Risk Factors for Transplant Outcomes in Children and Adolescents with Non-Malignant Diseases Following Allogeneic Hematopoietic Stem Cell Transplantation

Background: The objective of this study was the analysis of transplant outcomes and survival in children treated with allogeneic hematopoietic cell transplantation (alloHCT) for non-malignant disorders, with a focus on risk factor analysis of transplant-related mortality (TRM).

Material/Methods: The treatment outcome was analyzed retrospectively in 10 consecutive years in 4 pediatric transplant centers in Poland. To compare the outcomes, patient data were analyzed according to the diagnosis, age at transplant, donor type, stem cell source, conditioning regimens, transplanted CD34+ cells dose, and pediatric TRM score.

Results: From 183 analyzed patients, 27 (14.8%) died, all of them due to transplant-related complications. TRM occurred more frequently in matched unrelated donor (MUD) transplant recipients vs. matched sibling donor (MSD) transplant recipients (p=0.02); in peripheral blood (PB) recipients vs. bone marrow (BM) recipients (p=0.004); and in patients receiving >5×10^6/kg CD34+ cells (p<0.0001). OS differed significantly according to underlying disease comparing to other diagnoses. Lower survival was found in patients transplanted from MUD (p=0.02). OS was higher in patients receiving BM (p=0.001) and in those receiving ≤5×10^6/kg CD34+ cells (p<0.001). Multivariate analysis showed lower probability of TRM in BM recipients (p=0.04). The probability of TRM was higher in SCID patients (p=0.02) and in patients receiving >5×10^6/kg CD34+ cells (p=0.0001).

Conclusions: Underlying disease, stem cell source, and CD34+ dose higher than 5×10^6/kg were the most important risk factors for TRM, and they all affected OS.

MeSH Keywords: Adolescent • Child • Hematopoietic Stem Cell Transplantation • Risk Factors

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/915330
Background

Indications for allogeneic hematopoietic cell transplantation (alloHCT) for non-malignant disorders in pediatric patients are based on EBMT recommendations, which are published on a regular basis [1–4]. In severe aplastic anemia (SAA), alloHCT from a matched sibling donor (MSD) is a treatment of choice; matched unrelated donor (MUD) HCT is performed when previous immunosuppressive therapy has failed. In inherited bone marrow failure syndromes (IBMFS) such as Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), hematologic manifestation of the disease and cancer predisposition can be cured with HCT. Primary immunodeficiencies are a heterogeneous group of disorders. In severe combined immunodeficiency syndrome (SCID), alloHCT is the only feasible treatment. In other primary immunodeficiencies (PID), including Wiscott-Aldrich syndrome (WAS), autoimmune lymphoproliferative syndrome (ALPS), hemophagocytic lymphohistiocytosis (HLH), or DNA breakage repair disorders, and in some inborn errors of metabolism (IEM) such as mucopolysaccharidosis type I, or osteopetrosis, alloHCT may be effective and is recommended [1–4].

Indications for allogeneic HCT in non-malignant hematopoietic disorders in children are expanding because of improving results of HCT over the last decades [1–5]. Successful outcome of alloHCT may be influenced by various factors that can increase the incidence of serious procedure-related complications, and thereby affect overall survival. They may be related not only to transplant procedure, but also to the condition of the patient before HCT. Some children may have had previous infections or toxicities connected to the treatment before HCT, even if they do not have accompanying chronic diseases or organ dysfunctions [6–10]. The realistic estimation of survival probability after HCT compared to other treatment modalities may be helpful in the final decision of treatment method. The question is whether the transplant-related mortality (TRM) can be accurately predicted based on a risk assessment before HCT.

The aim of this study was to analyze risk factors for TRM to assess their effect on transplant outcome in children with non-malignant disorders, undergoing allogeneic HCT.

Design of the study

Treatment outcome was analyzed in a retrospective study on children with non-malignant diseases treated with allogeneic HCT in 10 consecutive years from 2006 to 2015 in 4 pediatric centers in Poland. Data were retrieved from institutional databases. All patients gave their consent for the individual transplant center to store the data. Approval for the study was given by the institutional committee. This study was a retrospective analysis of patient data. Given the retrospective nature of the study, the requirement for obtaining informed consent from each patient was waived.

To compare the outcome, patients were analyzed according to the diagnosis, age at transplant, donor type, stem cell source, conditioning regimens, transplanted CD34+ cells dose, and pediatric TRM score. This has been published by Matthes-Martin et al. and is defined as a sum of points depending on 3 risk factors: donor type, age at transplantation, and disease status (0 points for matched sibling donor, age ≥10 years at the time of HCT, and all non-malignant diseases; 1 point for alternative donors, age >10 years, and advanced malignant disease at the time of HCT) [5]. In non-malignant patients, such stratification results in 3 risk groups: low risk (score 0), intermediate risk (score 1), and high risk (score 3).

Material and Methods

All consecutive patients with non-malignant diseases treated with first allogeneic HCT over a 10-year period in 4 pediatric transplant departments in Poland were enrolled for analysis. Medical records of 183 children were analyzed. There were 112 boys (61.2%) and 71 girls (38.8%).

Transplant characteristics

Matched donors were specified as 10/10 and 9/10 match by HLA high-resolution typing. Conditioning regimens were in line with current EBMT recommendations [4]. Conditioning was considered myeloablative (MAC) when full-dose busulfan (4 mg/kg/day for 4 days) was used, and it was considered non-myeloablative (non-MAC) when fludarabine, cyclophosphamide, low-dose TBI (1-2 Gy), low-dose busulfan (1 mg/kg/day for 2–4 days), or ATG alone were used. Reduced-toxicity conditioning (RTC) was based on treosulfan (10–14 g/m² for 3 days, age-dependent). The diagnosis and management of GvHD, as well as supportive care and infections prophylaxis, were provided according to EBMT guidelines and center procedures.

Definitions

The main outcomes analyzed were transplant-related mortality (TRM) and overall survival (OS). TRM was defined as death resulting from any cause connected with transplant procedure. For estimating OS, death from any cause was considered an event. Surviving patients were censored at last follow-up.

Statistical methods

Statistical analysis was performed using SPSS IBM Statistics (Version 24) and R package version 3.4.1 (survival library version 2.41-3). Non-parametric tests used were Pearson’s chi-square...
test and the chi-square test with simulating p values, which are insensitive to small numbers, and the Kruskal-Wallis test was used for group comparison. OS was estimated using Kaplan-Meier method and log-rank tests. Multivariate analysis of OS was performed with a cause-specific proportional hazard model (Cox model). Statistical significance was considered P<0.05.

Results

Table 1 shows patient characteristics depending on age at transplant, donor type, stem cell source, conditioning type, stem cell dose, and TRM score. Detailed diagnoses of patients are presented in Table 2.

The median age of the analyzed patients was 7.8 years (range, 0.06–19.8). Median follow-up was 3.66 years (0.2–11.8 years). All of the SCID patients were younger than 10 years at time of HCT.

At the time of HCT, 6/18 (33.3%) SCID patients had an active infection: 1 had rotavirus infection, 1 had BCG-itis; 1 had interstitial pneumonia of unknown etiology; 1 had respiratory syncytial virus (RSV) pneumonia, candida infection, 1 had CMV, ADV, and norovirus infection, and 1 had CMV interstitial pneumonia. In 2 of these patients, sepsis occurred before transplantation and had already resolved before HCT.

Eighty-eight (48.0%) children received non-MAC, 57 (31.1%) received MAC, and 38 children received (20.8%) RTC. In 179 children (97.8%), cyclosporin was used as graft-versus host disease (GvHD) prophylaxis: alone (43 patients) or in combination with methotrexate (114 patients) or MMF (22 patients). Two patients received tacrolimus and 2 received MMF alone as GvHD prophylaxis. MUD transplant recipients received antithymocyte globulin (ATG) as T-cell depletion, and MMD transplant recipients received ex-vivo T-cell depleted grafts.

Transplant-related mortality

Depending on the donor type, TRM occurred more frequently in MUD and MMD HCT compared to MSD transplant recipients (p=0.02). TRM was more frequent in PB recipients compared to in BM recipients (p=0.004), and in patients who...
Table 2. Detailed diagnoses in analyzed patients.

| Group of patients (n) | Detailed diagnoses | Number of patients |
|-----------------------|--------------------|--------------------|
| All (183) | | 183 |
| SAA (70) | Hemophagocytic lymphohistiocytosis (HLH) | 17 |
| | Wiscott-Aldrich syndrome (WAS) | 9 |
| | Hyper IgM syndrome | 4 |
| | Autoimmune lymphoproliferative syndrome (ALPS) | 3 |
| PID (38) | Autoimmune lymphoproliferative syndrome (ALPS) | 17 |
| | Inborn errors of metabolism (NBS) | 6 |
| | Common variable immunodeficiency (CVID) | 1 |
| | IL-10 receptor deficiency | 1 |
| IBMFS (25) | Fanconi anaemia | 13 |
| | Blackfan-Diamond anaemia | 6 |
| | Shwachman-Damond syndrome | 3 |
| SCID (18) | Omenn syndrome | 5 |
| | T (+), B (+), NK (+) | 10 |
| IEM (11) | X-linked adrenoleukodystrophy | 6 |
| | Osteopetrosis | 4 |
| | Mucopolysaccharidosis type 1 | 1 |

SAA – severe aplastic anaemia; PID – primary immunodeficiency; SCID – severe combined immunodeficiency; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of metabolism.

Table 3. Risk factors of transplant-related mortality.

| Risk factor | All patients | Patients n | TRM n (%) | p-Value |
|-------------|--------------|------------|-----------|---------|
| Diagnosis   | SAA          | 70         | 8 (11.4%) | p=0.055 |
| | PID          | 38         | 9 (27.9%) |
| | IBMFS       | 25         | 2 (8.0%) |
| | CGD         | 21         | 1 (4.8%) |
| | SCID        | 18         | 7 (33.3%) |
| | IEM         | 11         | 1 (9.1%) |
| Age         | ≤10 years   | 110        | 16 (14.5%) | p=0.63 |
| | >10 years   | 73         | 8 (11.0%) |
| Donor type  | MUD         | 125        | 24 (19.2%) | p=0.02 |
| | MSD         | 52         | 2 (3.8%) |
| | MMD         | 6          | 2 (33.3%) |
| Stem cell source | BM     | 130        | 13 (9.2%) | p=0.004 |
| | PB          | 48         | 14 (29.9%) |
| | CB          | 5          | 0 (0.0%) |
| Conditioning type | Non-MAC   | 88         | 13 (14.8%) | p=0.86 |
| | MAC         | 57         | 7 (14.0%) |
| | RTC         | 38         | 6 (16.7%) |
| Stem cells dose | >5×10⁶/kg | 55         | 17 (30.9%) | p<0.0001 |
| | ≤5×10⁶/kg  | 128        | 10 (7.9%) |
| TRM score   | 0          | 20         | 1 (5.0%) | p=0.36 |
| | 1          | 120        | 19 (15.8%) |
| | 2          | 43         | 8 (18.6%) |

SAA – severe aplastic anaemia; PID – primary immune deficiency syndrome; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of metabolism; TRM – transplant related mortality; PB – peripheral blood, BM – bone marrow; CB – cord blood; MSD – matched sibling donor; MUD – matched unrelated donor; MMD – mis-matched donor; non-MAC – nonmyeloablative conditioning; MAC – myeloablative conditioning; RC – reduced toxicity conditioning.
received >5×10⁶/kg CD34 in comparison to those who were
given ≤5×10⁶/kg (p<0.0001).

TRM occurred more frequently in SCID patients compared to
other diagnoses, but the difference was at the border of sig-
nificance (p=0.055). SCID patients in most cases (61.1%) re-
ceived >5×10⁶/kg CD34+ cells. There was no statistically sig-
nificant difference in the occurrence of TRM depending on age
at transplant, conditioning type, and pediatric TRM score. Risk
factors for transplant-related mortality are shown in Table 3.

GvHD was diagnosed in 38 patients (20.8%): acute GvHD in
30 and chronic in 8. There was no statistically significant dif-
ference in acute and chronic GvHD occurrence depending on
diagnosis, stem cell source, donor type, and CD34+ cells dose.
Acute GvHD occurred more frequently in children age 10 years
and younger at time of HCT: 4/110 (21.8%) children ≤10 years
vs. 6/73 (8.2%) >10 years (p=0.01). None of the patients age
>10 years developed cGvHD, and it was diagnosed in 8/110
children age ≤10 years (p=0.015).

**Survival**

Overall survival (OS) in the entire group of patients was 85%
at the median observation time of 3.66 years, as well as at the
maximum (11.23 years) observation time. OS differed signifi-
cantly according to underlying disease, and was 95% in CGD
patients, 92% in IBMFS patients, 91% in IEM patients; 89% in
SAA patients; 75% in non-SCID PID patients, and 65% in SCID
patients (p=0.022).

Significantly lower survival was observed in patients transplanted
from MMD (67%) and MUD (81%) compared to those transplanted
from MSD (96%) (p=0.02). After excluding 6 patients transplanted
from MMD, the OS was also significantly lower in patients
transplanted from MUD compared to MSD (p=0.012). OS was
significantly higher in patients receiving BM as a graft source
compared to those who received PB (89.6% and 69.8%, respectively) (p=0.0007). CB transplants were excluded from the analysis due to the small number of such patients. Statistically higher OS was observed in patients receiving £5×10^6/kg CD34+ cells (92%) compared to those receiving >5×10^6/kg (68%) (p<0.001). OS did not differ according to sex and age at HCT or according to conditioning type and TRM score stratification.

**Risk factor analysis**

In univariate analysis, the probability of TRM was significantly lower: HR 0.19 for MSD recipients (95% CI 0.04–0.80) (p=0.02), HR 0.33 in patients receiving BM as stem cell source (95% CI 0.16–0.70) (p=0.004), and HR 4.53 in patients receiving ≤5×10^6/kg CD34+ cells (95% CI 2.07–9.9) (p=0.0001). For patients diagnosed with SCID, predicted TRM was HR 6.02, which was higher than in patients with other diagnoses (95% CI 1.33–11.06) (p=0.01). Prediction of TRM events according to diagnosis, donor type, stem cell source, and CD34+ cells dose is presented in Figures 1 and 2. Multivariate analysis showed that 3 factors affect TRM: (1) stem cell source, with lower probability of TRM in BM recipients: HR 0.44 (95% CI 0.2–0.96) (p=0.04); (2) diagnosis, with higher probability of TRM in SCID: HR 6.02 (95% CI 1.34–26.95) (p=0.02); and (3) CD34+ cell dose, with higher probability of TRM in recipients of ≥5×10^6 cells/kg: HR 4.53 (95% CI 2.07–9.9) (p=0.0001) (Table 4).

**Causes of deaths**

There were 156 patients still alive at the end of the study (85.2%), and 27 patients (14.8%) had died, all due to transplant-related complications. The causes of death with patient details are presented in Table 5.

**Discussion**

Patients with non-malignant diseases treated with HCT constitute a heterogeneous group in terms of diagnoses. In our cohort of patients, TRM was observed more frequently in patients with SCID, and these children had the lowest survival. According to Gennery et al., significantly lower survival was observed in SCID patients transplanted from unrelated and mismatched related donors (69% and 66%, respectively) compared to matched related donors (90%) [6]. In the same study, the absence of respiratory impairment, or viral infection before transplantation, were associated with better prognosis on multivariate analysis [6]. According to an analysis of SCID patients by Heimall et al., the average survival for patients who underwent HCT was about 70% at 3 years after transplantation [7]. This may be the consequence of prolonged immunosuppression and previous life-threatening infections, observed especially in severely immunocompromised patients. In another study of this same group, 2-year overall survival in SCID patients was lower in those transplanted with active infection [8]. In our analysis, 6/18 patients (33.3%) with SCID had active infection at the time of HCT, and 2 patients with SCID died due to infections. Infection was the most common cause of death in the whole analyzed cohort.

**Table 4. Cox multiple regression for transplant-related mortality.**

| ID | Independent variables (all but age dichotomized) | HR | 95% confidence interval for HR | p | Cox regression p |
|----|-------------------------------------------------|----|-------------------------------|---|-----------------|
|    | Donor Type: MSD                                 | 0.11| 0.01–1.63                     | 0.10 |                 |
|    | Donor Type: MMD                                 | 0.84| 0.17–4.18                     | 0.83 |                 |
|    | Sex: M                                          | 0.99| 0.45–2.12                     | 0.99 |                 |
|    | Pediatric TRM score: 1                          | 0.53| 0.02–13.15                    | 0.70 |                 |
|    | Pediatric TRM score: 2                          | 0.39| 0.01–28.49                    | 0.67 |                 |
|    | Age                                             | 1.07| 0.91–1.26                     | 0.38 | 0.004           |
|    | Disease: SCID                                   | 6.02| 1.34–26.95                    | 0.02 |                 |
|    | Disease: PID                                    | 2.74| 0.82–9.12                     | 0.10 |                 |
|    | Disease: Others                                 | 0.56| 0.15–2.02                     | 0.38 |                 |
|    | Stem Cell Source: BM                            | 0.44| 0.12–0.96                     | 0.04 |                 |
|    | CD 34+ cells: >5×10^6/kg                       | 4.53| 2.07–9.9                      | 0.0001 |                 |

Input variables: Donor Type + Sex + Pediatric TRM score + Age + Disease + Stem Cell Source + CD 34+ cells dose.
### Table 5. Causes of mortality in analyzed patients.

| No. | sex | Age at HCT years | Diagnosis | Donor type | Stem cell source | CD34+ cells dose ×10^6/kg | Cause of death | Accompanying complications |
|-----|-----|------------------|-----------|------------|-----------------|--------------------------|----------------|----------------------------|
| 1   | M   | 0.3              | SCID-Ommen s. | MUD        | PB              | 9.3                      | Organ failure | Renal failure, IFI         |
| 2   | F   | 7.5              | SAA        | MUD        | BM              | 8.5                      | Infection     | Bacterial infection (unknown pathogen), graft failure |
| 3   | F   | 8                | SAA        | MUD        | PB              | 13                       | Infection     | Fungal infection of CNS    |
| 4   | F   | 10.2             | PID– NBS   | MSD        | BM              | 3.5                      | Infection     | CMV reactivation, graft failure |
| 5   | F   | 0.6              | SCID– T–, B– NK+ | MUD      | PB              | 7.9                      | Infection     | Idiopathic pneumonia       |
| 6   | F   | 14.5             | SAA        | MUD        | BM              | 1.7                      | Infection     | CMV reactivation           |
| 7   | M   | 0.3              | SCID– Ommen s. | MMFD      | PB              | 14                       | Organ failure | Respiratory failure, EBV, IFI |
| 8   | M   | 13.2             | IBMFS– FA  | MUD        | PB              | 5.9                      | Infection     | Bacterial sepsis (unknown pathogen) |
| 9   | M   | 10.5             | PID– HLH   | MMUD       | BM              | 4.4                      | Organ failure | CNS bleeding, CMV reactivation |
| 10  | M   | 7.6              | SAA        | MUD        | BM              | 1.84                     | Infection     | CMV reactivation           |
| 11  | F   | 1.4              | SCID– T–, B– NK+ | MUD      | PB              | 9.06                     | Infection     | Sepsis (pseudomonas)       |
| 12  | M   | 4.5              | SCID– T–, B– NK+ | MUD      | PB              | 6.09                     | Organ failure | CNS bleeding               |
| 13  | F   | 11.3             | SAA        | MUD        | PB              | 1.5                      | Infection     | Encephalopathy             |
| 14  | M   | 13.3             | SAA        | MUD        | PB              | 7                        | Infection     | Pulmonary aspergillosis    |
| 15  | M   | 10.8             | SAA        | MUD        | BM              | 1.9                      | GvHD IIIo     | Renal failure, CMV reactivation |
| 16  | F   | 0.4              | IEM– osteopetrosis | MUD    | BM              | 6.6                      | GvHD IVo      | Infection (unknown pathogen) |
| 17  | M   | 9                | CGD        | MUD        | BM              | 2.6                      | Infection     | IFI                       |
| 18  | M   | 0.25             | PID– HLH   | MUD        | BM              | 4.0                      | GvHD IIIo     | CMV reactivation, VOD      |
| 19  | F   | 2                | SCID– T–, B– NK+ | MUD      | BM              | 5.42                     | Organ failure | GvHD IIo                  |
| 20  | F   | 15               | PID– hiper IgM symdr. | MSD    | BM              | 4.26                     | Infection     | Bacterial sepsis (Klebsiella pneumoniae) |
| 21  | F   | 17               | SAA        | MUD        | PB              | 4.32                     | Organ failure | VOD, gastrointestinal (GI) bleeding |
| 22  | M   | 15.5             | SAA        | MUD        | PB              | 7.5                      | Infection     | Pneumonia (unknown pathogen) |
| 23  | M   | 1.8              | PID– WAS   | MUD        | PB              | 5.6                      | Infection     | Pneumonia (unknown pathogen) |
| 24  | M   | 0.8              | PID– WAS   | MUD        | PB              | 7.8                      | cGvHD         | IFI, pneumonia             |
| 25  | M   | 1.5              | PID– HLH   | MUD        | PB              | 6.5                      | Organ failure | Respiratory failure, renal failure, GvHD |
| 26  | F   | 7                | IBMFS– FA  | MUD        | BM              | 1.8                      | Organ failure | Respiratory failure, renal failure, GvHD |
| 27  | M   | 1.5              | PID– HLH   | MUD        | BM              | 5.3                      | Infection     | Viral infection, RSV pneumonia |

SAA – severe aplastic anaemia; PID – primary immune deficiency syndrome; IBMFS – inherited bone marrow failure syndrome; CGD – chronic granulomatous disease; IEM – inborn errors of methabolism; NBS – Nijmegen Breckage Syndrome; FA – Fanconi anaemia; WAS – Wscott-Aldrich syndrome; HLH – limphohistiocytosis; CNS – central nervous system; GvHD – graft versus host disease; IFI – invasive fungal infection; CMV – cytomegalovirus; RSV – respiratory syncytial virus; VOD – venoclusive disease; PB – peripheral blood; BM – bone marrow; MSD – matched sibling donor; MUD – matched unrelated donor; MMFD – mis-matched family donor; MMUD – mis-matched unrelated donor.
patients receiving BM. Bacigalupo et al. reported that PB as the stem cell source was a negative predictor of survival in patients transplanted for SAA [9]. Studies by Eapen et al. on SAA patients showed that stem cell source was an important risk factor for survival, and BM was the preferred graft source in SAA patients, with lower mortality after BM compared to PB [10,11]. Several analyses show that PB stem cells and higher CD34+ dose tend to be associated with increased mortality and lower survival due to GvHD [12,13]. In our analysis, CD34+ cells dose, stem cell source, and underlying disease had no effect on acute and chronic GvHD, although CD34+ cells dose >5×10^6/kg was associated with higher incidence of TRM and lower OS. Many studies found that higher CD34+ cell dose improved engraftment and had no effect on severe GvHD and TRM in children [14–16], but other studies found a correlation between low CD34+ dose and worse survival [17,18]. According to Rembürger et al., in patients treated for malignancies, those given a very high CD34+ cell dose (≥11×10^6/kg) had decreased rates of survival [19]; stem cell dose was an important risk factor for survival when connected with graft source. Patients who received PB containing <11.0×10^6/kg CD34+ cells had significantly better OS compared with those receiving BM, regardless of cell dose. The study found that PB CD34+ cell dose ≥11×10^6/kg was correlated with reduced OS and increased mortality rate [19].

In our cohort, univariate analysis showed that OS was significantly lower in children transplanted from MUD compared to MSD. Several authors showed that patients transplanted from unrelated donors have lower survival and higher TRM [17–20]. Locatelli et al. reported an estimated OS of 87% in patients with FA when the donor was an HLA-identical sibling vs. 40% in MUD transplants [21]. Roy et al. reported outcomes of 61 transplanted BDA patients, with 76% 3-year OS after MSD HSCT, and 39% OS after MUD HSCT [20]. In SAA patients, the OS was 89% in our cohort, which is in line with other studies, in which OS varied from 91% to 86% after MSD HCT. In patients after failed immunosuppressive therapy (IST) treated with MUD HCT, OS was lower but still improving [22–24].

Recommended conditioning regimens have changed in recent years and now differ. In our cohort, conditioning type had no effect on TRM and OS. The results an analysis by Burroughs et al. of patients with non-malignant diseases indicate that RTC conditioning is effective and improves survival due to its lower toxicity [25]. However, Al Mulla et al. showed that reduced-toxicity conditioning was not significantly less toxic than myeloablative in pediatric and adolescent patients undergoing allogeneic HCT [26]. In our study, pediatric TRM score had no effect on TRM and OS, probably because the type of non-malignant disease was not included in the TRM stratification, and according to our analysis, the underlying disease affected survival after HCT.

This study has some limitations. The population was not homogeneous, as the underlying disease varied among the analyzed groups. The retrospective nature of the study, as well as the extended time of data collection and hence the changes of guidelines and standards of care during that time, could also have affected the results. Nevertheless, our results should be of value in investigating the causes of TRM in children with non-malignant diseases undergoing allogeneic HCT. Further research is needed to assess the effects of different risk factors on HCT outcome. In addition, prospective studies would allow gathering larger and more homogeneous populations of patients.

Predicting the outcome of HCT based on pretransplant factors is important for clinical practice. Despite the introduction of procedures that reduce the risk of TRM, it is necessary to assess such a risk individually before making a transplant decision.

**Conclusions**

In our study, SCID diagnosis, PB as stem cell source, and CD34+ dose higher than 5×10^6/kg were the most important risk factors for TRM in patients with non-malignant diseases treated with HCT, and they all appear to affect OS.

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