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Title page

Overuse of thrombopoietin receptor agonists driven by suboptimal response is associated with myelofibrosis in pediatric immune thrombocytopenia

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Declarations

Clinical Trial Registration Number:

This study is not a clinical trial and therefore does not have a clinical trial registration number.

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The authors confirm the absence of any conflicts of interest. No pharmaceutical companies were involved in the study's design, data collection, analysis, or manuscript preparation.

Author Contributions:

R.W. and JY.Ma. designed the protocol for this analysis. JY.Ma. verified the data and conducted the statistical analyses. J.J., J.M., H.L., L.Z., W.Y., S.Z., and Y.W. contributed to patient management. Data collection suitable for analysis was performed by XY.Ma., X.L., Y.H., S.D., and C.L. JY.Ma. wrote the manuscript. Z.C., X.C., and R.W. reviewed the paper, offered critical feedback on its intellectual content, and granted final approval. All co-authors reviewed the report, contributed suggestions regarding its content, and agreed to submit the manuscript.

Data Availability Statement:

This study utilized original data acquired with approval from the Institutional Review Board. Due to privacy and ethical restrictions, these data are not publicly accessible. Requests for data access may be directed to the corresponding author.

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To the Editor,

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia resulting from immune-mediated platelet destruction and impaired platelet production[1, 2]. For pediatric patients with persistent or chronic ITP, thrombopoietin receptor agonists (TPO-RAs), including eltrombopag, romiplostim, and avatrombopag, have become a cornerstone of second-line therapy, effectively stimulating megakaryopoiesis to raise platelet counts and reduce bleeding risk[3-5]. However, a significant clinical dilemma shadows the use of TPO-RAs: the risk of inducing or exacerbating bone marrow myelofibrosis (MF)[6, 7]. In adults, prolonged TPO-RA exposure has been associated with the development of reticulin fibrosis, a process driven by TPO-induced megakaryocyte hyperplasia and the subsequent release of pro-fibrotic cytokines, primarily transforming growth factor-beta (TGF-β)[8, 9]. Although this fibrosis is often low-grade and reversible upon drug discontinuation in adults, the potential for persistent fibrosis or progression remains critical in the pediatric population, particularly for difficult-to-treat patients whose severe bleeding phenotypes preclude the safe discontinuation of these agents.

Data on TPO-RA-associated MF in the pediatric population are scarce and inconsistent[10]. A critical knowledge gap persists regarding the MF risk in patients who fail to achieve a stable response from TPO-RA. In clinical practice, managing these cases often involves escalating doses beyond approved labels or switching between different TPO-RA agents, subjecting the bone marrow to supraphysiological thrombopoietic stimulation. This raises a pivotal question: is the risk of MF primarily a function of cumulative TPO-RA exposure duration, or is it linked to treatment intensity? To address this, we conducted a study to explore the factors associated with MF in pediatric ITP patients receiving TPO-RAs. Our objectives were to: (1) determine the rate of clinically significant fibrosis in a cohort requiring bone marrow re-evaluation due to a suboptimal response; (2) identify the clinical factors associated with MF, specifically disentangling the effects of treatment duration versus treatment intensity; and (3) assess the reversibility of fibrosis following TPO-RA discontinuation.

We performed a retrospective cohort study at the Hematology Department of Beijing Children's Hospital, a national referral center, between January 2020 and November 2025. The study was approved by the Institutional Review Board of Beijing Children's Hospital (Approval No. [2025]-Y-325-D) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective design. We included patients aged 1 to 18 years with a confirmed diagnosis of chronic ITP according to the 2021 Chinese guidelines[11] who had received TPO-RA therapy for at least six months. A key inclusion criterion was the performance of a bone marrow biopsy for clinical re-evaluation, prompted by a suboptimal response or loss of efficacy. Treatment intensification (dose escalation or switching) was typically prompted by an initial suboptimal response (failure to achieve

platelet count ≥30×10⁹/L and at least a 2-fold increase from baseline within 1 month of a stable dose) or a subsequent loss of response (platelet count declining to <30×10⁹/L after an initial response, or recurrence of clinically significant bleeding), per International Consensus criteria[2] . All patients underwent comprehensive diagnostic evaluation, including genetic testing when clinically indicated, to strictly exclude congenital thrombocytopenias, secondary ITP and concurrent hematologic malignancy.

Myelofibrosis was graded from MF-0 to MF-3 based on the European Consensus criteria[12] and dichotomized into clinically insignificant fibrosis (MF grade 0/1) and clinically significant fibrosis (MF grade ≥2). TPO-RA overdose was defined as any dose exceeding the maximum recommended pediatric weight-based dosage for each specific agent (eltrombopag >1.5 mg/kg/day, avatrombopag >1 mg/kg/day, hetrombopag >0.15 mg/kg/day, and romiplostim >10 μg/kg per weekly dose)[3-5]. All bone marrow specimens were independently reviewed by two expert hematopathologists blinded to clinical information; discrepancies were resolved through consensus discussion with a third senior hematopathologist. Variables with a *P*-value <0.1 in univariable analysis were entered into a multivariable binary logistic regression model using backward stepwise selection. Multicollinearity was assessed with the variance inflation factor. Time-to-event analysis was performed using the Kaplan-Meier method and multivariable Cox proportional hazards regression models.

A total of 54 patients were included, with a median age at biopsy of 7.8 years. The cohort represented a heavily pretreated population, with a median of 3.0 (IQR, 2.0-3.8) prior ITP treatment lines before TPO-RA initiation. Clinically significant fibrosis was identified in 14 patients (25.9%). The baseline characteristics, stratified by MF grade, are presented in Table 1. The distribution of specific TPO-RA agents used prior to bone marrow biopsy was: eltrombopag (70.4%), avatrombopag (64.8%), hetrombopag (24.1%), and romiplostim (9.3%). Notably, avatrombopag usage (100.0% vs. 52.5%, *P*=0.001) and the sequential use of multiple TPO-RA agents (85.7% vs. 40.0%, *P*=0.005) were significantly more frequent in the MF ≥2 group compared to the MF 0-1 group. Detailed distribution data are presented in Supplementary Table S2. The 100% avatrombopag usage in the MF ≥2 group likely reflects treatment refractoriness rather than a direct causal role, as these patients typically received avatrombopag after failing initial TPO-RAs, consistent with their higher switching rate. In univariable analysis, the MF ≥2 group had a markedly higher incidence of TPO-RA overdose (64.3% vs. 27.5%; *P*=0.024), more frequent agent switching (median 2.0 vs. 1.0 switches; *P*=0.002), longer total TPO-RA duration (23.9 vs. 16.6 months; *P*=0.018), and longer duration of overdose exposure (3.0 vs. 0.0 months; *P*=0.013). Among the 20 patients with TPO-RA overdose, the median maximum administered dose was 168.5% (IQR, 126.5%-211.0%) of the recommended upper limit, and the median duration of overdose exposure was 7.8 months (IQR, 2.0 - 12.5 months). The concurrent complete blood count and

peripheral blood smear findings at the time of biopsy are presented in Supplementary Table S1. Notably, there were no significant differences in platelet count, white blood cell count, neutrophil count, or hemoglobin levels between the two groups (all $P > 0.05$), and no teardrop cells were observed on peripheral blood smears in any patient. This suggests that even in the MF ≥2 group, the fibrosis had not yet progressed to a stage that severely compromised peripheral blood hematopoiesis.

To rigorously identify the independent risk factors, we developed a data-driven multivariable logistic regression model. Given the correlation between the binary overdose status and the continuous overdose duration variable, we compared models incorporating each metric. The model incorporating the binary overdose status yielded superior fit and discriminatory power (AIC=50.1, AUC=0.863) compared to the model using continuous overdose duration (AIC=54.0, AUC=0.825). In the final optimal model, TPO-RA overdose (adjusted odds ratio aOR=4.41, 95% CI: 1.04–18.58; P=0.043) and the number of TPO-RA switches (aOR=4.00, 95% CI: 1.49–10.76; P=0.006) emerged as the sole independent predictors of developing MF ≥2 (Table 2).

Kaplan-Meier analysis confirmed that TPO-RA overdose was associated with a significantly shorter time to MF ≥2 development (Log-rank test P=0.005) (Figure 1). Furthermore, a multivariable Cox proportional hazards model revealed that TPO-RA overdose was a significant independent predictor of accelerated MF development (adjusted hazard ratio aHR=4.63, 95% CI: 1.36–15.76; P=0.014). While the duration of overdose was also significantly associated with MF in univariable analysis (OR=1.12 per month, P=0.033), its effect was superseded by the occurrence of overdose itself and the frequency of agent switching in the final multivariable models. This indicates that the intensity of supraphysiological exposure, characterized by off-label dose escalation and frequent agent rotation in non-responsive patients, is primarily associated with accelerated fibrosis.

Among the 14 patients with MF ≥2, eight underwent a follow-up bone marrow biopsy after a median of 6 months. All five patients who discontinued TPO-RA therapy and transitioned to alternative immunomodulatory agents showed regression of fibrosis (two to MF-0, three to MF-1). In contrast, the three patients who continued TPO-RA therapy showed persistent MF ≥2. This suggests that fibrosis is reversible upon drug withdrawal but maintained by continued TPO-RA exposure.

Our findings provide clinical evidence supporting the concept that MF risk is intrinsically linked to the intensity of supraphysiological bone marrow stimulation. For patients who respond well to standard doses, long-term therapy carries a moderate but manageable risk. However, in the context of a suboptimal response, escalating doses beyond approved limits or frequently switching between different TPO-RA agents creates a high-risk scenario. The

significantly higher usage of avatrombopag and multiple TPO-RAs in the MF ≥2 group reflects this pattern of treatment intensification in difficult-to-treat patients. While dose adjustments within the approved label range are standard and appropriate practice, the strategy of escalating beyond maximum recommended limits and maintaining such doses over time should be strongly reconsidered. For patients who remain unresponsive at the maximum approved dose, clinicians should prioritize a timely switch to alternative immunomodulatory therapies such as rituximab or daratumumab, rather than prolonged off-label TPO-RA intensification[13-15].

We acknowledge several limitations. The retrospective, single-center design may limit generalizability. The observed MF prevalence of 25.9% is specific to our highly selected, high-risk population and should not be extrapolated to the general pediatric ITP population on TPO-RAs. In conclusion, our study provides compelling evidence that the overuse of TPO-RAs, specifically overdosing and frequent agent switching in patients with a suboptimal response, are the primary independent risk factors for MF in pediatric ITP. This finding calls for greater vigilance in TPO-RA dosing and a shift in management, moving away from prolonged off-label TPO-RA intensification towards switching to alternative immunomodulatory therapies.

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Table 1. Baseline Characteristics of the Study Cohort

Characteristics	Total (n=54)	MF 0-1 (n=40)	MF ≥ 2 (n=14)	*P*-value
Demographics and Disease History				
Age at biopsy, years, median (IQR)	7.8 (5.9-10.7)	7.7 (6.0-10.5)	8.8 (6.0-13.0)	0.580
Male sex, n (%)	26 (48.1)	21 (52.5)	5 (35.7)	0.358
Disease duration at admission, months, median (IQR)	26.5 (21.2-54.0)	25.5 (22.0-52.5)	36.0 (20.2-68.2)	0.553
Prior treatment lines, median (IQR)	3.0 (2.0-3.8)	3.0 (2.0-3.2)	3.0 (2.0-3.8)	0.885
Prior rhTPO use, n (%)	23 (42.6)	14 (35.0)	9 (64.3)	0.069
TPO-RA Treatment Parameters				
Total TPO-RA duration, months, median (IQR)	18.5 (13.7-30.0)	16.6 (12.4-28.2)	23.9 (17.8-36.4)	**0.018**
Number of TPO-RA switches, median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (2.0-3.0)	**0.002**
TPO-RA overdose, n (%)	20 (37.0)	11 (27.5)	9 (64.3)	**0.024**
Overdose duration, months, median (IQR)	0.0 (0.0-3.5)	0.0 (0.0-1.1)	3.0 (0.0-10.4)	**0.013**
Maximum dose among overdose patients (% of upper limit), median (IQR)	168.5 (126.5-211.0)	155.0 (122.5-194.5)	181.0 (143.0-250.0)	0.301

Abbreviations: MF, myelofibrosis; IQR, interquartile range; rhTPO, recombinant human thrombopoietin; TPO-RA, thrombopoietin receptor agonist.

Continuous variables are presented as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as count (percentage) and compared using Fisher's exact test. Bold P-values indicate statistical significance ($P < 0.05$).

Table 2. Univariable and Multivariable Logistic Regression Analysis for Factors Associated with Myelofibrosis (Grade ≥2)

Variables	Univariable OR (95% CI)	*P*-value	Multivariable aOR (95% CI)	*P*-value
TPO-RA overdose (yes vs. no)	4.75 (1.30-17.32)	**0.018**	4.41 (1.04-18.58)	**0.043**
Number of TPO-RA switches	4.10 (1.61-10.47)	**0.003**	4.00 (1.49-10.76)	**0.006**
Overdose duration (per month)	1.12 (1.01-1.25)	0.033	-	-
Total TPO-RA duration (per month)	1.03 (1.00-1.07)	0.055	-	-
Prior rhTPO use	3.34 (0.94-11.92)	0.063	-	-
Disease duration at admission	1.02 (1.00-1.04)	0.064	-	-
Age at biopsy	1.05 (0.89-1.23)	0.573	-	-
Male sex	0.50 (0.14-1.77)	0.283	-	-
Prior treatment lines	1.00 (0.63-1.58)	0.993	-	-

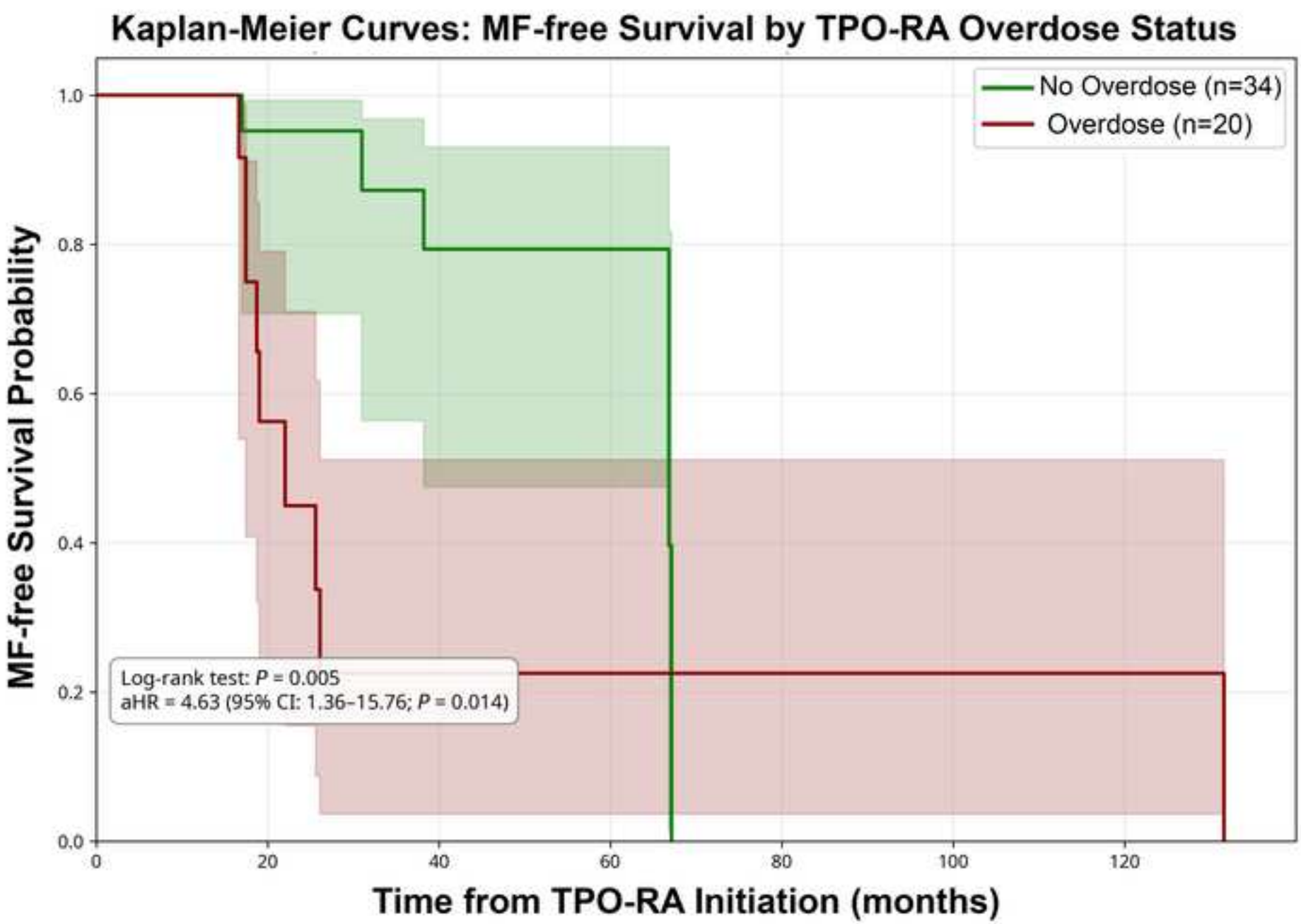
Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; rhTPO, recombinant human thrombopoietin; TPO-RA, thrombopoietin receptor agonist.

Variables with P < 0.1 in univariable analysis were evaluated for collinearity. Given the correlation between binary TPO-RA overdose and continuous overdose duration, models incorporating each metric were compared. The model incorporating binary overdose status was selected as it demonstrated superior fit (AIC=50.1 vs 54.0) and discriminatory power (AUC=0.863 vs 0.825). The final multivariable model was derived using backward stepwise selection. Bold P-values indicate statistical significance (P < 0.05).

Figure 1. Kaplan-Meier estimates of myelofibrosis-free survival in pediatric ITP patients according to TPO-RA overdose status.

Kaplan-Meier curves show the probability of remaining free from clinically significant myelofibrosis (MF grade ≥2) over time, stratified by the occurrence of TPO-RA overdose (red line) versus no overdose (green line). The shaded areas represent the 95% confidence intervals. The statistical significance between the two survival curves was determined using the log-rank test (P=0.005). A multivariable Cox proportional hazards regression model, adjusted for the number of TPO-RA switches, confirmed that TPO-RA overdose is an independent predictor of accelerated MF development (adjusted hazard ratio [aHR] = 4.63, 95% CI: 1.36–15.76; P=0.014).

Abbreviations: ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist; MF, myelofibrosis; CI, confidence interval.


Kaplan-Meier Curves: MF-free Survival by TPO-RA Overdose Status
No Overdose (n=34)
Overdose (n=20)
MF-free Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
Time from TPO-RA Initiation (months)
Log-rank test: P = 0.005
aHR = 4.63 (95% CI: 1.36–15.76; P = 0.014)

Supplementary Materials

Overuse of thrombopoietin receptor agonists driven by suboptimal response is associated with myelofibrosis in pediatric immune thrombocytopenia

Table S1. Complete Blood Count and Peripheral Blood Smear Findings at the Time of Bone Marrow Biopsy

Characteristics	Total (n=54)	MF 0-1 (n=40)	MF ≥ 2 (n=14)	*P*-value
Platelet count, ×10⁹/L, median (IQR)	55.0 (15.0-112.0)	51.0 (15.0-92.5)	76.0 (16.2-125.8)	0.621
White blood cell count, ×10⁹/L, median (IQR)	9.8 (6.8-11.1)	9.2 (7.0-11.3)	10.1 (7.3-11.1)	0.701
Neutrophil count, ×10⁹/L, median (IQR)	6.6 (3.8-8.3)	5.5 (3.7-8.0)	7.3 (5.2-10.2)	0.246
Hemoglobin, g/L, median (IQR)	119.0 (106.0-130.0)	121.0 (109.5-130.0)	112.5 (104.5-126.5)	0.167
Teardrop cells on peripheral smear, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000

Abbreviations: MF, myelofibrosis; IQR, interquartile range.

Continuous variables are presented as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as count (percentage) and compared using Fisher's exact test.

Table S2. Distribution of Specific TPO-RA Agents Used Prior to Bone Marrow Biopsy

TPO-RA Agent Exposure	Total (n=54)	MF 0-1 (n=40)	MF ≥ 2 (n=14)	*P*-value
Eltrombopag, n (%)	38 (70.4)	29 (72.5)	9 (64.3)	0.735
Avatrombopag, n (%)	35 (64.8)	21 (52.5)	14 (100.0)	**0.001**
Hetrombopag, n (%)	13 (24.1)	7 (17.5)	6 (42.9)	0.075
Romiplostim, n (%)	5 (9.3)	2 (5.0)	3 (21.4)	0.103
Multiple TPO-RAs used, n (%)	28 (51.9)	16 (40.0)	12 (85.7)	**0.005**

Abbreviations: MF, myelofibrosis; TPO-RA, thrombopoietin receptor agonist.

Categorical variables are presented as count (percentage) and compared using Fisher's exact test. Note that patients could have been exposed to more than one TPO-RA agent due to switching, hence the percentages do not sum to 100%.