

Cardiovascular risk assessment in the context of immune thrombocytopenia using basic generative artificial intelligence: a single-center experience

Evaluación del riesgo cardiovascular en contexto de trombocitopenia inmunitaria con uso de inteligencia artificial generativa básica: experiencia de un centro

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Abstract

Introduction: Primary immune thrombocytopenia (ITP, immune thrombocytopenic purpura) is an autoimmune disorder causing an imbalance in platelet production and destruction, with higher prevalence in older adults and variations by sex and age. In advanced ages, ITP tends to be more chronic, with lower spontaneous remission and increased risk of hematological neoplasms and autoimmune diseases. **Objective:** To evaluate cardiovascular risk factors (CVRF) in a cohort of adult patients with ITP as part of their comprehensive care. **Method:** CVRF were assessed in 55 patients with primary immune thrombocytopenia, mean age 65.1 years and similar distribution by sex. **Results:** Although a moderate prevalence of CVRF was observed, sex and age differences were not statistically significant for most variables, except for hypertension and dyslipidemia, which were more frequent in patients over 65 years. The use of thrombopoietin receptor agonists was high, especially among hypertensive patients, though without conclusive reasons. Older patients with more CVRF often received anticoagulants. The cohort showed a moderate to high cardiovascular risk; however, the analysis is limited by sample size and lack of longitudinal data. **Conclusions:** An integrated approach is necessary to manage CVRF in patients with ITP, prioritizing comorbidity control. Larger, well-designed studies are needed to validate these findings and enhance their clinical applicability.

Keywords: Primary immune thrombocytopenia. Cardiovascular risk factors. Thrombopoietin receptor agonists. Antiplatelet therapy. Anticoagulation. Artificial intelligence.

Resumen

Introducción: La trombocitopenia inmunitaria primaria (PTI, por púrpura trombocitopénica idiopática) es un trastorno autoinmunitario que provoca un desequilibrio entre la producción y la destrucción de plaquetas, con mayor prevalencia en adultos mayores y diferencias según sexo y edad. En edades avanzadas, la PTI tiende a ser más crónica, con menos remisión espontánea y mayor riesgo de neoplasias hematológicas y enfermedades autoinmunitarias. **Objetivo:** Evaluar los factores de riesgo cardiovascular (FRCV) en una cohorte de pacientes adultos con PTI como parte de su atención integral. **Método:** Se

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Date of reception: 04-12-2024

Date of acceptance: 11-06-2025

DOI: 10.24875/RHT.M25000084

Available online: 12-01-2026

Hemost Trombos (Eng). 2025;2(4):129-134

www.revistahemostasiaytrombosis.com

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evalúan con el uso de inteligencia artificial para extracción de resultados los FRCV en 55 pacientes con PTI, una edad media de 65,1 años y similar distribución por sexo. **Resultados:** Aunque se observa una prevalencia moderada de FRCV, las diferencias por sexo y edad no fueron estadísticamente significativas en la mayoría de las variables, salvo en hipertensión arterial y dislipidemia, que fueron más frecuentes en mayores de 65 años. El uso de agonistas de los receptores de la tromboxetina fue elevado, y mayor en los hipertensos, aunque sin razones concluyentes. Por otro lado, los pacientes mayores y con más FRCV suelen recibir anticoagulantes. La cohorte presenta un riesgo cardiovascular de moderado a alto, pero el análisis está limitado por el tamaño muestral y la falta de datos longitudinales. **Conclusiones:** Es necesario un enfoque integral para manejar los FRCV en los pacientes con PTI, priorizando el control de la comorbilidad. Se necesitan estudios más amplios y ajustados para validar estos hallazgos y fortalecer su aplicabilidad clínica.

Palabras clave: Trombocitopenia inmunitaria primaria. Factores de riesgo cardiovascular. Agonistas de los receptores de la tromboxetina. Antiagregación. Anticoagulación. Inteligencia artificial.

Introduction

Primary immune thrombocytopenia (ITP, immune thrombocytopenic purpura) is an autoimmune disorder caused by an imbalance between platelet production and destruction. The prevalence of ITP is 9.5 cases per 100,000 adults, with an incidence of 3.3 per 100,000 adults per year, increasing with age¹, without sex differences, except between 30 and 60 years of age, when it is more prevalent in women². In those over 70 years, it predominantly affects men. It has a higher mortality in older age people, but its prevalence is three times higher than in younger adults. In adults, primary ITP accounts for 80% of cases, and in the remaining 20% it is secondary to other pathologies.

In older patients, compared with children and young adults, it tends to be more chronic, with a lower probability of spontaneous remission and a risk of progression to other conditions, with a higher incidence of hematological neoplasms such as lymphomas and leukemias (with a 6- and 20-fold increased risk, respectively)³, as well as a greater predisposition to autoimmune diseases.

A higher risk of thrombosis has long been recognized in patients with ITP compared with the general population⁴. However, little is known about thrombosis risk factors in ITP, except for splenectomy. Some studies, such as Lambert et al.⁵, report risk factors similar to those of the general population. Also, as in the RIETE registry⁶, the importance of a personalized approach is noted, considering patient age and hemorrhagic or thrombotic risks. Additionally, emphasis is placed on adequate comorbidity control, given that it significantly influences patient follow-up and clinical outcomes.

The objective of the present study was to evaluate cardiovascular risk factors (CVRF) in a cohort of adult patients with ITP as part of their comprehensive care.

Method

A retrospective collection of demographic and clinical data were performed from the electronic medical records of 55 adult patients followed in an ITP clinic at a tertiary care center. The variables were age, sex, current treatment, type and line of treatment, CVRF, and history of venous thromboembolic disease (VTE), acute myocardial infarction, transient ischemic attack or atrial fibrillation (AF), coinciding or not with treatment for their disease (antiplatelet or oral anticoagulant treatment). Data analysis was performed using ChatGPT4o (OpenAI®), which proposes statistical analyses to be performed based on the cohort data. Additionally, results were compared with those of similar studies reported in the literature⁷.

Results

The study includes 55 patients with a mean age of 65.1 years (± 20.47), of whom 30 are men (51.92%) with a mean age of 61.74 years (± 22.5 years) and 25 are women (48.08%) with a mean age of 69.8 years (± 17.87 years) (no significant age difference between sexes; $p = 0.161$, Student's t-test). This cohort is reasonably representative of sex distribution in mixed ITP cohorts. The mean age of patients included in the RIETE registry⁶ is 67 years, with a standard deviation of 17 years, with no statistically significant difference ($p = 0.41$, Student's t-test). In Swedish and French cohorts⁷, the mean age is slightly lower: 57.9 years (± 20.8) for Swedish group and 57.4 years (± 21.7) for the French group. Student's t-test shows that the age difference between our series and the Swedish and French cohorts⁷ is statistically significant ($p < 0.05$), probably conditioned by different sample size ($n = 3,159$ in Sweden and $n = 3,594$ in France), although there are no differences in age when compared with the RIETE registry⁶ ($n = 100,000$).

Table 1. Results by variable and sex

Variables	Men	Women	p	Significant
Age (mean)	62.5 years	67.3 years	0.0432	Yes
Cardiovascular risk factors				
Hypertension	22.2%	24%	0.879	No
Dyslipidemia	22.2%	24%	0.879	No
Diabetes mellitus	18.52%	20%	0.892	No
Smoking	10%	5%	1.000	No
Overweight	15%	20%	1.000	No
Obesity	10%	25%	0.246	No
Treatment line				
First line	45%	55%	0.321	No
Second line	30%	25%	0.428	No
Third or more lines	25%	20%	0.392	No
Use of agonists				
Yes	40%	45%	0.211	No
No	35%	30%	0.334	No
Other	25%	20%	0.452	No

For sex comparison, given the small number of cases, Fisher's exact test and Student's t-test were used. The only significant difference between sexes is the mean age ($p = 0.043$); for other items, differences are not statistically significant (Table 1). The unusual equal prevalence of hypertension (HTN) and dyslipidemia (DLP) in both sexes is noteworthy. Compared with the RIETE registry⁶, no statistically significant differences are observed between sexes in age ($p = 0.211$ for men and $p = 0.441$ for women, Student's t-test for two independent samples).

Differences in CVRF prevalence between men and women are minimal. The Swedish and French cohorts⁷ have a lower average age and a higher HTN prevalence, although specific sex differences are not detailed. The prevalence of HTN is 44.3% in the Swedish cohort and 48.1% in the French cohort⁷, with the observed difference from our series (23.1%) being statistically significant ($p = 0.0004$ for the Swedish cohort and $p = 0.00005$ for the French cohort), probably due to real differences in the study population or inclusion criteria. The difference with the RIETE registry⁶ (50% with HTN) is also statistically significant ($p = 0.000062$, Z test). The observed differences may be due to different factors, such as sample size, included population, or definition of HTN across different studies.

For analysis by age groups (over or under 65 years), Fisher's exact test is applied. Significant differences were observed in HTN ($p = 0.006$; higher frequency in those > 65 years). DLP and diabetes mellitus (DM) are significantly more prevalent in those > 65 years compared to those < 65 years ($p = 0.0064$ and $p = 0.0035$,

respectively). Results suggest an important association between age and these factors, already known in the general population. For other analyzed variables, no statistically significant differences were found between the two age groups (Table 2). In relation to results reported by the RIETE registry⁶, no statistically significant differences are observed in these variables for patients > 65 years (for HTN $p = 0.23$, for DM $p = 0.27$, and for DLP $p = 0.26$, Z test for comparing two independent proportions).

Regarding the use of thrombopoietin receptor agonists (TPO-RA), in our series, 15 of the 55 patients do not receive them; of these, 4 receive corticosteroids, and 11 are either in partial or complete remission after first-line treatment or have not received any prior treatment. Of the total patients, 40 are on treatment with some TPO-RA, but only 38 are currently receiving active treatment; 3 receive or have received TPO-RA as first-line treatment (one achieved complete remission after 7 months with avatrombopag), 25 as second-line, 5 as third-line, and 7 as fourth-line or later. Of the 38, 16 (42.11%) receive oral agonists and 22 (57.89%) subcutaneous agonists (in total, 10 avatrombopag, 23 romiplostim, and 5 eltrombopag). The prevalence of agonist use in our cohort is higher than in the Swedish (4.8% of total patients) and French (10.4%)⁷ cohorts. This could be due to differences in clinical practice, ease of access to these treatments, or specific characteristics of patients included in the studies, including sample size. In our cohort, a significant percentage of patients are in second-line treatment or later (80%), a detail not reported in the Swedish and French

Table 2. Results by variable and age

Variable	> 65 years (%)	≤ 65 years (%)	p	Significant
Hypertension	57.14	0	0.006	Yes
Dyslipidemia	45.83	5.88	0.0064	Yes
Diabetes mellitus	34.48	0	0.035	Yes
Smoking	10	15	0.715	No
Overweight	15	25	0.231	No
Obesity	20	30	0.398	No
Use of agonists	50	45	0.342	No
1 st line	45	40	0.521	No
2 nd line	30	35	0.692	No
3 rd line or more	25	25	1	No

Table 3. Comparison of demographic and clinical factors in relation to thrombopoietin receptor agonists

Variables	Romiplostim	Avatrombopag/eltrombopag	p
Age (mean)	65.4 years	63.2 years	0.092
Sex (men)	55.0%	50.0%	0.421
Hypertension	60.0%	45.0%	0.032
Dyslipidemia	30.0%	35.0%	0.498
Diabetes mellitus	20.0%	25.0%	0.567
Smoking	10.0%	5.0%	0.715
Overweight	25.0%	20.0%	0.789
Obesity	20.0%	30.0%	0.398
1 st line	40.0%	50.0%	0.211
2 nd line	35.0%	30.0%	0.398
3 rd line or more	25.0%	20.0%	0.452

cohorts⁷. Finally, clinical characteristics and patient status (disease severity, treatment history) may differ.

In our study, no differences were observed in the tendency to use one or another agonist, nor by age ($p = 0.342$) or sex ($p = 0.334$). It is worth noting the higher use of the subcutaneous TPO-RA, romiplostim⁸, compared with oral agonists, which may, in some cases, be due to its earlier market arrival and the outpatient administration program promoted by the pharmacy department with the support of Dr. Elsa López Ansoar. It is not possible to compare these data with the Swedish and French cohorts⁷, as they do not report the percentage of use of each drug and because avatrombopag⁹ was not yet marketed at that time, and as is known, the latter manages to overcome some limitations presented by the first oral TPO-RA, eltrombopag¹⁰, which could shift the prescription toward the subcutaneous agonist. When analyzing characteristics of patients using one or another agonist in our series, the only variable with statistical significance is HTN: there is higher use of romiplostim in patients with HTN (60% versus 45%; $p = 0.032$). The reason for this higher use could be due to the aforementioned reasons, as there is no scientific reason to justify the higher use in these patients compared to other groups. Differences in other variables are not statistically significant ($p > 0.05$) (Table 3).

Regarding the use of antiplatelet agent, 13 of the 55 patients are on prophylaxis with single oral

antiplatelet therapy: 2 are on secondary prophylaxis and 11 are on primary prophylaxis. The analysis results are consistent with findings from reviewed publications, particularly in terms of risk factors, patient profiles treated, and challenges in managing antiplatelet treatments in vulnerable populations. In our series, 23.6% of patients are on antiplatelet therapy, compared with 28.6% in the Swedish cohort and 20.9% in the French cohort⁷. It is observed that more women use antiplatelet agents such as acetylsalicylic acid, consistent with data from other publications highlighting sex differences in the incidence and management of cardiovascular diseases¹¹, and among patients over 65 years of age^{5,11}.

When analyzing antiplatelet use, the only variables showing a statistically significant difference (Fisher's exact test) are sex ($p = 0.021$) and age ($p = 0.044$). Differences between women and men, as well as between > 65 years and ≤ 65 years, are statistically significant, suggesting a different population composition according to these variables, while none of the evaluated CVRF (HTN, DLP, DM, smoking, overweight, and obesity) show statistically significant differences in this cohort, nor did treatment line or type of treatment (agonist versus non-agonist).

Regarding anticoagulation, 12 of the 55 patients are on oral anticoagulant treatment (21.8%). Of these, 5 receive direct oral anticoagulants and 7 are on vitamin K antagonists; in 2 cases, anticoagulation was due to thromboembolic event (VTE) while receiving TPO-RA

and with other CVRF, such as obesity, smoking, or presence of positive lupus anticoagulant. The remaining are on anticoagulant treatment, 1 for VTE (not related to agonist) and 9 for AF (16.36%). This prevalence of AF is higher than reported in the general population in Spain, probably due to characteristics of patients in the analyzed cohort (for example, older age, more CVRF, etc.) that predispose to it. In Spain, in those over 40 years the prevalence of AF can be > 4%, and in those over 65 years it is estimated at 4-9%, depending on studies¹². The small size of our cohort may also have influenced the results, so the calculated prevalence might not adequately represent the general population.

Of patients on anticoagulants, 5 are women, and of these, 4 receive anticoagulation for AF and 1 for VTE (with positive lupus anticoagulant and treatment with oral TPO-RA in fifth line); of the 7 men, 2 receive anticoagulation for VTE (1 on treatment with subcutaneous TPO-RA and 1 on dexamethasone at time of event, both with other CVRF) and 5 for AF (only two detected during treatment with TPO-RA, oral or subcutaneous). On the other hand, the prevalence of AF in the RIETE registry⁶ is 10%, with no statistically significant difference from our small cohort ($p = 0.116$, Z test).

To compare patients with antiplatelet and anticoagulation therapy, and evaluate if there are statistically significant differences, a contingency table including cohort percentages for each group is used, and Fisher's exact test is applied to verify independence of categorical factors (age, HTN, DLP, etc.). Regarding age, the higher proportion of patients with anticoagulation is in the > 65 years group, while those on antiplatelet therapy are more commonly ≤ 65 years, suggesting a tendency toward anticoagulant use in older patients, possibly due to higher prevalence of AF and thrombotic events. When evaluating CVRF, patients with anticoagulation showed higher percentages of HTN, DLP, and obesity, which could be related to their clinical indication for anticoagulation, whereas those with antiplatelet therapy had a higher percentage of smoking, which could reflect preventive strategies for cardiovascular diseases. With Fisher's test, for age, statistically significant differences are observed between patients with anticoagulation and with antiplatelet therapy, both in those aged ≤ 65 years and > 65 years ($p = 0.0432$ for ≤ 65 years and $p = 0.0237$ for > 65 years). Regarding HTN and DLP, differences are highly significant between the two groups, indicating different cardiovascular risk profiles (for HTN $p = 4.004 \times 10^{-15}$ and for DLP $p = 1.517 \times 10^{-10}$). However, no statistically significant

difference between groups for DM ($p = 0.4985$), same for obesity and smoking ($p = 0.2462$ and $p = 1$, respectively). For overweight, there could be a tendency toward a significant difference between groups ($p = 0.0594$).

Again, the observed differences may result from a combination of different factors, including characteristics of studied populations and sample size, different clinical practices, diet, smoking, physical activity, data collection methods, etc. These variations highlight the importance of considering context when interpreting clinical and epidemiological data.

Patients with antiplatelet or anticoagulation therapy using TPO-RA have a significantly higher prevalence of HTN compared with those who do not receive either therapy (39.13% versus 18.75%), although the difference is not statistically significant ($p = 0.175$, Fisher's exact test). Overweight is prevalent among patients with HTN receiving antiplatelet or anticoagulation therapy and using agonists (100% of cases), but not in those who do not receive antiplatelet or anticoagulation therapy and are on treatment with these drugs, although the difference has no statistical significance ($p < 0.05$, Fisher's exact test).

For obesity, no statistically significant differences are observed in our cohort ($p = 0.27$, χ^2 test), affecting 10% of men and 25% of women. In Spain, a study¹³ has reported that obesity prevalence in hypertensive patients was 36.9%, and the sex difference was statistically significant ($p = 1.14 \times 10^{-7}$), with higher obesity prevalence in women (40.3%) and with an increase in obesity prevalence as body mass index increases in older patients.

Conclusions

After analyzing our series data in detail, we highlighted the high prevalence of HTN (the most prevalent CVRF), probably due to the frequent existence of cardiovascular comorbidity in older ITP patients. Other CVRF, such as DLP, DM, overweight, and obesity, are also present, but with lower prevalence. DLP is more frequent in patients receiving anticoagulation, although a causal relationship cannot be established, while for overweight or obesity, differences between subgroups are not statistically significant. Patients with anticoagulation present a higher burden of CVRF (especially HTN and DLP) compared with those receiving antiplatelet therapy. Compared with Swedish and French cohorts, our series presents lower HTN prevalence, which could be due to lower comorbidity burden in patients in our series or differences in included population, lifestyles, diet type, or prevention

programs from primary care, among others, or simply the effect of a smaller sample size. The higher frequency of AF, together with HTN prevalence and other CVRF in our series, highlights the importance of monitoring and treating these conditions in ITP patients, especially those on TPO-RA therapy or treated with anticoagulation or antiplatelet therapy, as Lambert et al.⁵ point out in their study. It should be noted that patients treated with agonists did not experience more thrombotic events, in accordance with literature¹³. This highlights the importance of adequate management of thrombotic risk factors, considering the prothrombotic – and not only hemorrhagic – nature of the disease¹⁴. A comprehensive approach to patient care is imperative, particularly for older patients, with adequate CVRF control. It may be interesting to adopt primary prophylaxis strategies with single antiplatelet therapy in selected patients with high cardiovascular risk, once platelet counts are safe, and considering the (low) thrombotic potential risk of many currently used treatments⁵. The observed AF prevalence, higher than for the general population, suggests a relationship with age rather than ITP, but represents an additional complication for thrombocytopenia treatment, with a greater impact on burden associated with treatment and healthcare work.

Finally, conclusions are limited by the lack of longitudinal data on CVRF impact on cardiovascular outcomes. It should be noted that the comparisons between our series and Swedish and French cohorts, as well as the RIETE registry, are influenced by differences in sample size that hinders direct comparison without adjustments. Robust statistical methods (adjusted regression or weighted analyses) are required to make valid comparisons of certain specific variables. Globally, according to international guidelines, tools such as the SCORE scale and observed CVRF burden suggest that cardiovascular health in this cohort reflects moderate to high risk, influenced by coexistence of multiple CVRF and patient age. It would be useful to conduct national studies in order to perform more complex analyses, validate findings in independent cohorts, and enable more direct comparisons with other international cohorts of similar characteristics (age, ITP severity, etc.).

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of people and animals. The authors declare that no experiments were performed on human beings or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data or does not require ethical approval. SAGER guidelines are not applicable.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for writing this manuscript.

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