

## Retrospective study

# Secondary failure of platelet recovery after allogeneic hematopoietic stem cell transplantation in pediatric acquired aplastic anemia: Incidence, risk factors, and clinical outcomes

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Secondary failure of platelet recovery (SFPR) poses a significant risk for life-threatening complications following hematopoietic stem cell transplantation (HSCT). However, the incidence, clinical outcomes, and risk factors associated with SFPR in the context of allogeneic HSCT (allo-HSCT) for pediatric patients with acquired aplastic anemia (AA) remain unclear. We conducted a retrospective review of 86 consecutive acquired AA children who underwent allo-HSCT at our center from December 2017 to November 2023. The 1-year cumulative incidence of SFPR was found to be 11.6% (95% confidence interval [CI]: 6.2%-21.1%). The median time to SFPR was 2 months (range: 1-5 months) post-transplantation. To clarify the risk factors for SFPR, 9 SFPR cases and 69 non-SFPR cases were further analyzed. Multivariable analyses revealed that age, pre-transplantation body mass index (BMI) and a history of grade III-IV acute graft-versus-host disease (aGVHD) were the most significant predictors for SFPR post-transplantation ( $p < 0.05$ ). Additionally, we found that the 2-year overall survival rate was significantly lower in children with SFPR compared to those without (74.1% vs. 96.7%;  $p < 0.005$ ). Ultimately, 4 patients achieved full platelet count recovery, with 2 patients becoming transfusion-independent. However, 1 patient still requires periodic platelet transfusions, and 2 patients unfortunately died. Among the 6 patients who received thrombopoietin receptor agonist therapy, an overall response rate of 66.6% was observed, suggesting the potential efficacy of this treatment approach in managing SFPR. This study underscores the need for vigilant monitoring of platelet recovery in pediatric HSCT recipients and highlights the need for further research into the etiology of SFPR to improve clinical outcomes.

## INTRODUCTION

Survival after hematopoietic stem cell transplantation (HSCT) for acquired aplastic anemia (AA) has improved significantly in recent decades.<sup>1,2</sup> Sustained hematopoietic recovery is pivotal to the success of HSCT in AA. However, clinicians have noted that even when patients achieve initial hematopoietic reconstitution and retain complete donor-derived hematopoietic cells, they may subsequently develop refractory thrombocytopenia.<sup>3,4</sup> This phenomenon, known as secondary failure of platelet recovery (SFPR), affects 12-26% of patients post-transplantation ac-

cording to previous reports.<sup>5-7</sup> Patients with SFPR lose their initial platelet reconstitution, which leads to increased risks of severe bleeding events and other life-threatening complications, or requirement for transfusions after transplantation. Current therapeutic strategies for SFPR are constrained, and the associated prognosis remains poor.

Several risk factors have been associated with SFPR after allogeneic HSCT, including transplants from unrelated donors, graft-versus-host disease (GVHD) prophylaxis regimens, severe acute GVHD (aGVHD), conditioning involving busulfan, cyclophosphamide and total body irradiation, stem cell dosage, and infections—particularly cy-

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tomegalovirus (CMV) reactivation.<sup>5,6</sup> However, data on SFPR after allogeneic HSCT (allo-HSCT) in pediatric AA patients are still limited.

This study aims to investigate the incidence, clinical management, outcomes, and risk factors associated with SFPR in pediatric patients with AA post-HSCT.

## MATERIALS AND METHODS

### PATIENT SELECTION

In this retrospective analysis, we reviewed a consecutive series of 86 acquired AA children who underwent allo-HSCT as their first HSCT at the Institute of Hematology and Blood Diseases Hospital in Tianjin, China, from December 2017 to November 2023. All pediatric patients' guardians gave informed consent before participation in this study. Patients who developed graft failure after allo-HSCT (n=5) or died of any cause within 30 days post-transplantation without hematopoietic reconstitution (n=3) were excluded from further analysis. Consequently, the remaining cohort, comprising 78 patients, was utilized to estimate the cumulative incidence of secondary failure of platelet recovery (SFPR).

### DEFINITIONS

The timeline for SFPR was calculated from the date of HSCT to the date of clinical diagnosis. SFPR was defined as the first of seven consecutive days of platelet counts  $<20 \times 10^9/L$  or a requirement of platelet transfusions within 7 days after primary platelet recovery was achieved. Patients who had graft rejection or disease relapse within 30 days after the onset of SFPR were regarded as those without SFPR, in accordance with previous studies.<sup>7</sup> Neutrophil engraftment was identified as the first of three consecutive days with an absolute neutrophil count exceeding  $0.5 \times 10^9/L$ , while platelet engraftment was defined as the first of seven consecutive days with an unsupported platelet count above  $20 \times 10^9/L$ . Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) DNAemia was defined as the presence of  $>1000$  DNA copies/mL in blood by quantitative polymerase chain reaction (PCR) assays.<sup>8,9</sup> A human leukocyte antigen (HLA) mismatch was identified as having at least one antigen discrepancy between the donor and recipient. Both aGVHD and chronic GVHD (cGVHD) were diagnosed and graded according to established criteria.<sup>10</sup> Body mass index (BMI) was categorized according to World Health Organization BMI-for-age standards. Overall survival (OS) was calculated as the period from the date of transplantation to the date of death from any cause or the last follow-up point.

### STATISTICAL ANALYSIS

The last follow-up for all survivors was conducted on February 25th, 2024. All clinical data were analyzed utilizing R software (version 4.4.1). Continuous variables were summarized as median (range) and compared using the Mann-Whitney U test, while categorical variables were presented as counts and percentages and compared using the chi-square test or Fisher's exact test. Univariable analysis was

performed based on logistic regression models, and potential risk factors (p-value  $<0.10$ ) were further analyzed in multivariable analysis. The final model was determined using stepwise multiple logistic regression with the "MASS" package.<sup>11</sup> Furthermore, the Kaplan-Meier method was employed to estimate survival curves. All statistical tests were two-tailed, and a p-value  $<0.05$  was considered to indicate statistical significance. The cumulative incidence rate (CIR) of SFPR was calculated using Gray's method, considering death without SFPR as a competing event.

## RESULTS

### CHARACTERISTICS OF PATIENTS WITH SFPR OR NON-SFPR

A total of 78 pediatric patients with acquired AA who underwent allo-HSCT were included. The median age was 8 (range, 2-17) years, and 60.2% were male. Pre-transplant, 52.6% were diagnosed with very severe AA (VSAA). The donor types for HSCT were as follows: 59.0% received grafts from haploidentical donors (Haplo), 28.2% from matched sibling donors (MSD), and 12.8% from unrelated umbilical cord blood (UCB). Additional general characteristics of the patients are presented in [Table 1](#).

### INCIDENCE OF SFPR AND OTHER CLINICAL EVENTS BEFORE SFPR ONSET

The median time to SFPR was 2 (range, 1-5) months post-transplantation ([Supplemental Figure 1](#)). The 1-year CIR of SFPR was 11.6% (95% CI: 6.2%-21.1%). Among the SFPR cohort, the median times to neutrophil and platelet engraftment were both 14 days post-transplantation. Four patients (44.4%) had developed grades III-IV aGVHD prior to the onset of SFPR. Additionally, 3 patients (33.3%) experienced CMV reactivation, transplantation-associated thrombotic microangiopathy (TA-TMA), and hemorrhagic cystitis (HC), respectively. Furthermore, 2 individuals had evidence of EBV activation and early bloodstream infection, respectively. Full cohort characteristics are detailed in [Table 2](#).

### RISK FACTORS FOR SFPR

We subsequently explored whether patients' characteristics, HSCT program, and early post-transplantation complications could predict the incidence of SFPR. The results of the univariate logistic regression analysis for SFPR are presented in [Supplementary Table 1](#). Subsequently, we selected indicators with P-values  $< 0.1$  for inclusion in the multivariate analysis. On the latter, age, BMI and III-IV aGVHD (p-value  $<0.05$ ) were identified as the most significant predictors for SFPR ([Table 3](#)). These findings suggest that special attention should be given to patients with abnormal BMI and those who have experienced severe aGVHD, as they may be at higher risk for the development of SFPR.

**Table 1. Demographic and Clinical Characteristics of Patients with SFPR or non-SFPR.**

| Characteristic                                  | Total<br>n=78       | SFPR<br>n=9         | non-SFPR<br>n=69    |
|-------------------------------------------------|---------------------|---------------------|---------------------|
| Age, years, median (range)                      | 8 (2-17)            | 10 (6-17)           | 8 (2-17)            |
| Male, n (%)                                     | 47 (60.2)           | 7 (77.8)            | 40 (58.0)           |
| BMI, n (%)                                      | 48 (61.5)           | 2 (22.2)            | 46 (66.7)           |
| Normal                                          | 14 (17.9)           | 3 (33.3)            | 11 (15.9)           |
| Overweight                                      | 12 (15.4)           | 2 (22.2)            | 10 (14.5)           |
| Obesity                                         | 4 (5.1)             | 2 (22.2)            | 2 (2.9)             |
| Thinness                                        |                     |                     |                     |
| VSAA, n (%)                                     | 41 (52.6)           | 5 (55.6)            | 36 (52.2)           |
| AA course, months, median (range)               | 4 (1-105)           | 12(2-56)            | 4 (1-105)           |
| GVHD prophylaxis, n (%)                         | 70 (89.7)           | 8 (88.9)            | 62 (89.9)           |
| CSA based                                       | 8 (10.3)            | 1 (11.1)            | 7 (10.1)            |
| TAC based                                       |                     |                     |                     |
| SF level, ng/mL, median (range)                 | 335.1 (29.8-1667.0) | 303.2 (102.5-499.4) | 337.8 (29.8-1667.0) |
| Donor age, years, median (range)                | 28 (0-55)           | 37 (8-55)           | 24 (0-53)           |
| Related Donor source, n (%)                     | 68 (87.2)           | 9 (100.0)           | 59 (85.5)           |
| Stem cell source, n (%)                         | 21 (26.9)           | 3 (33.3)            | 18 (26.1)           |
| BM+PB                                           | 46 (59.0)           | 6 (66.7)            | 40 (58.0)           |
| PB                                              | 1 (1.3)             | 0 (0.0)             | 1 (1.4)             |
| BM                                              | 10 (12.8)           | 0 (0.0)             | 10 (14.5)           |
| CB                                              |                     |                     |                     |
| Donor-recipient sex match, n (%)                | 42 (53.9)           | 7 (77.8)            | 35 (50.7)           |
| HLA match 9~10/10, n (%)                        | 35 (44.9)           | 2 (22.2)            | 33 (47.9)           |
| ABO blood group match, n (%)                    | 39 (50.0)           | 5 (55.6)            | 34 (49.3)           |
| Reduced intensity Conditioning regimen, n (%)   | 60 (76.9)           | 9 (100.0)           | 51 (73.9)           |
| Graft characteristics                           | 10.0 (0.3-21.3)     | 10.7 (10.0-15.0)    | 10.0 (0.3-21.3)     |
| MNCs (×10 <sup>8</sup> /kg), median (range)     | 2.6 (0.1-11.7)      | 3.3 (1.2-5.0)       | 2.5 (0.1-11.7)      |
| CD34+cells(×10 <sup>6</sup> /kg), median(range) |                     |                     |                     |
| Donor type, n (%)                               | 46 (59.0)           | 7 (77.8)            | 39 (56.5)           |
| Haplo                                           | 22 (28.2)           | 2 (22.2)            | 20 (29.0)           |
| MSD                                             | 10 (12.8)           | 0 (0.0)             | 10 (14.5)           |
| UCB                                             |                     |                     |                     |

VSAA: very severe aplastic anemia; CSA: cyclosporin; TAC: tacrolimus; SF: serum ferritin ; BM : bone marrow ; PB : peripheral blood ; MNCs : total number of mononuclear cells transfused; Haplo: haploidentical donors; MSD: matched sibling donors; UCB: unrelated umbilical cord blood.

**Table 2. Clinical events before SFPR onset after allo-HSCT.**

| Events                                      | SFPR<br>n=9  | non-SFPR<br>n=69 |
|---------------------------------------------|--------------|------------------|
| Neutrophil engraftment, day, median (range) | 14 ( 11-17 ) | 13 (10-27)       |
| Platelet engraftment, day, median (range)   | 14 ( 12-30 ) | 15 (8-124)       |
| III-IV aGVHD, n (%)                         | 4 (44.4)     | 12 (17.4)        |
| EBV DNAemia, n (%)                          | 2 (22.2)     | 8 (11.6)         |
| CMV DNAemia, n (%)                          | 3 (33.3)     | 27 (39.1)        |
| TA-TMA, n (%)                               | 3 (33.3)     | 7 (10.1)         |
| Early bloodstream infections, n (%)         | 2 (22.2)     | 8 (11.6)         |
| HC, n (%)                                   | 3 (33.3)     | 24 (34.8)        |

III-IV aGVHD: grades III-IV acute graft-versus-host disease; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; TA-TMA: transplantation-associated thrombotic microangiopathy; HC: hemorrhagic cystitis.

## MANAGEMENTS AND OUTCOMES OF SFPR

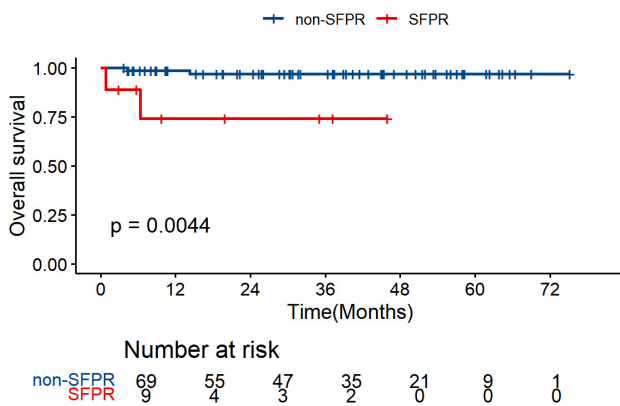
Treatment strategies for the 9 patients with SFPR, included platelet transfusions, thrombopoietin receptor agonists (TPO-RAs), recombinant human thrombopoietin (rhTPO),

and glucocorticosteroid (Shown in [Table 4](#)). Ultimately, 4 patients (patients 3, 4, 5, and 7) achieved full platelet count recovery. In 2 cases (patients 2 and 9), the interventions resulted in a state of transfusion independence, with absolute platelet values consistently above  $20 \times 10^9/L$ , although not

**Table 3. Multivariate analysis for factors associated with SFPR in children with aplastic anemia after transplantation.**

| Variables                 | Adjusted OR for all patients (95% CI) | P value |
|---------------------------|---------------------------------------|---------|
| Age(year)                 | 1.431 (1.087-2.049)                   | 0.023   |
| BMI (kg /m <sup>2</sup> ) | Ref                                   |         |
| Normal                    | 14.069 (1.378-276.396)                | 0.040   |
| Overweight                | 16.793 (1.103-486.145)                | 0.055   |
| Obesity                   | 51.813(2.646-2107.124)                | 0.015   |
| Thinness                  |                                       |         |
| III-IV aGVHD              | 24.585 (2.557-519.787)                | 0.014   |

BMI: Body mass index; III-IV aGVHD: grades III-IV acute graft-versus-host disease

**Figure 1. The overall survival of pediatric patients with SFPR.**

returning to the normal range. Patient 1 did not experience recovery and remained dependent on platelet transfusions. Two patients (nos. 6 and 8) succumbed to severe pneumonia. The treatment outcomes are shown in [Supplemental Figure 1](#).

Among the five patients treated with avatrombopag and the one treated with eltrombopag, three regained normal platelet counts, and one became independent of platelet transfusions, yielding an overall response rate of 66.6%.

### IMPACT OF SFPR ON OS

With a median follow-up period of 32 (range, 0.8 to 75.1) months), the 2-year OS rate for the entire cohort was 94.3% (95% CI 89.1-99.9). Notably, a significant difference in OS was observed between patients with and without SFPR (74.1% versus 96.7%;  $p < 0.005$ ) ([Figure 1](#)).

### DISCUSSION

Acquired AA in children is a severe hematological disorder that seriously not only endangers children's physical and mental health, but also imposes a heavy economic burden on families and society, while consuming substantial public health resources. In the case of SAA/VSAA and transfusion-dependent AA, allo-HSCT is a key therapeutic option. In our studies, the 2-year OS rate for the whole cohort was

94.3% (95% CI 89.1-99.9), which indicates a marked improvement in prognosis for pediatric patients with AA.

SFPR, as an important complication following HSCT, is associated with life-threatening hemorrhage, negatively impacting the quality of survival in pediatric patients. Previous research has mostly focused on adult allogeneic transplants or autologous transplants,<sup>6</sup> with only a few reports addressing SFPR in the context of pediatric allo-HSCT. In our study, 11.6% (9/78) of the children developed SFPR (95% CI: 6.2%-21.1%) within 1-5 months post-transplantation. This incidence appears to be slightly lower than that observed in adults, which ranges from 12% to 26%.<sup>5-7</sup> Although older age in our cohort seems to correlate with a higher risk of SFPR, this observation does not firmly establish that age plays a significant role in the incidence of SFPR, given the limited studies comparing different age groups.

Importantly, the etiology of SFPR is not yet fully understood. Some specialists<sup>12</sup> have suggested an association between SFPR and aGVHD. Research has shown that patients with SFPR/aGVHD have significantly higher levels of inflammatory cytokines IL-2R and TNF-R1, indicating a dysregulated immune response. Additionally, pathways critical to hematopoiesis and immune responses are under-expressed in CD34+ cells isolated from SFPR/aGVHD patients, suggesting a direct impact on hematopoietic function. Our multifactorial analyses seem to support these findings, highlighting the need for further investigation into the relationship between SFPR and aGVHD. Interestingly, we identified abnormal BMI as a potential risk factor for the development of SFPR. Previous research has reported<sup>13,14</sup> that both obesity and low BMI can increase the risk of aGVHD after post-transplantation. In our study, 7/9 patients with SFPR had abnormal BMIs (3 cases of overweight, 2 cases of obesity, and 2 cases of thinness), with only 2 cases simultaneously developing grades III-IV aGVHD. This suggests a complex interplay between BMI, aGVHD, and SFPR that warrants further exploration. As for CMV reactivation, contrary to a previous report by Zhao et al.,<sup>15</sup> which suggested a higher incidence of CMV reactivation in SFPR patients, our findings indicate that out of 9 patients in the SFPR group, only 3 had CMV with an average viral load of 5707.67 CMV DNA copies/mL in the serum. This was lower than the average of 8095.67 CMV DNA copies/mL observed in 27 non-SFPR patients

**Table 4. Demographic and Clinical Profiles for SFPR Patients**

| <i>Patients</i> | <i>Age<br/>(Years)</i> | <i>Gender</i> | <i>Disease<br/>type</i> | <i>Donor<br/>Type</i> | <i>Neutrophil and<br/>Platelet Engraftment<br/>(Days)</i> | <i>SFPR<br/>Onset<br/>Time<br/>(Days)</i> | <i>Transplant-related complications</i>           | <i>treatments</i>                                        | <i>outcome</i>              |
|-----------------|------------------------|---------------|-------------------------|-----------------------|-----------------------------------------------------------|-------------------------------------------|---------------------------------------------------|----------------------------------------------------------|-----------------------------|
| 1               | 8                      | Male          | VSAA                    | MSD                   | 14,13                                                     | 60                                        | None                                              | TPO-RAs, MSC                                             | Transfusion-<br>dependent   |
| 2               | 10                     | Male          | NSAA                    | Haplo                 | 11,12                                                     | 45                                        | HC, blood stream infection, II<br>aGVHD           | TPO-RAs, glucocorticosteroid                             | Transfusion-<br>independent |
| 3               | 6                      | Male          | SAA                     | Haplo                 | 11,12                                                     | 35                                        | TA-TMA, IV aGVHD                                  | TPO-RAs, glucocorticosteroid,<br>MSC, IVIG               | recovery                    |
| 4               | 11                     | Male          | VSAA                    | Haplo                 | 17,21                                                     | 150                                       | CMV DNAemia                                       | TPO-RAs                                                  | recovery                    |
| 5               | 11                     | Male          | VSAA                    | MSD                   | 12,12                                                     | 55                                        | CMV DNAemia, III aGVHD                            | Glucocorticosteroid, rhTPO                               | recovery                    |
| 6               | 8                      | Male          | NSAA                    | Haplo                 | 11,14                                                     | 22                                        | blood stream infection                            | Immunosuppressant dose<br>reduction                      | Dead                        |
| 7               | 10                     | Female        | VSAA                    | Haplo                 | 15,16                                                     | 90                                        | CMV DNAemia, EBV DNAemia,<br>HC,TA-TMA, III aGVHD | TPO-RAs                                                  | recovery                    |
| 8               | 11                     | Male          | VSAA                    | Haplo                 | 14,22                                                     | 71                                        | EBV DNAemia, TA-TMA, IV<br>aGVHD                  | TPO-RAs, glucocorticosteroid                             | Dead                        |
| 9               | 17                     | Male          | SAA                     | Haplo                 | 17,30                                                     | 60                                        | HC, I aGVHD                                       | Immunosuppressant dose<br>reduction, glucocorticosteroid | Transfusion-<br>independent |

SAA: severe aplastic anemia; NSAA: non-severe aplastic anemia; VSAA: very severe aplastic anemia; Haplo: haploidentical donors; MSD: matched sibling donors; CMV: cytomegalovirus; EBV: Epstein-Barr virus; TA-TMA: transplantation-associated thrombotic microangiopathy; HC : hemorrhagic cystitis; IVIG: intravenous immunoglobulin; TPO-RAs: thrombopoietin receptor agonists; rhTPO: recombinant human thrombopoietin; MSC: mesenchymal stem cell.

with CMV reactivation, suggesting that the role of CMV in SFPR may be more complex than previously thought.

In recent years, TPO-RA is becoming increasingly important in the treatment of patients who develop thrombocytopenia due to various causes.<sup>3,16-18</sup> Among the 6/9 patients with SFPR, who received TPO-RA monotherapy or combination therapy, the overall response rate was 66.6%. As reported,<sup>19</sup> rhTPO has also demonstrated efficacy in the treatment of SFPR. In our cohort, platelet counts gradually returned to normal in one patient who received rhTPO and methylprednisolone. However, restricted by the limited number of cases, we are unable to compare the efficacy of different treatment regimens. Further in-depth mechanistic studies are needed to guide us to more efficient clinical treatments.

The present study encompasses several limitations. The single-center retrospective design and limited cohort size (particularly the low SFPR incidence yielding few positive cases) may compromise statistical power and increase the risk of model overfitting. Multivariable regression analyses were potentially limited by an inadequate events-per-variable (EPV) ratio, raising concerns about parameter estimate stability. Finally, the absence of external validation restricts generalization of findings. While univariate analyses were conducted to mitigate these constraints, confirmation through larger prospective cohorts remains essential. Future studies with larger numbers of patients are needed to validate our findings and to explore the associations identified in this preliminary analysis.

In summary, our findings revealed that 11.6% of pediatric patients who underwent transplantation developed SFPR which was not due to relapse or graft rejection. We identified abnormal BMI and severe aGVHD were significant risk factors associated with SFPR. Additionally, SFPR had a significant adverse effect on OS. Therefore, novel approaches to determine the underlying etiology of SFPR will be required to improve the outcome of patients with SFPR.

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## AUTHORS' CONTRIBUTION - CREDIT

*Conceptualization:* Ye Guo; *Methodology:* Yuanyuan Ren, Lipeng Liu; *Formal analysis and investigation:* Yue Shang; *Writing - original draft preparation:* Yue Shang; *Writing - review and editing:* Xin Wang, Chaoqian Jiang, Xia Chen, Yang Wan, Aoli Zhang, Xiaoyan Zhang, Fang Liu, Li Zhang, Yumei Chen, Yao Zou, Xiaojuan Chen, Wenyu Yang; *Funding acquisition:* Ye Guo ; *Resources:* Xiaofan Zhu, Ye Guo; *Supervision:* Ye Guo

## COMPETING OF INTEREST – COPE

No competing interests were disclosed.

## ETHICAL CONDUCT APPROVAL – HELSINKI – IACUC

The study design and methods complied with the Declaration of Helsinki and were approved by the Ethics Committee and Institutional Review Board of the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College.

## INFORMED CONSENT STATEMENT

All authors and institutions have confirmed this manuscript for publication.

## DATA AVAILABILITY STATEMENT

All are available upon reasonable request.

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## REFERENCES

1. Shimano KA, Narla A, Rose MJ, et al. Diagnostic work-up for severe aplastic anemia in children: Consensus of the North American Pediatric Aplastic Anemia Consortium. *American Journal of Hematology*. 2021;96(11):1491-1504. doi:[10.1002/ajh.26310](https://doi.org/10.1002/ajh.26310)
2. Xu ZL, Huang XJ. Haploidentical stem cell transplantation for aplastic anemia: the current advances and future challenges. *Bone Marrow Transplant*. 2021;56(4):779-785. doi:[10.1038/s41409-020-01169-7](https://doi.org/10.1038/s41409-020-01169-7)
3. Yan F, Lu N, Gu Z, et al. Eltrombopag in the treatment of patients with persistent thrombocytopenia after haploidentical peripheral blood stem cell transplantation: a single-center experience. *Ann Hematol*. 2022;101(2):397-408. doi:[10.1007/s00277-021-04706-6](https://doi.org/10.1007/s00277-021-04706-6)
4. Tanaka T, Inamoto Y, Yamashita T, et al. Eltrombopag for Treatment of Thrombocytopenia after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2016;22(5):919-924. doi:[10.1016/j.bbmt.2016.01.018](https://doi.org/10.1016/j.bbmt.2016.01.018)
5. Xie Y, Yang G, Pan L, et al. Development of a nomogram to predict the risk of secondary failure of platelet recovery in patients with  $\beta$ -thalassemia major after hematopoietic stem cell transplantation: a retrospective study. *Therapeutic Advances in Hematology*. Published online May 9, 2024. doi:[10.1177/20406207241245190](https://doi.org/10.1177/20406207241245190)
6. Bruno B, Gooley T, Sullivan KM, et al. Secondary failure of platelet recovery after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2001;7(3):154-162. doi:[10.1053/bbmt.2001.v7.pm11302549](https://doi.org/10.1053/bbmt.2001.v7.pm11302549)
7. Akahoshi Y, Kanda J, Gomyo A, et al. Risk Factors and Impact of Secondary Failure of Platelet Recovery After Allogeneic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2016;22(9):1678-1683. doi:[10.1016/j.bbmt.2016.06.003](https://doi.org/10.1016/j.bbmt.2016.06.003)
8. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. *Clinical Infectious Diseases*. 2017;64(1):87-91. doi:[10.1093/cid/ciw668](https://doi.org/10.1093/cid/ciw668)
9. Lin F, Han T, Zhang Y, et al. The Incidence, Outcomes, and Risk Factors of Secondary Poor Graft Function in Haploidentical Hematopoietic Stem Cell Transplantation for Acquired Aplastic Anemia. *Front Immunol*. 2022;13. doi:[10.3389/fimmu.2022.896034](https://doi.org/10.3389/fimmu.2022.896034)
10. Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplant*. 2018;53(11):1401-1415. doi:[10.1038/s41409-018-0204-7](https://doi.org/10.1038/s41409-018-0204-7)
11. Venables WN, Ripley BD, Venables WN. *Modern Applied Statistics with S*. 4th ed. Springer; 2002. doi:[10.1007/978-0-387-21706-2](https://doi.org/10.1007/978-0-387-21706-2)
12. Huang A, Zhao X, Li M, et al. Suppression of Hematopoietic Primitive Cells in Patients with Secondary Failure of Platelet Recovery after Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2020;26(10):1840-1854. doi:[10.1016/j.bbmt.2020.06.003](https://doi.org/10.1016/j.bbmt.2020.06.003)
13. Khuat LT, Le CT, Pai CCS, et al. Obesity induces gut microbiota alterations and augments acute graft-versus-host disease after allogeneic stem cell transplantation. *Sci Transl Med*. 2020;12(571):eaay7713. doi:[10.1126/scitranslmed.aay7713](https://doi.org/10.1126/scitranslmed.aay7713)
14. Paviglianiti A, Dalle JH, Ayas M, et al. Low Body Mass Index Is Associated with Increased Risk of Acute GVHD after Umbilical Cord Blood Transplantation in Children and Young Adults with Acute Leukemia: A Study on Behalf of Eurocord and the EBMT Pediatric Disease Working Party. *Biol Blood Marrow Transplant*. 2018;24(4):799-805. doi:[10.1016/j.bbmt.2017.12.790](https://doi.org/10.1016/j.bbmt.2017.12.790)
15. Zhao Y, An S, Bi H, et al. Evaluation of Platelet Parameters in Patients With Secondary Failure of Platelet Recovery and Cytomegalovirus Infection After Hematopoietic Stem Cell Transplantation. *Clin Appl Thromb Hemost*. 2023;29:10760296231157741. doi:[10.1177/10760296231157741](https://doi.org/10.1177/10760296231157741)
16. Gao F, Zhou X, Shi J, et al. Eltrombopag treatment promotes platelet recovery and reduces platelet transfusion for patients with post-transplantation thrombocytopenia. *Ann Hematol*. 2020;99(11):2679-2687. doi:[10.1007/s00277-020-04106-2](https://doi.org/10.1007/s00277-020-04106-2)
17. Zhou M, Li T, Zhang P, Lai Y, Sheng L, Ouyang G. Herombopag for the treatment of persistent thrombocytopenia following hematopoietic stem cell transplantation. *Ann Hematol*. 2024;103(5):1697-1704. doi:[10.1007/s00277-024-05711-1](https://doi.org/10.1007/s00277-024-05711-1)

18. E KG, S YK, F Y, et al. Eltrombopag treatment in thrombocytopenia following hematopoietic stem cell transplantation: A multicenter real-world experience. *Leukemia research*. 2024;140. doi:[10.1016/j.leukres.2024.107484](https://doi.org/10.1016/j.leukres.2024.107484)

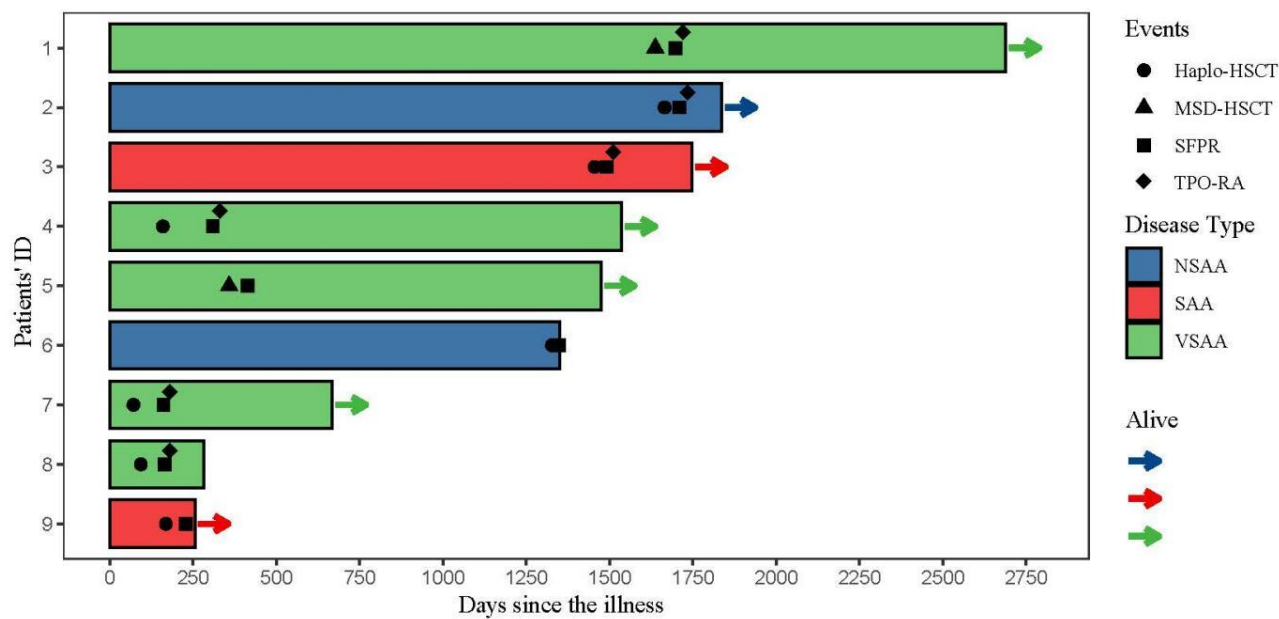
19. Cao Y, Wang M, Shen B, et al. Efficacy of Recombinant Human Thrombopoietin for the Treatment of Secondary Failure of Platelet Recovery After Allogeneic HSCT. *Clin Appl Thromb Hemost*. 2022;28:10760296211068037. doi:[10.1177/10760296211068037](https://doi.org/10.1177/10760296211068037)

## SUPPLEMENTAL MATERIAL

**Supplemental Table 1. Univariate analysis for factors associated with SFPR in children with aplastic anemia after transplantation.**

|                                                       | Univariate logistic analysis |         |
|-------------------------------------------------------|------------------------------|---------|
|                                                       | OR (95%CI)                   | P value |
| Gender                                                | Ref                          | 0.267   |
| Male                                                  | 2.538(0.564-17.873)          |         |
| Female                                                |                              |         |
| Age (year)                                            | 1.234(1.004-1.548)           | 0.052   |
| BMI                                                   | Ref                          | 0.059   |
| Normal                                                | 6.273(0.935-52.243)          | 0.150   |
| Overweight                                            | 4.600(0.504-42.309)          | 0.011   |
| Obesity                                               | 23.000(1.993-319.918)        |         |
| Thinness                                              |                              |         |
| Time from diagnosis to transplantation (month)        | 1.000(0.999-1.001)           | 0.301   |
| Disease type                                          |                              |         |
| SAA/NSAA                                              | Ref                          |         |
| VSAA                                                  | 1.146(0.280-4.973)           | 0.849   |
| Conditioning regimen intensity                        |                              |         |
| MAC                                                   | Ref                          |         |
| RIC                                                   | 2.002×107(0.000-NA)          | 0.992   |
| Conditioning regimen scheme                           |                              |         |
| Non-BU                                                | Ref                          |         |
| BU-based                                              | 6.736×107(0.000-NA)          | 0.993   |
| Donor and recipient ABO blood                         |                              |         |
| Not matched                                           | Ref                          |         |
| matched                                               | 0.956(0.180-7.253)           | 0.960   |
| Donor and recipient sex                               |                              |         |
| Not matched                                           | Ref                          |         |
| matched                                               | 3.400(0.758-23.925)          | 0.144   |
| HLA match                                             |                              |         |
| 5-8/10                                                | Ref                          |         |
| 9-10/10                                               | 0.312(0.044-1.399)           | 0.164   |
| Relative donor                                        | Ref                          | 0.994   |
| No                                                    | 1.764×107(0.000-NA)          |         |
| Yes                                                   |                              |         |
| Total number of mononuclear cells transfused (×108/L) | 1.118(0.947-1.357)           | 0.218   |
| Total number of CD34+ cell transfused (×106/L)        | 1.045(0.721-1.410)           | 0.791   |
| Pretransplant ferritin (ng/ml)                        | 0.993(0.962-1.025)           | 0.677   |
| Early bloodstream infections                          | Ref                          | 0.379   |
| No                                                    | 2.179(0.291-11.098)          |         |
| Yes                                                   |                              |         |
| CMV DNAemia                                           | Ref                          | 0.737   |
| No                                                    | 0.778(0.154-3.214)           |         |
| Yes                                                   |                              |         |
| EBV DNAemia                                           | Ref                          | 0.095   |
| No                                                    | 3.813(0.701-17.838)          |         |
| Yes                                                   |                              |         |
| III-IV aGVHD                                          | Ref                          | 0.072   |
| No                                                    | 3.800(0.837-16.550)          |         |
| Yes                                                   |                              |         |
| Hemorrhagic cystitis                                  | Ref                          | 0.932   |
| No                                                    | 0.938(0.185-3.893)           |         |
| Yes                                                   |                              |         |
| TA-TMA                                                | Ref                          | 0.067   |
| No                                                    | 4.439(0.802-21.308)          |         |
| Yes                                                   |                              |         |

SAA: severe aplastic anemia; NSAA: non-severe aplastic anemia; VSAA: very severe aplastic anemia; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; BU: busulfan; CMV: cytomegalovirus; EBV: Epstein-Barr virus; TA-TMA: transplantation-associated thrombotic microangiopathy; BMI: Body mass index; III-IV aGVHD: grades III-IV acute graft-versus-host disease



Supplemental Figure 1. The timeline of pediatric patients with SFPR.