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Late Effects in Pediatric Allogeneic Hematopoietic Stem Cell Transplantation for Nonmalignant Diseases: Proxy- and Patient-Reported Outcomes

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A B S T R A C T

Survival rates in pediatric hematopoietic stem cell transplantation (HSCT) for nonmalignant diseases have improved due to advances in conditioning regimens, donor selection, and prophylaxis and treatment of infections and graft-versus-host disease. Insight into the long-term patient-reported outcomes (PROs) after pediatric HSCT for nonmalignant disease is lacking but essential for optimal shared decision making, counseling, and quality of care. The purpose of this research was to determine long-term patient-reported outcomes in allogeneic pediatric HSCT for nonmalignant diseases and to compare these results with Dutch reference data. This single-center cohort study evaluated PROs (PedsQL 4.0, PROMIS item banks), self- or proxy-reported, among patients at ≥2 years after pediatric allogeneic HSCT for nonmalignant disease. Mean scores were compared with those of the Dutch general population. Of 171 eligible patients, 119 participated, for a 70% response rate. The median patient age was 15.8 years (range, 2 to 49 years), and the median duration of follow-up was 8.7 years (range, 2 to 34 years). Indications for HSCT included inborn errors of immunity (n = 41), hemoglobinopathies (n = 37), and bone marrow failure (n = 41). Compared with reference data, significantly lower scores were found in adolescents (age 13 to 17 years) on the Total, Physical Health, and School Functioning PedsQL subscales. Significantly more Sleep Disturbance was reported in children (age 8 to 18 years). On the other hand, significantly better scores were seen on PROMIS Fatigue (age 5 to 7 years) and Pain Interference (age 8 to 18 years) and, in adults (age 19 to 30 years), on Depressive Symptoms and Sleep Disturbance. This study showed better or comparable very long-term PROs in patients after pediatric HSCT for nonmalignant diseases compared with the reference population. Children and adolescents seem to be the most affected, indicating the need for supportive care to prevent impaired quality of life and, more importantly, to amplify their long-term well-being.

Allogenic pediatric hematopoietic stem cell transplantation (HSCT) is an intensive, curative treatment for an increasing number of patients with nonmalignant diseases [1], including inborn errors of immunity (IEI), hemoglobinopathies (HB), and inherited and acquired bone marrow failure (BMF) disorders. HSCT for nonmalignant diseases differs substantially from HSCT for malignant diseases in various aspects with respect to health status (including comorbidity) and health-related quality of life (HRQoL) pre-HSCT, and applied conditioning regimens. Over the last several decades, advances in conditioning

Abbreviations: BMF, bone marrow failure; CAT, computer adapative test; GvHD, graft versus host disease; HB, hemoglobinopathies; HRQoL, health related quality of life; HSCT, hematopoietic stem cell transplantation; ICHOM, International Consortium for Health Oucomes Measurement; IEI, inborn errors of immunity; IRT, item response theory; PRO, patient-reported outcome; PROM, patient-reported outcome measure

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regimens, donor selection, and prophylaxis and treatment of infections and graft-versus-host disease (GVHD) have led to improved survival [2]. The indications for HSCT are expanding in the broad spectrum of nonmalignant diseases. Given the challenges in determining the best treatments for nonmalignant diseases, insight into long-term HRQoL after HSCT is of utmost importance [3].

Current late effects research is focused mainly on clinical outcomes, such as survival, immune reconstitution, chronic GVHD (cGVHD), and gonadal dysfunction. However, to properly determine the late effects after this intensive treatment, the patients' overall well-being, which includes HRQoL, is also essential, especially when comparing outcomes with those of conservative treatment and following HSCT. HRQoL is assessed using validated patient-reported outcomes (PROs). As defined by the US Food and Drug Administration (FDA), a PRO is "a measurement based on a report that comes directly from the patient about the status of a patient's condition without amendment or interpretation of the patient's response by a clinician or anyone else" [4]. The use of PROs can objectify the patients' overall well-being and provides a better view of long-term outcomes after pediatric HSCT for nonmalignant diseases.

International comparisons of HRQoL in pediatric HSCT has proven difficult owing to the wide variety of patient-reported outcome measures (PROMs) in use worldwide [5]. Furthermore, PROMs and PRO domains used in previous research differ for children and adults (eg, Pediatric Quality of Life [PedsQL] 4.0 and Short Form Health Survey 36), posing a challenge in longitudinal long-term follow-up [6]. In the evaluation of long-term outcomes in patients with pediatric HSCT for nonmalignant diseases, HRQoL research is limited, and reported results are inconsistent. Although in-depth insight into the long-term PROs and HRQoL in patients after pediatric HSCT for nonmalignant diseases is lacking, it is essential for optimal counseling and shared decision making, as well as for improving HSCT treatment strategies and comprehensive care programs for late effects after HSCT.

With this in mind, in the present study we aimed to determine long-term patient-reported outcomes in allogeneic pediatric HSCT for nonmalignant diseases and compare these results to Dutch reference data in different age groups, as well as to assess associations between these results with the primary disease, complications, and HSCT characteristics. Based on previous research and expert opinion, we hypothesized that patients with a pediatric HSCT for nonmalignant disease would have impaired HRQoL compared with the reference Dutch general population [7,8].

METHODS

Study Design and Participants

In this single-center cross-sectional study, patient- and proxy-reported outcome data were collected online between December 2020 and March 2021. The inclusion criterion was ≥2 years after undergoing pediatric allogeneic HSCT for a nonmalignant disease at the Willem Alexander Children's Hospital, Leiden University Medical Center. The exclusion criterion was inadequate knowledge of the Dutch language or psychological inability to fill in questionnaires, as determined by the primary physician at the late effects follow-up outpatient clinic. This study was approved by the Medical Ethical Committee Leiden, The Hague, Delft (N20.181). All participants provided written informed consent; for patients age ≤15 years, assent was given by (both) caregivers.

Measures

Patients completed questionnaires in the digital KLIK PROM portal (www.hetklikt.nu) [9]. PRO domains from the International Consortium for Health Outcomes Measurement standard set "Overall Pediatric Health" were selected [10]. Validated PROMs were age-appropriate and selected based on Dutch availability and optimal international comparison (Supplementary Table S1).

PedsQL

The Dutch version of the generic PedsQL 4.0 was used for children (proxy report for age 2 to 4 years and 5 to 7 years, self-report for age 8 to 12 years), adolescents (self-report for age 13 to 17 years), and young adults (self-report for age 18 to 30 years) [11–13]. The PedsQL consists of 4 scales: Physical Health (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). Scoring is on a 5-point Likert scale (ranging from "never" to "almost always"), with a 7-day recall period. All scales can be combined into a total score. Psychosocial health can be assessed through a combined score of Emotional Functioning, Social Functioning, and School Functioning. Higher scores represent a better HRQoL (range, 0 to 100). Additionally, the "Worry" subscale of the Dutch version of the PedsQL Stem Cell Transplant Module was used for children (proxy report for age 5 to 7 years, self-report for age 8 to 12 years) and adolescents (self-report for age 13 to 18 years) [14].

PROMIS Measures

The validated Dutch-Flemish PROMIS item banks used were Anxiety, Anger, Depressive Symptoms, Fatigue, Pain Interference, Pain Intensity, Sleep Disturbance, Mobility, Physical Function, Peer Relationships, Satisfaction with Social Roles and Activities, and Cognitive Function (Supplementary Table S1) [15–26]. The PROMIS item banks were used for children (proxy report for age 2 to 4 years and 5 to 7 years, self-report for age 8 to 12 years), adolescents (self-report for age 13 to 17 years), and adults (self-report for age ≥18 years). PROMIS item banks were administered as a computerized adaptive test, which selects items based on previously completed responses, aiming for the minimum number of items needed for a reliable score [27]. If Dutch computerized adaptive test versions were not available, short forms were used. PROMIS item banks use a 5-point Likert scale (ranging from "never" to "almost always"), with a 7-day recall period. The use of the US Item Respons Theory (IRT) model results in T scores, where 50 is the mean score of the US general population with a standard deviation of 10. A higher score indicates more of the item present. The PROMIS item bank Pain Intensity uses a scale of 0 to 10.

Patient Characteristics

Patient characteristics obtained from the medical files were age, sex, underlying disease, conditioning regimen, stem cell source, donor relation, acute GVHD, and cGVHD. Underlying disease was divided into 3 groups: IEI, HB, and BMF disorders. Conditioning regimens were grouped into busulfan-based, treosulfan-based, cyclophosphamide-based, cyclophosphamide with total body irradiation/thoracoabdominal irradiation, fludarabine-based. and no conditioning. Additionally, patients (age >18 years) or their caregivers (for those age 2 to 18 years) completed a sociodemographic questionnaire about themselves (age, county of birth, educational level, employment, marital status).

Statistical Analyses

All statistical analyses were performed using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics were compared by underlying disease using the Fisher exact test or Kruskal-Wallis rank-sum test. Internal reliability (Cronbach α coefficient) for PedsQL 4.0 was considered as acceptable if >.6 [28]. Additionally, mean PedsQL scores were compared to Dutch reference data [29–33] using an independent-samples *t* test and are presented as mean difference scores. PROMIS T scores were compared to either the Dutch or US reference mean using 1-sample *t* tests. Dutch PROMIS reference data for young adults (age 19 to 30 years) and adults (age 31 to 49 years) were provided by the Dutch Flemish PROMIS Health Organization. For some PROMIS item banks, Dutch reference data were not available; if so, US reference data were used (mean T score, 50 ± 10) for comparison. Reference data were not available for the PedsQL Stem Cell Transplant subscale "Worry." Effect sizes (Cohen d and Glass Δ) were calculated [34]. Univariate robust linear regression analyses were performed for correlations between patient characteristics and PedsQL 4.0 scores. Owing to small sample sizes, multivariate analyses could not be performed on the PedsQL 4.0 data. Univariate and multivariate linear regression analyses were performed for patient characteristics and PROMIS item banks correlation, except for PROMIS Pain Intensity owing to different types of measurement (scale scores versus T scores). Covariates evaluated were age at baseline, age at HSCT, sex, diagnosis, and country of birth. cGVHD was not included in this analysis owing to its low occurrence rate. Bonferroni correction was used to correct for multiple testing.

RESULTS

One hundred nineteen of 171 eligible patients (70%) participated in this study (Figure 1), of whom 72 (61%) were male.

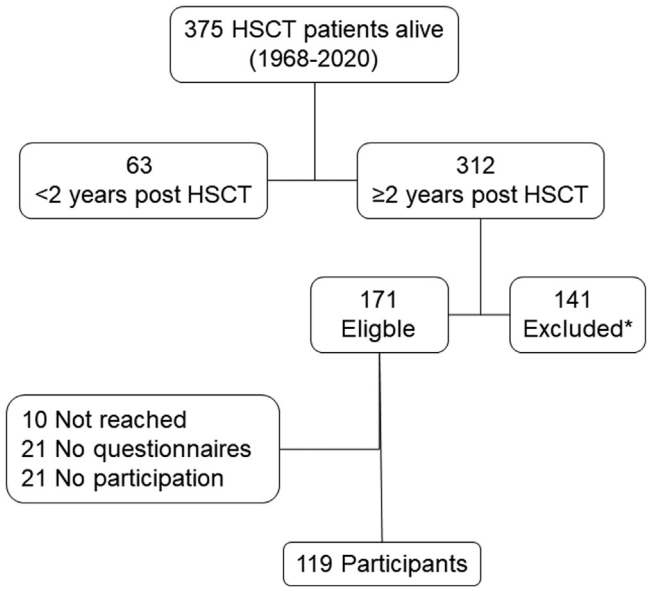

Figure 1. Flowchart showing inclusion and exclusion of patients. *Second HSCT (n = 2), autologous HSCT (n = 2), not at late effects follow-up outpatient clinic (n = 5), at request of primary physician (n = 7), development of myelodysplastic syndrome (n = 1), lost to follow-up (n = 124).

The median duration of follow-up was 8.7 years (range, 2.1 to 33.6 years) (Table 1). The underlying disease was categorized as IEI in 41 patients, as HB in 37, and as BMF in 41 (Supplementary Table S2). Conditioning regimens were mainly busulfan-based (34%), treosulfan-based (41%), or cyclophosphamide-based (17%) (Supplementary Table S3). IEI patients were significantly younger than HB and BMF patients. Of the HB patients, 81% were, or had at least 1 parent, born in a foreign country, a significantly higher proportion compared with IEI and BMF patients. Age-appropriate PedsQL questionnaires (Supplementary Table S2) were available for 109 patients and were completed by 105 (96%). Age-appropriate PROMIS item banks were available for 117 patients and were completed by 105 (90%). Demographic data did not differ significantly between the patients who did not complete all questionnaires and those who did.

PedsQL: Comparison with the Dutch General Population

The number of patients in the age category 2 to 4 years (n = 2) was insufficient for further analysis. Table 2 presents mean difference scores compared to Dutch reference data by age category (raw mean scores are provided in Supplementary Table S4). The school subscale in children (age 5 to 7 years) was not reliable (Cronbach α = .32), and thus was not used. Significantly, lower scores compared to the Dutch population were found in adolescents (age 13 to 17 years) on the Total, Physical Health, and School Functioning subscales. Children (age 2 to 12 years) and young adults (age 18 to 30 years) reported no significantly different scores compared to the Dutch population (Table 2). Mean scores on the PedsQL Stem Cell Transplant subscale "Worry" were 91.3 $\pm$ 8.3 for children age 5 to 7 years, 87.9 $\pm$ 10.4 for children age 8 to 12 years, and 68.7 $\pm$ 13.5 for adolescents age 13 to 18 years (Supplementary Table S5). There are no reference data available for this module.

PROMIS Item Banks: Comparison to Dutch General Population

Figure 2 presents mean difference scores compared to Dutch reference data by age category (Supplementary Table S6; raw mean scores provided in Supplementary Table S7). Children age 5 to 7 years had lower Fatigue scores, and children age 8 to 18 years reported less Pain Interference compared with the reference population. Children age 8 to 18 years reported more Sleep Disturbance, and young adults (age 19 to 30 years) reported significantly less Sleep Disturbance. Additionally, young adults (age 19 to 30 years) reported fewer Depressive Symptoms and greater satisfaction with Social Roles and Activities. Score in adults (age >30 years) were not significantly different from those of the reference population. Mean Pain Intensity scores were .0 $\pm$ 1.8 in young adults (age 19 to 30 years) and -.4 $\pm$ 3.0 in adults (age >30 years) and were not significantly different than Dutch reference data.

PedsQL: Correlations

In children age 5 to 7 years, univariate robust linear regression analysis showed significantly higher scores on Total (B, 20; 95% confidence interval [CI], 8.7 to 32), Social Functioning (B, 22; 95% CI, 8.3 to 36) and Psychosocial Health (B, 16; 95% CI, 6.7 to 26) scores in the BMF group compared with the IEI group. Additionally, higher Social Functioning (B, 7.0; 95% CI, 3.7 to 10) and Psychosocial Health (B, 4.2; 95% CI, 1.8 to 6.7) scores were seen in children of older age at HSCT. In adolescents (age 13 to 17 years), lower Physical Health scores (B, -27; 95% CI, -38 to -16) were seen in females. In young adults (age 18 to 30 years), lower Social Functioning score (B, -1.2; 95% CI, -2.0 to -.37) were seen in patients of older age at HSCT. No significant differences were seen in children age 8 to 12 years (Supplementary Table S8).

PROMIS Item Banks: Correlations

Univariate linear regression analysis showed significantly better scores for males than for females on Fatigue (B, 5.9; 95% CI, 2.2 to 9.7), Pain Interference (B, 5.9; 95% CI, 2.6 to 9.2), and Mobility (B, -6.1; 95% CI, -10 to -2.1). Patients of older age at HSCT reported more Anxiety (B, .44; 95% CI, .13 to .75), Fatigue (B, .55; 95% CI, .18 to .92), and Pain Interference (B, .49; 95% CI, .16 to .81). Patients of older age at measurement reported more Anxiety (B, .30; 95% CI, .11 to .49) and Fatigue (B, .38;

Table 1
Demographic Characteristics by Diagnosis

Characteristic	Total (N = 119)	IEI* (N = 41)	HB† (N = 37)	BMF‡ (N = 41)	*P* Value
Male/female, n	*72/47*	30/11	21/16	21/20	.11
Age at first HSCT, yr, median (IQR)	*5.5 (2.0-11.0)*	2.4 (.9-5.2)	8.5 (3.5-12.1)	7.9 (3.5-11.3)	<.001
Age at baseline, yr, median (IQR)	*15.8 (10.6-22.3)*	15.9 (9.7-18.3)	16.3 (13.7-21.3)	14.6 (10.6-28.4)	.5
Follow-up duration, yr, median (IQR)	*8.7 (4.2-15.4)*	9.8 (7.2-15.5)	7.8 (3.4-12.6)	6.4 (3.6-17.2)	.12
Stem cell source, n					<.001
Bone marrow	*101*	27	34	40	
Peripheral blood stem cells	*10*	7	2	1	
Cord blood	*7*	7	0	0	
Bone marrow and cord blood	*1*	0	1	0	
Donor relation, n					.037
Matched related donor	*44*	9	15	20	
Unrelated donor	*61*	28	15	18	
Mismatched related donor	*14*	4	7	3	
Conditioning strategy, n					.012
Myeloablative conditioning	*112*	35	37	40	
Reduced-intensity conditioning	*7*	6	0	1	
Acute GVHD, n					.5
Grade 0-1	*109*	37	35	37	
Grade II	*4*	1	2	1	
Grade III	*6*	3	0	3	
cGVHD, n					.4
No GVHD	*104*	37	31	36	
Limited	*6*	1	4	1	
Extensive	*9*	3	2	4	
Multiple HSCTs, n	*15*	5	9	1	.054
Country of birth: The Netherlands, n (%)§	*64 (60)*	28 (78)	4 (12)	32 (86)	<.001
Unknown	*12*	5	3	4	
Education level, n (%)¶					.017
High	*36 (34)*	16 (44)	5 (15)	15 (41)	
Intermediate	*48 (45)*	15 (42)	16 (47)	17 (46)	
Low	*23 (21)*	5 (14)	13 (38)	5 (14)	
Unknown	*12*	5	3	4	
Paid employment, n (%)¶	*87 (82)*	32 (91)	22 (65)	33 (89)	.006
Unknown	*13*	6	3	4	
Marital status, n (%)¶					.5
Married or living together	*75 (70)*	23 (64)	24 (71)	28 (76)	
Single/separated/widowed	*32 (30)*	13 (36)	10 (29)	9 (24)	
Unknown	*12*	5	3	4	

In the event of multiple HSCTs, the conditioning regimen for the first HSCT is reported.

* Conditioning regimens: no conditioning, n = 1; busulfan-based, n = 24; treosulfan-based, n = 16.

† Conditioning regimens: busulfan-based, n = 7; treosulfan-based, n = 29; cyclophosphamide + low-dose total body irradiation/thoracoabdominal irradiation, n = 1.

‡ Conditioning regimens: busulfan-based, n = 9; treosulfan-based, n = 4; cyclophosphamide-based, n = 20; cyclophosphamide + low-dose total body irradiation/thoracoabdominal irradiation, n = 6; fludarabine-based, n = 2.

§ Children age <18 years were considered Dutch if at least 1 caregiver reported The Netherlands as their country of birth.

¶ For children age <18 years, caregivers' sociodemographic data were used. The highest educational level from both caregivers was selected. Paid employment was categorized if at least 1 caregiver had paid employment.

Table 2
Mean Difference Scores Compared with the Dutch General Population (PedsQL 4.0)

Domain	Age 5-7 yr (N = 15), mean Δ (95% CI)	d	Age 8-12 yr (N = 20), mean Δ (95% CI)	d	Age 13-17 yr (N = 35), mean Δ (95% CI)	d	Age 18-30 yr (N = 36), mean Δ (95% CI)	d
Total score	-7.72 (-14.66 to -.77)	-.13	-2.41 (-7.36 to 2.55)	-.04	**-8.70 (-14.15 to -3.25)**	-.14	-.91 (-5.47 to 3.66)	-.01
Physical health	-14.17 (-26.18 to -2.17)	-.14	-3.06 (-7.44 to 1.33)	-.06	**-13.43 (-20.04 to -6.81)**	-.17	-3.31 (-9.50 to 2.88)	-.04
Emotional functioning	4.40 (-3.26 to 12.06)	.07	-1.92 (-8.83 to 4.99)	-.02	-3.94 (-10.82 to 2.93)	-.05	2.33 (-3.40 to 8.06)	.03
Social functioning	-8.06 (-16.04 to -.06)	-.12	4.76 (-2.02 to 11.54)	.06	-3.08 (-9.48 to 3.33)	-.04	2.83 (-1.93 to 7.59)	.04
School/work functioning	-9.15 (-15.37 to -2.93)*	-.17	-9.02 (-16.57 to -1.47)	-.11	**-11.55 (-18.61 to -4.49)**	-.14	-4.03 (-9.95 to 1.88)	-.05
Psychosocial health	-4.27 (-10.05 to 1.51)	-.09	-2.06 (-8.07 to 3.95)	-.03	-6.19 (-11.81 to -.58)	-.09	.38 (-4.02 to 4.77)	.01

d indicates Cohen d; $P < .008$ (Bonferroni correction).

* Cronbach α coefficient <.6.

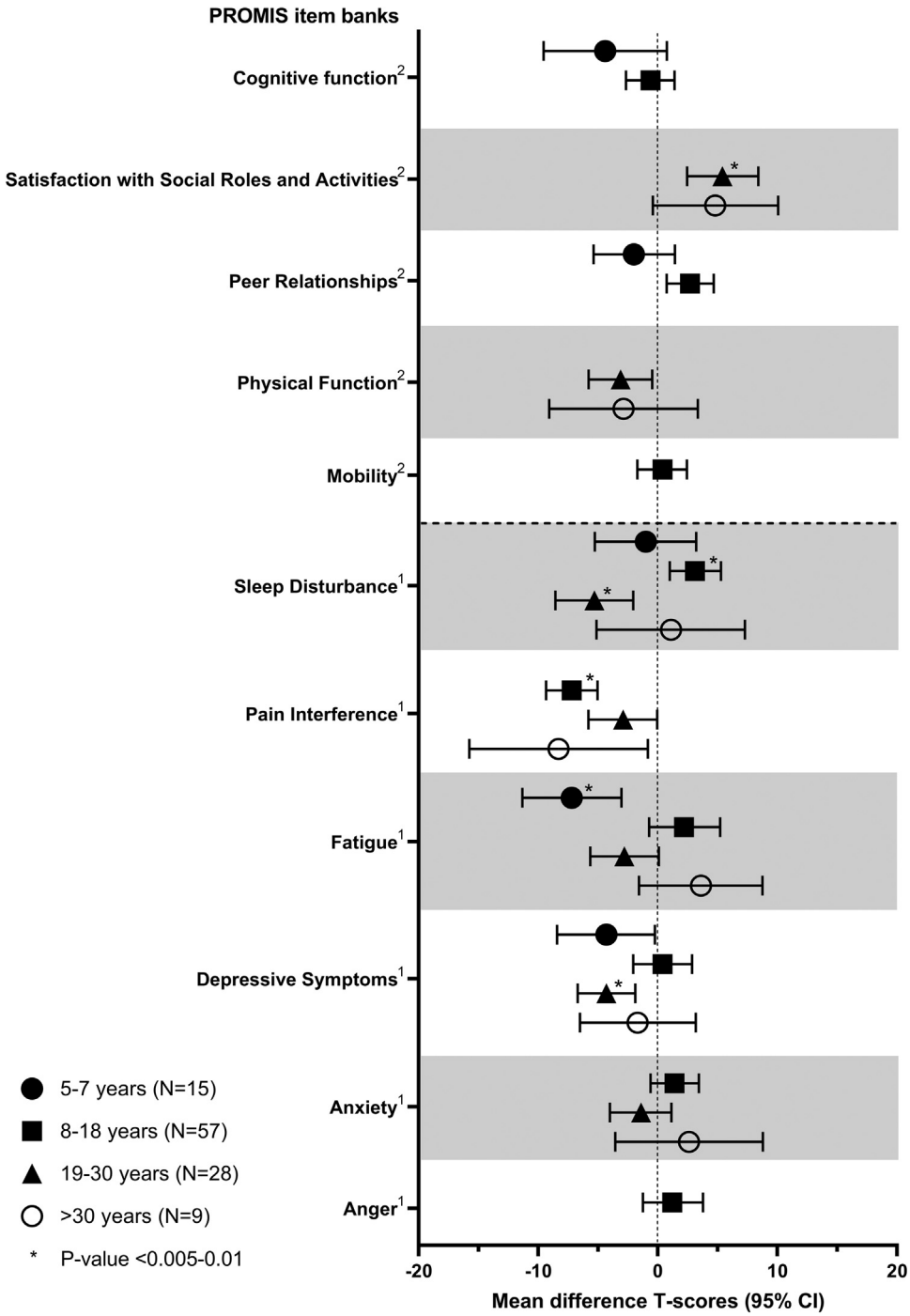

Figure 2. Mean difference scores compared to the Dutch general population (PROMIS item banks). [1]Higher scores indicate more symptoms; [2]higher scores indicate better functioning.

95% CI, .17 to .58) (Tables 3 and 4). Multivariate regression analysis showed no correlations (Supplementary Table S9).

DISCUSSION

Our study provides insight into the long-term PROs after pediatric HSCT for nonmalignant diseases. This study compared PedsQL and PROMIS outcome data to scores of the general population. Remarkably, in contrast to our hypothesis, we observed better or comparable HRQoL scores in, mostly, (young) adults after HSCT compared to the reference population. Previous research on long-term overall HRQoL has shown mixed findings, with some studies reporting comparable HRQoL to reference data [6,35-38] and others reporting impaired HRQoL [7,8,39]. However, these studies differ in their selection of PROMs, duration of follow-up, and indications for HSCT (malignant and nonmalignant diseases), which must be considered when comparing results.

This study has several strengths. Two different PROMs were used, which strengthens outcome reports and is unique in this research setting. An overall HRQoL view is provided by PedsQL, and a more in-depth view is provided by the use of PROMIS item banks with the use of different

Table 3
Univariate Linear Regression Analysis for PROMIS Item Banks

Covariate	Anger*		Anxiety*		Depressive Symptoms*		Fatigue*		Sleep Disturbance*		Pain Interference*	
	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)
Age group			93		109		108		107		93	
5-7 yr		–		–		Reference		Reference		Reference		–
8-18 yr		–		Reference		-.6 (-5.2 to 4.1)		-.8 (-6.3 to 4.7)		1.5 (-3.2 to 6.1)		Reference
19-30 yr		–		**5.4 (2.0 to 8.8)**		2.1 (-3.0 to 7.3)		4.4 (-1.7 to 10)		-3.8 (-8.9 to 1.3)		5.2 (1.5 to 8.9)
>30 yr		–		**8.5 (3.2 to 14)**		3.5 (-3.3 to 10)		11 (3.0 to 19)		2.3 (-4.4 to 9.1)		3.7 (-2.0 to 9.5)
Sex	56		93		109		108		107		93	
Male		Reference		Reference		Reference		Reference		Reference		Reference
Female		1.0 (-4.3 to 6.2)		3.6 (.4 to 6.8)		3.2 (.1 to 6.3)		**5.9 (2.2 to 9.7)**		1.5 (-1.7 to 4.8)		**5.9 (2.6 to 9.2)**
Diagnosis	56		93		109		108		107		93	
IEI		Reference		Reference		Reference		Reference		Reference		Reference
HB		-2.2 (-8.4 to 4.0)		2.6 (-1.4 to 6.7)		-.0 (-4.0 to 3.9)		3.8 (-1.0 to 8.6)		1.3 (-2.7 to 5.4)		4.8 (.6 to 9.0)
BMF		-1.9 (-8.0 to 4.2)		3.1 (-.8 to 7.0)		.2 (-3.4 to 3.9)		3.5 (-1.0 to 8.0)		.9 (-2.8 to 4.6)		2.6 (-1.4 to 6.6)
Age at first HSCT	56	.2 (-.4 to .7)	93	**.4 (.1 to .8)**	109	.3 (-.0 to .6)	108	**.6 (.2 to .9)**	107	-.1 (-.4 to .2)	93	**.5 (.2 to .8)**
Age at baseline	56	.22 (-.6 to 1.1)	93	**.3 (.1 to .5)**	109	.2 (-.0 to .3)	108	**.4 (.2 to .6)**	107	-.10 (-.3 to.1)	93	.3 (.1 to .5)
Country of birth	46		83		99		98		97		83	
Netherlands		Reference		Reference		Reference		Reference		Reference		Reference
Other		-2.8 (-8.2 to 2.7)		-.9 (-4.4 to 2.6)		-2.4 (-5.6 to .7)		-2.1 (-6.2 to 2.1)		3.0 (-.3 to 6.4)		-.1 (-3.8 to 3.7)

P values differ owing to different numbers of items (Bonferroni): $P < .008$ for Anger, $P < .006$ for Anxiety, Depressive Symptoms, Fatigue, Sleep Disturbance, and Pain Interference.

* Higher scores indicate more symptoms.

Table 4
Univariate Linear Regression Analysis for PROMIS Item Banks

Covariate	Mobility*		Physical Function*		Peer Relationships*		Satisfaction with Social Roles and Activities*		Cognitive Function*	
	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)	N	B (95% CI)
Age group			36		71		36		66	
5-7 yr		–		–		Reference		–		Reference
8-18 yr		–		–		1.6 (-2.5 to 5.7)		–		3.8 (-.84 to 8.4)
19-30 yr		–		Reference		–		Reference		–
>30 yr		–		-2.9 (-8.4 to 2.6)		–		-3.1 (-8.9 to 2.6)		–
Sex	57		36		71		36		66	
Male		Reference		Reference		Reference		Reference		Reference
Female		**-6.1 (-10 to -2.1)**		-4.0 (-8.6 to .67)		-1.4 (-4.9 to 2.2)		.41 (-4.7 to 5.5)		1.7 (-2.3 to 5.7)
Diagnosis	57		36		71		36		66	
IEI		Reference		Reference		Reference		Reference		Reference
HB		-1.8 (-6.9 to 3.3)		-6.9 (-13 to -.77)		-.39 (-4.6 to 3.8)		-6.6 (-13 to -.17)		2.0 (-2.8 to 6.8)
BMF		-.24 (-5.3 to 4.8)		-3.7 (-9.2 to 1.9)		2.0 (-2.0 to 6.0)		-5.5 (-11 to .30)		.90 (-3.7 to 5.5)
Age at first HSCT	57	-.29 (-.76 to .19)	36	-.35 (-.80 to .10)	71	-.35 (-.74 to .04)	36	-.58 (-1.0 to -.14)	66	.16 (-.29 to .61)
Age at baseline	57	-.14 (-.85 to .57)	36	-.25 (-.63 to .13)	71	.00 (-.43 to .44)	36	-.22 (-.63 to .18)	66	.29 (-.23 to .81)
Country of birth	47		36		61		36		59	
Netherlands		Reference		Reference		Reference		Reference		Reference
Other		.81 (-3.7 to 5.4)		-5.5 (-11 to .31)		1.3 (-1.9 to 4.6)		-5.2 (-11 to 1.0)		3.0 (-1.1 to 7.1)

* Higher scores indicate better functioning.*P* values differ owing to different numbers of items (Bonferroni): $P < .008$ for Mobility, $P < .007$ for Physical Function, Peer Relationships, Satisfaction with Social Roles and Activities, and Cognitive Function.

PRO domains. Moreover, with PROMIS item banks, longitudinal follow-up over the course of life and international evaluation are possible. Second, the study has a high response rate (70%), a long duration of follow-up, and well-distributed age categories. Finally, the broad selection of PROs was based on international standards (International Consortium for Health Outcomes Measurement) and was aimed to provide an overview of HRQoL.

Children age 8 to 18 years showed the most varied HRQoL scores compared with the reference population. Poorer HRQoL was seen for Physical Health in adolescents (age 13 to 17 years), whereas Mobility on the PROMIS item bank was comparable to that of the US reference population. Regression analysis was limited owing to our small sample size, and research on physical health in adolescents after pediatric HSCT is scarce, leaving the question of whether HSCT or disease characteristics could have influenced these results unanswered. In young adults, physical health varies, as noted by the review of Parsons et al. [35] that found low rates of functional loss and lowest physical health scores in mostly young adults, in contrast to our results, in which (young) adults seem to be thriving. School functioning was also significantly lower in adolescents (age 13 to 17 years), whereas cognitive functioning on the PROMIS item was not different than the US reference data. Differences in these PRO domains lie in questions about school absence at the PedsQL questionnaire, indicating more school absences due to illness or hospital visits compared with the reference data, whereas the PROMIS item bank is focused more on memory and reading comprehension. The comparable scores on cognitive functioning are in line with the current literature showing stable long-term cognitive functioning in pediatric HSCT survivors [35]. Finally, less pain interference was reported in children age 8 to 18 years, which differs from what has been reported for pediatric HSCT in mainly malignant diseases [7], indicating that pain interference is less present in HSCT survivors with nonmalignant diseases. Unfortunately, owing to the lack of reference data for the PedsQL Stem Cell Transplant subscale "Worry," a comparison with the general population was not possible; however, it is remarkable that adolescents (age 13 to 18 years) reported the lowest scores compared to other age groups, which is in line with the generic PedsQL 4.0 results.

Young adults (age 19 to 30 years) had less sleep disturbance compared to the reference population, whereas children age 8 to 18 years reported greater sleep disturbance. Little is known about sleep disturbances post-HSCT. Graef et al. [40] reported daytime sleepiness in 20% to 30% of pediatric HSCT survivors, a higher rate than seen in their reference population. However, this PROM is aimed at measuring daytime sleepiness, in contrast to the PROMIS item, which is focused more on falling asleep. Furthermore, it was hypothesized that multiple factors could have influenced sleep (eg, high-dose chemotherapy, total body irradiation, steroid use, GVHD, pulmonary condition, endocrine function) rather than a single factor [40]. In the general Dutch population, sleep disturbance has proven to not be unidimensional in children, adolescents, and young adults, which could explain the contradictory results reported in these age groups [33,41]. Young adults reported fewer depressive symptoms, in contrast to most studies of pediatric HSCT survivors [8,38]. The review of Di Giuseppe et al. (2020) found that depressive symptoms were more prevalent in pediatric HSCT survivors (malignant and nonmalignant diseases) compared with healthy children and pediatric cancer survivors who did not undergo HSCT [8]. This might indicate that HSCT itself has an impact on HRQoL, and that there might be a difference between HSCT survivors with malignant or nonmalignant disease. However, comparisons between these groups are difficult owing to differences in PROM use in these studies.

In both children age 5 to 7 years and adults age >30 years, HRQoL was comparable to that of the reference population. HRQoL research in adults (age >30 years) is very limited, because of the limited follow-up in most studies. Even though additional analysis was restricted owing to our small sample size, these data are promising for long-term HRQoL, in which adults seem to have adapted to their HSCT morbidity. In children age 5 to 7 years, even better scores were seen on PROMIS Fatigue, which has not been reported in the literature to date [5,7,8].

Regression analysis was restricted owing to our small sample size, in which we could control for confounding to only a limited extent. Therefore, we performed explorative analyses for correlations between HRQoL and HSCT, cGVHD, and disease characteristics. Overall, better HRQoL (PedsQL) was seen if patients were younger at HSCT, were male, or had BMF as the underlying disease. Similar results were seen on the PROMIS item banks Fatigue, Pain Interference, and Mobility compared with PedsQL data if patients were younger at HSCT or were male. Owing to a low incidence of post-HSCT complications in our cohort, statistical analysis of HRQoL and cGVHD was not possible. Multivariate analyses showed no correlation. In the Dutch general population, females report less favorable HRQoL than males [30,31]. In addition, female HSCT survivors have been shown to report lower physical health scores than males [42–44]. Younger age at HSCT was associated with better HRQoL, a result not previously reported in the literature. Previous studies have focused on age at measurement instead of age at HSCT. In young patients, HRQoL might not yet be impaired prior to HSCT. Greater well-being prior to intensive treatment could result into better long-term outcomes.

This study has some limitations. First, this is a single-center study in which most patients underwent HSCT before 2000. Most of these patients were referred to their healthcare professional closer to home, explaining the large number lost to follow-up. Owing to our small sample size and low prevalence of cGVHD, regression analysis was restricted. Second, during this study there were COVID restrictions, which could have affected the patients' overall well-being. Third, we did not measure HRQoL before HSCT; with a baseline measurement, associations with HSCT characteristics could be more evident. Fourth, Bonferroni correction was used to correct for multiple testing, possibly leading to an increase in type II errors. However, when looking at the 95% CIs of the PROMIS items, our main conclusions would not change. Finally, Dutch reference data are not yet available for some PROMIS item banks, mainly for the age category 2 to 4 years.

This is the first study that provides insight into long-term PROs in patients after HSCT in childhood for nonmalignant diseases. Surprisingly, we found better or comparable long-term PROs in patients after pediatric HSCT for nonmalignant diseases compared with the reference population. Moreover, this study provides the possibility for international comparisons and longitudinal follow-up for children and adults, and we recommend that future studies use an international adaptable PROM, such as PROMIS, to achieve this. More attention is needed for Physical Health, School Functioning, and Sleep Disturbance. Children and adolescents seem to be the most affected, indicating the need for supportive care to

prevent impaired quality of life and, more importantly, to amplify their long-term well-being. Moreover, these results offer the first evidence to empower these patients in their impressive resilience after high-intensity treatment. When evaluating HSCT outcome data, the overall well-being of patients should be evaluated, which includes HRQoL. Future application of PROs during and after HSCT treatment can be useful to timely initiate preventive or preemptive (para) medical support if needed; therefore, we recommend integrating PROs in standard HSCT care.

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Data availability: The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.12.024.

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