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Patient and Caregiver Health-related Quality of Life and Caregiver Burden While Awaiting Heart Transplantation: Findings From the Sustaining Quality of Life of the Aged: Heart Transplant or Mechanical Support (SUSTAIN-IT) Study

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Background. We sought to compare change over time (baseline to 2 y) in health-related quality of life (HRQOL) between older (60–80 y) patients awaiting heart transplantation (HT) with mechanical circulatory support (MCS) versus without MCS and their caregivers and caregiver burden. **Methods.** This study was conducted at 13 United States sites. Patient HRQOL was examined using the EuroQol 5-dimensional questionnaire (EQ-5D-3L) and Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12). Caregiver measures included the EQ-5D-3L and Oberst Caregiving Burden Scale, measuring time on task and difficulty. Analyses included analysis of variance, χ^2 , and linear regression. **Results.** We enrolled 239 HT candidates ($n = 118$ with MCS and $n = 121$ without MCS) and 193 caregivers ($n = 92$ for candidates with MCS and $n = 101$ for candidates without MCS). Baseline differences in HRQOL were observed between HT candidates with and without MCS: EQ-5D-3L visual analog scale (VAS) score (67.7 ± 17.6 versus 54.1 ± 23.3 , $P < 0.001$) and KCCQ-12 overall summary score (59.9 ± 21.0 versus 48.9 ± 21.6 , $P < 0.001$), respectively. HT candidates with MCS had significantly higher EQ-5D-3L VAS scores and KCCQ-12 overall summary score across time versus without MCS. Baseline EQ-5D-3L VAS scores did not differ significantly between caregivers of HT candidates with and without MCS (84.6 ± 12.9 versus 84.3 ± 14.4 , $P = 0.9$), respectively, nor were there significant between-group differences over time. Caregivers for HT candidates with MCS reported more task difficulty (range: 1 = not difficult to 5 = extremely difficult) versus caregivers for those without MCS at baseline (1.4 ± 0.5 versus 1.2 ± 0.3 , $P = 0.004$) and over time. **Conclusions.** Understanding differences in HRQOL and caregiver burden among older HT candidates with and without MCS and their caregivers may inform strategies to enhance HRQOL and reduce burden.

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After medical/surgical and psychosocial/behavioral evaluation, United States patients with advanced heart failure (HF), who are acceptable candidates for heart transplantation (HT) and choose to undergo transplant, are listed with the

United Network for Organ Sharing (UNOS). In recent years, the number of HTs performed in North America has increased to <3000 annually.¹ The proportion of recipients >60 y of age continues to increase, and approximately 50% of patients

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await HT with durable mechanical circulatory support (MCS) (primarily left ventricular assist devices [LVADs]).¹

Recent national median time to HT was 6.0 mo.² In 2015, the proportion of candidates on the UNOS waitlist for <1, 1–2, and 2–4 y was approximately 60%, 20%, and 15%, respectively.³ Notably, waitlist time varies considerably among HT candidates based on many factors, including donor compatibility, medical urgency, geographic factors, blood type, body mass index, human leukocyte antibody screening, and gender.³

Among HT candidates on the UNOS waitlist during 2018, 4.9% died without transplant, and 4.8% were removed without transplant due to their condition worsening.² There is a paucity of data on other outcomes for HT candidates and their caregivers, specifically health-related quality of life (HRQOL). Studies have demonstrated that patient HRQOL is poor before HT and improves after transplant in, on average, middle-aged patients.^{4,6} There are few longitudinal studies of HRQOL of caregivers of HF patients, and most literature is focused on caregivers of patients with chronic HF on medical therapy.^{7,8} Furthermore, most studies of caregiver burden are cross-sectional and also focused on caregivers of medically treated patients with chronic HF,⁸ although some literature addresses burden in caring for patients with MCS.⁹ To our knowledge, there are no studies of change over time in HRQOL of older HT candidates and their caregiver, nor caregiver burden before HT. Additionally, HRQOL and burden may differ based on pretransplant management strategies (ie, HT candidates with MCS versus without MCS), which may differentially inform strategies to enhance patient and caregiver HRQOL and reduce caregiver burden before transplant.

Therefore, we sought to compare baseline and change over time (baseline to 2 y) in HRQOL between older HT candidates with MCS versus those without MCS and their caregivers and caregiver burden prior to HT. We hypothesized that as follows:

1. (a) Baseline HRQOL of HT candidates without MCS is lower compared with HT candidates with MCS and (b) HRQOL of HT candidates without MCS decreases over time, while HRQOL of candidates with MCS remains stable.
2. (a) Baseline HRQOL of caregivers of HT candidates without MCS is lower compared with caregivers of HT candidates with MCS and (b) HRQOL of caregivers of HT candidates without MCS decreases over time, while HRQOL of caregivers of candidates with MCS remains stable.
3. (a) Baseline caregiver burden (time spent on task and task difficulty) is higher for caregivers of HT candidates with MCS compared with caregivers for HT candidates without MCS and (b) caregiver burden remains stable over time for both groups.

We defined HRQOL as “the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient”¹⁰ and used the theoretical framework by Spilker and Revicki,¹⁰ (modified to include caregiver outcomes) to guide our research because it is focused on the influence of disease and treatment on HRQOL.

MATERIALS AND METHODS

Design, Settings, and Sample

This report is an analysis of patients enrolled in the Sustaining Quality of Life of the Aged: Heart Transplant or Mechanical Support study. Sustaining Quality of Life of the Aged: Heart Transplant or Mechanical Support is an observational study conducted at 13 United States sites, whose primary

aim is to compare HRQOL outcomes in older (60–80 y) advanced HF patients who undergo HT or long-term MCS (ie, destination therapy) from before to 2 y after these surgeries. In this report, we used a longitudinal comparative design, focused on patients awaiting HT and their caregivers. Participants were recruited between October 1, 2015, and December 31, 2018, after patients were listed with UNOS. HT candidates and their caregivers were divided into 2 groups: those enrolled with MCS and those enrolled without MCS. Guided by intention to treat principles, if HT candidates received MCS after study enrollment, they and their caregivers remained in the group without MCS.

Patient inclusion criteria were advanced HF, 60–80 y of age, able to speak, read, and understand English, and listed with UNOS for HT, with or without MCS. Both second and third generation Food and Drug Administration-approved and investigational MCS (specifically LVADs) were allowed. HT candidates with MCS could have had one or more devices. HT candidates listed for retransplant, multiple organ transplant, and those with right or biventricular ventricular assist devices were excluded from the study. Caregiver inclusion criteria were being identified as the primary caregiver by the transplant candidate, an unpaid family member or friend who helped the patient with self-care, age ≥21 y, and able to speak, read, and understand English. This study is in compliance with the International Society for Heart and Lung Transplantation Ethics Statement and was approved by all site Institutional Review Boards. Participants provided written informed consent. The lead institution protocol number is STU00200851, and the original Institutional Review Board approval number is STU00200851.

Data Collection/Procedures

Baseline self-report assessments were administered as follows: (1) for HT candidates with MCS and their caregivers: after listing with UNOS and MCS implant, and (2) for HT candidates without MCS and their caregivers: after listing with UNOS. Subsequently, self-report data were collected from HT candidates and their caregivers every 6 mo until transplant. Patients completed 2 assessments of HRQOL. The EuroQol 5-dimensional questionnaire (EQ-5D-3L)¹¹ is a 6-item generic measure of HRQOL that includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with 3 levels of response: no problems, some/moderate problems, and extreme problems) and a visual analog scale (VAS) (0 [worst]–100 [best] imaginable health state). The Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12)¹² is a HF-specific measure of HRQOL that has 4 domains (symptom frequency, physical limitations, social limitations, and quality of life) which when combined, creates an overall summary score (OSS). With a score range of 0–100, lower scores represent more severe symptoms and/or limitations and worse quality of life. Caregivers completed a brief health history, the EQ-5D-3L, and the Oberst Caregiving Burden Scale (OCBS¹³). The OCBS is a 15-item measure of physical, logistical, and emotional tasks of caregiving with 2 subscales that measure perceived time spent on tasks (1 = none to 5 = a great amount of time) and task difficulty (1 = not difficult to 5 = extremely difficult). These assessments are relevant to this sample of older patients awaiting HT and their caregivers and are psychometrically supported. Clinically important differences for the EQ-5D-3L^{14,15} and the KCCQ-12¹² are 10 and 5 points, respectively.

Patient baseline demographic characteristics (eg, age, gender, race, marital status, educational level, work status, and insurance) and clinical variables (eg, cause of HF, medical/surgical history,

New York Heart Association [NYHA] class, UNOS status, etc) were collected from medical records by sites and/or securely downloaded directly from the Society of Thoracic Surgeons Interagency Registry for Mechanically Assisted Circulatory Support for HT candidates with MCS. Caregiver demographic characteristics and clinical variables were collected via self-report.

Statistical Analyses

Demographic characteristics, clinical variables, and assessments were summarized using means and SD, medians and first/third quartile, or counts and percentages, as appropriate. If <15% of item-level data were missing, they were singly imputed using the within-group respondent mean (continuous variables) and mode (categorical variables), to avoid cross-group contamination. No imputation was used for the KCCQ-12, per scoring instructions. Group comparisons (ie, analysis of variance or χ^2 tests) were used to test hypotheses 1 (a), 2 (a), and 3 (a) regarding baseline HT candidate HRQOL, caregiver HRQOL, and caregiver burden, respectively.

Unadjusted and adjusted linear regression models for longitudinal data were used to test hypothesis 1 (b) regarding change (within and between groups) in HT candidate HRQOL from baseline to 24 mo. Separate models were created using the EQ-5D-3L VAS score and KCCQ-12 OSS. Adjustment variables, all evaluated at the time of enrollment, included age, gender, race, body mass index, length of time on waitlist, NYHA class, method of paying for medical care, cause of HF, UNOS status, and comorbidities (diabetes, pulmonary hypertension, stroke, and arrhythmias). Separate unadjusted and adjusted linear regression models were used to test hypotheses 2 (b) and 3 (b) regarding change (within and between groups) in caregiver HRQOL and caregiver burden from baseline to 24 mo, respectively. Adjustment variables included caregiver age, gender, and comorbidities (kidney disease, autoimmune disease, anxiety, and seizures). For all regression models, statistical significance was established at the 2-sided 5% level,

and no multiplicity adjustments were made. All analyses were performed using SAS v 9.4 (SAS Institute, Cary, NC) and R v 3.6.1 (R Foundation, 2020).

RESULTS

Of 649 HT candidates listed with UNOS, 369 (57%) were approached, and of those approached, 241 (65%) were enrolled (118 with MCS, 121 without MCS, and 2 ineligible who were withdrawn), with a final sample size = 239 (Figure 1). From the sample of 241 enrolled HT candidates, 194 caregivers were enrolled (92 caregiver for candidates with MCS, 101 caregivers for candidates without MCS, and 1 ineligible caregiver who was withdrawn), with a final sample size = 193 (Figure 1). The majority of HT candidates were male, white, married, and educated beyond high school with a mean age = 64.2 ± 3.1 y (Table 1); while the majority of caregivers were female, white, spouses of the patient, and educated beyond high school with a mean age = 60.4 ± 9.1 y (Table 2). No between-group differences were found for patient and caregiver demographic characteristics. Patient clinical characteristics differed by group for NYHA class and UNOS status at enrollment, while the average number of comorbidities at enrollment was similar between groups (Table 1). Notably, more HT candidates with MCS had a history of stroke and pulmonary hypertension compared with HT candidates without MCS. Also, adverse events occurred in each group over time. Major infection and major bleeding occurred in $\geq 50\%$ of HT candidates with MCS, while worsening HF occurred in 64% of HT candidates without MCS (Table S1, SDC, <http://links.lww.com/TXD/A381>). Lastly, 42% of HT candidates with MCS required hospitalization during the 2-y follow-up period compared with 92% of candidates without MCS (Table S1, SDC, <http://links.lww.com/TXD/A381>). The average number of comorbidities did not generally differ between caregiver groups (Table 2).

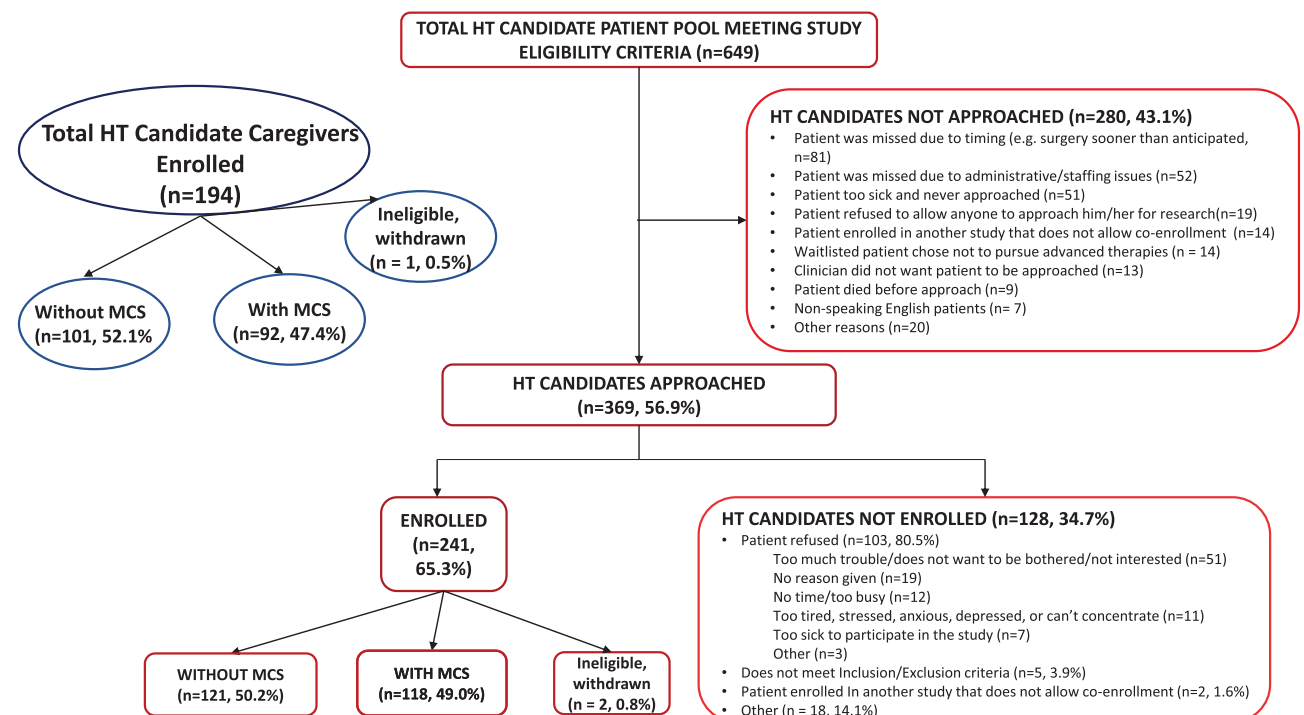


FIGURE 1. Heart transplantation (HT) candidate and caregiver enrollment. MCS, mechanical circulatory support.

TABLE 1.
Patient demographic and clinical characteristics at baseline

Variable	N available cohort (per group)	Entire cohort (n = 239)		HT candidates with MCS (n = 118)		HT candidates without MCS (n = 121)		P
Age, mean ± SD, y	239 (118, 121)	64.2	± 3.1	64.4	± 3.3	64.0	± 2.9	0.295
Gender (male), n (%)	239 (118, 121)	193	(81%)	99	(84%)	94	(78%)	0.223
Race (white), n (%)	236 (118, 118)	197	(83%)	94	(80%)	103	(87%)	0.115
Marital status: married/domestic partners, n (%)	237 (116, 121)	184	(78%)	89	(77%)	95	(79%)	0.741
Education (> than high school), n (%)	230 (109, 121)	152	(66%)	69	(63%)	83	(69%)	0.397
Currently working, n (%)	239 (118, 121)	45	(19%)	22	(19%)	23	(19%)	0.943
Insurance type, n (%)	239 (118, 121)							0.211
Medicare/Medicaid		130	(54%)	69	(58%)	61	(50%)	
Private insurance		109	(46%)	49	(42%)	60	(50%)	
Heart failure cause, n (%)	239 (118, 121)							0.318
Ischemic cardiomyopathy		101	(42%)	55	(47%)	46	(38%)	
Dilated cardiomyopathy		122	(51%)	57	(48%)	65	(54%)	
Other		16	(7%)	6	(5%)	10	(8%)	
NYHA class at study enrollment, n (%)	233 (113, 120)							<0.001
I		18	(8%)	16	(14%)	2	(2%)	
II		56	(24%)	43	(38%)	13	(11%)	
III		111	(48%)	39	(35%)	72	(60%)	
IV		48	(21%)	15	(13%)	33	(28%)	
INTERMACS profile at enrollment, n (%)	113 (113, 0)							
Profile 1		21	(19%)	21	(19%)	NA		
Profiles 2–3		71	(63%)	71	(63%)	NA		
Profiles 4–7		21	(19%)	21	(19%)	NA		
UNOS status at enrollment, n (%)	239 (118, 121)							<0.001
1A		44	(18%)	16	(14%)	28	(23%)	
1B		138	(58%)	87	(74%)	51	(42%)	
2		44	(18%)	5	(4%)	39	(32%)	
7		13	(5%)	10	(8%)	3	(2%)	
Length of time on UNOS waitlist at enrollment, median (Q1, Q3), d	239 (118, 121)	99.0	(22.0, 357.0)	217.0	(71.0, 457.0)	29.0	(9.0, 159.0)	<0.001
Length of time on UNOS waitlist until HT, median (Q1, Q3), d	160 (67, 93)	251.5	(61.0, 629.0)	507.0	(255.0, 825.0)	94.0	(43.0, 330.0)	<0.001
Length of time on MCS from implant to enrollment, median (Q1, Q3), d	118 (118, 0)	352.0	(171.0, 692.0)	352.0	(171.0, 692.0)	NA	NA	
LVEF (closest to date of surgery), n (%)	95 (42, 53)							0.287
>50 (normal)		3	(3%)	1	(2%)	2	(4%)	
40–49 (mild)		4	(4%)	1	(2%)	3	(6%)	
30–39 (moderate)		7	(7%)	1	(2%)	6	(11%)	
20–29 (moderate/severe)		30	(32%)	12	(29%)	18	(34%)	
<20 (severe)		44	(46%)	22	(52%)	22	(42%)	
Not recorded/documentated		7	(7%)	5	(12%)	2	(4%)	
Number of comorbidities, mean ± SD	239 (118, 121)	4.0	± 1.9	4.2	± 2.1	3.9	± 1.8	0.233
Hypertension, n (%)	239 (118, 121)	137	(57%)	67	(57%)	70	(58%)	0.867
Hyperlipidemia, n (%)	239 (118, 121)	139	(58%)	68	(58%)	71	(59%)	0.869
Arrhythmia, n (%)	239 (118, 121)	130	(54%)	69	(58%)	61	(50%)	0.211
Diabetes, n (%)	239 (118, 121)	96	(40%)	53	(45%)	43	(36%)	0.139
History of smoking, n (%)	237 (116, 121)	91	(38%)	37	(32%)	54	(45%)	0.044
Myocardial infarction, n (%)	239 (118, 121)	80	(33%)	40	(34%)	40	(33%)	0.891
Chronic kidney disease, n (%)	239 (118, 121)	74	(31%)	39	(33%)	35	(29%)	0.490
Pulmonary hypertension, n (%)	239 (118, 121)	44	(18%)	28	(24%)	16	(13%)	0.036
Obesity (body mass index >30 kg/m ²), n (%)	239 (118, 121)	46	(19%)	24	(20%)	22	(18%)	0.672
Stroke, n (%)	239 (118, 121)	34	(14%)	23	(19%)	11	(9%)	0.021
History of cancer, n (%)	239 (118, 121)	26	(11%)	11	(9%)	15	(12%)	0.445

HT, heart transplantation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NYHA, New York Heart Association classification; Q1, first quartile; Q3, third quartile; UNOS, United Network for Organ Sharing.

At enrollment, median length of time on the UNOS waitlist was significantly longer for HT candidates with MCS versus without MCS (Table 1). HT candidates with MCS had been on LVAD support for a median of 352 d before study enrollment.

Sixteen HT candidates enrolled without MCS received an LVAD while on the waitlist (mean = 78 ± 87 d after enrollment).

Of the 239 HT candidates, 160 underwent transplant. Median time on the UNOS waitlist for those who were

TABLE 2.
Caregiver demographic and clinical characteristics at baseline

Variable	N available cohort (per group)	Cohort (n = 193)		Caregivers of HT candidates with MCS (n = 92)		Caregivers of HT candidates without MCS (n = 101)		P
Age, mean ± SD, y	188 (88, 100)	60.4	± 9.1	59.6	± 8.6	61.1	± 9.5	0.257
Gender (male), n (%)	193 (92, 101)	33	(17%)	11	(12%)	22	(22%)	0.070
Race (white), n (%)	186 (88, 98)	159	(85%)	74	(84%)	85	(87%)	0.609
Marital status: married/domestic partner, n (%)	186 (88, 98)	170	(91%)	81	(92%)	89	(91%)	0.765
Relationship to patient = spouse, n (%)	186 (88, 98)	162	(87%)	79	(90%)	83	(85%)	0.302
>High school education, n (%)	185 (87, 98)	134	(72%)	60	(69%)	74	(76%)	0.320
Currently working, n (%)	180 (84, 96)	91	(51%)	42	(50%)	49	(51%)	0.889
Perception that health will be affected by being a caregiver (range 0–10, most/least affected)	185 (87, 98)	8.6	± 1.8	8.6	± 1.8	8.7	± 1.9	0.807
Number of previous surgeries, mean ± SD	184 (87, 97)	2.7	± 2.3	2.6	± 2.3	2.9	± 2.3	0.350
Number of comorbidities, mean ± SD	185 (87, 98)	2.3	± 2.2	2.4	± 2.4	2.2	± 2.0	0.551
Arthritis, n (%)	185 (87, 98)	58	(31%)	27	(31%)	31	(32%)	0.930
Hypertension, n (%)	185 (87, 98)	56	(30%)	24	(28%)	32	(33%)	0.454
Hypercholesterolemia, n (%)	185 (87, 98)	46	(25%)	21	(24%)	25	(26%)	0.829
Anxiety, n (%)	185 (87, 98)	27	(15%)	18	(21%)	9	(9%)	0.027
Depression, n (%)	185 (87, 98)	27	(15%)	14	(16%)	13	(13%)	0.587
Gastrointestinal disease, n (%)	185 (87, 98)	28	(15%)	16	(18%)	12	(12%)	0.244
Diabetes, n (%)	185 (87, 98)	23	(12%)	10	(11%)	13	(13%)	0.716
Thyroid disease, n (%)	185 (87, 98)	28	(15%)	11	(13%)	17	(17%)	0.373
Cancer, n (%)	185 (87, 98)	22	(12%)	11	(13%)	11	(11%)	0.766

HT, heart transplantation; MCS, mechanical circulatory support.

transplanted differed significantly by group, with HT candidates with MCS having longer waitlist times (Table 1). Seventy-nine candidates were not transplanted (22 still on the UNOS waitlist, 39 withdrawn, and 18 died). Of the 39 transplant candidate withdrawals, 19 candidates with MCS moved to long-term MCS (ie, destination therapy) and were censored, 13 experienced deterioration in their medical condition and further study was deemed inappropriate, and 7 had other reasons. Caregivers for the 39 withdrawn patients were also withdrawn.

Patient and caregiver group sizes from baseline through 3.5 y while awaiting transplant are demonstrated in Figures 2 and 3. The most frequent reasons for a decrease in participant sample sizes over time were patient transplant, patient death, and participant withdrawal from the study.

Rates of completion of baseline self-report assessments were very high (ie, HT candidates = 99% and caregivers = 94%). Completion rates of assessments every 6 mo between 6 and 24 mo before HT were somewhat lower (HT candidates, range = 89%–100% and caregivers, range = 72%–100%).

Baseline and Change in HRQOL of HT Candidates Over Time

At baseline, EQ-5D VAS scores differed significantly between HT candidates with MCS and HT candidates without MCS (67.7 ± 17.6 versus 54.1 ± 23.3 , $P < 0.001$), respectively (Table 3). Scores for all EQ-5D-3L dimensions (ie, % report of problems) did not differ significantly between groups at baseline (HT candidates with MCS range = 27%–60% versus HT candidates without MCS range = 21%–65%) (Table 3). Both groups reported the most problems with usual activities (60%–65%). From baseline to 24 mo, there was no significant change in EQ-5D VAS scores of HT candidates with MCS, and significant change in adjusted VAS scores of HT candidates without MCS, which increased from baseline to 6 mo and then declined (adjusted $P = 0.033$) (Figure 4A). Group

comparisons across time revealed a significant difference in EQ-5D VAS scores between HT candidates with versus without MCS, with VAS scores being higher in the transplant candidates with MCS (Figure 4A).

At baseline, the KCCQ-12 OSS differed significantly between HT candidates with MCS versus without MCS (59.9 ± 21.0 versus 48.9 ± 21.6 , $P < 0.001$), respectively (Table 3). KCCQ-12 domains differed significantly at baseline between groups for symptom frequency, quality of life, and social limitations, with lower scores in HT candidates without MCS (Table 3). For both groups, the KCCQ-12 OSS did not change significantly from baseline to 24 mo (Figure 4B). Similar to EQ-5D-3L VAS group comparisons, HT candidates with MCS had significantly higher KCCQ-12 OSS across time versus those without MCS (Figure 4B).

Baseline and Change in HRQOL of Caregivers for HT Candidates Over Time

Baseline EQ-5D VAS scores were high and did not differ significantly between caregivers of HT candidates with MCS and caregivers of HT candidates without MCS (84.6 ± 12.9 versus 84.3 ± 14.4 , $P = 0.9$), respectively (Table 4). Caregiver report of problems for the EQ-5D-3L dimensions was similar between groups (overall range = 1%–45%) (Table 4). Caregivers reported the most problems with pain/discomfort. From baseline to 24 mo, significant differences in HRQOL were found for caregivers of HT candidates with MCS (adjusted $P = 0.0003$) but not for caregivers of HT candidates without MCS (Figure 4C). Caregiver EQ-5D VAS scores did not differ significantly between groups over time.

Baseline and Change in Caregiving Burden of Caregivers of HT Candidates Over Time

Baseline OCBS scores for perceived time spent on tasks was moderate and did not differ significantly between caregivers

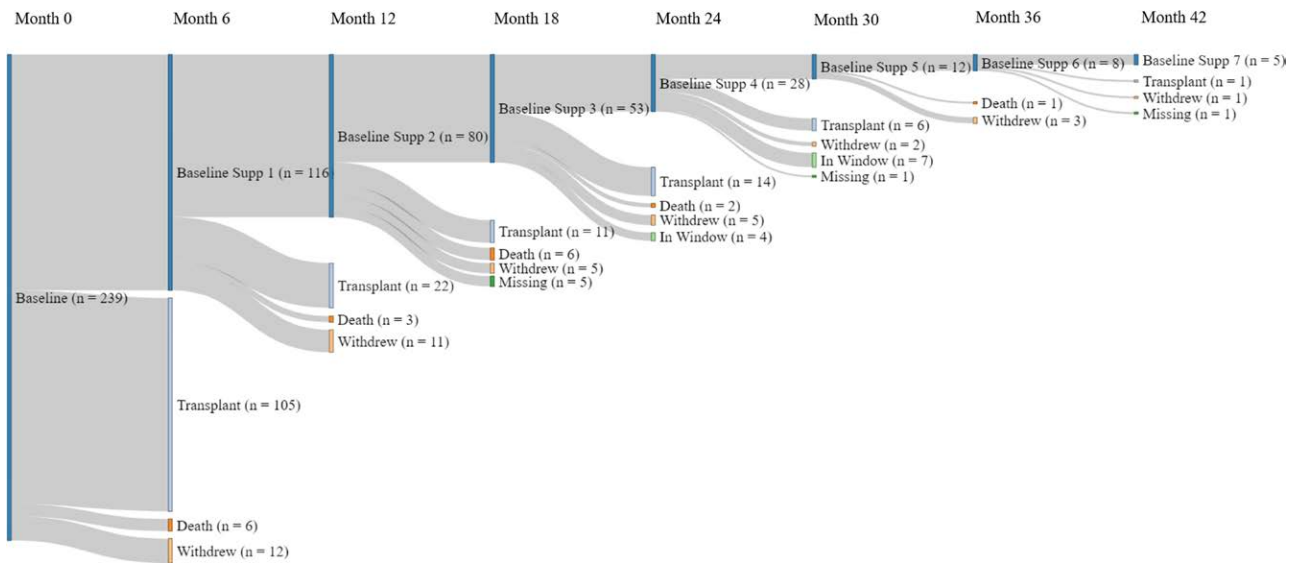


FIGURE 2. Sankey diagram for change in heart transplantation candidate sample size from baseline (month 0) to 42 mo (baseline supplement 7), including number of patients in the study at each time point, withdrawals, in window, missing data, death, and transplant.

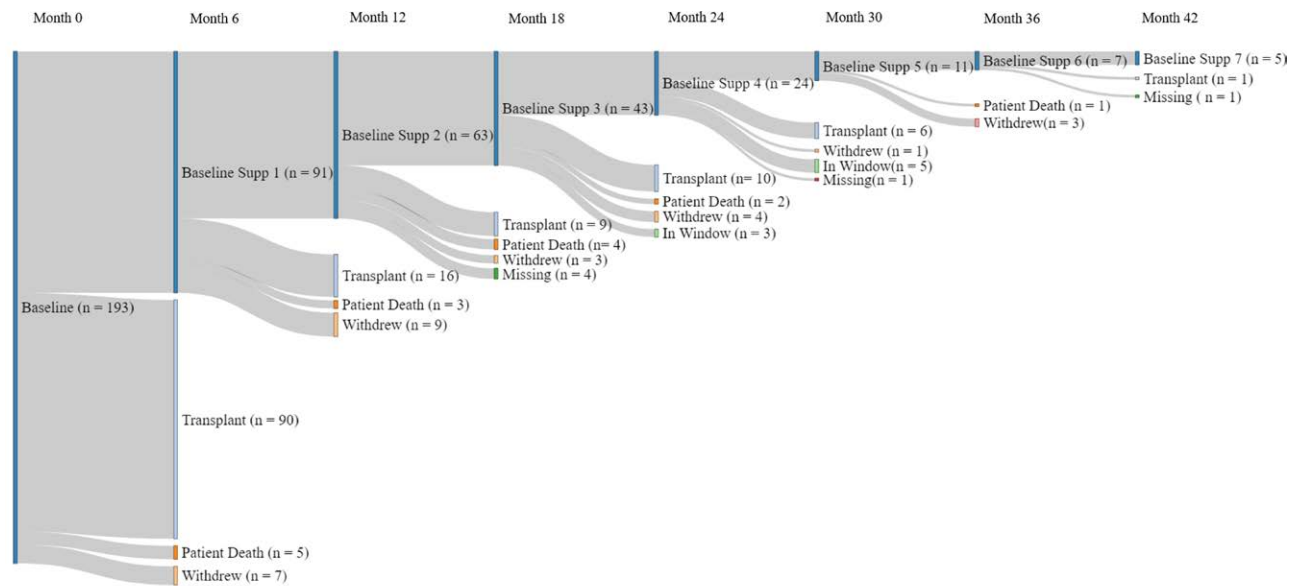


FIGURE 3. Sankey diagram for change in heart transplantation candidate caregiver sample size from baseline (month 0) to 42 mo (baseline supplement 7), including number of caregivers in the study at each time point, caregiver withdrawal, caregiver in window, caregiver with missing data, patient transplant, and patient death.

of HT candidates with MCS versus caregivers of HT candidates without MCS (time = 2.4 ± 0.7 versus 2.2 ± 0.7 , $P = 0.1$); however, while perceived difficulty was low, differences were detected between groups (difficulty = 1.4 ± 0.5 versus 1.2 ± 0.3 , $P = 0.004$), respectively (Table 4). From baseline to 24 mo, change in time spent on caregiving was not significant within groups nor between groups (Figure 5). Similarly, there was no significant change in task difficulty over time for both groups (Figure 5). However, caregivers of HT candidates with MCS reported more difficulty providing care than HT candidates without MCS over time (adjusted $P = 0.005$).

DISCUSSION

Guided by the theoretical framework of Spilker and Revicki,¹⁰ our novel findings provide important insights on

differences in HRQOL over time based on pre-HT treatment strategy and actionable targets to enhance HRQOL and reduce caregiver burden for older patients with advanced HF and their caregivers while awaiting HT. At baseline, HT candidates without MCS had lower overall HRQOL compared with those awaiting HT with MCS which supported hypothesis 1a. Over 24 mo, overall HRQOL remained stable in the HT MCS group (partially supporting hypothesis 1b); however, while the overall HRQOL trajectory for HT candidates without MCS varied over time (using the EQ-5D VAS); it did not change over time using the KCCQ-12 OSS. Hypotheses 2a and 2b were not supported, as caregiver HRQOL did not differ between groups at baseline, and HRQOL varied over time for caregivers of HT candidates with MCS but did not change over time for caregivers of HT candidates without MCS. Regarding caregiver burden, hypothesis 3a was partially

TABLE 3.
Patient self-report questionnaires at baseline

Variable	N available cohort (per group)	Entire cohort (n = 239)	HT candidates with MCS (n = 118)	HT candidates without MCS (n = 121)	P
EQ-5D-3L VAS score, mean ± SD	238 (118, 120)	60.8 ± 21.8	67.7 ± 17.6	54.1 ± 23.3	<0.001
EQ-5D-3L VAS score, binned, n (%)	238 (118, 120)				<0.001
0–24		13 (5%)	2 (2%)	11 (9%)	
25–49		47 (20%)	9 (8%)	38 (32%)	
50–74		99 (42%)	57 (48%)	42 (35%)	
75–100		79 (33%)	50 (42%)	29 (24%)	
EQ-5D-3L mobility (% problems), n (%)	237 (118, 119)	118 (50%)	54 (46%)	64 (54%)	0.217
EQ-5D-3L self-care (% problems), n (%)	237 (118, 119)	57 (24%)	32 (27%)	25 (21%)	0.271
EQ-5D-3L usual activities (% problems), n (%)	238 (118, 120)	149 (63%)	71 (60%)	78 (65%)	0.441
EQ-5D-3L pain/discomfort (% problems), n (%)	237 (118, 119)	120 (51%)	54 (46%)	66 (55%)	0.135
EQ-5D-3L anxiety/depression (% problems), n (%)	237 (118, 119)	73 (31%)	41 (35%)	32 (27%)	0.190
KCCQ-12 physical limitation, mean ± SD	233 (117, 116)	56.1 ± 26.1	58.8 ± 26.4	53.4 ± 25.6	0.118
KCCQ-12 symptom frequency, mean ± SD	238 (118, 120)	65.5 ± 24.5	70.6 ± 22.4	60.6 ± 25.6	0.002
KCCQ-12 quality of life, mean ± SD	238 (118, 120)	42.9 ± 26.8	50.5 ± 26.9	35.4 ± 24.5	<0.001
KCCQ-12 social limitation, mean ± SD	232 (115, 117)	53.0 ± 28.6	59.6 ± 25.6	46.6 ± 29.9	<0.001
KCCQ-12 overall summary score, mean ± SD	238 (118, 120)	54.4 ± 22.0	59.9 ± 21.0	48.9 ± 21.6	<0.001
KCCQ-12 overall summary score, binned, n (%)	238 (118, 120)				0.005
0–24		23 (10%)	7 (6%)	16 (13%)	
25–49		79 (33%)	30 (25%)	49 (41%)	
50–74		89 (37%)	53 (45%)	36 (30%)	
75–100		47 (20%)	28 (24%)	19 (16%)	

EQ-5D VAS, EuroQol visual analog scale, score range 0 = worse to 100 = best imaginable health state; EQ-5D-3L, dimension with 3 response levels: no problems, some/moderate problems, and extreme problems (combined into problems); HT, heart transplantation; KCCQ-12, Kansas City Cardiomyopathy Questionnaire-12, domain and overall summary score ranges: 0 = worse to 100 = best health status; MCS, mechanical circulatory support.

supported, as at baseline, caregivers of candidates with MCS reported more task difficulty than caregivers of candidates without MCS but perceived time spent on caregiving tasks was similar between groups. Lastly, hypothesis 3b was partially supported as time spent on tasks did not change over time for either group, but caregivers of HT candidates with MCS reported more task difficulty than caregivers of candidates without MCS over time.

Differences in overall HRQOL between older HT candidates with versus without MCS for up to 2 y on the UNOS waiting list deserve comment. These differences in HRQOL were clinically important differences (ie, ≥ 10 points using the EQ-5D VAS and ≥ 5 points using the KCCQ-12 OSS).^{12,14,15} Better HRQOL reported by HT candidates with MCS over time, compared with those on medical therapy, most likely represents the positive effects of MCS on reducing HF symptoms, despite comorbidities and adverse events. Furthermore, variation in HRQOL for HT candidates without MCS over 2 y may be related to episodic worsening of HF, supported by our findings of higher rates of rehospitalization for HT candidates without MCS compared with HT candidates with MCS, and 16 HT candidates on medical therapy who subsequently required MCS. Findings from Heo et al,¹⁶ who reported that change in HF symptoms is associated with change in HRQOL are also supportive of our findings. Similarly, Flint et al,¹⁷ identified 3 possible health status trajectories of older outpatients with HF and reported that all 3 groups improved at 3 mo, but those with moderate or poor health status trajectories had worse health status at 1-y follow-up.

Our domain-specific HRQOL findings provide therapeutic targets. The majority of all HT candidates reported problems with usual activities, mobility, and pain/discomfort. These problem areas should be discussed with patients to determine

if any of them are actionable. Consult for further assessment and follow-up with physical/occupational therapy and outpatient rehabilitation may be helpful to address these problems. Consult with other services may also be beneficial. For example, HT candidates with musculoskeletal disorders such as degenerative spine and arthritic conditions, which are common in older patients, may benefit from consult with orthopedics and rheumatology.

We also determined that HRQOL of caregivers of HT candidates was high (using the EQ-5D-3L VAS) and is similar to the general population with some chronic conditions (using unadjusted EQ-5D_{index} scores).¹⁸ Notably, Pressler et al⁷ found that HRQOL of caregivers of patients with chronic HF (NYHA class I-IV) was only fair (using the SF.12). Additionally, Jaarsma et al,¹⁹ and others determined that HRQOL of caregivers of patients with advanced HF, compared with the general population, was impaired.²⁰ However, Goetzinger et al²¹ reported that caregivers of solid organ transplant candidates, including HT candidates, were generally well adjusted with minimal depression and anxiety. Worse HRQOL of caregivers of patients with advanced chronic diseases versus caregivers of patients awaiting transplant may be related to caregiver expectations of improved patient outcomes after transplant.

Our finding of no change over time in HRQOL in caregivers of patients without MCS is similar to findings from Pressler et al⁷ who reported no change over 8 mo in HRQOL of caregivers of patients with chronic HF. However, our finding that caregivers of HT candidates with MCS had improved HRQOL from baseline to 2 y later must be interpreted cautiously, as the amount of improvement was small and not a clinically important difference.^{14,15} Lastly, while caregiver overall HRQOL was high, 30% and 43% of the entire sample reported problems with anxiety/depression and pain/

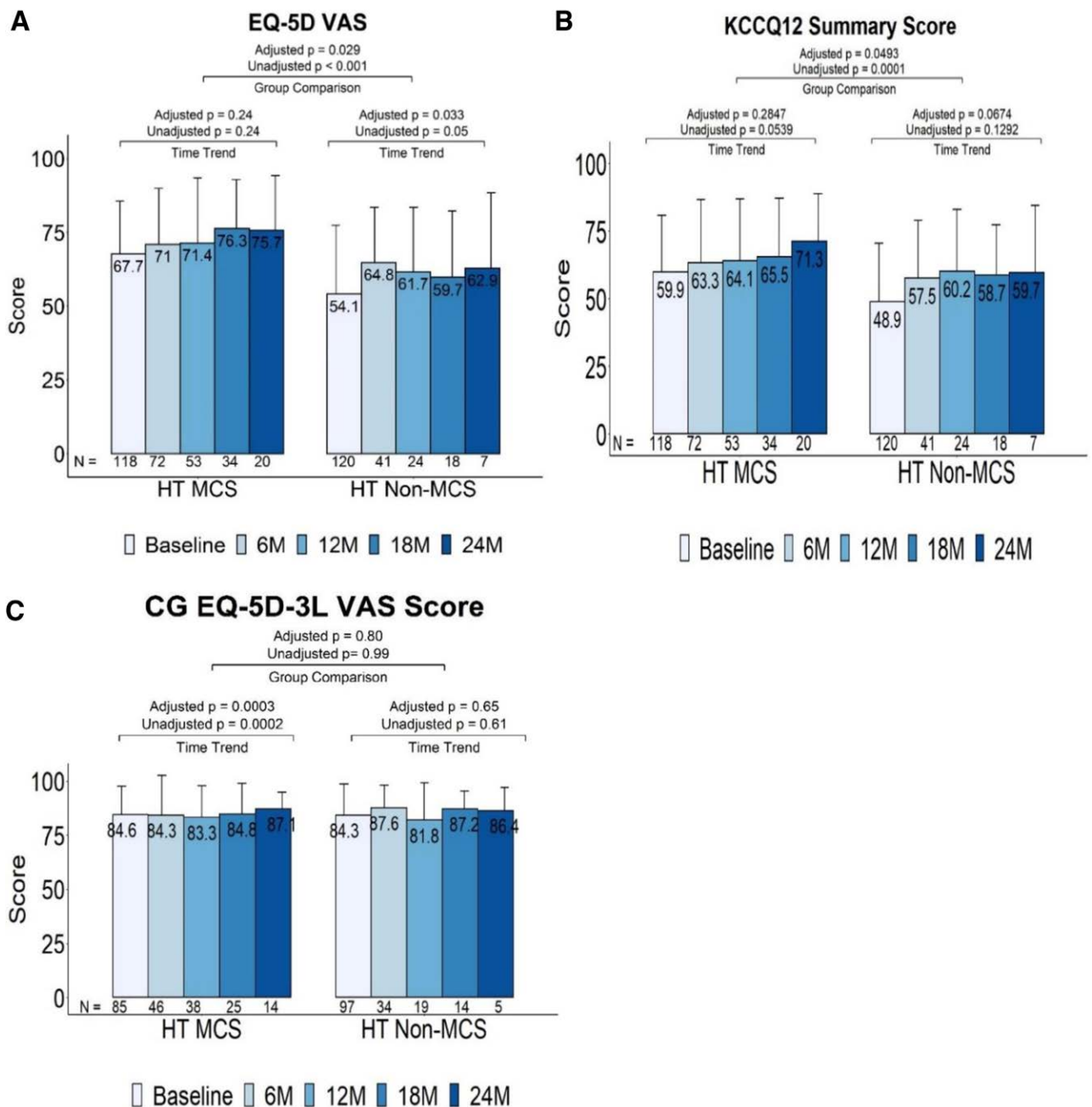


FIGURE 4. (A and B), Change in health-related quality of life (HRQOL) of heart transplantation (HT) candidates over time; (C) change in HRQOL of caregivers of HT candidates over time. CG, caregiver; EQ-5D-3L, EuroQol 5-dimensional questionnaire; HT, heart transplantation; HT MCS, HT candidate with MCS; HT non-MCS, HT candidate without MCS; MCS, mechanical circulatory support; KCCQ-12, Kansas City Cardiomyopathy Questionnaire-12; and VAS, visual analog scale.

discomfort, respectively, which may require intervention. Clinicians caring for HT candidates have an opportunity to support their caregivers. However, few studies have examined interventions for caregivers of patients with advanced HF; additional research is needed.¹⁹

We found that caregiver burden was higher (ie, more difficult) for those caring for HT candidates with MCS compared with those caring for HT candidates without MCS. While caregiver task difficulty was low for both groups and the between-group difference was small, these differences may be due to the need for caregivers of HT candidates with MCS to learn and apply new and complex skills in device management (eg, changing driveline dressings, troubleshooting

device alarms, and changing controllers, if needed). Pressler et al,⁷ who also used the OCBS, reported low perceived time on tasks and low task difficulty in patients with chronic HF, both of which improved over 8 mo. They also reported differences when patients were grouped by symptom burden; such that caregivers of patients with more symptoms of HF reported more task difficulty than caregivers of patients with fewer HF symptoms.⁷ These findings are somewhat similar to our report of more difficulty caring for HT candidates with MCS, as the presence of MCS in our study and having more HF symptoms in the Pressler et al⁷ study both may have resulted in higher intensity of caregiving. Magasi et al²² also found that role loss, loss of social, and leisure activities and being the sole caregiver

TABLE 4.
Caregiver self-report questionnaires at baseline

Variable	N available cohort (per group)	Cohort (n = 193)	Caregivers of HT candidates with MCS (n = 92)	Caregivers of HT candidates without MCS (n = 101)	P
EQ-5D VAS score, mean ± SD	182 (85, 97)	84.4 ± 13.7	84.6 ± 12.9	84.3 ± 14.4	0.880
EQ-5D-3L VAS scores, n (%)	182 (85, 97)				0.705
0–24		1 (1%)	0 (0%)	1 (1%)	
25–49		3 (2%)	2 (2%)	1 (1%)	
50–74		29 (16%)	13 (15%)	16 (16%)	
75–100		149 (82%)	70 (82%)	79 (81%)	
EQ-5D-3L mobility (% problems), n (%)	182 (85, 97)	28 (15%)	16 (19%)	12 (12%)	0.229
EQ-5D-3L self-care (% problems), n (%)	182 (85, 97)	3 (2%)	2 (2%)	1 (1%)	0.485
EQ-5D-3L usual activities (% problems), n (%)	182 (85, 97)	22 (12%)	11 (13%)	11 (11%)	0.741
EQ-5D-3L pain/discomfort (% problems), n (%)	182 (85, 97)	79 (43%)	38 (45%)	41 (42%)	0.741
EQ-5D-3L anxiety/depression (% problems), n (%)	182 (85, 97)	54 (30%)	27 (32%)	27 (28%)	0.563
OCBS time, mean ± SD	181 (85, 96)	2.3 ± 0.7	2.4 ± 0.7	2.2 ± 0.7	0.138
OCBS difficulty, mean ± SD	181 (85, 96)	1.3 ± 0.4	1.4 ± 0.5	1.2 ± 0.3	0.004

EQ-5D VAS, EuroQol visual analog scale, range: 0 = worse to 100 = best imaginable health state; EQ-5D-3L, dimension with 3 response levels: no problems, some/moderate problems, and extreme problems (combined into problems); HT, heart transplantation; MCS, mechanical circulatory support; OCBS difficulty, Oberst Caregiving Burden Scale, difficulty of tasks, range: 1 = not difficult to 5 = extremely difficult; OCBS time, Oberst Caregiving Burden Scale, time spent on tasks, range: 1 = none to 5 = great amount of time spent.

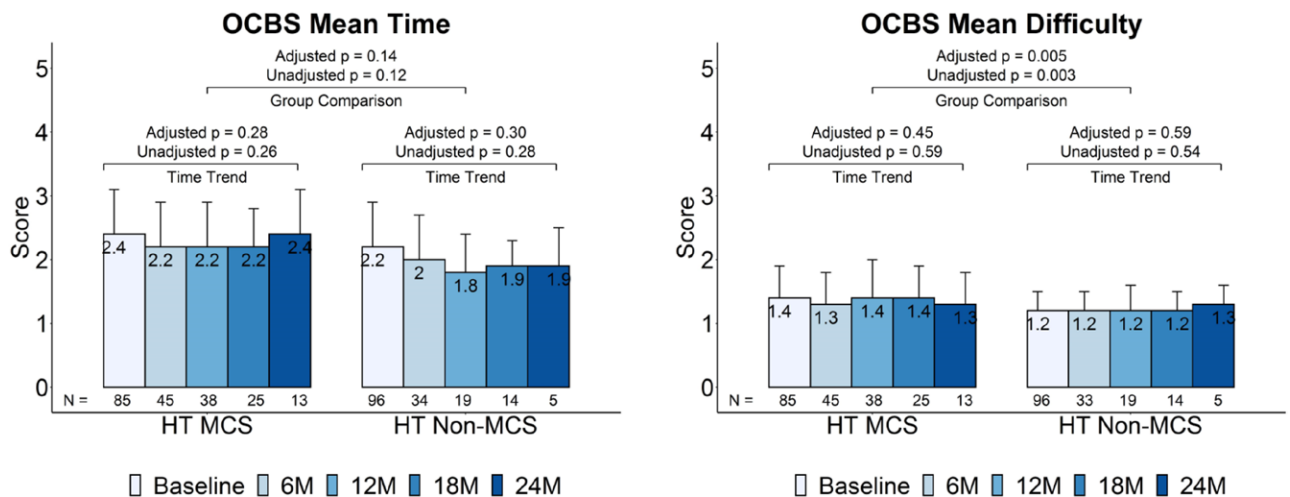


FIGURE 5. Change in caregiving burden of caregivers for heart transplantation (HT) candidates over time. Oberst Caregiving Burden Scale (OCBS) time spent on tasks, range: 1 = none to 5 = great amount of time spent; Task difficulty, range: 1 = not difficulty to 5 = great difficulty. HT MCS, caregiver of HT candidate with mechanical circulatory support; HT non-MCS, caregiver of HT candidate without MCS; MCS, mechanical circulatory support.

of an MCS patient intensified caregiver burden. Clinician understanding of caregiver burden and reasons for perceived burden, including reasons directly and indirectly related to caregiving, provide opportunities for caregiver support. More research of caregiving of patients with advanced HF and in particular caregiving for older HT candidates is needed. Bidwell et al²³ suggest that this research be conducted at the level of the dyad in order to address the needs of patients and caregivers together.

Limitations of our study included that our sample of advanced HF patients were listed for HT and, therefore, not representative of advanced HF patients in general. We also had challenges in recruitment (ie, of those older HT candidates eligible to participate, several were too sick and were either not approached or approached and refused participation), which may have contributed to overestimation of HRQOL. It is very important to understand recruitment barriers in order to identify strategies to enhance recruitment. Barriers to study recruitment, especially among minorities and patients with end-stage chronic diseases, include challenges

related to research teams (eg, communication/approach during the recruitment process) and patient issues (eg, acuity of illness, trust, and logistical issues [eg, transportation and time commitment]).²⁴⁻²⁶ Addressing barriers may increase study enrollment. Examples include improving communication (eg, honesty and active listening to patient concerns during recruitment), facilitating trust (eg, training staff on sociocultural factors of populations being considered for recruitment), and removing logistical barriers (eg, financial compensation for time and travel expenses).^{24,26}

Other limitations were that our HT candidate and caregiver samples were relatively homogenous by age, race, gender, and marital status which may limit generalizability to other older advanced HF patient and caregiver populations in the United States, although participants were broadly geographically representative of the United States, and potentially other countries, depending upon their demographic characteristics. Notably, 83% of HT candidates and 85% of their caregivers were white, which is higher than reported in the United States in general (ie, 60%).²⁷ Additionally, by 24 mo, sample sizes were small,

due to transplant, patient death, and study withdrawal, which also may have influenced findings. Lastly, HT candidate group differences in length of time on the UNOS waitlist at enrollment and until HT may have influenced our findings.

Conclusions

HT candidates with MCS experienced higher HRQOL over time than those awaiting HT without MCS. While caregiver HRQOL was high, caregivers of HT candidates with MCS reported more caregiving burden compared to caregivers of HT candidates without MCS. Our findings have important clinical implications. As wait times for HT can be quite long, we recommend that clinicians assess HRQOL (overall and by domain) of both HT candidates and their caregivers and caregiver burden which may guide treatment for HT candidates and support for their caregivers and may also contribute to improved HRQOL for both after HT.

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