.896 | <br>0.527-2.841<br>0.442-8.139 | <br>0.640<br>0.390 | - | - | - |
| **Risk factor of coronary artery disease** | 5.155 | 2.288-11.611 | <0.001 | - | - | - |
| **Splenectomy** | 1.426 | 0.545-3.731 | 0.470 | - | - | - |
| **Venous thrombosis history** | 3.758 | 0.892-15.829 | 0.071 | 5.429 | 1.097-26.869 | 0.038 |

Variables that had significance levels of p<0.25 in univariate analysis were identified as candidate variables for the multivariate model. ATE: Arterial thromboembolic event; OR: odds ratio; CI: confidence interval; AF: atrial fibrillation.

without splenectomy [20]. In our study, it was observed that ATE developed in the late period (median 136 months) in splenectomized patients. Furthermore, no statistically significant difference was identified in splenectomy rates between Group 1 and 2.

Saldanha et al. [21] described a correlation between the number of platelets and the development of thromboembolic events. We did not observe such a relationship; only 20 of our patients had a platelet count above $100x10^9$/L at the time of thrombosis and 8 of those patients were not receiving any treatment for pITP. Platelet counts were below $30x10^9$/L in only 5 (13.5%) cases. The finding of platelet counts being below $100x10^9$/L in 46% of patients suggests that low platelet counts may not offer protection against ATE. In the study by Saldanha et al. [21], age of >60 years, atrial fibrillation, cancer, chronic kidney damage, hypertension, cardiovascular disease, obesity, history of thrombosis, being male, smoking and antiphospholipid antibody (aPL) positivity were identified in multivariate analysis as significant risk factors for thrombosis [21]. Diz-Küçükkaya et al. [22] reported that 5-year thrombosis-free survival was lower in pITP patients with aPL positivity. However, in our study, only 1 of 30 patients had anticardiolipin IgM, while 7 patients were not evaluated for aPL. The limitations of this study include its multicenter nature, the small number of analyzed patients, and the fact that aPL status was not evaluated for all patients.

## Conclusion

Atherosclerosis develops from early adulthood and accelerates with age, inflammation, lifestyle factors, and medications. Therefore, all adult patients with pITP should be monitored for age-appropriate atherosclerotic risk factors. In pITP patients, thrombocytopenia is predominantly associated with bleeding; however, ATEs may occur even in cases of low platelet counts. In long-term follow-up, cases should be evaluated not only in terms of platelet counts but also in terms of risk factors that increase the risk of thrombosis, even in the untreated period. The occurrence of ATEs, especially during the thrombocytopenic period, poses significant challenges in terms of treatment and management, often resulting in substantial morbidity. Furthermore, it is crucial to acknowledge that the risk of arterial thrombosis in pITP may escalate both in the absence of treatment and during the treatment period. To reduce the risk of thrombosis, the use of treatment options with minimal thrombosis side effects may be a safe management method for patients who are elderly, have comorbidities, or have a history of venous thrombosis. However, the limited availability of drugs with minimal thrombosis risk, such as fostamatinib, poses a significant challenge. Consequently, all pITP guidelines recommend that the treatment of pITP be individualized and incorporate the consideration of age-related disorders to prevent morbidity and mortality.

### Ethics

**Ethics Committee Approval:** This study was approved by Trakya University Faculty of Medicine's Ethics Committee (protocol code: TÜTF-GOBAEK 2023/503, decision no: 01/32, date: 08.01.2024).

**Informed Consent:** A patient consent statement was obtained from all patients.

### Footnotes

### Authorship Contributions

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

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