Pediatric Blood & Cancer

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RESEARCH ARTICLE

Hematopoietic Recovery and Safety Following Early Romiplostim Administration After Pediatric HSCT: A Prospective Randomized Pilot Study

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Received: 31 May 2026 | **Revised:** 30 June 2026 | **Accepted:** 10 July 2026

ABSTRACT

Background: Delayed platelet recovery remains a frequent and clinically significant complication following hematopoietic stem cell transplantation (HSCT) in children, contributing to increased transfusion burden, bleeding risk, and prolonged hospitalization. Thrombopoietin receptor agonists (TPO-RAs), including romiplostim, have demonstrated activity in post-transplant thrombocytopenia; however, prospective pediatric data on their early post-transplant use are limited. We evaluated the safety and potential effects of early romiplostim administration on platelet and hematopoietic recovery following pediatric HSCT.

Methods: In this prospective, open-label, randomized pilot study conducted at a tertiary care center in India, children aged 1–18 years undergoing autologous or allogeneic HSCT were randomized (1:1) to receive standard post-transplant care with or without romiplostim. Romiplostim (5 μg/kg subcutaneously) was administered on Days +1 and +8 post-transplant (or Days +5 and +12 for haploidentical transplants with post-transplant cyclophosphamide). The primary endpoint was time to platelet engraftment (platelet count $\geq 20 \times 10^9$/L for 3 consecutive days without transfusion). Secondary endpoints included platelet transfusion requirements, platelet nadir, platelet counts on Day +28, time to platelet count $\geq 50 \times 10^9$/L, neutrophil recovery, bleeding, and thrombotic events.

Results: Thirty-two children were enrolled (romiplostim $n = 17$; control $n = 15$). Median time to platelet engraftment was comparable between the romiplostim and control groups (12 vs. 12.5 days; $p = 0.88$), with no significant difference on Kaplan–Meier analysis. Platelet transfusion requirements, platelet nadir, and time to platelet count $\geq 50 \times 10^9$/L were also similar between groups. By Day +28, higher platelet counts were observed in the romiplostim arm, with exploratory subgroup analysis demonstrating higher platelet counts following allogeneic HSCT. Romiplostim recipients also demonstrated higher absolute neutrophil counts on Day +28. No thrombotic events, severe bleeding episodes, or drug-related serious adverse events were observed.

Conclusion: Early administration of romiplostim following pediatric HSCT was safe and well tolerated, with no significant treatment-related toxicity observed. Although it did not shorten time to platelet engraftment, exploratory analyses demonstrated

higher Day +28 platelet and neutrophil counts, generating the hypothesis that romiplostim may support sustained hematopoietic recovery. These findings require confirmation in larger, adequately powered multicenter studies before conclusions regarding efficacy can be drawn.

1 | Introduction

Hematopoietic stem cell transplantation (HSCT) remains a potentially curative therapy for various malignant and nonmalignant pediatric disorders. However, thrombocytopenia is a frequent and often prolonged post-transplant complication, as platelets are typically the last hematopoietic lineage to recover. Delayed platelet engraftment or persistent thrombocytopenia is associated with increased transfusion requirements, prolonged hospitalization, and higher morbidity and mortality. The etiology is multifactorial, involving decreased marrow production due to myelotoxic conditioning, poor graft function, graft-versus-host disease–mediated marrow suppression, stromal injury, viral reactivation, and transplant-associated endothelial injury with peripheral platelet destruction [1–4].

Although platelet transfusions remain the standard supportive strategy, their benefit is transient and associated with complications, including alloimmunization, transfusion reactions, refractoriness, and infectious risks. Effective pharmacologic approaches to enhance platelet recovery following HSCT remain limited [5–9].

Thrombopoietin (TPO) is the principal regulator of megakaryocyte proliferation and platelet production through binding to the thrombopoietin receptor (c-MPL or TPO-R). Second-generation thrombopoietin receptor agonists (TPO-RAs), including romiplostim and eltrombopag, stimulate platelet production without inducing cross-reactive antibodies that limited earlier thrombopoietic agents. Romiplostim, a peptide–Fc fusion protein that binds the extracellular domain of TPO-R, promotes megakaryocyte maturation and platelet production through activation of the JAK–STAT and MAPK signaling pathways. Beyond megakaryopoiesis, TPO-R signaling has also been implicated in hematopoietic stem cell maintenance, progenitor cell survival, and multilineage hematopoietic recovery [10–14].

Romiplostim is currently approved for chronic immune thrombocytopenia and has demonstrated encouraging activity as rescue therapy for delayed platelet recovery following HSCT. However, evidence regarding its early use following transplantation remains limited, particularly in children. Most available studies have evaluated TPO-RAs in adults with persistent thrombocytopenia or secondary platelet failure after HSCT, while prospective pediatric data are lacking.

Therefore, we conducted a prospective randomized pilot study to evaluate the safety and potential effects of early romiplostim administration on platelet and hematopoietic recovery in children undergoing autologous or allogeneic HSCT.

2 | Methods

2.1 | Study Design and Setting

This was a prospective, open-label, randomized pilot study conducted in the Division of Pediatric Oncology, Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), New Delhi, between March 2024 and December 2025. The study was approved by the Institutional Ethics Committee and registered prospectively with the Clinical Trials Registry of India (CTRI/2024/03/064716). Written informed consent was obtained from parents or legal guardians, and assent was taken from children, as applicable.

2.2 | Participants

Children aged 1–18 years undergoing hematopoietic stem cell transplantation (HSCT) for malignant or nonmalignant disorders were eligible. Both autologous and allogeneic transplant recipients were included. Exclusion criteria were prior exposure to thrombopoietic agents, history of thrombotic events, lack of parental consent, second HSCT, bone marrow not in remission at transplant, reduced-intensity conditioning, or umbilical cord blood transplantation.

2.3 | Randomization and Masking

Eligible subjects were randomized (1:1) to the intervention or control arm using computer-generated block randomization, with variable block sizes and stratification by transplant type (autologous or allogeneic) to ensure balanced distribution. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes held by an independent resident not involved in the trial or analysis. The study was open-label; no placebo control was used.

2.4 | Sample Size Calculation

Data from a retrospective cohort of 36 children who underwent HSCT in our unit showed that the mean time to platelet engraftment was 17.9 days with a standard deviation of 6.8 days. Twenty percent of patients in this cohort achieved platelet engraftment within 12 days.

Using these assumptions, and considering an expected mean time to platelet engraftment of 12 days following intervention, the calculated sample size was 21 patients per arm (alpha 0.05, power 80%, allocation ratio 1:1). However, given feasibility constraints related to the limited pediatric HSCT population and

the exploratory nature of the study, this trial was conducted as a pilot randomized study.

2.5 | Intervention and Control

Participants in the intervention arm received romiplostim 5 μg/kg subcutaneously (outer lateral deltoid, 45° angle) on Day +1 and Day +8 post-transplant. For patients undergoing haploidentical HSCT with post-transplant cyclophosphamide (PtCy), doses were administered on Day +5 and Day +12. Romiplostim was supplied by Zydus Lifesciences Ltd., reconstituted, and stored as per the manufacturer's instructions. The company had no role in study design, data collection, or analysis.

All participants received standard institutional post-HSCT care, including granulocyte colony-stimulating factor (G-CSF), as indicated. The control arm received standard care alone without placebo.

2.6 | Study Assessments and Monitoring

Complete blood counts (CBC) were performed daily from transplant day until platelet engraftment, and subsequently at each follow-up until a platelet count $\geq 50 \times 10^9$/L was achieved, and on Day +28. CBCs were analyzed using an automated hematology analyzer at the AIIMS Hematology Laboratory.

Patients were prospectively monitored throughout hospitalization and during follow-up visits for adverse events. Prespecified adverse events of special interest included venous or arterial thromboembolic events and clinically significant bleeding (WHO Grade ≥3). In cases of clinical suspicion, thrombotic events were evaluated using Doppler ultrasonography or CT (computed tomography) angiography, as appropriate. Bone marrow examinations to assess reticulin fibrosis were not performed routinely and were undertaken only when clinically indicated. Similarly, endothelial complications such as transplant-associated thrombotic microangiopathy or sinusoidal obstruction syndrome were managed according to institutional clinical protocols, but were not prospectively collected as predefined study endpoints. An independent Data and Safety Monitoring Board (DSMB) comprising a pediatrician, statistician, and subject expert periodically reviewed safety and mortality data.

2.7 | Endpoints and Definitions

The primary endpoint was the number of days to platelet engraftment, defined as the first of 3 consecutive days with platelet count $\geq 20 \times 10^9$/L without transfusion for ≥72 h.

Secondary endpoints included:

- Total platelet transfusion volume (mL/kg) until platelet engraftment.
- Platelet nadir (lowest platelet count post-transplant).
- Platelet count on Day +28.
- Days to achieve platelet count $\geq 50 \times 10^9$/L.
- Incidence of clinically significant bleeding (≥Grade 3, WHO 2013 bleeding scale).
- Thrombotic events within 3 months of the last romiplostim dose.

Exploratory analyses included evaluation of neutrophil engraftment and hematopoietic recovery parameters. Exploratory and subgroup analyses were prespecified as hypothesis-generating. Given the pilot nature of the study, no adjustment for multiple comparisons was performed, and these analyses should be interpreted cautiously.

2.8 | Statistical Analysis

Data were entered in Microsoft Excel and analyzed using Python. Data distribution was assessed using the Shapiro–Wilk test. Continuous variables were summarized as mean (SD) or median (interquartile range [IQR]) depending on normality; categorical variables were presented as counts and percentages.

- Between-group comparisons were performed using Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for non-normal data.
- Categorical variables were analyzed with Fisher's exact or chi-square tests.
- Time-to-event analysis for platelet engraftment was conducted using the Kaplan–Meier method with log-rank testing.

A *p*-value less than 0.05 was considered statistically significant for all analyses. Exploratory and subgroup analyses were considered hypothesis-generating.

3 | Results

3.1 | Patient Enrollment and Baseline Characteristics

A total of 32 children undergoing hematopoietic stem cell transplantation (HSCT) were enrolled between March 2024 and December 2025, and randomized into the intervention arm (romiplostim, $n = 17$) and the control arm ($n = 15$). Two participants (one in each group) did not achieve platelet engraftment and were included in time-to-event analyses (Figure 1).

The mean age at transplant was comparable between the intervention and control groups (7.2 vs. 6.7 years). Overall, 47% of patients were female (nine in the intervention arm and six in the control arm). Nineteen (59%) patients underwent allogeneic HSCT, while 13 (41%) underwent autologous HSCT. The underlying indication was malignant disease in 24 patients (75%) and nonmalignant disorders in eight patients (25%), with similar distribution across both study arms. Common malignant indications included Hodgkin lymphoma, neuroblastoma, hemophagocytic lymphohistiocytosis, and acute myeloid leukemia, while nonmalignant indications included mucopolysaccharidosis, X-linked adrenoleukodystrophy, and Gaucher disease.

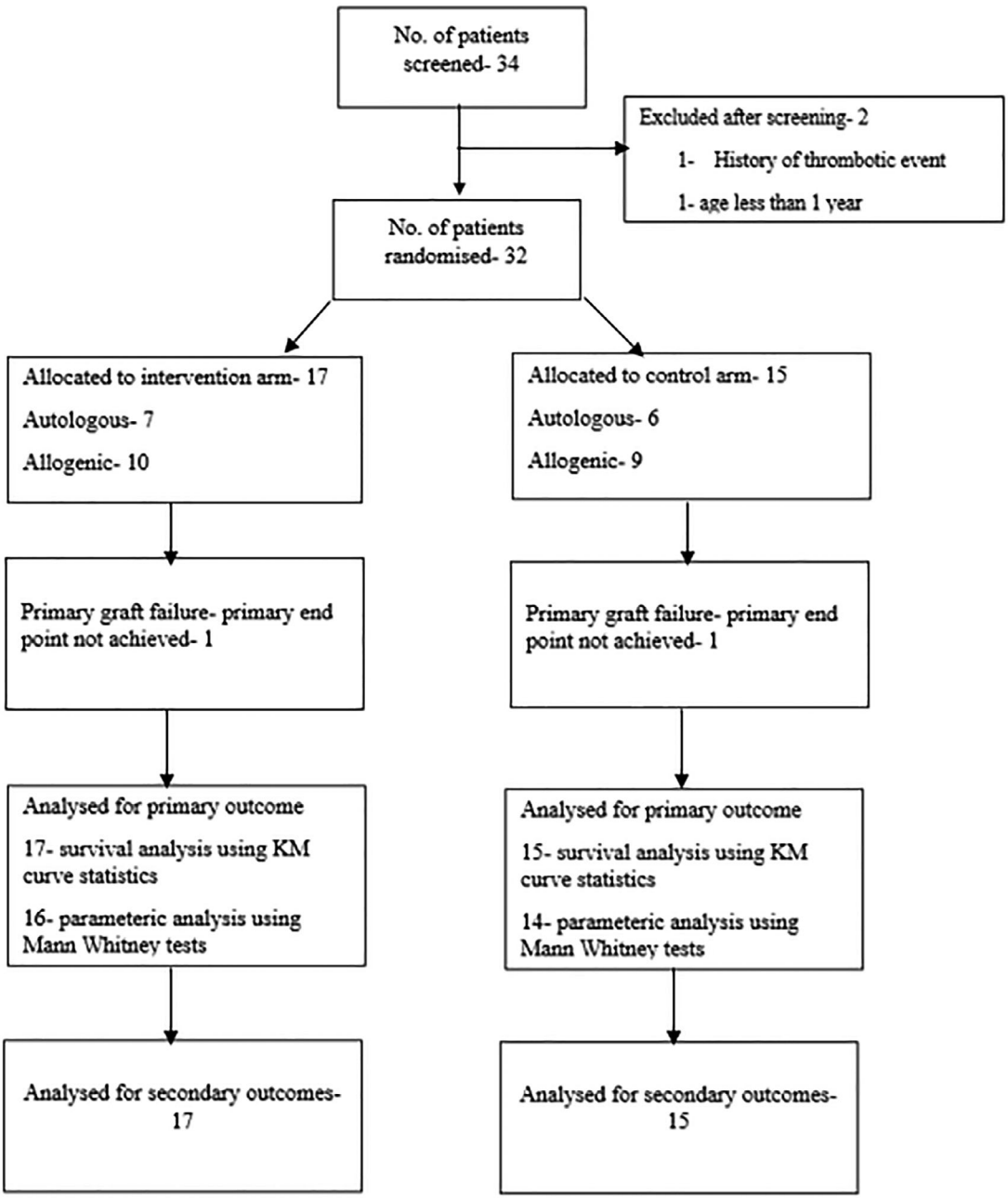

FIGURE 1 | CONSORT study flow diagram.

Pre-transplant variables, including remission status, cumulative anthracycline and alkylator exposure, donor characteristics (for allogeneic HSCT), and stem-cell dose (median 6.8 × 10^6/kg in controls vs. 6.3 × 10^6/kg in the intervention arm), were comparable between groups (Table 1).

3.2 | Primary Outcome: Time to Platelet Engraftment

The median time to platelet engraftment was 12 days (IQR: 11–18.75) in the romiplostim group and 12.5 days (IQR: 11–16.75) in the control group (p = 0.88) (Table 2). Kaplan–Meier analysis similarly demonstrated no significant difference in platelet engraftment kinetics between groups (log-rank $p = 0.66$) (Figure 2).

Comparable engraftment times were observed across autologous, allogeneic, and malignant transplant subgroups, suggesting that early romiplostim administration did not significantly alter early platelet engraftment kinetics in the study cohort.

3.3 | Secondary Outcomes

3.3.1 | Platelet Transfusion Requirement

The cumulative platelet transfusion volume was similar between the romiplostim and control arms (median 14 vs. 17 mL/kg; p

TABLE 1 | Baseline characteristics of the study cohort.

Characteristics	Intervention arm ($n = 17$)	Control arm ($n = 15$)	Total ($n = 32$)	p-value
Age (mean ± SD)	7.29 ± 3.75	6.73 ± 3.05	7.03 ± 3.44	0.67
Female gender, *n* (%)	9 (53)	6 (40)	15 (47)	0.52
Type of HSCT—stratified group, *n* (%)				0.94
Autologous	7 (41)	6 (40)	13 (41)	
Allogenic	10 (59)	9 (60)	19 (59)	
Indication for HSCT, *n* (%)				0.70
Malignant	12 (71)	12 (80)	24 (75)	
Nonmalignant	5 (29)	3 (20)	8 (25)	
Disease distribution, *n* (%)				0.90
Hodgkin lymphoma	5 (29)	2 (13)	7 (22)	
Neuroblastoma	1 (5.9)	4 (27)	5 (16)	
Retinoblastoma	1 (5.9)	0 (0)	1 (3.1)	
HLH	1 (5.9)	3 (20)	4 (13)	
AML	1 (5.9)	1 (6.8)	2 (6.3)	
APML	1 (5.9)	0 (0)	1 (3.1)	
ALL	0 (0)	1 (6.8)	1 (3.1)	
JMML	2 (12)	0 (0)	2 (6.3)	
X ALD	1 (5.9)	1 (6.8)	2 (6.3)	
MPS	4 (24)	1 (6.8)	5 (16)	
Gaucher	0 (0)	1 (6.8)	1 (3.1)	
MDS	0 (0)	1 (6.8)	1 (3.1)	
Stem cell dose CD34 cells in million per kg bodyweight Median (IQR)	6.30 (5.5–8.5)	6.80 (5.7–9.9)	6.7 (5.50–9.00)	0.620
Cumulative anthracycline exposure pre-transplant (mg/m^2) Median (IQR) (malignant transplants)	150 (0–300)	130 (0–230)	150 (0–265)	0.61
Cumulative alkylator exposure pre-transplant (mg/m^2) Median (IQR) (malignant transplants)	2250 (0–4500)	3900 (0–4700)	3500 (0–4500)	0.73
Gender of the donor (allogenic transplants), Female	3 (30)	3 (33.33)	6 (31.57)	1
Age of the donor (years) (allogenic transplants) Median (IQR)	33.5 (14–36)	34 (18–36)	32 (16–36)	0.83
HLA match type, *n* (%) (allogenic transplants)	6 (60)	7 (78)	13 (68)	1
Haploidentical matched	4 (40)	2 (22)	6 (32)	

TABLE 2 | Comparison of primary outcome—Time to platelet engraftment.

Variable	Intervention arm	Control arm	*p*-value
Days to platelet engraftment Median (IQR)	12.0 (11–18.75)	12.5 (11–16.75)	0.88
Days to platelet engraftment in the autologous transplant group Median (IQR)	21 (15–23)	17.5 (11–32)	0.94
Days to platelet engraftment in the allogeneic transplant group Median (IQR)	11 (10–12.5)	12.5 (11–15.25)	0.173
Days to platelet engraftment in the malignant transplant group Median (IQR)	13.5 (12–21.5)	13 (11–20)	0.62

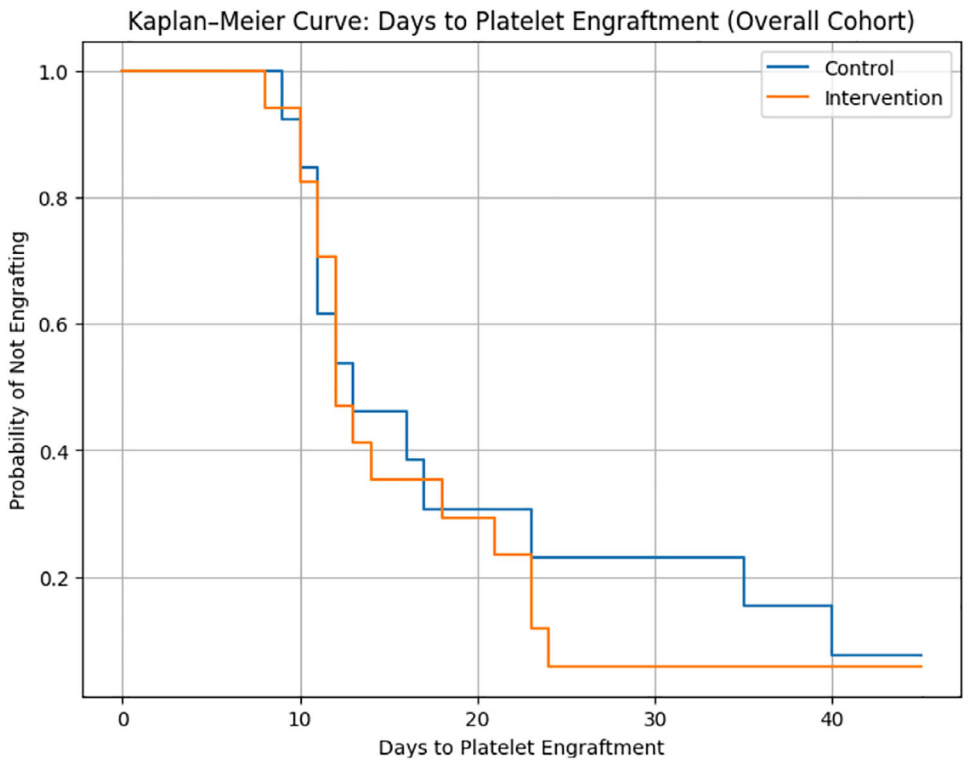

FIGURE 2 | Survival curve depicting time to platelet engraftment.

= 0.26). Subgroup analyses likewise demonstrated no significant differences in transfusion requirements across autologous, allogeneic, or malignant transplant subsets (Table 3).

3.3.2 | Platelet Count on Day +28

By Day +28, median platelet counts were numerically higher in the intervention arm compared with controls (175×10^3/μL [IQR: 94–365] vs. 145×10^3/μL [IQR: 56–175]), although the overall difference did not reach statistical significance ($p = 0.26$). Exploratory subgroup analyses demonstrated higher platelet counts in the allogeneic HSCT subgroup receiving romiplostim (310×10^3/μL vs. 156×10^3/μL; $p = 0.048$). These findings should be interpreted cautiously because of the limited subgroup sample size and the absence of adjustment for multiple comparisons. Similar trends toward higher platelet counts were observed in malignant and autologous transplant subgroups, although these differences were not statistically significant (Table 4).

3.3.3 | Platelet Nadir

The platelet nadir was comparable between groups (median 10×10^3/μL in both arms; $p = 0.70$). No significant differences were observed following stratification by transplant type or disease category.

TABLE 3 | Comparison of secondary outcomes.

Variable	Intervention arm	Control arm	*p*-value
Volume of platelets transfused (mL/kg) Median (SD)	14 (8–20)	17 (7.5–33.5)	0.264
Nadir platelet count (cells/mm^3) Median (IQR)	10,000 (8000–10,000)	10,000 (6500–15,000)	0.701
Time to reach a platelet count of 50,000 cells/mm^3 Median (IQR)	14.0 (12–22.25)	14.5 (12–21.50	0.98

TABLE 4 | Comparison of platelet count on Day +28.

Variable	Intervention arm	Control arm	*p*-value
Platelet count on Day +28 (cells/mm^3) Median (IQR)	175,000 (94,000–365,000)	145,000 (94,000–187,500)	0.26
Platelet count on Day +28 in autologous transplant group (cells/mm^3) Median (IQR)	120,000 (94,000–153,500)	104,000 (33,250–138,750)	0.47
Platelet count on Day +28 in allogeneic transplant group (cells/mm^3) Median (IQR)	310,000 (186,250–432,500)	156,000 (100,000–165,000)	0.041
Platelet count on Day +28 in malignant transplant group (cells/mm^3) Median (IQR)	170,000 (114,500–295,000)	132,000 (93,250–161,250)	0.11

3.3.4 | Time to Achieve Platelet Count $\geq 50 \times 10^9$/L

The median time to achieve platelet count $\geq 50 \times 10^9$/L was similar between the intervention and control groups (14 days [IQR: 12–22] vs. 14.5 days [IQR: 12–21]; $p = 0.98$). Comparable findings were observed across autologous, allogeneic, and malignant transplant subgroups.

3.3.5 | Exploratory Analysis: Neutrophil Recovery

Median time to neutrophil engraftment was comparable between the two groups (13 days [IQR: 10.75–16.75] vs. 12 days [IQR: 11.25–14.75]; $p = 0.81$), with no significant subgroup differences observed across malignant, allogeneic, or autologous transplants.

However, by Day +28, children in the romiplostim arm demonstrated higher absolute neutrophil counts compared with controls (median 3.56×10^3/μL vs. 2.30×10^3/μL; $p = 0.04$). Exploratory subgroup analysis also demonstrated higher Day +28 neutrophil counts within the malignant transplant subgroup receiving romiplostim (median 3.76×10^3/μL vs. 1.99×10^3/μL; $p = 0.04$) (Table 5). Again, these findings should be interpreted cautiously given the small subgroup size and absence of adjustment for multiple comparisons.

3.3.6 | Safety

Romiplostim was well tolerated. No venous or arterial thromboembolic events, Grade ≥3 bleeding events, or treatment-limiting toxicities were observed in either study arm. No patient required treatment discontinuation or dose modification because of adverse events. No graft failures attributable to the study intervention were identified. Routine bone marrow assessments for reticulin fibrosis were not performed as part of the study protocol, and no clinically indicated bone marrow examination demonstrated findings attributed to romiplostim therapy. Likewise, no clinically significant endothelial complications considered attributable to the study intervention were identified during follow-up. All deaths and serious adverse events were independently reviewed by DSMB for causality assessment.

4 | Discussion

Thrombocytopenia following hematopoietic stem cell transplantation (HSCT) remains a major clinical challenge, particularly in pediatric recipients, where delayed platelet recovery contributes substantially to transfusion burden, prolonged hospitalization, and increased morbidity. In this prospective randomized pilot study, early administration of romiplostim following HSCT was safe and feasible but did not significantly shorten the time

TABLE 5 | Exploratory analysis—Comparison of time to neutrophil engraftment and absolute neutrophil counts on Day +28.

Variable	Intervention arm	Control arm	*p*-value
Days to neutrophil engraftment Median (IQR)	13.0 (10.75–16.75)	12.0 (11.25–14.75)	0.81
Neutrophil count on Day +28 (cells/mm^3) Median (IQR)	3560 (3190–4270)	2300 (1155–2880)	0.04
Neutrophil count on Day +28 (cells/mm^3) Median (IQR) (malignant subgroup)	3760 (3137–4217)	1990 (1167–2672)	0.01

to platelet engraftment. However, exploratory analyses demonstrated signals suggesting improved sustained platelet and neutrophil recovery following transplantation. However, exploratory analyses demonstrated higher Day +28 platelet and neutrophil counts, generating the hypothesis that early romiplostim administration may support sustained hematopoietic recovery. Given the pilot nature of the study, these findings should be interpreted cautiously and require confirmation in larger prospective studies.

4.1 | Pathophysiological Basis and Rationale for TPO-RA Use

Post-transplant thrombocytopenia is multifactorial, resulting from the combined effects of myeloablative conditioning, delayed megakaryocytic maturation, poor graft function, immune-mediated destruction, infections, and endothelial injury. Thrombopoietin (TPO), produced mainly by the liver, is the key physiological regulator of megakaryopoiesis. Pharmacologic activation of its receptor (c-MPL) using TPO-RAs such as romiplostim and eltrombopag has demonstrated potential to improve platelet recovery in various hematologic conditions, including chronic immune thrombocytopenia and post-HSCT thrombocytopenia [4].

Romiplostim, a peptibody analog that binds to the extracellular domain of c-MPL, stimulates megakaryocyte proliferation and differentiation without neutralizing endogenous TPO. Its weekly dosing schedule and predictable pharmacokinetic profile make it attractive for use in the post-transplant setting. Preclinical studies have also suggested broader hematopoietic effects, including support of progenitor cell proliferation and multilineage marrow recovery. Several adult studies have demonstrated that romiplostim can safely improve platelet recovery in delayed engraftment or secondary platelet failure following HSCT, although prospective pediatric data remain limited [15–25].

4.2 | Primary Outcome

In the present study, early administration of romiplostim did not significantly reduce time to platelet engraftment compared with standard care (median 12 vs. 12.5 days; $p = 0.88$). Kaplan–Meier analysis similarly demonstrated no significant difference in platelet engraftment kinetics between groups ($p = 0.66$). Comparable findings were observed across autologous, allogeneic, and malignant transplant subgroups.

These findings are consistent with those reported by Scordo et al. (2023), who observed similar platelet engraftment kinetics in adults receiving early romiplostim following HSCT [19]. In contrast, Surya Prakash et al. (2024) demonstrated earlier platelet recovery among multiple myeloma patients receiving romiplostim following autologous transplantation, although that study involved a more homogeneous adult population undergoing melphalan-based conditioning [25]. The absence of a significant difference in early engraftment kinetics in our cohort may reflect the small sample size, clinical heterogeneity, and differences in transplant characteristics between pediatric and adult populations.

4.3 | Secondary and Exploratory Outcomes

Although early platelet engraftment kinetics were similar between groups, exploratory analyses showed numerically higher platelet counts on Day +28 in romiplostim recipients. This difference was statistically significant within the allogeneic HSCT subgroup. Similar trends toward higher platelet counts were observed in malignant and autologous transplant subsets.

Our findings parallel observations by Scordo et al., who reported improved platelet counts on Days +21 and +30 despite similar early engraftment kinetics [19]. Together, these observations suggest that romiplostim may preferentially influence sustained megakaryopoiesis and post-engraftment platelet production rather than the initial timing of platelet recovery. The pharmacodynamic effects of TPO receptor activation support this hypothesis, as stimulation of c-MPL signaling promotes megakaryocyte maturation and platelet shedding from already engrafted progenitors.

Exploratory analyses also demonstrated higher absolute neutrophil counts on Day +28 among children receiving romiplostim, despite comparable neutrophil engraftment times between groups. Scordo et al. similarly reported improved hemoglobin recovery among patients receiving romiplostim following HSCT [19]. These findings raise the possibility that TPO-R signaling may contribute to broader hematopoietic recovery beyond megakary-

opoiesis alone. Experimental studies have demonstrated that the TPO–MPL signaling axis plays an important role in hematopoietic stem cell quiescence, self-renewal, and proliferation of multipotent $CD34^+$ progenitor cells, providing biologic plausibility for multilineage hematopoietic effects.

4.4 | Safety and Tolerability

Romiplostim was well tolerated, with no Grade ≥3 adverse events, thrombotic complications, or clinically significant bleeding episodes observed during follow-up. No patient required treatment discontinuation or dose modification. The absence of thrombotic events is consistent with the favorable safety profile reported in previous adult studies evaluating TPO-RAs following HSCT. These findings support the feasibility of early romiplostim administration even during the immediate post-conditioning period, when endothelial activation and coagulopathy risks may be increased. It should be acknowledged that routine bone marrow evaluation for reticulin fibrosis and systematic surveillance for endothelial complications were not incorporated into the study protocol. Accordingly, the present findings support the short-term clinical safety and feasibility of early romiplostim administration, but do not exclude rare or subclinical toxicities that require evaluation in larger studies with longer follow-up.

4.5 | Clinical Interpretation

The principal contribution of the present study is the demonstration that early romiplostim administration following pediatric HSCT is feasible and was well tolerated in this pilot cohort. Although romiplostim did not significantly alter early platelet engraftment kinetics, exploratory findings of higher Day +28 platelet and neutrophil counts suggest a potential biologic effect on post-engraftment hematopoietic recovery. Given the pilot nature of the study, these findings should be considered hypothesis-generating and require confirmation in adequately powered multicenter studies before conclusions regarding efficacy can be drawn. Importantly, no excessive thrombocytosis or thrombotic toxicity was observed. Given its once-weekly administration and favorable tolerability profile, romiplostim may represent a feasible supportive strategy warranting further investigation in pediatric HSCT recipients.

4.6 | Comparison With Existing Literature

Most prior studies evaluating romiplostim following HSCT have focused on rescue therapy for persistent thrombocytopenia or secondary platelet failure rather than early prophylactic administration. Hartranft et al. reported median response times of approximately 35 days among adults treated for secondary platelet failure, while dose-finding studies following cord blood transplantation demonstrated improved but statistically nonsignificant platelet recovery [18].

The present study extends existing literature by prospectively evaluating early romiplostim administration in a pediatric HSCT cohort. The observed increase in Day +28 platelet counts despite unchanged early engraftment kinetics mirrors findings from adult studies suggesting that TPO-RAs may primarily influence sustained post-engraftment megakaryocyte activity rather than initial engraftment timing. These observations may be particularly relevant in settings of delayed marrow recovery or impaired hematopoietic reserve.

4.7 | Strengths and Limitations

The principal strengths of this study include its prospective randomized design, inclusion of both autologous and allogeneic HSCT recipients, and comprehensive evaluation of hematologic and clinical outcomes in a pediatric population. The study additionally addresses an important evidence gap regarding early TPO-RA use following pediatric HSCT.

However, several limitations should be acknowledged. Although the calculated sample size was 21 patients per arm, the planned recruitment target could not be achieved because of the limited number of eligible pediatric HSCT recipients during the study period. Consequently, this pilot study was underpowered to detect modest differences in platelet engraftment kinetics. In addition, the inclusion of both autologous and allogeneic transplantation, malignant and nonmalignant disorders, and different transplant platforms introduced substantial clinical heterogeneity, limiting the interpretation and generalizability of subgroup analyses. These subgroup analyses were exploratory, were not adjusted for multiple comparisons, and should therefore be regarded as hypothesis-generating. Long-term follow-up evaluating marrow fibrosis, clonal evolution, and sustained hematologic outcomes was not feasible within the study period. Additionally, concomitant factors influencing platelet recovery, including viral reactivation and graft-versus-host disease, were not systematically stratified.

4.8 | Future Directions

The favorable safety profile and exploratory hematopoietic findings observed in this study support further evaluation of romiplostim following pediatric HSCT. Larger multicenter randomized studies are required to validate these findings, identify patient populations most likely to benefit, and determine optimal timing and dosing strategies. Comparative studies evaluating romiplostim alongside other thrombopoietin receptor agonists, including eltrombopag, may further clarify differences in hematopoietic effects and long-term recovery patterns. Mechanistic studies evaluating the influence of TPO-RAs on progenitor cell recovery and marrow microenvironment repair may additionally improve understanding of their role in post-transplant hematopoiesis.

5 | Conclusion

This prospective randomized pilot study demonstrates that early romiplostim administration following pediatric HSCT is feasible and was well tolerated, without evidence of significant treatment-related toxicity. Although no improvement in the primary end-

point of platelet engraftment was observed, exploratory analyses demonstrated higher Day +28 platelet and neutrophil counts, generating hypotheses regarding a potential role for romiplostim in sustained hematopoietic recovery. Larger adequately powered multicenter studies are required to confirm these exploratory observations.

Ethics Statement

This study was approved by the Institutional Ethics Committee and registered prospectively with the Clinical Trials Registry of India (CTRI/2024/03/064716). Written informed consent was obtained from parents or legal guardians, and assent was taken from children, as applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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