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Analysis

Physical, Mental, and Social Health of Adult Patients with Sickle Cell Disease after Allogeneic Hematopoietic Stem Cell Transplantation: A Mixed-Methods Study

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A B S T R A C T

Patients with sickle cell disease (SCD) experience a considerable physical and psychosocial disease burden. In recent years, the application of allogeneic hematopoietic stem cell transplantation (HSCT) to treat adults with SCD has increased. A thorough understanding of patients' physical, mental, and social health before and after cure is needed to meet the needs of this growing group of patients. We aimed to explore the perspectives of adult SCD patients on the changes in their experienced health and personal life goals after being cured. A mixed-methods approach was used, comprising a semistructured interview and a set of 9 Patient Reported Outcomes Measurement Information System (PROMIS) measures. Adult SCD patients who underwent HSCT at least 1 year earlier were eligible to participate in the study. Interviews were thematically analyzed using MAXQDA software. PROMIS T scores were compared with reference scores of the general population using SPSS Statistics. Ten patients participated in the study; their median age was 29.5 years (range, 19 to 49 years), and their median time since HSCT was 2.7 years (range, 1.0 to 3.5 years). Themes from the interviews were (1) pain/living pain free, (2) physical well-being, (3) mental well-being, (4) perspective/ outlook, (5) education/work, (6) family/friends, and (7) activities/ participation. Following the PROMIS framework, we described these themes in a narrative synthesis according to health domain and categorized in 4 chronological time phases: before HSCT, first year post-transplantation, current situation, and future expectations. Physical health improved greatly, but transplantation-related toxicity, ongoing pain from avascular osteonecrosis, and fatigue negatively impacted quality of life in some patients. Furthermore, emotional struggles during the post-transplantation period were common, and patients expressed a need for psychological help. Patients reported improvements in social health and the ability to pursue personal life goals. The mean T scores of all PROMIS measures fell within the normal symptom limits compared with reference data of the general population, although, large variations were observed among the participants, matching our qualitative findings. In general, adult SCD patients experienced improved physical, mental, and social health after cure by HSCT and were able to pursue personal life goals. Yet they found themselves confronted with a new and unfamiliar reality that brought different challenges. Pain due to irreversible avascular osteonecrosis continued to have a negative impact. Clinicians should aim to help patients have realistic expectations before transplantation and offer timely psychological care.

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INTRODUCTION

Patients with sickle cell disease (SCD) suffer from chronic hemolytic anemia, painful vaso-occlusive crises (VOC), and cumulative (ischemic) organ damage, resulting in increased morbidity and mortality [1,2]. A US population-based analysis showed that the median age at death is 43.4 years for females and 40.8 years for males with SCD [3]. Additionally, the psychological burden of living with SCD is high, with many patients experiencing stress, anxiety, low self-efficacy, and/or depressive symptoms [4–6]. The various physical and mental symptoms of SCD, as well as frequent hospitalizations, have a negative impact on the patients' ability to participate in social, educational, and occupational activities [7–9].

Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the sole established curative treatment option for patients with SCD [10,11]. Advances in supportive care, modifications to conditioning regimens, and the use of haploidentical donors have made HSCT a viable treatment for SCD patients [11–15]. In a recent study, overall survival and disease-free survival following HSCT in adult SCD patients were 93% and 85%, respectively [14]. Transplantation-related complications include graft-versus-host disease (GVHD), allograft rejection, and infections, with incidence varying depending on the conditioning regimen, patient age, and donor type [13,16]. Patient-reported physical and psychological well-being is being increasingly recognized as an important outcome measurement. However, a systematic evaluation of the effects of HSCT on health-related quality of life (HRQOL)—the self-reported impact on physical, mental, and social well-being—of SCD transplantation recipients is lacking [17]. This is particularly true for the adult SCD population. Improvement of all health domains may be expected after HSCT, yet this is not self-evident [18–20]. Irreversible organ damage, such as avascular osteonecrosis (AVN), cognitive impairment, and psychosocial problems, potentially could have an ongoing influence on the experienced health and future perspective of SCD patients, even after successful transplantation. In addition, personal factors such as coping abilities and preceding expectations of living a healthy life might influence the perception of success or failure of treatment.

Therefore, a better understanding of the effects of HSCT on physical, mental, and social health of patients with SCD is essential for clinicians to be able to meet the needs of this growing group of patients. In the present study, we aimed to explore the perspectives of adult SCD transplantation recipients on the changes in their experienced health and personal life goals after cure by HSCT.

METHODS

Study Design and Research Team

This study was conducted at the Amsterdam University Medical Center, a tertiary care center specialized in SCD and allogeneic HSCT care. A mixed methods approach was used, comprising qualitative interview data and a quantitative questionnaire component.

The study was performed in accordance with the Declaration of Helsinki. Approval of the Institutional Review Board of the Amsterdam University Medical Center was obtained (reference no. W21_247). The research team included medical doctors (E.D., E.N., and B.B.), a BSc/Masters student of medicine (S. N.), psychologists (L.H. and M.M.v.M.), and specialized pediatric/MSc (H.M.) and transplantation (L.S. and G.H.) hematology nurses.

Participant Selection and Treatment

SCD patients were eligible if they met the following criteria: (1) treatment with matched sibling donor or haploidentical donor HSCT at least 1 year earlier, (2) age ≥16 years, (3) ability to provide informed consent, and (4) fluency in Dutch or English language. Patients were invited to participate by their attending physician (E.N.). Informed consent was provided by each participant.

Patients with an available matched sibling donor underwent nonmyeloablative conditioning (alemtuzumab/3 Gy total body irradiation) as described by Hsieh et al. [15], preceded by a 3-month preconditioning phase with hydroxyurea and azathioprine. Sirolimus was provided as GVHD and rejection prophylaxis for at least 1 year. The conditioning for haploidentical bone marrow transplantation consisted of antithymocyte globulin, fludarabine, cyclophosphamide, thiotepa, and total body irradiation (2 Gy). Post-transplantation cyclophosphamide was administered as part of GVHD prophylaxis along with mycophenolate mofetil and sirolimus [21].

Data Collection and Analysis

Qualitative

A semistructured interview, face-to face or via videoconference, was conducted with each participant by 1 interviewer (E. D.) or 2 interviewers (E.D. and S.N.). The interviewers did not have a current healthcare provider relationship with any participants. Interviews were audiotaped and transcribed verbatim. The interview topic list (Supplementary Data, Appendix 1) was based on the clinical experience of 2 researchers (E.N. and E.D.) and the phases of undergoing an HSCT. The topic list was reevaluated throughout the study. Interviews were continued until data saturation was reached, meaning that no new codes were generated during the last 2 interviews. MAXQDA version 10 was used for qualitative data analysis. The consolidated criteria for reporting qualitative research (COREQ) checklist was followed to ensure comprehensive reporting [22]. Two researchers (E.D. and S.N.) conducted the coding. Thematic analysis was used, guided by the following steps: (1) familiarization of data; (2) initial independent open coding; (3) generating themes; (4) validity and reliability of themes; (5) defining and naming themes; and (6) interpretation and reporting [23,24]. Codes and themes were discussed within the research team and categorized in 4 time phases: (1) before HSCT, (2) first year after transplantation, (3) current situation (time of interview), and (4) future expectations. Although generated through open coding, relevant themes of each time phase were further categorized in physical, mental, and social health using the PROMIS framework. The narrative synthesis of the results of the interviews is presented for each time phase. Additionally, representative quotes are provided to illustrate and highlight patients' experiences and perceptions.

Quantitative

Sociodemographic and transplantation data were collected through a short questionnaire and from medical records and summarized with descriptive statistics (SPSS Statistics version 25; IBM, Armonk, NY). Participants were asked to complete a set of 9 Patient-Reported Outcomes Measurement Information System (PROMIS) measures using the online KLIK PROM portal [25]: (1) Pain Interference, (2) Physical Function, (3) Sleep Disturbance, (4) Fatigue, (5) Anxiety, (6) Anger, (7) Depression, (8) Ability to Participate in Social Roles and Activities, and (9) Satisfaction with Participation in Social Roles. Computer adaptive testing was used for all item banks except for

Table 1
Patient and transplant characteristics

Sex, female/male n		4/6
Age at HSCT yr, median (range)		29.5 (19-49)
Time since HSCT yr, median (range)		2.7 (1-3.5)
Marital status, *n*	Married/living together Single	1 9
Education, *n*	Higher (tertiary) education*	1
	Secondary (vocational) education Below secondary education	8 1
Paid job at time of interview, *n*	Paid job	5
	Incapacitated for work	5
Country of birth, *n*	Europe: The Netherlands (6), United Kingdom (1)	7
	Africa: Angola (1), Congo (1), Uganda (1))	3
Genotype, *n*	HbSS/HbS 0	9/1
Treatment before HSCT, *n*	Hydroxyurea	6
	Exchange/periodic RBC transfusions	4
SCD morbidity and coexisting conditions before HSCT, *n*	VOC (≥2/year)	8
	Cholecystectomy	7
	AVN	7
	ACS	7
	Retinopathy	3
	Stroke (overt)	1
	Nephropathy	1
	Pulmonary hypertension	1
Donor/conditioning *n*	MSD/Alemtuzumab/3 Gy TBI	9
	Haplo/ATG+Flu+Cyclo+Thio+2 Gy TBI, PTCy	1
Adverse events ≥ grade 2, *n*	GvHD (GI) grade 2	2
	Sirolimus-related toxicity - oral ulcers (6) - hyperlipidemia (4) - body aches (4) - acne (2) - hypertension (1)	9
	Viral reactivation (VZV)	1
	Infections - norovirus (2) - catheter-related bloodstream infection (1)	3
	Immunological - AIHA (1) - Hypothyroidism (1)	2
	Stroke	1
Hospital readmissions, *n*	1 or 2 readmissions	3
	≥ 3 readmissions	2
Total readmission days, *median (range)*		10 (6-23)

* Higher education is defined as education leading to award of an academic degree.
HSCT, hematopoietic stem cell transplantation; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis; AVN, avascular osteonecrosis; ACS, acute chest syndrome; MSD, matched sibling donor; Haplo, haploidentical donor; TBI, total body irradiation; ATG, antithymocyte globulin, Flu, fludarabine; Cyclo, cyclophosphamide, Thio, thiotepa, Gy, Gray; PTCy, post-transplantation cyclophosphamide, GvHD, graft-versus-host disease; GI, gastro-intestinal; VZV, varicella zoster virus; AIHA, auto-immune hemolytic anemia.

Anger (Short Form 5a). PROMIS results were visualized presenting the standardized T score of each measure per participant and per group (mean ± SD) T scores; SPSS Statistics) in a heat map using the PROMIS colors and cutpoints for symptom severity: green for normal limits, yellow for mild impairment, orange for moderate impairment, and red for severe impairment. For the Anger scale, T scores were calculated using the HealthMeasures Scoring Service [26]. Generally, the height of PROMIS T scores depends on the concept being measured; for example, a high T score on item bank Anxiety is unfavorable, whereas a high T score on item bank Physical Function represents a favorable outcome. Cutpoints vary by PROMIS measure and are based on the SD. We used mean T scores and cutpoints provided by the Dutch-Flemish PROMIS National Center and HealthMeasures as references [27,28].

RESULTS

Participant Characteristics

Ten patients were included in the study (60% female; median age, 29.5 years). One patient was considered for participation but did not meet the eligibility criteria because of a language barrier. Another patient was not approached because of contemporaneous medical issues. All included patients had

Table 2
Overview of Main Results from the Semistructured Interviews

Themes		Phase before HSCT	HSCT, First Year Post-HSCT	Current Situation	Future Expectations
Physical health	Pain	Frequent VOCs; hospitalizations; chronic pain/AVN; opioid use	Body aches (sirolimus-related); no VOCs	Living pain-free/different pain; irreversibility of AVN	Hope for further improvement
	Physical well-being	Chronic fatigue; feeling cold; chronic medication; chronic blood transfusions; worsening symptoms with age	More energy/feeling different; hair loss; weight gain; toxicity of medication; hospitalization due to complications	Feeling healthy; more energy/fatigue; being able to do sports, swim, cycle; no more blood transfusions	Leading an active life; worries about fertility
Mental health	Mental well-being	Feelings of depression, isolation, traumatization, anxiety, stress; feeling close to death; knowing how to live with SCD; familiarity with SCD; lack of psychological guidance	Feelings of relief, grief; importance of being mentally ready for transplantation/timing; emotional processing of SCD; lack of psychological guidance	Feeling cured; no regrets; ongoing emotional processing of SCD; discrepancy between expectations and outcomes	Optimistic about future; fear of SCD coming back
	Perspective/outlook	Living day-to-day; unpredictability of SCD; taking everything into account; knowledge of short life expectancy	Opening of a new world; adjusting to many new possibilities; sticking to SCD patterns	Feeling independent; feeling free; taking ownership of one's own life	Make plans; dare to picture future; hope for longer life
Social health	Education and work	Falling behind at school; missing out on job opportunities; diminished ability to work	Stop working or studying	Back to studying; found/searching for job	Continue to study; find job/start business; financial worries
	Family and friends	Dependency; feeling a burden for others	Relief for family; support of family and friends	Changed relationships; being a better parent; greater independence	Wanting to start a family
	Activities and participation	Incomprehension by others; missing out on life experiences; unable to do sports, cycle, swim	Loneliness/isolation due to hygiene restrictions	Achieved goals: driver's license, swimming diploma; pursuing hobbies	Being able to travel; pursuing hobbies

successful engraftment. The median time since HSCT was 2.7 years (range, 1.0 to 3.5 years). Only 1 patient was still using immunosuppressive medication. The participants suffered from various pretransplantation comorbidities and post-transplantation complications, ranging from mild to severe. Table 1 provides an overview of patient and transplantation characteristics.

Qualitative Findings

Semistructured interviews, with a mean duration of 48 minutes (range, 30 to 70 minutes), were conducted between October 2021 and May 2022. Thematic analysis revealed 7 themes highlighting the experiences of participants before, during, and after undergoing HSCT: (1) pain/living pain-free, (2) physical well-being, (3) mental well-being, (4) perspective/outlook, and impacts on (5) education and work, (6) family and friends and (7) activities and participation (Table 2). No extra topics were added to the topic guide during the interviewing phase.

Before HSCT

Physical health. Suffering from pain before HSCT is a theme that resonated strongly with most participants. Patients felt that painful VOCs and pain due to AVN had a great influence on their life. Moreover, various interviewees emphasized that VOCs also had an impact on their family members. Not having to experience pain anymore was an important motivation for undergoing an HSCT. Besides pain, patients found it unpleasant to feel tired often. They also used chronic medication or received (exchange) RBC transfusions, which were demanding and placed a burden on their lives.

[about living with SCD] *"I just was someone that was sick very often." Patient 3*

"I couldn't take it [frequent pain crises] *anymore, I really couldn't. I was ready for it* [transplantation]*; I would have rather died than have another crisis." Patient 9*

"You feel that when you are having a crisis, they [family] *don't really know what to do. You see that they care for you and that they want to take the pain from you. But they can't do anything." Patient 8*

Mental health. The physical and social impairments of living with SCD had a great mental impact. SCD made patients feel insecure, lonely, depressed, anxious and/or stressed. Sometimes incomprehension by others, such as unpleasant encounters with teachers or even health care professionals, added to those feelings. Two patients felt close to death shortly before HSCT and believed that they would not have had much longer to live.

"It [SCD] *was a tormentor, that's what I called it." Patient 2*

"I was, to put it briefly, basically traumatized by it [SCD]*." Patient 3*

"It puts a certain weight on your shoulders knowing you have SCD." Patient 4

The unpredictability of SCD felt debilitating and made it hard to pursue plans. Patients lived on a day-to-day basis. Participants had accepted SCD, and it felt normal to them. Living with SCD was familiar, as they had not known another life. Patients had adjusted their lifestyle to SCD, which often meant taking it slow and avoiding activities that they otherwise would have liked to engage in.

"*The future was tomorrow; it was like that." Patient 6*

"*Well, I used to think, I have sickle cell, I won't get old anyway, you know? I thought, ah, I won't get 50 or something. I just lived my life, I'll see, you know*?" *Patient 2*

Social health. VOCs and frequent hospitalizations throughout their lives caused patients to feel that they were lagging behind their peers. Participants reported missing out on school lessons and suggested that they might have performed better at school or professionally had they not had SCD. Patients experienced limitations in engaging in social activities and sports, such as swimming, cycling, and fitness.

"It's not like I had to quit school completely, but I could have done something else than what I'm doing now if I hadn't had SCD. It is like that." Patient 4

"I really had to watch out how I lived my life. That was hard because you're young and you want to be able to do anything. So, I really missed out on a lot when I was younger." Patient 7

First year post-transplantation

Physical health. Almost without exception, participants described the transplantation process as hard but worth it. Most experienced some side effects, such as fever, headaches, skin problems, hair loss, gastrointestinal disturbances, body aches, menstrual irregularities, and/or weight gain. Despite recalling that they had been informed about these side effects, they often came as a surprise. Some patients had to be rehospitalized because of complications, which felt like a setback and occurred unexpectedly. On the other hand, interviewees reported having a lot of energy shortly after the transplantation, feeling no pain, and no longer feeling cold all the time. One participant said that his health went from 0% to 100% in just a few weeks' time.

"It [transplantation] *was hard, but we were working towards something and with SCD it was just going nowhere." Patient 6*

Mental health. Regarding the mental impact of undergoing HSCT, we observed a high degree of ambivalence. On the one hand, participants found it emotionally difficult to process that they did not have SCD anymore and struggled to adjust to the new situation. In hindsight, they felt that timing of HSCT and mental preparation was more important than expected. Interviewees reported feeling left alone with this process and wishing for psychological guidance before and after HSCT. Some reported that psychological help was offered only after they requested it. On the other hand, many participants felt great mental relief after their transplantation.

"And I did it [transplantation], *but emotionally I feel like something was taken away from me." Patient 5*

"Ha! I said good riddance and I don't miss it [SCD]. *I don't want it. No, I am happy it's gone. (. . .) Yeah, I was born with it, yes, but I didn't want it, didn't ask for it." Patient 10*

After HSCT, some participants needed time to internalize that they were cured. They described sticking to SCD patterns at first. Being able to swim in cold water or ride a bike brought intense happiness to many participants, but others were reluctant and still in disbelief that these actions would not cause a VOC.

"I went to the city center by bike, and I was soaking wet. I went home and I was ready to get sick that night. I went to bed, prepared everything [pain medication] *like I always used to do in that situation. And I woke up the next morning and everything was still there. I looked at myself like wow, I did not get sick." Patient 9*

Social health. In general, patients described the transplantation as a big relief for their family and friends, from whom they also received a lot of support. Some participants stopped school or work to undergo the transplantation and felt isolated because of hygiene restrictions during the first year after transplantation.

"My mother once went upstairs in that first year after the transplantation with a sigh: 'And now I can finally sleep. Sometimes I went into your room to check if you were alive, if you were still breathing." Patient 1

"The transplantation was not only of benefit for myself, but also for my family. I would have done everything to not have crises anymore and take that powerless feeling from them." Patient 8

Current situation

Physical health. Most interviewees considered living a pain-free life to be one of the biggest benefits of undergoing transplantation. Not being hospitalized for VOCs any longer and not having to live with the constant threat of VOC added to that gain. Participants who underwent chronic RBC transfusions before HSCT also described feeling as if a large burden was lifted from them. This included not having to undergo venous punctures every few weeks and taking iron chelation medication.

"It starts with the pain, that is where it always starts for me. It's just the pain. So that the pain is gone now is the biggest gain." Patient 6

"I'm not in pain anymore. I had never experienced that before [the transplantation], *I feel, I just feel normal. Like, no pain, nothing!" Patient 2*

Two patients still experienced daily debilitating pain from AVN, which differed from the pain they had experienced before HSCT. Both patients realized that they had achieved some important gains following transplantation, but feelings of disappointment about their current health and ongoing pain still dominated their lives. Three participants also reported feeling fatigued despite now-normal blood counts. Another patient who viewed her transplantation as a great success was still emotional about having to live with a half-sided paralysis that she had developed from a childhood

stroke. Despite now being cured, the half-sided paralysis affected her physical appearance and practical abilities.

> [about feeling cured] *"Theoretically yes, because it is like that. On paper and when you look at my blood, than you do not see sickle cells anymore. But the irreversible physical damage* [AVN], *(. . .). You can't cure what has already happened." Patient 3*

Mental health. Participants described a difference between feeling physically cured and mentally cured from SCD. The mental impact of having had SCD their whole life was not cured by the transplantation process. In fact, mental processing took longer than the physical recovery and was still ongoing for some interviewees. Again, patients expressed a need for psychological counseling during this phase. Looking back made some participants emotional. One interviewee reported that only now that she was cured was she able to talk about the depression and anxiety she had experienced in the past. In the past, she preferred not to be confronted with those feelings by others and neglected the mental impact that SCD had on her.

> [about processing SCD and HSCT] *"It all happens so fast now. And that is, eh, I just want life to stop for a second so that I can think about everything." Patient 1*

> "*I feel like I am emotionally and mentally lagging behind others or something. Like I am only now processing the sadness from the past. Like I am only letting it out now. And that is all because of SCD." Patient 6*

Social health. Many possibilities opened up to patients after HSCT, which often led to a more physically and socially active life. On the one hand, they reported feeling thankful and happy about that, but on the other hand, they described being overwhelmed and not knowing what to do with the energy at first. They had to get used to planning activities or making choices about their personal and professional life.

> "*I noticed that when I was cured it felt like a whole new world opened up to me, so I wanted to do everything all at once." Patient 6*

At the time of the interview, many participants had already achieved life goals and/or were pursuing dreams. These included hobbies such as sports, cycling, and swimming but also getting a drivers' license or a job, buying a car or house, and for many patients, traveling. Some patients who were also parents described that they were now able to be a better parent for their children.

> *"For example, I can now ride a bike with my children. That is something I really wanted to do in the past. But when I rode a bike in the past, I would be in the hospital the next day, so that was not an option. And now I can bring my little one to school by bike." Patient 5*

Future expectations

Physical health. Two patients with ongoing pain from AVN hoped for further physical improvement, probably through joint replacement surgery. A small group of females were concerned about fertility. They recalled being told that the treatment probably would not have a negative influence on fertility but experienced menstrual irregularities, which made them feel uneasy.

Mental health. Some participants worried about SCD coming back. One patient found it hard to adjust to less frequent hospital visits, because seeing his normal blood counts regularly gave him confidence about being cured. The majority of participants felt assured about the success of the transplantation and did not worry about it. Most patients were optimistic about the future, their mindset was changed, and they allowed themselves to make plans.

> *[about SCD coming back] "That is my fear. Because sometimes when something hurts, I think: it's back." Patient 2*

> *"Now I just want to live. I want to do everything I used to be afraid of. I just want to experience it all. So yes, I just want to live. It turned out really well for me." Patient 1*

Social health. Many participants planned to return to school or hoped to find a different job, but some also experienced financial worries about the future. Not all participants were able to work (yet), and others had no work experience because of SCD. Now that she was officially cured, one interviewee worried about her income support, which she received from the Dutch government because she was officially declared unfit for work before the transplantation. This uncertainty made her feel insecure.

> *"Will I be able to work normally, to support my family?" Patient 5*

> *"In many ways, my future was very bleak because I was sick. Where was I going to work? I wasn't thinking about doing hard jobs or going back to school. But now I can see the world is at my feet. I can do what I want if I want. The only limitation with me now is money." Patient 10*

Many patients were hoping to live longer because of the transplantation. One participant looked forward to seeing his children grow up, something he could not imagine while having SCD. Others reported wanting to start a family or get in a serious relationship. Many participants felt less dependent on others and experienced more ownership of their lives.

> *"I see it* [the future] *colorful. I don't want to stay in the country, I want to travel, see the world. I also want to keep studying." Patient 4*

Quantitative Findings

All patients completed 9 PROMIS measures at the time of the interview (1.0 to 3.5 years post-transplantation). The results were visualized as a heat map comprising the T scores of each measured outcome per participant (Table 3). Compared with the general population, mean T scores of our study participants fell within normal limits for all tested PROMIS measures; however, we observed a wide variety of T scores among the participants. One group of patients consisting of 5 patients (50%), including the only haploidentical transplant recipient, scored within normal limits on 8 or 9 of the 9 PROMIS measures (patients 1, 4, 6, 7, and 10). The median age at HSCT of these participants was 25 years (range, 19 to 45 years). One patient was rehospitalized for bone fracture after trauma, unrelated to the HSCT or SCD. Each of the 5 participants in this

Table 3
Results of PROMIS Measures, Completed at the Time of the Interview (Median, 2.7 years [Range, 1.0 to 3.5 Years] Post-Transplantation)

	Physical health				Mental health			Social health	
Patient	Pain interference	Physical function	Sleep disturbance	Fatigue	Anxiety	Anger	Depression	Ability to Participate in Social roles and Activities	Satisfaction with Social Roles and Activities
1	51.6	47.7	45.4	42.7	52.2	50.4	55.9	53.4	52.9
2	51.6	48.0	41.7	44.3	47.0	37.9	47.9	40.4	40.3
3	65.8	35.5	60.0	60.1	57.3	48.8	53.0	36.1	39.7
4	55.8	46.1	61.1	51.1	47.4	52.8	46.8	56.1	51.0
5	55.8	39.9	51.5	61.7	60.6	56.5	64.8	43.0	43.7
6	41.0	62.4	42.0	47.3	48.7	48.1	48.4	58.2	51.7
7	44.9	51.9	53.2	34.0	42.8	41.6	53.1	55.6	51.7
8	70.2	35.5	52.2	69.9	62.5	64.8	65.1	38.0	33.5
9	61.3	34.7	45.0	46.9	46.4	46.3	47.3	40.2	42.4
10	57.8	55.7	46.9	50.5	53.1	49.8	52.0	51.6	44.8
Mean T-score	**55.6**	**45.7**	**49.9**	**50.8**	**51.8**	**49.7**	**53.4**	**47.3**	**45.2**
SD	8.9	9.4	6.9	10.5	6.5	7.5	6.8	8.5	6.5
Mean T-score Dutch population	**54.9**	**49.8**	**49.7**	**49.1**	**49.9**	**50***	**49.6**	**50.6**	**47.5**
SD	8.6	10.8	9.8	10.8	10.1	10*	10.0	9.5	8.3
Normal limits**									
Mild impairment**									
Moderate impairment**									
Severe impairment**									

* Mean T-score U.S. population as Dutch reference data for this outcome is missing.
** Symptom categories are based on mean T-scores and cut-points of reference populations as provided by the Dutch-Flemish PROMIS® National Center and Health-Measures.net. Cut-points vary per PROMIS® measure and are based on the standard deviation.

group with favorable PROMIS scores also reported having a paid job.

Two patients (20%) scored within the mild or moderate symptom range on at least 2 items (patients 2 and 9), whereas the remaining 3 participants (30%) scored within mild or moderate impairment symptom limits on ≥6 of 9 items (patients 3, 5, and 8). The median age of these 5 participants was 32 years (range, 28 to 48 years). All but 1 of the hospital readmissions in this group were in patients with less favorable PROMIS results. Reasons for hospital readmissions included GVHD, infections, treatment for impending graft failure, and stroke. Moreover, this group of 5 patients reported being incapacitated for work.

DISCUSSION

This mixed methods study evaluated the experiences and perceptions of adult patients before, during, and after allogeneic HSCT as a cure for SCD. SCD patients generally experience improvement of physical, mental, and social health and are able to pursue life goals after HSCT. However, the new post-transplantation reality also confronts patients with challenges that potentially can influence their HRQOL. Pain due to irreversible AVN continues to have a negative impact.

The mean PROMIS T scores of all participants were comparable to those of the Dutch general population, and qualitative data show that the SCD transplant recipients were satisfied with the effects of HSCT on their physical, mental, and social health. Physical health improved greatly for most participants, but transplantation toxicity, ongoing pain and fatigue negatively impacted the life of some. Likewise, mental health improved for almost all participants, but emotional struggles during the post-transplantation period were common. Regarding social health, patients could engage in sports, travel, and pursue a career or further education. For most patients, their perspective changed from living life on a day-to-day basis with physical complaints to pursuing personal life goals while leading an active life.

Interestingly, mean PROMIS T scores of our study group fell within the normal limit category compared with the general population. Previous studies have validated PROMIS measures in SCD patient populations and showed a strong correlation between PROMIS T scores and SCD severity [29,30]. Compared with the general population, SCD patients were shown to score worse on several PROMIS item banks, including Physical Functioning, Pain Interference, Fatigue, Depressive Symptoms, and Anxiety [30–32]. Therefore, based on our finding that mean T scores of our adult SCD transplant recipients fell within normal limits on the 9 PROMIS measures tested, it could be concluded that the study participants currently experience normal physical, mental, and social health, which most likely would reflect an improvement.

Two important observations should be acknowledged, however. First, we noticed a great diversity of PROMIS T scores among the study participants; 3 of the 10 participants scored notably worse than the other 7, indicating a poorer health experience in these patients compared with the general population and the other participants. These patients had already developed extensive organ damage prior to HSCT, were incapacitated for work, and tended to be older and to have experienced more complications after HSCT. Qualitative data of these patients revealed that they were less satisfied with the results of the HSCT, and that their expectations about living pain-free and without hospitalizations were not met. The 2 participants with daily pain from AVN did not view their transplantation as a complete cure from SCD, regardless of successful engraftment and withdrawal of immunosuppressive medication. Therefore, it seems that the severity of preexisting AVN and transplantation toxicity accounted for the subjective success of

HSCT in our cohort, an observation also reported by others [19,20]. Gallo et al. [19] reported the lowest HRQOL scores among patients with failed HSCT and with AVN. Likewise, no improvement in physical functioning at 1 year post-transplantation was found in an adult SCD population, in which 6 of 13 participants suffered from AVN in multiple joints [33]. Another study with 22 patients with a relatively young median age of 22.5 years and no report of previous AVN found significant improvement in Physical Function and Pain Interference [18]. Taken together, these findings argue for early transplantation before the occurrence of irreversible organ damage, especially AVN.

Second, our qualitative data show that SCD patients who scored within normal limits on most PROMIS items undeniably viewed their transplantation as successful and reported significant improvements in many aspects of their lives. Nevertheless, many of these participants also described the transplantation process as physically and mentally challenging. Before transplantation, SCD forced them to live an adjusted lifestyle, which they often accepted and normalized. Acceptation and normalization of SCD was previously described by Constantinou et al. [6] in a qualitative study of children with SCD. After cure, SCD transplant recipients found themselves confronted with a new reality for which they needed time and professional guidance to adjust to. Study participants described being overwhelmed by their improved physical abilities and new social or occupational possibilities, even though they valued these changes as improvements. It should be recognized that patients acknowledged great satisfaction about the transplantation on one hand but nonetheless had once sought or still needed psychological counseling on the other hand. The ongoing impact of SCD on mental and social health should not be underestimated; mental repercussions or even trauma from having had SCD should be addressed in the post-transplantation period, and appropriate help should be offered. Psychologists with experience in working with SCD patients and allogeneic HSCT recipients seem most appropriate to bring about the required knowledge and skills needed for this specific patient population. Additional counseling by social workers or specialized nurses could be valuable for patients with financial or social problems, which are common among SCD patients [34,35] and might persist after physical cure from SCD.

Only 3 other qualitative studies have focused on the experiences of small groups of adult SCD patients after HSCT [19,20,36]. Many of our findings overlap with those identified in the previous studies, for example, the relief of being pain-free and welcoming new goals and opportunities. Two studies also emphasized the importance of addressing psychosocial and contextual life challenges in the care plan, as well as possible benefits from hearing the experiences of other recipients [19,20]. Abu al Hamayel et al. [36] conducted a qualitative study on pain experiences of adult SCD patients after HSCT. Interestingly, patients in this study described a shift in their experienced pain from VOC to a different kind of pain after HSCT, which persisted for at least 1 year post-transplantation but often resolved completely thereafter [36]. Similarly, some of our patients also described a different pain after HSCT, which often was attributed to the use of sirolimus. These body aches resolved after discontinuation of sirolimus at approximately 1 year post-transplantation. Abu al Hamayel et al. also elaborated on patients' reluctance to use opioids after transplantation, which was confirmed by our study. No longer having to use chronic (pain) medication was described as an important benefit of undergoing transplantation.

Limitations of the present study are linked to its cross-sectional design. Although the PROMIS results at the time of the interview showed consistency with the results of the interviews and further validated our data, future research should aim at a longitudinal research design. PROMIS measures have been shown to be responsive over time in SCD patients and thus are useful measures before and during long-term follow-up [31,32]. Although we gained many novel insights from the qualitative data of this study, future research also should include interviews before transplantation to avoid recall bias. Additional work is also needed to evaluate the pertinence of our findings after other curative treatment modalities, such as gene therapy approaches, and in more SCD patients undergoing haploidentical donor transplantation. Although toxicity profiles of the various curative treatment modalities might differ, most of described themes are likely to apply to all cured adult SCD patients, regardless of the curative approach applied.

In conclusion, adult SCD HSCT recipients are confronted with a new reality after being cured. Regardless of whether this reality measures up to their expectations or is valued as an improvement, they face challenges that call for awareness. A deeper understanding of the complex consequences of undergoing a curative treatment on the physical, mental, and social health of adult SCD patients is essential to ensure optimal care. Future research should aim to include more qualitative and HRQOL measures in clinical transplantation and gene therapy studies. Clinicians can use the insights gained from the present study and other studies to recognize the needs of SCD patients undergoing curative treatments, manage their expectations beforehand, and provide SCD patient-tailored pretransplantation and post-transplantation psychological care.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.01.001.

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