Received: 17 September 2024 | Accepted: 29 January 2025

DOI: 10.1002/hem3.70100

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Changes in the quality of life of adults with sickle cell disease following allogeneic stem cell transplantation: A mixed-methods, prospective cohort study

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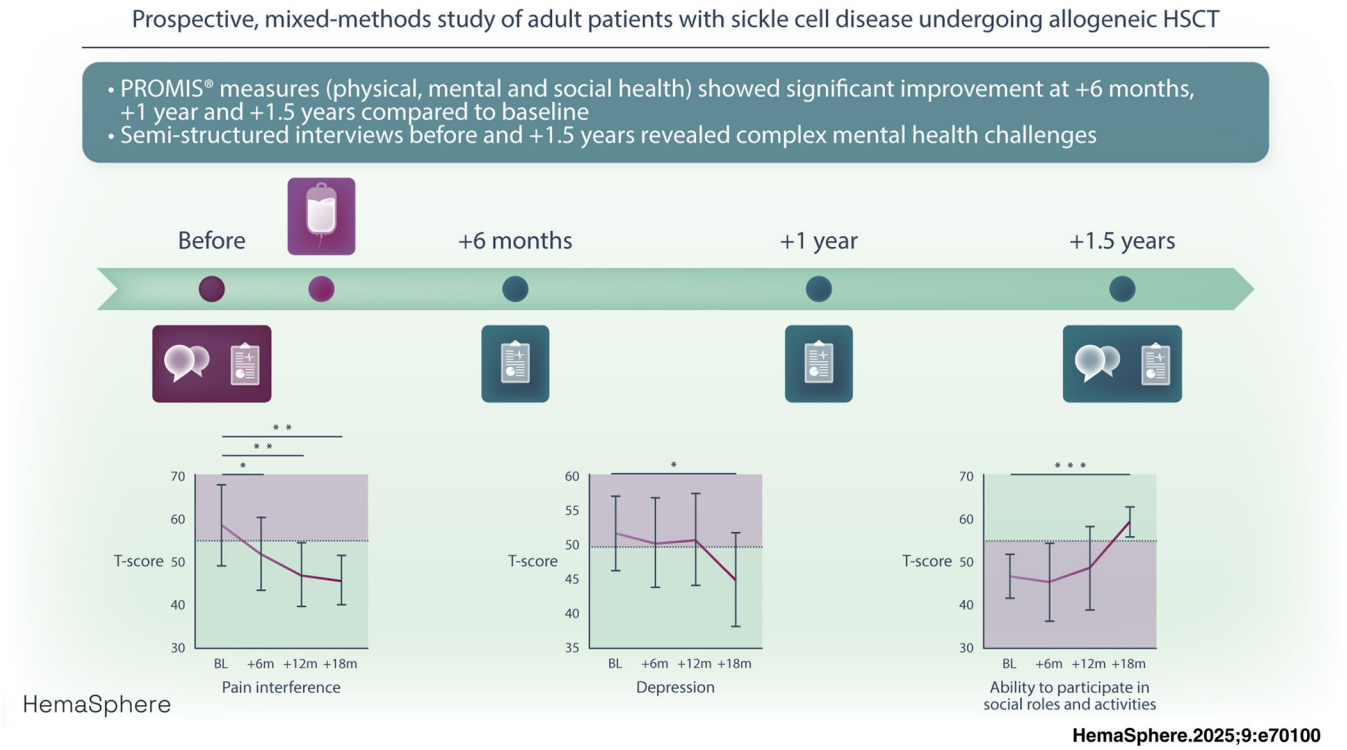
Graphical Abstract



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Changes in the quality of life of adults with sickle cell disease following allogeneic stem cell transplantation: A mixed-methods, prospective cohort study

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Abstract

Advances in conditioning regimens have made non-myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) a viable curative option for adults with sickle cell disease (SCD). However, prospective studies comparing pre- and post-transplant patient-reported health outcomes are scarce. Therefore, in a prospective, mixed-methods cohort study in adults with SCD undergoing HSCT, we tested the hypothesis that physical, mental, and social health improves after HSCT relative to baseline. We compared 9 Patient-Reported Outcomes Measurement Information System (PROMIS®) measures at 6, 12, and 18 months post-transplant to baseline and general population values. Semi-structured interviews were conducted pre- and post-transplant that were thematically analyzed (MAXQDA). Seventeen patients (7 females, 10 males; median age 26 years) underwent matched sibling (9) or haploidentical donor (8) transplantation. Compared to baseline, pain interference ($p = 0.008$), physical function ($p < 0.001$), fatigue ($p = 0.001$), anxiety ($p = 0.016$), anger ($p = 0.037$), and the ability to ($p < 0.001$) and satisfaction with ($p < 0.001$) social roles and activities improved at 18 months. Compared to reference values, physical function, sleep disturbance, fatigue, anxiety, and the ability to and satisfaction with social roles and activities *T*-scores were significantly worse at baseline but comparable or better after 18 months. Thematic analysis of the interviews revealed high satisfaction with improved physical and social abilities alongside complex mental health challenges, including processing the psychological aftermath of SCD, dealing with transplant-related toxicity, adjustment challenges, and identity conflicts. In conclusion, while physical, mental, and social health improves after HSCT, the effects on mental health can be complex and warrant psychosocial support early in the process of curative therapies.

INTRODUCTION

Sickle cell disease (SCD) is a monogenetic disease characterized by chronic hemolytic anemia, recurrent painful vaso-occlusive events, and both acute and chronic organ complications. Consequently, patients with SCD experience a significantly decreased quality of life and shorter life expectancy compared to the general population.[1–3]

In recent years, allogeneic hematopoietic stem cell transplantation (HSCT) has emerged as a viable curative treatment for adult patients with SCD, facilitated by the development of less intensive,

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non-myeloablative conditioning regimens.[4,5] Patients experiencing recurrent vaso-occlusive events and/or (progressive) organ complications nonresponsive to disease-modifying therapies, such as hydroxyurea, are eligible for HSCT in middle- and high-income countries.[6,7] Studies in adults with SCD report overall survival and disease-free survival rates of >94% and >85%, respectively.[8–10] Furthermore, as haploidentical HSCT has emerged as a viable option in patients lacking a matched sibling donor, allogeneic HSCT is increasingly offered to adults with SCD.[4,8]

Nevertheless, the effects of HSCT on the quality of life in adults with SCD are largely unknown. Although an improvement in quality of life is expected following a cure, HSCT is an intensive treatment with the potential for significant toxicities, which might impact patient-reported outcomes. The only prospective evaluation of patient-reported outcomes in 17 adolescents and adults with SCD undergoing HSCT found a significantly improved physical function and pain interference after 1 year.[11] However, this study did not include a qualitative evaluation with interviews, and the follow-up was only 1 year, a period during which patients generally still use immunosuppression and are recovering from transplant-related toxicity. Three other small retrospective studies have investigated the effects of HSCT on the quality of life of adults with SCD using mixed methods between 1 and 3.5 years after transplantation.[12–14] These studies revealed that patients with successful transplants are generally able to pursue their life goals but that avascular necrosis and fatigue can seriously impact the quality of life of some patients.

To mitigate the potential influence of recall bias and to enable a comparison of patient-reported post-transplant outcomes with baseline values, we conducted a longitudinal assessment of patient-reported outcomes measurement information system (PROMIS®) measures, along with a before-and-after qualitative evaluation of health-related quality of life, in a unique prospective mixed-methods study of adults with SCD undergoing allogeneic HSCT. We hypothesized that patient-reported physical, mental, and social health will improve after HSCT, as compared to baseline. As the use of immunosuppression and other prophylactic medication, frequent outpatient clinic visits, and lifestyle restrictions during the first 12 months post-transplant can negatively affect mental and social health, we postulated that evaluation at 18 months post-transplant might provide a better reflection of the quality of life after HSCT.

METHODS

Study design

This prospective study was conducted at Amsterdam UMC (The Netherlands), a tertiary care center specializing in SCD and allogeneic HSCT care. A mixed-methods approach was employed, using PROMIS® measures completed at baseline and at 6, 12, and 18 months post-transplant, along with qualitative data obtained from semi-structured interviews conducted at baseline and between 12 and 18 months post-transplant. The study adhered to the Declaration of Helsinki and received approval from the Institutional Review Board of the Amsterdam UMC (W21_247#21.274).

Participant selection and treatment

Patients with SCD aged 16 years or older who were planned to undergo matched sibling donor or haploidentical donor HSCT were eligible for participation. Patients were invited to take part in the study by their transplant physician (ED, EN). All patients provided written informed consent.

Briefly, patients with a matched sibling donor received three months of preconditioning with azathioprine/hydroxyurea followed by alemtuzumab (1 mg/kg total dose) and total body irradiation (3 Gy) conditioning and GvHD prophylaxis with sirolimus for at least 1 year.[9] The haploidentical bone marrow transplantation regimen consisted of anti-thymocyte globulin (total dose 4.5 mg/kg Day −9 to −7), fludarabine (30 mg/kg Day −6 to −2), cyclophosphamide (14.5 mg/kg Day −6 and −5), thiotepa 10 mg/kg (Day −7), TBI (2 Gy), and GvHD-prophylaxis with post-transplant cyclophosphamide (50 mg/kg Day +3 and +4) and mycophenolate mofetil and sirolimus.[8]

Data collection

Patient characteristics and transplantation data were retrieved from medical records.

At baseline and at 6, 12, and 18 months post-transplantation, all participants completed the following nine PROMIS® measures using the online KLIK PROM portal (https://www.hetklikt.nu/): (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 and Activities. Except for Anger (short form 5a), we used computer adaptive testing (CAT).[15] For the Anger scale, we calculated *T*-scores using the HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice).

Two semi-structured interviews were conducted with the first 10 consecutive participants; before the start of the (pre)conditioning phase and after approximately 12–18 months post-transplant. Interviews were held by one interviewer (ED or SN), who did not have a current healthcare provider relationship with the participant; either face-to-face or videoconference interviews were conducted. We used an interview topic list (Table S1).

Data analysis

Patient characteristics were described using frequencies and percentages for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables, depending on the distribution. For comparisons of baseline characteristics between treatment groups, a Mann–Whitney *U* test or χ^2 test was used. For correlation analyses, Spearman's or Pearson's Correlation was used, as appropriate. All statistical analyses were performed using IBM SPSS Statistics, version 25. A two-sided p-value < 0.05 was considered statistically significant.

PROMIS® measures

All PROMIS® measures were classified into the domains of physical, mental, or social health. The higher the PROMIS® *T*-score, the more you have of the construct that is being measured. For example, a high *T*-score on item bank Fatigue is unfavorable, whereas a high *T*-score on item bank Physical Function represents a positive outcome. Score cut points (mild, moderate, severe impairment) vary per PROMIS® measure based on the standard deviation. We used mean *T*-scores and cut points provided by the Dutch-Flemish PROMIS® National Center and HealthMeasures as reference data (https://www.dutchflemishpromis.nl/normgegevens_21_32.html).[16–18] Furthermore, in accordance with previous studies, a 3-point difference in *T*-score was considered clinically meaningful.[19,20]

The mean (±standard error, SE) *T*-score was computed for each PROMIS® measure at the different time points for all patients and per treatment group (matched sibling donor versus haploidentical donor

transplant). For comparisons of *T*-scores between baseline and the different post-transplantation time points, a paired *t*-test was used. Only cases with two available *T*-scores (pairs) were included; missing data were not imputed. For comparisons of mean *T*-scores between the two treatment groups, an unpaired *t*-test was used. For comparisons between our cohort and reference values of the general population, a one-sample *t*-test was used.

Semi-structured interviews

All interviews were audiotaped and transcribed verbatim; thereafter, we used MAXQDA version 10 for the qualitative data analysis. We followed the consolidated criteria for reporting qualitative research (COREQ) checklist to ensure comprehensive reporting.[21] Two researchers (ED, SN) conducted the coding and thematic analysis of the data.[22] Codes and themes were discussed within the research team. Relevant themes were further categorized in physical, mental, and social health using the PROMIS® framework, with a focus on the description of the theme before and after transplantation.

RESULTS

Patient characteristics

Seventeen patients (median age 26 years (range 18–46), 7 females/10 males; 9 matched sibling donor/8 haploidentical donors) participated in the study and completed the PROMIS® measures before and at least once after transplantation (Table 1). We found no significant difference in age ($p = 0.437$) or sex ($p = 0.092$) between the two treatment groups (matched sibling donor or haploidentical donor transplant). Of all patients, the first consecutive 10 patients also participated in the qualitative part of the study. All patients engrafted successfully and had either already stopped or were in the process of tapering and stopping immunosuppressive agents at the time of the interview.

TABLE 1 Patient and transplant characteristics.

	Quantitative (PROMIS®) *N* = 17	Qualitative (interviews) *N* = 10
Age at HSCT (years), median (range)	26 (18–46)	25 (19–46)
Sex, female/male, *N*	10/7	2/8
Genotype, *N*		
HbSS/HbSb0	13	10
HbSC/HbSb+	4	0
SCD-related comorbidity pre-HSCT, *N*		
Vaso-occlusive events (≥2/year)	13	7
Stroke (venous)	2	1
Avascular osteonecrosis	5	2
Priapism	1	1
Chronic exchange transfusions	4	2
Donor, *N*		
Matched sibling donor	9	7
Haploidentical donor	8	3
Transplant toxicity CTCAE grade ≥3, *N*		
– (Neutropenic) fever, infectious complications	7	4
– Pure red cell aplasia	1	1
– Skin rash/acne >30% BSA with severe symptoms	1	1
– Preemtive treatment for declining donor chimerism	3	2
– Severe pain requiring hospitalization	1	0
– Hemorragic cytitis requiring hospitalization	2	1
– Pulmonary embolism	1	0
Psychological counseling, *N*		
Before and/or after transplantation	11	6
Offered, but declined	4	2
None	2	2

Physical health

Quantitative findings

Figure 1A presents the mean *T*-scores for the four distinct PROMIS® measures within the physical health domain across various time points. Compared to reference values of the Dutch general population, baseline (pre-transplant) values of physical function ($p < 0.001$), sleep disturbance ($p = 0.007$), and fatigue ($p < 0.001$) were significantly worse (Table 2). Pain interference at baseline did not differ from the mean *T*-score of the general population ($p = 0.152$). Compared to baseline values, significant improvements in pain interference ($p = 0.008$), physical function ($p < 0.001$), and fatigue ($p = 0.001$) were noted at the 18-month post-transplantation assessment. A clinically meaningful improvement (indicated by a 3-point difference on the *T*-score scale) was evident as early as 6 months post-transplantation. There were no differences between patients with a matched sibling donor and those with a haploidentical donor or between males and females (data not shown) at any time point. At baseline, age was not associated with worse *T*-scores in the physical health domain, but at +6 months post-transplantation, older age was associated with worse pain interference ($r = 0.572$, $p = 0.027$), worse physical functioning ($r = -0.551$, $p = 0.022$), worse sleep disturbance ($r = 0.570$, $p = 0.017$), and more fatigue ($r = 0.612$, $p = 0.009$).

At the last follow-up (+18 months), pain interference ($p < 0.001$) and physical function ($p < 0.001$) were significantly better than reference values of the general population, while sleep disturbance ($p = 0.852$) and fatigue ($p = 0.052$) at the last follow-up were comparable to the general population.

Qualitative findings

Prior to transplantation, most patients commonly experienced pain from vaso-occlusive events, frequently precipitated by physical exertion, thereby limiting their engagement in daily activities, including sports. Many patients described fatigue as their most debilitating symptom and often characterized themselves as being in poor physical conditions. Additional symptoms included priapism and feeling cold all the time. The majority of patients felt more like a patient (versus person) because of the impact of the disease on their daily routines. When questioned about their aspirations and expectations, patients mentioned their primary motivations for undergoing transplantation to be the prospect of achieving a life devoid of pain and hospital admissions, prevention of (further) organ

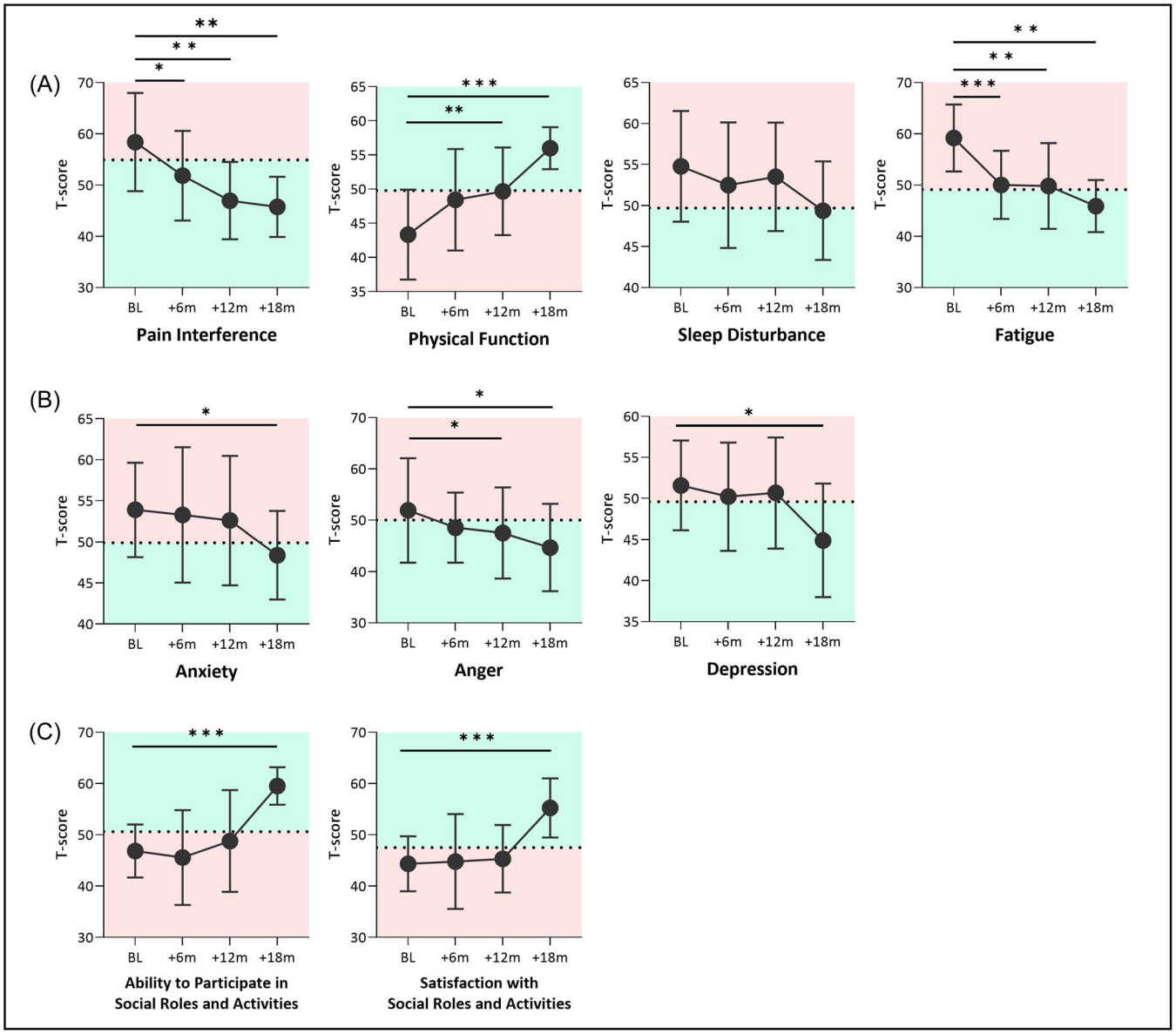

FIGURE 1 **Mean (standard deviation) *T*-scores of PROMIS® measures completed before (BL, baseline) and +6, +12, and +18 months after allogeneic hematopoietic stem cell transplantation (HSCT)**. Each time point after HSCT was compared to the baseline using a paired *t*-test. The horizontal dotted line reflects the *T*-score of the general population. A decrease on a symptom scale reflects an improvement, whereas a decrease on a functional scale reflects a deterioration (green and red colors, respectively). **(A)** Physical health domain. **(B)** Mental health domain. **(C)** Social health domain. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

deterioration, extension of their lifespan, and cessation of physical distress from recurrent blood draws. On the other hand, worries among patients included concerns regarding susceptibility to infections and surrounding potential alterations in physical appearance post-transplantation, such as hair loss and skin complications.

Following transplantation, the participants uniformly reported having no vaso-occlusive painful events anymore, a heightened energy level, and an increased capacity for prolonged engagement in sports and other activities. They also noted a reduction in the need for sleep and the disappearance of jaundiced conjunctivae. Adverse physical manifestations of the transplantation procedure included weight gain, (temporary) hair loss, skin complications, susceptibility to infections, and infertility. Overall, patients reported a markedly improved physical health compared to their pre-transplantation state. Nonetheless, they continued to identify with a patient identity and not a healthy individual as long as medication regimens persisted. Illustrative quotes are presented in Table 3.

Mental health

Quantitative findings

At baseline, the mean *T*-score for anxiety was significantly worse than the general population ($p = 0.011$), and those for anger and depression were comparable with ($p = 0.462$ and $p = 0.156$, respectively) the general population (Table 2). At +18 months, anxiety ($p = 0.016$), anger ($p = 0.037$), and depression ($p = 0.025$) showed a significant improvement when compared to baseline (Figure 1B, Table 2). We found no differences between patients with a

TABLE 2 Mean *T*-scores of study cohort and reference values of the general Dutch population.

		General population[a]	Baseline		+6 months		+12 months		+18 months		Comparison of post-HSCT time points with baseline (Bl) values			Comparison of pre- and post-HSCT time points with general population (Gp)			
		T-score	*T*-score		*T*-score		*T*-score		*T*-score		+6 m vs. Bl	+12 m vs. Bl	+18 m vs. Bl	Bl vs. Gp	+6 m vs. Gp	+12 m vs. Gp	Gp vs. +18 m
Health domain	PROMIS® item bank	mean (SD)	mean (SD)	*N*	mean (SD)	*N*	mean (SD)	*N*	mean (SD)	*N*	*p*-value[b]	*p*-value[b]	*p*-value[b]	*p*-value[c]	*p*-value[c]	*p*-value[c]	*p*-value[c]
Physical	Pain Interference[e]	54.9 (8.6)	58.4 (9.6)	17	51.8 (8.7)	15	47.0 (7.5)	13	45.7 (5.9)	12	0.049	0.001	0.008	0.152	0.197	0.003	<0.001
	Physical Function[f]	49.8 (10.8)	43.3 (6.6)	17	48.4 (7.4)	17	49.7 (6.6)	14	56.0 (3.1)	12	0.335	0.006	<0.001	<0.001	0.459	0.943	<0.001
	Sleep Disturbance[e]	49.7 (9.8)	54.8 (6.8)	17	52.5 (7.7)	17	53.5 (6.6)	15	49.4 (6.0)	12	0.241	0.370	0.054	0.007	0.153	0.043	0.852
	Fatigue[e]	49.1 (10.8)	59.2 (6.5)	17	50.0 (6.7)	17	49.8 (8.4)	15	45.9 (5.1)	12	<0.001	0.005	0.001	<0.001	0.576	0.748	0.052
Mental	Anxiety[e]	49.9 (10.1)	53.9 (5.7)	17	53.3 (8.2)	17	52.6 (7.8)	15	48.4 (5.4)	12	0.677	0.357	0.016	0.011	0.110	0.206	0.348
	Anger[e]	50.0[d] (10.0)	51.9 (10.2)	17	48.6 (6.8)	16	47.5 (8.9)	14	44.7 (8.5)	12	0.207	0.012	0.037	0.462	0.399	0.315	0.053
	Depression[e]	49.6 (10.0)	51.6 (5.5)	17	50.2 (6.6)	17	50.7 (6.8)	15	44.9 (7.0)	12	0.333	0.400	0.025	0.156	0.706	0.550	0.038
Social	Ability to Participate in Social Roles and Activities[f]	50.6 (9.5)	46.9 (5.2)	17	45.6 (9.3)	16	48.8 (9.9)	14	59.5 (3.7)	12	0.821	0.682	<0.001	0.009	0.046	0.507	<0.001
	Satisfaction with Social Roles and Activities[f]	47.5 (8.3)	44.3 (5.4)	17	44.8 (9.3)	16	45.3 (6.6)	13	55.3 (5.8)	12	0.569	0.681	<0.001	0.028	0.262	0.257	<0.001

Note: The red color indicates a significantly worse mean *T*-score, whereas the green color indicates a significantly better mean *T*-score, as compared to the comparator. Non-significant *p*-values indicate comparable mean *T*-scores.

Abbreviations: Bl, baseline; Gp, general population; m, months; SD, standard deviation.

[a]Reference *T*-scores of the general Dutch population, provided by the Dutch-Flemish PROMIS National Center.[19–21]

[b]Paired *t*-test, compared with baseline.

[c]One-sample *t*-test, comparison with reference *T*-scores of the general population.

[d]For Anger, the reference value of the general US population was used (not available for Dutch population).

[e]Symptom scale: a higher score = worse.

[f]Functional scale: a higher score = better.

TABLE 3 Representative quotes from semi-structured interviews.

		Interview before transplantation	Interview after transplantation
Physical health			
"Fatigue"	Pt. 5	"Even when I sleep 8 hours, I will be fit for 1 hour and then be tired again."	"It turns out that my body can be quite strong when I do not have sickle cell anymore."
	Pt. 4	"It is the fatigue, rather than the pain, that withholds me from doing the things I would like to do."	"I am less tired and have more energy. I sleep better and that is also because I have more peace of mind."
"Doing sports"	Pt. 6	"Next to the pain crises that come along with sickle cell disease, I notice that I have to be very careful when it comes to sports and with pushing your physical boundaries."	"I can push myself to my limits [physically], without getting sick."
Mental health			
"Anxiety"	Pt. 4	"I feel anxious a lot and I don't like to go outside alone. You do not know what is going to happen. […]. One of my biggest fears is that somebody might accidently bump into me and that my spleen, which is twice the normal size, would hurt tremendously. And that I would be all alone."	"It feels as if the light switch was switched on. It is hard to explain when you have not experienced it, but this is the best description I can give. As if you are sitting in a dark room and somebody switches on the light, and then, you are on!"
"Normalization of sickle cell disease and new life"	Pt. 1	"Despite the limits of sickle cell disease, I have had a nice life. I have learned to live with it and I have just accepted it. I try to make the best of it."	"I feel weird. Being a patient seems to belong to an old life, another life. When I walk through the halls of the hospital and see my doctors, it does not fit into my world anymore. I see them, I talk to them, but it feels as if we are talking together about somebody else." "This is a life reset, I have been updated to a new level that I have never seen, never tasted, never had. And it is only now that I have the feeling that I am alive and among people."
"Identity" and "Adapting to life without sickle cell disease"	Pt. 10	"Maybe it sounds silly, but I have never accepted my sickle cell disease, maybe because I don't feel sick every day. I don't look sick, so it is hard. I find it hard to have sickle cell disease." "Maybe it will be like, it is over and we will not talk about it anymore. […] I expect myself to say: I am better, and huh? Sickle cell disease, what is that?"	"I have to organize my life now without sickle cell disease. […] All these things that I have experienced, all the pain that I have felt. It is as if I miss this and I don't feel myself. I have only noticed this recently, I have to discover who I am again."
	Pt. 6	"I expect to be a bit overwhelmed by everything that is new."	"It is a loss, yes, and that is good. […] But now, I sometimes have the feeling that I am living a life that I was not supposed to live."
Social health			
"Work"	Pt. 1	[About not being able to work for a year after the transplantation] "What's a year of your life if you can be cured? Nothing weights against that."	[About work after transplantation] "I have experienced this, chemotherapy and radiation and all that, and now life is smiling at me, but I cannot go back to my old work. I could, but it does no longer reflect the person I've become."
	Pt. 7	"I am sick more often than an average person. For an employer, that is just really annoying."	"I am now working, yes. But I would like to be an actor and make music."
"Friends and family"	Pt. 3	[About the impact of sickle cell disease on friendship] "I say 'no' more often than other people. Maybe that is the reason I find it hard to make real good friends."	"I can now think of how my life will be when my child is 18, or 20, or 25."

matched sibling donor and those with a haploidentical donor, and no significant correlations between age and mental health PROMIS *T*-scores were found at any time point (data not shown). At +6 and +18 months post-transplantation, female patients scored worse for anger compared to male patients (mean *T*-scores 53.7 vs. 44.9, $p = 0.007$ and 52.2 versus 40.9, $p = 0.041$, respectively). At +6 months post-transplantation, females also scored worse for depression (54.9 vs. 46.9, $p = 0.015$).

When comparing the *T*-scores of the last follow-up with those of the general population, depression was significantly better ($p = 0.038$), while anger and anxiety were similar to the general population.

Qualitative findings

Prior to transplantation, patients exhibited varying coping strategies with regard to their SCD, including either acceptance and normalization or denial of the illness, adopting a lifestyle as if they were not afflicted. The disease significantly impacted the psychological functioning of several patients, manifesting in increased introversion and diminished self-confidence. Some patients felt being stigmatized as lazy. Many patients experienced anxiety resulting from uncertainties, physical symptoms, and a fear of death during the vaso-occlusive painful events. The awareness of a reduced life expectancy was continuously present among the majority of patients and limited making plans for the future. Anger did not emerge as a theme from the interviews.

Patients hoped to feel relieved post-transplantation and expressed curiosity about their future quality of life. They did not anticipate missing SCD and generally believed they would not encounter mental health issues afterward. Patients perceived transplantation as their only option, accompanied by apprehension regarding its success, leading many to postpone making plans until they attained more certainty about the outcome. Past disappointments with SCD fostered skepticism regarding the success of the transplantation. One patient feared that being cured would impose pressure to excel in life.

Following the HSCT, many patients described the first post-transplant year as mentally demanding. They struggled with adjusting to the absence of SCD and initially hesitated to engage in activities that previously triggered vaso-occlusive events. Nearly all patients required several weeks to months to adapt to their new physical possibilities. Positive outcomes included a feeling of newfound time and peace in life because of the expectation of a longer lifespan. The transplant alleviated numerous worries and negative emotions and increased resilience among patients. One patient felt as having two distinct identities before and after the HSCT. Nonetheless, challenges persisted, including feelings of being overwhelmed, disbelief, mistrust, isolation, and loneliness. One patient felt that life had already been predetermined by SCD, rendering it too late for significant change. When asked about feeling cured, patients expressed ambivalence, citing the ongoing need for medication, the looming threat of graft failure, and being a sickle cell carrier, which undermined their sense of complete recovery. Additionally, many patients described worrying about sickle cell disease coming back.

Psychological support was offered to most patients (Table 1), who generally felt that this was important and helpful. Patients who did not have psychological care before or after the transplantation process expressed that this would have helped them, or should have started earlier. Patients also would have liked to have more contact with fellow patients for support. Some patients mentioned that their primary caretakers or children should have had more psychosocial support as well.

Social health

Quantitative findings

When compared to the general population, the ability to participate in social roles and activities and the satisfaction with social roles and activities were significantly worse in our cohort at baseline ($p = 0.009$ and $p = 0.028$, respectively; Table 2). Figure 1C displays the mean *T*-scores for the ability to participate in and the satisfaction with social roles and activities before and after HSCT. Compared to baseline, both outcome measures improved significantly after 18 months (both $p < 0.001$). No differences between patients with a matched sibling donor and those with a haploidentical donor or males and females were observed at any time point (data not shown). At baseline, there was no correlation between age and *T*-scores, but at +6 months post-transplantation, older age was associated with a poorer ability to participate in social roles and activities ($r = -0.630$, $p = 0.009$).

At the last follow-up, both social health mean *T*-scores were significantly better compared to the general population (both $p \leq 0.001$).

Qualitative findings

Prior to undergoing transplantation, some patients expressed difficulties in establishing or maintaining genuine friendships while coping with SCD. In contrast, the majority emphasized the presence of robust family ties, albeit acknowledging the significant impact imposed by the disease on family dynamics. While many described the adverse effects of SCD on their educational or occupational pursuits, some reported a heightened drive to excel professionally despite their condition. All patients experienced a pronounced negative impact of SCD on their ability to partake in recreational activities such as traveling, attending festivals, or engaging in (winter) sports. Post-transplantation aspirations included career advancement, entrepreneurship, increased educational attainment, and, on a personal level, the desire to start a family and achieve greater independence. Concerns regarding homesickness during hospitalization and the potential loss of friendships were prevalent among patients when discussing their expectations.

Following transplantation, the majority of patients reported improved social integration with friends and enhanced familial harmony. Strong bonds with family members and partners persisted for most individuals. However, some patients described negative encounters, including feelings of disappointment with family and friends during the transplantation process because of a lack of support. Some patients described significant troubles and anxiety experienced by their caregivers or immediate family members. Patients who had children expressed concerns about the initial impact of transplantation on their children, particularly regarding limitations in physical interaction and play during the first months. Almost all patients were satisfied with their ability to work or study and to improve their professional careers.

DISCUSSION

We present the findings of a unique prospective, mixed-methods study examining the changes in the physical, mental, and social health of adult patients with SCD undergoing HSCT.

Overall, prior to transplantation, patient-reported outcomes were worse compared to reference values of the general population. Over the course of 18 months post-transplantation, mean *T*-scores improved to levels that were comparable with or even exceeded

reference values of the general population. Outcomes within the physical domain demonstrated improvement as early as 6 months following transplantation, most likely due to the normalization of hemoglobin values and resolution of SCD-related vaso-occlusive events. It is noteworthy, that older age was associated with worse *T*-scores in the physical health domain at 6-months post-transplantation, suggesting that older patients need more time for their physical recovery after HSCT. The improvement in patient-reported outcomes related to social activities was only observed after 18 months. This delayed improvement is likely attributable to lifestyle constraints imposed during immunosuppressive therapy. A possible explanation for why patients scored higher than the general population in the physical and social health domains could be that, having previously been chronically ill, they feel especially grateful for their improved health. This gratitude may lead them to view their well-being more positively compared to others. Additionally, they may have been benefiting from strong medical and psychosocial support, which further enhanced their sense of physical and social well-being. Our findings of an improved health-related quality of life following HSCT are supported by earlier findings in children with SCD.[23–26] Furthermore, in 31 adult patients with SCD, significant improvements in physical, emotional, and functional well-being, measured with the Functional Assessment of Cancer Therapy General (FACT-G) questionnaire, have been observed after HSCT.[27] Research on quality of life outcomes after gene therapy in patients with SCD is still scarce. However, recently published data from 44 patients with SCD who underwent one-time treatment with exagamglogene autotemcel showed clinically meaningful improvements on the Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) and EuroQoL Visual analog Scale (EQ-VAS).[28]

To our knowledge, there are no studies that directly compare the effect of HSCT to that of standard therapy (hydroxyurea and/or chronic red blood cell transfusions) on health-related quality of life. In children with SCD, regular transfusion therapy resulted in a better overall health-related quality of life compared to children not receiving transfusion therapy.[29] For patients using hydroxyurea, significant improvements were reported in the severity of pain episodes, frequency of hospitalizations, and the need for blood transfusions, resulting in an improved quality of life, as assessed through qualitative interview data.[30,31] Nevertheless, most of the patients included in our study were using hydroxyurea before the transplantation and still had significantly worse PROMIS® *T*-scores compared to the general population and their own paired values after transplantation. This suggests that the beneficial effects of HSCT on patient-reported quality of life are superior to the effects of hydroxyurea despite transplantation-related toxicities.

Although all three mental health PROMIS® measures (Anxiety, Depression, and Anger) demonstrated a significant improvement in our patient cohort, these changes were less pronounced compared to those in physical and social health scores, and females tended to have worse anger and depression *T*-scores, compared to males. Meanwhile, thematic analysis of the interview data unveiled diverse mental health challenges during the first year after the transplantation that is difficult to capture using standardized questionnaires. Firstly, following physical rehabilitation and alleviation of SCD-related physical symptoms, there is often a need for mental recovery and psychological processing. This addresses the challenges associated with having had SCD, such as feelings of insecurity, anxiety, and guilt. Anxiety regarding needles and blood draws may also require therapy. Secondly, some patients need to psychologically process and adapt to specific unexpected transplant-related toxicities, for example, alterations in physical appearance or reduced fertility, which can have a great impact on their mental health. New worries might also arise after transplantation, such as the fear of SCD coming back. Thirdly, patients may encounter identity dilemmas wherein they must navigate through a changed reality and find a new role, not only within their own values, interests, and aspirations but also within family structures, friends, employment, and other societal constructs. The (fear of) loss of identity after being cured from a chronic disease has earlier been described in patients with epilepsy and hemophilia and is referred to as "burden of normality."[32–34] This phenomenon results from having to adjust to the psychological experience of leading a symptom-free life.[32,35] To our knowledge, the concept of "burden of normality" has not yet been documented in patients with SCD. However, it is plausible that adult patients with SCD who undergo curative treatments may experience a similar phenomenon. Our findings highlight the importance of a mixed-methods approach, incorporating both patient-reported outcome measures and interviews.

Interestingly, we observed no differences in the improvements in PROMIS® scores between the matched sibling donor and haploidentical donor transplantation recipients, suggesting equal improvement in quality of life after HSCT despite the different donor types and conditioning regimens. However, these findings need to be confirmed in a larger patient cohort. Another clear challenge of our study is that we were only able to assess patients who were alive and that none of our patients experienced graft failure, a complication that would most likely have negatively impacted patient-reported outcomes.[12,13]

This study's strengths lie in its robust methodology, including a prospective design and the use of well-validated instruments, which enhance the reliability and validity of our findings. The improvement in average PROMIS® *T*-scores, which we observed, is encouraging and can be used to counsel future patients. Meanwhile, the longitudinal qualitative data demonstrate the life-altering shift that occurs after transplantation. While prior to transplantation, most patients focused on their debilitating physical symptoms and social limitations imposed by SCD, we noticed that after transplantation, their focus changed toward addressing mental challenges, identity, and future aspirations. The involvement of specialized nurses and psychologists is essential for many patients to navigate through this process. Furthermore, the requirement for professional support is independent of the medical success of the transplantation and should at least be explored and offered to patients, even those who do not experience significant transplant-related complications. Our findings support the observation of previous small studies that addressing psychosocial challenges is perceived as an important part of the transplantation process and should be incorporated into a comprehensive care path for patients with SCD undergoing allogeneic HSCT.[13,14] Therefore, instead of only offering a consultation with a psychologist before HSCT, we have now implemented an early intervention strategy involving a case manager who engages with patients prior to transplantation and a mandatory consultation with a psychologist. The involvement of a social worker is determined based on the case manager's discretion.[36]

The findings of our study are relevant to a large and growing number of SCD patients, as HSCT is increasingly considered in adults with SCD. Psychosocial support throughout the transplant journey is essential for patients to cope with the (post-)transplant challenges and the altered reality and opportunities that follow curative therapy. Involving a clinical psychologist, a case manager, specialized nurses, and a social worker is likely to contribute to the success of curative treatments for adult patients with SCD. Furthermore, these findings are likely applicable to SCD patients undergoing other curative treatments such as gene editing and gene therapy.

In conclusion, patient-reported outcomes of adult patients with SCD undergoing matched sibling or haploidentical donor

transplantation improved during the first 18 months post-transplantation, with the most profound changes observed in pain interference, physical functioning, fatigue, and social participation. The effects of HSCT on mental health are more complex and include many positive effects as well as difficulties with adjustment and processing the psychological aftermath of SCD. Incorporation of psychosocial care and patient-reported outcome measures into the treatment plan of SCD patients undergoing HSCT is needed to improve the transplant outcomes and patient experience.

ACKNOWLEDGMENTS

The authors extend their gratitude to all the patients who participated in the study for their time and willingness to share their personal experiences.

AUTHOR CONTRIBUTIONS

Conceptualization: Elisabeth Dovern, Maud M. van Muilekom, Lotte Haverman, Erfan Nur. *Data analysis*: Elisabeth Dovern. Sterre J. A. M. Nijland performed the coding. Elisabeth Dovern, Sterre J. A. M. Nijland, Maud M. van Muilekom, Annemarie M. J. Braamse, Lotte Haverman, and Erfan Nur interpreted the coding and performed the thematic analysis. Elisabeth Dovern performed the statistical analysis of quantitative data. *Writing (original draft)*: Elisabeth Dovern. *Supervision*: Erfan Nur. *Funding*: Erfan Nur. *Writing (review and editing)*: All authors critically reviewed the data and first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

M. R. D. served as medical advisor in developing the CTX001 Early Economic Model; consulted for the Forma Pharmaceutical company about sickle cell disease in 2021 and 2022; and served on the steering committee for a Novartis-sponsored phase 2 trial to prevent priapism in men with sickle cell disease. B. B.: Novartis, Sanquin, GBT/Pfizer, (research funding); GBT/Pfizer, BMS/Celgene, (advisory board consultancy); Novo Nordisk, Sanofi (honoraria for lectures and podcasts). E.N.: Novartis (research funding, consultancy, speakers bureau); Vertex (speakers bureau). The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

FUNDING

This project was supported by Amsterdam UMC Research Foundation and Dutch Sickle Cell Fund: 24632 (ASPIRE).

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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