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# Immune Thrombocytopenia in Finnish Children and Adolescents: A Population-Based Cohort Study

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**Keywords:** ITP | paediatric | thrombocytopenia

## ABSTRACT

**Aim:** Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children. This study aimed to describe the diagnostics, patient characteristics, and treatment strategies regarding children with ITP, as well as identify risk factors for chronic disease.

**Methods:** This study included 403 Finnish children aged under 16 years at diagnosis, who were first diagnosed with ITP between 2006 and 2020.

**Results:** Of the 367/403 patients with complete follow-up data, 242 (65.9%) recovered within three months. Chronic ITP developed in 25.9% of the children. Severe bleeding events occurred in 3.7% of them, with no intracranial bleeding events or deaths reported. Pharmacological treatment was administered to 40.2% of the patients. An elevated risk of chronic ITP was found in the children presenting with an insidious disease onset, female gender, higher age, higher platelet counts, and an absence of recent viral infections. As many as 83.3% of the patients with an insidious disease onset and no recent infections developed chronic ITP.

**Conclusion:** Most of the children with ITP experienced short and uncomplicated disease courses. Chronic illness was more likely when the disease onset was insidious, the platelet count was not extremely low, and there was no recent history of an infection.

## 1 | Introduction

Primary immune thrombocytopenia (ITP) is an immune-mediated disorder characterised by a low platelet count in the context of an otherwise normal blood count and an absence of other underlying diseases [1]. ITP is the most common cause of thrombocytopenia in childhood, affecting approximately 2–5 children per 100 000 annually [2, 3]. The diagnosis is based on the exclusion of genetic reasons and other underlying disorders by the clinician; no laboratory tests or clinical parameters are currently available to ascertain the diagnosis. Increased knowledge has resulted in an increase in definitive diagnoses of inherited thrombocytopenia, but ITP remains the most common diagnosis among patients with isolated thrombocytopenia [4–6]. ITP is classified according to its duration: newly diagnosed (< 3 months), persistent (3–12 months) and chronic disease (> 12 months) [1].

Current guidelines recommend a strategy of watchful waiting in uncomplicated cases with mild to moderate bleeding. Based on these guidelines, pharmacological treatment is needed when the

**Abbreviations:** ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin.

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**Summary**

- Most children with immune thrombocytopenia (ITP) require no treatment, and three out of four fully recover from ITP within 12 months of diagnosis.
- Severe bleeding events occurred in <4% of patients and only with platelet counts below $20 \times 10^9$/L.
- As many as 83.3% of the children with ITP who had an insidious onset of symptoms and no history of recent infections developed chronic ITP.

disorder causes bleeding requiring immediate medical attention, or when no spontaneous recovery has been achieved and the child's activities must be overly restricted [4, 7, 8]. Splenectomy is reserved for chronic, complicated cases that do not respond to other treatments [4, 9]. In clinical practice, treatment strategies vary among clinicians, hospitals, and countries. Since the publication of updated guidelines by the International Working Group on ITP in 2010 and the American Society of Hematologists in 2011, the proportion of patients with an applied strategy of watchful waiting has been reported to have increased [10–14]. Previous studies have shown that most patients receive medical treatment, and although watchful waiting is currently suggested in most cases, recent studies have indicated that the majority of patients undergo treatment due only to low platelet counts [15–18].

Chronic ITP has been reported to develop in 20%–30% of patients with childhood ITP [15, 19–21]. While severe bleeding events are rare, restrictions on physical activities and daily life are commonly ordered to prevent bleeding [22]. In chronic cases, such restrictions last longer, and repeated follow-up laboratory tests and pharmacotherapy may be required [4]. This may cause a severe burden and influence the quality of life of an otherwise healthy child [23]. Researchers have investigated risk factors for chronic disease, and predictive clinical scoring systems have been developed [24–27]. It is essential to understand the factors associated with chronic disease to guide clinicians in both differential diagnostics as well as treatment and follow-up considerations.

The most recent Nordic cohort study on childhood ITP is by Rosthøj et al. (2003), dating back two decades, and with the exception of a brief report by Andersson et al. (2023) on intracranial haemorrhages, no Nordic studies have been conducted since the international guidelines have been updated [17, 28]. Our objectives were to describe the clinical characteristics, diagnostic and treatment strategies of patients with ITP in contemporary practice; to identify factors associated with treatment responses, as well as to identify risk factors for chronic disease.

## 2 | Methods

### 2.1 | Study Design

This was a retrospective, population-based cohort study. Children and adolescents diagnosed with primary ITP between 2006 and 2020 and aged under 16 at diagnosis were identified from the records of the participating hospitals based on the International Classification of Disease (ICD-10) codes for thrombocytopenia (D69.1–D69.6). Four university hospitals in Finland participated in the study. The exclusion criteria were secondary ITP, inherited thrombocytopenia, neonatal alloimmune thrombocytopenia, drug-induced thrombocytopenia, misclassified patients (e.g., leukaemia, Henoch-Schönlein purpura, and aplastic anaemia), and clear laboratory errors. Transient mild leukopenia or leukocytosis due to, for example, an acute viral infection or mild anaemia due to iron deficiency were not considered exclusion criteria. The study adhered to the principles of the Declaration of Helsinki. Permission to use hospital records was obtained from the Finnish Social and Health Data Permit Authority (Findata). According to Finnish law, no informed consent is required for register-based studies.

### 2.2 | Data Collection

Data were manually collected from the medical records of each participating hospital by clinicians. The data were gathered and managed using the Research Electronic Data Capture (REDCap) tool hosted by Indiana University [29, 30]. Information on patient characteristics, laboratory results, diagnostics, follow-ups, and treatments for ITP was obtained from the hospitals' medical records. The data were pooled and pseudonymized by Findata, after which the pooled data were reviewed in the coordinating study centre.

### 2.3 | Definitions

ITP was defined as thrombocytopenia with a reported platelet count $<100 \times 10^9$/L and the exclusion of other causes. A complete response was defined as a platelet count $>100 \times 10^9$/L; a partial response was considered as platelets >30 but $<100 \times 10^9$/L, and no response was defined as a platelet count $<30 \times 10^9$/L after treatment. The response was considered sustained if platelet counts did not drop below the response criteria at any point during further follow-up. ITP was classified based on duration as newly diagnosed (0–3 months), persistent (3–12 months), and chronic (>12 months). Bleeding symptoms were graded according to the recommendations of the international consensus report by Provan et al. [1, 4]. Recovery was defined as platelet counts permanently exceeding $100 \times 10^9$/L. Acute infection at diagnosis was defined as recent or ongoing symptoms of an acute flu or flu-like infection at the time of ITP diagnosis. An insidious onset was defined as a history of symptoms of thrombocytopenia, including abnormal bleeding, bruises, or petechia, for more than 4 weeks before diagnosis.

### 2.4 | Data Analysis and Statistics

The mean values of the platelet counts and patients' ages at diagnosis across groups by ITP duration were examined using variance analysis with Brown–Forsythe's test and the Games–Howell correction for pairwise post hoc tests. The distribution of the clinical characteristics, examinations, and forms of treatment between the three groups was assessed using the chi-square test.



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Standard and forward stepwise multivariate logistic regressions were used to evaluate possible factors associated with favourable responses to pharmacological treatments and increased risk of chronic disease in patients with ITP. The variables included in the models were age at diagnosis, gender, the lowest measured platelet count, an insidious disease onset, a history of a recent acute infection, vaccinations less than one month before diagnosis, and a positive family history of thrombocytopenia. Responses to intravenous immunoglobulin (IVIG), corticosteroids, and other medications were analysed separately for each group. Kaplan–Meier analysis was performed to assess the patients' time to recovery. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA).

## 3 | Results

### 3.1 | Patient Characteristics

Data were collected from 506 patients diagnosed with isolated thrombocytopenia. After reviewing these data, 103 patients were excluded due to unmet diagnostic criteria or an established diagnosis other than ITP, leaving a total of 403 (79.7%) patients with a diagnosis of ITP (Figure 1). Follow-up data were incomplete for 36 patients. Among the 367 patients with complete follow-up data, the duration of ITP was less than 3 months in 242 (65.9%) patients, 3–12 months in 30 (8.2%) patients and >12 months in 95 (25.9%) patients.

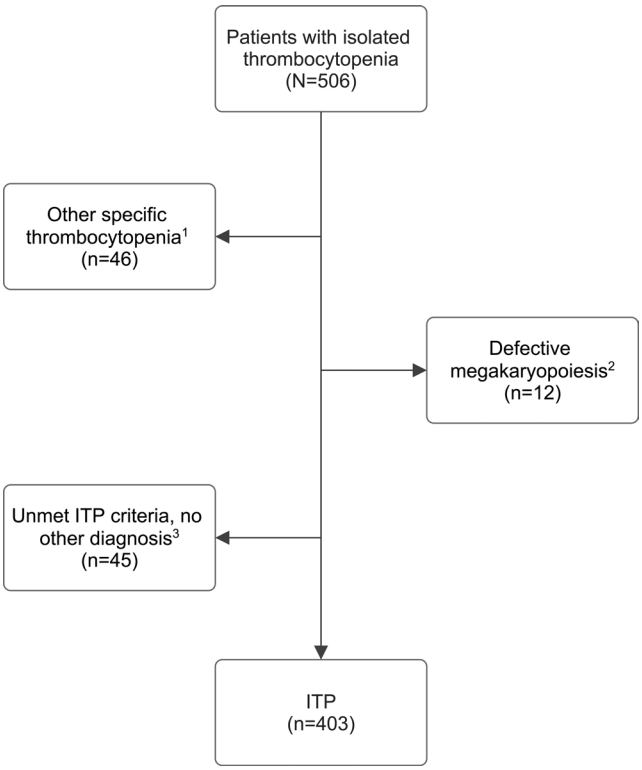


**FIGURE 1** | Study flow. ITP, immune thrombocytopenia. [1]Other diagnosis causing thrombocytopenia (e.g., inherited disorders and certain infectious diseases). [2]Defects in megakaryopoiesis found in bone marrow samples or peripheral blood smears. [3]No reported platelet count $<100\times10^9$/L, or clinical features or family history strongly suggestive of other diagnoses.

The patients' characteristics are presented in Table 1. The mean age of the patients was 6.5 ± 4.8 years, and it was distributed as follows: 5.6 ± 4.5 in the newly diagnosed cases, 6.4 ± 5.5 in the persistent cases, and 8.6 ± 4.8 years in the chronic cases. Statistically significant differences were found between the ages of the newly diagnosed and chronic cases ($p<0.001$). A slight male predominance was found, with 225 (55.8%) male patients. Seasonal variation was found with bimodal incidence peaks in autumn (September–October) and spring (March–May) (Figure 2). The mean lowest measured platelet count for all the patients was 22 ± 28 × 10 [9]/L, with a median of 8 × 10 [9]/L. Minor differences were observed between the three groups, with a slight tendency toward higher platelet counts in the chronic patients, but these differences were not statistically significant ($p=0.218$).

### 3.2 | Bleeding

At diagnosis, 281 (69.7%) patients reported bleeding symptoms, including bruises, petechiae, epistaxis, other mucosal bleeding or any other bleeding symptom. Severe (grade 3 or 4) bleeding events occurred in 15 (3.7%) patients. No patients died due to the complications of thrombocytopenia, and no intracranial bleeding events were reported. Severe bleeding was observed only in patients with low platelet counts, as follows: 14/15 patients with severe bleeding had platelet counts below 10 × 10 [9]/L, and one patient had a platelet count of 12 × 10 [9]/L.

### 3.3 | Treatment

A total of 162 (40.2%) patients received pharmacological treatment for ITP. Among those treated, 90 (55.6%) had newly diagnosed ITP; 14 (8.6%) persistent ITP, and 44 (27.2%) chronic ITP, with the remaining 14 (8.6%) having incomplete follow-up data. The treatment options used in the cohort were IVIG, corticosteroids, eltrombopag, and rituximab. The first-line treatment was IVIG in 152/162 (93.8%) patients, followed by corticosteroids in 10/162 (6.2%) patients. Also, 41/162 (25.3%) patients required more than one line of treatment. All the patients with severe bleeding events received first-line treatment with IVIG, and five patients required second-line treatment with corticosteroids. Three patients who had recurrent bleeding despite pharmacological treatment underwent splenectomy, and their platelet counts subsequently normalised. The treatment paths are illustrated in Figure 3. Alongside pharmacological and surgical treatments, platelet transfusions had been administered to 27 (6.7%) patients.

Any documented response was observed in 126/152 (82.9%) patients treated with IVIG, 36/44 (81.8%) with corticosteroids, and 8/9 (88.9%) with rituximab or eltrombopag. A complete response was observed in 98/152 (64.5%) patients treated with IVIG, 26/44 (59.1%) with corticosteroids, and 4/9 (44.4%) with rituximab or eltrombopag. The response was sustained in 66/152 (43.4%) patients treated with IVIG, 14/44 (31.8%) with corticosteroids, 1/8 (12.5%) with eltrombopag, and no patients who received rituximab.

No characteristics predicting a more favourable response could be identified using multivariate regression analysis for any of the pharmacological treatment options (Table S1).



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**TABLE 1** | Clinical characteristics of patients with ITP by disease duration.

| | All patients ($N=403$) | 0–3 months ($n=242$) | 3–12 months ($n=30$) | >12 months ($n=95$) | Missing follow-up data ($n=36$) |
|---|---|---|---|---|---|
| Age at onset (years) | 6.5 ± 4.8 | 5.6 ± 4.5 | 6.4 ± 5.5 | 8.6 ± 4.8 | 7.42 ± 4.7 |
| Lowest measured platelet count ($n \times 10^9$/L) | 23 ± 28.3 | 22 ± 27.9 | 16 ± 20.1 | 27 ± 32.3 | 24 ± 24.9 |
| Male gender | 225 (55.8%) | 150 (62.0%) | 13 (43.3%) | 47 (49.5%) | 15 (41.7%) |
| Insidious onset[a] | 49 (12.2%) | 8 (3.3%) | 2 (6.7%) | 33 (34.7%) | 6 (16.7%) |
| Bleeding symptoms at diagnosis | 281 (69.7%) | 186 (76.9%) | 22 (73.3%) | 53 (55.8%) | 20 (55.6%) |
| Acute infection at onset[b] | 114 (28.3%) | 87 (36.0%) | 7 (23.3%) | 13 (13.7%) | 7 (19.4%) |
| Vaccinations before onset[c] | 31 (7.7%) | 24 (9.9%) | 3 (10.0%) | 4 (4.2%) | 0 (0.0%) |
| Peripheral blood smear examined | 173 (42.9%) | 99 (40.9%) | 13 (43.3%) | 52 (54.7%) | 9 (25.0%) |
| Bone marrow examined | 157 (39.0%) | 45 (18.6%) | 12 (40.0%) | 71 (74.7%) | 30 (83.3%) |
| Abdominal ultrasound examined | 134 (33.3%) | 52 (21.5%) | 11 (36.7%) | 60 (63.2%) | 11 (30.6%) |
| Spleen enlarged | 12 (3.0%) | 5 (2.1%) | 0 (0.0%) | 2 (2.1%) | 1 (2.8%) |
| Severe bleeding[d] | 15 (3.7%) | 8 (3.3%) | 3 (10.0%) | 3 (3.2%) | 1 (2.8%) |
| Pharmacological treatment | 162 (40.2%) | 90 (37.2%) | 14 (46.7%) | 44 (46.3%) | 14 (38.9%) |
| Positive family history of TP | 38 (9.4%) | 19 (7.9%) | 1 (3.3%) | 17 (17.9%) | 1 (2.8%) |
| Genetic tests done[e] | 23 (5.7%) | 1 (0.4%) | 2 (6.7%) | 19 (20.0%) | 1 (2.8%) |

*Note:* Values stated as *n* (%) or mean ± SD.
Abbreviation: ITP, immune thrombocytopenia.
[a]Bruises or petechiae > 4 weeks before the diagnosis.
[b]Symptoms of an acute flu or flu-like infection at or shortly before the onset of ITP.
[c]Vaccination documented < 1 month before the onset of ITP.
[d]Severe (grade 3 or 4) bleeding events requiring medical attention.
[e]Low proportion of patients tested for genetic reasons is due to exclusion of patients with confirmed genetic diagnoses.

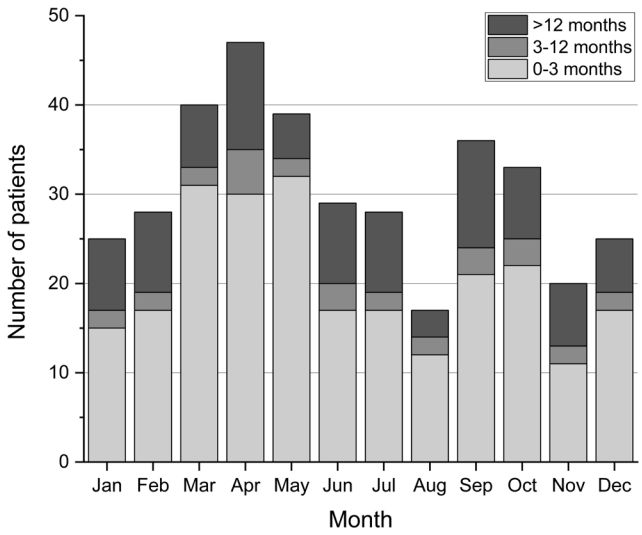


**FIGURE 2** | Seasonal variation. X-axis: Months from January to December; y-axis: Number of patients diagnosed with immune thrombocytopenia (ITP) per month. Bimodal incidence peaks for ITP were found during typical peaks of respiratory viral infections (i.e., spring and autumn). Patients with sufficient follow-up data: $N=367$.

### 3.4 | Chronic ITP

Of the 367 patients with follow-up data available, 95 (25.9%) developed chronic disease. The female patients experienced prolonged disease more often. During the first 3 months, 150/225 (66.7%) male patients and 92/178 (51.7%) female patients recovered; 48/178 (27.0%) female patients developed chronic disease compared to 47/225 (20.9%) male patients. These differences were statistically significant ($p=0.017$).

Forward stepwise multivariate logistic regression analysis was used to identify risk factors for chronic ITP. Higher age, an insidious onset, an absence of acute infection at diagnosis, and a higher platelet count were associated with an increased risk of chronicity (Table 2). The strongest predictive factors were an absence of acute infection and an insidious disease onset. In this regard, 30/36 (83.3%) patients without recent infections and with an insidious onset of symptoms developed chronic ITP. The standard multivariate regression model including all the candidate variables gave the same results.

Among the patients with chronic disease, sustained remission was documented in 36/95 (37.9%) individuals, with follow-up



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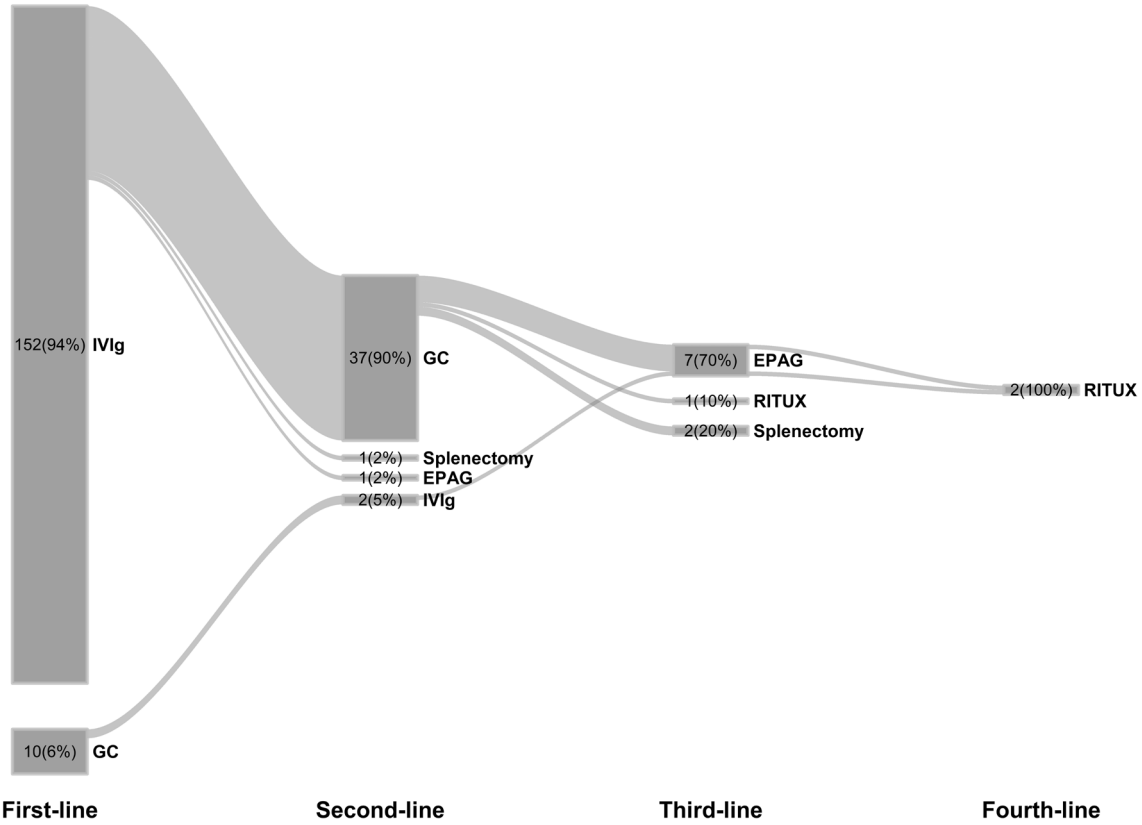


**FIGURE 3** | Alluvial plot of treatment paths of patients with ITP. EPAG, eltrombopag; GC, any form of treatment with corticosteroids; IVIG, intravenous immunoglobulin; RITUX, rituximab. [Correction added on 27 May 2025, after first online publication: Figure 3 was updated.]

**TABLE 2** | Forward stepwise multivariate logistic regression analysis of risk factors for developing chronic disease in patients with ITP.

| Factor | aOR | 95% confidence interval | *p* |
|---|---|---|---|
| Age at diagnosis (years) | 1.14 | 1.07–1.21 | < 0.001* |
| Insidious onset[a] | 17.15 | 7.45–39.52 | < 0.001* |
| Acute infection at diagnosis[b] | 0.25 | 0.12–0.52 | < 0.001* |
| Platelet count | 1.01 | 1.00–1.02 | 0.021* |

*Note:* Chronic ITP = disease duration > 12 months.
Abbreviation: aOR, adjusted odds ratio.
[a]Symptoms of thrombocytopenia including bleeding, bruises or petechiae > 4 weeks before the diagnosis.
[b]Recent or ongoing symptoms of an acute flu or flu-like infection at the time of ITP diagnosis.
*Significant at the < 0.05 level.

extending up to 13 years before remission. Follow-up times varied due to the retrospective nature of the study, with a median follow-up of 0.54 years (IQR 0.18–1.64), ranging from 0 to 15.91 years. For chronic cases, the mean follow-up time was 4.49 years (SD 3.40 years). Recovery over time is illustrated in Figure 4.

## 4 | Discussion

The present population-based study offers a longitudinal perspective on the diagnostics, management, and follow-up of Finnish children diagnosed with ITP over a 15-year period. The results align with those of earlier cohort studies on paediatric ITP. The majority of the 403 patients examined reached normal platelet counts rapidly, while chronic disease developed in 25.9% of those with follow-up data available. Severe bleeding events were rare, and there were no fatal events. Most of the patients fared well with watchful waiting. Pharmacological treatment was administered to 162 (40.2%) patients. No factors predicting a favourable response to treatment could be identified. Risk factors for chronic disease included an insidious disease onset, higher age, a higher platelet count, and an absence of a recent (viral) infection at diagnosis. Female gender was also associated with a prolonged disease course.

We report one-fourth of all patients developing chronic disease, which is in accordance with the results of previous studies [15, 19, 21]. A slight overestimation in our findings is possible because only tertiary hospitals were included in the study, which potentially led to an increased representation of chronic cases requiring treatment or further investigation. Previous studies have identified several risk factors for chronic disease, including higher age, a higher platelet count, female gender, an insidious onset of symptoms, and an absence of infections or vaccinations administered recently prior to the disease's onset [19, 21, 24–26]. Our results are in line with these findings. Notably, an insidious onset strongly indicated a chronic disease, especially when combined with an absence of a recent infection. This association is likely to be even stronger in practice, considering that patients with inherited platelet disorders and other specific causes of thrombocytopenia were excluded from the present analysis.



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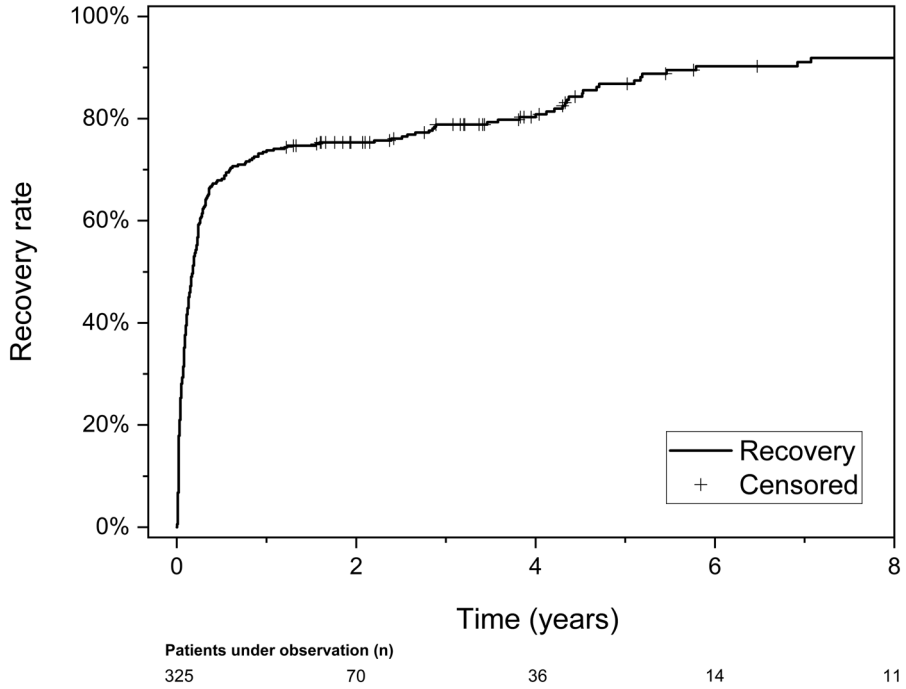


**FIGURE 4** | Kaplan–Meier curve of time to recovery. The curve shows the recovery and follow-up times of patients with ITP. Accurate follow-up data were not available for all the cases. For clarity, the scale was cut to 8 years of follow-up, although a single patient recovered after 13 years of follow-up, and the longest follow-up time of a patient not recovering was 15.91 years.

Hence, an early-on approach of extended diagnostic evaluation including genetic testing appears beneficial for this subgroup of patients. This is particularly relevant given the current costs and availability of, for example, whole exome sequencing and thrombopoietin-receptor agonist treatment compared to the costs and burden of repeated blood sampling and restrictions on leisure time activities for safety reasons.

Many chronic cases of ITP resolve over time, even after years of follow-up [31]. In a previous Nordic cohort prospective study, half of the patients with chronic ITP recovered within 5 years. In a Turkish study, 15% of patients recovered after the first 12 months of follow-up [12, 32]. In our cohort, sustained, documented remission was reached in 36/95 (37.9%) patients with chronic disease. Due to the nature of this study, the duration of follow-up varied among the chronic cases, with the shortest follow-up being two years and the longest nearly 16 years. Therefore, some chronic cases that were not reported as resolved would certainly have reached remission given enough time. Indeed, the potential for ITP to resolve even after years from the disease's onset is highlighted by a child in our cohort who spontaneously recovered from ITP after 13 years of follow-up.

Current treatment guidelines recommend a strategy of watchful waiting for patients without significant bleeding, in contrast to former guidelines recommending treatment based on a patient's platelet count [4, 33]. In our study, very few individuals had severe bleeding events, despite most patients not receiving treatment. The international guidelines by Provan et al. (2019) advocate for IVIG as the primary first-line option to increase platelet counts in paediatric patients with more severe bleeding symptoms, while corticosteroids should be used when bleeding symptoms are mild (grade 1 or 2) and treatment is considered necessary or if there is no response to IVIG. Combination therapy with IVIG, intravenous corticosteroids, and platelet transfusions is recommended as an emergency treatment for life-threatening bleeding [4]. Previous studies have found that children treated with IVIG have better immediate responses, which are sustained at 48 h, compared to those treated with corticosteroids; also, treatment with corticosteroids is associated with serious adverse effects when used in the long term [14, 34]. In our study, IVIG was the most common first-line treatment, with corticosteroids used as a second-line option when required. In some refractory cases, the thrombopoietin-receptor agonist eltrombopag or rituximab was used. The differences we report in the proportions of sustained responses can be attributed to IVIG being the first-line option in most cases, followed by spontaneous remission as part of the natural course of the disease, while persisting and chronic cases of ITP required additional treatment with other medications. Notably, in many cases, treatment responses were not permanent and did not appear to affect overall prognoses.

A previous Nordic cohort study of ITP reported seasonal variation, with 70/112 (62.5%) Finnish patients being diagnosed between October and March [19]. In the present study, no winter bulk of cases was observed, but a bimodal distribution following respiratory virus epidemics in spring and autumn was found (Figure 2). This underlines the connection between the onset of ITP and viral infections. The differences with the previous study conducted on the same population may be due to secular changes in the epidemics of respiratory viral infections.

Examining peripheral blood smears helps distinguish ITP from underlying malignancies and inherited platelet disorders characterised by abnormalities in platelet size [33, 35, 36]. In our study, we found that peripheral blood smears had not been routinely examined in all the patients and participating centres, whereas bone marrows had been obtained even in some newly



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diagnosed cases. For patients presenting as typical newly diagnosed ITP cases, checking peripheral blood smears might seem unnecessary if the blood count normalises quickly during follow-up. However, taking peripheral blood smears may reduce the need for bone marrow investigations, potentially allowing for the early discovery of genetic disorders.

Our population-based study design, combined with a systematic approach to data collection, represents the main strength of this study. The inclusion of only tertiary hospitals may have led to missing follow-up data and bias toward more severe cases. To minimise this, patients with insufficient data and known to have been followed up in other units were excluded from the risk analyses. However, retrospectively collected data may not always encompass all desired information. In our case, some potentially relevant parameters or laboratory markers might never have been explored, and some symptoms and characteristics may not have been documented. These variations in data quality and completeness may introduce information bias.

## 5 | Conclusions

Most children with ITP experience uncomplicated disease courses, recover shortly after diagnosis, and do not typically require further investigations or treatment. Severe bleeding events are very rare. Most of the patients who are considered to require pharmacological therapy respond to first-line treatment with IVIG or corticosteroids. Chronic disease is more likely to develop when the disease onset is insidious, the patient is older, the platelet count is not extremely low, and there is no history of a recent acute viral infection. Chronic ITP has the potential to resolve even years after diagnosis.

### Author Contributions

**Lauri-Matti Kulmala:** writing – original draft, funding acquisition, investigation, formal analysis, visualization, project administration, writing – review and editing. **Henri Aarnivala:** supervision, writing – review and editing, funding acquisition, formal analysis, conceptualization, methodology, investigation, visualization, project administration. **Tytti Pokka:** writing – review and editing, formal analysis. **Anu Huurre:** formal analysis, writing – review and editing. **Liisa Järvelä:** writing – review and editing, formal analysis. **Sauli Palmu:** writing – review and editing, formal analysis. **Tuuli Pöyhönen:** formal analysis, writing – review and editing. **Riitta Niinimäki:** supervision, writing – review and editing, formal analysis, visualization, conceptualization, methodology, investigation, funding acquisition, project administration.

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### Conflicts of Interest

The authors declare no conflicts of interest.

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