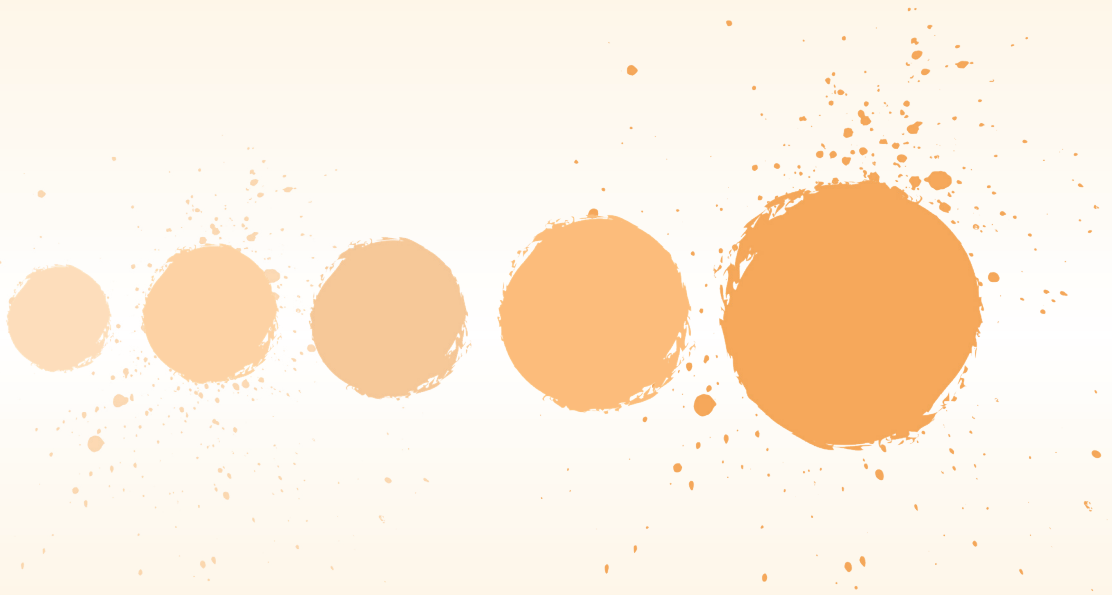
Patient-Centered Value-Based Healthcare in Long-term Follow-up after Pediatric Stem Cell Transplantation for Nonmalignant Diseases



Joëll E. Bense

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Colophon

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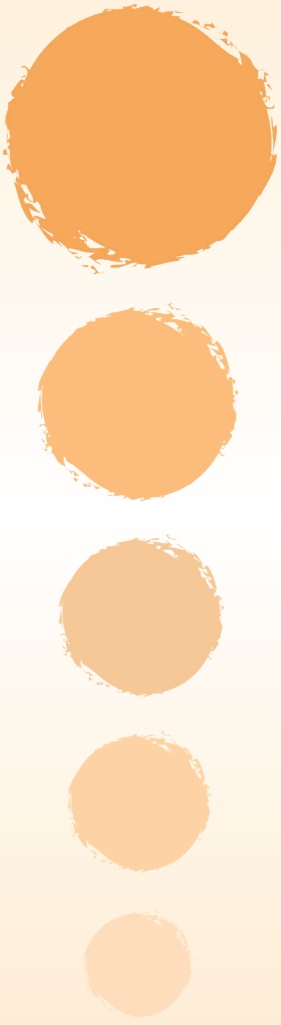

Chapter 1

General introduction

PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR NONMALIGNANT DISEASES

Allogeneic pediatric hematopoietic stem cell transplantation (HSCT) is an intensive, curative treatment for an increasing number of patients with nonmalignant diseases (1). HSCT is a high intensity treatment, in which conditioning regimens are required for achieving positive HSCT outcome (2). Conditioning regimens consists primarily of a combination of chemotherapy and immunosuppressants. Due to chemotherapy and immunosuppressants, children have (transiently) impaired immunity and are at risk for (severe) complications, such as organ toxicity and infections. In the setting of allogeneic HSCT there is a risk of graft versus host disease (GVHD), which itself, but also the treatment, could result in severe complications (1). Immune reconstitution takes several months or, in rare cases, even years, during which supportive care and restrictions due to impaired immunity are gradually phased out.

In the setting of nonmalignant diseases, the indications for HSCT include inborn errors of immunity (IEI), hemoglobinopathies (HB), and inherited and acquired bone marrow failure (BMF) disorders (3, 4). Some of these diseases are (acutely) life-threatening, while others are characterized by a chronic, progressive, and disabling life-shortening course and decreased quality of life. HSCT is aimed at curing hematologic and immunologic deficiencies. However, some nonmalignant diseases involve multiple organ systems. The non-hematologic or non-immunologic related deficiencies are still present, or could arise, after HSCT, as it would in non-transplanted patients, even if the hematopoietic system is fully replaced and become of health donor origin (5). The possible pre-existing disease manifestations could affect the HSCT procedure itself (e.g., drug choice in the presence of pre-existing renal impairment in sickle cell disease), as well as the post-transplant follow-up.

In the last decades advances in conditioning regimens, donor selection, and prophylaxis and treatment of infections and GvHD have resulted in improved survival (4, 6). With these advances, an increasing number of patients are being transplanted, or being considered for HSCT, while until recently they would receive conservative, non-curative therapy. Consequently, the long-term physical and psychosocial outcomes of HSCT are becoming increasingly important.

LATE EFFECTS: DEVELOPMENTS & SCREENING GUIDELINES

After pediatric HSCT late effects can arise, due to the HSCT procedure itself or due to the underlying disease (5). Knowledge of late effects is required to adjust treatment modalities to prevent or limit late effects, and to offer supportive care. To gain a better understanding of late effects, a screening follow-up program is in place at the

Leiden University Medical Center (LUMC). Patients transplanted in childhood for a nonmalignant disease enter this program from two years after HSCT onwards. Since late effects can also occur many years after pediatric HSCT, the follow-up program continues throughout adulthood. The Late Effects Comprehensive Care & Follow-up (LEEF) program annually screens patients for physical and mental health.

At the start of the LUMC follow-up program, the national screening guidelines of late effects after childhood cancer were used (7). However, HSCT for nonmalignant diseases differs substantially from HSCT for malignant diseases with respect to applied conditioning regimens. Further, patients differ in comorbidity, health status, and health related quality of life (HRQoL) pre-HSCT. Moreover, the underlying disease itself can be a predisposing factor for the occurrence (of severity) of late effects after HSCT. To provide adequate care, screening guidelines for pediatric HSCT for nonmalignant diseases are necessary. Currently, international guidelines are mostly expert-opinion-based rather than evidence-based, and are predominantly aimed at late effects of childhood cancer (7-9).

To establish an evidence-based screening guideline for pediatric HSCT for nonmalignant diseases research is essential. Current late effects research is mainly focused on clinical outcomes such as survival, immune reconstitution, chronic GvHD, growth, endocrine and gonadal dysfunction. However, to properly determine the late effects after this intensive treatment, study of patients' overall well-being is essential too, including HRQoL and psychosocial outcomes.

LATE EFFECTS COMPREHENSIVE CARE & FOLLOW-UP (LEEF) PROGRAM: PROVIDING OPTIMAL CARE

In addition to screening for late effects and looking at overall well-being, the Late Effects Comprehensive Care & Follow-up program is also aimed at providing optimal care, which is adjusted to patients' needs throughout life. Whether optimal care is provided should not solely be up to the healthcare professional (HCP), but should also be defined by the patient. Patient involvement in the development and evaluation of the LEEF program is therefore essential. Patients' healthcare perspectives and what is of importance to them, is fundamental to evaluate the value of the provided care.

VALUE-BASED HEALTHCARE

In recent years, the healthcare system has gradually moved towards a system of value-based healthcare (VBHC). With VBHC Porter and Teisberg seek to create value in healthcare by achieving the best possible outcomes that matter to people at the lowest cost (10). However, the implementation strategies of VBHC has faced

persistent challenges (11). Therefore, Porter and Lee created a strategic agenda and described six VBHC components: (1) organize into integrated practice units (IPUs), (2) measure outcomes and costs for every patient, (3) move to bundled payment for care cycles, (4) integrate care delivery across separate facilities, (5) expand excellent services across geography, and (6) build an enabling information technology platform (12).

While the relevance and necessity of VBHC have become increasingly evident in healthcare, the implementation of VBHC has proven to be a challenge (11, 13). Firstly, the definition of VBHC turns out to be open to interpretation and the strategic value agenda by Porter and Lee is incomplete (14-18). Van der Nat et al (2022) suggested to add four components to the existing VBHC components: (1) set up value-based quality improvement, (2) integrate value in patient communication, (3) invest in a culture of value delivery (education), and (4) build learning platforms for healthcare professionals (Figure 1) (19). Secondly, shared decision making (SDM) is often seen as part of the VBHC principles (14, 20). SDM is not emphasized in Porter's definition since the model is aimed at the patient group level and outcomes are used for benchmarking (10, 12). As stated by van der Nat et al (2022), when outcomes, such as clinical outcomes and PROMs, become a part of the conversation between the healthcare professional and patient, SDM and VBHC intersect (19). The authors assert, 'Experts in both fields advocate the use of PROMs and clinical outcomes in shared-decision making as an opportunity to strengthen value-based healthcare' (19). Thirdly, there is ambiguity regarding the inclusion of patient experiences in the VBHC principles. Teisberg et al (2020) stated not to see patient experiences as value, since VBHC focuses primarily on improving health outcomes, and perceives patient experiences as a result of the delivered care (21). A different point of view is presented by Chatterjee et al (2015), who showed better clinical process and outcomes measures through higher patient satisfaction scores (22). In addition, in the setting of VBHC, the Netherlands Federation of University Medical Centers (NFU) defined health outcomes as clinical outcomes (e.g. hormonal function, graft function, kidney function), patient-reported outcomes (e.g. physical function, sleep disturbance, cognitive function), and patient-reported experiences (23).

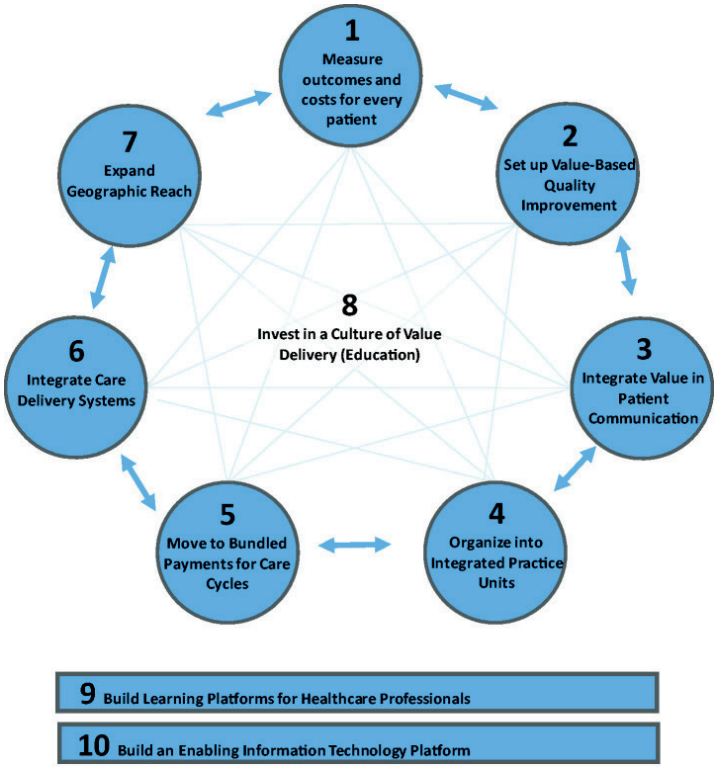

Figure 1. VBHC components: extended version by van der Nat et al (2022) (19)

Although there is no consensus on the definition of and implementation strategies for VBHC, it is evident that VBHC principles are increasingly being applied in current healthcare. With the aim of providing optimal care, the VBHC principles were implemented at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases. In our view, with an emphasis on the patient perspective, VBHC posits a combination of improved health outcomes through better processes of care, enhanced incorporation of patient experience, and optimal use of effort and costs (Figure 2).

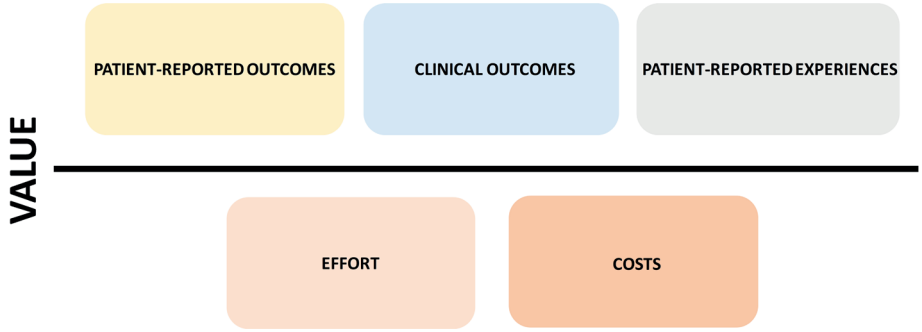

Figure 2. VBHC at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases

GAPS OF KNOWLEDGE

In 2018, the first steps towards a long-term follow-up program after pediatric HSCT for nonmalignant diseases at the LUMC had been taken which was based on guidelines and experiences of follow-up after childhood cancer (7). Currently, international screening programs and consensus on long-term follow-up after pediatric HSCT for nonmalignant diseases, including follow-up continuing into adulthood, are lacking. There is limited research in the field of late effects of pediatric HSCT for nonmalignant diseases, research predominantly has focused on late effects of childhood cancer (8, 9). However, knowledge on late effects is essential to adjust the screening guidelines for providing optimal care.

VBHC has predominantly been implemented in care paths aimed at managing acute or chronic diseases, with the primary goal of symptom control. Lessons learned from these care paths have been adapted to similar care paths. However, there is a lack of knowledge of VBHC implementation in care paths where the focus solely lies on screening, where active disease and symptoms are lacking. Additionally, there is no VBHC implementation experience in care paths involving multiple age categories, including children, adolescents, and adults.

When initiating VBHC in comprehensive care follow-up programs after pediatric HSCT for nonmalignant diseases, the need for accurately assessing the patient's overall well-being becomes more pressing. By integrating research into the VBHC initiation, the gap of knowledge on late effects and overall well-being in patients after this type of HSCT is addressed, while providing care of value.

AIM AND OUTLINE OF THIS THESIS

The first aim of this thesis was to evaluate the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric stem cell transplantation for nonmalignant diseases at the LUMC, regarding various late effects and health-related quality of life. The second aim was to implement and evaluate aspects of value-based healthcare at the LEEF program.

Part I of this thesis focuses on the long-term clinical outcomes of pediatric HSCT for nonmalignant diseases. At the beginning of this thesis a screening guideline for late effects of pediatric HSCT for nonmalignant diseases was developed and is described in **Chapter 2.** Integrated in this guideline are the endocrine late effects, which are described in **Chapter 3.**

Part II of this thesis focuses on patient-reported outcomes and patient-reported experiences in pediatric HSCT for nonmalignant diseases. **Chapter 4** describes the long-term psychosocial impact of this high-intensive treatment. Additionally, the long-term parental distress of parents of children transplanted is addressed in **Chapter 5**. Lastly, **Chapter 6** describes the long-term patient-reported outcomes of pediatric HSCT for nonmalignant diseases.

Part III of this thesis focuses on the implementation and evaluation of VBHC at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases. **Chapter 7** describes the value of value of using patient-reported outcomes for health screening during long-term follow-up after stem cell transplantation in children with nonmalignant diseases. Finally, **Chapter 8** addresses the lessons learned from the VBHC implementation at the LEEF program.

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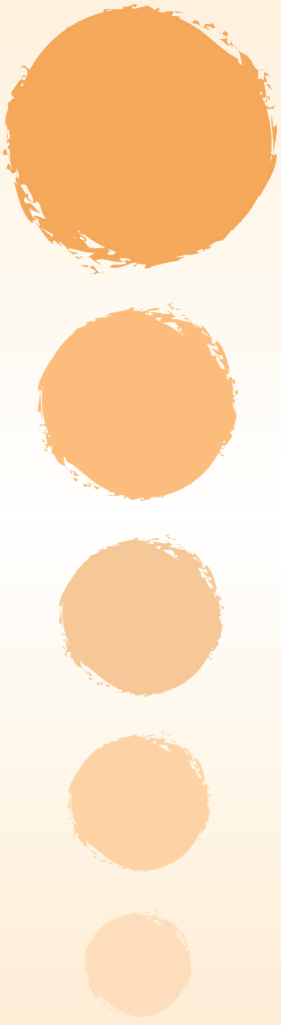

Chapter 2

Screening guideline for late effects after pediatric stem cell transplantation or cell therapy for nonmalignant diseases

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SUMMARY

Hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative treatment for various nonmalignant diseases, such as bone marrow failure, hemoglobinopathies, and immunologic disorders, particularly in pediatric patients. After the high-intensity clinical treatment and short-term outpatient follow-up, long-term follow-up is recommended, typically starting two years after HSCT. Successful long-term follow-up programs have been established in (pediatric) oncology, where HSCT is part of a broader treatment, such as the LATER and BETER outpatient clinics. However, follow-up after HSCT for nonmalignant diseases is often fragmented and lacks integration into a standardized care path, despite the similar intensive therapy and increased risk of long-term health effects. The (inter)national guidelines for Late Effects after childhood cancer are based on treatment modalities rather than underlying diseases. In patients with a nonmalignant indication for HSCT, the underlying disease itself may be a predisposing factor for the development or worsening of late effects after HSCT. Therefore, a new supplementary guideline has been developed for late effects follow-up after (pediatric) stem cell transplantation for nonmalignant diseases. The guideline provides screening recommendations for both children and adults, emphasizing lifelong care. Further research on late effects after HSCT with nonmalignant diseases is needed to optimize treatment and reduce or prevent late effects. Moreover, increased knowledge of these late effects will facilitate the optimization of post-treatment care and allow for tailored follow-up based on specific disease entities and treatment modalities.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is increasingly being used as a curative treatment for various nonmalignant diseases, such as bone marrow failure, hemoglobinopathies, and immunological disorders (1). Innovations in the prevention and treatment of acute complications, such as infections and graft-versus-host disease (GVHD), have led to increasing survival rates. Additionally, an increasing number of patients are being transplanted or considered for HSCT, even those who previously received conservative, non-curative therapies. With a growing population of HSCT survivors, long-term outcomes are becoming more relevant.

Following HSCT, patient receive outpatient monitoring for acute complications and evaluation immune recovery. However, patients are also at risk of long-term health effects (late effects). At the national expertise center in Leiden, long-term follow-up (figure 1) begins two years after treatment, implemented through a life-course approach according to value-driven care methodology. In this Late Effects & Comprehensive Care (LEEF) care path after HSCT, both physical and mental health are evaluated.

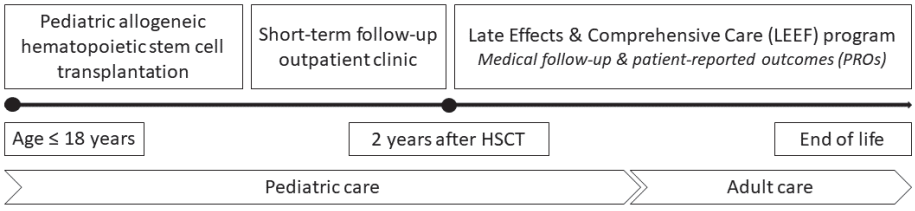

Figure 1. Late Effects & Comprehensive Care (LEEF) care path for pediatric stem cell transplantation

From the field of pediatric oncology, where HSCT can be part of broader treatment, several successful long-term follow-up programs have been established, such as the LATER and BETER clinics (2). However, follow-up after HSCT for nonmalignant diseases is often fragmented and not integrated into a standardized care path, despite the application of similar intensive therapies with an increased risk of long-term health effects. The (inter)national Late Effects guidelines for childhood cancer are based on treatment modalities rather than underlying diseases (2-18). In patients with a nonmalignant indication for HSCT, the underlying condition may be a predisposing factor for the development or worsening of late effects after HSCT. Therefore, a new additional guideline has been developed specifically for the follow-up of late effects after pediatric HSCT for nonmalignant diseases, which

has been approved by the Dutch pediatric hematology and pediatric infectious diseases-immunology sections. Table 1 provides an overview of the screening modules. To adapt follow-up recommendations from malignant to nonmalignant diseases, three articles were used that provide recommendations for follow-up after HSCT for bone marrow failure, hemoglobinopathies, and immune deficiencies (19-21). Additionally, literature research was conducted for each module. The guideline provides screening recommendations for both children and adults, thus focusing on life-course care. For complications from the original underlying disease, which are unrelated to the HSCT procedure, we refer to the guidelines for the specific underlying disease. In the current conditioning regimens for HSCT with nonmalignant diseases, radiotherapy is not routinely applied. For late effects due to other therapies used for nonmalignant HSCT diseases (such as anthracyclines, radiotherapy), we refer to the (inter)national Late Effects guidelines for childhood cancer (2-18). This article serves as an explanatory document for the follow-up guideline of late effects after pediatric stem cell transplantation or cell therapy with benign hematological, metabolic, or immunological diseases.

Table 1. Modules of the guideline for the follow-up of late effects after pediatric stem cell transplantation or cell therapy with benign hematological, metabolic, or immunological diseases.

Modules	Modules
General recommendations	Cardiovascular evaluation
Immune System: Spleen	Renal evaluation
Immune System: Graft function	Liver evaluation
Immune System: Vaccinations	Metabolic syndrome
Iron overload	Neurology evaluation
Endocrinology: Growth	Neurocognitive evaluation
Endocrinology: Thyroid function	Psychosocial and fatigue
Endocrinology: Female gonadal function	Audiology evaluation
Endocrinology: Male gonadal function	Ophthalmology evaluation
Endocrinology: Adrenal function	Oral health
Endocrinology: Bone health	Dermatology evaluation
Pulmonary evaluation	Secondary malignancies

ADOPTED RECOMMENDATIONS FROM (INTER)NATIONAL LATE EFFECTS GUIDELINES FOR CHILDHOOD CANCER

Certain recommendations from the (inter)national Late Effects guidelines for childhood cancer have been directly or mostly adopted for this guideline, and further elaboration is not provided in this article (2-18). These modules include the following:

general recommendations, thyroid, adrenal, cardiovascular, renal, liver, neurology, neurocognitive, audiology, ophthalmology, dermatology evaluation, oral health, and secondary malignancy.

IMMUNE SYSTEM: SPLEEN, GRAFT FUNCTION, VACCINATIONS

In the context of HSCT for pediatric cancer, a different approach applies to evaluating the immune system, and recommendations are only provided for evaluating spleen function. An effective functional test for splenic function is currently not available (21). Therefore, it is important to accurately define the risk groups with abnormal spleen function. It is stated that post-HSCT patients with pre-existing sickle cell disease should be considered functionally asplenic. For additional measures regarding asplenia, the working group refers to the National Coordination of Infectious Disease Control (LCI) guideline 'Asplenia' and the Dutch Pediatric Society (NVK) guideline 'Prevention of infections in people with (functional) hyposplenism and asplenia'.

In HSCT with a malignant disease, achieving 100% donor chimerism is important due to the required Graft-versus-Leukemia effect. In HSCT with a nonmalignant disease, the goal is also to achieve 100% donor chimerism, but depending on the HSCT indication, adequate outcomes can be achieved with <100% donor chimerism and adequate graft function. The late effects of mixed chimerism and the long-term course of chimerism are not yet known. Therefore, no risk groups are identified in the evaluation of graft function, and it is advised to screen everyone (standard laboratory tests: complete blood count, leukocyte differentiation, immunoglobulin G, A, and M; additional laboratory tests: chimerism, lymphocyte subsets). In the case of abnormal immune recovery and function, a modified monitoring approach may be pursued in consultation with a pediatric immunologist.

Revaccinations are indicated after adequate immune recovery following HSCT. If immune recovery is delayed, the revaccination process may take place more than two years after HSCT, and vigilance for infections is advised. If immune recovery is inadequate or pulmonary issues are present, the revaccination program should be tailored in consultation with a pediatric infectious disease specialist/immunologist.

IRON OVERLOAD

Iron overload has toxic effects on multiple organs and is considered a risk factor for the development of various late effects after HSCT (22). Iron overload is associated with increased iron uptake due to the underlying diseases, chronic transfusion

requirements pre-HSCT, or persistent transfusion requirements post-HSCT. Currently, there are shifts in choices for screening methods, with MRI T2* serving as the gold standard. In the (inter)national guidelines for Late Effects after childhood cancer, the indication for an MRI T2* is based on serum ferritin levels (persistently >500ng/ml) (17). However, due to the weak correlation between ferritin and MRI T2* values and based on expert opinion, which suggests that iron overload can also be diagnosed in patients with serum ferritin <500ng/ml, this recommendation has not been adopted. In patients undergoing HSCT with a nonmalignant disease, the underlying disease is added as a risk factor for iron overload due to dyserythropoiesis and increased intestinal iron absorption (e.g., β-thalassemia, congenital dyserythropoietic anemia, Blackfan Diamond anemia). Since iron overload often occurs pre-HSCT, a single evaluation of iron status at the start of long-term follow-up should be sufficient. If the MRI T2* shows no abnormalities, the follow-up can be concluded unless there are (recurring) transfusion requirements post-HSCT. If frequent evaluation of iron status is needed, for example during iron chelation therapy, ferritin and transferrin saturation can be determined until normal values are reached. Subsequently, a MRI T2* should be performed to evaluate the iron status.

ENDOCRINOLOGY: GROWTH, GONADAL FUNCTION, ADRENAL FUNCTION, BONE HEALTH

Risk factors for endocrine late effects include young age at HSCT (due to increased risk of growth and puberty problems), chemotherapy (either for underlying disease or as conditioning for HSCT), and high-dose corticosteroids (23). Additionally, the underlying disease plays a role as the risk of endocrine late effects, such as growth problems, may already be increased in some diseases pre-HSCT. Iron overload in the hypothalamic-pituitary (HP) region or endocrine organs can also lead to problems in the HP axis.

In the (inter)national guidelines for Late Effects after childhood cancer, the predisposing factor of the underlying disease is not considered in relation to growth. However, research in this population has shown that the underlying disease may have a greater impact on growth problems than the HSCT itself, with the final height of 21% of men and 8% of women being more than 2 standard deviations below the mean parental height (24). It is recommended to measure height and weight annually until the patient has reached full adult height.

Evaluation of gonadal function involves assessing both puberty development and fertility. The (inter)national guidelines for Late Effects after childhood cancer describe precocious puberty in brain tumors or treatment in the brain (3). However, these risk factors do not apply to the HSCT group with nonmalignant indications.

Possible abnormalities include (hyper/hypogonadotropic) hypogonadism, which can lead to delayed puberty. It is recommended to evaluate puberty development (Tanner stages) until reaching full adult stage. Gonadal function can be further evaluated in (post)pubertal patients through laboratory tests (FSH, LH, estradiol/testosterone). The (inter)national guidelines for Late Effects after childhood cancer recommend performing laboratory tests only in the presence of symptoms (3, 5). However, recent research within the HSCT patient group with nonmalignant diseases has shown gonadal dysfunction in 55% of females and 39% of males (24). The risk of gonadal dysfunction is higher in patients with Busulfan-based conditioning compared to Treosulfan-based conditioning. Lower plasma levels of busulfan do not reduce the risk of gonadal dysfunction (25). In addition to hypergonadotropic hypogonadism caused by chemotherapy, iron overload can lead to hypogonadotropic hypogonadism, particularly in males (24). With this high cumulative incidence of gonadal dysfunction, it is advised to perform additional evaluations at least at the age of 11 in girls and consider repeating them annually. An AMH (Anti-Müllerian hormone) measurement can provide support in the evaluation. In women showing signs of premature ovarian failure in laboratory tests, caution should be exercised regarding fertility prospects, and these patients should still be counseled for contraception. In (post)pubertal boys, it is recommended to primarily determine testosterone levels and, if abnormal, perform additional FSH and LH measurements (3, 6). Testicular volume may be reduced in the context of gonadal dysfunction. Regarding fertility evaluation, a post-pubertal semen analysis conducted by a fertility specialist is considered the gold standard. Both women and men with a desire for children should be referred to a clinical geneticist for counseling on the genetic transmission of the underlying disease.

Regarding reduced bone density and osteonecrosis, the recommendations are adopted from the (inter)national guidelines for Late Effects after childhood cancer. When initiating growth hormone treatment, caution should be exercised regarding the occurrence of epiphysiolysis, particularly in patients with (pre-existing) thalassemia. The etiology of this is not yet known.

PULMONARY EVALUATION

Pulmonary abnormalities can be present prior to HSCT due to the underlying disease, such as in sickle cell disease, or as a result of previous infections in immunological diseases (21). Pulmonary arteriovenous malformation and lung fibrosis are seen in patients with dyskeratosis congenita (19). These abnormalities cannot be detected through pulmonary function test, and symptoms may also develop later in life. Pre-existing pulmonary damage may not always be identifiable before HSCT since

pulmonary function testing is typically feasible from the age of 6 years onwards. To date, there is no evidence of new damage occurring longer than 2 years after HSCT. Therefore, at present, pulmonary function testing at the start of long-term follow-up and a minimum age of 6 years are considered sufficient.

METABOLIC SYNDROME

Metabolic syndrome has various definitions and is a combination of impaired glucose metabolism or diabetes, dyslipidemia, overweight, and hypertension. Table 2 presents the definition of metabolic syndrome from the Dutch Pediatric Society (NVK) guideline on obesity. The (inter)national Late Effects after childhood cancer guideline currently do not have a specific module on metabolic syndrome, but they may address individual components in separate modules (3). In children under the age of 10, a diagnosis of metabolic syndrome is not possible. However, it is important to be vigilant if components of metabolic syndrome are present in these young patients. For children aged >16 years, adult criteria are applied. It is recommended to measure height, weight, BMI, and blood pressure (annually until growth is completed, then every 2 years). Laboratory tests include a (fasting) lipid profile and serum glucose (with HbA1c, if necessary) every five years.

Table 2. Criteria for Metabolic syndrome according to the Dutch Pediatric Society (NVK) guideline on obesity.

Age (years)	Waist circumference	Triglycerides serum	HDL-cholesterol serum	Bloodpressure	Fasting serum glucose
10-16	≥ P90	≥ 1.7 mmol/L	<1.03 mmol/L	Syst > 130 mmHg Diast > 85 mmHg	≥ 5.6 mmol/L
>16	BMI > 30	≥ 1.7 mmol/L	<1.03 mmol/L males <1.29 mmol/L females	Syst > 130 mmHg Diast > 85 mmHg	≥ 5.6 mmol/L

PSYCHOSOCIAL AND FATIGUE

A HSCT is a high-intensity treatment that has a direct impact on the lives of patients and their families, especially during hospitalization. Due to the (risk of) late effects, the treatment can also have long-term impacts. Therefore, within the LEEF care path, the overall health, including mental aspects, is evaluated. A comprehensive assessment focusing on school/work, depression, anxiety, post-traumatic stress, suicidal thoughts, and fatigue is recommended. Patient-reported outcomes (PROs) can assist in this screening process. Within the LEEF program, PROs are integrated into the consultation process. Patients complete online patient-reported outcome

measures (PROMs) prior to their appointment. Table 3 shows the various PROMs currently used. The outcomes of the online questionnaires are discussed during a multidisciplinary meeting. If any concerns are identified, the consultation can be adjusted, and if necessary, additional consultations with other specialists can be arranged. During the consultation, the outcomes are reviewed together with the patient and, if applicable, their parents or caregivers. This systematic use of PROMs allows for the comprehensive assessment, further clarification and interpretation of patient-reported outcomes.

Table 3. Patient-reported outcome measures (PROMs) within the LEEF care path

PROM	Completed by:
Sociodemographic	Age ≤18 years: parents Age ≥ 19 years: patient
Medical history	Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Anxiety	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Depressive symptoms	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Fatigue	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Mobility / PROMIS Physical functioning	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Pain intensity	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Peer relationships/ PROMIS Satisfaction with participation in social roles	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Sleep disturbance	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient
PROMIS Anger	Age ≤ 7 years: not applicable Age ≥ 8 years: patient
PROMIS Cognitive function	Age ≤ 4 years: not applicable Age ≤ 7 years: parents Age ≥ 8 years: patient

CONCLUSION

HSCT for a nonmalignant disease is a rare and high-intensity treatment in which late effects can occur years after the treatment. In order to establish uniformity, the guidelines for follow-up after childhood cancer have been adapted for patients undergoing HSCT for nonmalignant diseases, taking into account differences in treatment modalities and predisposing factors related to the underlying diseases. Further research on late effects after HSCT for nonmalignant diseases is necessary to optimize the treatment and reduce (late) effects. The goal is not only to improve survival rates but also to strive for a better quality of life. This knowledge also contributes to the optimization of lifelong care and patient-centered follow-up, recognizing that appropriate post-HSCT care is of utmost importance for optimal well-being and societal participation.

GUIDELINES FOR PRACTICE

- In the Late Effects & Comprehensive Care (LEEF) care path, screening for physical and mental health is conducted.
- Take the underlying disease (morbidities and predisposing factors) into consideration during follow-up after HSCT.
- In screening, consider not only late effects related to the HSCT procedure but also (pre)disposing factors of the original disease beyond hematopoiesis.
- For late effects related to other therapies used for nonmalignant HSCT diseases (such as anthracyclines, radiotherapy), in the absence of scientific evidence for tailored recommendations, we refer to the (inter)national guidelines for Late Effects after childhood cancer.

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Summary of recommendations - Guideline for screening of late effects after pediatric stem cell transplantation or cell therapy for benign hematological, metabolic or immunological diseases

General recommendations

Who needs surveillance?

- All HSCT patients

What type of diagnosis/abnormalities occur?

- Type of diagnosis/abnormalities will be discussed in the relevant modules.

What surveillance modality should be used?

- Measure height, weight and BMI
  - If ≤ 18 years of age: annually
  - If > 18 years of age: every 5 years
- Give advice:
  - Maintain a physically active lifestyle
  - Maintain a healthy weight
  - Eat a healthy diet, according to the current national guidelines
  - Use adequate sun protection measures
  - Attend regular six-monthly or yearly dental examinations
  - Quit smoking and/or reduce exposure to second-hand smoke
  - Avoid alcohol excess

What should be done when abnormalities are identified?

- Consider referral to physical therapist if the patients has special needs.
- Consider referral to a dietician or refer for a combined lifestyle intervention for weight management.
- Treat patients with hypertension according to the current national guidelines, or refer to appropriate HCP.

Immune system: spleen

Who needs surveillance?

HSCT patients (treated) with:

- Splenectomy
- Underlying disease: sickle cell disease (functional asplenia)

What type of diagnosis/abnormalities occur?

- Patients with (functional) asplenia have an increased risk for severe infections with encapsulated organisms (S. pneumoniae, Hemophilus influenzae B, or Neisseria meningitidis). Severe infections can be prevented by vaccinations en antibiotic prophylaxis.

What surveillance modality should be used?

- Keep considering patient with pre-existence (functional) asplenia after HSCT
- Consider testing Howell-Jolly bodies
  - Be aware of the diagnostic limitations of this tests: a negative result does not exclude splenic dysfunction and provides no reliability about spleen function. Currently, there is no other available to test the spleen function.

What should be done when abnormalities are identified?

- Treat according to the current national guidelines: LCI richtlijn 'Asplenie'.

Immune system: Graft function

Who needs surveillance?

- All HSCT patients

What type of diagnosis/abnormalities occur?

- Decrease in donor chimerism, possibly ending in graft failure
- Cytopenia and/or cGVHD
- If immune system is impaired: increased risk for (opportunistic) infections and auto-immunity

What surveillance modality should be used?

- Regular* evaluate graft function and immune reconstitution:
  - CBC & reticulocytes
  - Leukocytes differentiation
  - IgG and IgM
- Consider regular additional analyses:
  - Donor chimerism (granulocytes/peripheral blood mononuclear cell)
    - If indicated: specific cell chimerism
- Lymphocyte subsets (immunophenotyping):
    - T cells: CD4, CD8, CD4/CD45RA+, CD4/CD45RO, CD8/CD 45RA+, CD8/CD45RO, optional: TREC analyses
    - B cells : CD19, CD20, B cell subset analyses (CD19+/CD27+/IgD-)
    - NK cells: CD3-/CD16+/of CD56
- Adjust frequency if indicated by (pediatrician-)immunologist.

What should be done when abnormalities are identified?

- Counsel on preventive measures, infection monitoring, antibiotic prophylaxis, antifungal prophylaxis if:
  - CD4 cells < 200 u/L
  - Impaired T cell function
  - Prolonged supraphysiological doses of corticosteroids

* 2 to 5 years post-HSCT: annually | 5 to 11 years post-HSCT: every 3 years | > 11 years post-HSCT: every 5 years

Immune system: Vaccination

Who needs surveillance?

- All HSCT patients

What type of diagnosis/abnormalities occur?

- Be aware for infections if vaccinations are not (fully) complete.

What surveillance modality should be used?

- Evaluate immune reconstitution in advance of vaccinations:
- CD4 cells <200 u/L
- Relative contraindications for live-attenuated vaccines:
  - cGVHD treated with systemic glucocorticoids
  - Severe hypogammaglobulinemia
  - Severe auto-immunity
  - Severe infection
    - Consider inactivated vaccines
- Administer vaccinations according to (inter)national guidelines
  - National guidelines: Dutch National Immunisation Program, Dutch guideline Asplenia
  - Internationl guidelines: Ljungman et al (2009), Guilcher et al (2021)
- Consider titer evaluation 4-6 weeks after last vaccination
- Consider influenza vaccine for patients with:
  - Pulmonary problems
  - Risk for severe infections

What should be done when abnormalities are identified?

- Consult (pediatrician-)immunologist
  - Unprotective titers: consider booster vaccination & evaluate titers
  - For additional diagnostics or treatment

Iron overload

Who needs surveillance?

HSCT patients (treated) with:

- Multiple red blood cell (RBC) transfusions pre-HSCT, during HSCT, and post-HSCT
- Underlying disease: ineffective erythropoiesis, increased intestinal iron absorption
    - For example: Diamond-Blackfan Anemia, beta thalassemia, Congenital Dyserythropoietic Anemia

What type of diagnosis/abnormalities occur?

- Iron overload can occur in multiple organs and can lead to liver cirrhosis, cardiomyopathy, arrhythmia, heart failure, endocrine dysfunction, skin disorders, joint problems, or malignancy .
- Consequences of iron overload will be discussed in the related modules

What surveillance modality should be used?

- (If not recently executed) Perform MRI T2* (heart & liver) at entry into the long-term follow-up program
    - Surveillance is completed if no iron load is detected:
        - Restart surveillance when patient becomes transfusion-dependent.
        - Discuss with or refer to a (pediatrician-)hepatologist or gastroenterologist for possible liver biopsy if there are liver abnormalities.
- Monitor ferritin and transferrin saturation levels if frequent iron overload assessment is needed:
    - Consider MRI T2* to assess iron overload if ferritin and transferrin saturation levels are within normal limits.

What should be done when abnormalities are identified?

- Start with chelation therapy (phlebotomy or chelating agents)

Endocrine system: Growth

Who needs surveillance?

- All HSCT patients

What type of diagnosis/abnormalities occur?

- Short stature
- Growth deceleration

What surveillance modality should be used?

- Measure height and weight
  - Annually
- Additional analysis according to national protocols (e.g., NVK richtlijn 'Triage en Diagnostiek van Groeistoornissen bij kinderen')

What should be done when abnormalities are identified?

- Refer to pediatrician-endocrinologist if:
  - Deceleration in linear growth
  - Absence of pubertal growth spurt
  - Growth -1SD below target height
- Additional analysis and treatment according to national protocols (e.g., NVK richtlijn 'Triage en Diagnostiek van Groeistoornissen bij kinderen', NVK richtlijn 'Groeihormoonbehandeling na hematopoietische stamceltransplantatie')

Endocrine system: thyroid function

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Underlying disease: RS SCID
  - Conditioning regimen: alkylating agents
  - Complications: iron overload

What type of diagnosis/abnormalities occur?

- (Sub)clinical hypothyroidism
- (Sub)clinical hyperthyroidism

What surveillance modality should be used?

- A medical history/anamnesis focused on symptoms of hypothyroidism and/or hyperthyroidism.
- Measure TSH and fT4:
  - If ≤ 18 years of age: annually
  - If > 18 years of age: every 2 to 3 years
- Female survivors attempting pregnancy:
  - Measure TSH and fT4 prior to attempting pregnancy and, if needed, periodically during pregnancy

What should be done when abnormalities are identified?

- Repeat TSH and fT4 if results are (borderline) abnormal.
- Refer to an (pediatrician-)endocrinologist if results are repeatedly abnormal.

Endocrine system: female gonadal function

Who needs surveillance?

- All HSCT patients
- High risk patients
  - Iron overload (confirmed by MRI T2* or high probability)
  - Conditioning regimven: alkylating agents

What type of diagnosis/abnormalities occur?

- Delayed puberty
  - Age ≥ 13 years: absence of first signs of puberty (Tanner <M2)
- Hypogonadotropic hypogonadism
- Hypergonadotropic hypogonadism
- Fertility problems

What surveillance modality should be used?

- A medical history/anamnesis:
  - Age of puberty onset and pubertal development
  - Annual Tanner evaluation until reaching adulthood
  - Age of menarche, menstrual cycle
  - If sexually active: sexual dysfunction
  - Discuss desire to have children and genetic counseling
- Consider to measure FSH, LH, estradiol/testosterone, and SHBG annually
  - Measure:
  - By default at 11 years of age. Repeat if necessary.
  - failure to initiate or progress through puberty at
  - In case of failure to initiate or progress through puberty, amenorrhea, or irregular menstrual cycles
    - Consider AMH measurement
  - If suspicion of premature ovarian insufficiency
    - Consider AMH measurement

What should be done when abnormalities are identified?

- (Pre-)pubertal females
  - Refer to (pediatrician-)endocrinologist if:
    - Absence of first signs of puberty (Tanner <M2) by 13 years of age
    - Primary amenorrhea by 16 years of age

- Post-pubertal females
  - In case of irregular menstrual cycles with suspicion of premature ovarian insufficiency, or who desire assessment about possible future fertility:
    - Refer to gynecologist, fertility physician, or (pediatrician-) endocrinologist
    - Consider hormone replacement therapy
  - If at risk for genetic transmission of underlying disease:
    - Refer to clinical geneticist

Endocrine system: Male gonadal function

Who needs surveillance?

- All HSCT patients
- High risk patients
  - Iron overload (confirmed by MRI T2* or high probability)
  - Conditioning regimen: alkylating agents

What type of diagnosis/abnormalities occur?

- Delayed puberty
  - Age ≥ 15 years: testicular volume < 4 ml
- Hypogonadotropic hypogonadism
- Hypergonadotropic hypogonadism
- Impaired spermatogenesis
- Testosterone deficiency
- Physical sexual dysfunction

What surveillance modality should be used?

- (Pre-)pubertal males
  - Annual medical history/anamnesis and physical examination focused on hypothalamic-pituitary axis (HPA) problems.
  - Height measurement and Tanner evaluation until reaching adulthood.
  - Consider morning testosterone if aged <9 years
    - In the presence of clinical signs of hypogonadism, or of previous low-normal or borderline testosterone concentrations, or if it is not possible to obtain an early morning blood sample, it is reasonable to measure LH concentration in addition to testosterone.
- Post-pubertal males
  - Annual medical history/anamnesis and physical examination for hypothalamic-pituitary axis (HPA) problems and sexual dysfunction.
  - Consider morning testosterone
    - In the presence of clinical signs of hypogonadism, or of previous low-normal or borderline testosterone concentrations, or if it is not possible to obtain an early morning blood sample, it is reasonable to measure LH concentration in addition to testosterone.
  - Discus paternity
    - Who desire assessment about possible future fertility:
      - Refer to fertility physician for semen analysis
        - Clinical measurement of testicular volume, FSH and inhibin B may be in whom semen analysis has been declined or is not possible

- and who desire assessment about possible future fertility. Be aware of the diagnostic limitations of these tests that may result in false positives or false negatives.

What should be done when abnormalities are identified?

- Refer to (pediatrician-)endocrinologist if:
  - Clinical signs of hypothalamic-pituitary axis (HPA) problems
  - Signs of delayed puberty
- Refer to fertility physician if:
  - Severe oligospermia (sperm counts ≤ 5x106/ml) or if laboratory results suggest testosterone deficiency or unsuccessful attempts to conceive ≥ 6 months (regardless of sperm count)
- Refer to andrology, endocrinology or urology if:
  - Symptoms suggesting physical sexual dysfunction
- If at risk for genetic transmission of underlying disease:
  - Refer to clinical geneticist

Endocrine system: Adrenal function

Who needs surveillance?

HSCT patients (treated) with:

- Prolonged supraphysiological doses of corticosteroids, at least 2 weeks continuously
  - All dose forms (e.g., tablets, creams, inhaled corticosteroids)
- Iron overload (confirmed by MRI T2* or high probability)

What type of diagnosis/abnormalities occur?

- Primary, secondary, and tertiary adrenal insufficiency

What surveillance modality should be used?

- Measure morning cortisol if
  - Suspected adrenal insufficiency
  - Risk factors for adrenal insufficiency
- Evaluate the hypothalamic-pituitary axis (HPA): NVK richtlijn 'Glucocorticoïden, afbouwen van glucocorticoïden bij kinderen'

What should be done when abnormalities are identified?

Refer patients with low morning cortisol to (pediatrician-)endocrinologist.

Endocrine system: Bone health

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Prolonged supraphysiological doses of corticosteroids, at least 2 weeks continuously
  - Methotrexate
  - Hypogonadism
  - Growth hormone deficiency
  - Growth hormone treatment
  - Iron overload (confirmed by MRI T2* or high probability)
  - Dyskeratosis Congenita
  - Diamond-Blackfan Anemia
  - Underweight or low BMI
  - Male
  - Caucasian
  - Reduced physical activity
  - Smoking (current, or in the past)

What type of diagnosis/abnormalities occur?

- Reduced bone mineral density
- Osteonecrosis
- Epiphysiolysis
  - If treated with growth hormone

What surveillance modality should be used?

<u>Reduced bone mineral density</u>

- Medical history/anamnesis for:
  - Risk factors: insufficient intake of calcium and vitamin D, decreased physical activity, comorbidity
  - Symptoms: back pain, fractures
- Measure 25(OH)D, ionized calcium (albumin-corrected), PTH, and phosphate
  - Every 5 years
- Consider a DXA scan
  - Preferably in post-pubertal patients
  - Repeat if indicated

Osteonecrosis

- Medical history/anamnesis for symptoms
  - Every 5 years

Epiphysiolysis

- If currently treated with growth hormone:
  - Medical history/anamnesis for acute lower extremity pain (especially hip pain)
  - Educate about emergency assessment if lower extremity pain is present

What should be done when abnormalities are identified?

- Recommend adequate calcium and vitamin D intake, and adequate physical activity according to guidelines for the general population.
- Encourage reduction of risk behavior (smoking, alcohol consumption).
- Recommend nutritional supplements in underweight patients.
- Refer patients with osteoporosis to (pediatrician-)endocrinologist.
- Refer patients with suspected osteonecrosis to orthopedic surgeon.
- Refer patients with growth hormone treatment and acute lower extremity pain to orthopedic surgeon for emergency assessment.

Pulmonary evaluation

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Dyskeratosis Congenita
  - SCID
  - Sickle cell disease
  - Underlying pulmonary disease

What type of diagnosis/abnormalities occur?

- Pulmonary fibrosis
- Obstructive or restrictive pulmonary diseases
- Bronchiolitis obliterans (pulmonary chronic GVHD)

What surveillance modality should be used?

- All HSCT patients:
  - Medical history/anamnesis for symptoms
    - If ≤ 18 years of age: annually
    - If > 18 years of age: every 5 years
  - Pulmonary function test (spirometry and diffusing capacity for carbon monoxide)
    - Once at entry into long-term follow-up program and >6 years of age
    - Repeat if indicated
  - Recommend:
    - Avoid tobacco, quit smoking and/or reduce exposure to environmental smoke
  - If respiratory complaints
    - Recommend annual seasonal influenza vaccination
    - Consider pneumococcal vaccination (according to (inter)national guidelines).
- High risk patients:
  - Dyskeratosis Congenita
    - Consider annual pulmonary function test
    - Consider ultrasound in patients suspected for pulmonary arteriovenous malformations
  - SCID
    - Consider annual pulmonary function test

What should be done when abnormalities are identified?

- Repeat pulmonary function test if:
  - Respiratory complaints
  - Abnormal physical examination
- Refer, or consult with, patients with pulmonary symptoms or abnormal pulmonary function to a (pediatrician-)pulmonologist.

Cardiovascular evaluation

Who needs surveillance?

HSCT patients (treated) with:

- Iron overload (confirmed by MRI T2* or high probability)
- Sickle cell disease
- Cardiomyopathy
    - In patients with/after chronic anemia

What type of diagnosis/abnormalities occur?

- Hypertension
- Cardiomyopathy
- Pulmonary hypertension
    - In patients with sickle cell disease

What surveillance modality should be used?

- All HSCT patients:
    - Blood pressure measurement
        - Annually
    - Consider lipid profile evaluation
        - Every 5 years
        - Advance measurement if patient is overweight or hypertension is present
- Iron overload (confirmed by MRI T2* or high probability):
    - Consider ECG and/or echocardiogram to exclude asymptomatic cardiomyopathy
- Sickle cell disease:
    - Consider echocardiogram to exclude tricuspid regurgitation if not previously evaluated
        - Repeat in patients with clinical symptoms for tricuspid regurgitation

What should be done when abnormalities are identified?

- Refer patients with asymptomatic cardiomyopathy to (pediatrician-) cardiologist.
    - If iron overload present: see module ‘iron overload’.

Renal evaluation

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Pre-existent renal impairment
  - Nephrotoxic drugs
  - Sickle cell disease

What type of diagnosis/abnormalities occur?

- Hypertension
- Glomerular dysfunction
- Tubular dysfunction

What surveillance modality should be used?

All HSCT patients:

- Education about caution in the use of NSAIDs
- Measure height and blood pressure
  - Annually
- Glomerular function (every 5 years)
  - Serum creatinine (eGFR)
    - Consider: Cystatin C
  - Urine albumin-to-creatinine ratio
- Tubular function (every 5 years)
  - Serum potassium, phosphate, magnesium, albumin en bicarbonate
    - Consider: sodium, calcium, uric acid
  - Urine: glucosuria, albumin-to-creatinine ratio
    - Consider: beta-2-microglobulin (or alpha-1-microglobulin)

What should be done when abnormalities are identified?

- Refer to (pediatrician-)nephrologist if:
  - Proteinuria
  - Chronic kidney disease
- Patients with hypertension:
  - Consider 24-hour blood pressure measurement
  - Treat according to local or national guidelines
  - Evaluate metabolic syndrome: see module ‘metabolic syndrome’

Liver evaluation

Who needs surveillance?

- All HSCT patients
- High risk patients
  - Dyskeratosis Congenita
  - Sickle cell disease
  - Iron overload (confirmed by MRI T2* or high probability)
  - Liver chronic GVHD

What type of diagnosis/abnormalities occur?

- Liver fibrosis or cirrhosis
- Hepatocellular liver injury
- Hepatobiliary dysfunction
- Biliary tract injury
- Liver synthetic dysfunction
- Hepatic iron overload

What surveillance modality should be used?

- Medical history/anamnesis and physical examination focused on liver abnormalities
  - For example: hepatosplenomegaly, spider naevi or pruritus
- Serum liver enzyme concentrations (ALT, AST, gGT, ALP, bilirubin (total and conjugated fraction)
  - Once at entry into long-term follow-up program
  - Consider annual measurement in high risk patients

What should be done when abnormalities are identified?

- If abnormal serum liver enzyme concentrations:
  - Between 1-2 x ULN: repeat the test within 1 year.
  - 2x ULN: repeat the test within 2 months.
- If persistent liver abnormalities
  - Refer to (pediatrician-)gastro-enterologist or hepatologist if there is no obvious explanation (alcohol, medication, obesity).
  - Counsel about avoidance of alcohol intake and drugs with hepatic drug metabolism.
  - Consider hepatitis A and B virus immunization
  - Counsel about importance of measures to maintain liver health:
    - Cautious use or avoidance of alcohol intake
    - Maintain a healthy weight and lifestyle
- Precautions to reduce viral transmission to household and sexual contacts in survivors with chronic HBV/HCV infection

Metabolic syndrome

Who needs surveillance?

- All HSCT patients

What type of diagnosis/abnormalities occur?

- If ≥ 10 years of age:
  - See table 3 for metabolic syndrome criteria.
    - Includes impaired glucose metabolism or diabetes, dyslipidemia, overweight/increased waist circumference, and hypertension.
- If <10 years of age:
  - Criteria of metabolic syndrome are not applicable.
  - Individual metabolic syndrome components may be present.

What surveillance modality should be used?

- Measure height, weight, BMI, and blood pressure
  - Annually until reaching adulthood and every 2 years thereafter
- (Fasting) lipid profile and glucose (optionally with HbA1c)
  - Every 5 years

What should be done when abnormalities are identified?

- Refer to appropriate HCP or general practitioner for treatment.

The Dutch national guideline (NVK richtlijn 'Diagnostiek en behandeling van obesitas bij volwassenen en kinderen') can be used to support diagnostics and treatment.

Neurology evaluation

Who needs surveillance?

HSCT patients (treated) with:

- Dyskeratosis Congenita
- SCID
- Sickle cell disease
- Pre-existent neurological abnormalities (confirmed on radiological imaging)

What type of diagnosis/abnormalities occur?

- Cerebrovascular accidents (CVA)
- Epilepsy
- Vascular abnormalities

What surveillance modality should be used?

- All HSCT patients
  - Medical history/anamnesis and physical examination focused on neurological abnormalities
  - Discuss the importance of controlling cardiovascular and stroke risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking and low levels of physical activity)
    - Every 5 years
- In patients with pre-existent neurological abnormalities (confirmed on radiological imaging)
  - Consider imaging as appropriate
  - Refer to, or consult, a neurologist, neurosurgeon or vascular specialist

What should be done when abnormalities are identified?

- Consider imaging as appropriate
- Refer to, or consult, a neurologist, neurosurgeon or vascular specialist

Neurocognitive evaluation

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - (Neurological) complications during HSCT treatment with clear signs of mental changes
  - Medical problems that affect brain function
  - Underlying syndromic conditions with developmental delay or intellectual disabilities

What type of diagnosis/abnormalities occur?

- Neurocognitive problems include cognitive domains of academic and school performance, attention, executive functions, intelligence, language, memory, processing speed or visual-motor integration.

What surveillance modality should be used?

- Medical history/anamnesis for school function and/or work
  - If < 18 years of age: every 2 years
  - If > 18 years of age: every 5 years

What should be done when abnormalities are identified?

Refer to a (neuro)psychologist for a formal neuropsychological evaluation.

Psychosocial and fatigue

Who needs surveillance?

- All HSCT patients

What type of diagnosis/abnormalities occur?

- Psychosocial problems include dependent living, educational problems, relationship problems, social withdrawal, under-employment or unemployment, anxiety, behavioral problems, depression, post-traumatic stress, and suicidal ideation.
- Fatigue is defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.

What surveillance modality should be used?

- Medical history/anamnesis for school function and/or work, depression anxiety, post-traumatic stress, and suicidal ideation and fatigue
    - If indicated:
        - Physical examination and/or perform diagnostics

What should be done when abnormalities are identified?

- Refer to appropriate HCP (e.g., psychiatrist, psychologist, or social worker) for further diagnostic and risk assessment

Audiology evaluation

Who needs surveillance?

HSCT patients (treated) with:

- Ototoxic drugs (chemotherapy, chelating agents, antibiotics)
- Underlying disease:
  - Dyskeratosis Congenita
  - ADA-SCID
  - RD-SCID (AK2 deficiency)

What type of diagnosis/abnormalities occur?

- Hearing loss
- Tinnitus

What surveillance modality should be used?

- If ≥ 6 years of age: consider pure tone conventional audiometry testing at 1000-8000 Hz.
- If < 6 years of age: consider extensive testing by audiologist every year, to begin no later than the end of treatment.
- Advance audiology evaluation if indicated.

What should be done when abnormalities are identified?

- Refer to an otorhinolaryngologist, audiologist or auditory clinic if:
  - Symptoms suggesting hearing loss or tinnitus are present
  - Abnormal audiological test results showing a loss of more than 15 dB absolute threshold level (1000-8000 Hz)

Ophthalmology evaluation

Who needs surveillance?

HSCT patients (treated) with:

- Prolonged supraphysiological doses of corticosteroids, at least 2 weeks continuously
- Sickle cell disease
- Dyskeratosis Congenita
- Chelation therapy
- GVHD
- CMV infection

What type of diagnosis/abnormalities occur?

- Cataract
- Retinopathy (sickle cell disease, dyskeratosis congenita)
- Sicca syndrome (GHVD)
- CMV retinitis

What surveillance modality should be used?

- All HSCT patients:
  - Medical history/anamnesis and physical examination for cataract and other eye problems
    - Every 5 years
- High risk patients:
  - Consider referral to ophthalmologist or ocular specialist for retinal screening

What should be done when abnormalities are identified?

- Refer to ophthalmologist or ocular specialist

Oral health

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Age at HSCT < 7 years

What type of diagnosis/abnormalities occur?

- Dental caries
- Dental developmental problems (especially if treated at a young age or having suffered from poor nutritional condition)
- Xerostomia
- Periodontal disease

What surveillance modality should be used?

- Recommend dentist checkup
  - Every 6 months to 1 year
  - Inform the dentist on the increased risk on dental problems after HSCT.

What should be done when abnormalities are identified?

- Refer to specialist dental care or orthodontist

Dermatology evaluation

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Conditioning regimen: busulfan

What type of diagnosis/abnormalities occur?

- Reduced hair growth
- Alopecia
- Skin cGVHD
- Scars

What surveillance modality should be used?

- Medical history/anamnesis and physical examination for skin abnormalities
- Discus potential negative psychological effects

What should be done when abnormalities are identified?

- Discuss availability of cosmetic solutions and/or psychological support

*For skin cancer evaluation: see module secondary malignancy

Secondary malignancy

Who needs surveillance?

- All HSCT patients
- High risk patients:
  - Predisposing syndromes or genetic mutations

What type of diagnosis/abnormalities occur?

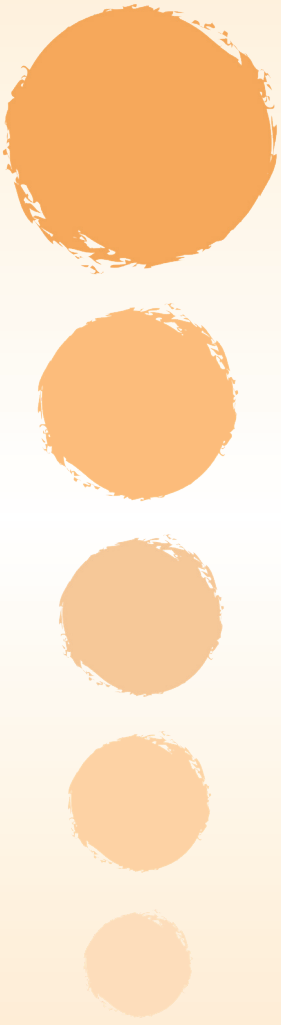
- Acute myeloïde leukemia of myelodyplastic syndrome
- Oral cancer (Dyskeratosis congenita, oral GVHD)
- Skin cancer (melanoma, basal cell carcinoma, cutaneous squamous cell carcinoma)
- Other solid tumors (e.g., osteosarcoma, colorectal cancer, breast cancer)

What surveillance modality should be used?

- Medical history/anamnesis and physical examination (including skin evaluarion and palpation of the thyroid gland)
  - Every 2 years
- Recommend self-examination for new spots and changing moles
  - Every 6 months
- Family history for malignancies
  - Every 5 years
- General advice:
  - Discuss the importance of prompt reporting of new symptoms or masses
  - Discuss healthy lifestyle recommendations
  - Encourage reduction of risk behavior (smoking, alcohol consumption, drug use, sun exposure)
  - Encourage HPV vaccination (according to national guidelines) and consider advising safe sexual practices
  - Encourage participation in the national cancer screening programs, unless more intensive or earlier surveillance is specified in the guidelines

What should be done when abnormalities are identified?

- Perform the appropriate diagnostic tests.
- Refer to the appropriate HCP.
- Refer patients with (suspicion of) a hereditary cancer to clinical geneticist to determine individualized surveillance methods.



Chapter 3

Late endocrine effects after hematopoietic stem cell transplantation in children with nonmalignant diseases

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ABSTRACT

The number of children undergoing hematopoietic stem cell transplantation (HSCT) for nonmalignant diseases has increased in recent years. Endocrine complications are common after HSCT for malignant diseases, while little is known about long-term prevalence and risk factors in children transplanted for nonmalignant diseases. We retrospectively evaluated gonadal function, near adult height and thyroid function in 197 survivors of pediatric HSCT for hemoglobinopathies (n = 66), inborn errors of immunity/metabolism (n = 74) and bone marrow failure disorders (n = 57); median follow-up was 6.2 years (range 3.0-10.5). Gonadal dysfunction occurred in 55% of (post)pubertal females, was still present at last assessment in 43% and was more common after busulfan- than treosulfan-based conditioning (HR 10.6, CI 2.2-52.7; adjusted for HSCT indication). Gonadal dysfunction occurred in 39% of (post)pubertal males, was still present at last assessment in 32% and was less common in those who were prepubertal compared to (post)pubertal at HSCT (HR 0.11; CI 0.05-0.21). Near adult height was more than 2 SDS below mean parental height in 21% of males and 8% of females. Hypothyroidism occurred in 16% of patients; 4% received thyroxin treatment. In conclusion, endocrine complications, especially gonadal dysfunction, are common after pediatric HSCT for nonmalignant conditions. In females, treosulfan seems less gonadotoxic than busulfan. Careful long-term endocrine follow-up is indicated.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) provides an established curative treatment for an increasing variety of nonmalignant diseases (1). Nonmalignant indications for HSCT include hemoglobinopathies (HBP), bone marrow failure syndromes (BMF), inborn errors of immunity (IEI) and inborn errors of metabolism (IEM). The growing number of indications, continuous developments in HSCT approaches and the ongoing improvements in survival have led to a growing population of survivors who are at risk of developing late effects. Endocrine complications, such as growth impairment and gonadal dysfunction, are among the most frequent late effects after HSCT for malignant diseases. However, little is known about the prevalence and risk factors of long-term endocrine complications in children transplanted for nonmalignant diseases. Factors that may affect the incidence and severity of endocrine complications such as underlying disease, age at HSCT, pretransplant therapies, conditioning agents including irradiation, use of high dose steroids, chronic graft versus host disease (GvHD) and iron overload differ between children with malignant and nonmalignant diseases (2-4). Therefore, knowledge gained from studies of late effects after HSCT for malignant diseases may not apply to patients with nonmalignant diseases.

The aim of this study is to evaluate the cumulative incidence of gonadal dysfunction, thyroid dysfunction and growth failure in individuals who had received an HSCT in childhood for nonmalignant diseases. We hypothesize that the incidence of late endocrine effects in children transplanted for nonmalignant diseases is lower than what has been described after HSCT for malignant indications, as we expect they received less toxic treatment pre-HSCT, less toxic conditioning regimens and less irradiation therapy. Identifying the incidence of, and risk factors for, late endocrine effects is crucial for 1) optimizing treatment regimens to improve outcome after HSCT in children, 2) improving shared decision making before HSCT by providing patients and their parents accurate and complete information on potential risks and benefits of HSCT and 3) developing optimal clinical guidelines for screening of endocrine late effects (5).

METHODS

Study design

This retrospective non-interventional single-center study included all patients, aged 0-18 years, with a nonmalignant disease who had received an HSCT at the Department of Pediatrics at the Leiden University Medical Center in the Netherlands between 1997 and 2018 and were alive 2 years post-transplant (Fig 1). Exclusion

criteria were re-transplantation, no data available on the outcome measures of the study and death within 2 years post-transplant. Patients were evaluated by a transplantation specialist and pediatric endocrinologist for a clinical and laboratory assessment pre-transplantation and yearly after transplantation at the outpatient clinic. Clinical assessment included assessment of symptoms suggestive of endocrine complications (such as amenorrhea), auxological measurements, evaluation of the growth chart, assessment of bone age with an X-ray of the left hand, evaluation of pubertal stage and palpation of the thyroid gland. At each visit the following laboratory measurements were performed: gonadotrophins, testosterone in boys, estradiol in girls, thyroid stimulating hormone (TSH), Free Thyroxin (FT4), Insulin-like Growth Factor 1 (IGF-1) and Insulin-like Growth Factor Binding Protein-3 (IGF-BP3). The study protocol was assessed by the local medical ethical committee who determined that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study. The need for informed consent was waived.

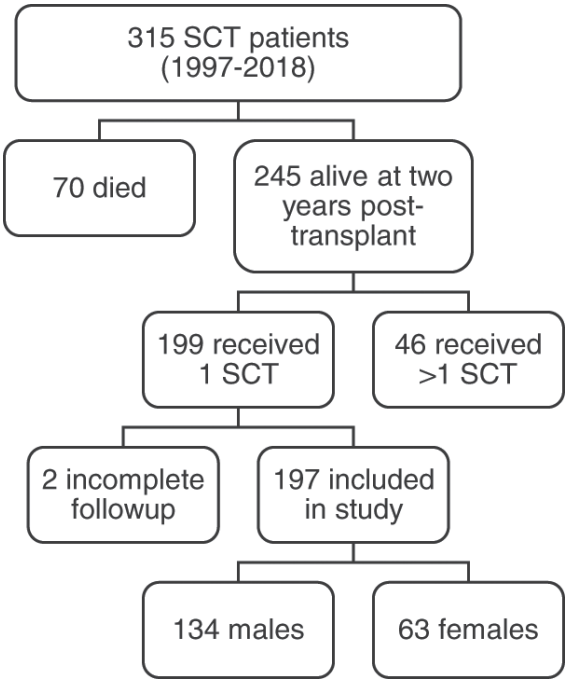

Fig 1. Flow chart showing inclusion and exclusion of patients.

Data collection

Patient characteristics were collected from the medical files including sex, age, underlying disease and conditioning regimen. Indications for HSCT were classified as IEI/IEM, HBP or BMF; blood cell disorders such as paroxysmal nocturnal hemoglobinuria were included in the BMF group (for all diagnoses included in these groups see Supplementary Table 1). Conditioning regimens were divided into five main categories: busulfan-based, treosulfan-based, chemotherapy with total abdominal irradiation (TAI)/total body irradiation (TBI), others and no conditioning (for specific regimens see Supplementary Table 2).

Data were collected on three main endocrine late effects after transplantation: gonadal dysfunction, thyroid complications and growth failure. Data were abstracted from medical charts by two of the authors (LCdK and JEB).

Definitions and outcome measures

Gonadal dysfunction

Patients at Tanner stage ≥G2 or ≥B2 were classified as (post)pubertal and were included in the analysis of gonadal dysfunction (6, 7). Patients diagnosed with gonadal dysfunction before HSCT were excluded from this analysis. Gonadal dysfunction (elevated gonadotrophins) and hypogonadotropic hypogonadism (low estradiol/testosterone with gonadotrophins below/within reference range) were recorded (for exact definitions see Supplementary Table 3) (8). Use of hormone replacement therapy (HRT) or oral contraceptives after HSCT, ovarian tissue cryopreservation prior to HSCT, and the use of a GnRH agonist (GnRHa) at the time of HSCT were recorded.

Thyroid complications

Patients diagnosed with hypothyroidism before HSCT were excluded from this analysis. Overt primary hypothyroidism (elevated TSH and FT4 below reference range), subclinical hypothyroidism (elevated TSH with normal FT4), central hypothyroidism (TSH within/below reference range with FT4 below reference range) and hyperthyroidism (suppressed TSH and elevated FT4) were recorded (for exact definitions see Supplementary Table 3) (9, 10).

Growth failure

Patients (temporarily) treated with growth hormone before or after HSCT were excluded from this analysis. Height standard deviation scores (SDS) for age and sex were calculated using reference data reported by de Onis et al. and Garza et al. (11, 12). Near adult height (NAH) was analyzed in all patients with a chronological age ≥14 years for boys and ≥12 years for girls, who fulfilled at least one of the following

criteria: height velocity <2 cm/year or bone age >16 years for boys and >14 years for girls according to Greulich and Pyle (13). NAH was compared to mid-parental height (MPH) (14). Short stature (SS) was defined as NAH < -2 SDS.

Statistical analysis

Continuous outcomes were compared between groups with a Mann-Whitney U test. Differences in categorical factors between groups were analyzed by the Pearson's chi-square test or Fisher's exact test. Two-tailed P-values of <0.05 were considered statistically significant. Univariate logistic regression analyses were performed to evaluate risk factors for outcomes calculating odds ratios. Risk factors evaluated were age at HSCT, gender, diagnosis, conditioning regimen, donor type, puberty stage at HSCT and acute GVHD and, in the analysis of gonadal dysfunction, the use of a GnRHa. When large and significant differences were seen in follow-up duration multistate Cox models (Supplementary Fig 1) were used to compare groups and to calculate hazard ratios (HR) using R 4.1.0 (15).

RESULTS

Patient characteristics

The study included 197 patients, 134 males and 63 females. Median age at HSCT was 5.7 years (IQR 2.9-11.3 years) and median follow-up was 6.2 years (IQR 3.0-10.5 years). Underlying diseases were IEI/IEM (n=74), HBP (n=66), and BMF (n=57) (Table 1). Patients with IEI/IEM were significantly younger at HSCT and follow-up duration was significantly longer. The majority of patients had received busulfan-based (46%) or treosulfan-based (34%) myeloablative conditioning. The remainder was treated with chemotherapy with low dose irradiation (4%), no conditioning (2%), or others (fludarabine with cyclophosphamide (11%), cyclophosphamide (2%), other (2%)). The conditioning regimen was significantly different between IEI/IEM, HBP and BMF (Table 1).

Table 1. Patient characteristics.

	Total ***N*=197**	**IEI/IEM** ***N*=74**	**HBP** ***N*=66**	**BMF** ***N*=57**	***p*** **value**
Male / female	134/63	55/19	46/20	33/24	0.13
Age at transplantation, years, median (IQR)	5.7 (2.8-11.3)	3.0 (0.9-6.7)	8.5 (4.9-14.1)	7.9 (4.4-13.1)	<0.001
Age at last assessment, years, median (IQR)	14.7 (9.7-18.7)	13.7 (8.9-17.8)	15.7 (12.4-18.4)	14.9 (9.9-19.2)	0.3
Follow-up duration, years, median (IQR)	6.2 (3.0-10.5)	8.4 (4.4-12.4)	5.4 (2.9-8.5)	5.1 (2.6-10.1)	0.01
Conditioning regimens					<0.001
Busulfan based	90 (46%)	50 (68%)	22 (33%)	18 (32%)	
Treosulfan based	66 (34%)	20 (27%)	41 (62%)	5 (9%)	
TAI-based	8 (4%)	0 (0%)	1 (2%)	7 (12%)	
Others	30 (15%)	1 (1%)	2 (3%)	27 (47%)	
None	3 (2%)	3 (4%)	0 (0%)	0 (0%)	
Donor relation					<0.001
Matched related donor	76 (39%)	20 (27%)	30 (45%)	26 (46%)	
Mismatched related donor	23 (12%)	4 (5.4%)	15 (23%)	4 (7.0%)	
Unrelated donor	98 (50%)	50 (68%)	21 (32%)	27 (47%)	
Stem cell source					0.1
BM	159 (81%)	54 (73%)	53 (80%)	52 (91%)	
CB	15 (7.6%)	10 (14%)	4 (6.1%)	1 (1.8%)	
Other/Undefined	1 (0.5%)	0 (0%)	1 (1.5%)	0 (0%)	
PBSC	22 (11%)	10 (14%)	8 (12%)	4 (7.0%)	
aGvHD					0.14
Grade 0-I	175 (89%)	62 (84%)	59 (89%)	54 (95%)	
Grade II-III[a]	22 (11%)	12 (16%)	7 (11%)	3 (5%)	

IEI/IEM inborn errors of immunity/metabolism, HBP hemoglobinopathies, BMF bone marrow failure disorders, BM bone marrow, CB cord blood, PBSC peripheral blood stem cells, aGvHD acute graft versus host disease.
[a]There were no patients with grade IV aGvHD.

Gonadal function in females

At last follow-up 44 of 63 females were (post)pubertal and included for evaluation of gonadal function. At time of HSCT 19 of them (43%) were (post)pubertal; median age at HSCT was 8.9 years (IQR 6.1-14.2 years) and median age at last visit 17.5 years (IQR 15.6-21.2).

Gonadal dysfunction occurred in 24 of these 44 (55%) patients and was still present at last assessment in 19/44 females (43%) (Table 2 and Fig 2). Median time from HSCT to diagnosis of gonadal dysfunction was 1.0 year (IQR 0.6-7.8 years), median age at diagnosis of gonadal dysfunction was 14.0 years (IQR 11.5-15.3 years). In five females, gonadotrophin levels decreased over time with eventual recovery of gonadal function. No females were diagnosed with hypogonadotropic hypogonadism.

Twenty-one patients received HRT, which could be discontinued in six. Four out of eight patients who had undergone cryopreservation of one ovary developed gonadal dysfunction, of whom three received HRT. Ten patients received GnRHa treatment during HSCT; five of them developed gonadal dysfunction and from two no follow-up data on gonadal function were available. Gonadal dysfunction was significantly more common in females who received busulfan-based compared to treosulfan-based conditioning, 16/17 (94%) versus 5/15 (33%). Bivariate multistate analysis, including HSCT indications, showed a HR for busulfan versus treosulfan of 10.6 (95%CI 2.2-52.7, p=0.004) and a HR for BMF versus IEI/IEM of 0.2 (95%CI 0.05-0.8, p=0.03, Supplementary Table 4).

Table 2. Female gonadal dysfunction and risk factors

	Gonadal dysfunction	**No gonadal dysfunction**	**p-value[a]**
	N=24	**N=20**	
Pubertal status at HSCT			0.4
Prepubertal	12 (48%)	13 (52%)	
(Post)pubertal	12 (63%)	7 (37%)	
Conditioning			<0.001
Busulfan based	16 (94%)	1 (6%)	
Treosulfan based	5 (33%)	10 (67%)	
TBI/TAI based	2 (100%)	0 (0%)	
Others	1 (10%)	9 (90%)	
Underlying disease			0.01
Inborn errors of immunity/metabolism	11 (85%)	2 (15%)	
Bone marrow failure disorders	5 (31%)	11 (69%)	
Hemoglobinopathies	8 (53%)	7 (47%)	

HSCT hematopoetic stem cell transplantation, TAI total abdominal irradiation, TBI total body irradiation.
[a]Univariate analysis by Fisher's exact test.

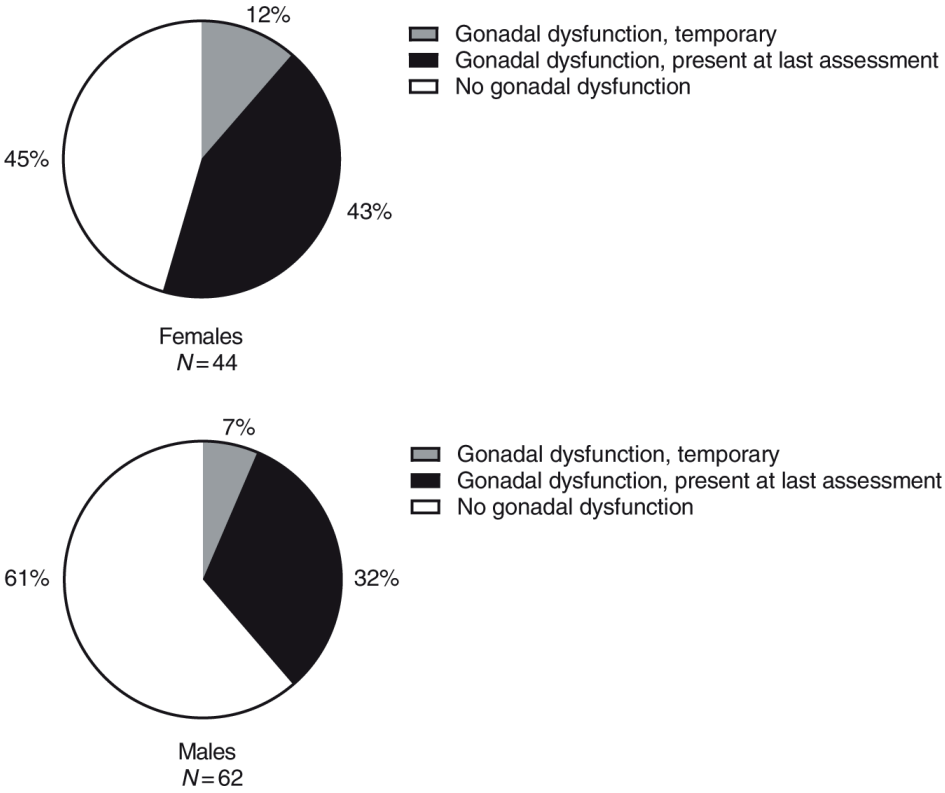

Fig 2. Gonadal dysfunction by gender

Gonadal function in male patients

At last follow-up 67 of 134 males were (post)pubertal of whom 62 patients were included for evaluation of gonadal function. One patient was excluded due to missing data and four patients were excluded because of gonadal dysfunction prior to HSCT. At time of HSCT 19 (31%) were (post)pubertal, median age at HSCT was 7.6 years (IQR 4.1-13.2 years) and median age at last visit was 18.6 years (IQR 15.1-21.1 years).

In 24/62 (39%) gonadal dysfunction was observed, which was still present at last assessment in 20/62 (32%) (Table 3 and Fig 2). Median time from HSCT to diagnosis of gonadal dysfunction was 4.4 years (IQR 1.0-11.1 years), median age at diagnosis of gonadal dysfunction was 15.9 years (IQR 14.9-17.7 years). Hypogonadotropic hypogonadism was seen in two males. In one pituitary iron overload was suspected based on high serum ferritin levels after chronic transfusion therapy because of beta-thalassemia. Two males received HRT because of hypergonadotropic (n=1) or mixed (n=1) hypogonadism.

Table 3. Male gonadal dysfunction and risk factors

	Gonadal dysfunction	No gonadal dysfunction	p value[a]
	N=24	N=38	
Pubertal status at HSCT			
Prepubertal	12 (28%)	31 (72%)	0.04
(Post)pubertal	12 (63%)	7 (37%)	
Conditioning			0.009
Busulfan based	17 (46%)	20 (54%)	
Treosulfan based	2 (14%)	12 (86%)	
TBI/TAI based	2 (40%)	3 (60%)	
Others	3 (50%)	3 (50%)	
Underlying disease			0.13
Inborn errors of immunity/metabolism	7 (29%)	17 (71%)	
Bone marrow failure disorders	9 (53%)	8 (47%)	
Hemoglobinopathies	8 (38%)	13 (62%)	

HSCT hematopoetic stem cell transplantation, TAI total abdominal irradiation, TBI total body irradiation.
[a]Univariate analysis by Fisher's exact test.

Gonadal dysfunction was significantly less common in males who were prepubertal versus (post)pubertal at HSCT (28% versus 63%, HR 0.11; 95%CI 0.05-0.21, p<0.001, Table 3). In males who received busulfan-based conditioning 46% developed gonadal dysfunction, compared to 14% in patients with treosulfan-based conditioning; this difference was not statistically significant (HR 3.1; 95%CI 0.7-13.3, p=0.14)

Thyroid complications

Data on thyroid function were available from 189 of 197 patients. Two were excluded from this analysis because of a diagnosis of hypothyroidism prior to HSCT. Thirty-four patients (18%) developed thyroid complications after a median duration of 21.0 months (IQR 11.0 - 27.0 months) post-HSCT. One female was diagnosed with papillary thyroid carcinoma 16 years after HSCT; she had received TAI (4 Gy). In 29 patients (16%) hypothyroidism was diagnosed (overt, n=7; subclinical, n=19; or central, n=3). Primary or central hypothyroidism was still present at last assessment in 8 of 187 patients (4%). All six patients (3%) with primary hypothyroidism had positive thyroid peroxidase (TPO) antibodies. In one patient the sibling donor had (in retrospect) also been diagnosed with auto-immune hypothyroidism. No association was found between the underlying diagnosis of patients with auto-immune hypothyroidism compared to patients with normal thyroid function after HSCT. All six patients showed complete chimerism and had no endocrine dysfunction before HSCT. Fourteen patients (7%) required thyroxin treatment. In patients who

received busulfan-based conditioning 24% developed hypothyroidism, compared to 8% in patients with treosulfan-based conditioning (HR 1.6; CI 0.6-4.5, p=0.31). Hypothyroidism was observed in 1/8 patients who received TAI (4 Gy).

Transient hyperthyroidism occurred in four patients (2%). Anti-TSH receptor antibodies were positive in one and anti-TPO antibodies were positive in two of these patients.

Growth

Growth hormone treatment was used in 18 of 197 patients and these were excluded from the analysis. At last visit, 79 of 179 patients had reached NAH (44%) and in 60 of them MPH was known (Supplementary Table 5). Overall, median height SDS did not significantly change between HSCT and last follow-up, with a median change of 0.0 SDS (IQR -0.6-0.4). Nineteen percent of patients had SS (NAH < -2 SDS). In 7 of 34 males (21%) and 2 of 26 females (8%) NAH was more than 2 SDS below MPH; five of them already had a height more than 2 SDS below MPH at HSCT (Fig 3 and Supplementary Table 5). Univariate regression analysis did not identify factors associated with distance of NAH to MPH more than 2 SDS.

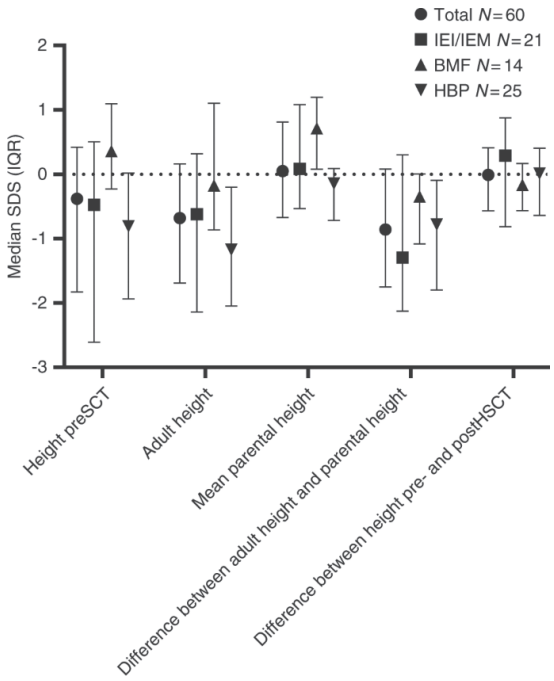

Fig 3. Growth outcomes by underlying condition

Multiple endocrine complications

To investigate to what extent gonadal dysfunction, thyroid complications and growth failure cluster, we calculated the number of endocrine complications per patient in 54 patients who had reached NAH and were (post)pubertal at last visit. In total, 33 patients (61%) had at least one endocrine complication and 25 patients (46%) had a complication that was still present at last assessment (Fig 4). Eleven (20%) had more than one endocrine complication and seven (13%) more than one complication present at last assessment.

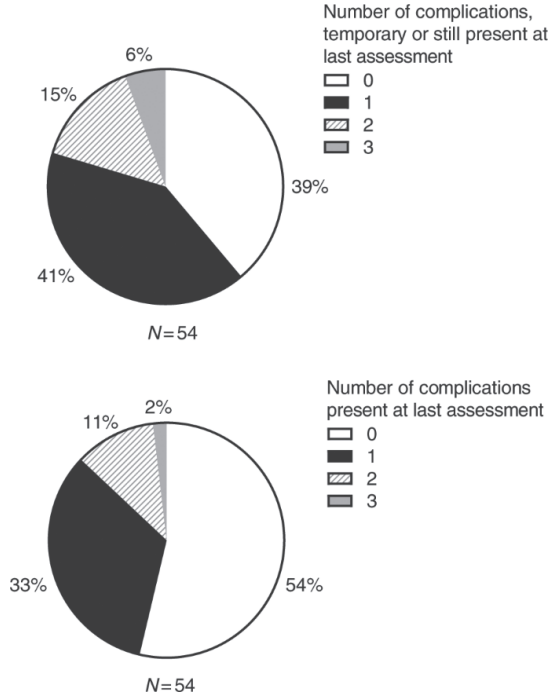

Fig 4. Frequency of multiple complications

DISCUSSION

The aim of our study was to identify the prevalence of, and risk factors for, late endocrine effects after HSCT in children transplanted for nonmalignant diseases to optimize treatment regimens, improve shared decision making before HSCT with patient and parents and aid in developing optimal clinical guidelines for screening of late effects. Our study reports a high cumulative incidence of 61% of endocrine complications in survivors of pediatric HSCT for nonmalignant diseases. Previous studies, mainly in malignant diseases, showed a similar incidence of endocrine complications after HSCT, ranging from 59 to 65% (16-18). This may seem surprising, as children with malignant disease have usually received more extensive chemotherapy and/or irradiation prior to HSCT. However, in children transplanted for nonmalignant diseases factors other than the conditioning may contribute to endocrine complications, such as iron overload due to chronic transfusions, the use of immunosuppressive agents and the underlying diseases themselves.

Gonadal dysfunction

Gonadal dysfunction was the most frequent endocrine complication in both females and males, seen in respectively 55% and 39%. We demonstrate that females were more likely to develop gonadal dysfunction after busulfan- than after treosulfan-based conditioning and in males a similar trend was seen. Previous studies, mainly of HSCT for malignant diseases, reported a similarly high risk of gonadal dysfunction after busulfan-based conditioning in both males and females (19-25). We also observed an increased risk of gonadal dysfunction in males who were (post)pubertal at HSCT. This is in line with other reports (26-28), although the opposite has also been reported (29). All parents and patients should be counseled about the risk of gonadal dysfunction and should be offered fertility preservation prior to HSCT, in particular patients with busulfan conditioning and males that are (post)pubertal at HSCT. The significantly higher risk of gonadal dysfunction after busulfan needs be taken into account when selecting a conditioning regimen. In addition, animal studies are providing insight into the mechanisms by which gonadal damage occurs, which will hopefully lead to future strategies to prevent gonadal toxicity due to conditioning (30, 31). However, factors other than conditioning-related toxicity may also play a role in certain patient groups, as a recent study found that endocrinopathies including primary ovarian insufficiency frequently occurred among individuals with immunodeficiencies who had not been transplanted (32). We also observed a particularly high rate of gonadal dysfunction among females with IEI/IEM (11/13). Further research is necessary to unravel the role of underlying genetic defects and immune dysregulation in the pathophysiology of gonadal dysfunction in order to identify ways to improve outcome.

Several guidelines on follow-up after HSCT for HBP, BMF or SCID, recommend annual assessment of pubertal progress and laboratory evaluation of gonadal function

starting 12 months after HSCT or without specifying when screening should start (5, 33, 34). Based on the high incidence of gonadal insufficiency among females, the finding that half of them were diagnosed with this complication within 1 year post-HSCT and the fact that most required treatment we recommend earlier screening, from 6 months post-HSCT to ensure early detection and appropriate treatment of hypogonadism (Table 4). Importantly, several individuals had temporary gonadal dysfunction with elevated gonadotrophin levels in the initial post HSCT period that normalized over time indicating recovery of gonadal function, as has been reported in previous studies in patients transplanted for severe aplastic anemia (SAA) or malignancies (35-38). Patients should be counselled about the possibility of ovarian recovery and advised about contraceptive measures.

Table 4. Recommendations for endocrine follow-up in nonmalignant HSCT survivors

Endocrine system	Follow-up recommendations
Growth	Measure height and weight annually. In case of short stature and/or growth deflection perform laboratory evaluation for short stature and determine bone age. Refer patients with poor growth to an endocrinologist to consider GH treatment.
Thyroid	Perform thyroid function tests (TSH, free T4) annually. Refer patients with abnormal results to an endocrinologist for advice on treatment.
Gonads - females	Evaluate Tanner stage and menstrual cycle annually until adulthood. In females aged ≥11 years: • Measure sex steroid and gonadotropin levels (FSH, LH, estradiol) annually until menarche has occurred; thereafter repeat in case of menstrual irregularities amenorrhea or in case of wish to evaluate with regard to fertility. • Consider measuring Anti-Mullerian hormone (AMH) at least once. Refer patient with pubertal delay, amenorrhea and/or abnormal laboratory results to an endocrinologist or gynaecologist for advice on treatment.
Gonads - males	Evaluate Tanner stage annually until adulthood. In males aged ≥12 years: • Measure sex steroid and gonadotropin levels (FSH, LH, testosterone). Consider repeating these measures annually. • Repeat measures in case of symptoms/signs suggestive of hypogonadism. • Consider measuring Inhibin B at least once. Refer patient with pubertal delay, abnormal progression of puberty and/or abnormal laboratory results to an endocrinologist or andrologist for advice on treatment.

We recommend screening at 6 months post HSCT, 12 months and then annually.

Thyroid function

In our cohort 18% of patients developed thyroid complications and 7% were treated with thyroxin. The overall reported incidence of thyroid disease in survivors of HSCT in childhood for malignant and nonmalignant diseases is similar, with incidences ranging from 10-24% (39-41). A number of mechanisms may explain abnormalities in thyroid function after HSCT. In our cohort, all patients with persistent primary hypothyroidism (3%) had anti-TPO antibodies pointing to immune mediated endocrine dysfunction. Auto-immune hypothyroidism in transplanted children has been observed in previous studies with a similar incidence (42), while in the general population a lower incidence has been reported, around 1-2% (43). An unexplained GvHD-like phenomenon is suggested to play a role (40, 42, 44, 45), which is supported by a study that found thyroid dysfunction to be 8.4 times more likely after HSCT with an unrelated donor compared to matched sibling donors (46) and the absence of development of auto-immune thyroid dysfunction with use of T cell-depleted grafts (42). Furthermore, the underlying conditions are suggested to explain some of the thyroid complications as the risk of thyroid disease is elevated in for example IPEX, Fanconi anemia and beta-thalassemia (44, 47-49). Our study did not show an association with diagnosis, GvHD, donor type, serotherapy or chimerism and although thyroid dysfunction was more common in the group with busulfan- compared to treosulfan-based conditioning this difference was not statistically significant. Previous studies have shown that even radiation free conditioning seems to increase the risk of thyroid dysfunction and found a trend toward more thyroid dysfunction after myeloablative compared to reduced intensity conditioning (40, 41). In total, 35% of patients developed thyroid dysfunction more than 2 years post HSCT and were asymptomatic at diagnosis stressing the importance of prolonged annually screening.

Growth

In our study height SDS did not change between HSCT and last follow-up, in line with several previous studies in both nonmalignant (SCD and TM) and malignant diseases when using radiation-free conditioning (50-53). Nonetheless, almost 20% of patients ended with a short NAH and 21% of males and 8% of females had a NAH more than 2 SDS below MPH. One study reported a similar incidence of SS of 15% at last visit (not final height) in TM patients treated with HSCT. However, another study reported no significant difference between height at last follow-up and mid-parental height in patients with SCD (16, 52).

The high incidence of growth failure, frequently already present preSCT, suggests underlying conditions themselves rather than HSCT may play a large role in growth impairment. Many diagnoses are associated with SS including TM, SCD, Fanconi

anemia and several IEI/IEM syndromes (54-57). Our study did not show that SS or difference between adult height and MPH was associated with factors as age at HSCT, gender, pubertal stage, diagnosis, GvHD and donor type.

Previous studies report conflicting results to what extent busulfan based conditioning causes growth impairment (58, 59). The current study did not find an association of poor growth outcome with any of the conditioning regimens. Given the high prevalence of SS, which was likely underestimated due to exclusion of patients treated with growth hormone, growth monitoring is warranted and in those with growth failure growth hormone treatment may be considered (60-62).

To our knowledge this is one of the largest studies investigating multiple endocrine complications after HSCT in children with nonmalignant diseases. The strengths of the study are the large cohort and the systematic long-term follow-up in which dedicated pediatric endocrinologists performed a yearly clinical and biochemical evaluation. The variety of primary diagnoses also is a strength on the one hand, but this, together with the range of different conditioning regimens, also makes it difficult to determine the individual factors associated with endocrine complications. Large registries, such as the EBMT registry, should allow future studies among larger cohorts with a specific diagnosis rather than the broad diagnostic groups used in the current study, and assessment of the interaction of that specific diagnosis with the transplant process and other relevant factors that may modify outcome (such as iron overload in HBP). This will be necessary to define diagnosis-specific strategies to prevent endocrine complications and to develop diagnosis-specific recommendations for follow-up, as are currently available for some diagnoses (5, 33, 34).

Although the median duration of follow-up in the current study was over 6 years, this might still have been insufficient to evaluate long-term complications and potential recovery over time in all patients. Other limitations are the exclusion of patients with re-transplantation or death within 2 years after HSCT which constitutes a risk of bias and exclusion of 18 patients treated with growth hormone which might have caused an underestimation of the negative impact of HSCT on growth. Lastly, we were unable to assess infertility due to the relatively young age of the cohort in the current study, but this is an essential part of gonadal function and certainly deserves further investigation. In addition, impact on quality of life of the various endocrine complications needs to be evaluated.

In conclusion, this study shows that the majority of patients treated with HSCT for nonmalignant conditions during childhood developed one or more endocrine complications. Gonadal dysfunction was the most common late effect seen in

55% of females and 39% of males, whereas SS and thyroid dysfunction occurred in nearly 20%. Therefore, we recommend counseling about endocrine late effects and the option of fertility preservation before HSCT and at least yearly evaluation of growth, pubertal development and thyroid function starting 6 months post-HSCT. Busulfan based conditioning was associated with a significantly higher risk of developing gonadal dysfunction in females. This should be taken into account when deciding upon conditioning regimens. Further research is necessary to gather diagnosis-specific knowledge on endocrine complications after HSCT and the pathophysiology in order to develop strategies to prevent these complications and refine recommendations for follow-up.

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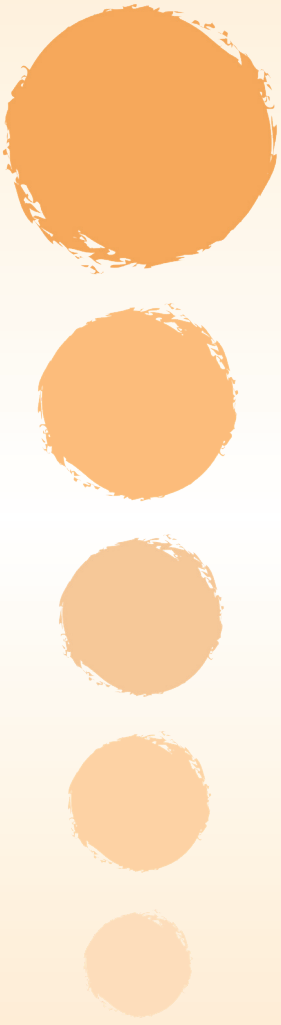

Chapter 4

Exploring the long-term psychosocial Impact of paediatric haematopoietic stem cell transplantation for nonmalignant diseases

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ABSTRACT

Introduction

An understanding of the long-term psychosocial impact of paediatric haematopoietic stem cell transplantation (HSCT) for nonmalignant diseases is needed to optimize pre-HSCT counselling, supportive care and long-term follow-up programmes after HSCT for this group of patients and caregivers.

Methods

This qualitative study included 14 patients who underwent transplantation for a nonmalignant disease during childhood. In-depth interviews were held online to explore patients' perspectives on the long-term psychosocial impact of HSCT on their lives. The results were analysed based on the Grounded Theory approach.

Results

Patients' median age at the time of the interview was 19 years (range: 14–49), and the median years after HSCT was 12 years (range: 3–33). Four main themes were identified: (1) doing okay, (2) experiencing persistent involvement with healthcare services, (3) influence on relationships with loved ones and (4) impact on the patient's life course. Subthemes extracted were doing okay, feeling of being cured, health limitations, sense of vulnerability, ongoing connection to the hospital, acceptance, friendship, family relations, development of own identity, not taking life for granted, social development, impact on (school) career and thinking about the future.

Conclusions

Patients reported active coping strategies and resilience after this high-impact treatment. The data highlight the need for patient-adjusted supportive care, indicating more need for supportive care in the long-term outpatient clinic.

Patient Contribution

This study included patients as participants. Caregivers were approached if patients were below a certain age. Additionally, preliminary results were presented during a patient conference day.

INTRODUCTION

Paediatric allogeneic haemotopoietic stem cell transplantation (HSCT) is a curative treatment option for various malignant and nonmalignant diseases.[1] The list of indications for paediatric HSCT for nonmalignant diseases is increasing and is commonly divided into three categories: haematologic (e.g., severe aplastic anaemia, sickle cell disease), metabolic (e.g., Hurler's disease), or immunological (e.g., severe combined immunodeficiency) diseases.[2] Some of these diseases are life-threatening, others are life shortening and decrease quality of life. Due to ongoing advances in HSCT procedures and concomitant improvements in survival, the long-term physical and psychosocial outcomes of HSCT are becoming increasingly important.[3,4] While the psychosocial outcomes of HSCT for malignant indications have been characterized, data are scarce for patients with a nonmalignant disease.[5-8] The most frequently described long-term psychosocial effects of HSCT for childhood cancer are: anxiety, depression, posttraumatic stress reactions and behavioural and social problems. Both mental and physical late effects are likely to have a negative impact on patients' quality of life.[5,7,9-11] Many children with nonmalignant diseases have already been coping with morbidity and chronic disease in the years before HSCT, often resulting in impaired quality of life.[12,13] HSCT is generally well known as curative treatment for malignant diseases, this does not however apply to nonmalignant diseases resulting into lack of peer support for these patients. There are no separate patients' associations for HSCT patients with nonmalignant diseases, as there are for patients with paediatric cancer.

A better understanding of the long-term psychosocial impact of undergoing paediatric HSCT for nonmalignant diseases is needed to optimize pre-HSCT counseling, supportive care and long-term follow up programmes after HSCT for this group of patients. In this study, we explored patients' perspectives on the long-term psychosocial impact of HSCT on their lives.

METHODS

Study Design and Participants

A qualitative descriptive design was used to determine patients' perspectives on the long-term psychosocial impact of HSCT on their lives. In-depth interviews were held by videoconference, due to COVID-19 restrictions, from April-May 2021. Patients were interviewed one-on-one, and invited to be accompanied by their caregivers if they preferred. Companions were instructed to interfere as little as possible. The researcher conducted the interview using a topic guide consisting of open questions (Supporting Information Table S1). All interviews were video-

recorded and transcribed verbatim. Field notes were taken about the researchers' reflections on the interview themes. Data collection continued until data saturation was reached, which was defined as no new findings emerging in the analysis of the three latest consecutive interviews. The research team consisted of four researchers with expertize in the HSCT field and qualitative research: L.t.W. (BSc, Master student, Medicine), J.B. (MSc, PhD candidate paediatrics), A.h.P. (PhD, cognitive psychologist) and A.d.P. (MD, PhD, paediatrician-hematologist). All interviews were performed by an independent researcher (L.t.W.), who did not have any (treatment) relationship with the participants. This was made clear to the participants before the start of the interviews. The study protocol was approved by the medical ethics committee of Leiden University Medical Center (N20.181). Participants were approached by telephone (J.B.), had received complete study information and provided written informed consent. At age 15 or younger additional assent was provided by (both) caregivers.

All patients who underwent an HSCT during childhood for a nonmalignant disease in the Willem Alexander Children's Hospital in Leiden, The Netherlands were eligible to participate in this study. Further eligibility criteria included HSCT 2 or more years ago, being ≥12 years of age at the time of the interview and having adequate knowledge of the Dutch or English language. Patients were selected using purposeful sampling based on age (age categories 12-18, 18-25, >25) and diagnosis (inborn errors of immunity, bone marrow failures, haemoglobinopathies).

Data Analysis

Interviews were thematically analysed to find common patterns using the comprehensive 10 step method of the Qualitative Analysis Guide of Leuven (Supporting Information Table S2), which is based on the Grounded Theory associated with Charmaz.[14-21] The whole process consisted of constant comparison and continuous checking of the interview data. Each transcript was analysed by two independent researchers. The researcher who conducted the interviews was a permanent part of the data collection and analysis process. The other researchers on the team (J. B., A. h. P., A. d. P.) alternated in the role of second coder and analyser of the transcripts. Each step was first performed by the researchers individually, after which they came together to compare their findings and discuss discrepancies until consensus was reached about key storylines, coding fragments, categorizing concepts and interpreting the data. Data collection and analysis took place parallel to each other. Final coding was entered into the qualitative data analysis software ATLAS.ti (version 8).[22] In addition, the COREQ checklist for qualitative studies was used for explicit and comprehensive reporting (Supporting Information Table S3).[23]

RESULTS

Eighteen participants were approached, and fourteen participants were willing to participate, with an equal gender distribution. Ages ranged from 14 to 49 years, and the interview took place at a median of 12 years (range: 3–33) after HSCT. Six participants were long term (2–10 years) after HSCT, and eight were very long term (>10 years) after HSCT. Indications for HSCT were inborn errors of immunity (n = 4), haemoglobinopathies (n = 4) or bone-marrow failures (n = 6) (Table 1). The median interview duration was 35 min (range: 27–57). One participant preferred company from an adult caregiver. From the coding and categorizing of data, four main themes on psychosocial impact of paediatric HSCT emerged: (1) Doing Okay, (2) Experiencing persistent involvement with healthcare services, (3) Influence on relationships with loved ones and (4) Impact on participant's life course. Illustrative quotations are given per theme (Tables 2–5).

Table 1. Patient characteristics (*N* = 14)

Characteristics	Median (range)
Gender	
Male	7
Female	7
Age at HSCT (in years)	10 (1–18)
Age at interview (in years)	19 (14–49)
Years since HSCT	12 (3–33)
Diagnosisa	
Inborn errors of immunity	4
Haemoglobinopathies	4
Bone marrow failures	6
Second HSCT	2

Abbreviation: HSCT, haematopoietic stem cell transplantation.
[a] Conditioning regimens were busulphan-based (*n* = 3), treosulphan-based (*n* = 4), cyclophosphamide + TBI/TAI (*n* = 2), cyclophosphamide-based (*n* = 3), fludarabine-based (*n* = 1), no conditioning (*n* = 1). In the case of multiple HSCTs, the conditioning regimen of the first HSCT is reported.

Doing okay

Doing okay

Almost all participants reported that they were ‘doing okay’ in their daily life. The participants were able to live the life they wanted and were feeling good. Many participants experienced late effects or needed medical treatment at the time of the interview. At the same time, the participants reported hardly any inconvenience in daily life from the disease and transplantation-related late effects.

Feeling of being cured

The participants were positive about their recovery after HSCT. However, some participants mentioned that the recovery took a long time, and that they had experienced some setbacks (e.g., slow immune reconstitution, sequelae of graft-vs.-host disease). The majority of the participants reported considering themselves as cured from the original disease, and had been able to leave the HSCT procedure behind them at some point.

Experiencing persistent involvement with healthcare services

Health limitations

The participants reported limitations in daily life due to late effects/complications of the HSCT. Multiple late effects were reported, such as loss of fertility, alopecia, skin abnormalities or growth abnormalities. Fatigue was one of the most frequently experienced side effects, mainly during the first few years after transplantation. All participants experienced physical, social and emotional limitations due to the side effects. As a consequence, some participants reported limitations in daily activities and needed medical care. In addition, the participants indicated that they had needed to make adjustments in daily life and had had to learn and rebuild life skills after the transplantation (e.g., rebuilding physical health, and only gradually returning to school).

Sense of vulnerability

The participants reported feeling more susceptible to health issues compared to their peers. A few participants still did not feel completely healthy and reported being afraid of the possibility of experiencing new complications or disease recurrence. The participants reported frequent hospital visits for follow-up and were aware of the possible late effects. Additionally, the participants were warned of possible health hazards, such as a COVID-19 infection. All these factors exacerbated the participants' sense of vulnerability. For example, one participant stopped pursuing her healthcare study after her physician had warned her about her increased susceptibility to a COVID-19 infection.

Ongoing link with the hospital

Many participants needed medical help after the HSCT (e.g., consulting a psychologist or social worker, undergoing trauma therapy, participating in online psychological self-help programmes, having operations, being admitted to the hospital, undergoing additional hospital checks, getting revaccinations and undergoing fertility treatments). Help was frequently sought at the initiative of the participant or was offered by the hospital. Some participants indicated that, in retrospect, medical

help after discharge from the hospital had been insufficient or wished they had sought help sooner. Furthermore, the participants visited the hospital frequently for check-ups, used medication on a daily basis or regularly had memories about the HSCT and the hospital. Some participants admitted that they experience the physical examinations and additional tests at the hospital as unpleasant. A few participants mentioned not being compliant with the therapy, as they did not notice that it made any difference to their overall condition. Lastly, nearly all of the participants mentioned occasionally looking back on the HSCT and hospital admission. These memories were generally positive and pleasant. A few participants reported experiencing anger or fear while thinking back to the HSCT.

Acceptance

The participants indicated having a degree of acceptance on various aspects related to HSCT. The participants got used to the regular check-ups and examinations at the hospital, and some stated that it helped them to feel more certain about their physical status. Additionally, the participants reported accepting the side effects. A few participants reported feeling unique because of the side effects. Lastly, the participants accepted that they had received a transplantation and felt relieved from the burden of the original disease. The participants accepted the HSCT as part of themselves and of their lives.

Influence on relationships with loved ones

Friends

For most participants, the HSCT did not affect current friendships. The participants felt supported by their friends, and after returning to school, most participants rejoined friends without problems. When encountering new friends, the participants informed them about the HSCT and current relevant side effects. One participant reported losing friends due to the HSCT.

Family relations

Some participants experienced changes in family relations as a result of the HSCT. Family relations had become closer and more equal (e.g., parent–child equality). The participants underlined receiving a lot of family support, both during and after the HSCT. However, a few participants mentioned that family relations had been damaged or that they had become more dependent on their family due to the HSCT. Some of their family members were very concerned and protective in the first few years after transplantation. The participants sometimes experienced this as annoying, but generally understood it well. Some participants had received stem cells from a family member. The experiences and thoughts about family donor tissue

varied greatly, ranging from experiencing it as nice and personal to the feeling of being indebted to that family member.

Impact on participants' life course

Development of own identity

Some participants struggled with existential questions, for example, who they are without the disease. Furthermore, the participants mentioned wanting to be independent and to make their own choices without being restricted by the HSCT. A number of participants underlined feeling different from their peers sometimes. In addition, some participants mentioned that it took a while to get used to the idea of having received stem cells from an unknown donor, and how this had raised questions about their 'self'.

Not taking life for granted

Having undergone transplantation during childhood means that the participants had faced issues of life and death at a young age, and some reported taking life less for granted. The participants reported being grateful for their lives and health. A few participants reported being proud of life achievements, in view of the health challenges that they had faced. Moreover, some participants described the HSCT as life-saving and were generally grateful for having received the HSCT.

Social–emotional development

A much-discussed topic included the (dreaded) reactions of others to the visible physical consequences of the HSCT, such as alopecia, low voice, skin abnormalities or growth abnormalities. The participants mentioned regularly receiving comments or questions, mostly from strangers, leading to feelings of insecurity. A few participants admitted to avoiding public places because of these reactions, which made them feel restricted in establishing relationships. Some participants felt unsure about whether they would be perceived to be attractive by (potential) partners. Moreover, due to (anticipated risk of) infertility, some participants were afraid to disappoint their partner. The participants felt uncertain about acceptance by new friends. Experiencing stress before returning to school or feeling unable to keep up in class had led to experiencing a social gap with classmates. Furthermore, some participants reported having difficulties expressing emotions, as they lagged behind in learning how to regulate their emotions.

Impact on (school) career

Many participants did not advance to the next grade in the year they underwent HSCT and were frequently absent from school due to side effects (such as fatigue) in the first few years after HSCT. A few participants had felt restricted in terms of

career options due to the HSCT. The fear of complications or relapse or simply being confronted with memories of the HSCT had discouraged them from making more challenging school choices or pursuing particular career choices (such as not aiming for a higher school level, or prematurely terminating a study).

Thinking about the future

Most participants stated that their HSCT experience would not play a role in the future. Some reported concerns, for example, finding a job, given physical limitations, finding a partner, the extent to which late effects would remain and whether or not they will be able to have children. Some participants hoped that limitations due to late effects would diminish with time, or that goals could be achieved (e.g., improvement in physical health, being able to have children or to obtain a driver's license).

Table 2. Illustrative quotations from Theme 1 'Doing okay'

Subtheme	Sex	Age	Quotation
Doing okay	♀	16	'Yes, I'm doing really well. Besides the use of medication of course, I do not longer suffer from the transplantation. Or it's not that I notice in my daily life that, well, I've been transplanted. No, I'm just doing well'.
	♂	26	'Yes, I'm doing well. I am feeling comfortable in my own skin, and I don't experience consequences of the transplantation'.
Feeling of being cured	♂	14	'When I got out of the hospital and I was able to do things again, I basically left it all behind and started doing the things I like'.
	♂	18	'It just feels like nothing has ever happened. Like I'm completely cured'.
	♂	18	'Due to the transplantation I am able to do a lot more things. I feel normal now. Before the transplantation I really liked doing sports, but I always felt limited. Now, I don't feel that way anymore. When I am exercising, I can see myself growing and getting stronger. That feels great. So, that's how the transplantation has affected me'.

Table 3. Illustrative quotations from Theme 2 'Experiencing persistent involvement with healthcare services'

Subtheme	Sex	Age	Quotation
Health limitations	♀	20	'I was very tired for a long time, and I was not able to do all the things my peers were able to do. And that's still there every now and then. I really have to think about my daily schedule; when I'm doing X, Y, Z today, then I should skip this tomorrow, because otherwise it would be too tiring'.
	♂	14	'The left side of my body was paralyzed and is still functioning worse than my right side. However, it's not problematic as I use my right side the most. I write with my right hand. Some of my fingers can't move individually, which is somewhat annoying. But besides, it doesn't really bother me anymore'.
Sense of vulnerability	♀	49	[About checkups in the hospital]—'So, on the one hand it's nice it's all being monitored. On the other hand, it also stirs things up a lot. The week in advance I'm really, well, not upset, but caught up by it. I know that my body is not as strong as someone else's body without a transplantation. So, every check-up I face with the thought "oh god, what will be it this time"'.
	♀	20	'I've seen how fragile life can be and that's still stuck in my head. Still, the possibility of that happening again scares me'.
Ongoing connection to the hospital	♀	20	'But what came up recently, is I have difficulties undergoing examinations in the hospital. The transplantation is [x] years ago and mentally, I'm done with it'.
	♀	49	[About unfulfilled desire for having children]—'So I went to see a social worker a few years ago for support. At that time all my friends got pregnant, which was really intense. Despite new insights, it still remains a thing'.
Acceptance	♂	18	[About skin manifestations]—'It is what it is, and it belongs to me. And at some point, I embraced it'.
	♀	16	[About checkups in the hospital]—'Actually, it's all normal now. I got used to it and no longer I think "oh I have to go to the hospital". It's just a normal part of my life right now'.

Table 4. Illustrative quotations from Theme 3 'Influence on relationships with loved ones'

Subtheme	Sex	Age	Quotation
Friendship	♀	49	'Friends always visited me at the hospital. So eventually when you're back, you're just part of the group again. And it feels like nothing's happened'.
	♀	20	'Especially because I've lost friends due to my overload of emotional baggage. And I can understand that, but that's kind of... [...] When I make new friends it's just like "hey, I'm blind and I've had a stem cell transplantation". And that's something which influences me every day. So, that's quite anxious'.
Family relations	♀	16	'They're the best parents I could wish for. When I need their help, they're always there for me. They always support me with everything'.
	♂	28	'But my mother is always concerned. She has always said "take care of yourself" or "no, don't go" or "don't do it, just stay home"'.
	♀	16	'My parents told me a lot about how things went and what it was like. That really makes me emotional. Because when my mother talks about that time, she starts to cry. It makes me realize it actually is very serious'.
	♀	17	'But, compared to now, we grew apart. We're no longer the family of before and during the transplantation. That's a pity, because, for example my sisters grew up too. They wanted to continue with their lives and moved out. And now, it's just that I notice my family is not as close as it was in the past'.
	♀	29	'It's beautiful that my brother was my donor. So, that's nice, it's something personal. It would be different if it had been an unknown donor. So it's nice that my brother could do this as he was also very young at that time'.

Table 5. Illustrative quotations from Theme 4 'Impact on patient's life course'

Subtheme	Sex	Age	Quotation
Development of own identity	♀	17	'I'm really trying to find my identity. I am looking for who I am without the disease or who I am without the process of transplantation'.
	♂	26	'And that's a thing I learned this last year. That I should go my own way and not always do the things my mother does. That woke me up mentally and made me see I had to develop myself'.
	♀	16	'Of course you have to catch your breath, because it is a completely different person inside you. I received the immune system of someone else and have to get used to that'.
Not taking life for granted	♂	18	'I believe that as a kid you don't think about the consequences or the dark side of certain things. As the result of exposure, at some point, you start to think differently about those things. And you don't know how to deal with that yourself, because you're actually too young for that'.
	♀	29	'You really have to be aware of the fact that no one has promised you a new day. So, that's something you must be aware of in life. Because yes, you're alive, but it also could have ended differently. So, that's really something I remind myself of frequently'.

Table 5. Continued Illustrative quotations from Theme 4 'Impact on patient's life course'

Subtheme	Sex	Age	Quotation
Social development	♀	16	'People look at me strangely, as if I am a strange creature. People don't think it's normal that I'm short which gives me the feeling of not belonging here. That makes me feel sad and then I just don't dare going outside anymore. I then prefer to stay at home and not meet up with people'.
	♂	28	'It's hard when you get to know someone who wants to become a mother. It was very difficult to tell her it might not work out'.
	♀	40	'That was a really scary thing, to return to my old school. I didn't know my classmates anymore and it felt like a new school again'.
	♀	20	'Socially, I couldn't keep up very well. For example, I once in class heard two children behind me talking about 'oh we were at a party this weekend and the police came' and then I thought "are you proud of that?". That just felt like a very big gap, that they were concerned about such things while I was focusing on the next time I had to visit the hospital to get my blood checked and whether that would be okay or not. That created a big gap between me and my classmates'.
Impact on (school) career	♀	16	'Last year, my grades were pretty good and there was an opportunity to level up at school. Then we finally decided not to, because if I get sick for 2-3 weeks this winter, would I still be able to handle it? Or with corona for example, I could maybe become a vulnerable group when it would get worse. Therefore, with choices I think twice about "would it be wise?"'.
	♂	14	'And also, when I was allowed to get back to school again, it was very difficult to notice that I actually couldn't keep up as I was just too tired'.
(Worrying about) the future	♂	28	'So uh, I only hope I have kids then. [...] We only had an investigation once and then the doctors said the chance of getting pregnant in a natural way is not very big. But that was only one test, and with testing once, you will not always see all results. Yes, I think we have to do two more tests'.
	♀	16	'Because, if I want to get married, I have to find a man my height because, I can't be with a man who is much taller than me. So, I'll just have to see how things go'.
	♂	14	'As soon as my physical endurance is good again, I will no longer suffer from it'.

DISCUSSION

This study provides a qualitative exploration of the long-term psychosocial impact among survivors of paediatric HSCT for nonmalignant disease. The literature to date mainly focuses on patients with malignant conditions. Moreover, approaches using quantitative measures (e.g., questionnaires) are dominant in this field, which do address possible psychosocial topics, but are insufficient to provide broader insight on the psychosocial burden. This study reveals four main life areas in which patients experience the psychosocial impact of the HSCT. First, patients indicate that they are *doing okay* and feel cured from their original disease. Second, patients continue to *experience involvement with healthcare services* their entire life. This is mainly due to persisting side effects which negatively affect patients in their daily functioning, contribute to a sense of vulnerability and make them seek out medical support. Patients experience having a continuous attachment to the hospital, while at the same time, they downplay and accept side effects, check-ups in the hospital and having experienced the HSCT to a large extent. Third, HSCT *changes family relations and friendships* both in positive and negative ways. Lastly, HSCT *interferes with patients' course of life* in terms of their social development, progress in (school) career, development of identity and how they see the future.

Our study reveals some similarities to what has been observed in childhood cancer patients treated with HSCT. These patients also experienced social problems, social withdrawal, physical problems, changes in family relations, fear of disease recurrence, the desire to been seen as normal and impact on (school) career. Other similarities are the acceptance of serious side effects, ongoing use of medication, regular hospital check-ups and the feeling of being cured after HSCT.[5,8,24,25] The latter has also been reported among sickle cell disease patients after HSCT.[12] A study on cancer patients who sought psychotherapeutic help after HSCT found that patients felt different, lost contact with friends and showed family dependency[26], which is similar to our results. In contrast to what was reported in the former studies, the patients in our study did not experience symptoms of anxiety, depression, or ask themselves 'what if I didn't have received the HSCT'.[5,7,24] These complaints may be less common in patients with nonmalignant disorders, or may not have been experienced or expressed by the patients who participated in the interviews.

Unique psychosocial themes that emerged in our study include experiencing a continuous attachment to the hospital, not taking life for granted, the search for one's own identity and thinking about the future. Strikingly, a number of patients expressed remarkable contradictions between and within themes. More in detail, patients mentioned that they were doing okay (Theme 1), while also expressing feelings of vulnerability (Theme 2). In addition, patients indicated having a good relationship with friends, but sometimes also perceive a social gap with peers (Theme 3). Patients mentioned impactful limitations,

such as experiencing a persisting connection with healthcare services, having to deal with late effects on a daily basis and the HSCT influencing their life course. It has to be noted that most patients tended to tone down the limitations they experience. Clearly, these limitations play a significant role in the patients' lives, but accepting them or trying to accept them has become part of their identity. The extent to which patients accept side effects and check-ups at the hospital is remarkable. It indicates that patients have developed active coping strategies and resilience.

This study has a number of strengths. First, purposeful sampling of participants allowed to obtain a diverse study population, and there was a wide age range at the time of the interview and years since transplantation, which is key when exploring a topic. Second, the research team consisted of people with different professional backgrounds, and their different perspectives helped in identifying and interpreting the various themes and subthemes. Third, the interviewer was independent from the care team of the participants. This made it easier for the participants to feel free in openly sharing and discussing their feelings and experiences without fear of consequences for their care. Some limitations of this study need to be considered as well. First, some of the patients indicated that they did not know whether particular psychosocial experiences were fully attributable to the HSCT, or (also) to other conditions or life events. Second, the COVID-19 pandemic compelled us to hold the interviews digitally, which may have had some influence on the flow of the interview. Third, over the years treatment has been optimized. Patients undergoing transplants now may experience different psychosocial effects than the patients included in our study, of whom a substantial number had undergone transplantation in an earlier time period. Finally, due to the long time since undergoing HSCT, there is a possibility of recall bias.

CONCLUSION

This study reveals four main life areas in which patients experience the psychosocial impact of the HSCT. A number of clinical practice recommendations for improving healthcare can be formulated based on this study. Patients may not have been offered supportive care services after discharge. We recommend the initiation of individualized medical support directly after discharge.[25,27] Furthermore, making medical support an addressed topic at the hospital check-ups will add value in post-HSCT supportive care initiation, for example, using clear validated patient-reported outcome measures to initiate conversation about medical support. In future research, the long-term psychosocial impact of paediatric HSCT for nonmalignant diseases should be studied among larger patient samples and their caregivers, ideally in a multicentre setting. This would allow identification of priorities for

psychosocial support. The present study clearly points to a need to integrate pre-emptive psychosocial support in the multidisciplinary care pathways during HSCT treatment and follow-up for children with nonmalignant diseases.

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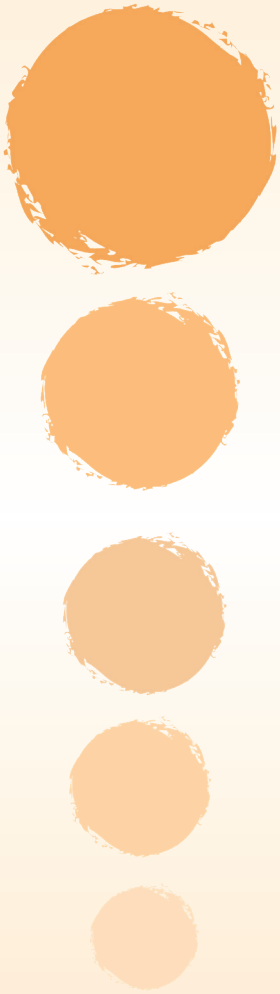

Chapter 5

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.

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.

METHODS

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.

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), 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 form 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).

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. 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.

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.

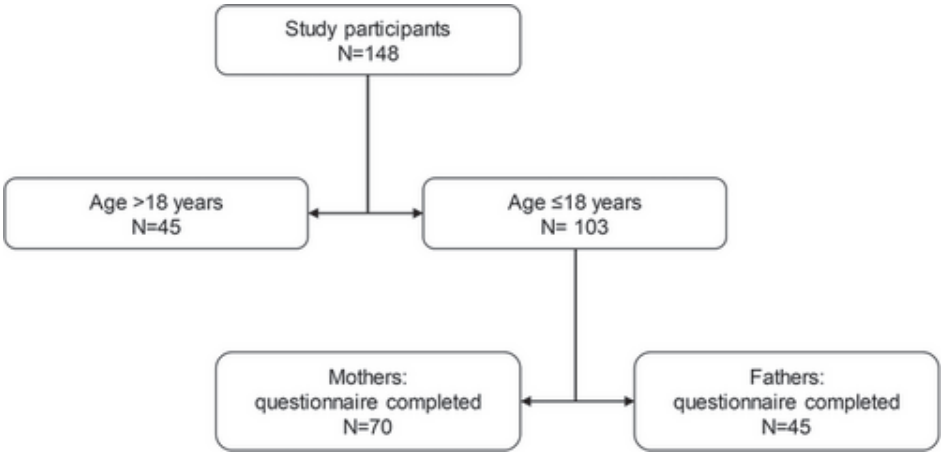

Figure 1. Flow chart of participants. All parents of pediatric hematopoietic stem cell transplantation (HSCT) recipients eligible for inclusion are shown.

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).

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	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.

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).

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

Table 3. Continued 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***
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
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

Table 3. Continued 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*
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.

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).

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).

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). 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).

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).

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).

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, which is in line with a qualitative study in parents of leukemia survivors.[5] In that study by Forinder et al (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 et al's (2004) study, 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 warranted. 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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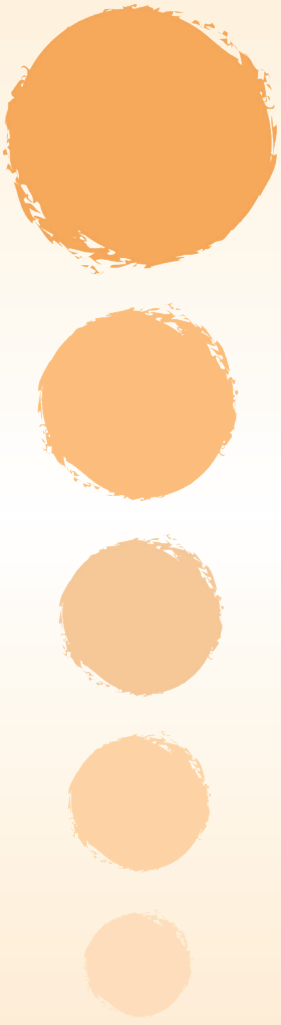

Chapter 6

Late effects in pediatric allogeneic hematopoietic stem cell transplantation for nonmalignant diseases: proxy- and patient-reported outcomes

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ABSTRACT

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.

INTRODUCTION

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 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 due 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 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).

MATERIAL AND 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 criteria was patients ≥2 years after undergoing pediatric allogeneic HSCT for a nonmalignant disease at the Willem Alexander Children's Hospital, Leiden University Medical Center. The exclusion criteria was inadequate knowledge of the Dutch language or psychological inability to fill in questionnaires, as determined by the primary physician at the late effects and 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

Validated PROMs were age-appropriate and selected based on Dutch availability and optimal international comparison (Supplementary Table S1). (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. 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.

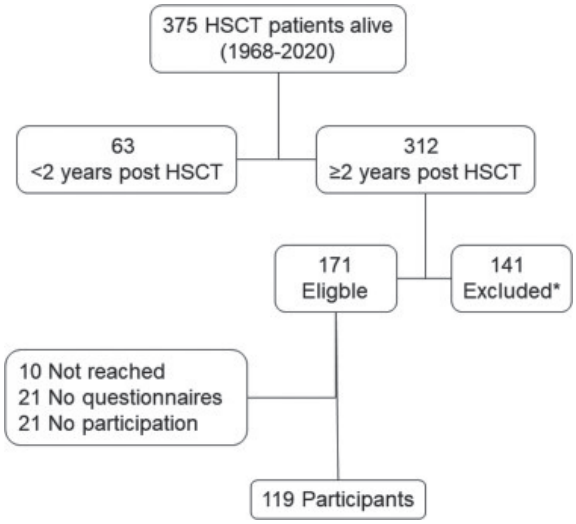

Figure 1. Flowchart showing inclusion and exclusion of patients. *Second HSCT (n = 2), autologous HSCT (n = 2), not at late effects follow-up outpatient clinic (n = 5), at request of primary physician (n = 7), development of myelodysplastic syndrome (n = 1), lost to follow-up (n = 124).

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	

Table 1. Continued Demographic Characteristics by Diagnosis

Characteristic	Total (N = 119)	IEI* (N = 41)	HB† (N = 37)	BMF‡ (N = 41)	*P* Value
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.

PedsQL: comparison to 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 ± 8.3 for children age 5 to 7 years, 87.9 ± 10.4 for children age 8 to 12 years, and 68.7 ± 13.5 for adolescents age 13 to 18 years (Supplementary Table S5). There are no reference data available for this module.

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.

PROMIS item banks: comparison to Dutch general population

Figure 2 present mean difference scores compared to Dutch reference data per age category (Table S6; for raw mean scores see Table S7). Children (5-7 years) show lower Fatigue scores and children (8-18 years) reported less Pain Interference than the reference population. Children (8-18) years reported more Sleep Disturbance, while young adults (19-30 years) reported this significantly less. Additionally, young adults (19-30 years) reported fewer Depressive Symptoms and reported higher Satisfaction with Social Roles and Activities. Adult scores (>30 years) were not significantly different from those of the reference population. Pain Intensity scores in young adults (19-30 years) and adults (>30 years) were 0.0 (SD 1.8) and -0.4 (SD 3.0), respectively, and were not significantly different compared to Dutch reference data.

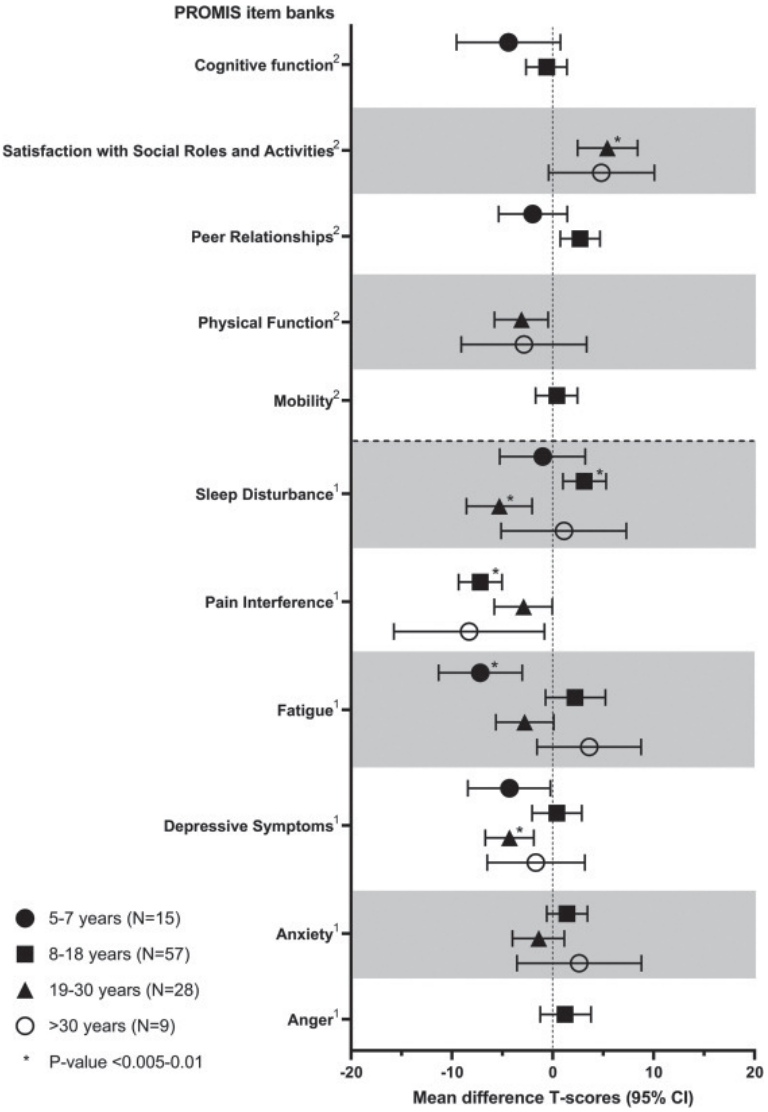

Figure 2. Mean difference scores compared to the Dutch general population (PROMIS item banks). [1]Higher scores indicate more symptoms; [2]higher scores indicate better functioning.

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

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)

* Higher scores indicate more symptoms.
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.**

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.**

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 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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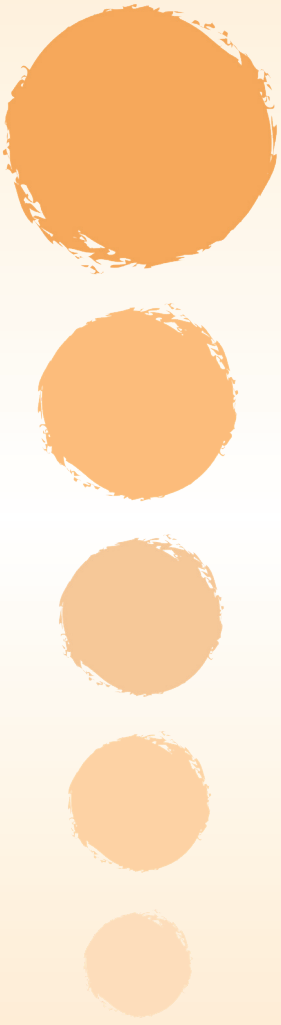

Chapter 7

The value of using patient-reported outcomes for health screening during long-term follow-up after pediatric stem cell transplantation for nonmalignant diseases

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ABSTRACT

Introduction

The assessment of using patient-reported outcomes (PROs) within comprehensive care follow-up programmes, specifically focused on health screening, remains largely unexplored. PROs were implemented in our late effects and comprehensive care programme after paediatric hematopoietic stem cell transplantation (HSCT) for nonmalignant diseases. The programme focuses solely on screening of physical and mental health and on discussing PROs during the consultation.

Methods

The primary method of this study was semistructured interviews to explore the perspective of both patients and healthcare providers' (HCP) on the use of PROs, which were thematically analyzed. Additionally, an explorative quantitative approach with patient-reported experience measures (PREMS) was used, with a pretest–posttest design, to assess whether the use of PROs was accompanied by more patient-centred care.

Results

From the patient-interviews (N = 15) four themes were extracted: use of PROs (1) help to discuss topics; (2) make the patients feel understood; (3) create a moment of self-reflection; and (4) make consultations more efficient. Pre- and postimplementation analysis of PREMs (N = 40) did not show significant differences in terms of patient-centeredness.

Conclusion

Our results demonstrate the added value of integrating PROs for health screening purposes within the long-term follow-up programme after paediatric HSCT, as perceived by both patient and HCP. With the active use of PROs, patients are stimulated to consciously assess their health status.

Patient Contribution

This study included patients as participants. Caregivers were approached if patients were below a certain age. Additionally, preliminary results were shared with all patients (including nonparticipants) during a patient conference day.

INTRODUCTION

Patient-reported outcomes (PROs) are increasingly applied in hematopoietic stem cell transplantation (HSCT) for the purpose of collecting data for research or monitoring symptoms.[1,2] However, PROs can also be used to better understand the patients' needs, and to support shared decision-making (SDM).[3,4] Integrating PROs into routine care offers the healthcare provider (HCP) the opportunity to identify essential topics and address problems early on, provide personalized support, make timely referrals, and consequently improve quality of care.[5,6] PROs have been incorporated into the late effects (LEEF) and comprehensive care follow-up programme after paediatric allogeneic HSCT for nonmalignant diseases. The integration of PRO in this programme was part of the implementation of value-based healthcare in this care path, aiming to enhance healthcare quality further.

HSCT has proven to be an intensive, curative treatment option for various severe paediatric diseases, including nonmalignant disorders such as inborn errors of immunity, hemoglobinopathies and bone marrow failure syndromes.[7,8] Due to the HSCT procedure, consisting of chemotherapy and immunosuppressants, or due to the underlying disease, potential late effects can arise, such as gonadal dysfunction, renal insufficiency and cognitive problems, which consequently impair health-related quality of life.[9-14] Proper screening for these late effects requires a dedicated long-term follow-up programme, which has been implemented at the Leiden University Medical Center (LUMC) in the Netherlands, providing comprehensive care from 2 years after HSCT onwards.[9,10] The programme includes annual monitoring of both physical and mental health (Supporting Information S1: Figure 1), and continues throughout adulthood due to the potential for late effects to occur even many years after paediatric HSCT.

Current research on the value of PROs in healthcare has predominantly focused on diseases where intervention efficacy, symptom control, or cure were the primary treatment objectives.[6,15] However, the value of PROs has not been investigated in care paths for screening programmes, where active healthcare utilization and overt disease symptoms may be absent. Therefore, the aim of this study was to explore patients', caregivers' and HCPs' experiences with the active use of PROs during consultations in the late effects and comprehensive care (LEEF) programme after paediatric HSCT for nonmalignant diseases. Furthermore, the study aimed to evaluate the impact of PRO use on patient-centred care.

MATERIALS AND METHODS

PRO implementation

PROs were implemented in routine care in the LEEF programme in September 2021 (Figure 1). PRO domains from the International Consortium for Health Outcomes Measurement Standard Set 'Overall Paediatric Health' have been selected by consensus among both patients and the clinical team of the LEEF programme.[16] Age-appropriate and validated patient-reported outcome measures (PROMs) were identified and selected based on their availability in Dutch (Supporting Information S1: Table 1). 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.[17-28] Patients completed PROMs before their consultation using the digital KLIK PROM portal (www.hetklikt.nu).[29] In addition, patients completed a symptom checklist (Supporting Information S1: Table 2). The HCP retrieved the PRO results in an electronic PROfile and discussed them with the patient during the consultation, for which the HCPs received training.[30]

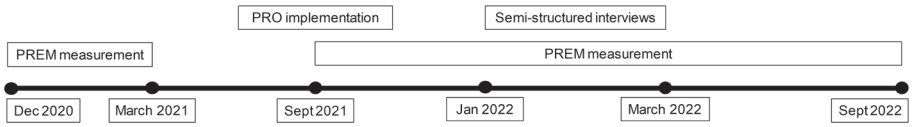

Figure 1. Overview measurements over time. Shown are the measurements within this study over time. The measurements involve PREMs, PRO measures, and semistructured interviews. PREM, patient-reported experiences measures; PRO, patient-reported outcome.

Design

The primary method of this study was semistructured interviews to explore the perspective of both patients and HCPs on the use of PROs. Additionally, in anticipation of changes related to patient-centeredness, an explorative quantitative approach was used, with a pretest–posttest design, to assess whether the use of PROs was accompanied by more patient-centred care (Figures 1 and 2).

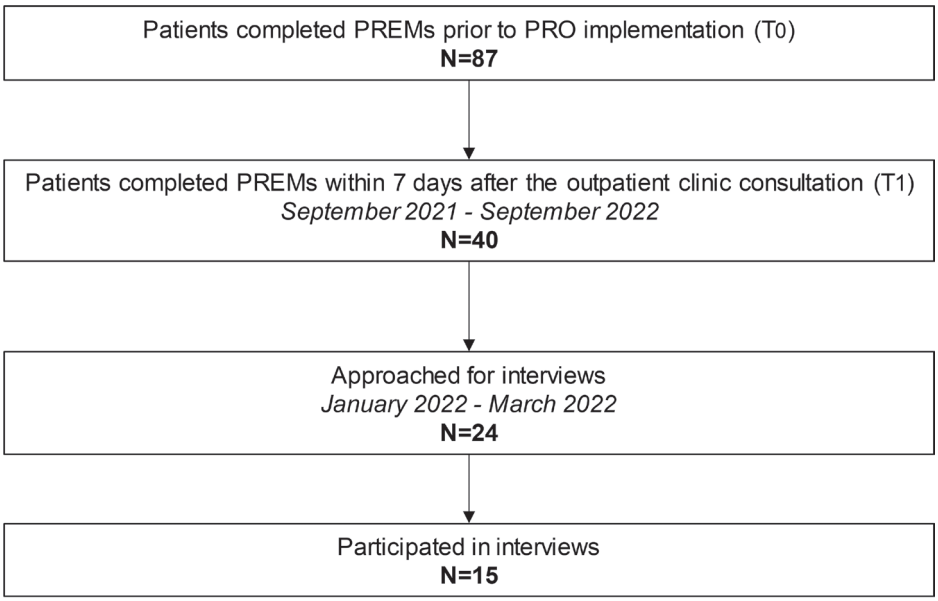

Figure 2. Flowchart showing inclusion of patients. Shown are the inclusion of patients in semi-istructured interviews and in the pretest–posttest design with PREMs. PREM, patient-reported experiences measures; PRO, patient-reported outcome.

Participants

Patients' inclusion criteria for both the interviews and the pretest–posttest study were: (1) allogeneic HSCT in childhood for a nonmalignant disease at the Willem-Alexander Children's Hospital with a follow-up of at least 2 years; (2) active follow-up at the LUMC outpatient clinic (LEEF programme); (3) completion of PROMs before the consultation; (4) Dutch- or English-speaking. Participants received complete study information and were recruited by telephone or in-person. This study was approved by the medical ethics committee of Leiden—The Hague—Delft (N20.181). Written informed consent was obtained from all participants. For participants aged 15 years or younger, additional assent was obtained from (both) caregivers. All HCPs (N = 3) involved in the LEEF programme were included.

Measures

Patient Characteristics

Patient characteristics obtained from the medical files were age, gender and underlying disease (inborn errors of immunity, hemoglobinopathies and bone marrow failure disorders).

Interviews with patients

Semistructured interviews were held from January to March 2022 to explore the patients' perspective on PRO use in all consecutive patients visiting the outpatient clinic. Participants were selected using convenience sampling. Interviews were held in-person or by video conference, depending on the participant's preference. Two researchers (F. Z. and N. G.) who were not involved in the patient's care, conducted the interviews. For participants below the age of 12, one-on-one interviews were conducted with their parents, while participants ages 12 and above had the choice of being interviewed individually, with their parents, or together. The initial interview topic guide created by the researchers (J. B., H. M. and A. h. P.) was revised after the first three interviews, as it was found to focus excessively on the questionnaires themselves (PROMs) rather than the use of PROs during the consultation (Supporting Information S1: Table 3).

Interviews with HCPs

To gain a comprehensive understanding of the use of PROs within the LEEF programme, HCPs were interviewed as well. Currently, three HCPs who use PROs work at the outpatient clinic. Two independent researchers (F. Z. and N. G.) took turns conducting the interviews with the HCPs. The topic guide created by researchers (J. B., F. Z. and N. G.) was adapted from the patients' topic guide (Supporting Information S1: Table 4).

Patient-reported experience measures (PREMs)

Two PREMs were used to assess if the use of PROs added value in terms of patient-centred care. PREMs were selected by the research team based on expert opinion. The Person-Centred Coordinated Care Experience Questionnaire (P3CEQ) consists of 11 items and is divided into two subscales: person-centeredness (eight items), and care coordination (five items).[31-33] The Revised Patient Perception of Patient-Centeredness Questionnaire (PPPC-R) consists of 18 items with three factors: (1) healthcare process (eight items); (2) context and relationship (eight items) and (3) roles (two items).[34] Both PREMs were translated into Dutch language level B1 by the Dutch Centre of Expertise on Health Disparities (Pharos institute), and were approved by an independent test panel (N = 3). Participants completed the PREMs in the digital KLIK PROM portal on two separate occasions: T_0) in before PRO implementation; T_1) within 7 days after the outpatient clinic consultation (Figure 1). If participants were below 16 years of age, their caregiver completed the PREMs. Inclusion for the PREM analysis closed 1 year after PRO implementation, ensuring that all patients who participated in the T_0 had the opportunity to participate in the T_1 measurement.

Analysis

Interviews

All interviews were recorded, transcribed verbatim and information was depersonalized. All interviews were conducted in Dutch. The participants' interviews were thematically analyzed using the Qualitive Analysis Guide of Leuven (Supporting Information S1: Table 5).[35-38] This guideline consists of a step-by-step method for analyzing qualitative data. Each researcher (J. B., F. Z. and N. G.) read and summarized the interviews, followed by the creation of conceptual interviews schemes. In these first steps, the relevant information from each interview is selected and clustered into different topics. After individual analysis, the researchers (J. B., F. Z. and N. G.) compared their findings, discussed their interpretation of the data, and reached consensus on a list of concepts (codes) linked to passages in each interview, enabling the identification of recurrent themes. Data collection and analysis took place simultaneously to enhance efficiency. Data collection continued until data saturation was reached, which was defined as no new upcoming themes in the analysis of the last three consecutive interviews. Finally, concepts were clustered into main themes and subthemes using the qualitative data analysis software ATLAS.ti (version 9).[39] The HCPs' (N = 3) interviews were analyzed in the context of the themes identified from the patients' interviews. This approach was taken due to the small group size, which prevented data saturation from being achieved.

PREMs

Statistical analysis of the PREM data was performed using SPSS version 25.[40] Mean scores of P3CEQ and PPPC-R at T_0 vs. T_1 were compared using paired sample t-tests. A $p < .05$ was considered statistically significant. The PREM analysis was performed after the completion of interview analysis, and the PREM results were not available to the HCPs or interviewers. Participants who were interviewed completed both PREMs before the interview to avoid influencing the PREM scores.

RESULTS

Interviews with patients

In total, 15 of the 24 patients approached were interviewed after which data saturation was reached. Among the participants, eight out of 15 were male, ranging in age from 8 to 37 years (Table 1). The median interview duration was 21 min (range: 11–46 min). Supporting Information S1: Table 6 shows details from nonparticipants (N = 9). Upon coding and categorizing the data, four main themes emerged: (1) use of PROs help to discuss topics; (2) evaluating the PROs make the patients feel understood; (3) completing the PROs create a moment of self-reflection; (4) use of PROs make the consultation more efficient. Additionally, participants were specifically asked about the usefulness of PROs and opportunities for improvement of use of PROs.

Table 1. Interviews: Patient characteristics (N = 15).

Characteristics	Median (range)
Gender, *N*	
Male	8
Female	7
Age at HSCT (years)	3 (1–15)
Age at interview (years)	17 (8–37)
Years since HSCT	11 (3–28)
Diagnosis, *N*	
Inborn errors of immunity	5
Hemoglobinopathies	5
Bone marrow failures	5
Second HSCT	2
Interview duration (min)	21 (11–46)
Interview setting, *N*	
Video conference	9
In person	6
Interview composition, *N*	
Participant	6
Parent of the participant	5
Participant and their parent	4

Abbreviation: HSCT, hematopoietic stem cell transplantation.

Most participants completed the questionnaires (PROMs) independently, while some younger participants required assistance from their caregivers. Due to

COVID-19 restrictions, participants over 18 years of age discussed the PROs with their doctor over the phone and were unable to view their results. Paediatric participants discussed their PROs during in-person consultations at the LUMC and had the possibility to review their results together with the HCP as they discussed it. Illustrative quotations are given per theme (Tables 2–5 and Supporting Information S1: Tables 7 and 8).

Table 2. Illustrative quotations from Theme 1 'Use of PROs help to discuss topics'.

Subtheme	Sex	Age	Quotation
Discussing the PROs to start the conversation	♂	11	*I think it provides [name HCP] the right tools to start a conversation, so that you don't have to start asking questions out of the blue*. [Caregiver about discussing PROs]
	♀	12	*… and then its looked upon to try to understand how the patient is going through life, if she is supported, if she is happy or not happy, if there are potential gaps, if she is deeply unhappy, you name it*. [Caregiver about discussing PROs]
	♀	17	*I thought it was better, because with the questionnaires you can really think clearly about everything beforehand and if you're at the appointment, well then you'll also forget half of it*.
	♀	30	*… it's nice, because then I can address it if I have something on my mind. And most of the time, as I said before, she acts upon this and takes action, so that's really nice*. [About discussing PROs]
Impact of discussing PROs	♀	13	*It's more like, all the HCPs know me better than I know them, so that makes it hard, because I only see them once a year*. [Caregiver about discussing emotionally charged subjects]
	♂	8	*The only thing that I'm thinking about is that, because your child is always sitting right next to you, I don't want to keep talking as if he is not there. So I consciously choose to not always discuss everything, except for when it's urgent, then I would dare to point that out*. [Caregiver about discussing certain topics]
	♂	37	*It's a difficult subject. And by confronting people that are not necessarily burdened by these feelings, or well, burdened is maybe too strong, but simply don't have these feelings, well, it's not making it easier*. [About PROs on depression]

Abbreviations: HCP, healthcare provider; PRO, patient-reported outcome; ♀, female; ♂, male.

Table 3. Illustrative quotations from Theme 2 'Evaluating the PROs make the patient feel understood'.

Subtheme	Sex	Age	Quotation
Improvement of consultation preparation by the HCP	♂	37	*And she won't go through the questionnaire word for word, luckily, but I do notice that she asks substantive questions in such a way that I notice that she has read it, which I appreciate, because then I won't have done it for nothing and I can see that she is prepared*.
	♀	29	*When I filled it out, about how I felt in the last week and everything, so what you're supposed to do. I filled it in, and then [HCP] also responded to it. [HCP] did ask like: what's the reason you filled it out like this. So, I did find that nice*.
Patient feels supported	♀	16	*I just had the feeling that she like gets me and that she could relate with me, and I also appreciated the tips she gave me*. [About the HCP]
	♀	30	*I just feel really at ease when I come to you at the hospital. I mean, I really feel like a human being, you know, not just another number.*
	♀	20	*They help you understand what you mean exactly and they show a lot of commitment towards the questions you have.* [About the HCP]

Abbreviations: HCP, healthcare provider; PRO, patient-reported outcome; ♀, female; ♂, male.

Table 4. Illustrative quotations from Theme 3 'Completing the PROMs create a moment of self-reflection'.

Sex	Age	Quotation
♂	17	*He completed the questionnaires two days beforehand and well, then you talk about it, you talk about the whole process and about how his friends dealt with it and well, you get to have a moment in which you talk extensively about it*. [Caregiver]
♀	17	*I thought it was better, because with the help of the questionnaires you can really think clearly about everything*. [About filling in the PROMs]
♀	30	*Well, now we get the questionnaires that we have to fill in, so that's some sort of preparation*. [When asked about preparation before the consultation]

Abbreviations: PROM, patient-reported outcome measure; ♀, female; ♂, male.

Table 5. Illustrative quotations from Theme 4 'Use of PROs make the consultation more efficient'.

Sex	Age	Quotation
♂	8	*I think it's beneficial that you don't have to discuss everything, then it's mostly the things you answered with yes or the things that are urgent, that are being highlighted and I think that is better, that saves time.* [Caregiver]
♀	21	*The other things, well the other answers I gave, were not different from the last time, so like, we didn't necessarily have to discuss these things.*

Abbreviations: PRO, patient-reported outcome; ♀, female; ♂, male.

1. Use of PROs help to discuss topics

Discussing the PROs to start the conversation

Almost all participants briefly reviewed their PROs with their HCP, had discussed them and had decided together which topics needed more clarification. The participants were satisfied with the way the PROs had been discussed. Discussing the PROs helped the participants to gain clarity about the questions they had and helped to facilitate the discussion. Participants felt that through discussing the PROs, the HCP can extract topics that are essential for the patient more easily and address questions that arose from the PROs. This was perceived as valuable. Furthermore, participants reported that completing the PROMs prepared them to talk about sensitive or personal topics, such as mental wellbeing, instead of feeling overwhelmed when the HCP initiates these topics without prior notice. Lastly, a few participants mentioned that discussing the PROs served as a reminder to address specific issues with their HCP.

Impact of discussing PROs

The majority of participants reported that when discussing the PROs they felt safe to discuss any topic they desired, including sensitive or personal topics. However, a few participants considered certain aspects of the PROs to be too personal and therefore did not want to discuss them during the consultation. Additionally, two parents preferred to discuss topics without their children present in the consultation room.

2. Evaluating the PROs make the patients feel understood

Improvement of consultation preparation by the HCP

Many participants emphasized that PROs helped the HCP better prepare for the consultation. Additionally, they appreciated that the HCP already had insights into their emotional state. The participants felt that the HCP was able to focus more on their needs. One participant expressed the need to provide context on PRO-related issues during the consultation to enhance the understanding of specific PROs.

Patient feels supported

Participants appreciated the time and attention of the HCP to evaluate the PROs. In addition, most participants experienced a sense of trust and support during their interactions with the HCP. Many participants appreciated that by evaluating the PROs, their well-being was actively monitored and were overall satisfied with the consultation.

3. Completing the PROs create a moment of self-reflection

Completing the PROs prompted several participants to reflect on their current well-being, their transplantation experience, and everything they have been through since then. It also helped them to reveal issues for which they needed support. Many participants perceived the request to complete the PROMs as a way to prepare for the consultation, as it invited them to reflect on essential aspects of their lives. Parents found that the PROs served as a conversation starter with their children on topics such as alcohol and drug use. However, a few participants perceived completing the PROs as mentally challenging and considered some questions as being too personal, such as the PROM regarding depressive symptoms.

4. Use of PROs make the consultation more efficient

Some participants reported that using PROs made the consultation more efficient. The HCP was already aware of the most prominent issues, allowing irrelevant topics to be skipped or briefly touched upon, which was also preferred by half of the participants. A few participants noticed that their answers were directly transferred into their medical file, which meant the participants did not have to answer certain questions again.

5. Additional results

Participants were specifically asked about the usefulness of PROs and opportunities for improvement of use of PROs.

Usefulness of PROs

While some participants did not personally perceive PROs as valuable because they did not have any problems to report, all participants emphasized the importance of PROs for those in need, healthcare improvements and research purposes. Some participants viewed the questionnaires within the context of active illness and treatment, and since they were already several years posttreatment, the PROs felt less relevant to them personally. However, participants could easily imagine that the PROs might be relevant to other patients. Most participants did not view completing the PROs as burdensome. Half of the participants regarded PROs as a valuable tool for monitoring the overall well-being and health of all patients.

Opportunities for improvement of use of PROs

Nearly all participants considered the implementation of PROs to be an improvement of care. PRO content was clear and appropriate for the consultation. However, the number of questions in the PROMs was excessive and some participants preferred to skip topics they considered irrelevant. Certain questions were sometimes perceived as too personal and detailed for an online questionnaire. One participant also noted that certain PROMs emphasized negative aspects too much and lacked a positive approach. Some participants thought that the recall period of the PROMs was inappropriate and wished for an extended timeframe. Lastly, a few participants found the completion of PROs challenging due to the language level of the PROs and requested support from caregivers.

Interviews with HCPs

Two of the three HCPs worked with paediatric patients and one with adult patients. The median interview duration was 44 min (range: 39–47). All HCPs perceived that the use of PROs improve the consultations, improve insight into patients' overall well-being, and help to recognize and prepare topics needing attention during the consultation. The HCPs also noted that discussing the PROs led to more in-depth conversations and made it easier to discuss personal subjects, such as sexuality, as patients had already reflected on them and were not caught off-guard. However, the HCPs emphasized the need to verify patients' interpretation of the PROs and to conform or clarify any PRO-related issues. The HCPs noticed that patients were better prepared for consultations and were more involved in their care. This resulted in improved equality and reciprocity in the HCP–patient interactions, and improved SDM after PRO implementation. However, one HCP perceived a sense of detachment due to patients answering personal questions online instead of in person. All HCPs reported that consultations became more efficient due to improved preparation, although the time requires for consultation preparation had increased both for HCPs and patients. Nevertheless, the HCPs experienced that with PROs, patients and HCPs were better prepared, facilitating SDM.

PREM

PRO implementation was evaluated by two PREMs (P3CEQ, PPPC-R) regarding patient-centeredness before (T_0) and after PRO implementation (T_1). T_1 measurement ended 1 year after PRO implementation and included 40 patients. Twenty-three patients were male. Age at T_1 ranged from 6 to 42 years (Table 6). Mean scores at T_0 and T_1 from the P3CEQ and PPPC-R were not significantly different (Table 7). There was a trend ($p = .09$) for more attention to the factor 'context and relationship' (PPPC-R). Within this factor, per item analysis in this factor showed significant improvement

in the perceived compassion from HCPs (mean [T_0]: 1.3, SD: 0.6; mean [T_1]: 1.1, SD: 0.5; 95% confidence interval [CI]: 0.01–0.4) and trust in HCPs (mean [T_0]: 1.2, SD: 0.5; mean [T_1]: 1.0, SD: 0.3; 95% CI: 0.04–0.4).

DISCUSSION

This study aimed to explore the value of using PROs during consultations in the late effects and comprehensive care (LEEF) programme after paediatric HSCT for nonmalignant diseases. Four key themes emerged from the data. First, use of PROs helped to discuss topics and facilitate the conversation. Discussing the PROs guided an efficient consultation with a focus on the topics perceived as most relevant to the individual patient. Second, evaluating PROs made the patients feel understood and supported. The patient and HCP noticed mutual preparation before the consultation, resulting in more tailored follow-up questions. Third, completing the PROs created a moment of self-reflection for patients and parents. Fourth, use of PROs made the consultation more efficient due to better preparation. In addition to the four key themes, patients and caregivers had varying perceptions of the usefulness of PROs, both in positively and negatively.

When comparing our results to previous studies, several aspects must be considered, as PRO implementation and the use of PROs vary substantially across studies.[41-44] According to a review from Carfora et al.[44] on the patient perspective regarding the use of PROs in clinical care, it is evident that various PROMs were utilized. The variations in PROMs used across studies can have implications for factors such as the length and number of questions in the PROMs, whether the PROMs were generic or disease-specific, the extent to which the PROs were discussed during consultations, and whether visual aids were used to aid in the interpretation of PRO results. These variations could potentially influence patients' perceptions of the usefulness of PROs in their care. Nonetheless, there are many similarities between these studies and our results.

In line with previous research, use of PROs improved patient–physician communication, which could facilitate SDM.[44-46] Although SDM was not explicitly addressed by patients or HCPs, there are elements of SDM that were highlighted in the interviews. Moreover, with the use of PROs, patients felt understood and supported by their HCP. HCPs reported a better understanding of their patient, enabling them to address personal topics more effectively. These factors could enhance the exploration of patient's values, thereby supporting SDM. Overall, research into the connection between SDM and the use of PROs in general has predominantly been conducted in a restricted range of care paths, rather than in

care paths centred around health screening, such as the LEEF programme.[47] Further research is needed to explore the association between the use of PROs and SDM.

Certain topics mentioned in the interviews also correspond to the quantitative analysis in this study. Although the evaluation using PREMs showed no significant difference in overall patient-centeredness after PRO implementation, detailed analysis did reveal a trend for more attention to the factor 'context and relationship', specifically related to the perceived compassion from HCPs and trust in HCPs. This factor also evaluates to which extent patients are comfortable discussing their problems with their HCP. These topics have been especially positively highlighted in the interviews, providing further support to the observed trend in the PREMs. Unfortunately, due to the small sample size, possible significant differences could not be demonstrated.

PRO implementation impacted patients as well. Use of PROs was valuable for self-reflection and made patients feel more in control of their care, which is in line with previous research.[44,49] However, the literature also suggests that self-reflection could be potentially stressful for patients.[41,44] From our interview data, it remains uncertain whether self-reflection had resulted in stress. In the days prior and after the consultation prompted some patients to reflect on their time of hospitalization and the initial months following their discharge. This often led them to engage in discussions about this with their family. Still, it is not evident if this type of reflection induced stress.

Regarding possible effects of the use of PROs in the consultations, HCPs reported increased efficiency due to use of PROs, which has been described in the literature.[44,48] However, in this study we did not measure the consultation duration nor the time devoted to certain topics. Further research is needed to assess the efficiency of the consultations when using PROs. There have been studies where PROs were utilized as a tool for evaluating active symptoms and determining the need for a health check at the hospital. However, providing context to PRO results was deemed essential by both patients and HCPs.[44,50] Additionally, HCPs expressed the preference for PROs to complement rather than replace regular consultations. The HCPs highlighted that PROs should be used as an additional resource in the overall care process, providing valuable information to enhance patient–physician communication.[44,51]

This study has multiple strengths. First, this study is a multiple methods study. Most studies have either used quantitative measures or qualitative measures, such as focus groups. Second, the research team consisted of individuals from diverse professional backgrounds. This interdisciplinary collaboration brought different expertize and perspectives to the study, enhancing the identification of a wide range of themes and subthemes. However, there are also some limitations that should be acknowledged.

First, this study did not conduct interviews before PRO implementation, precluding a comparison from pre- to postimplementation. Second, not all participants were able to review their PRO results since their consultation was conducted by phone. As a result, participants could not always determine whether the topics discussed were influenced by the PRO results. Third, in addition to PROMs patients completed a symptom checklist. Although the difference between PROMs and the symptom checklist was clear to HCPs, this may have been less clear to patients. The interviewers were aware of this issue and asked for clarification when necessary. Fourth, there was a lack of PREMs specifically aimed at evaluating PRO implementation. However, we expected differences regarding patient-centeredness based on literature and expert opinions, and therefore chose the PREMs accordingly.[3,44] Fortunately, the themes derived from the interview data aligned with the PREM factors, providing additional support for the findings. Fifth, the sample size was too small to have sufficient power to assess changes regarding patient-centeredness. However, our results suggest the late effects and comprehensive care programme might already perceived to be focused on patient-centred care. This was evident when comparing the P3CEQ results to Dutch adults with a chronic condition, suggesting that the programme had already achieved a relatively high level of patient-centeredness.[33] It is possible that further improvement in patient-centeredness might be challenging to detect, as the programme was already performing well in this aspect. Lastly, there might be a potential bias in the study due to exclusion of patients who did not complete PROs, possibly underestimating the perceived usefulness and difficulty of the PROMs. Topics addressed in the participants' interviews, such as language level, number of questions and personal inquiries, could be contributing factors. Reasons for not completing PROs should be further investigated.

CONCLUSION

Overall, our results indicate that the use of PROs for screening purposes in the late effects and comprehensive care programme after paediatric HSCT is valuable from both patient's and HCP's perspectives. It is important to note that completing PROs should not replace routine consultations, as patients and HCPs have expressed the importance of providing context to the PRO results. The use of PROs can lead to more efficient consultations by addressing the essential topics identified through PRO analysis. Moreover, with the active use of PROs there might be a shift towards a more mutual patient–HCP relationship, in which patients are stimulated to consciously assess their health status. Future research could focus on linking PRO results to psychosocial and clinical outcomes, enabling further optimization of PROs as a screening tool and provide valuable insights into the relationship between PROs and patients' overall well-being.

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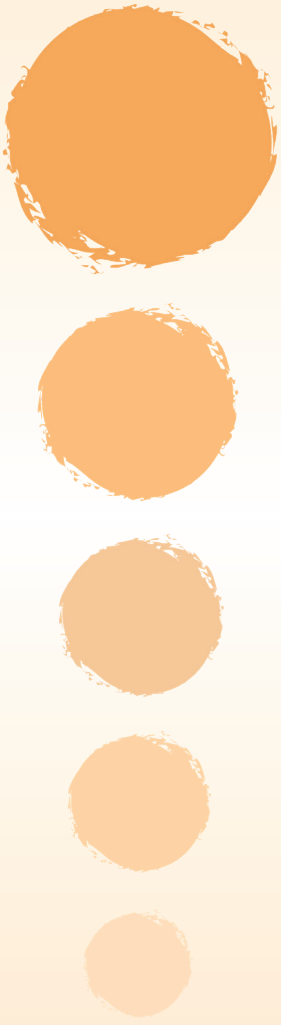

Chapter 8

Appropriate healthcare represents life-course care: a blueprint for the implementation of value-based healthcare

Shared decision-making at the Late Effects & Comprehensive Care (LEEF) program after pediatric stem cell transplantation

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Qruxx (2023). https://www.qruxx.com/passende-zorg-is-levensloopzorg-een-blauwdruk-voor-implementatie-van-waardegedreven-zorg/

INTRODUCTION

With the slogan 'Care of Value,' the Leiden University Medical Center (LUMC) initiated the implementation of Value-Based Healthcare (VBHC) in 2020. The principles of VBHC can be presented in a formula (figure 1). Currently, VBHC implementation tools tend to focus on optimizing individual VBHC elements (1). However, an integrated approach reveals interconnections between the elements and enables the scientific measurement of implementation effects across multiple levels.

To date, VBHC is known in disease-specific standardized care paths. However, care paths focused on life-course care exist as well. The LUMC provides life-course care for patients who have received a high-intensity treatment during childhood, such as a stem cell transplantation. A stem cell transplantation involves chemotherapy as preparation, followed by prolonged hospitalization(s) and an intense recovery period of over one year. This treatment aims to cure the underlying disease, but it also carries long-term consequences such as fertility issues or kidney damage. Providing this care extends beyond the boundaries of a single healthcare organization, with age being a significant factor. Therefore, the departments of Pediatrics and Internal Medicine collaborate intensively to deliver comprehensive care in these cases.

The perspectives of the patient and their family members has been the starting point for the implementation of VBHC in the Late Effects & Comprehensive Care (LEEF) program after pediatric stem cell transplantation This approach has facilitated shared decision-making throughout the entire process. In this article, we discuss the seven components of the blueprint for VBHC implementation (figure 2), which provide guidance for implementing VBHC in similar care paths.

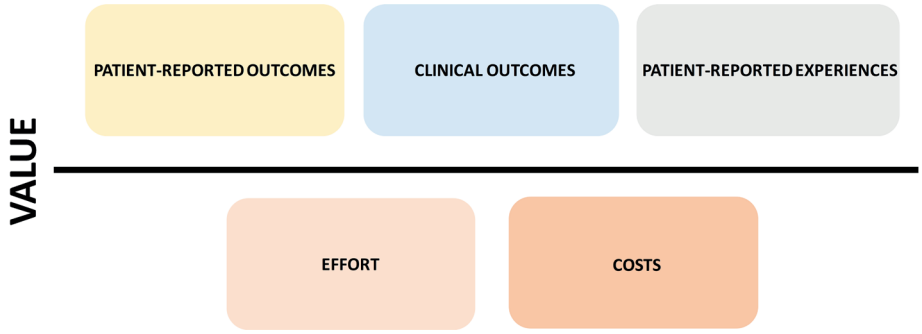

Figure 1. Value-based healthcare components

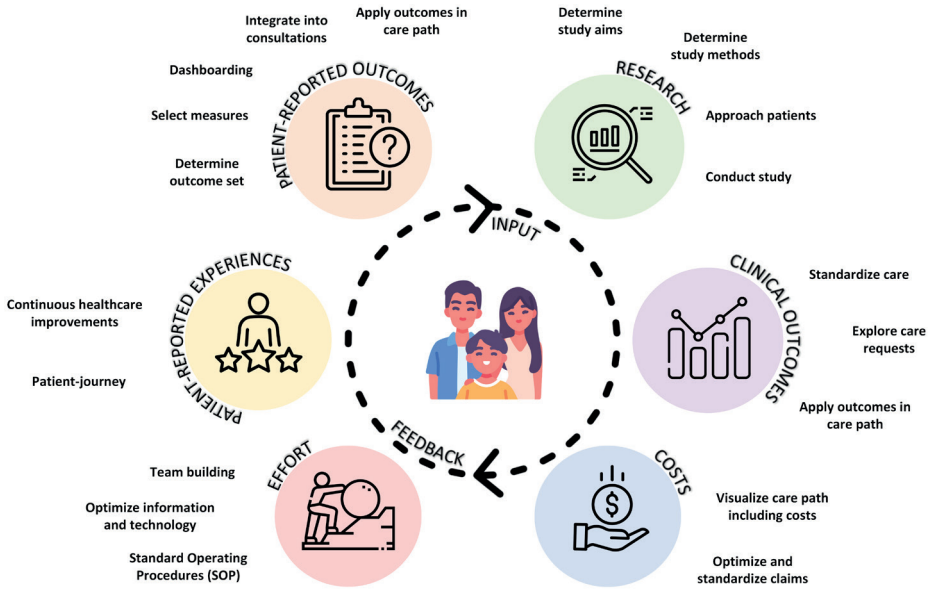

Figure 2. Value-based healthcare (VBHC) implementation at the Late Effects & Comprehensive Care (LEEF) program after pediatric stem cell transplantation. This figure presents all VBHC components with the patient at the center. The patient is involved in all VBHC components, and this involvement is ensured through a cyclical process: gathering input from the patient and providing feedback to the patient.

PATIENT JOURNEY

To this day, shared decision-making is mainly known in the context of setting up a course of treatment. However, shared decision-making remains essential even after the initial treatment. Outcome data are crucial for this purpose, but the first step involves the identification of patients' core values and needs. Therefore, a patient conference day was organized, where patients and their family members, together with the VBHC implementation team, created a patient journey. During this process, questions such as 'what went well? and, 'what could have been improved?' were addressed. To avoid bias, the entire patient population was involved rather than a small sample. Based on the feedback from patients, improvement projects were initiated in collaboration with health care providers (HCPs). Patients receive feedback on these processes through annual patient conferences, where new input from patients is being collected as well. Through this cycle, patient involvement, and thus the essence of shared decision-making, are continuously ensured.

PATIENT-REPORTED OUTCOMES (PROS): FROM LITERATURE TO (OUTPATIENT) CLINICAL PRACTICE

The measurement of PROs is an important element of VBHC. There are different purposes for PRO measurement, including scientific research, determining the need for follow-up appointments, and integration into clinical consultations. Within the Late Effects & Comprehensive Care (LEEF) program after pediatric HSCT, PROs have been implemented in routine care and serve as a screening and interview tool during consultations.

Determining the PRO set requires a thorough approach with input from the patient and their family members. After all, HCP-driven items addressed during the consultation may not always align with patient-driven items. Therefore, the entire patient population was asked about which PRO domains are of importance to them. The PRO domains were selected based on ICHOM's internationally standardized outcome sets 'Overall Pediatric Health' (2). The PRO domains were assessed through written questionnaires ('how often do you experience …' & 'how much does … affect you?'). A ranking of PRO domains was presented during the patient conference day, where patients prioritized PRO domains based on their significance and impact on daily life, according to the ICHOM methodology. Subsequently, HCPs used this ranking to assemble a PRO set. During this process, a critical questions was posed: "can we provide assistance if a patient reports difficulties in this specific PRO domain?".

After establishing the PRO set, a search was conducted using literature review and PRO implementation tools for matching validated Patient-Reported Outcome Measures (PROMs). Consideration was given to 1) patient burden (maximum number of PROMs; does one PROM cover multiple PRO domains?), 2) if the PROM covers the entire PRO domain, 3) if the PROM is specific enough for the PRO domain, and 4) available languages. Additionally, it was of interest to 5) ensure longitudinal follow-up, so PROMs can be applied across all age groups (ensuring life-course care). Finally, 6) suitability for (inter)national comparison/benchmarking was also assessed.

To capture the outcomes effectively, it is essential to select an PROM portal that allows both patients and parents/caregivers to complete PROMs and to have insights in their outcomes through data visualization. Therefore, KLIK (Kwaliteit van Leven in Kaart; www.hetklikt.nu) was selected. Patients of all ages can use the same digital portal to complete PROMs and observe trends over time, ensuring longitudinal follow-up.

To ensure reliable PRO implementation, a baseline measurement was performed. All patients were asked to complete the PROMs. The outcomes were presented during a patient conference day, where patients prioritized the PRO domains once again.

Subsequently, the PRO set was adjusted and implemented in the care path. Important decisions made during this process included: 1) determining the measurement points in the care path, including frequency, 2) patient approach (method and timing of providing patient instructions), and 3) reaching consensus on how to use PROs during consultations.

REDUCTION OF NO-SHOW RATES AND IMPROVED PREPARATION

In the LEEF program after pediatric HSCT, patients annually visit the outpatient clinic. This standardized visit is chosen as a fixed measuring point. If the PROMs are not completed two weeks in advance of the appointment, patients are approached by telephone. An additional benefit is the reduction of 'no shows' since patients are being reminded of their appointment. PRO evaluation, along with the available medical information, has become part of the consultation preparation. If there are specific healthcare questions, it is considered whether this can be integrated directly into the consultation. For instance, combining the appointment with a pediatrician-endocrinologist if there are concerns about growth or fertility. This approach has enhanced efficiency and reduced the number of hospital visits. During the consultation, PROs are discussed with the patient using graphical representations of the results in the PROM dashboard.

PRO implementation has been evaluated by patients, family members, and HCPs, revealing that they are better prepared for the appointment. Furthermore, the essence of their concerns is discussed more effectively, and the consultations are more efficient. Based on this evaluation, the PRO set has been further optimized. The results of the evaluation will be presented at the next patient conference day, where patients will be asked to provide feedback. This approach ensures that the PRO-set remains continuously evolving, incorporating current patient input.

COMPLETE OUTCOME SET

By sharing their experiences through the patient journey, patients have provided valuable insights. Health care providers (HCPs) used these insights to establish improvement projects, including: 1) transition of care between HCPs, 2) information resources (digital information written at language level B1, accessible on a per phase basis) and 3) psychosocial support. Patient experiences also play a significant role in evaluating the implementations of VBHC, assessing with each adjustment whether it adds value to care.

"Is it normal for this to happen to me?" and "What can I expect in the future?". To address these patient queries, a guideline has been developed in which the follow-up after pediatric HSCT has been standardized. In addition to HCP-initiated research, patient-initiated research also takes place. The research questions are derived from patient input, contributing to a high level of patient engagement in the study. This requires reciprocity between HCPs and patients, whereby research outcomes are fed back to patients. Here, patients are given the choice to receive or decline hearing the, potential impactful, outcomes.

Currently, efforts are underway to develop a complete outcome set that integrates clinical outcomes and patient-reported outcomes (PROs) as the reported outcome measure. Thus, the treatment outcome can be evaluated in the context of optimal well-being.

COSTS

When assessing the costs associated with the standardized care path, it was found that there was no care product available to cover the expenses of this care. Consequently, a successful application for a care product was submitted to the Dutch Healthcare Authority (Nederlandse Zorgautoriteit). As a result, the care product for the this LEEF program is now available.

ASSURANCE

The collaboration among HCPS has resulted in the formation of a cohesive team that actively involves patients and their family members. Optimization of documentation (ICT standardization in the electronic medical files) has led to quality assurance, such as conducting uniform consultations among different HCPs. Through this optimization process (ICT standardization in the medical history, physical examination, and additional examinations), the data had become suitable for (scientific) evaluation purposes. Furthermore, the work processes within the outpatient clinic are safeguarded by Standard Operating Procedures (SOPs), with fixed evaluation intervals for continuous quality improvement.

RESEARCH

In this care pathway, a scientific baseline measurement has been chosen to evaluate healthcare adjustments. In a longitudinal study, both clinical and patient-reported outcomes are collected (3-5). The PRO evaluation shows that these are comparable, or even better, compared to the Dutch population (6). PRO implementation has been

evaluated using patient-reported experiences (questionnaires and interviews) and had no negative effect on patient-centeredness (7). In addition, interviews have revealed positive effects, including that the use of PROs 1) helps to discuss topics, 2) makes patients feel understood, 3) creates a moment of self-reflection and 4) makes consultations more efficient (7). While scientific evaluation may extend the VBHC implementation period, it leads to concrete (evidence-based) improvements to the care path.

CONCLUSION

Using this blueprint for VBHC implementation, we aim to share tools for similar complex multidisciplinary life-course care paths. The key messages for VBHC implementation are as follows: 1) start with the entire patient population to assess patient needs, 2) place scientific evaluation at the core to ensure the sustainability of VBHC elements and provide feedback on results to patients, and 3) implementation of the all VBHC components contributes to broad quality improvement, continuously enhancing treatment based on optimal patient well-being.

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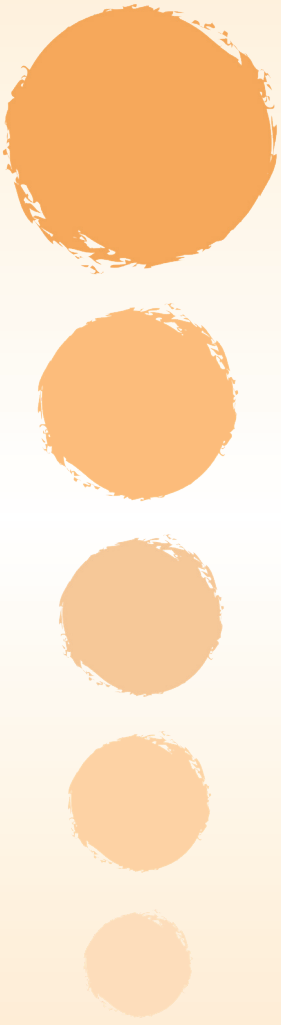

Chapter 9

General discussion

The Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases at the Leiden University Medical Center (LUMC) is aimed at screening for late effects. Additionally, overall well-being is evaluated. If additional care is needed, the patient is referred to an appropriate healthcare professional (HCP) or general practitioner for diagnostics and treatment, providing customized care for the patient. The LEEF program after pediatric HSCT for nonmalignant diseases at the LUMC originates from 2018 and was based on guidelines and experiences of follow-up after childhood cancer (1). There is limited research in the field of late effects of pediatric HSCT for nonmalignant diseases, since research predominantly has focused on late effects of childhood cancer (2, 3). However, knowledge on late effects after pediatric HSCT for nonmalignant diseases is essential to adjust the screening guidelines for providing optimal care.

In line with the recent trend of many healthcare systems moving towards a system of value-based healthcare (VBHC), VBHC was implemented in 2020 in the LEEF program at the LUMC. In our view, with an emphasis on the patient perspective, VBHC posits a combination of improved health outcomes through better processes of care, enhanced incorporation of patient experience, and optimal use of effort and the lowest possible costs. However, experience with VBHC implementation in care paths solely focused on screening, such as follow-up programs after pediatric HSCT, was lacking. Additionally, there was no experience with VBHC implementation in care paths involving multiple age categories, including children, adolescents, and adults.

The first aim of this thesis was to evaluate the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric stem cell transplantation for nonmalignant diseases at the LUMC, and includes the assessment of various late effects and health-related quality of life. The second aim was to implement and evaluate aspects of VBHC at the LEEF program. This general discussion describes lessons learned from the VBHC implementation in the Late Effects Comprehensive Care & Follow-up (LEEF) program and suggests possible future directions for VBHC implementation in similar comprehensive care programs.

PATIENT INVOLVEMENT: "IF YOU WANT TO GO FAST, GO ALONE. IF YOU WANT TO GET FAR, GO TOGETHER." – *AFRICAN PROVERB*

Healthcare is primarily organized to fix health problems, where patients turn towards HCPs when they experience health problems, instead of preventing health complications. Evidence-based protocols and guidelines are aimed at achieving the best possible health outcomes. However, the patient perspective on the recommended care is often lacking in these guidelines. Instead, it is up to

individual patients and HCPs, with the help of shared-decision making, to customize the recommended care in order to achieve the best possible outcomes at the lowest possible cost and effort. In the evaluation of value of care, in our view the patient perspective is essential. Therefore, with the aim of adding value to care, patient involvement is essential throughout the VBHC implementation process. This thesis describes various ways of involving patients in VBHC within the Late Effects Comprehensive Care & Follow-up (LEEF) program.

At the start of the VBHC implementation within LEEF program after pediatric HSCT in the LUMC, a patient conference day was held in January 2020. Prior to this day, patients were asked to provide input on elements of care they wanted more information about and express what they considered most important regarding their own health. This approach, which did primarily not involve HCPs, revealed care topics that had not been anticipated by the HCPs. It was the first hint of the different perspectives of HCPs and patients on the appraisal of health.

The need to explore the patients' perspective had further led to a qualitative research project on the long-term psychosocial impact of pediatric HSCT for nonmalignant diseases (**chapter 4**). Four main life areas in which patients experience the psychosocial impact of the HSCT were identified. First, most patients reported to be doing okay and had the feeling of being cured. Second, patients experienced persistent involvement with healthcare services. In some cases, this was due to health limitations, which required additional care. In addition, even though patients reported the feeling of being cured, they experienced a sense of vulnerability. The vulnerability was partly due to the recurring hospital checkups within the late effects follow-up program. Still, most patients had accepted that they had received a HSCT with the long-term follow-up as a consequence. Third, the HSCT had influenced the relationships with loved ones in both positive and negative ways. Fourth, the HSCT had an impact on the patient's life-course. Patients were aware of the fact that they should not take life for granted. Additionally, they sometimes had difficulties with the development of their own identity and social skills. The HSCT had sometimes influenced their school or career choices. Lastly, some patients reported the HSCT was (expected to be) of influence on their future. A lesson learned from this research was the need to individualize supportive care and create a setting in which patients' needs can be addressed. In addition, awareness was created about the possible impact of the hospital checkups on patients, and it emphasizes the necessity of care coordination. Lastly, patients downplayed and accepted side effects, and showed a remarkable resilience after this high intensity treatment.

The current literature on experiences with VBHC implementation shows differences in the level of patient involvement (4-7). Some care paths have no patients involved

in their VBHC processes (4). Other care paths do involve patient, but struggle with the frequency and design of patient involvement (5). Various forms of patient involvement are described, such as individual patient involvement (one patient gives continuously feedback), focus groups, and patient organizations (e.g., disease specific organization, Netherlands Patient Federation). Some care paths involve patients on a consultation basis, while some have integrated patient involvement in their VBHC processes (4). From the perspective of HCPs, patient involvement is perceived as useful to some, but not all VBHC components (5). Patients are predominantly involved in developing the care path and developing (standard) patient-reported outcomes sets (4, 7, 8). In addition, care paths report difficulties on how to translate the individual patient perspectives to the whole population (4). In line with our implementation strategy, Heijsters et al (2022) view patients as members of the value team: 'this ensures the inclusion of wishes and needs of the patient group in the enhancement of the care process and that relevant outcomes are selected to measure in a later stage' (6).

Through the involvement of our entire patient population at the start of our VBHC implementation and the related research projects, patients have been stimulated, not only to participate in their own healthcare, but also in research (**chapter 8**). Patients express interest to receive research updates during consultations and at patient conference days. While discussing the latest results with patients, new patient-initiated research questions arise, and the cycle repeats itself as shown in figure 1. In addition, patients have reported to feel acknowledged in their problems by having been asked to provide feedback on scientific results during the consultation and at patient conference days. Overall, patient-involvement integrated in the care path, in VBHC implementation, and research has resulted in an improved collaboration between patients and HCPs. The reciprocity between patients and HCPs is essential in this collaboration.

HEALTHCARE PROVIDER (HCP) INVOLVEMENT: EXPERTISE

After the first patient conference day, in which patients evaluated the care path and defined relevant care topics to be addressed, HCPs came together to evaluate the input provided by patients. The input from patients was not always disease- or HSCT-specific. Therefore, all involved HCPs of the LEEF program (e.g., doctors, nurses, psychologists, social workers) were invited and participated in the VBHC implementation. HCPs categorized and prioritized the input from patients, and complemented this information with a HCP perspective.

To provide knowledge for patients, and to gain expertise in this specific population, a guideline for late effects screening after pediatric HSCT for nonmalignant diseases

was developed (**chapter 2**). Up to that point, the follow-up program used the (inter)national late effects guidelines after childhood cancer (1). The guidelines for childhood cancer survivors approach surveillance recommendations on treatment modality and do not take the underlying disease into account (2, 3). However, the underlying disease (especially in nonmalignant diseases that are frequently characterized by non-hematopoietic manifestations/pre-existing disease burden) can be a predisposing factor for late effects. The modules from the (inter)national late effects guidelines after childhood cancer were adapted, after literature review, grading evidence, and expert opinion (2, 9-25). The first steps towards international consensus on the guideline for ate effects screening after pediatric HSCT for nonmalignant diseases have been taken.

INTEGRATING CLINICAL OUTCOMES, PATIENT-REPORTED OUTCOMES AND EXPERIENCES: EVALUATING OVERALL WELL-BEING

At the first patient conference day and during consultations, patients had requested to investigate long-term endocrine function, specifically gonadal function, which was in line with the request from HCPs. In **chapter 3**, the late endocrine effects after pediatric HSCT for nonmalignant diseases have been shown. In this study, growth, thyroid function, and gonadal function were studied based on the routine annual post-HSCT evaluations by a pediatrician-endocrinologist. Our results show a high cumulative incidence (61%) of at least one late endocrine effect in patients after pediatric HSCT for nonmalignant diseases. Specifically, the cumulative incidence of gonadal dysfunction was high in both females and males (55% and 39%, respectively). Females with busulfan-based conditioning were more at risk for developing gonadal dysfunction compared to females with treosulfan-based conditioning. It was known from previous research that busulfan is often associated with gonadal dysfunction (26). The number of studies on gonadotoxic effect of treosulfan is very limited. Furthermore, these studies have very small sample sizes (26). Our study thus constitutes the largest study comparing busulfan and treosulfan. Moreover, these results had led to a follow-up study on the level of exposure of busulfan and treosulfan in relation to gonadal function (27). Results from this study showed, in contrast to many hypotheses on gonadal toxicity, that reduced intensity busulfan conditioning does not lower the risk of gonadal dysfunction (27). Based on our results, we recommend further research on possible predisposing factors of the underlying disease, iron overload, or other contributing factors to gonadal dysfunction. Unfortunately, the follow-up duration in our study was insufficient to evaluate fertility problems, and further research, preferably in a multicenter setting, is necessary.

From an HCP perspective, it could be assumed that late effects, such as gonadal dysfunction, are associated with impaired HRQoL and have an impact on the patients' life. **Chapter 6** of this thesis describes the long-term patient-reported outcomes (PROs) after pediatric HSCT. Comparable, or more favorable, long-term PROs were seen compared to the Dutch general population. These results contrasted with our hypothesis, which was based on previous studies, mainly in childhood cancer survivors, of impaired long-term HRQoL after pediatric HSCT for nonmalignant diseases. Most of these previous studies used varying PROMs, included a limited number of age-categories, and had shorter follow-up duration, making comparison with our results difficult. Unique in our study was the use of PROMIS item banks, facilitating longitudinal follow-up in all age-categories. With the aim of international comparison, PRO domains were selected from the International Consortium for Health Outcomes Measurement standard set 'Overall Pediatric Health'. In this broad selection of PRO domains, results show that more attention is needed for physical health, school functioning, and sleep disturbance.

During the preparation for our research on long-term PROs (**chapter 6**), we had to select a proper control group for this population, which turned out to be difficult. From a methodological perspective, patients with similar diseases who did not receive a HSCT would give the best comparison. However, the disease severity often determines the HSCT indication. Patients with severe disease manifestations are usually considered more eligible for HSCT. In clinical practice, during consultations and at patient conference days, patients ask 'am I healthy?', 'am I normal?', or 'am I capable of doing everything I want to do, just like my peers?'. In addition, patients have reported to feel cured from their original disease (**chapter 4**). So, patients compare themselves to others in their surroundings. Therefore, the overall Dutch general population was deemed a more relevant control group, which consisting of people both with and without chronic diseases.

The combination of positive results of the long-term PROs and the high cumulative incidence of gonadal dysfunction in this population raises the question if patients with late effects have impaired HRQoL compared to patients without late effects. This topic has partially been addressed in our explorative study on long-term psychosocial impact of HSCT (**chapter 4**). Results have shown that patients downplay their late effects, and generally feel good, implying that the association of late effects and HRQoL may not be present, or to a lesser extent than expected. Unfortunately in our studies, additional analysis on associations with late effects, such as gonadal dysfunction, and PROs was not possible due to small sample sizes. Moreover, not all late effects have yet been investigated in this population. Studies in larger cohorts of HSCT survivors are required to explore whether specific late effects are particularly associated with HRQoL perception.

As of yet, overall well-being has been evaluated from the patient's perspective (late endocrine effects, long-term PROs, and long-term psychosocial impact of pediatric HSCT). However, overall well-being is also influenced by the patients (social) environment. Patients have reported the HSCT has influenced their relationships with loved ones, in both positive and negative ways (**chapter 4**). In **chapter 5** of this thesis long-term parental distress and everyday problems in caregivers of pediatric HSCT recipients for nonmalignant diseases was assessed. Parental outcomes were, mostly, comparable to those of parents of children with a CC. However, when compared to parents of healthy children, there were indicators for long-term parental distress after pediatric HSCT, and problem domains differed between mothers and fathers. Mothers of HSCT recipients reported more problems in the parenting domain compared to controls. Specifically, mothers experienced problems with the child's autonomy, and had difficulties dealing with their child's emotions and with talking about the disease and/or its consequences with their child. Fathers of HSCT recipients reported emotional problems, such as feeling tense or nervous and depression. Currently, parental supportive care is mainly offered during the acute hospitalization phase. A lesson learned from this research was the (variable) need for parental supportive care, which should not remain restricted to the acute hospitalization phase, but should also be actively offered at the Late Effects Comprehensive Care & Follow-up (LEEF) program.

CARE PATH OPTIMIZATION

With VBHC implementation various processes within the care path have been addressed and first steps towards care path optimization have been made (**chapter 8**). First, the care path was visualized using the Metro Mapping methodology (28, 29). Metro Mapping approached the care path as a Metroline in which multiple layers are visible, including decision points from a patients' perspective, information, involved HCPs and patient companions, and the physical context. Essentially, the patient-journey and medical care path are combined. In doing so, awareness is increased of the impact of adjustments, not only of the targeted process, but also of the non-targeted processes in the care path. In our experience, presenting the visualized care path (the Metroline) to all involved HCPs has led to a better understanding of VBHC processes among HCPs, acceptance of adjustments, and better collaboration between HCPs. HCPs became more aware of the care provided by other HCPs, encompassing both the intramural and extramural care settings.

In **Chapter 6** of this thesis we assessed the long-term PROs after pediatric HSCT. Projecting our results on current clinical practice in the follow-up program after pediatric HSCT, it became clear that not all PRO domains from the study were a

regular topic addressed during the consultation. Specifically, sleep disturbance was only addressed if indicated by the HCP (e.g., if symptoms of fatigue were present), or was reported by the patient themselves. Consequently, as part of the VBHC implementation, PROs have been incorporated into the LEEF program. Patients complete online PROMs in advance of their consultation. The PRO results are being evaluated by HCPs, after which alterations to the consultation can be made if indicated. For example, when there are musculoskeletal problems, a physiotherapist can already be added to the appointment on the same day. During the consultation the HCP discusses the PROs with the patient. An evaluation of this PRO implementation has been described in **chapter 7**. Patients and HCPs were interviewed on their perceptions of the use of PROs during consultations. Perspectives from patients and HCPs on the use of PROs were mostly in line. Use of PROs was perceived to help discuss topics and facilitate conversations. More sensitive subjects, such as sexuality, were addressed more easily due to better preparation from patients and HCPs. In addition, with the use of PROs consultations became more efficient and topics important to the patient were discussed. PRO use led to a moment of self-reflection and made patients look back at the HSCT and their recovery afterwards. With the use of PROs patients felt more understood and supported by their HCP. HCPs experienced that the use of PROs improved their insight into patients' overall well-being. However, the HCPs highlighted the need to check the patients' interpretation of the PROMs and confirm or clarify the PROs. The HCPs noticed patients were better prepared for the consultation and were more involved in their care. This had included improving equality and reciprocity in the doctor-patient interactions and improved shared decision making after PROM implementation.

MOVEMENT TOWARDS PATIENT CENTERED LIFELONG CARE

In recent years, healthcare systems are gradually moving towards a system based on VBHC (5, 6, 30, 31). In addition, the 2023 Integral Healthcare Agreement in the Netherlands (Integraal Zorg Akkoord) states that healthcare has to be value-based, thereby acknowledging this development (32). Sharing knowledge in VBHC implementation is essential to support this ongoing development.

The aim of this thesis was to implement and evaluate aspects VBHC at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric stem cell transplantation for nonmalignant diseases. By pioneering with both the expertise of the HCP and patient (family) experiences, with HCPs, patients and their families working together and sharing knowledge, we have worked towards adding value to care. **Chapter 8** of this thesis describes lessons learned from the VBHC

implementation at the LUMC LEEF program after pediatric HSCT. Figure 1 presents the steps of VBHC implementation. Involving the patients at the start of the VBHC implementation, and exploring the patients' needs, leads to new, and sometimes unexpected, perspectives towards healthcare. One of the key messages was that implementing individual VBHC elements does not automatically lead to bringing the VBHC elements together. Furthermore, integrating research in VBHC is essential to secure and continue these ongoing processes and helps, based on our experiences, to keep everyone, patients, their families, and HCPs, motivated. Through the lessons learned and sharing this knowledge, we are working towards (inter)national benchmarking for the long-term follow-up after pediatric HSCT for nonmalignant diseases. The LEEF program strives to provide standardized care wherever possible while ensuring personalized care when necessary.

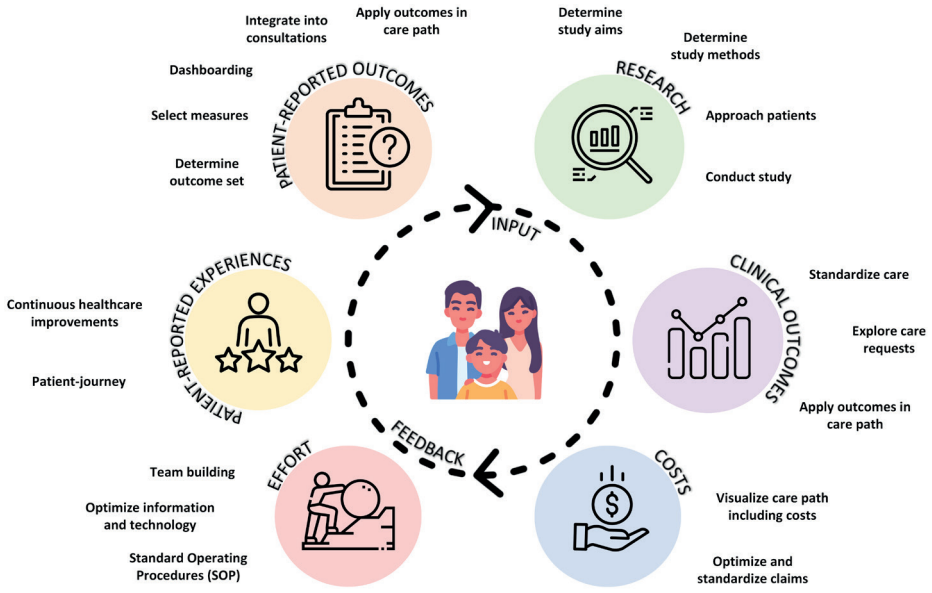

Figure 1. Value-based healthcare (VBHC) implementation at the late effects comprehensive care & follow-up program (LEEF) program after pediatric HSCT for nonmalignant disease

FUTURE PERSPECTIVES

By pioneering with integrating research into VBHC implementation at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT

for nonmalignant diseases at the LUMC, we have observed that this approach continuously advances the processes for optimizing the care path. In this regard, maintaining the patient perspective as a priority is essential, which needs to be continuously explored and revised during patient conference days and in day-to-day evaluation. Therefore, future studies should not solely focus on determining the late effects after pediatric HSCT for nonmalignant diseases, but also assess the impact of these late effects (e.g., gonadal dysfunction) on quality of life.

In this thesis, PROs have demonstrated their value in research, such as long-term quality of life studies, but they have also proven to be valuable when used in clinical practice. The evaluation of PROs for both research purposes and clinical use can be expanded within the broader care path of pediatric stem cell transplantation. PROs can be applied, for example, prior to transplantation and shortly after transplantation, to assess the overall well-being of the patient and support shared decision-making. When discussing long-term HSCT outcomes, it is not solely about survival rates, but PROs are integral to capturing these long-term outcomes. The integration of PROs into the late effects screening program, and therefore assessing overall well-being, should also be internationally adopted by similar comprehensive care programs.

By sharing our knowledge regarding late effects after pediatric stem cell transplantation and VBHC implementation with colleagues outside the field of HSCT, we have discovered significant similarities in the late effects and overall well-being following high-intensity treatments during childhood. This presents an opportunity for others also to explore a collaborative approach in providing supportive care and treatment. Therefore, we advocate for generalized integrated follow-up programs to optimize support and treatment, aiming to improve overall wellbeing of these patients and empower patients and their families throughout their lifetime.

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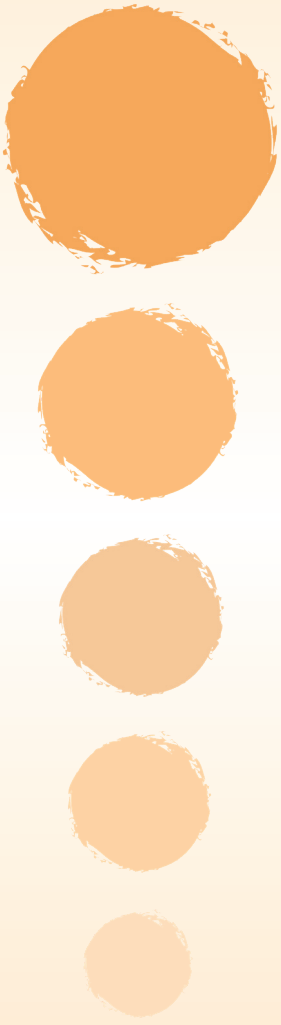


Chapter 10

Nederlandse samenvatting

STAMCELTRANSPLANTATIE

Een allogene hematopoietische stamceltransplantatie (HSCT) is een intensieve behandeling waarmee genezing van zowel oncologische (bijv. leukemie), als niet-oncologische aandoeningen (bijv. sikkelcelziekte) wordt beoogd. Hematopoietische stamcellen zitten in het beenmerg en vormen de bron van al onze bloedcellen:

- Rode bloedcellen (erythrocyten): zorgen voor transport van zuurstof in het lichaam.
- Witte bloedcellen (leukocyten): zorgen voor bescherming tegen ziekteverwekkers.
- Bloedplaatjes (trombocyten): zorgen voor bloedstolling, zodat bloedingen stelpen.

Bij een HSCT worden de stamcellen van de patiënt vervangen door stamcellen van een donor. Vanuit de donorstamcellen wordt vervolgens opnieuw een bloed- en afweersysteem gevormd. Patiënten worden voorbereid middels conditionering, welke bestaat uit (intensieve) chemotherapie en immunosuppressiva (medicijnen welke het afweersysteem onderdrukken). Door chemotherapie en immunosuppressiva hebben kinderen (tijdelijk) verminderde afweer en lopen ze risico op (ernstige) complicaties, zoals orgaantoxiciteit en infecties. Het duurt enkele maanden of, in zeldzame gevallen, zelfs jaren voordat het afweersysteem zich herstelt.

Binnen de niet-oncologische, meestal aangeboren, aandoeningen waarbij HSCT als curatieve behandeling wordt ingezet, zijn een viertal groepen te onderscheiden: aangeboren afweerstoornissen, rode bloedcelaandoeningen (bijv. hemoglobinopathieën), aangeboren of verworven beenmergfalen en stofwisselingziektes. Sommige van deze aandoeningen zijn direct levensbedreigend. Andere aandoeningen kenmerken zich door een chronisch, progressief beloop met verminderde kwaliteit van leven en lagere levensverwachting. Een HSCT geneest de hematologische en immunologische verschijnselen van de aandoening. Echter, de eventuele ziekte-uitingen in andere organen of weefsels, zoals de nieren of de lever, worden veelal niet (direct) beïnvloed door de HSCT en kunnen peristeren of manifest worden na een geslaagde HSCT. De mogelijke al bestaande ziekteverschijnselen (co-morbiditeit) kunnen van invloed zijn op de uitvoerbaarheid van het HSCT-proces zelf, bijvoorbeeld de keuze van medicijnen in het geval van nierproblemen bij sikkelcelziekte, en voor de follow-up na HSCT.

LATE EFFECTEN NA STAMCELTRANSPLANTATIE

Na een HSCT kunnen late effecten optreden, zowel als gevolg van de HSCT-procedure zelf als van de onderliggende ziekte. Het optreden van late effecten is bekend geworden door chemotherapie en bestralingsbehandeling van oncologische patiënten, waarbij onderzoek aantoonde dat er ook op de lange termijn orgaanschade kan optreden door chemotherapie en/of bestraling. Dit is met name bekend geworden voor de patiënten met kanker op de kinderleeftijd. Voor deze groep is door de Stichting Kinderoncologie Nederland (SKION) een follow-up programma opgezet waarbij patiënten na kinderkanker standaard worden gescreend op diverse late effecten via de LATER richtlijn. Aangezien chemotherapie een integraal onderdeel is van de behandeling bij een HSCT was het eveneens van belang om het screenen op late effecten na HSCT te benadrukken. werd ook het belang van screenen op late effecten na HSCT relevant. In eerste instantie lag de nadruk op het screenen van patiënten met een oncologische aandoening. Later werd ook aandacht besteed aan het onderzoeken van late effecten bij patiënten met een niet-oncologische aandoening, waarbij chemotherapie, vergelijkbaar met de oncologische aandoeningen, deel uitmaakt van het HSCT-proces.

Vanaf 2 jaar na de HSCT worden patiënten, zowel kinderen als volwassenen jaarlijks gescreend op late effecten in het Leids Universitair Medisch Centrum (LUMC). Deze polikliniek heet de Late Effecten Follow-up (LEEF) polikliniek. Late effecten kunnen elk orgaansysteem betreffen, zoals de huid, nieren en lever. Naast de fysieke gezondheid wordt ook gekeken naar het mentale welzijn.

In deze video's wordt beknopt uitgelegd wat een HSCT inhoudt, zowel tijdens de klinische opname als de poliklinische follow-up.

1.
Wat is een stamceltransplantatie

2.
In het ziekenhuis

3.
Hoe gaat het verder thuis

PATIËNTGERICHTE WAARDEGEDREVEN ZORG

Naast het screenen op late effecten wordt binnen het LEEF zorgpad ook gestreefd naar het bieden van optimale zorg, waarbij de zorg afgestemd is op de behoefte van de patiënt gedurende het hele leven. In de afgelopen jaren beweegt het gezondheidszorgsysteem geleidelijk naar een systeem van waardegedreven zorg (Patient-Centered Value-Based Healthcare, VBHC). VBHC streeft naar het creëren van waarde door de beste mogelijke resultaten te behalen tegen de laagst mogelijke effort en kosten. VBHC elementen betreffen klinische uitkomsten, patiënt-gerapporteerde uitkomsten (kwaliteit van leven), patiëntervaringen, kosten en effort. Eenduidige implementatiestrategieën ontbreken, maar de principes van VBHC worden in toenemende mate al toegepast binnen de gezondheidszorg. Binnen dit onderzoeksproject werden de VBHC-principes geïmplementeerd in het LEEF zorgpad.

EVALUEREN VAN LATE EFFECTEN NA KINDERSTAMCELTRANSPLANTATIE MET EEN NIET-ONCOLOGISCHE AANDOENING

Deel I van dit proefschrift richt zich op de lange termijn klinische resultaten van HSCT voor niet-oncologische aandoeningen op de kinderleeftijd. Bij de start van het LEEF zorgpad werden aanvankelijk de richtlijnen van late effecten na kinderkanker gebruikt. Echter, de behandeling voor oncologische aandoeningen op de kinderleeftijd (inclusief het onderdeel HSCT) verschilt aanzienlijk ten opzichte van de behandeling van die bij kinderen met een niet-oncologische aandoening. Dit betreft met name de aard van de soms intensieve en/of langdurige voorbehandeling en de gezondheidsstatus en kwaliteit van leven voorafgaand aan de HSCT. Bovendien kan de onderliggende ziekte zelf een predisponerende factor zijn voor het optreden van late effecten na HSCT. **Hoofdstuk 2** omschrijft de ontwikkeling van een screeningsrichtlijn voor late effecten na kinderstamceltransplantatie met een niet-oncologische indicatie. Geïntegreerd in deze richtlijn zijn de late endocriene effecten, beschreven in **hoofdstuk 3**. De endocriene late effecten betreffen groei, schildklier- en gonadale functie (geslachtshormonen). Hierin wordt vastgesteld dat in 61% van de patiënten sprake is van ten minste één laat endocrien effect. Tevens wordt een hoog percentage gonadale dysfunctie gezien bij zowel vrouwen als mannen (respectievelijk 55% en 39%). Vrouwen met een conditionering op basis van busulfan liepen een groter risico op het ontwikkelen van gonadale dysfunctie in vergelijking met vrouwen met een conditionering op basis van treosulfan. Verder onderzoek is nodig om ook vruchtbaarheid te evalueren, wat momenteel niet haalbaar bleek gezien de gemiddelde leeftijd en follow-up duur van onze onderzoekspopulatie.

Deel II van dit proefschrift richt zich op patiënt-gerapporteerde uitkomsten en ervaringen na kinderstamceltransplantatie. **Hoofdstuk 4** beschrijft de lange termijn psychosociale impact van de HSCT behandeling. Hieruit zijn vier thema's naar voren gekomen: 1) zich goed voelen, 2) aanhoudende betrokkenheid van de gezondheidszorg, 3) invloed op relaties met dierbaren en 4) invloed op de levensloop van de patiënt. Het onderzoek heeft duidelijk gemaakt dat het essentieel is om de ondersteuning op de individuele patiënt af te stemmen (Patient-Centered VBHC). Bovendien werd de mogelijke impact van frequente ziekenhuiscontroles op patiënten duidelijk, met daarbij de noodzaak voor zorgcoördinatie. Tot slot minimaliseerden en accepteerden patiënten somatische bijwerkingen en toonden een opmerkelijke veerkracht na deze intensieve behandeling. Deze kennis is direct toepasbaar in de voorlichting en begeleiding tijdens en na het HSCT traject. Daarnaast helpen deze inzichten de LEEF zorgpad-organisatie te optimaliseren.

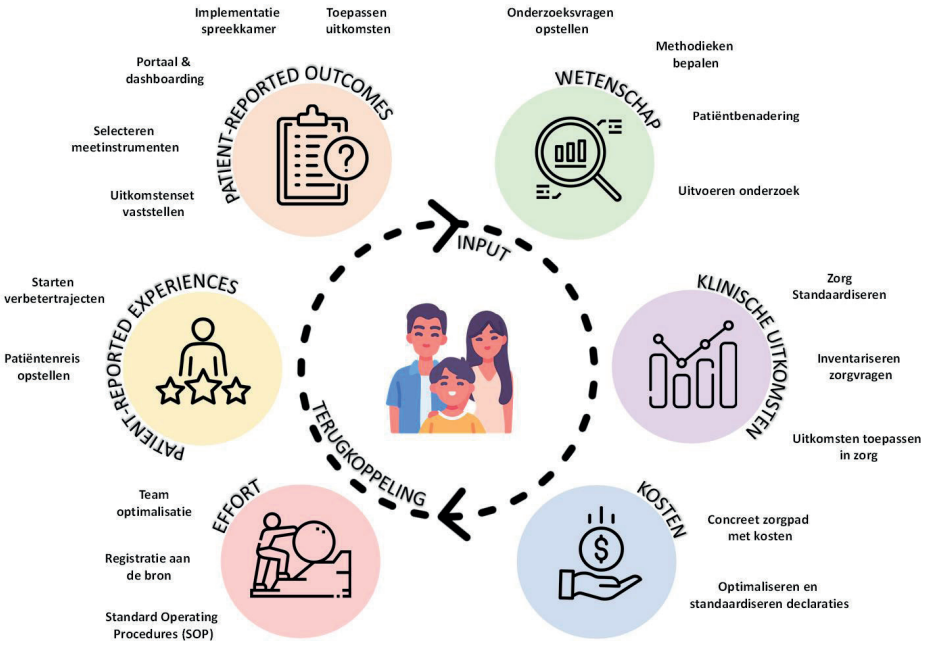
In **hoofdstuk 5** worden de lange termijn alledaagse problemen van ouders van getransplanteerde kinderen geëvalueerd. De uitkomsten voor ouders van getransplanteerde kinderen zijn over het algemeen vergelijkbaar met die van ouders van kinderen met een chronische aandoening. Echter, in vergelijking met ouders van gezonde kinderen ervaren ouders van getransplanteerde kinderen meer stress in het dagelijks leven. De gebieden waarop problemen worden ervaren verschillen tussen moeders (opvoedingsproblemen) en vaders (emotionele problemen). Momenteel wordt ondersteunende zorg voor ouders voornamelijk aangeboden tijdens de ziekenhuisopname. Een leerpunt uit dit onderzoek was de (variabele) behoefte aan ondersteunende zorg voor ouders, die idealiter niet beperkt blijft tot tijdens de ziekenhuisopname, maar juist ook actief moet worden aangeboden direct na HSCT en in het LEEF zorgpad om daarmee eventuele behoefte aan deze zorg al vroegtijdig te herkennen en aan te bieden.

Ten slotte beschrijft **hoofdstuk 6** de lange termijn patiënt-gerapporteerde uitkomsten (kwaliteit van leven) na kinderstamceltransplantatie. Dit is een van de eerste studies waarin kwaliteit van leven met hetzelfde (internationale) meetinstrument wordt gemeten in diverse leeftijdsgroepen van zowel kinderen als volwassenen. Het biedt daarmee de kans om lange termijn follow-up op het gebied van kwaliteit van leven van alle leeftijdsgroepen te waarborgen en daarmee ook internationaal de resultaten te kunnen vergelijken (benchmarking). In vergelijking met de referentiegroep (leeftijds-gematchte controlepersonen) wordt vergelijkbare of zelfs gunstigere lange termijn kwaliteit van leven gezien bij patiënten na kinderstamceltransplantatie met een niet-oncologische indicatie. Dit wordt vaker gezien bij patiënten na een intensieve behandeling of ziekte, waarbij zij zich realiseren dat gezondheid en daardoor 'normaal' kunnen functioneren niet vanzelfsprekend is. Deze studie laat zien dat meer aandacht nodig is voor de fysieke gezondheid, het functioneren op

school en mogelijke slaapstoornissen. Tevens suggereert deze studie dat speciale aandacht nodig is voor de groep 8 tot 18 jarige gezien deze patiëntengroep de meest variabele scores op de verschillende domeinen van kwaliteit van leven lieten zien.

IMPLEMENTEREN EN EVALUEREN VAN WAARDEGEDREVEN ZORG ELEMENTEN BINNEN HET LEEF ZORGPAD

Deel III van dit proefschrift richt zich op de implementatie en evaluatie van VBHC gezondheidszorg binnen het LEEF zorgpad. **Hoofdstuk 7** beschrijft de waarde van het gebruik van door patiënten-gerapporteerde uitkomsten voor gezondheidsscreening tijdens lange termijn follow-up na HSCT. Patiënt-gerapporteerde uitkomsten worden met behulp van online vragenlijsten verzameld welke voor het poliklinisch bezoek wordt ingevuld. De uitkomsten worden vervolgens voorbereid door het behandelteam en besproken met de patiënt in de spreekkamer. Uit de interviews met zowel patiënten als zorgverleners komt naar voren dat met behulp van patiënt-gerapporteerde uitkomsten 1) onderwerpen makkelijker worden besproken, 2) het leidt tot een moment van zelfreflectie, 3) het leidt tot een efficiënter consult en 4) de patiënten zich beter begrepen voelen. De implementatie van patiënt-gerapporteerde uitkomsten heeft geleid tot een verbetering van gelijkheid en wederkerigheid tussen arts en patiënt, en een verbeterde gedeelde besluitvorming. Tot slot behandelt **hoofdstuk 8** de lessen die zijn geleerd uit de implementatie van waardegedreven gezondheidszorg in het LEEF zorgpad. Met behulp van deze blauwdruk (figuur 1) voor waardegedreven zorg-implementatie beogen we handvatten te delen voor vergelijkbare complexe multidisciplinaire levensloopzorgpaden. De kernboodschappen voor waardegedreven zorg-implementatie zijn 1) start met input van de gehele patiëntenpopulatie voor inventarisatie van patiëntbehoeftes, 2) zet wetenschappelijke monitoring en evaluatie centraal voor bestendiging van evidence-based VBHC-elementen en koppel resultaten terug aan patiënten, en 3) implementatie van het gehele waardegedreven zorg draagt bij aan brede kwaliteitsverbetering om zo vanuit optimaal welzijn van de patiënten de behandeling te blijven verbeteren.



Figuur 1. VBHC elementen en implementatie binnen het LEEF zorgpad

CONCLUSIES EN TOEKOMSTPERSPECTIEF

Het doel van dit proefschrift was om de basis te leggen voor implementatie en evaluatie van passende zorg middels de VBHC principes voor patiënten na kinderstamceltransplantatie met een niet-oncologische indicatie in het LEEF zorgpad. De wetenschappelijke kennis op dit gebied is nog schaars en daarmee biedt dit proefschrift waardevolle inzichten vanuit een pionierende fase met directe klinische toepassing. Door de centrale rol van de ervaringen van patiënten (en hun families), aangevuld met expertise van de diverse betrokken zorgverleners tijdens de ontwikkeling en wetenschappelijk evaluatie van het LEEF zorgpad, hebben we ernaar gestreefd waarde toe te voegen aan de zorg.

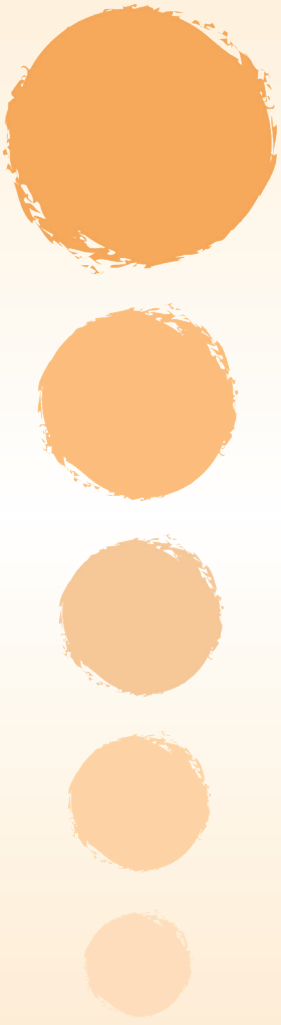
Door te pionieren met de integratie van wetenschappelijk onderzoek in de VBHC-implementatie in het LEEF zorgpad, hebben we gezien dat de verbetercyclus voor optimalisatie van het zorgpad geborgd blijft. Het patiëntenperspectief blijft hierin essentieel, welke continu moet worden geëxploreerd in de spreekkamer (ten behoeven van individuele zorg) en tijdens patiëntendagen (ten behoeve van zorgpad-

organisatie). Toekomstige studies moeten zich daarom niet alleen richten op het bepalen van de klinische late effecten na kinderstamceltransplantatie (bijv. gonadale dysfunctie), maar ook op de impact van deze late effecten op de kwaliteit van leven.

In dit proefschrift hebben patiënt-gerapporteerde uitkomsten hun waarde aangetoond in zowel onderzoek (lange termijn kwaliteit van leven), als in klinische toepassing (in de spreekkamer). Deze manier van toepassing van patiënt-gerapporteerde uitkomsten kan in het gehele zorgpad van kinderstamceltransplantatie worden geïmplementeerd, bijvoorbeeld vóór HSCT en kort na HSCT. Bij het vaststellen van lange termijn resultaten van kinderstamceltransplantaties gaat het niet alleen om overlevingspercentages, maar zijn juist patiënt-gerapporteerde uitkomsten essentieel voor de bredere waardering van de uiteindelijke uitkomst van deze behandeling. De integratie van patiënt-gerapporteerde uitkomsten in het screeningsprogramma voor late effecten, en daarmee het beoordelen van het algehele welzijn, kan ook internationaal van grote meerwaarde zijn in de evaluatie, vergelijking en het optimaliseren van soortgelijke uitgebreide zorgprogramma's.

Door onze kennis te delen over late effecten na kinderstamceltransplantatie en de implementatie van een levensloop-zorgpad op basis van de VBHC methodiek buiten het transplantatieveld (bijvoorbeeld neonatologie en aangeboren hartafwijkingen), hebben we overeenkomstige thema’s geïdentificeerd in de lange termijn follow-up van hoog-intensieve behandelingen op de kinderleeftijd. Door de krachten hierin te bundelen, kan een levensloop-zorgpad worden vormgegeven met toepassing van de juist expertise met de juiste zorg op de juiste plek. Zo kan passende zorg geboden worden voor alle patiënten na hoog-intensieve behandeling op de kinderleeftijd.

We pleiten daarom voor levensloopgerichte follow-up programma’s voor kinderen én volwassenen na hoog-intensieve behandeling op de kinderleeftijd om de ondersteuning en behandeling te optimaliseren, met als doel het algehele welzijn van deze patiënten en hun families te verbeteren voor een optimale toekomst.



Appendices

List of abbrevations

List of publications

Curriculum Vitae

Dankwoord

List of abbrevations

AMH = anti-Müllerian hormone

BMF = bone marrow failure

BMI = Body Mass Index

BMT = bone marrow transplantation

CC = chronic condition

cGVHD = chronic graft versus host disease

COVID = corona virus disease

CVA = cerebrovascular accident

Distress Thermometer for Parents (DT-P)

FSH = follicle stimulating hormone

FT4 = free thyroxin

GVHD = graft versus host disease

HBP = hemoglobinopathies

HCP = health care professional

HPA = hypothalamic-pituitary axis

HPV = humane papillomavirus

HRQoL = health related quality of life

HRT = hormone replacement therapy

HSCT = hematopoietic stem cell transplantation

ICHOM = International Consortium for Health Outcomes Measurement

IEI = inborn errors of immunity

IEM = inborn errors of metabolism

IGF = insulin-like growth factor

LCI = Landelijke Coördinatie Infectieziektebestrijding

LEEF = Late Effects Follow-up

LH = luteinizing hormone

NAH = near adult height

NFU = Netherlands Federation of University Medical Centers

NVK = Nederlandse Vereniging voor Kindergeneeskunde

PRE = patient-reported experience

PREM = patient-reported experience measure

PRO = patient-reported outcome

PROM = patient-reported outcomes measure

PTH = parathyroid hormone

SAA = severe aplastic anemia

SDM = shared-decision making

SCID = severe combined immunodeficiency

SS = short stature

TAI = total abdominal irradiation

TBI = total body irradiation

TSH = thyroid stimulating hormone

VBHC = value-based healthcare

List of publications

This thesis

Bense, J.E., Lankester, A.C., Bresters, D., Versluys, A.B., Louwerens, M., & de Pagter, A.P.J. (2023). Leidraad late effecten follow-up na kinderstamceltransplantatie of celtherapie voor benigne hematologische, metabole of immunologische indicatie - Screening guideline for late effects after pediatric stem cell transplantation or cell therapy for nonmalignant diseases Nederlands Tijdschrit voor Hematologie.

Submitted

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de Kloet, L.C.#, **Bense, J.E**#., van der Stoep, M., Louwerens, M., von Asmuth, E.G.J., Lankester, A.C., de Pagter, A.P.J., & Hannema, S. E. (2022). Late endocrine effects after hematopoietic stem cell transplantation in children with nonmalignant diseases. Bone Marrow Transplant, 57(10), 1564-1572. https://doi.org/10.1038/s41409-022-01755-x

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Curriculum Vitae

Joëll Bense is geboren op 31 mei 1993 in Venlo. In 2011 behaalde zij haar VWO-Atheneum diploma aan het Valuascollege in Venlo. Vervolgens volgde ze gedurende één jaar de studie Gezondheidswetenschappen in Maastricht. In 2012 startte ze met haar studie Geneeskunde. Aan het einde van haar bachelostudie kwam ze voor het eerst in aanraking kwam met de stamcelgeneeskunde en ervoer de klinische kant hiervan tijdens haar semi-artsstage bij de afdeling kinderstamceltransplantatie. Ze behaalde haar masterdiploma in december 2018. Direct daarna ging ze aan de slag als arts-assistent kindergeneeskunde in het Spaarne Gasthuis in Haarlem. Na een jaar werkervaring te hebben opgedaan, begon ze in januari 2020 aan haar promotietraject bij de kinderstamceltransplantatie van het Leids Universitair Medisch Centrum. Dit deed ze onder begeleiding van prof. dr. A.C. Lankester, prof. dr. A.M. Stiggelbout en dr. A.P.J. de Pagter. Het promotietraject rondde ze succesvol af in maart 2023. Daarna ging ze werken als arts-assistent kindergeneeskunde bij het Reinier de Graaf Ziekenhuis in Delft. Per 1 januari 2024 is Joëll gestart met haar opleiding tot kinderarts in het Leids Universitair Medisch Centrum.

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