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Original Article

Clinical Impact of Eltrombopag-Associated Iron Chelation in Adults with Immune Thrombocytopenia: A Multicenter Real-World Study

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Abstract. *Background*: Eltrombopag (ELT) is an established thrombopoietin receptor agonist (TPO-RA) for chronic immune thrombocytopenia (ITP), yet accumulating translational evidence indicates clinically relevant iron-chelating activity. Adult primary ITP–focused data characterizing longitudinal iron trajectories during ELT remain limited. We assessed whether ELT exposure is independently associated with iron deficiency (ID) in routine practice.
***Methods*: In this multicenter retrospective study, adults with ITP were evaluated with longitudinal monitoring of platelet count, ferritin, transferrin saturation (Tsat), hemoglobin (Hb), and mean platelet volume (MPV). Within-patient change was defined as the difference between baseline and follow-up (Δ). Outcomes were compared by ELT exposure and dose strata. Multivariable linear regression was used to identify independent determinants of Δ-ferritin, adjusting for age, gender, relapse status, and iron replacement therapy (IRT).**
***Results*: The cohort included 283 adults with ITP; 110 received ELT (median 25 months). ELT was associated with greater declines in ferritin and Tsat ($p<0.001$), with a dose-graded effect across 25–75 mg and earlier iron depletion at higher dose intensity. In relapsed patients not receiving ELT, the mean Δ-ferritin was positive and did not differ by bleeding status. In multivariable linear regression, ELT was the dominant independent predictor of lower Δ-ferritin (B≈−79.8 µg/L, $p<0.001$), whereas age, gender, and relapse were not significant; IRT attenuated ferritin decline but did not negate ELT effects.**
***Conclusion*: ELT exposure was independently associated with ID, supporting a clinically meaningful ELT-related iron chelation phenotype in routine practice. Monitoring and timely correction of ID during ELT therapy may mitigate a modifiable contributor to fatigue during follow-up.**

Keywords: Immune Thrombocytopenia; Eltrombopag; Iron Deficiency; Ferritin; Fatigue.

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Introduction. Immune thrombocytopenia (ITP) is an acquired autoimmune disorder defined by isolated thrombocytopenia, arising from immune-mediated platelet clearance and impaired platelet production.[1] The pathophysiology reflects coordinated humoral and cellular immune dysregulation, wherein platelet-directed autoantibodies drive accelerated peripheral clearance, while cytotoxic T cells target bone marrow (BM) megakaryocytes (MKs) and impair thrombopoiesis.[2] Clinically, ITP exhibits a broad hemorrhagic spectrum, ranging from petechiae and mucocutaneous bleeding to life-threatening hemorrhage.[3] First-line approaches, including corticosteroids and IVIG, primarily aim to attenuate immune-mediated platelet destruction. Nevertheless, corticosteroids achieve sustained remission in only ~20% of patients at 6 months, whereas most relapse or develop refractory disease, necessitating second-line strategies such as thrombopoietin receptor agonists (TPO-RAs).[4]

Eltrombopag (ELT) is an orally bioavailable, non-peptidyl TPO-RA that stimulates thrombopoiesis by selectively binding the transmembrane domain of c-Mpl. Receptor engagement activates JAK/STAT signaling, thereby enhancing proliferation and differentiation of MK progenitors.[5] ELT is approved for adults with chronic ITP (cITP) who have an inadequate response to first-line therapies.[6] In addition to its thrombopoietic activity, ELT binds iron with high affinity and has been shown to reduce intracellular labile iron, thereby influencing systemic iron handling. Experimental studies report chelator-like activity comparable to that of deferoxamine and deferasirox, supported by cellular permeability that permits access to intracellular iron pools, including those within hepatocytes, macrophages, and hematopoietic cells.[7–10]

Accordingly, we sought to characterize ELT-associated iron depletion in an adult cITP cohort by longitudinally profiling iron indices, with particular emphasis on within-patient ferritin change (delta (Δ)-ferritin) as a pragmatic marker of treatment-related shifts in iron stores. Given emerging evidence that iron deficiency (ID) may contribute to persistent fatigue, a prevalent and clinically meaningful complaint in cITP that adversely affects health-related quality of life,[11,12] we examined the potential clinical relevance of ELT-associated iron depletion. By integrating ELT exposure metrics with longitudinal trajectories of iron stores and accounting for the multifactorial drivers of iron depletion in cITP, we aimed to determine whether ELT-related chelation represents an underrecognized contributor to symptom burden and functional impairment in adult cITP.

Methods. Adult patients diagnosed with ITP and followed at the Hematology Departments of Trakya University Faculty of Medicine, Manisa Celal Bayar University, and the University of Health Sciences Hamidiye Faculty of Medicine, and at Bakırköy Dr. Sadi Konuk Training and Research Hospital were retrospectively screened in this multicenter study. Eligible patients were required to have a confirmed ITP diagnosis according to International Working Group (IWG) criteria[13] and have more than one ferritin/Tsat evaluated during follow-up. Demographic and baseline clinical characteristics were collected, including age, gender, and comorbidity profile. Platelet count, ferritin, transferrin saturation (Tsat), hemoglobin (Hb), and mean platelet volume (MPV) were recorded at diagnosis and at follow-up, and iron parameters were evaluated longitudinally in relation to ELT exposure. Within-patient changes were expressed as Δ (delta) values calculated as baseline minus follow-up (Δ-ferritin [µg/L], Δ-Tsat %, and Δ-Hb gr/dl), such that negative Δ-ferritin values indicated a decline in ferritin during follow-up. Treatment-related variables comprised of first-line management (initial corticosteroid regimen, response to the first course, and steroid-related adverse events (AEs)) and subsequent treatment lines and treatment-associated toxicities. Treatment response was evaluated according to IWG criteria.[13] For patients receiving ELT, dosing and treatment duration (months), and clinical course were documented, including relapse occurrence, bleeding at relapse, and escalation to third-line therapy.ID was defined as serum ferritin <15 µg/L in healthy adults, and anemia as Hb <130 g/L in men and <120 g/L in nonpregnant women in accordance with World Health Organization (WHO) recommendations.[14,15] The multicenter study was approved by the Ethics Committee of the participating institution and conducted in accordance with the Declaration of Helsinki. Following ethical approval (TÜTF-GOBAEK 2025/446; approval date: 17 November 2025), patient data were retrospectively reviewed for the period June 2018 to March 2025.

Statistical analyses were performed using IBM SPSS Statistics v27. Continuous variables are presented as mean ± SD or median (IQR), and categorical variables as n (%). Distributions were assessed using the Explore procedure and graphical inspection. Between-group comparisons were conducted using Pearson's χ^2 test or Fisher's exact test for categorical variables and the Mann–Whitney U test for two-group comparisons of continuous variables, with Δ values compared after stratification by ELT exposure (users vs non-users). One-way ANOVA was used to compare more than two groups when the distributional assumptions were met.

Independent association between ELT exposure and Δ-ferritin was evaluated using multiple linear regression with prespecified covariates, including ELT exposure, age, gender, relapse status, and iron replacement therapy (IRT). Regression results are reported as unstandardized coefficients (B) with SEs, t statistics, 95% CIs, and two-sided p-values. Model assumptions were examined using residual-versus-fitted and normal P–P plots and the Durbin–Watson statistic; influential observations were screened using Cook's distance, and multicollinearity was assessed using tolerance and variance inflation factors. Statistical significance was defined as p<0.05.

Results. The cohort included 283 adults with ITP (mean age 51 years), of whom 204 (72.1%) were women. Hypertension, diabetes mellitus, and coronary artery disease were present in 84 (30.7%), 48 (17.0%), and 28 (9.9%) patients, respectively. At diagnosis, the mean platelet count was 23 × 10^9/L (range 1–110) with MPV 11 fL; baseline ferritin was 69.9 µg/L, Tsat 23.7%, and Hb 12.6 g/dL. Bleeding at presentation occurred in 190 patients (67.1%) and was predominantly mucocutaneous. Among treated patients, an initial steroid response per IWG criteria[13] was achieved in 179 (63.2%). Relapse occurred in 202 patients (71.3%) after initial corticosteroid success. Subsequent-line therapies are summarized in **Table 1**.

Overall, 110 patients received ELT for a median of 25 months (mean 35.4), most commonly at 25 mg (n=40) or 50 mg (n=65), with 75 mg used in a small subset (n=5). In ELT-treated patients, mean Hb declined from 12.5 at diagnosis to 12.1 gr/dl at follow-up, mean ferritin declined from 84 µg/L to 31 µg/L (Δ-ferritin −52.74 µg/L) and Tsat decreased from 26% to 19%; compared with non-ELT patients (Δ-ferritin +17.7 µg/L, Δ-Tsat +4.6%, and Δ-Hb +0.9 gr/dl), both Δ-ferritin (Mann–Whitney U=2660.5, Z=−10.214, p<0.001; mean ranks 79.69 vs 181.62) and Δ-Tsat (U=4776.5, Z=−7.061, p<0.001; mean ranks 98.92 vs 169.39) were significantly lower in ELT users detailed in **Table 2**. Mean time to hypoferritinemia was 8.3 months in the ELT group. A dose–response pattern was observed across ELT strata, with progressively greater ferritin declines at higher doses (mean Δ-ferritin −44.12 µg/L at 25 mg, −56.4 µg/L at 50 mg, and −73.38 µg/L at 75 mg). In time-to-event analysis, Kaplan–Meier curves showed early separation that was statistically significant (p=0.009), although the overall correlation was borderline by log-rank (p=0.092) (**Figure 3**). Distributions of Δ-ferritin and Δ-Tsat were examined across genders; both females and males demonstrated declines in the ELT-treated group. Neither gender (p=0.436) nor age (p=0.636) showed a significant association in bivariate analyses (**Figure 1A-2A**).

Iron deficiency anemia (IDA) and ID occurrences were noted in detail (**Table 2**), and IRT was administered to 72 patients (25.4%). Among ELT users, 94 (85.5%) and 104 (94.5%) did not have ID and IDA at diagnosis (p=0.022 and p=0.046, respectively). During follow-up, ID was more frequent in ELT users (40/60 with ID were on ELT) (p<0.001). In a binary logistic model, ≥50 mg (vs 25 mg) was associated with a non-significant increase in ID risk (OR 1.81, 95% CI 0.90–3.65; p=0.098). IRT was used in 35.5% of ELT-treated patients across dose strata (25 mg: 13/40; 50 mg: 24/65; 75 mg: 2/5), and although Δ-ferritin remained negative in all groups, ferritin decline was significantly attenuated among IRT recipients (**Figure 1C**; Mann–Whitney p<0.001). Δ-ferritin did not correlate with ELT duration (p=0.688). Among relapsed patients, Δ-ferritin (mean −15.48 µg/L,

Table 1. Demographic, Clinical Characteristics and Treatment Patterns Of 283 Adults Diagnosed with Immune Thrombocytopenia.

Characteristics	n = 283
Gender, n (%)	
Female	204 (72.1)
Male	79 (27.9)
Age at diagnosis, years	
Mean (Range)	51 (18-80)
Comorbidities, n (%)	
Hypertension (HT)	87 (30.7)
Diabetes Mellitus (DM)	48 (17)
Coronary Artery Disease	28 (9.9)
Primary Response to Corticosteroids	
No steroids received	37 (13.1)
No response	54 (19.1)
Primary Response	192 (67.8)
Relapse, n (%)	202 (71.4)
Bleeding at Relapse, n (%)	66 (23.3)
Second Line Therapy	
None	81 (28.6)
Corticosteroids	52 (18.3)
Eltrombopag	68 (24)
IVIG	59 (20.8)
Rtx	4 (1.4)
Splenectomy	13 (4.6)
IVIG Received, n (%)	105 (37.1)
Eltrombopag Received, n (%)	110 (38.9)
25mg	40 (14.1)
50mg	65 (23)
75mg	5 (1.8)
Eltrombopag Received, months	
Mean - Median	35 - 25
Splenectomy, n (%)	26 (9.2)
Third Line Therapy	
None	234 (82.7)
Corticosteroids	4 (1.4)
Eltrombopag	23 (8.1)
Romiplostim	6 (2.1)
IVIG	4 (1.4)
Rtx	6 (2.1)
Splenectomy	6 (2.1)

Data are presented as n (%). IVIG indicates intravenous immunoglobulin; Rtx, rituximab; HT, hypertension; DM, diabetes mellitus. Eltrombopag dose strata reflect the maximum documented daily dose (25, 50, or 75 mg), and ELT duration is shown as mean and median months among ELT-exposed patients.

Table 2. Longitudinal Changes in Iron Indices and Hematologic Parameters from Diagnosis to Follow-Up, Stratified by Eltrombopag Exposure.

Laboratory Values	At Diagnosis	At Control
Entire Cohort, n:283	**Mean**	**Mean**
• Ferritin, µg/L	69.9	60.27
• Tsat, %	23.7	23.5
• Hb, gr/dl	12.6	13
• Platelets, × 10⁹/L	23	-
• MPV, fL	11	-
Iron Deficiency (ID), n (%)	61 (21.6)	60 (21.2)
Iron Deficiency Anemia (IDA), n (%)	28 (9.9)	27 (9.5)
Non-ELT users, n:173	**Mean**	**Mean**
• Ferritin, µg/L	60.9	78.7
• Tsat, %	21.84	26.4
• Hb, gr/dl	12.6	13.5
• ID	45 (26)	22 (12.7)
• IDA	20 (11.6)	9 (5.2)
ELT users, n:110	**Mean**	**Mean**
• Ferritin, µg/L	84	31.2
• Tsat, %	26.6	19
• Hb, gr/dl	12.54	12.19
• ID	16 (14.5)	40 (36.4)
• IDA	6 (5.5)	18 (16.4)

ITP: Immune Thrombocytopenia, **ELT:** Eltrombopag, **ID:** Iron Deficiency, **IDA**: Iron Deficiency Anemia. **Tsat:** Transferrin Saturation. ID and IDA are reported as n (%). Δ-ferritin and Δ-Tsat were calculated as follow-up minus diagnostic values for ferritin (µg/L) and Tsat (%), respectively; negative values indicate a decline over time.

Table 3. Bivariate Associations Between Δ-ferritin and Key Clinical Variables.

Predictor	Groups	Δ-ferritin (µg/L)	Mann-Whitney U test values (Associations with Δ-ferritin)			
		Mean (Min to Max) - SD	Mean Rank	U	Z	p value
Gender	Male	-12.6 (-170 to 236) – 71.2	135.9	7577	-0.779	0.436
	Female	-6.98 (-255 to 156) – 47.9	144.3			
ELT use	No	**13.7 (-78 to 236) - 35**	**181.62**	**2660.5**	**-10.214**	**<0.001**
	Yes	**-43.65 (-255 to 156) – 62.9**	**79.69**			
IRT use	No	-10.5 (-243 to 236) – 57.5	139.9	7172.5	-0.706	0.480
	Yes	-2.9 (-255 to 156) – 48.2	147.8			
Relapse	No	**8.6 (-78 to 75.8) – 26.3**	**173.87**	**5599.5**	**-4.148**	**<0.001**
	Yes	**-15.4 (-255 to 236) - 62**	**129.22**			

ELT: eltrombopag **IRT:** iron replacement therapy. Data are presented as mean (minimum–maximum) ± SD (standard deviation). Δ-ferritin denotes the change in serum ferritin (µg/L) between baseline and follow-up. The Mann–Whitney U test is a non-parametric method for comparing two independent groups. Mann–Whitney test statistic: U, Z: standardized normal approximation of. Mean rank reflects the average rank of Δ-ferritin values within each group. Two-sided p values are reported.

Mann–Whitney U=5599.5, Z=−4.148, p<0.001; mean rank 129.22 vs 173.87) and Δ-Tsat was lower (mean −3.16%, Mann–Whitney U=5609.5, Z=−4.133, p<0.001 mean rank 129.27 vs 173.75), indicating significant reductions in ferritin and Tsat with relapse, shown in **Figure 1B** and **2B**. Among relapsed patients not receiving ELT, mean changes were positive (Δ-ferritin: +25.8 µg/L; Δ-Tsat: +5.4%; Δ-Hb: +0.5 g/dL). Δ-ferritin did not differ by bleeding status at relapse. (p=0.116), relapse status was incorporated into our multivariable model. All bivariate associations used to inform covariate selection for multivariable analyses are summarized in **Table 3**.

In a multiple linear regression model evaluating independent determinants of Δ-ferritin (age, gender, relapsed ITP, ELT exposure, IRT), ELT exposure emerged as the dominant independent predictor of Δ-ferritin (B=−79.809 µg/L, p<0.001), whereas age (B=0.249, p=0.351), gender (B=−0.346, p=0.975), and relapse status (B=12.857, p=0.294) were not significant. IRT showed a positive association with Δ-ferritin (B=+23.041, p=0.056), indicating a trend toward less negative Δ-ferritin among recipients, all values detailed in **Table 4**. In multivariable linear regression with Δ-Tsat

Figure 1: Distribution of Δ-ferritin (μg/L) by ELT exposure; stratified by gender (A), relapse status (B), IRT (C)

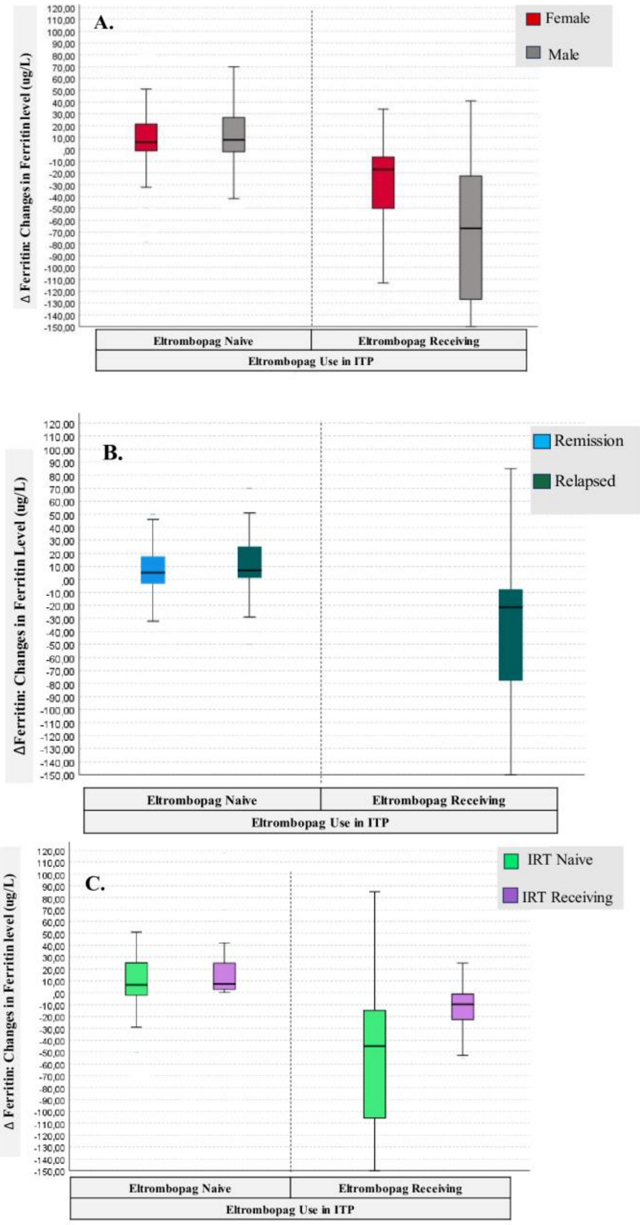
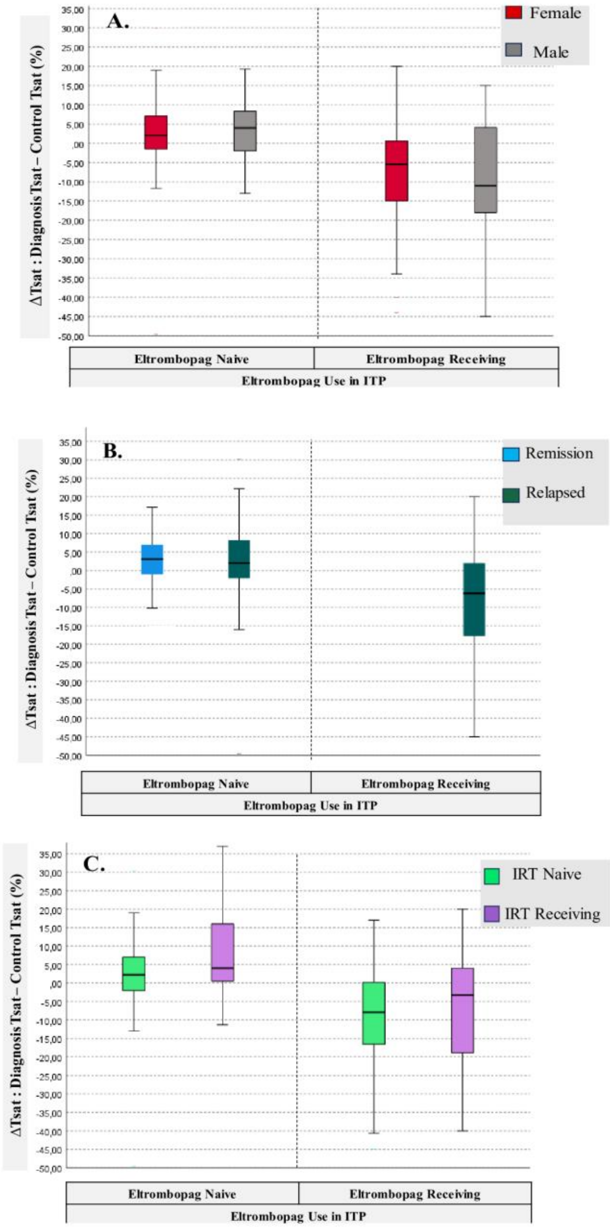


Figure 2: Distribution of Δ-TSAT (%) by ELT exposure; stratified by gender (A), relapse status (B), IRT (C)



ELT: Eltrombopag, **Tsat**: Transferrin Saturation, **IRT:** Iron Replacement Therapy, **Δ**: Delta value; calculated by value at diagnosis – value at follow-up under ELT therapy

(%) as the dependent variable, ELT exposure was independently associated with a greater decline (B=−11.99%, 95% CI −15.46 to −8.51; p<0.001), whereas gender (B=−0.78%, 95% CI −4.05 to 2.49; p=0.639) and relapse status (B=−0.25%, 95% CI −4.01 to 3.51; p=0.898) were not associated; shown in **Figure 2A–C**.

Discussion. In contemporary adult ITP practice, management frequently transitions from initial corticosteroid control toward strategies that sustain hemostatic platelet counts, and TPO-RAs have become a central second-line pillar[1] as clinicians balance efficacy, tolerability, comorbidity burden,[16] and patient preference. Within this landscape, ELT is widely used to reduce bleeding risk and maintain platelet stability,[5] yet accumulating translational evidence suggests pharmacologic effects beyond receptor agonism. In particular, ELT has been shown to act as an intracellular iron chelator, mobilizing labile iron and facilitating net iron efflux by forming an iron–drug complex, potentially via mechanisms that are not fully dependent on canonical TPO receptor signaling.[7,17,18] This mechanistic profile renders iron status a clinically meaningful complement

Table 4. Multiple Linear Regression for Predictors of Δ-ferritin (μg/L) and Δ-Tsat (%).

Variable	B		SE		β		t		p value		95% C.I (Min to Max)	
Iron Value	**ΔFerritin μg/L**	**ΔTsat %**	**ΔFerritin μg/L**	**ΔTsat %**	**ΔFerritin**	**ΔTsat**	**ΔFerritin**	**ΔTsat**	**ΔFerritin**	**ΔTsat**	**ΔFerritin μg/L**	**ΔTsat %**
Age	0.249	-0.041	0.267	0.042	0.053	-0.054	0.934	-0.968	0.351	0.334	-0.27 to 0.77	-0.12 to 0.04
Gender	-0.346	0.471	10.954	1.720	−0.002	0.015	-0.032	0.274	0.975	0.784	-21.9 to 21.2	-2.9 to 3.8
ELT exposure	**-79.809**	**-12.353**	**11.191**	**1.757**	**-0.452**	**-0.438**	**-7.132**	**-7.030**	**< 0.001**	**< 0.001**	**-101.8 to -57.7**	**-15.8 to 8.8**
Relapsed ITP	12.857	-0.952	12.234	1.921	0.067	-0.031	1.501	-0.495	0.294	0.621	-11.2 to 36.9	-4.7 to 2.8
IRT	**23.041**	**3.943**	**11.983**	**1.882**	**0.117**	**0.125**	**1.923**	**2.096**	0.056	**0.037**	**-0.55 to 46.6**	**0.24 to 7.6**

ITP: Immune Thrombocytopenia, **ELT:** Eltrombopag, **IRT:** Iron Replacement Therapy. **B**: Unstandardized Coefficient (μg/L), **SE**: Standard Error, **β**: Standardized Coefficient, **CI**: Confidence Interval. Δ-ferritin defined as ferritin at follow-up minus ferritin at diagnosis (μg/L). Δ-Tsat defined as follow-up Tsat minus Tsat at diagnosis (%). Categorical variables coded as: ELT (1=yes, 0=no), relapse (1=yes, 0=no), iron therapy (1=yes, 0=no), gender (1=male, 0=female). p values <0.05 considered significant.

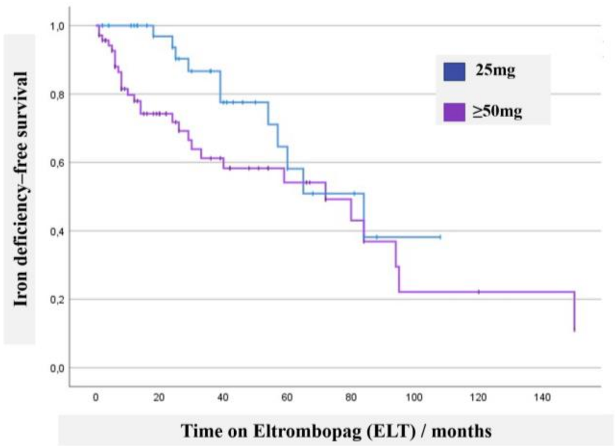


Figure 3. Kaplan–Meier Analysis of Iron Deficiency–Free Survival (Ferritin <15 μg/L) During Eltrombopag (ELT) Therapy Stratified by Dose Intensity (25 Mg Vs ≥50 Mg) In Adult ITP Patients. Iron deficiency was defined as ferritin <15 μg/L (event=1), with time measured in months on ELT; patients without iron deficiency were censored at the last follow-up. Survival curves were compared using the log-rank (Mantel–Cox) test and the Breslow (generalized Wilcoxon) test. The overall difference between groups was not statistically significant by log-rank (p=0.092), whereas the Breslow test indicated a statistically significant early divergence, consistent with separation of the ≥50 mg curve during earlier follow-up (p=0.009). The ≥50 mg category comprised 50–75 mg dosing (75 mg, n=5).

to platelet-centered monitoring in patients receiving ELT.

Clinical observations in other disease contexts support the plausibility of ELT-associated perturbations in iron homeostasis. In BM failure syndromes, prolonged exposure has been linked to progressive declines in ferritin levels, even among initially iron-overloaded patients,[8] and cumulative dosing has been associated with incident ID in aplastic anemia (AA) cohorts.[19] Pediatric ITP experience has similarly suggested an ELT-related chelation phenotype and proposed clinical benefit from prompt IRT when ID is recognized.[20] Despite the expanding clinical use of ELT, systematic multicenter evidence delineating iron homeostasis in exclusively adult primary ITP cohorts remains limited, providing the rationale for the present analysis. Within this framework, our multicenter data demonstrate longitudinal declines in ferritin and Tsat during ELT exposure, consistent with heightened susceptibility to treatment-period iron depletion. These findings are clinically salient when considered alongside patient-reported outcomes from the ITP World Impact Survey, which consistently identifies fatigue as a dominant and persistent burden and one that patients often prioritize more than clinicians.[12] While fatigue was not directly measured and causal inference is not possible in this retrospective design, the convergence of mechanistic evidence for ELT-mediated iron chelation, the recognized contribution of ID to fatigue even in the absence of overt anemia,[21,22] and the observed erosion of iron indices during ELT therapy supports the plausible hypothesis that treatment-emergent ID may contribute to fatigue in a subset of adult ITP patients.

We additionally evaluated clinically relevant covariates that could modify or confound these relationships. Given the female predominance of the cohort (72%) and the higher background prevalence of ID during menstruating years, gender and age were examined as potential modifiers of Δ-ferritin; however, neither remained independently associated with Δ-ferritin after accounting for ELT exposure, supporting the predominance of treatment-related effects. Relapse status was also considered, given its potential association with bleeding and compensatory stimulation of megakaryopoiesis (MKP), a process that requires iron across key stages of MK maturation.[23] Although major bleeding was not documented, analyses restricted to relapsed patients indicated that ferritin decline was more pronounced in ELT-treated individuals, suggesting that the decline in ferritin was more closely associated with ELT exposure than with relapse status alone. IRT emerged as a clinically relevant co-intervention in this setting. Most ELT-treated patients did not have ID at baseline, indicating that the subsequent erosion of iron indices developed during follow-up rather than reflecting pre-existing deficiency. Approximately one-third of ELT recipients received IRT to counter evolving ID, and ferritin decline appeared attenuated among supplemented patients (**Figure 1C**), consistent with partial preservation of iron stores when replacement is provided. Nonetheless, iron indices did not fully stabilize, with continued downward drift despite supplementation, suggesting that ELT-associated effects on iron handling may persist even in the presence of IRT and reinforcing the need for structured surveillance rather than reactive supplementation alone.

Importantly, the association between ELT and iron depletion remained evident after adjustment for covariates, with ELT exposure emerging as the dominant independent determinant of both Δ-ferritin and Δ-Tsat. Although ferritin is an acute-phase reactant and inflammatory markers such as CRP were not uniformly available, the concordant decline in Tsat supports the interpretation that the observed pattern reflects true iron depletion regardless of inflammation. In ELT-treated patients, Δ-ferritin was not meaningfully associated with treatment duration but showed a dose-dependent decline, and **Figure 3** shows earlier ferritin depletion in patients receiving ≥50 mg compared with 25 mg. Given concentration-dependent effects of ELT on MKP[23] and pharmacokinetic evidence of substantially higher systemic exposure at 75 mg,[18] it is biologically plausible that iron chelation is more pronounced at higher dose intensity, providing a mechanistic rationale for the dose-stratified patterns observed in our cohort.

Several limitations merit emphasis. Baseline ferritin was more consistently recorded in patients hospitalized for bleeding and or severe thrombocytopenia, whereas iron studies were less frequently obtained in outpatient settings. As a relatively novel indicator of functional iron restriction, soluble transferrin receptor (sTfR) has been demonstrated to be more sensitive than ferritin, which is directly affected by inflammation. However, given the retrospective multicenter design, sTfR was unavailable, and platelet–iron index associations were not prespecified. These constraints nonetheless point to a clear clinical implication: iron indices should be obtained at baseline and reassessed at defined intervals during follow-up, particularly in patients receiving higher-dose and/or prolonged ELT therapy, to enable timely identification and management of clinically meaningful iron depletion. Such surveillance complements the customary emphasis on platelet counts and bleeding phenotype in routine ITP care and may help address a potentially modifiable contributor to fatigue in adult ITP cohorts.

Conclusions. In this multicenter adult primary ITP cohort, ELT exposure was independently associated with iron depletion and development of ID, supporting a clinically relevant ELT-related iron chelation phenotype in routine practice. The association persisted despite a predominantly non-ID baseline profile, concomitant IRT in a subset, and relapse occurring largely without major documented bleeding across age and gender strata, making relapse-related bleeding-driven iron loss an unlikely primary explanation. Taken together, these results extend observations from BM failure syndromes and pediatric ITP, address limited adult ITP-specific evidence on ELT-associated ID, and suggest that treatment-emergent iron depletion may represent a modifiable contributor to fatigue during longitudinal care.

Data availability statement. Adult patients with primary ITP followed at Trakya University Faculty of Medicine, Manisa Celal Bayar University, and University of Health Sciences Hamidiye Faculty of Medicine Bakırköy Dr. Sadi Konuk Training and Research Hospital were retrospectively screened, and clinical and laboratory data were abstracted from available medical records for the period June 2018 to March 2025.

Ethical approval. The study was approved by the Ethics Committee of the participating institution and conducted in accordance with the Declaration of Helsinki (TÜTF GOBAEK 2025/446; approval date: 17 November 2025).

Consent to participate: Given the retrospective design and use of routinely collected clinical data, the requirement for individual informed consent was handled in accordance with the institutional ethics approval.

Author Contributions. Study design and conceptualization was coordinated by Elif Gulsum Umit and Ufuk Demirci. Ahmet Yigitbasi and Guray Aygun coordinated data extraction and dataset assembly, with multicenter data collection and curation supported by Fehmi Hindilerden, Nese Varli, Elif Aksoy, Emine Gulturk, and Eren Arslan Davulcu. Ahmet Yigitbasi performed the statistical analyses, conducted the literature review, and drafted the initial manuscript. Elif Gulsum Umit and Ahmet Muzaffer Demir provided substantive consultancy and mentorship. All authors reviewed the manuscript, contributed to revisions, and approved the final version for submission.

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