# Evaluation of paediatric immune thrombocytopenia patients with clinical and laboratory findings: emphasizing the role of monocytosis

Şefika Akyol, Özlem Tüfekçi, Şebnem Yılmaz and Hale Ören

**We aimed to investigate the relationship between demographics, clinical features, laboratory findings including monocytosis and clinical course in children with immune thrombocytopenia (ITP). Data of 100 ITP patients were analysed. Complete blood count findings of the patients at certain time points were evaluated to classify the disease as acute, persistent and chronic. An effect of sex on chronicity was not observed ($P = 0.166$). Of the patients enrolled in the study, 38% ($n = 38$) had chronic course. The mean age of patients with the chronic course was $7 \pm 4.1$ years, which was significantly higher than the other groups ($P = 0.007$). Sixty-five percent ($n = 13$) of the patients presenting with mucosal bleeding and 27.4% ($n = 20$) of the patients presenting with skin bleeding became chronic ($P = 0.008$). MPV was found to be significantly high in chronic ITP patients ($P = 0.049$). Monocytosis was noted in 80% of the patients at diagnosis. Intravenous immunoglobulin was used in 84% of the patients with acute ITP; 33% of them developed chronic ITP. The age at diagnosis, presence of mucosal bleeding and increased MPV on admission were high-risk factors for the development of the chronic course. Monocytosis was detected in 80% of the patients on admission, and it may play a role in the pathogenesis of ITP.** *Blood Coagul Fibrinolysis* **33:315–321** **Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.**

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## Introduction

Immune thrombocytopenia (ITP) is a disease characterized by shortening of platelet life span and decrease in platelet count in peripheral blood with the presence of immune dysregulation resulting in the development of antibodies against platelets [1]. ITP is one of the most common causes of bleeding disorders and thrombocytopenia in childhood and is characterized by isolated thrombocytopenia (peripheral blood platelet count $<100 \times 10^9$/l) in a patient who is otherwise completely normal [1,2].

According to the latest classification of the 2019 American Society of Hematology (ASH), acute ITP is defined as thrombocytopenia lasting for the first 3 months after diagnosis, persistent ITP for 3–12 months and chronic ITP for more than 12 months [3]. ITP usually presents with acute purpura, petechiae and/or mucosal haemorrhages following a viral infection or vaccination [4]. Regardless of the platelet count, observation is essential in the management of the patient with ITP. Severe bleeding occurs in 3–5% of patients [5]. Treatment options mostly include intravenous immunoglobulin, steroid, anti-D immunoglobulin and thrombopoietin receptor agonists (TPO-RAs) and rituximab. Concomitantly, platelet transfusion may be considered in life-threatening bleeding situations [6]. Rituximab is a mAb targeting the CD20 antigen. It is aimed to reduce the precursor plasma cells that produce antibodies with the anti-CD20 effect [7].

In pathogenesis, increased destruction and decreased production via antiplatelet antibodies are proposed basically. Indeed, on the basis of recent research, pathogenesis is much more complicated. Although the pathogenesis of ITP is not fully understood and clarified, the loss of immune tolerance has an important place. And as a result, monocytes, macrophages and dendritic cells are the most prominent cells involved in destruction in the reticuloendothelial system. Monocytes are the precursors of dendritic cells (antigen-presenting cells), and numerical changes in different monocyte subgroups in the pathogenesis of ITP have been reported in the literature [8–10]. Changes in monocyte subsets and cytokine releases in ITP are still highly studied topics to elucidate the pathogenesis, as well as to determine its relationship with the clinical course and to predict the clinical course.

In this study, we aimed to investigate the relationship between demographics, clinical features, laboratory findings, especially monocytosis, and clinical courses in children and adolescents with ITP.

## Materials and methods

In our study, demographic data, complaints, complete blood count findings on admission, treatment modalities

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and treatment responses of 100 patients diagnosed with ITP who were admitted to Dokuz Eylül University Pediatric Hematology Department between December 2009 and January 2021 were evaluated. Data were obtained retrospectively from patient hospital files. Complete blood count findings of the patients at the time of admission (before treatment), at the end of the third month and after 12 months were evaluated to classify the disease as acute, persistent and chronic disease [3]. Treatment modalities were noted for each patient. Complete remission (improvement) was defined as platelet count at least 100 000 cells/μl. The leukocyte subgroup values were determined as absolute counts and percentages. Monocytosis was defined as an absolute monocyte count of more than 500–800 cells/μl and the normal range for age was taken into account. Mean monocyte counts were considered as 600 cells/μl for the first 2 months of life, 500 cells/μl for 1–6 years and 400 cells/μl for 6–16 years [10–12]. Patients diagnosed with secondary thrombocytopenia, hereditary thrombocytopenia and autoimmune diseases such as systemic lupus erythematosus were excluded.

Data were analysed using SPSS version 22.0. Continuous variables were expressed as mean ± standard deviation (normal distribution) or median (skewed distribution). Categorical variables were expressed in frequency or as a percentage. The one-way analysis of variance (ANOVA, normal distribution), Kruskal–Wallis H (skewed distribution) test and chi-square tests (categorical variables) were used to determine any statistical difference between the means and proportions of the groups. Univariate Cox regression model was used to evaluate the association between age and chronicity. A $P$ value of less than 0.05 was considered statistically significant.

## Results

Out of 100 patients, 45 (45%) were girls and 55 (55%) were boys. An effect of sex on chronicity was not observed ($P = 0.166$). The mean age on admission was 5.4 years ± 4.2 years and the median age was 4.2 years (4 months–16 years). When the ages of the patients were evaluated, 24% were less than 2 years old, 32% were 2–5 years old and 44% were more than 5 years old. The mean age of patients with the chronic course was 7 ± 4.1 years and was significantly higher than those with acute/persistent course (mean age 4.5 ± 4.1 years) ($P = 0.007$). When the effect of age at diagnosis on the clinical course was evaluated, the chronic course was observed significantly more frequently in patients who were more than 4.2 years old (ROC analysis, Fig. 1, AUC: 703, $P < 0.001$, sensitivity and specificity 67.3–68.8). Five patients (5%) were vaccinated within 3 weeks before diagnosis. Thirty-nine percent ($n = 39$) of the patients had a history of upper respiratory airway infection between 15 days and 1 month before admission.

Seventy-three percent of the patients ($n = 73$) presented with skin bleeding and 20% with mucosal bleeding ($n = 20$). Epistaxis was present in 13 patients (65%), bleeding gum in six (30%) and blood in stool in one (5%). Thrombocytopenia was detected incidentally in seven patients (7%). The clinical course was acute in 47%, chronic in 38% and persistent in 15%. Information about patient characteristics, clinical course and complaints on admission are given in Table 1. Sixty-five percent ($n = 13$) of the patients presenting with mucosal bleeding and 27.4% ($n = 20$) of the patients presenting with skin bleeding became chronic, and this difference was statistically significant ($P = 0.008$). Of the patients who presented with skin bleeding, 54.8% ($n = 40$) had an acute course. A chronic course was observed in 57% of the patients who were diagnosed incidentally. About 52.2% ($n = 23$) of 44 patients admitted after vaccination/infection had an acute course and 38.6% ($n = 17$) had a chronic course. There were five patients diagnosed with ITP in the postvaccine period (vaccinated within 3 weeks before diagnosis) and 39 patients after infection. All patients who developed ITP after vaccination experienced an acute course of the disease.

Treatment modalities of the patients are given in Table 2. As IVIG was the predominant choice as first-line treatment, the effect of treatment modality on the clinical course could not be analysed. Of those patients who received IVIG at initial diagnosis, 33% ($n = 28$) developed the chronic disease. Out of 11 patients taking steroids, 54% ($n = 6$) became chronic ($P = 0.189$). Second-line treatment was required in 46% of the patients and third-line treatment was required in 25%.

At initial diagnosis, platelet counts of patients with acute, persistent and chronic ITP showed no statistically significant difference ($P = 0.143$) (Table 3). Monocytosis was detected in 80% of the patients on admission. Evaluation of monocyte counts of the patients is summarized in Table 4. There was no statistically significant difference between mean monocytes values in acute, persistent and chronic patients. In the acute course group, 80.5% of patients (n:38) had monocytosis at diagnosis, with a mean platelet improvement time of 7.97 ± 13.1 days and a median platelet improvement time of 4.5 days (2–79 days). On the contrary, monocytosis was not detected in 19% ($n = 9$) of patients in the acute course group. The mean platelet improvement time of these patients was 10.4 ± 11.3 days, and the median platelet improvement time was 6 (3–30 days) days. Although there was statistically no significant difference between the two groups ($P = 0.67$), this may be due to the small number of patient groups. In the persistent course group, 66.6% of patients had monocytosis at diagnosis, and the mean platelet improvement time was 7.87 ± 3.52 months, median 7.5 (4–13 months) months. In the group without monocytosis, the mean platelet improvement time was 7 ± 2.94 months, median 7 (4–10 months) months, and

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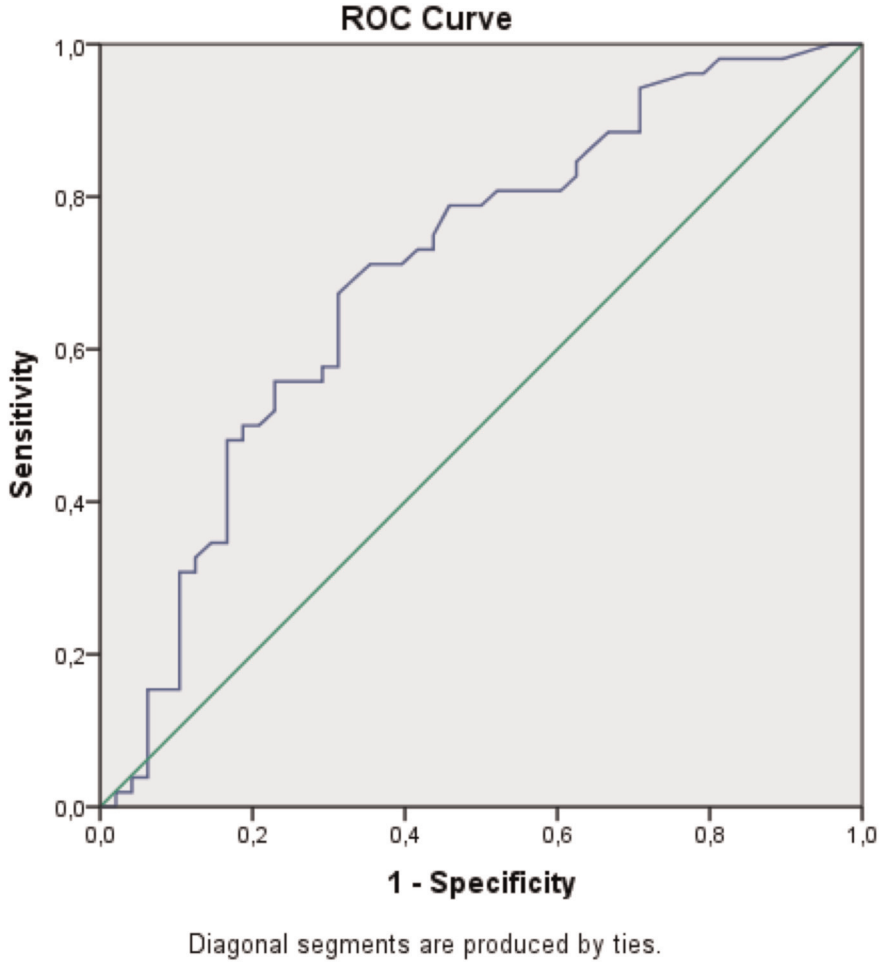
**Fig. 1**




Receiver operating characteristic curve analysis for age (AUC: 703, $P < 0.001$, sensitivity and specificity 67.3–68.8).

statistically no significant difference was found ($P = 0.8$). In the chronic course group, monocytosis was found in 84% ($n = 32$) patients at diagnosis. Monocytosis was present at diagnosis in 12 (80%) of 15 patients who recovered. Detailed complete blood count results on admission are summarized in Table 3.

**Table 1 Patient demographics**

| Demograhics | *N* | % |
|---|---|---|
| Sex | | |
| Female | 45 | 45 |
| Male | 55 | 55 |
| Clinical course | | |
| Acute | 47 | 47 |
| Persistent | 15 | 15 |
| Chronic | 38 | 38 |
| Complaint | | |
| Skin bleeding | 73 | 73 |
| Mucosal bleeding | 20 | 20 |
| Epistaxis | 13 | 65 |
| Bleeding gum | 6 | 30 |
| Blood in stool | 1 | 5 |
| Incidental | 7 | 7 |

The mean improvement time in acute ITP was 8.8 ± 12.8 days (2–79 days), and the mean improvement in persistent ITP was 6.8 ± 2.5 months (4–11 months).

**Table 2 Treatment modalities of the patients**

| | *n* (%) |
|---|---|
| First-line treatment | |
| Observation | 5 (5%) |
| IVIG | 84 (84%) |
| Steroid | 1 (1%) |
| Steroid + IVIG | 10 (10%) |
| Second-line treatment | 7 (15%) |
| IVIG | 15 (33%) |
| Steroid | 20 (43%) |
| Thrombopoietin receptor agonists | 3 (6%) |
| Splenectomy | 1 (2%) |
| Third-line treatment | |
| Steroid | 5 (20%) |
| Steroid + IVIG | 5 (20%) |
| Thrombopoietin receptor agonists | 11 (44%) |
| Splenectomy | 2 (8%) |
| Other: RTX | 1 (4%) |
| CSA | 1 (4%) |

CSA, cyclosporine A; IVIG, intravenous immunoglobulin; RTX, rituximab.

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**Table 3 Haemogram values of the patients with acute, persistent and chronic course**

| | Acute course ($n=47$) | Persistant course ($n=15$) | Chronic course ($n=38$) | *P* |
|---|---|---|---|---|
| Haemoglobin (g/dl) | | | | |
| Mean ± SD | 11.5 ± 1.27 | 11.7 ± 1.56 | 12 ± 0 0.93 | 0.121 |
| Median (Min-Max) | 11.4 (8.5–14.4) | 11.9 (6.9–13.7) | 12 (10.2–13.9) | |
| Platelet count (cells/μl) | | | | |
| Mean ± SD | 9040 ± 6734 | 14 600 ± 22 693 | 14 400 ± 17 642 | 0.143 |
| Median (Min-Max) | 7000 (1000–28 000) | 6000 (3000–93 000) | 8500 (1000–69 000) | |
| Mean platelet volume (fL) | | | | |
| Mean ± SD | 8.8 ± 1.4 | 9.18 ± 1.51 | 9.57 ± 1.46 | 0.049 |
| Median (Min-Max) | 8.8 (5.9–11.7) | 9.3 (6.9–11.9) | 9.5 (3.9–12.3) | |
| Leukocyte count (cells/μl) | | | | |
| Mean ± SD | 9555 ± 2784 | 8480 ± 4000 | 9456 ± 2711 | 0.444 |
| Median (Min-Max) | 9200 (3300–15 800) | 7200 (4000–19 900) | 8800 (4900–17 100) | |
| Absolute neutrophil count (cells/μl) | | | | |
| Mean ± SD | 4034 ± 2146 | 3486 ± 1647 | 4,234 ± 1686 | 0.443 |
| Median (Min-Max) | 3500 (500–10 200) | 3500 (1200–7000) | 3900 (1700–8100) | |
| Absolute lymphocyte count (cells/μl) | | | | |
| Mean ± SD | 4455 ± 1718 | 4013 ± 2553 | 4168 ± 2015 | 0.683 |
| Median (Min-Max) | 4400 (1500–8700) | 3300 (1300–11 700) | 4200 (1200–10 700) | |
| Absolute monocyte count (cells/μl) | | | | |
| Mean ± SD | 808 ± 330 | 707 ± 343 | 768 ± 362 | 0.596 |
| Median (Min-Max) | 700 (400–2000) | 600 (400–1800) | 700 (300–2100) | |

Improvement was observed in 39% ($n=15$) of the patients diagnosed with chronic ITP (14–62 months).

## Discussion

ITP is a haematologic disease of autoimmune dysregulation characterized by increased platelet destruction and decreased production. ITP is diagnosed by exclusion of other causes of thrombocytopenia [13]. The incidence of ITP is 7.2–9.5/100 000 per year in children aged 1–14 years, and it is frequently seen between the ages of 2 and 5 years [1,2]. In our study, we found that 32% of our patients were in this age range. Although boys and girls appear to be equally affected, it has been reported to be more common in boys less than 4 years of age [2]. However, chronic ITP is more common in girls [14,15]. In the present study, 45% of our patients were female and no effect of sex on chronicity was observed. In previous studies and meta-analyses, being diagnosed at an older age was associated with an increased risk of developing chronic ITP, and it was reported that chronicity was more common in patients aged more than 8–11 years [16,17]. In our study, the mean age was 7 ± 4.1 years in the chronic patient group and there was a statistically significant difference; patients who were more than 4.2 years old had likely to have a chronic course.

Preceding infections and vaccines have been frequently studied for their role in the pathogenesis of ITP and their effects on clinical course. The absence of vaccination and infections prior to admission was significantly associated with chronic ITP [17–19]. In the present study, five patients were vaccinated before the onset of ITP and 39 patients have had an infection within the last month. None of the patients who developed ITP after vaccination showed chronic course. There was no significant relationship between the chronic course and the presence of infection before ITP development.

Usually, the first finding in ITP is petechiae, purpura, ecchymoses and/or mucosal bleeding in an otherwise healthy child. On admission, more than half of the patients have cutaneous and approximately 40% of patients have mucosal bleeding symptoms [20]. ITP

**Table 4 Evaluation of the monocyte counts of the patients**

| | Monocyte count according to age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Diagnosis | | Third month | | Sixth month | | Twelfth month | | Last follow-up | |
| ITP classification | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Acute | | | | | | | | | | |
| High | 38 | **80.8** | 31 | **72** | 22 | **81.4** | 19 | **63** | 30 | **63.8** |
| Normal | 7 | 14.8 | 8 | 18.6 | 1 | 3.7 | 4 | 13 | 8 | 17 |
| Low | 2 | 4 | 4 | 9 | 4 | 14.8 | 7 | 23 | 9 | 19.1 |
| Persistent | | | | | | | | | | |
| High | 10 | **66.6** | 8 | **53** | 8 | **66.6** | 7 | **87.5** | 9 | **64.2** |
| Normal | 3 | 20 | 4 | 26.6 | 2 | 16.6 | 1 | 12.5 | 4 | 28.5 |
| Low | 2 | 13 | 3 | 20 | 2 | 16.6 | | | 1 | 7.1 |
| Chronic | | | | | | | | | | |
| High | 32 | **84** | 26 | **72** | 20 | **60.6** | 26 | **68.4** | 26 | **68.4** |
| Normal | 3 | 7.8 | 7 | 19 | 9 | 27 | 9 | 23.6 | 7 | 18.4 |
| Low | 3 | 7.8 | 3 | 8 | 4 | 12 | 3 | 7.8 | 5 | 13.1 |

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Emergency Management Guideline Panel, including experts in haematology, emergency medicine, research methodology and patient representatives, identified the need for a standardized definition of a critical bleed [21]. A critical bleed was defined in two groups as [1] a bleed in a critical anatomical site, including intracranial, intraspinal, intraocular, retroperitoneal, pericardial or intramuscular with compartment syndrome; or [2] an ongoing bleed that results in haemodynamic instability or respiratory compromise. So, the clinical evaluation of bleeding symptoms is very important to plan treatment modality. In the present study, 73% of the patients had cutaneous and 20% had mucosal bleeding. None of our patients had a critical bleed according to the mentioned classification [21]. In some studies, it has been reported that patients with mucosal bleeding developed less chronic ITP than patients without mucosal bleeding [22,23]. On the contrary, in our patients admitted with mucosal bleeding symptoms, the development of chronic ITP was more frequent than in patients without mucosal bleeding. None of our patients had intracranial haemorrhage, but it should be kept in mind during follow-up of these patients, which may occur in 0.6% of the patients [24].

In previous literature, patients who received IVIG therapy, which is one of the most frequently chosen from the first-line therapies, had significantly less chronic disease [10,22,25–27]. In the present study, as IVIG is the predominant choice in first-line treatment, no significant effect on the chronic course could be demonstrated. In recent years, randomized clinical studies with different results have been conducted on this subject. A recent randomized controlled study compared IVIG treatment with observation strategy in newly diagnosed patients and they found that IVIG treatment at diagnosis did not result in lower chronicity [28]. However, IVIG led to less life-threatening bleeding and faster recovery of platelets. Steroid therapy may be another good choice for acute ITP treatment, but adverse effects may cause difficulties in management [29,30]. TPO-RAs and rituximab can be effective when used as second-line therapies [31–38]. Splenectomy may be a choice for chronic refractory cases with frequent bleeding [36]. Considering all these different treatment modalities, treatment should be individualized according to the patient's laboratory and clinical findings.

The relationship between complete blood count findings on admission and chronicity has been constantly studied in the literature. The most frequently studied parameters are the platelet count at diagnosis, mean platelet volume, haemoglobin (Hb) and white blood cell values. Although no significant relationship was found in our study, higher platelet counts on admission were found to be significantly associated with the development of chronic ITP in some previous studies [14,16]. In this regard, MPV is a frequently studied complete blood count parameter. MPV value at diagnosis was found to be significantly high in patients with the chronic course [39,40]. Similar results were obtained in our study. MPV may be high in these patients because of mediated thrombopoietic activity in a compensatory manner in response to the peripheral destruction of platelets [40]. Recently, an observational study conducted by Jeon *et al.* [41] demonstrated that immature platelet fraction (IPF), absolute immature platelet count (AIPC) and MPV are significantly higher in patients with autoimmune thrombocytopenia and these markers can be used as reflecting bone marrow's thrombopoetic activity.

In our study, we could not find an association between the Hb, total leukocyte and absolute lymphocyte counts on admission and development of chronic ITP. No significant difference was found in the literature regarding Hb values [15]. In studies evaluating the total leukocyte and absolute lymphocyte counts, both were found to be significantly lower on admission in the chronic course group compared with the other clinical courses of ITP [16,42]. Manzano *et al.* [13] analysed the fraction of lymphocytes in whole blood and demonstrated that patients who had no response to first and second-line treatments (NR-ITP) had a higher proportion of B lymphocyte cells. They reported that this increase could be due to a significant rise in the fraction of naive B cells. In chronic ITP, even though the absolute lymphocyte counts do not have significant importance in clinical course, the fractions of lymphocytes may be important in the pathogenesis.

Although the formation of autoantibodies against platelets have long been incriminated for the pathogenesis of ITP, it is now known that the mechanism is much more complicated [8,13]. There is an autoimmune dysregulation and increased antibody production from B cells, with changes in T cell depolarization with a mechanism in which imbalance in cellular immunity is fundamental [43]. In our study, absolute monocyte counts were high in 80% of our patients on admission. Monocytosis was present in acute, persistent and chronic ITP patients and mostly continued in all groups. Even though the mean platelet improvement time was shorter in the acute ITP patients who had monocytosis on admission, statistically, no significant difference was found. This result can be attributed to the small number of patients. In a recent study, similar to our results, it has been demonstrated that adult patients with ITP had higher monocyte counts than the healthy controls [13]. In that study, the fraction of classical monocytes was increased and the fraction of nonclassical monocytes was decreased in the untreated patients, who did not need treatment for at least 6 months, and in patients who showed NR-ITP. Monocytes are key components of both the innate and adaptive immune systems and act as precursors of dendritic cells [8]. Recently, monocytes have been divided into three subsets based on CD16 expression as classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$) and

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nonclassical ($CD14^{+}CD16^{++}$) [43–45]. Yang *et al.* [8] showed that the frequency of nonclassical monocytes was significantly increased in patients with active ITP, but decreased after complete remission. They also demonstrated that the intermediate subset was increased in acute ITP and produced the highest levels of tumour necrosis factor alfa and interleukin 1 beta. Furthermore, the nonclassical subset showed the highest capability of promoting platelet reactive T-cell proliferation and significantly promoted the secretion of interferon-gamma among the three subsets [8]. Monocytes are important cells that direct the T cell response through antigen processing, presentation and cytokine production [46]. Disruption of T cell homeostasis is also thought to be one of the important reasons for the loss of immune tolerance in ITP. In clinical studies, it has been shown that CD16+ proinflammatory monocytes stimulate the Th1 response in the pathogenesis of ITP, and suppression of the proinflammatory monocyte response as a possible therapeutic target has been attempted to be targeted *in vitro* [47]. As a result, monocyte increase may be one of the main causes of immune dysregulation and may play different roles in the pathogenesis of ITP.

In conclusion, ITP is a highly heterogeneous disease, and it is essential to predict the clinical course and individualize the treatment according to the patient. In the present study, the age at diagnosis, the presence of mucosal bleeding and increased. MPV on admission were found to be high-risk factors for the development of the chronic course. Monocytosis was detected in 80% of the patients on admission, which may play a role in the pathogenesis of ITP. Randomized controlled studies with larger participation are needed to elucidate it.

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The corresponding authors declare that the manuscripts reporting the results of experimental investigations conducted with humans state that the study protocol received institutional review board approval and that all participants provided informed consent in the format required by the relevant authorities and/or boards.

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### Conflicts of interest

All authors also disclose no conflict of interest that may have influenced either the conduct or the presentation of the research.

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