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RESEARCH ARTICLE

Prognostic Factors for Poor Outcome in Immune Thrombocytopenia

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Abstract

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by increased platelet destruction and impaired platelet production. Although most acute cases—particularly in children—resolve spontaneously or respond readily to first-line therapy, a significant subset of adult patients develop chronic, refractory, or complicated disease. Early recognition of poor prognostic factors is essential to guide management, optimize treatment sequencing, and prevent severe bleeding or unnecessary therapeutic exposure. This narrative review summarizes recent evidence (2018–2025) concerning the clinical, biological, immunological, and therapeutic determinants associated with adverse outcomes in adult ITP. We emphasize factors related to chronicity, treatment resistance, and bleeding risk to inform the development of personalized, risk-adapted therapeutic strategies.

Keywords: Immune Thrombocytopenia, Prognosis, Predictive Factors, Chronic ITP, Refractory ITP, Bleeding Risk.

1. Introduction

Immune Thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura, is an autoimmune disorder defined by a platelet count of $<100\times10^9$/L, driven by both antibody- and cell-mediated platelet destruction and concurrent megakaryocyte dysfunction [1, 2]. As one of the most common autoimmune cytopenias, ITP presents with a highly heterogeneous clinical course, spanning from transient mild thrombocytopenia to severe, chronic disease associated with significant hemorrhagic or thrombotic events [3]. Early identification of patients prone to a poor prognosis and progression to chronicity is therefore critical; initial predictors include the absence of a preceding infectious event, lack of bleeding manifestations, and poor response to initial corticosteroids [4]. Despite significant advances in therapeutic options, including thrombopoietin-receptor agonists (TPO-RAs) and novel agents like fostamatinib or FcRn inhibitors, many patients continue to experience relapses or require long-term management [5]. Identifying robust prognostic factors holds major implications for personalized care.

The overall goal of this narrative review is to critically analyze and synthesize the body of literature concerning the key prognostic factors in ITP, highlighting the transition from traditional clinical markers to modern immunologic and genetic biomarkers, and discussing how these evolving insights inform the development of personalized, risk-adapted therapeutic strategies.

2. Heterogeneity, Prognosis, and Therapeutic Challenges of ITP

ITP is a highly heterogeneous autoimmune disorder resulting from both antibody- and cell-mediated platelet destruction alongside defective megakaryocyte function [1, 2]. This heterogeneity is evident across the entire disease course. The clinical presentation itself varies widely, ranging from incidental findings of mild thrombocytopenia to

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life-threatening hemorrhagic complications, such as intracranial or severe gastrointestinal bleeding [3]. The subsequent disease evolution is equally unpredictable, encompassing spontaneous remission (observed in a substantial minority of adults), progression to chronic ITP (persistence beyond 12 months), or the state of refractoriness to standard treatments [4]. Furthermore, defining genuine cure remains challenging, as even patients achieving durable remission may experience late relapse. Compounding this complexity is the risk of iatrogenic complications, notably thrombosis associated with TPO-RA use, or infections following splenectomy [5]. Furthermore, ITP can evolve over time, necessitating reclassification as secondary ITP due to the later manifestation of an underlying associated condition, including systemic autoimmune diseases (e.g., systemic lupus erythematosus [SLE], antiphospholipid syndrome) or an occult lymphoproliferative disorder [6]. Consequently, identifying robust prognostic factors for chronic ITP and defining personalized treatment pathways holds major implications for realizing the goal of risk-adapted care and optimizing long-term outcomes.

3. Epidemiology and Prognostic Axes in ITP

TP affects approximately 2 to 4 adults per 100,000 per year globally, with incidence rates showing variation across different populations [7]. Epidemiological studies confirm a slight female predominance in adults before the age of 60, followed by a roughly equal sex distribution thereafter, highlighting the age-dependent shift in disease prevalence [8]. Prognosis in ITP is generally assessed along three main, interconnected axes, which are crucial for guiding therapeutic intensity and monitoring [1]. First, chronicity is defined as the persistence of thrombocytopenia (platelet count $<100\times10^9$/L) beyond 12 months after diagnosis, a trajectory seen in approximately two-thirds of adults. Second, treatment refractoriness refers to a lack of adequate response or subsequent relapse following standard first- and second-line treatments, typically including corticosteroids, intravenous immunoglobulins (IVIg), and often splenectomy [9]. This refractory state poses the greatest therapeutic challenge and is associated with a higher complication risk. Third, bleeding risk reflects the probability of life-threatening hemorrhage; this risk is dynamically modulated not only by the absolute platelet count but also by factors like advanced age, the presence of key comorbidities (e.g., hypertension, renal failure), and the use of concomitant antithrombotic medications [10]. Although overall ITP-attributable mortality has decreased dramatically in recent decades, patients with poor prognostic factors continue to face considerable morbidity and impaired quality of life (QoL) [11].

4. Age and Comorbidities as Key Prognostic Predictors of ITP

Among clinical variables, advanced age remains the strongest independent predictor of poor prognosis in ITP [10]. Patients older than 60 years exhibit a higher incidence of chronic disease, reduced initial response to standard therapies such as corticosteroids, and, most critically, increased bleeding-related mortality [10, 12] (Table 1). This vulnerability likely reflects a confluence of factors, including immuno-senescence (age-related decline in immune function) and the higher prevalence of comorbidities requiring concomitant antithrombotic therapy (e.g., aspirin or anticoagulants), which amplify the hemorrhagic risk [13-15]. The male sex has also been consistently associated with chronic evolution and suboptimal initial response in ITP, a finding demonstrated across several large multicenter cohorts [14]. The precise immunological basis for this sex-specific difference in ITP remains an area of ongoing investigation. Furthermore, the presence of secondary forms of ITP—those associated with underlying systemic disorders—significantly increases the likelihood of chronicity and refractoriness [6]. Key secondary etiologies include systemic autoimmune conditions, such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome; chronic viral infections, notably Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV); and lymphoproliferative disorders [6]. Finally, severe bleeding at presentation and the immediate need for urgent interventions (e.g., high-dose IVIg or platelet transfusions) may serve to identify patients with higher disease activity and, consequently, poor long-term disease control and increased risk of future complications [9]. These critical clinical presentations often necessitate a more aggressive and sustained therapeutic approach.

Table 1. *Clinical and Demographic Prognostic Factors Associated with ITP Chronicity (Adults).*

Factor	Association with Poor Prognosis / Chronicity	Notes for Clinicians	Reference
Advanced Age (>60 years)	Strongest independent predictor; higher incidence of chronic disease, reduced initial response to standard therapies, increased bleeding-related mortality.	Requires more aggressive initial risk stratification and management, especially for bleeding.	[11, 12]

Male Sex	Consistently associated with chronic evolution and suboptimal initial response.	A subtle but persistent predictor across cohorts; immunological basis under investigation.	[14]
Secondary Causes of ITP	Significantly increases likelihood of chronicity and refractoriness.	Screen for underlying systemic autoimmune diseases (SLE, aPLs), chronic viral infections (HIV, HCV), and lymphoproliferative disorders.	[15]
Absence of Preceding Infectious Event	Predictor of progression to chronic ITP at diagnosis.	Acute ITP often follows infection; absence may suggest primary, more recalcitrant autoimmunity.	[4]
Absence of Bleeding Manifestations at Onset	Identified as a predictor of progression to chronic ITP.	Patients with severe bleeding often receive aggressive, prompt treatment, which may alter disease course.	[4]
Platelet Count (>10x10^9/L) at Diagnosis	Identified as a predictor of progression to chronic ITP.	May indicate a less acute, more indolent process with higher propensity for chronicity.	[4]
Poor Response to Initial Corticosteroids	Strongly associated with progression to chronic or refractory disease.	Lack of sustained response after 3 weeks (prednisone ≥1 mg/kg/day) mandates consideration of earlier second-line.	[4, 1]

5. Hematologic and Biological Markers of ITP Poor Prognosis

Beyond clinical demographics, several baseline hematologic and bone marrow features have been strongly associated with poor ITP outcomes: a persistently very low platelet count (<10×10^9/L) at diagnosis is a powerful predictor of non-remission and early relapse, reflecting severe and rapidly destructive disease activity [16]. Similarly, evaluation of the bone marrow is prognostic, as abnormalities such as a decreased megakaryocyte number or significant morphological dysplasia suggest impaired endogenous platelet production, which often correlates directly with subsequent treatment resistance and chronicity [17]. Though non-specific, high levels of platelet-associated immunoglobulin (PAIg) may also reflect persistent, high-grade immune activation linked to a poor response to corticosteroids. In addition to these classical markers, recent advances in immunopathology have identified a series of immune and inflammatory biomarkers associated with chronic and refractory disease [18]: high levels of pro-inflammatory cytokines such as interleukin-17 (IL-17), B-cell activating factor (BAFF), and interferon-gamma (IFN-γ) are implicated in driving sustained B-cell activation, autoantibody production, and T-cell-mediated destruction [19]. Furthermore, biological hallmarks of treatment failure and sustained autoimmunity include increased cytotoxic CD8+T-cell activation and a low regulatory-to-effector T-cell ratio [20], suggesting a failure of immune tolerance mechanisms to suppress the platelet-specific autoimmune attack. These molecular and cellular markers hold significant promise for future risk stratification and for guiding the selection of targeted therapies, particularly immunomodulatory agents, in patients with refractory ITP.

Table 2. *Biological and Immunological Markers of Poor Prognosis and Resistance in ITP.*

Marker Category	Specific Marker	Association with Poor Prognosis / Resistance	Clinical Implication	Reference
Hematologic	**Persistently Very Low Platelet Count** (<10x10^9/L) at Diagnosis	Powerful predictor of non-remission and early relapse; reflects severe, rapidly destructive disease.	Immediate need for intervention; higher risk of severe bleeding; consideration of earlier aggressive therapy.	[16]
	Decreased Megakaryocyte Number / Morphological Dysplasia in Bone Marrow	Suggests impaired endogenous platelet production; correlates with treatment resistance and chronicity.	Indicates a potential defect in platelet production alongside destruction; TPO-RAs may be less effective alone, or require higher doses.	[17]

Humoral Immunity	**High Platelet-Associated Immunoglobulin (PAIg) Levels**	Reflects persistent, high-grade immune activation; linked to poor response to first-line agents.	While non-specific, high levels may indicate significant antibody-mediated destruction.	[1, 2]
	Persistent / High-Titer Anti-GPIIb/IIIa Antibodies	Strongly associated with chronic disease and reduced likelihood of spontaneous remission.	Indicates ongoing humoral attack; may predict better response to B-cell-targeted therapies (e.g., rituximab, FcRn inhibitors).	[21]
Cellular Immunity	**Elevated Pro-inflammatory Cytokines** (IL-17, BAFF, IFN-gamma)	Drive sustained B-cell activation, autoantibody production, and T-cell-mediated destruction.	Reflects persistent inflammatory milieu; suggests potential benefit from immunomodulatory agents targeting cytokine pathways.	[19, 18]
	Increased Cytotoxic $CD8^+$ T-cell Activation	Hallmark of sustained autoimmunity and treatment failure.	Indicates T-cell mediated destruction; may require therapies with T-cell immunomodulatory effects.	[20]
	Low Regulatory T-cell (Treg) / T helper 17 (Th17) Ratio	Reflects profound immune dysregulation; promotes greater disease severity, sustained autoimmunity, and steroid resistance.	Suggests failure of immune tolerance; potential targets for therapies aiming to restore immune balance.	[22]
Genetic	**Specific Genetic Susceptibility Loci** (HLA-DRB111, CTLA4 polymorphisms)	Support a heritable component to chronicity and severity.	Future role in advanced risk stratification and potentially tailored gene-based interventions.	[23]

6. Immunological and Genetic Drivers of Disease Chronicity

ITP is a paradigmatic autoimmune disorder defined by extensive humoral and cellular immune dysregulation that drives persistent platelet destruction and impaired production [18]. On the humoral side, the presence of persistent or high-titer anti-GPIIb/IIIa antibodies—targeting the most frequent platelet epitope—is strongly associated with chronic disease and a reduced likelihood of spontaneous remission, reflecting ongoing B-cell activation [21]. In parallel, cellular immune dysfunction is critical, evidenced by a profound imbalance between immune-suppressing and pro-inflammatory cells: specifically, decreased regulatory T cell (Treg) function and increased T helper 17 (Th17) cell activity [22]. This dysregulated Treg/Th17 ratio promotes greater disease severity, sustained autoimmunity, and often correlates with steroid resistance [22]. Furthermore, the identification of specific genetic susceptibility loci supports a significant heritable component to chronicity, with key polymorphisms implicated in genes like HLA-DRB1*11 and CTLA4 [23]. Collectively, these interwoven immunologic abnormalities—humoral attack, cellular dysregulation, and genetic predisposition—promote persistent platelet destruction and a failure to re-establish immune tolerance, thereby underpinning poor long-term outcomes in ITP.

7. The Critical Prognostic Value of Initial Treatment Response

The initial treatment response serves as a critical, early prognostic indicator in ITP management. Patients who fail to respond adequately to corticosteroids—typically defined as less than a twofold increase in platelet count after three weeks of prednisone at ≥1 mg/kg/day—are immediately flagged as being at high risk for progressing to chronic or refractory disease [1]. This lack of early efficacy suggests that the underlying immune dysfunction is too robust for control by broad immunosuppression alone. Similarly, patients exhibiting only transient responses to intravenous immunoglobulins (IVIg), where the platelet boost lasts less than four weeks, face an elevated risk of subsequent relapse and treatment dependence [24]. This transient nature indicates that while Fc receptor blockade temporarily halts platelet destruction, the core autoimmune mechanism remains unaddressed. The lack of an early, sustained response to either

corticosteroids or IVIg may suggest a deeper immune dysfunction or a non–immune-mediated component, necessitating further investigation. Furthermore, delayed initiation of second-line therapy—including rituximab or TPO-RAs or fostamatinib—has been consistently linked to an increased likelihood of chronicity and less favorable long-term outcomes [11]. This finding emphasizes the clinical imperative for timely escalation to more targeted or platelet-producing agents in high-risk individuals who fail to meet early response milestones.

8. Response and Refractoriness to Second-Line Therapies

Among second-line agents, TPO-RAs (including eltrombopag, romiplostim, and avatrombopag) have achieved high initial efficacy rates by stimulating megakaryopoiesis and platelet production [25]. However, a significant clinical challenge remains, as 10–20% of patients remain refractory to these agents or experience a loss of response over time [26]. This secondary treatment failure often reflects the overwhelming effect of persistent, immune-mediated platelet destruction that continues despite the increased output from the bone marrow (Table 3). Similarly, the B-cell depleting agent Rituximab induces long-term remission in only approximately 40% of cases at one year [27]. Specific predictors of rituximab failure are crucial for patient selection and include older age, very low platelet count at diagnosis, the presence of secondary autoimmune disease, and the persistence of activated cytotoxic T cells [27]. Splenectomy, while historically regarded as potentially curative in 60–70% of patients, remains ultimately ineffective in up to one-fifth of cases [28, 29]. Treatment failure after splenectomy is particularly noted in patients exhibiting significant extra-medullary platelet sequestration or those with an underlying lymphoproliferative disorder [28, 30]. Patients who fail to achieve a sustained response following corticosteroids, IVIg, and at least one standard second-line agent (TPO-RA or rituximab), or who fail splenectomy, constitute the truly refractory ITP subgroup, whose prognosis remains guarded despite the advent of modern therapies, underscoring the urgent need for novel therapeutic targets [29].

Table 3. *Response Rates and Predictors of Failure for Second-Line Agents in Adult ITP.*

Agent Class	Specific Agents (Examples)	Typical Long-Term Response / Remission Rates	Key Predictors of Failure / Suboptimal Response	Reference
TPO-RAs	Eltrombopag, Romiplostim, Avatrombopag	$\sim 60-80\%$ initial response, but $10-20\%$ refractory or lose response over time	Persistent, strong immune-mediated destruction despite increased production; presence of specific bone marrow abnormalities.	[25, 26]
B-cell Depleters	Rituximab	40% long-term remission at one year	Older age, very low platelet count at diagnosis, secondary autoimmune disease, and persistence of activated cytotoxic T cells.	[27]
Surgical	Splenectomy	60-70% curative historically; ineffective in up to 20%	Extra-medullary platelet sequestration; underlying lymphoproliferative disorders.	[28]
SYK Inhibitors	Fostamatinib	18-43% overall response in refractory patients (variable definitions)	Absence of robust SYK pathway activation; concomitant immune destruction pathways.	[36]
FcRn Inhibitors	Efgartigimod	20-25% response in refractory patients (depending on baseline IgG)	High baseline IgG levels; alternative mechanisms of platelet destruction not involving FcRn.	[36]

9. Bleeding Complications and Mortality of ITP

Severe bleeding remains the principal cause of ITP-related mortality and serious morbidity, with intracranial and gastrointestinal hemorrhages being the most feared complications. Although the bleeding risk increases sharply below 10×10^9/L platelets [31], this numerical threshold must be interpreted within a broader clinical context: elderly patients, individuals on anticoagulants or antiplatelet agents, and those experiencing a rapid decline in platelet count face a significantly higher danger, even at moderately low counts [31]. Paradoxically, despite the low platelet count, ITP is also associated with an increased thrombotic risk, notably elevated under TPO-RA therapy [32]. Thrombosis rates are estimated at 3–6% per year and are heightened in

specific high-risk subgroups, including older, obese, or antiphospholipid-positive patients [33]. Effectively balancing bleeding and thrombosis prevention is therefore an essential and delicate aspect of prognosis management. Overall mortality attributable to ITP has fallen below 1% in most contemporary series [33], yet it remains significantly higher among patients with refractory disease and those in the elderly population, underscoring the persistent prognostic challenges in these subgroups.

10. Quality of Life (QoL) as an Integral Prognostic Dimension

Beyond traditional hematologic parameters, Quality of Life (QoL) has emerged as an integral and indispensable prognostic dimension in the long-term management of ITP. Chronic ITP imposes a substantial psychological burden, often leading to distress, anxiety, and profound fatigue that may unfortunately persist even when adequate platelet counts are maintained [34]. This impairment in QoL is driven by factors such as the fear of relapse, the logistical and emotional burden of frequent blood monitoring, and the adverse effects associated with chronic therapies, all of which significantly contribute to impaired social and professional functioning [34]. Therefore, a comprehensive assessment of prognosis must encompass not only platelet response and survival but also the patient's physical and emotional well-being. To accurately capture these long-term, patient-centric effects, several validated patient-reported outcome measures (PROMs), such as the ITP-Patient Assessment Questionnaire (ITP-PAQ), are now being routinely incorporated into clinical trials and longitudinal studies [35].

11. Iatrogenesis of ITP Treatment: Balancing Risks and Benefits

While effective, ITP therapies carry specific risks that contribute significantly to patient morbidity, demanding a careful balance between disease control and treatment-related complications. First-line treatments, such as corticosteroids, are associated with well-known long-term sequelae, including osteoporosis, weight gain, metabolic syndrome, and infectious risk [36]. IVIg, while generally well tolerated, carry risks such as headache, aseptic meningitis, and, rarely, renal impairment or thrombotic events [37]. While effective in some patients, splenectomy is a major intervention associated with significant iatrogenic risks, notably the permanent threat of post-splenectomy sepsis and potentially higher rates of long-term cardiovascular events [28]. Furthermore, agents targeting production or destruction pathways are not benign: TPO-RAs are associated with an elevated thrombotic risk, particularly in high-risk patients (older, obese, or aPL-positive) [32], while the B-cell depleting agent rituximab is linked to infusion reactions, hypogammaglobinemia, and delayed-onset neutropenia [27]. Emerging therapies, such as SYK inhibitors (e.g., fostamatinib), require careful monitoring for hypertension and hepatotoxicity, and FcRn inhibitors necessitate vigilance regarding volume overload and infectious risk [38]. Managing this iatrogenic burden, therefore, constitutes a fundamental and complex aspect of chronic ITP management.

12. Precision Medicine and Future Directions in ITP Therapy

Recent advances in immunopathology and pharmacology are rapidly paving the way for precision medicine in ITP, shifting the focus towards targeted therapies that interrupt specific pathways driving platelet destruction or dysfunction. Novel targeted agents have demonstrated significant efficacy in heavily pretreated and refractory patients [36]. These agents include FcRn inhibitors (e.g., efgartigimod), which accelerate the catabolism of IgG autoantibodies; SYK inhibitors (e.g., fostamatinib), which block the spleen tyrosine kinase pathway crucial for Fcγ receptor signaling and subsequent platelet destruction; and complement inhibitors (e.g., sutimlimab), which target components of the complement cascade [36]. Beyond single-agent use, combination strategies are being investigated to maximize initial response and minimize chronicity; early Phase II/III trial results suggest that regimens such as steroids plus rituximab or the early introduction of TPO-RAs significantly reduce the risk of progressing to chronic disease [37]. The future of prognosis and therapy lies in the integration of diverse data streams. Combining clinical data with complex genetic and immunologic biomarkers through Artificial Intelligence (AI) models may soon enable real-time prognostic prediction and truly individualized therapy [38]. This sophisticated approach holds the potential to identify patients likely to achieve a durable remission with minimal treatment versus those who require early aggressive treatment escalation or specific novel targeted agents to manage their high-risk disease. Emerging prognostic scores integrating clinical variables, early treatment responses, and immunological biomarkers are reshaping the future of risk stratification in ITP.

Although still theoretical, emerging multivariate prognostic tools offer a promising framework for future risk stratification in ITP. If validated, such models could help identify patients at higher risk of chronic or refractory disease and eventually support earlier, individualized therapeutic decisions. As these approaches evolve, they may lay the groundwork for more proactive and truly personalized ITP management.

13. Conclusion: Towards Predictive and Precision Management in ITP

ITP remains a highly heterogeneous autoimmune disorder characterized by unpredictable clinical trajectories and outcomes. Prognosis is dictated by a convergence of clinical, hematologic, and immunologic factors. Poor prognostic indicators are now well-defined, spanning advanced age, male sex, secondary autoimmune or infectious causes (e.g., SLE, HIV), very low baseline platelet counts ($<10\times10^9$/L), and critically, a lack of sustained early response to first-line therapies (corticosteroids/IVIg). Immunologically, persistent anti-platelet antibodies (anti-GPIIb/IIIa) and dysregulated T-cell profiles (low Treg/Th17 ratio) worsen prognosis. Recognition of these diverse predictors is essential to guide therapeutic intensity, monitor bleeding/thrombotic risk, and ultimately improve patient outcomes. Although mortality is now rare in contemporary series, morbidity related to chronicity, bleeding complications, thrombotic events, and treatment burden remains significant, severely impairing the patient's QoL. The future of ITP management lies in prognostic precision: novel multivariate models, integrating clinical data with granular immunologic and genetic biomarkers—potentially driven by Artificial Intelligence (AI)—will allow for a more personalized and anticipatory approach. This paradigm shift will transform ITP from a reactive disease, managed in response to flares and complications, to a predictive and precision-managed disease, enabling timely, risk-adapted intervention and optimizing long-term patient well-being.

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Contributions

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