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RESEARCH ARTICLE

Long-term parental distress after pediatric hematopoietic stem cell transplantation for nonmalignant diseases

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Abstract

Background: Survival rates have continued to increase for pediatric hematopoietic stem cell transplantation (HSCT) for nonmalignant diseases. Despite the crucial role of caregivers in this high-intensity treatment, knowledge about long-term parental impact is lacking.

Procedure: This cross-sectional study assessed parental distress and everyday problems in parents of patients 2 years and older after pediatric HSCT for a nonmalignant disease using Distress Thermometer for Parents (DT-P), and compared outcomes to matched Dutch parents of healthy children and Dutch parents of children with a chronic condition (CC).

Results: Median follow-up was 5.3 years (interquartile range [IQR]: 2.9–8.6). Underlying diseases were inborn errors of immunity ($N = 30$), hemoglobinopathies ($N = 13$), and bone marrow failure ($N = 27$). Mothers of pediatric HSCT recipients ($N = 70$) reported comparable overall distress levels to mothers of healthy children, but experienced more distress related to parenting problems, specifically managing their child's emotions, discussing disease consequences, and fostering independence. Fathers of HSCT recipients ($N = 45$) reported higher overall distress levels and had more emotional distress compared to fathers of healthy children.

Conclusions: Overall, parental distress and everyday problems of parents of HSCT recipients are comparable to those of parents of children with CC. However, there is ongoing parental burden, both emotional and in parenting, long-term after HSCT compared to parents of healthy children, and the type of burden differs between mothers and fathers. These results indicate that individualized parental supportive care should not remain restricted to the acute hospitalization phase, but also be actively offered during long-term follow-up after pediatric HSCT.

KEYWORDS
hematopoietic stem cell transplantation, late effects, long-term follow-up, parental distress, parental outcomes, pediatric

Abbreviations: BMF, bone marrow failure; CC, chronic condition; COVID-19, coronavirus disease 2019; DT-P, Distress Thermometer for Parents; GvHD, graft-versus-host disease; HB, hemoglobinopathies; HSCT, hematopoietic stem cell transplantation; IEI, inborn errors of immunity.

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established curative treatment for an increasing number of patients with large variety of inherited or acquired nonmalignant diseases.[1] Survival rates have continued to increase by improving treatment and prevention of early transplant-related complications, such as infections and acute graft-versus-host disease (GvHD).[2] With the increasing number of pediatric HSCT patients surviving into adolescence and adulthood, insights into long-term outcomes of pediatric HSCT for nonmalignant diseases gain relevance. Despite the crucial role of caregivers in this high-intensity treatment, knowledge about long-term parental impact is lacking.

Pediatric HSCT is an intensive and high-impact treatment for patients as well as for their families.[3,4] Following hospitalization, the burden on the patient and family persists during the vulnerable recovery phase at home.[4] Parents have to provide both medical care and parental care, while attending to work, taking care of the family's financial situation, continuing societal participation, and maintaining familial relationships.[5,6] Over time, the (family-)environment gradually stabilizes and focus shifts toward long-term follow-up of HSCT and re-attending "normal life." However, due to (the risk of) persistence of disease manifestation, the occurrence of late effects, and life-long follow-up after HSCT, the burden on the patient and family may remain.

Outcomes of impact on caregivers of HSCT recipients have primarily been assessed in the setting of adult HSCT or childhood cancer.[7] However, the growing population of pediatric patients treated with HSCT for nonmalignant diseases, differs substantially from patients treated for malignant diseases with respect to health status (including comorbidity), health-related quality of life (HRQoL) pre HSCT, and applied conditioning regimens.[8,9]

To date, there are only few studies available on long-term parental outcomes after pediatric HSCT. High levels of parental distress have been reported, including parents experiencing anxiety, depressive symptoms, and burnout. Ongoing parental distress after pediatric HSCT could affect the societal participation of parents.[5] Moreover, ongoing parental distress could affect siblings as well.[5] These results stress the need for more insight into long-term parental outcomes after HSCT of the children during childhood in order to provide adequate supportive care, and finally improve quality of care for pediatric HSCT survivors.[10] Therefore, the aim of this study was to investigate the long-term parental distress in parents of children who received HSCT for a nonmalignant disease.

2 | METHODS

2.1 | Study design and participants

In this single-center cross-sectional study, parental distress was assessed in parents (or their legal guardians) of patients 2 years and older after pediatric HSCT for a nonmalignant disease in the Willem Alexander Children's Hospital at the Leiden University Medical Center, the Netherlands. Parents of patients aged less than 19 years at study enrollment were approached between December 2020 and November 2022. Exclusion criteria were an inadequate knowledge of the Dutch language. This study was approved by the Medical Ethical Committee Leiden—The Hague—Delft (N20.181). All participants gave written informed consent. If the patient's age was above 12 years, the patient's assent was also sought in addition to consent from (both) parents.

2.2 | Measures

The validated Distress Thermometer for Parents (DT-P) was used to assess parental distress and everyday problems.[11,12] The DT-P assesses overall distress using a thermometer score (scale range 0–10; score ≥4 indicates clinically elevated distress). Additionally, the DT-P assesses everyday problems regarding practical (seven items), social (four items), emotional (nine items), physical (seven items), cognitive (two items), and parenting domains (five items). Problem domain scores are the sum of the problem items (yes = 1, no = 0). A total problem domain score is the sum of all problem items.[11,12] Lastly, there are questions regarding perceived support from the social network, perceived lack of understanding from people concerning their situation, parental chronic illness, and whether or not the parent would like to talk to a professional about his or her situation. Internal reliability (Cronbach's alpha) of the DT-P ranges from .52 to .89.[11,12]

Parents completed a sociodemographic questionnaire about themselves (age, gender, country of birth, educational level, employment, marital status, number of children). Participants completed the questionnaires in the digital KLIK Patient-Reported Outcome Measure (PROM) portal (www.hetklikt.nu).[13] The DT-P was requested from both parents. If multiple DT-Ps were completed over time by a parent, the first completed DT-P was selected.

Patient characteristics obtained from their medical files were age, gender, date of birth, underlying disease, donor relation, date of HSCT, acute GvHD, chronic GvHD, and Lansky/Karnofsky performance score to quantify functional status of patients (scale range: 0 "unresponsive" to 100 "fully active, normal").[14] Underlying disease was divided into three groups: inborn errors of immunity (IEI; e.g., severe combined immunodeficiency), hemoglobinopathies (HB; e.g., sickle cell disease, thalassemia), and bone marrow failure (BMF; e.g., severe aplastic anemia, Blackfan Diamond anemia) disorders. Follow-up duration was categorized as long-term follow-up (2–5 years) and very long-term follow-up (>5 years).

2.3 | Statistical analysis

All statistical analyses were performed using R 4.1.3.[15] Propensity score matching on parents' sociodemographic characteristics was used to select matched controls from the Dutch normative data.[12,16] The Dutch normative data include parents of healthy children and parents of children with a chronic condition (CC).[12] DT-P outcomes of parents of HSCT recipients were compared to two groups: Dutch parents of healthy children and Dutch parents of children with CC.

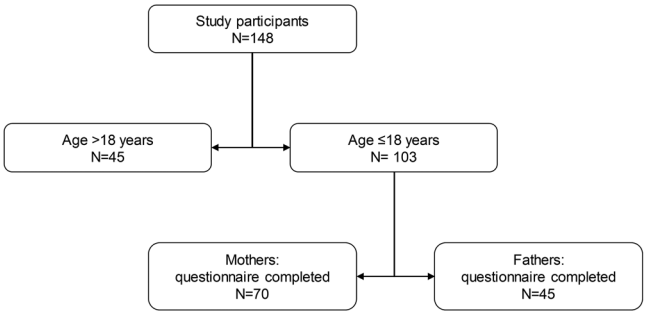

FIGURE 1 Flowchart of participants. All parents of pediatric hematopoietic stem cell transplantation (HSCT) recipients eligible for inclusion are shown.

Parent characteristics were compared to Dutch matched controls using Mann–Whitney *U* test, Pearson's chi-square test, or Fisher's exact test. DT-P (total) problem domain scores (Mann–Whitney *U* test), problem items, and additional questions (Pearson's chi-square test or Fisher's exact test) were compared to matched controls. Additionally, mothers and fathers of parent couples were compared: (total) problem domain scores (Wilcoxon signed-rank test), problem items, and additional questions (McNemar test). Lastly, long-term follow-up (2–5 years) and very long-term follow-up (>5 years) DT-P outcomes were compared: (total) problem domain scores (Mann–Whitney *U* test), problem items, and additional questions (Pearson's chi-square test). Statistically significant level was considered as *p*-values less than .05. With the aim of this study being to explore everyday problems of parents, Bonferroni correction was not applied to avoid type 2 errors.

3 | RESULTS

In total, 70 of 103 mothers (response rate 68%) and 45 of 103 fathers (response rate 44%) participated in this study (Figure 1). Reasons for not completing the DT-P were not assessed.

3.1 | Mothers of pediatric HSCT recipients compared to their controls

Compared to mothers of Dutch healthy controls, the children gender distribution differed significantly, with more males in the group of HSCT mothers (Table 1). In terms of nationality, a significantly lower percentage of mothers in the HSCT group were born in the Netherlands compared to the mothers of children with a CC (HSCT mothers 63%, controls [CC] 94%, $p < .001$). Median follow-up duration since HSCT was 5.3 years (interquartile range [IQR]: 2.9–8.6). Underlying diseases were IEI ($N = 30$), HB ($N = 13$), and BMF ($N = 27$) (Table 2).

Compared to mothers of healthy controls, HSCT mothers had comparable overall DT-P outcomes, except for parenting problems (Table 3). Mothers of pediatric HSCT recipients scored higher on the parenting problem domain score as well as on three parenting problem items: "dealing with the feelings of your child" (HSCT mothers 27%, controls 13%, $p = .035$), "talking about the disease/consequences with your child" (HSCT mothers 19.0%, controls 5.7%, $p = .020$), and "independence of your child" (HSCT mothers 23.0%, controls 7.1%, $p = .009$).

Compared to mothers of children with a CC, HSCT mothers had comparable overall DT-P outcomes, except for two problem items (Table 3). HSCT mothers reported less problems on the social problem item "interacting with your child(ren)" (HSCT mothers 10%, controls [CC] 29%, $p = .017$). However, HSCT mothers reported more problems on the emotional problem item "feeling tense or nervous" (HSCT mothers 53%, controls [CC] 33%, $p = .017$).

3.2 | Fathers of pediatric HSCT recipients compared to their controls

Compared to fathers of healthy parents, the children gender distribution differed significantly with more males in the group of HSCT fathers (Table 1). Regarding nationality, a significantly lower percentage of fathers in the HSCT group were born in the Netherlands compared to the fathers of children with a CC (HSCT fathers 60%, controls (CC) 98%, $p < .001$). Median follow-up duration since HSCT was 6.0 years (IQR: 3.1–8.7). Underlying diseases were IEI ($N = 18$), HB ($N = 13$), and BMF ($N = 14$ (Table 2).

Compared to fathers of healthy controls, HSCT fathers had comparable overall DT-P outcomes (Table 3). Fathers of pediatric HSCT recipients reported a higher frequency of clinically elevated distress (HSCT fathers 42%, controls 20%, $p = .023$). HSCT fathers scored higher on the emotional problem domain as well as on two emotional problem items: "depression" (HSCT fathers 40%, controls 20%, $p = .038$), "feeling tense or nervous" (HSCT fathers 49%, controls 20%, $p = .020$). Furthermore, HSCT fathers reported more problems on the practical problem item "leisure activities/relaxing" (HSCT fathers 36%, controls 11%, $p = .006$), psychical problem item "sleep" (HSCT fathers 42%, controls 22%, $p = .042$), and cognitive problem item "concentration" (HSCT fathers 33%, controls 13%, $p = .025$). HSCT fathers scored higher on the parental problem domain than their controls, but scores on the parenting problem items did not differ compared to controls. Additionally, HSCT fathers more often reported the desire to talk to a professional about their situation (HSCT father 24%, controls 8.9%, $p = .048$).

Compared to fathers of children with a CC, HSCT fathers had comparable overall DT-P outcomes, except for one problem item (Table 3). HSCT fathers reported less problems on the social problem item "interacting with your child(ren)" (HSCT fathers 11%, controls [CC] 29%, $p = .035$). Additionally, HSCT fathers reported less frequently of having an (chronic) illness themselves (HSCT fathers 18%, controls [CC] 40%, $p = .020$).

3.3 | Parent couples of pediatric HSCT recipients

In total 37 parent couples of pediatric HSCT recipients participated in this study (Table S1). Median age of mothers was 42.6 years (IQR: 37.4–46.5) and median age of fathers was 45.7 years (IQR: 40.4–49.8).

TABLE 1 Parents and their children who received HSCT: Matched controls on sociodemographic characteristics.

	Mothers					Fathers				
	HSCT *N* = 70	Control (healthy children) *N* = 70	*p*	Control (CC) *N* = 70	*p*	HSCT *N* = 45	Control (healthy children) *N* = 45	p	Control (CC) *N* = 45	*p*
Parents										
Age in years, median (IQR)	42.2 (37.1–46.8)	42.6 (38.9–46.2)	.6	42.2 (38.3–45.3)	>.9	46.0 (40.3–49.8)	45.4 (40.4–48.3)	.7	45.4 (41.7–49.1)	.7
Born in the Netherlands, *N* (%)	44 (63%)	51 (73%)	.2	66 (94%)	<.001	27 (60%)	28 (62%)	.8	44 (98%)	<.001
Education level, *N* (%)			.9		.3			.7		.7
High	31 (44%)	28 (40%)		29 (41%)		21 (47%)	25 (56%)		18 (40%)	
Intermediate	29 (41%)	32 (46%)		36 (51%)		19 (42%)	15 (33%)		20 (44%)	
Low	10 (14%)	10 (14%)		5 (7.1%)		5 (11%)	5 (11%)		7 (16%)	
Paid employment, *N* (%)	48 (69%)	51 (73%)	.6	52 (74%)	.5	36 (80%)	35 (78%)	.8	42 (93%)	.063
Marital status, *N* (%)			.8		>.9			>.9		.6
Married or living together	60 (86%)	62 (89%)		61 (87%)		44 (98%)	44 (98%)		42 (93%)	
Single/separated/widow	10 (14%)	8 (11%)		9 (13%)		1 (2.2%)	1 (2.2%)		3 (6.7%)	
Number of children, *N* (%)			.4		.3			.3		.7
1	15 (21%)	18 (26%)		12 (17%)		8 (18%)	10 (22%)		5 (11%)	
2	31 (44%)	35 (50%)		40 (57%)		20 (44%)	25 (56%)		21 (47%)	
≥3	24 (34%)	17 (24%)		18 (26%)		17 (38%)	10 (22%)		19 (42%)	
Child										
Age in years, median (IQR)	10.9 (7.6_15.3)	11.2 (7.4–15.4)	>.9	9.6 (6.6–14.7)	.4	10.6 (7.7–14.6)	10.5 (6.8–14.5)	.5	13.2 (7.9–16.1)	.2
Male gender, *N* (%)	50 (71%)	30 (43%)	<.001	43 (61%)	.2	31 (69%)	21 (47%)	.033	29 (64%)	.7

Note: $p < .05$. Educational level, highest educational level completed (low: primary education, lower vocational education, lower or middle general secondary education; intermediate: middle vocational education, higher secondary education, pre-university education; high: higher vocational education, university).

Abbreviations: CC, children with a chronic condition; HSCT, hematopoietic stem cell transplantation.

TABLE 2 HSCT characteristics of children of participating parents.

	Mothers $N = 70$	Fathers $N = 45$
Child		
Age at HSCT in years, median (IQR)	3.4 (1.5–7.5)	3.1 (1.6–7.2)
Years since HSCT, median (IQR)	5.3 (2.9–8.6)	6.0 (3.1–8.7)
2–5 years since HSCT	33 (47%)	18 (40%)
>5 years since HSCT	37 (53%)	20 (60%)
Underlying disease		
Inborn errors of immunity	30 (43%)	18 (40%)
Hemoglobinopathies	13 (19%)	13 (29%)
Bone marrow failures	27 (39%)	14 (31%)
2nd HSCT	6 (8.6%)	7 (16%)
aGVHD		
Grade 0–I	58 (33%)	40 (89%)
Grade II–III	12 (17%)	5 (11%)
cGVHD		
Limited	4 (5.7%)	3 (6.7%)
Extensive	5 (7.1%)	2 (4.4%)
Donor relation		
Matched related donor	19 (27%)	11 (24%)
Mismatched related donor	5 (7.1%)	6 (13%)
Unrelated donor	46 (66%)	28 (62%)
Lansky/Karnofsky performance score (range 0–100), mean (SD)	97.1 (6.9)	97.1 (7.1)
Lansky/Karnofsky performance score (range 0–100), *N* (%)		
70	2 (3.2%)	2 (4.8%)
80	2 (3.2%)	0 (0.0%)
90	8 (13%)	6 (14%)
100	50 (81%)	34 (81%)
Unknown	8	3

Abbreviations: aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.

Twenty-five mothers (68%) and 29 (78%) fathers had paid employment. Median follow-up duration since HSCT was 6.0 years (IQR: 3.0–8.8). Underlying diseases were IEI ($N = 14$), HB ($N = 6$), and BMF ($N = 17$) (Table S2). Overall, DT-P outcomes from mothers were comparable to fathers, except for parenting problems (Table S3). Mothers scored higher on the parenting problem domain score, as well as the parenting problem item "dealing with the feelings of your child" compared to fathers (mothers 35%, fathers 11%, $p = .016$).

3.4 | Long-term outcome compared to very long-term outcome: Mothers of pediatric HSCT recipients

Mothers of pediatric HSCT recipients ($N = 70$) were categorized into long-term follow-up (2–5 years post HSCT, $N = 33$) and very long-term follow-up (>5 years post HSCT, $N = 37$) (Table S4). Mothers with very long-term follow-up were significantly less often married or living together than mothers with long-term follow-up (long-term 97.0%, very long-term 76.0%, $p = .015$). Children of mothers in the very long-term follow-up group had a lower age at HSCT (long-term 5.5 years, very long-term 1.8 years, $p = .002$), and more often had IEI as HSCT indication (Table S4). Overall, DT-P outcomes between mothers with long-term and very long-term follow-up were comparable except for two emotional problem items (Table S5). Mothers with very long-term follow-up showed more problems with the emotional problem item "self-confidence" (long-term 8.1%, very long-term 30%, $p = .017$) and "fears" (long-term 14%, very long-term 33%, $p = .049$).

3.5 | Long-term outcome compared to very long-term outcome: Fathers of pediatric HSCT recipients

Fathers of pediatric HSCT recipients ($N = 45$) were categorized into long-term follow-up (2–5 years post HSCT, $N = 18$) and very long-term follow-up (>5 years post HSCT, $N = 27$) (Table S4). Child's median age at HSCT and IEI showed similar patterns as for the mothers (Table S4). Overall, DT-P outcomes between fathers with long-term and very long-term follow-up were comparable except for the problem item "finances/insurance" (long-term 33%, very long-term 0%, $p = .002$) (Table S5).

4 | DISCUSSION

This study aimed to investigate the long-term parental distress and everyday problems in parents of children who received HSCT for a nonmalignant disease. Mothers and fathers of pediatric HSCT recipients were compared to matched controls from the Dutch general population, including parents of healthy children and parents of children with a CC. This study revealed that overall, parental distress and everyday problems from parents of children who received HSCT were comparable to those of parents of children with a CC. However, when compared to parents of healthy children, there were indicators of long-term parental distress after pediatric HSCT, specifically regarding the emotional and parenting domain. Unique in this study is the use of Dutch matched controls to separately compare the outcomes of mothers and fathers of pediatric HSCT recipients. Previous studies, which focused primarily on mothers, often lacked control groups. Additionally, existing literature tends to focus on specific parental outcomes such as anxiety, depressive symptoms, and post-traumatic stress symptoms.[3,10,17–19] The validated DT-P used in this study is aimed to identify distress and everyday problems in parents, and provides a broader perspective on parental outcomes after pediatric HSCT.

Mothers of pediatric HSCT recipients showed more parenting-related problems compared to mothers of healthy children. In the parenting domain, mothers showed problems with their child's autonomy and experienced difficulties in dealing with their child's emotions,

TABLE 3 Parental distress outcomes: Parents of pediatric HSCT recipients matched with controls on sociodemographic characteristics.

	Mothers					Fathers				
	HSCT $N = 70$	Control (healthy children) $N = 70$	p	Control (CC) $N = 70$	p	HSCT $N = 45$	Control (healthy children) $N = 45$	p	Control (CC) $N = 45$	p
Thermometer score (0–10)										
Median (IQR)	4.00 (1.00–5.75)	4.00 (2.00–7.00)	.3	3.50 (2.00–7.00)	.2	3.00 (1.00–5.00)	2.00 (1.00–3.00)	.13	4.00 (1.00–7.00)	.2
Clinical (score ≥4), *N* (%)	39 (56%)	36 (51%)	.6	35 (50%)	.5	19 (42%)	9 (20%)	.023	24 (53%)	.3
Total problem scores, median (IQR)	6.50 (1.00–12.75)	6.00 (2.00–8.75)	>.9	6.00 (2.00–12.00)	>.9	6.00 (0.00–12.00)	2.00 (1.00–6.00)	.14	5.00 (1.00–12.00)	.9
Practical problems, median (IQR)	0.50 (0.00–2.00)	1.00 (0.00–2.00)	.7	1.00 (0.00–2.00)	.8	0.00 (0.00–2.00)	0.00 (0.00–1.00)	.2	1.00 (0.00–2.00)	.7
Housing, %	4 (5.7%)	3 (4.3%)	>.9	6 (8.6%)	.5	5 (11%)	3 (6.7%)	.7	0 (0%)	.056
Work/study, %	14 (20%)	19 (27%)	.3	15 (21%)	.8	13 (29%)	12 (27%)	.8	10 (22%)	.5
Finances/insurance, %	11 (16%)	10 (14%)	.8	9 (13%)	.6	6 (13%)	4 (8.9%)	.5	7 (16%)	.8
Housekeeping, %	13 (19%)	15 (21%)	.7	21 (30%)	.11	6 (13%)	6 (13%)	>.9	4 (8.9%)	.5
Transport, %	4 (5.7%)	3 (4.3%)	>.9	3 (4.3%)	>.9	5 (11%)	4 (8.9%)	>.9	2 (4.4%)	.4
Childcare/child supervision, %	11 (16%)	4 (5.7%)	.056	12 (17%)	.8	2 (4.4%)	1 (2.2%)	>.9	5 (11%)	.4
Leisure activities/relaxing, %	28 (40%)	19 (27%)	.11	23 (33%)	.4	16 (36%)	5 (11%)	.006	12 (27%)	.4
Social problems, median (IQR)	0.00 (0.00–0.75)	0.00 (0.00–1.00)	.3	0.00 (0.00–1.00)	.071	0.00 (0.00–1.00)	0.00 (0.00–0.00)	.2	0.00 (0.00–1.00)	.2
Dealing with (ex)partner, %	11 (16%)	9 (13%)	.6	15 (21%)	.4	7 (16%)	4 (8.9%)	.3	8 (18%)	.8
Dealing with family, %	6 (8.6%)	14 (20%)	.053	9 (13%)	.4	4 (8.9%)	2 (4.4%)	.7	5 (11%)	>.9
Dealing with friends, %	6 (8.6%)	4 (5.7%)	.5	6 (8.6%)	>.9	2 (4.4%)	2 (4.4%)	>.9	1 (2.2%)	>.9
Interacting with your child(ren), %	7 (10%)	12 (17%)	.2	20 (29%)	.005	5 (11%)	3 (6.7%)	.7	13 (29%)	.035
Emotional problems, median (IQR)	1.00 (0.00–4.00)	2.00 (0.00–3.00)	>.9	1.00 (0.00–3.75)	.4	1.00 (0.00–4.00)	0.00 (0.00–2.00)	.034	1.00 (0.00–3.00)	.8
Controlling emotions, %	19 (27%)	23 (33%)	.5	19 (27%)	>.9	8 (18%)	8 (18%)	>.9	14 (31%)	.14
Self-confidence, %	13 (19%)	18 (26%)	.3	16 (23%)	.5	9 (20%)	5 (11%)	.2	7 (16%)	.6
Fears, %	16 (23%)	9 (13%)	.12	8 (11%)	.073	8 (18%)	3 (6.7%)	.11	6 (13%)	.6
Depression, %	23 (33%)	27 (39%)	.5	28 (40%)	.4	18 (40%)	9 (20%)	.038	14 (31%)	.4
Feeling tense or nervous, %	37 (53%)	34 (49%)	.6	23 (33%)	.017	22 (49%)	9 (20%)	.004	21 (47%)	.8
Loneliness, %	9 (13%)	9 (13%)	>.9	10 (14%)	.8	6 (13%)	3 (6.7%)	.5	6 (13%)	>.9
Feelings of guilt, %	12 (17%)	15 (21%)	.5	14 (20%)	.7	6 (13%)	6 (13%)	>.9	3 (6.7%)	.5
Use of substances (e.g., alcohol, drugs, and/or medication), %	4 (5.7%)	4 (5.7%)	>.9	1 (1.4%)	.4	3 (6.7%)	0 (0%)	.2	1 (2.2%)	.6
Intrusive/recurrent thoughts about a specific event, %	24 (34%)	21 (30%)	.6	19 (27%)	.4	12 (27%)	7 (16%)	.2	11 (24%)	.8

(Continues)

TABLE 3 (Continued)

	Mothers					Fathers				
	HSCT $N = 70$	Control (healthy children) $N = 70$	p	Control (CC) $N = 70$	p	HSCT $N = 45$	Control (healthy children) $N = 45$	p	Control (CC) $N = 45$	p
Physical problems, median (IQR)	1.00 (0.00–4.00)	2.00 (0.00–3.00)	.8	2.00 (0.00–4.00)	.6	1.00 (0.00–3.00)	1.00 (0.00–2.00)	.3	1.00 (0.00–3.00)	.7
Eating, %	11 (16%)	8 (11%)	.5	9 (13%)	.6	4 (8.9%)	1 (2.2%)	.4	3 (6.7%)	>.9
Weight, %	17 (24%)	20 (29%)	.6	22 (31%)	.3	6 (13%)	6 (13%)	>.9	10 (22%)	.3
Sleep, %	27 (39%)	25 (36%)	.7	27 (39%)	>.9	19 (42%)	10 (22%)	.042	11 (24%)	.074
Fatigue, %	40 (57%)	43 (61%)	.6	37 (53%)	.6	19 (42%)	17 (38%)	.7	23 (51%)	.4
Out of shape/condition, %	21 (30%)	20 (29%)	.9	24 (34%)	.6	12 (27%)	8 (18%)	.3	10 (22%)	.6
Pain, %	16 (23%)	19 (27%)	.6	25 (36%)	.095	12 (27%)	8 (18%)	.3	11 (24%)	.8
Sexuality, %	8 (11%)	11 (16%)	.5	7 (10%)	.8	6 (13%)	4 (8.9%)	.5	8 (18%)	.6
Cognitive problems, median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	.12	0.00 (0.00–1.00)	.5	0.00 (0.00–1.00)	0.00 (0.00–0.00)	.056	0.00 (0.00–1.00)	.5
Concentration, %	25 (36%)	17 (24%)	.14	20 (29%)	.4	15 (33%)	6 (13%)	.025	12 (27%)	.5
Memory, %	23 (33%)	18 (26%)	.4	23 (33%)	>.9	13 (29%)	8 (18%)	.2	11 (24%)	.6
Parenting problems, median (IQR)	0.00 (0.00–2.00)	0.00 (0.00–0.00)	.009	0.00 (0.00–2.00)	.8	0.00 (0.00–1.00)	0.00 (0.00–0.00)	.022	0.00 (0.00–2.00)	>.9
Dealing with your child, %	9 (13%)	9 (13%)	>.9	16 (23%)	.12	7 (16%)	3 (6.7%)	.2	9 (20%)	.6
Dealing with the feelings of your child, %	19 (27%)	9 (13%)	.035	18 (26%)	.8	6 (13%)	3 (6.7%)	.5	9 (20%)	.4
Talking about the disease/consequences with your child, %	13 (19%)	4 (5.7%)	.020	8 (11%)	.2	6 (13%)	3 (6.7%)	.5	3 (6.7%)	.5
Independence of your child, %	16 (23%)	5 (7.1%)	.009	15 (21%)	.8	8 (18%)	3 (6.7%)	.11	7 (16%)	.8
Following advice about treatment/giving medication, %	4 (5.7%)	3 (4.3%)	>.9	8 (11%)	.2	5 (11%)	3 (6.7%)	.7	7 (16%)	.5
Additional questions										
Enough support from surroundings, %	60 (86%)	64 (91%)	.3	54 (77%)	.2	39 (87%)	43 (96%)	.3	35 (78%)	.3
People react with a lack of understanding, %	13 (19%)	10 (14%)	.5	17 (24%)	.4	8 (18%)	4 (8.9%)	.2	15 (33%)	.091
Do you have (chronic) illness yourself, %	16 (23%)	16 (23%)	>.9	24 (34%)	.13	8 (18%)	6 (13%)	.6	18 (40%)	.020
Would like to talk to a professional about situation—yes/maybe, %	18 (26%)	15 (21%)	.6	19 (27%)	.8	11 (24%)	4 (8.9%)	.048	14 (31%)	.5

Abbreviations: CC, children with a chronic condition; HSCT, hematopoietic stem cell transplantation.

which is in line with a qualitative study in parents of leukemia survivors.[5] In the study by Forinder (2004), parents expressed concerns on their child's psychosocial situation, such as the fear of their child feeling isolated or not belonging. Consequently, the natural process of child–parent independency became challenging and may also be applicable in parents of pediatric HSCT recipients.[5] Furthermore, mothers of pediatric HSCT recipients had more difficulties talking about the disease and its consequences with their child, as described in qualitative studies.[20,21] These studies report that due to the intensive nature of HSCT, looking back at the treatment and conversations about (possible) consequences of the disease can be emotional, painful, and therefore often avoided.[21] Other factors, such as the child's preference not to talk about their health status or the avoidance of certain topics, such as fertility, due to the child's age or to prevent deception, may contribute to these difficulties.[22] Additionally, with the divers nationalities of HSCT parents and the prevalence of different underlying diseases among various ethnicities, certain topics and diseases may be stigmatized.[23–25] The parenting problems in HSCT mothers were comparable to those of mothers of children with CC. Interestingly, HSCT mothers reported feeling more tense or nervous compared to mothers of children with CC, but the results were similar when compared to mothers of healthy controls. The difference in the Dutch reference data, where parents of healthy controls reported feeling more tense or nervous compared to parents of children with a CC, remains unknown.[12] These elevated levels of emotional distress, even very long-term after the treatment, emphasize the importance of implementing targeted interventions to sustain and enhance the emotional well-being of parents. Ultimately, this will lead to an improved quality of life for the pediatric patient.[26]

Fathers of pediatric HSCT recipients showed more emotional problems, such as feeling tense or nervous and depression, compared to fathers of healthy children. While higher rates of depression have been described in previous literature, the focus has primarily been on mothers of HSCT recipients.[17] Additionally, fathers of pediatric HSCT recipients faced more difficulties in leisure activities/relaxing, sleep, and concentration compared to controls, which has not yet been described in the literature. These factors, combined with the clinically elevated stress and the desire to talk to a healthcare professional, suggest that there may be insufficient support for fathers of HSCT recipients. Given the traditional gender roles and expectations related to parenting, where mothers often bear the primary responsibility for caregiving and emotional support, it is crucial to acknowledge that fathers also face unique challenges and may require targeted support to address their specific needs and concerns.

An additional unique element in this study is the analysis comparing parental outcomes within parent couples. When comparing mothers to fathers within parent couples, mothers reported more difficulties in dealing with their child's emotions. Ideally, such a parent-couple analysis would have been performed in our Dutch matched control group, but it was not possible as parent couples were not included in the Dutch normative dataset.[12]

Previous studies have shown a decrease in parental distress over time following HSCT.[27–29] Therefore, an additional analysis was performed to explore parental outcome differences between long-term (2–5 years) and very long-term (>5 years) follow-up duration after HSCT. Regarding the problems that previously showed significant differences from the Dutch matched controls (parenting and emotional problems), no differences were found between long-term and very long-term follow-up duration. However, mothers showed more problems with self-confidence and fears over time, which is in line with previous studies. In Forinder's study (2004), parents experienced anxiety due to the uncertainty regarding the risk of late effects.[5] Parental anxiety may have also been heightened due to the coronavirus disease 2019 (COVID-19) pandemic and the associated restrictions. Furthermore, fathers of pediatric HSCT recipients reported fewer financial problems over time. Coping with finance and juggling work with childcare had been a known struggle for caregivers of patients after HSCT.[5] These results could be attributed to optimized work-related and financial support for families, aiming to reduce the psychosocial long-term impact of the HSCT treatment.

This study had several limitations. First, there was a relatively low response rate among fathers of pediatric HSCT recipients, which is similar to those of other studies on parental outcomes.[17] Second, the study was conducted during a period of COVID-19 restrictions, which may have influenced reporting of parental problems. For example, there were fewer opportunities for leisure activities during the pandemic. Third, the study did not correct for multiple testing. As the first study to assess everyday problems for parents after pediatric HSCT, we prioritized avoiding type 2 errors over type 1 errors. Fourth, we did not perform a pre-HSCT measurement of parental distress. Pre-existing parental distress that might have been impacted by the HSCT remains undetected. Lastly, a risk analysis on the child's HSCT characteristics and parental distress was not performed, because the parental outcomes were predominantly comparable to Dutch matched controls. Additionally, previous studies already showed that HSCT factors, such as the child's age, type of diagnosis, and current disease status, do not significantly influence parental stress.[17]

This study provides a broad view of long-term parental distress and everyday problems in parents after pediatric HSCT for nonmalignant diseases. Overall, parental distress and everyday problems of parents of a child after HSCT are comparable to those of parents of children with a CC. However, there is ongoing parental burden long-term after HSCT compared to parents of healthy children, and the type of burden differs between mothers and fathers. While supportive care (emotional and practical support) is actively offered during the acute phase of hospitalization for HSCT treatment, parents do not always utilize this additional care due to their different coping strategies during hospitalization. When their child's health improves and direct medical care involvement is reduced, parents have to re-attend their normal way of life. However, while the direct consequences of HSCT treatment are diminished, the need for parental supportive care may persist or emerge. Our findings underscore the importance of providing comprehensive support for parents throughout the different stages of the HSCT process, even in long-term follow-up programs. Targeted interventions that address the specific needs of mothers and fathers, such as coping strategies, emotional support, and practical assistance, are war-

ranted. Further research is needed to explore the individual needs of parents and other family members (e.g., siblings) of patients after pediatric HSCT for nonmalignant diseases. Lastly, a longitudinal approach to assess parental distress, including a measurement before HSCT, could provide more insights into the HSCT factors that can contribute to parental distress. This information is needed to improve supportive care and foster resilience in parents, and ultimately improve quality of life of the pediatric HSCT patients even long-term after treatment.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no relevant financial or non-financial conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-1826. doi:10.1056/NEJMra052638
2. Passweg JR, Baldomero H, Chabannon C, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. *Bone Marrow Transplant*. 2021;56(7):1651-1664. doi:10.1038/s41409-021-01227-8
3. Packman W, Weber S, Wallace J, Bugescu N. Psychological effects of hematopoietic SCT on pediatric patients, siblings and parents: a review. *Bone Marrow Transplant*. 2010;45(7):1134-1146. doi:10.1038/bmt.2010.74
4. West CH, Dusome DL, Winsor J, Rallison LB. Falling down the rabbit hole: child and family experiences of pediatric hematopoietic stem cell transplant. *Qual Health Res*. 2020;30(7):1125-1138. doi:10.1177/1049732320912410
5. Forinder U. Bone marrow transplantation from a parental perspective. *J Child Health Care*. 2004;8(2):134-148. doi:10.1177/1367493504041872
6. Koch A, Kozhumam AS, Seeler E, Docherty SL, Brandon D. Multiple roles of parental caregivers of children with complex life-threatening conditions: a qualitative descriptive analysis. *J Pediatr Nurs*. 2021;61:67-74. doi:10.1016/j.pedn.2021.03.017
7. Beattie S, Lebel S. The experience of caregivers of hematological cancer patients undergoing a hematopoietic stem cell transplant: a comprehensive literature review. *Psycho-Oncol*. 2011;20(11):1137-1150. doi:10.1002/pon.1962
8. Sullivan KM, Parkman R, Walters MC. Bone marrow transplantation for non-malignant disease. *Hematology Am Soc Hematol Educ Program*. 2000;2000(1):319-338. doi:10.1182/asheducation-2000.1.319
9. Dietz AC, Duncan CN, Alter BP, et al. The second pediatric blood and marrow transplant consortium international consensus conference on late effects after pediatric hematopoietic cell transplantation: defining the unique late effects of children undergoing hematopoietic cell transplantation for immune deficiencies, inherited marrow failure disorders, and hemoglobinopathies. *Biol Blood Marrow Transplant*. 2017;23(1):24-29. doi:10.1016/j.bbmt.2016.10.004
10. Norberg AL, Forinder U. Different aspects of psychological ill health in a national sample of Swedish parents after successful paediatric stem cell transplantation. *Pediatr Blood Cancer*. 2016;63(6):1065-1069. doi:10.1002/pbc.25908
11. Haverman L, van Oers HA, Limperg PF, et al. Development and validation of the distress thermometer for parents of a chronically ill child. *J Pediatr*. 2013;163(4):1140-1146.e2. doi:10.1016/j.jpeds.2013.06.011
12. van Oers HA, Schepers SA, Grootenhuis MA, Haverman L. Dutch normative data and psychometric properties for the Distress Thermometer for Parents. *Qual Life Res*. 2017;26(1):177-182. doi:10.1007/s11136-016-1405-4
13. Haverman L, van Oers HA, Limperg PF, et al. Implementation of electronic patient reported outcomes in pediatric daily clinical practice: the KLIK experience. *Clin Pract Pediatr Psychol*. 2014;2:50-67. doi:10.1037/cpp0000043
14. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer*. 1984;53(9):2002-2007. doi:10.1002/1097-0142(19840501)53:9⟨2002::aid-cncr2820530933⟩3.0.co;2-w
15. R: A language and environment for statistical computing. Version 4.1.3. 2022. R Foundation for Statistical Computing. https://www.R-project.org/
16. Kane LT, Fang T, Galetta MS, et al. Propensity score matching: a statistical method. *Clin Spine Surg*. 2020;33(3):120-122. doi:10.1097/bsd.0000000000000932
17. Vrijmoet-Wiersma CM, Egeler RM, Koopman HM, Norberg AL, Grootenhuis MA. Parental stress before, during, and after pediatric stem cell transplantation: a review article. *Support Care Cancer*. 2009;17(12):1435-1443. doi:10.1007/s00520-009-0685-4
18. Riva R, Forinder U, Arvidson J, et al. Patterns of psychological responses in parents of children that underwent stem cell transplantation. *Psycho-Oncol*. 2014;23(11):1307-1313. doi:10.1002/pon.3567
19. Nam GE, Warner EL, Morreall DK, Kirchhoff AC, Kinney AY, Fluchel M. Understanding psychological distress among pediatric cancer caregivers. *Support Care Cancer*. 2016;24(7):3147-3155. doi:10.1007/s00520-016-3136-z
20. Yeung NCY, Cheung KC, Chau HC, et al. Transition from acute treatment to survivorship: exploring the psychosocial adjustments of Chinese parents of children with cancer or hematological disorders. *Int J Environ Res Public Health*. 2021;18(15):7815. doi:10.3390/ijerph18157815
21. White TE, Hendershot KA, Dixon MD, et al. Family strategies to support siblings of pediatric hematopoietic stem cell transplant patients. *Pediatrics*. 2017;139(2):e20161057. doi:10.1542/peds.2016-1057
22. Lahaye M, Aujoulat I, Vermylen C, Brichard B. Long-term effects of haematopoietic stem cell transplantation after pediatric cancer: a qualitative analysis of life experiences and adaptation strategies. *Front Psychol*. 2017;8:704. doi:10.3389/fpsyg.2017.00704
23. Middleton J, Calam R, Ulph F. Communication with children about sickle cell disease: a qualitative study of parent experience. *Br J Health Psychol*. 2018;23(3):685-700. doi:10.1111/bjhp.12311
24. Thomas VJ, Taylor LM. The psychosocial experience of people with sickle cell disease and its impact on quality of life: qualitative findings from focus groups. *Br J Health Psychol*. 2002;7(3):345-363. doi:10.1348/135910702760213724
25. Wesley KM, Zhao M, Carroll Y, Porter JS. Caregiver perspectives of stigma associated with sickle cell disease in adolescents. *J Pediatr Nurs*. 2016;31(1):55-63. doi:10.1016/j.pedn.2015.09.011
26. Bakula DM, Sharkey CM, Perez MN, et al. The relationship between parent distress and child quality of life in pediatric cancer: a meta-analysis. *J Pediatr Nurs*. 2020;50:14-19. doi:10.1016/j.pedn.2019.09.024

27. Vrijmoet-Wiersma CM, Egeler RM, Koopman HM, Bresters D, Norberg AL, Grootenhuis MA. Parental stress and perceived vulnerability at 5 and 10 years after pediatric SCT. *Bone Marrow Transplant*. 2010;45(6):1102-1108. doi:10.1038/bmt.2009.309
28. Barrera M, Atenafu E, Doyle J, Berlin-Romalis D, Hancock K. Differences in mothers' and fathers' psychological distress after pediatric SCT: a longitudinal study. *Bone Marrow Transplant*. 2012;47(7):934-939. doi:10.1038/bmt.2011.206
29. Lindahl Norberg A, Mellgren K, Winiarski J, Forinder U. Relationship between problems related to child late effects and parent burnout after pediatric hematopoietic stem cell transplantation. *Pediatr Transplant*. 2014;18(3):302-309. doi:10.1111/petr.12228

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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