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RESEARCH ARTICLE

# Immune or inherited thrombocytopenia? A population-based cohort study on children and adolescents presenting with a low platelet count

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## Abstract

**Background:** Thrombocytopenia is a common hematologic finding in children and adolescents. Immune thrombocytopenia (ITP) is the most common cause of this finding, but the differential diagnosis includes a growing list of genetic disorders. We aimed to report differences in phenotypes of patients with ITP, inherited platelet disorder (IPD)/primary immunodeficiency disorder (PID), and other causes, with a focus on differentiating ITP from inherited thrombocytopenia.

**Procedure:** This retrospective, population-based observational cohort from 2006 to 2020 involved 506 Finnish children under 16 years of age presenting with isolated thrombocytopenia.

**Results:** Of the 506 participants, 79.7% had ITP, 6.7% had IPD/PID, and 13.6% had other causes of thrombocytopenia. A platelet count of $\leq 12 \times 10^9$/L best distinguished between ITP and other reasons with a sensitivity of 60% and a specificity of 80%. Among patients with the lowest platelet count of less than $10 \times 10^9$/L, 95.9% had ITP, 3.3% had IPD/PID, and 0.8% had other causes. Severe bleeding events were reported in 20 patients (4.0%), but there were no cases of intracranial or fatal bleeding due to thrombocytopenia. Up to 50% of patients with a high suspicion of inherited thrombocytopenia remained without a specific diagnosis despite genetic testing.

**Conclusions:** ITP remains the most common cause of thrombocytopenia. A platelet count of $\leq 12 \times 10^9$/L often leads to an ITP diagnosis. Genetic disorders are rare but should be suspected in patients with persisting thrombocytopenia, especially with platelet counts constantly above $12 \times 10^9$/L, a positive family history, or atypical clinical features.

KEYWORDS
genetics, IPD, ITP, PID, thrombocytopenia

**Abbreviations:** IBMFS, inherited bone marrow failure syndrome; IPD, inherited platelet disorder; ITP, immune thrombocytopenia; PID, primary immunodeficiency disorder; ROC, receiver operating characteristics.

## 1 | INTRODUCTION

Thrombocytopenia is a common hematologic finding in children and adolescents. Immune thrombocytopenia (ITP), the most frequent cause, is an acquired immune-mediated disorder characterized by low platelet counts due to increased peripheral destruction of platelets or defects in platelet production.[1–4] ITP remains a diagnosis of exclusion with no specific diagnostic tests available.[5–7] Inherited platelet disorder (IPD) and primary immunodeficiency disorder (PID), among other causes, must be considered as alternatives.[8–10] The reported incidence of ITP ranges from 2.2 to 5.4 per 100,000 children annually.[11] Other causes of thrombocytopenia are very rare, with Wiskott–Aldrich syndrome at 1–10 per million cases and Bernard–Soulier syndrome at one per million cases annually.[8,12–16] Differentiating between ITP and other causes of thrombocytopenia remains a clinical challenge.[10] As the cost of genetic testing has decreased, gene panels and whole-genome sequencing have become accessible diagnostic tools for most clinicians. Consequently, the number of known genetic conditions causing thrombocytopenia is ever growing, and the increased knowledge on the pathophysiology behind different conditions causing thrombocytopenia enhances treatment- and follow-up-related decision-making.[8,9,12,14,17]

Several observational cohort studies on childhood ITP exist, with the most recent Nordic reports by Rosthøj et al. and Zeller et al. dating back two decades.[3,4,7,18,19] Several inherited forms of thrombocytopenia have recently been characterized, and many studies on the diagnostics and management of inherited thrombocytopenia have been published.[8,9,12,14,17,20] However, population-based studies with a focus on distinguishing between different causes of thrombocytopenia in children are lacking. In addition to the recent review by Grace and Lambert (2022), the registry study by Lee (2018) from Singapore is the sole prior study looking at the differences between ITP and non-ITP.[9,13]

We aimed to report all cases of childhood thrombocytopenia between 2006 and 2020 in Finland and to investigate potential phenotype differences among patients with ITP, IPD/PID, and other causes of low platelet count, with a focus on differentiating primary ITP from inherited thrombocytopenia.

## 2 | METHODS

### 2.1 | Study design

Four university hospitals in Finland participated in this retrospective, population-based, observational cohort study. The inclusion criteria were age less than 16 years at diagnosis of thrombocytopenia, first recorded between 2006 and 2020. Cases with mild anemia due to, for example, iron deficiency, or transient mild leukopenia, or leukocytosis due to, for example, acute viral infection were included. Exclusion criteria were secondary ITP, neonatal alloimmune and drug-induced thrombocytopenia, misclassified patients (e.g., leukemias, Henoch–Schönlein purpura, and aplastic anemia), and clear laboratory errors. The study adhered to the principles of the Declaration of Helsinki. As this was a register-based study, no informed consent was required according to the Finnish law.

### 2.2 | Data collection

The participants were identified from hospitals' medical records using International Classification of Diseases (ICD-10) codes for thrombocytopenia (D69.1–D69.6). Data were manually collected by the researchers from local patient records by using a specific case report form on the REDCap database, including patient characteristics, laboratory results, information on diagnostics, follow-up, and treatment of thrombocytopenia. Data were pooled and pseudonymized by the Finnish Social and Health Data Permit Authority (Findata), and then reviewed at the coordinating study center. Patients without documented thrombocytopenia (platelets never $<150 \times 10^9$/L) were excluded from the analysis, unless a diagnosis of an IPD had been established.

### 2.3 | Definitions

Thrombocytopenia was defined as a platelet count of less than $150 \times 10^9$/L. The lowest platelet count determined the severity of thrombocytopenia. ITP was defined according to international guidelines as a platelet count of less than $100 \times 10^9$/L and exclusion of other causes.[6] Patients with IPD/PID had a definite genetic diagnosis or phenotype-related findings leading to diagnosis. Patients with a confirmed cause of thrombocytopenia other than IPD/PID were classified as "Other," as were those with platelet counts of greater than $100 \times 10^9$/L, with no specific cause of thrombocytopenia found, as they did not meet the criteria for ITP.

A positive family history was defined as thrombocytopenia, abnormal bleeding tendency or petechiae, or a diagnosis of IPD or PID in first- or second-degree relatives. Bleeding symptoms were graded according to the updated international consensus report by Provan et al.[6]

### 2.4 | Data analysis and statistics

Mean values of laboratory results and patients' age at diagnosis between diagnosis groups were tested using variance analysis with Tukey's honestly significant difference or Games–Howell correction for post hoc tests. The distribution of the classified lowest platelet count between diagnosis groups and the classified duration of thrombocytopenia were assessed using the chi-square test. Receiver operating characteristic (ROC) analysis for platelet counts was used to determine the optimal cut-off value discriminating ITP patients from IPD/PID patients. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp.).

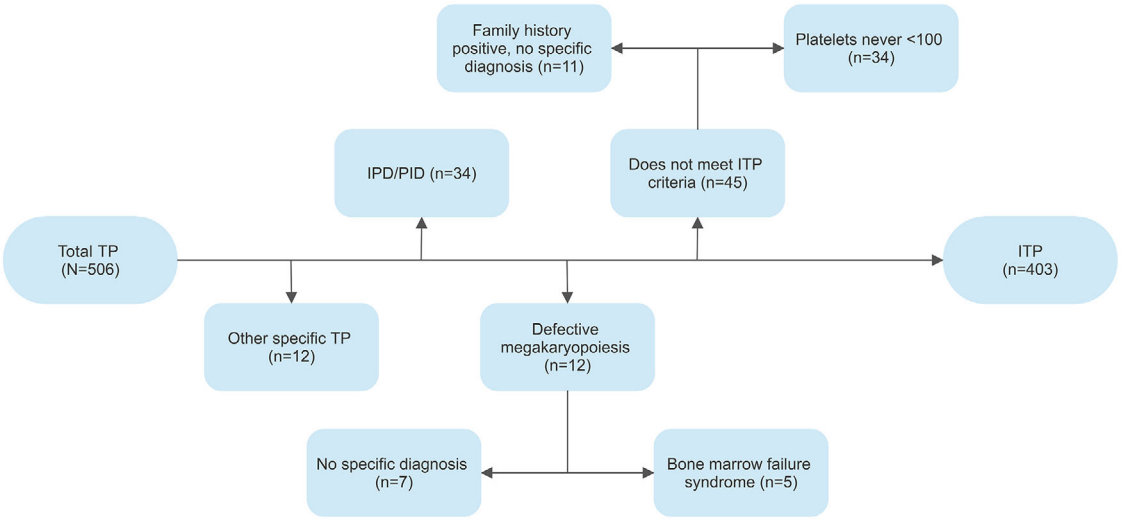


**FIGURE 1** Diagnostic flow of patients with thrombocytopenia. IPD, inherited platelet disorder; ITP, immune thrombocytopenia; PID, primary immune deficiency; TP, thrombocytopenia.

**TABLE 1** Clinical characteristics of patients with thrombocytopenia.

| | All patients ($N = 506$) | ITP ($n = 403$) | IPD/PID ($n = 34$) | Other ($n = 69$) |
|---|---|---|---|---|
| **Age at onset** (years) | 6.7 ± 4.9 | 6.5 ± 4.8 | 4.8 ± 4.9 | 8.8 ± 5.2 |
| **Lowest measured platelet level** ($n \times 10^9$/L) | 34.8 ± 40.7 | 22.7 ± 28.3 | 46.8 ± 36.6 | 100.2 ± 41.2 |
| **Time to definite diagnosis** | | | 2.3 ± 3.6 | |
| **Sex** | | | | |
| Male | 282 (55.7%) | 225 (55.8%) | 19 (58.3%) | 38 (54.4%) |
| **Positive family history** | 72 (14.2%) | 38 (9.4%) | 21 (61.8%) | 13 (18.8%) |
| **Acute infection at diagnosis** | 149 (29.4%) | 114 (28.3%) | 9 (25.0%) | 26 (38.2%) |
| **Peripheral blood smear examined** | 231 (45.7%) | 173 (42.9%) | 26 (76.5%) | 32 (46.4%) |
| Abnormal | 23 (10.0%) | 7 (1.7%) | 11 (32.4%) | 5 (7.2%) |
| **Bone marrow examined** | 208 (41.1%) | 157 (39.0%) | 16 (47.1%) | 33 (47.8%) |
| Abnormal | 29 (13.9%) | 10 (2.5%) | 5 (14.7%) | 14 (20.3%) |
| **Abdominal ultrasound examined** | 178 (35.2%) | 134 (33.3%) | 16 (47.1%) | 28 (40.6%) |
| Spleen enlarged | 20 (4.0%) | 12 (3.0%) | 3 (8.8%) | 5 (7.2%) |
| **Genetic tests done** | 67 (13.2%) | 23 (5.7%) | 28 (82.4%) | 15 (21.7%) |
| Causative mutation found | 33 (5.5%) | | 28 (82.4%) | 5 (7.2%) |

*Note*: Values stated as *n* (%) or mean ± SD. Other = patients with a confirmed cause of thrombocytopenia other than IPD/PID, and patients with no specific cause of thrombocytopenia found, not meeting ITP criteria.
Abbreviations: IPD, inherited platelet disorder; ITP, immune thrombocytopenia; PID, primary immune deficiency.

## 3 | RESULTS

### 3.1 | Incidence and characteristics

A total of 506 children and adolescents were included in the study. The diagnostic flow is shown in Figure 1. Three patients did not have recorded platelet counts of less than $150 \times 10^9$/L, but had a diagnosis of IPD. Descriptive data are presented in Table 1. A total of 403 (79.7%) patients had ITP, 34 (6.7%) had IPD/PID, and 69 (13.6%) were classified as "Other" thrombocytopenia. The mean age of the cohort was 6.7 ± 4.9 years at diagnosis (range: 0.00–15.86 years). For patients with ITP, the mean age was 6.5 ± 4.8 years; for those with IPD/PID, 4.8 ± 4.9 years; and for other thrombocytopenia, 8.8 ± 5.2 years. Patients with IPD/PID were younger than those with other diagnoses ($p = .002$), but there were no statistically significant differences between ITP and IPD/PID ($p = .093$). Abnormal findings in bone marrow samples were documented in 10 patients with ITP and peripheral blood smears of seven patients with ITP, but were later confirmed to

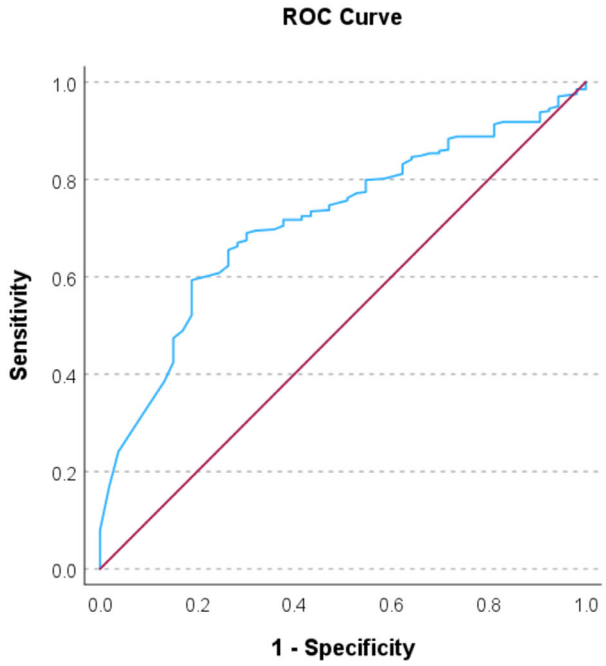


**FIGURE 2** Receiver operating characteristics (ROC) curve. Optimal cutoff point best distinguishing between immune thrombocytopenia and other thrombocytopenia at platelets 12 × $10^9$/L, at sensitivity of 60% and specificity of 80%.

be insignificant changes due to reactivity, deficiencies in iron or B-12 vitamins, or other nonspecific alterations not found in control samples.

## 3.2 | Platelet count and final diagnosis

Patients with ITP had the lowest measured platelet counts, with a mean of 22.7 ± 28.3 × $10^9$/L, while the mean lowest platelet count for patients with IPD/PID was 46.8 ± 37.3 × $10^9$/L and for those with other diagnoses 99.2 ± 41.8 × $10^9$/L. The differences were statistically significant between ITP and IPD/PID ($p < .001$), ITP and other thrombocytopenia ($p < .001$), and IPD/PID and others ($p < .001$). In the ROC analysis performed for patients with platelet counts less than 100 × $10^9$/L, a platelet count of 12 × $10^9$/L best distinguished between ITP and other causes, with a sensitivity of 60% and a specificity of 80% (Figure 2). Patients with the lowest platelet count of greater than 100 × $10^9$/L were excluded from the ROC analysis, as ITP by definition requires platelet counts of less than 100 × $10^9$/L. Out of the 243 patients with the lowest platelet count of ≤10 × $10^9$/L, 95.9% had ITP, 3.3% IPD/PID, and 0.8% had other causes. The distributions of lowest measured platelet counts between the diagnoses are shown in Figure 3.

## 3.3 | Genetics

A positive family history was reported in 72 (14.2%) patients. Of these, 38 (52.8%) were diagnosed with ITP, 21 (29.2%) with IPD/PID,

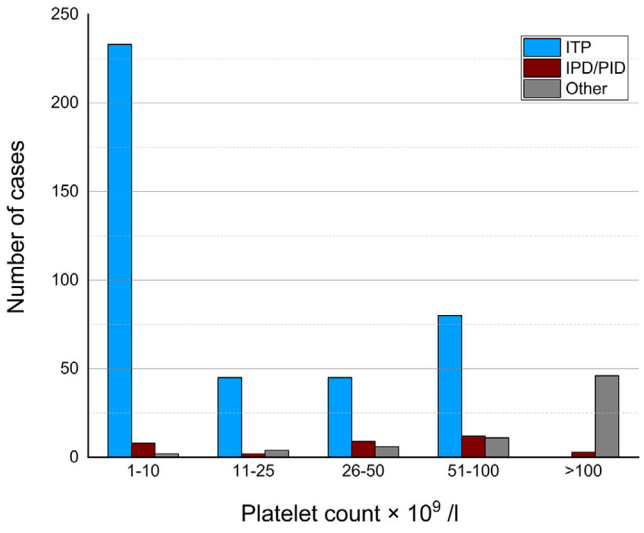


**FIGURE 3** Platelet count by diagnosis group. ITP, immune thrombocytopenia; IPD, inheritable platelet disorder; PID, primary immune deficiency.

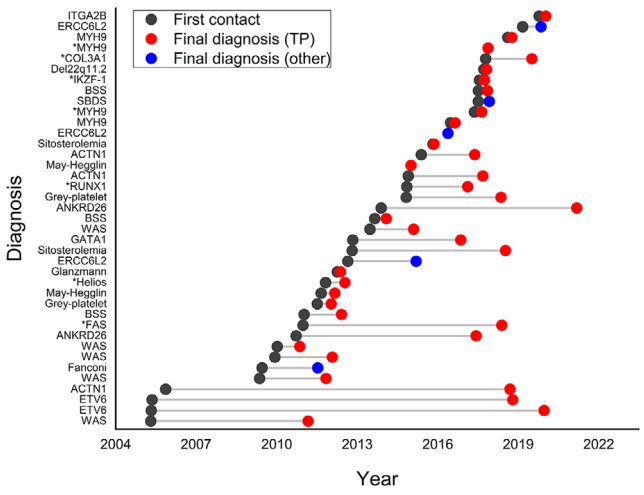


**FIGURE 4** Lollipop plot of 33 cases with genetic diagnoses showing timeline from first contact to final diagnosis: 28 patients with a diagnosis of thrombocytopenia, and five with other specific diagnoses presenting initially as isolated thrombocytopenia. BSS, Bernard–Soulier syndrome; SBDS, Swachman–Bodian–Diamond syndrome; TP, thrombocytopenia; WAS, Wiskott–Aldrich syndrome. Novel mutations marked with an asterisk (*).

and 13 (18.0%) with other thrombocytopenia. Genetic testing was performed in 66 (13.0%) of all patients with thrombocytopenia: single gene sequencing in 15 patients, a gene panel was examined in 43 patients, whole-exome sequencing in 12 patients, and whole-genome sequencing in one patient. Five patients underwent multiple rounds of genetic testing. A pathogenic mutation or a likely pathogenic mutation was found in 33 (50.0%) of the tested patients, leading to a specific diagnosis of IPD in 25 patients and PID in three patients (Figure 4). In seven patients, the variant found was a novel variant considered causative according to the geneticist (Figure 4). In addition,

**TABLE 2** Severe bleeding events by diagnosis groups and platelet count.

| | Nasal bleeding | Mucosal bleeding | Traumatic bleeding | Medical procedure-related bleeding |
|---|---|---|---|---|
| **ITP ($n = 403$)** | 11 (2.7%) | 3 (0.7%) | 1 (0.2%) | – |
| Platelets $<10 \times 10^9$/L | 10 (2.5%) | 3 (0.7%) | 1 (0.2%) | – |
| **IPD/PID ($n = 34$)** | 3 (8.8%) | 1 (2.9%) | – | 1 (2.9%) |
| Platelets $<10 \times 10^9$/L | 1 (2.9%) | – | – | – |
| **Total ($N = 506$)** | 14 (2.8%) | 4 (0.8%) | 1 (0.2%) | 1 (0.2%) |
| Platelets $<10 \times 10^9$/L | 11 (2.2%) | 3 (0.6%) | 1 (0.2%) | – |

Abbreviations: IPD, inherited platelet disorder; ITP, immune thrombocytopenia; PID, primary immune deficiency.

five patients classified as other thrombocytopenia had a mutation suggestive of inherited bone marrow failure syndrome (IBMFS): three patients with homozygous ERCC6L2 mutation, one with Shwachman–Diamond syndrome, and one with Fanconi anemia presenting only as thrombocytopenia. A total of 23 causative mutations (in 20 different genes) were identified. The rest of the cases with IPD ($n = 6$) were diagnosed based on phenotypical findings (including platelet morphology) and family history. Among the 33 patients with negative genetic results, 23 were ultimately classified as ITP (5.7% of all ITP patients) and 10 as other thrombocytopenia (9.7% of cases with thrombocytopenia other than ITP) due to proven defective megakaryopoiesis, or platelet count of greater than $100 \times 10^9$/L, and thus, not fulfilling the diagnostic criteria for ITP. Of the patients with a positive family history, 21 (29.2%) were tested for genetic disorders, and an explaining mutation was found in 18 (85.6%) of those tested.

For the patients with an established diagnosis of IPD or PID, the timeline from the first presentation at a tertiary clinic due to thrombocytopenia to a definite diagnosis is shown in Figure 4. The time to definite diagnosis was a median of 0.51 years (interquartile range [IQR]: 2.55 years), with a range of 0–14.63 years.

### 3.4 | Bleeding symptoms

Most patients presented with mild bleeding symptoms (petechia, bruises, epistaxis, etc.) at the initial presentation. Severe bleeding requiring medical attention was reported in 20/506 (4.0%) patients: 15/403 (3.7%) of the patients with ITP, and five of 34 (14.7%) patients with IPD/PID (Table 2). Most bleeding events occurred with platelet counts of less than $10 \times 10^9$/L in ITP patients, with one patient having a slightly higher platelet count at $12 \times 10^9$/L. Patients with IPD/PID experienced bleeding regardless of the platelet count, ranging $2–200 \times 10^9$/L. No severe bleeding was reported in patients with other causes of thrombocytopenia. One medical procedure-related bleeding event was documented after a tympanostomy. No intracranial hemorrhages or fatal bleeding were documented in the entire cohort.

## 4 | DISCUSSION

In this population-based retrospective cohort study, we identified 506 patients with isolated thrombocytopenia: 403 with ITP, 34 with IPDs or primary immune deficiencies, and 69 with other causes. ITP was the most common diagnosis, as expected, but a significant number of inherited causes of thrombocytopenia were also found. An observed platelet count of below $12 \times 10^9$/L was found to be highly specific for primary ITP as the ultimate diagnosis.

At presentation, age was not predictive of the final diagnosis of thrombocytopenia. Patients with IPD/PID were presented at variable ages, depending largely on the genetic etiology of the disease as well as on family history. Previous studies have reported age distributions of IPD/PID ranging widely. To our knowledge, no studies reporting differences in the age of onset of IPD/PID compared to ITP patients have been published, although ITP is often regarded as a disease of young children.[3,4,18,19,21–23]

In clinical practice, diagnosing ITP is generally straightforward, despite it being a diagnosis of exclusion. Bone marrow examination or genetic testing is reserved for cases presenting atypical clinical features or persistent cases of isolated thrombocytopenia.[2,5,6,9,24] Recent pediatric studies have suggested genetic testing in patients with thrombocytopenia presenting since early life and for ITP not responding to treatment, while cases with suggestive phenotypical or syndromic features or a positive family history may warrant early genetic testing.[6,25,26] Previous studies have reported significantly higher presenting platelet counts among patients with IPD/PID compared to patients with ITP.[27,28] Our results are in accordance with this observation, as patients with ITP more often had very low platelet counts, whereas those with IPD/PID showed variable platelet counts with a relatively even distribution, largely depending on the genetic disorder behind thrombocytopenia.

In the present study, 33 genetic causes were identified in 66 tested patients, which aligns with previous studies reporting up to 50% of patients with high suspicion for IPD/PID remaining without a definite diagnosis.[25,26,29] Most patients with a positive family history of

thrombocytopenia were not tested for genetic disorders, but the vast majority of those who were tested received a definite diagnosis. Considering the low number of IPD/PID diagnoses in patients with the lowest platelet count between 11 and 25 × $10^9$/L, our findings suggest that earlier genetic testing might be especially beneficial for patients with platelet counts persisting in the 26–100 × $10^9$/L range, especially in the context of a positive family history. Such patients are the ones with a higher likelihood of having clinically relevant variant mutations, for example, variants predisposing to leukemia. Patients with lower counts are more likely to remain with the diagnosis of ITP. Furthermore, the proportion of patients with ITP and lowest platelet counts between 51 and 100 × $10^9$/L in the present study may be an overestimation; patients with mild symptoms are less likely to undergo comprehensive genetic testing, leading to potential underdiagnosis of genetic causes for thrombocytopenia.

Gene panels and whole-exome sequencing have become accessible to most clinicians over the last two decades, shortening the timeline for exact diagnosis. In our cohort, the delay between first contact and final diagnosis significantly shortened during the last 5 years of the study period. However, the diagnostic lag appears unnecessarily long in some cases established in recent years. The recently described IBMFS and myeloid malignancy prone syndrome caused by homozygous ERCC6L2 mutations found in the present cohort, often initially presenting only as thrombocytopenia, underscores the necessity of timely genetic diagnosis to facilitate necessary therapeutic interventions in such diseases.[30]

Population-based studies on inherited thrombocytopenia in children are scarce. Cohort studies on inherited thrombocytopenia from Denmark and Italy have been published.[26–28,31] Leinøe et al. (2021) screened 106 Danish patients suspected of inherited thrombocytopenia by whole-genome and whole-exome sequencing, identifying a Danish founder variant of Bernard–Soulier syndrome (BSS) as the most frequent cause with a causative variant found in 50/106 patients.[28] Noris et al. (2012) screened 216 Italian patients with an unidentified non-syndromic, autosomal-dominant form of macrothrombocytopenia for the Bolzano variant, finding the Bolzano mutation causative in 42/216 cases.[27] The founder effect in Finland was evident in the overrepresentation of certain genetic disorders, such as the aforementioned ERCC6L2-related disease found in three of 66 tested patients in our cohort.[30] Other forms of inherited thrombocytopenia were present in our cohort sporadically, as expected.

Most cases of severe hemorrhage or bleeding requiring medical attention reportedly occur in patients with low platelet counts (<30 × $10^9$/L), but bleeding symptoms do not always correlate directly to the platelet count of a patient.[32–34] We report no intracranial hemorrhage or death due to thrombocytopenia despite 57.8% of patients with ITP presenting a platelet count of less than 10 × $10^9$/L. Patients with ITP had severe (grades 3–4) bleeding events rarely and only when their platelet count was ≤12 × $10^9$/L, whereas severe bleeding occurred in patients with IPD/PID with variable platelet counts (2–200 × $10^9$/L), highlighting the differences in pathogenesis and the necessity to plan the prevention and management of bleeding individually when a specific diagnosis for thrombocytopenia is established.

The strengths of our study are its population-based design and systematic data collection. Limitations arise from the exclusive inclusion of tertiary university hospital clinics, potentially biasing toward more complicated cases, and incomplete data due to a lack of documentation in some cases (e.g., follow-up in a different unit). The reliance on specific ICD-10 codes may exclude cases where a specific diagnosis is confirmed at first contact, which might lead to an underrepresentation of certain thrombocytopenia-related syndromes and genetic diagnoses, although such diagnoses are rarely established during the first visit.

## 5 | CONCLUSIONS

One out of five patients presenting with isolated thrombocytopenia in childhood receives a definitive diagnosis other than ITP. A platelet count below 12 × $10^9$/L in a child with isolated thrombocytopenia is highly suggestive of ITP. One possible solution to shorten the path to a definitive genetic diagnosis could be directing early genetic testing to patients with persistent thrombocytopenia constantly above 12 × $10^9$/L, not least in the presence of a positive family history or syndromic features. Bleeding management in patients with a definitive diagnosis of IPD/PID should be tailored individually, regardless of platelet count.

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### CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Research data are not shared due to local legislation.

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