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Change in health-related quality of life from before to after destination therapy mechanical circulatory support is similar for older and younger patients: Analyses from INTERMACS

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quality of life;
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age

BACKGROUND: Destination therapy left ventricular assist devices (DT LVADs) are being implanted in older adults on an increasing basis. Older patients have a higher risk for mortality and morbidity post-LVAD, which may impact their health-related quality of life (HRQOL). We aimed to determine the change in HRQOL by age from before implant to 1 year after DT LVAD implant and identify factors associated with the change.
METHODS: Data were collected from 1,470 continuous-flow DT LVAD patients at 108 institutions participating in INTERMACS from January 21, 2010 to March 31, 2012. Patients were divided into three cohorts: <60 years of age ($n = 457$); 60 to 69 years of age ($n = 520$); and ≥70 years of age ($n = 493$). HRQOL was measured using the generic EuroQol instrument (EQ-5D-3L). Data were collected pre-implant and 3, 6 and 12 months post-implant. Statistical analyses included descriptive statistics, Kaplan-Meier survival analyses and multivariable regression analyses.
RESULTS: HRQOL improved in all patients. Generally, older patients reported better HRQOL than younger patients pre-implant (≥70 years: mean 40; 60 to 69 years: mean 33; and <60 years: mean 31; $p < 0.0001$) and 1 year post-implant (≥70 years: mean 77; 60 to 69 years: mean 72; <60 years: mean 70; $p = 0.01$) using the EQ-5D visual analog scale (VAS), with 0 = worst imaginable health state and 100 = best imaginable health state. The magnitude of improvement in EQ-5D scores from pre-implant to 1-year post-LVAD implant was similar in all age groups (≥70 years: mean change 33; 60 to 69 years: mean change 35; <60 years: mean change 35; $p = 0.77$). Factors associated with improvement in HRQOL from before to 1 year after implant were a lower VAS score pre-implant and fewer rehospitalizations post-implant ($R^2 = 61.3\%$, $p < 0.0001$).

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CONCLUSIONS: Older patients reported better HRQOL than younger patients before and after LVAD implantation. The magnitude of improvement was similar for all age groups, with >70% of all patients showing clinically significant increases (>10 points on the VAS). Rehospitalization appears to reduce the magnitude of improvement.

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The number of people in the USA ≥65 years is projected to be 88.5 million in 2050, more than double the number of 40.2 million in 2010.[1] Because the prevalence of heart failure increases with age,[2] the estimated 50,000 to 500,000[3] patients with advanced heart failure is anticipated to include an increasing number of older individuals. Destination therapy (DT; intended for permanent use) mechanical circulatory support (MCS) is offered to older patients with advanced heart failure who are ineligible for heart transplantation as a consequence of advanced age and comorbidities.[4–7] In 2011, 38% (620 of 1,620) of MCS implants were DT cases, as reported by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS),[8] and their use in older adults has increased, with more DT MCS devices used in older vs younger patients during the period from 2006 to 2011 (<60 years: $n = 352$; ≥60 years: $n = 808$).[8]

Importantly, outcomes after MCS have improved over time. Patient survival 2 years after MCS (70%) is approaching that of heart transplantation (~80%).[4,9] Nevertheless, older age is a risk factor for decreased survival after MCS,[9] including DT MCS,[8] and is associated with increased morbidity after MCS (e.g., renal failure, stroke and gastrointestinal bleeding).[10,11] Health-related quality of life (HRQOL) outcomes also improve through 2 years after MCS.[12–15] However, adverse events and symptoms after MCS are risk factors for poor HRQOL and their increased incidence in older patients may diminish the HRQOL benefits in this population.[16,17] In contrast, we have previously reported that older patients have better short-term[18] and long-term[19] HRQOL outcomes after transplantation as compared with younger patients.

To address the gap in knowledge surrounding the HRQOL benefits of DT MCS in older patients, we examined these outcomes in INTERMACS, a prospective, multi-institutional registry of patients receiving MCS. We sought to assess change in HRQOL by age and identify factors associated with change in HRQOL from before to 1 year after DT MCS implant. We defined HRQOL as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient."[20]

Methods

Sample and sites

Data were collected retrospectively from adult (≥19 years) left ventricular assist device (LVAD) patients at 108 institutions that collected HRQOL data within INTERMACS. Patients were included if they received a U.S. Food and Drug Administration (FDA)-approved continuous-flow LVAD as a primary implant for DT between January 21, 2010 and March 31, 2012. Patients were divided into three cohorts based on age: <60 years; 60 to 69 years; and ≥70 years. Our rationale for using these subgroups is derived from the gerontology literature, which recognizes the diversity of old age by defining subgroups. Although there is no universal definition of subgroups, the field of cardiovascular research has used: 60 to 69 = young-old; 70 to 79 = middle-old; and 80^{+} = old-old.[21] We combined the middle-old and old-old DT MCS subgroups, as the sample size was very small at ≥80 years of age. Thus, our choice of <60 years, 60 to 69 years and ≥70 years supported our desire to understand whether the young-old DT MCS patients were more similar to adult DT MCS patients <60 years or the combined subgroups of middle-old and old-old DT MCS patients regarding HRQOL outcomes. Patients were followed through March 31, 2013 to enable each patient to have 1 year of post-implant follow-up.

Instrument

The five-dimension EuroQol questionnaire (EQ-5D-3L), a generic instrument, was used to measure HRQOL via patient self-report.[22,23] The EQ-5D-3L consists of five questions that assess the HRQOL dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[22,23] Patients were asked to rate the extent to which they had problems for each dimension using a three-level response format (no problems, some or moderate problems, extreme problems). This three-level response format has been used since initiation of the registry. A five-level response version of the EQ-5D became available after the launch of INTERMACS, but the three-level format has been used to maintain consistency. The EQ-5D-3L also includes an overall health status rating, using a vertical visual analog scale (VAS), with 0 = worst imaginable health state and 100 = best imaginable health state. Psychometric support for this instrument has been reported, including for patients with cardiovascular disease.[24,25]

Procedures

Institutional review board approval was received from all sites before INTERMACS participation. After providing informed consent, patients were enrolled in the registry. HRQOL and medical records were abstracted by research coordinators pre-implant (up to 30 days beforehand) and at 3, 6 and 12 months post-implant, or until device removal, re-implantation, transplant or death. When the EQ-5D-3L instrument was not completed, reasons for missing data were documented. Data were entered electronically into the INTERMACS database and analyzed by the data coordinating center at the University of Alabama, Birmingham.

Statistical analyses

Data were analyzed using SAS, version 9.1 (SAS, Inc., Cary, NC). Statistical analyses included Kaplan-Meier survival analyses, chi-square tests to compare frequencies, 1-way analysis of variance (ANOVA) to compare means (using all available data for each time period), paired *t*-tests to compare means (when complete data were

Table 1 Baseline (Pre-implant) Characteristics of MCS Recipients by Age[a]

Pre-implant characteristics	Total ($n = 1,470$)	Age <60 years ($n = 457$)	Age 60 to 69 years ($n = 520$)	Age ≥ 70 years ($n = 493$)	p-value
Demographic and behavioral characteristics					
Age at implant (mean years)	63.4 ± 11.8	49.0 ± 9.4	65.7 ± 2.9	74.1 ± 3.0	<0.0001
Male (%)	82	75	83	88	<0.0001
Race (% white)	75	55	83	86	<0.0001
Married at time of implant (%)	73	53	79	85	<0.0001
Beyond high school education (%)	50	42	50	58	<0.0001
Currently smoking (%)	11	22	10	4	<0.0001
Current alcohol abuse (%)	15	25	13	8	<0.0001
Current drug abuse (%)	2	7	1	0	<0.0001
Clinical characteristics					
Primary cardiac diagnosis (%)					
Ischemic cardiomyopathy	58	40	67	38	<0.0001
Dilated cardiomyopathy	38	56	29	32	<0.0001
Other	4	4	4	4	0.76
Co-morbidities (%)					
Diabetes	44	38	51	43	0.0004
CVA	8	7	10	7	0.16
Right heart failure (RVEF severe)	19	23	17	18	0.27
Pre-COPD	18	18	17	19	0.82
Cancer	13	12	15	12	0.22
NYHA Class IV (%)	76	75	79	75	0.21
Intra-aortic balloon pump (%)	26	27	26	25	0.79
Ventilator (%)	5	7	4	3	0.01
ECMO (%)	1	3	1	0	0.003
Dialysis (%)	2	2	1	1	0.20
INTERMACS profile at implant (%)					
1	11	15	11	7	0.0001
2	36	37	36	35	0.76
3	32	32	32	32	0.95
4	15	10	17	19	0.0003
5	3	2	3	4	0.26
6	2	2	1	2	0.44
7	1	1	1	1	0.49
Inotrope therapy (%)	78	82	78	75	0.03
Implantable cardioverter-defibrillator (%)	85	82	87	87	0.02
Temporary circulatory support (%)	15	18	16	13	0.07

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ECMO, extracorporeal membrane oxygenation; INTERMACS, Interagency Registry for Mechanically Supported Circulatory Support; MCS, mechanical circulatory support; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction.

[a]Those patients who were "too sick" were included and assigned a visual analog score = 0, and physical dimensions as "extreme problems."

available at the pre- and 1 year post-implant time periods) and multiple linear stepwise (forward) regression analyses. Distribution of change in VAS score was also examined over time and a priori, with a change of >10 units considered clinically relevant. This decision was based on the cancer literature, which estimates a change of 8 to 12 in VAS scores as a "minimally important difference" (MID) for self-rated health status among cancer patients.[26] We did not find MIDs for VAS scores in other disease states in the literature.

The EQ-5D VAS score is reported as a mean ± standard deviation, and dimension scores are reported as frequencies. A VAS rating of 0 was assigned to patients who were too sick to respond, based on the spread of the scores for those patients who responded. Data from the five dimensions were organized into two groups: Group 1, physical function/activities of daily living (dimensions = mobility, self-care, usual activities); and Group 2, pain/emotions (dimensions = pain/discomfort and anxiety/depression). This grouping was used because a response level of "extreme problems" was assigned (post hoc) to patients who were too sick to respond for the physical function/activities of daily living group to reduce the potential for overestimation of HRQOL in patients who were most severely ill. No assignment of responses was made for too sick patients in the pain/emotions group, as being too sick does not necessarily indicate extreme problems regarding pain or negative emotions. We performed sensitivity analyses to assess the influence of assignment of VAS scores for patients too sick to respond.

Multivariable regression analyses were conducted, combining the three age groups and including some basic transformations (age^2 and log age), using change in the VAS score from pre- to 1 year post-implant as the dependent variable. Independent variables included the institution at which the surgery was performed, pre-implant VAS score, demographic characteristics (age, gender, race, education, marital status), pre-implant clinical

variables (e.g., diagnosis, INTERMACS patient profile, New York Heart Association class, left ventricular ejection fraction <20%, severely decreased right ventricular function, cardiac index, pre-albumin, pre-implant interventions [i.e., inotropes, intra-aortic balloon pump, ventilator, dialysis, extracorporeal membrane oxygenation, implantable cardioverter-defibrillator] and presence of comorbidities [i.e., previous cancer, diabetes, cerebrovascular accident, peripheral vascular disease, chronic obstructive pulmonary disease, rheumatologic disease, current smoker, abuse of alcohol, abuse of drugs), concomitant surgery and post-operative adverse events within 1 year post-implant [i.e., bleeding, infection, neurologic dysfunction, psychiatric episode, device malfunction, rehospitalization]). These demographic and pre- and post-operative clinical variables were selected based on their potential to influence HRQOL. For example, comorbidities, such as diabetes, pre-implant interventions, including use of inotropes and adverse events after implant, such as device malfunction, can all influence change in HRQOL from before to after implant. Pre-implant interventions, comorbidities, concomitant surgery and adverse events were operationalized as dichotomous variables (i.e., present/not present). There were no outliers, and multicollinearity was minimal. Level of significance was $p < 0.05$ for all analyses.

Results

Between January 21, 2010 and March 31 2012, 1,470 patients (mean age 63.4 years, 82% male, and 75% white) enrolled in INTERMACS received primary continuous-flow DT LVADs. Sample size by age group was as follows: <60 years, $n = 457$ (31%); 60 to 69 years, $n = 520$ (35%); and ≥70 years, $n = 493$ (34%). Significant differences were detected among the age groups for demographic characteristics and pre- and post-implant variables (Table 1). Compared with the two older age groups, the youngest age group included the highest proportion of unmarried respondents, more non-white respondents, more women, more individuals with less than a high school education, and more individuals reporting substance abuse. Notably, fewer older patients were INTERMACS Profile 1, as compared with the two younger age groups. Survival did not differ among age groups (Figure 1).

EQ-5D-3L instrument completion rates overall and by age group

Rates of instrument completion were identified for all three age groups (Table 2). Before implant, 70%, 73% and 76% of data were available for patients <60 years, 60 to 69 years and ≥70 years, respectively, which included patients who were too sick to respond for whom the VAS score was assigned a 0. At 12 months after implant, EQ-5D completion rates for the three age groups ranged from 52% to 64%. After implant, very few patients were too sick to respond. Reasons for post-implant lack of survey completion were primarily administrative (e.g., patient not consented, no contact with the patient during the window of time that a survey was due) and patient's refusal to participate.

Differences in HRQOL by age group before and after DT LVAD implant

Differences in overall HRQOL (using the VAS score) among age groups were examined cross-sectionally within each time period and longitudinally from before to 1 year after DT LVAD implant (Table 3). Using all available data, differences were detected among the three age groups, with the older age group demonstrating the best overall HRQOL (≥70 years: mean 40; 60 to 69 years: mean 33; and <60 years: mean 31; $p < 0.0001$) before implant. Similarly, differences were detected among age groups at 1 year after implant, showing the best overall HRQOL in the oldest patients (≥70 years: mean 77; 60 to 69 years: mean 72; and <60 years: mean 70; $p = 0.01$). Overall HRQOL improved significantly in all three age groups from pre-implant to 1 year after DT LVAD implant, as per analyses with paired data.

Importantly, the amount of change in the VAS score across time did not differ by age group (≥70 years, mean change 33; 60 to 69 years: mean change 35; and <60 years: mean change 35; $p = 0.77$; Table 3). Sensitivity analyses, without assignment of 0 for the VAS (when patients were

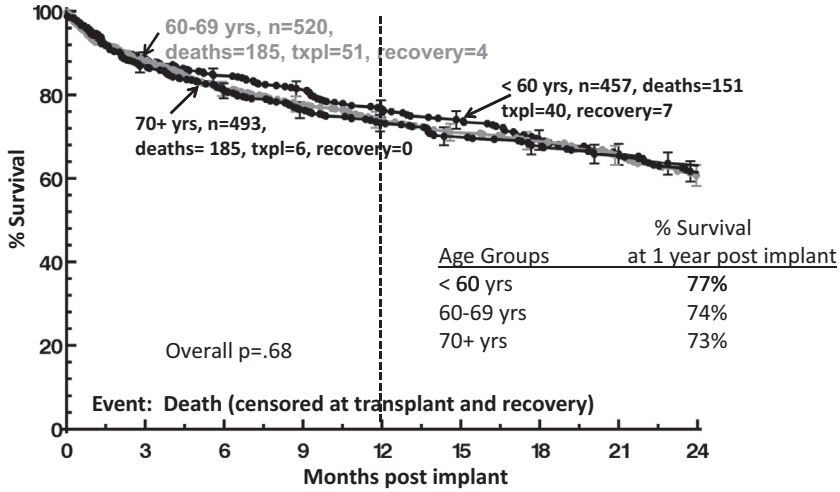


Figure 1 Survival analyses by age group.

Table 2 HRQOL Data Availability by Age Group

	< 60 years			60–69 years			70^{+} years			Totals		
Time-point	Exp	n^a	Too sick to respond to survey: VAS = 0	Exp	n^a	Too sick to respond to survey: VAS = 0	Exp	n^a	Too sick to respond to survey: VAS = 0	Exp	n^a	Too sick to respond to survey: VAS = 0
Pre-implant	457	318 (70%)	85 (27%)	520	377 (73%)	71 (19%)	493	377 (76%)	47 (12%)	1,470	1,072 (73%)	203 (19%)
3 months	406	205 (50%)	16 (8%)	463	234 (51%)	21 (9%)	440	242 (55%)	25 (10%)	1,309	681 (52%)	62 (9%)
6 months	381	194 (51%)	4 (2%)	429	237 (55%)	10 (4%)	411	249 (61%)	8 (3%)	1,221	680 (56%)	22 (3%)
12 months	323	169 (52%)	2 (1%)	359	207 (58%)	3 (1%)	351	223 (64%)	3 (1%)	1,033	599 (58%)	8 (1%)

Exp, expected; HRQOL, health-related quality of life; VAS, visual analog score.
[a]Includes patients who completed the survey and patients who were too sick to respond and were assigned a VAS score = 0.

too sick to respond), resulted in similar findings (i.e., similar improvement in mean VAS scores and similar amounts of change for the three age groups across time). The vast majority of patients in each age group demonstrated clinically meaningful improvement (i.e., >10 points) in their VAS scores from pre-implant to 1 year after DT LVAD implant (≥70 years: 74.3%; 60 to 69 years: 74.9%; <60 years: 73.4%; Table 4).

EQ-5D dimensions were also examined by age group cross-sectionally (within each time period) and longitudinally. Before DT LVAD implant, there were significant differences among the three age groups regarding reporting of problems for all five dimensions, with older patients reporting fewer problems than younger cohorts (Figures 2 and 3). Differences were not significant among the age groups at 12 months after implant for mobility, self-care and usual activities, although there was a trend toward younger patients having more problems with usual activities than the two older age groups (Figure 2a–c). However, the oldest patients reported fewer problems at 12 months after implant when compared with the two younger groups with regard to pain/discomfort and anxiety/depression (Figure 3a and b). For both physical function/activities of daily living (dimensions = mobility, self-care, usual activities) and pain/emotions (dimensions = pain/discomfort and anxiety/depression), patients in all three age groups reported significantly fewer problems from pre-implant to 1 year post-implant (Figures 2 and 3).

Multivariable analyses of factors related to HRQOL by age group

We assessed factors associated with change in overall HRQOL from pre-implant to 1 year post-implant using change in the VAS score from before to 1 year after implant as the dependent variable. Factors associated with improvement in HRQOL from before to 1 year after implant included lower VAS score pre-implant and fewer rehospitalizations after implant (R^2 = 61.3%, p < 0.0001; Figure 4). Age was not a significant variable either before or after adjustment for rehospitalization.

Discussion

Older patients reported better HRQOL than younger patients before and 1 year after DT LVAD implantation, yet overall HRQOL improved similarly, independent of age. The vast majority of patients in all three age groups improved overall HRQOL by >10 units from pre-implant to 1 year after LVAD implant, and the amount of change in HRQOL was similar for all three age groups across time. Rehospitalization was associated with less improvement in HRQOL from before to 1 year after implant. Notably, the youngest age group (<60 years) differed from the older age groups sociodemographically and behaviorally. Because younger patients are more commonly bridged to transplant with an LVAD, factors related to HRQOL in this younger DT cohort require further study. In other studies, older age is related to

Table 3 Mean VAS Scores for Adult Primary DT LVAD Patients

	<60 years		60–69 years		70+ years		
Time-point	*n*	Mean VAS	*n*	Mean VAS	*n*	Mean VAS	*p*-value
All available data							
Pre-implant	311	31.3	371	33.3	371	40.2	<0.0001
1-year follow-up	158	70.1	199	72.0	217	76.5	0.01
Paired data							
Pre-implant	124	35.8	144	37.7	167	44.4	0.02
1-year follow-up	124	70.7	144	72.7	167	77.0	0.03
Difference (1-year pre-implant)	124	34.9	144	35.0	167	32.6	0.77
P-value		<0.0001		<0.0001		<0.0001	

VAS, visual analog scale.

lower VAS scores and lower EQ-5D index scores (which correlate highly with VAS scores), including those patients with chronic conditions.[27,28] These findings are in contradistinction to our findings. The higher pre-implant VAS scores of older patients may have been due to being less sick (i.e., fewer older patients having INTERMACS Profile 1 at time of implant) than younger cohorts.

Our findings provide important new information about HRQOL with which to inform patients who are considering DT LVAD implant and should help guide more tailored care after implant by age group. For example, patients can be informed that HRQOL improves after DT LVAD implant, irrespective of age. Also, it is important to inform patients about the risk of rehospitalization and its potential effect on HRQOL after implant.

The LVAD and heart transplant literature partially support our findings. Adamson et al[29] compared HRQOL between younger (<70 years, $n = 25$) and older (≥70 years, $n = 30$) patients from a single institution whose implant strategies were bridge to transplant or DT. Both groups had improved HRQOL from baseline to 6 months after implant, with no difference between groups, perhaps because their sample sizes were small. We reported that older heart transplant recipients were more satisfied with HRQOL, had less negative affect and depression, and had better overall functioning than younger and middle-aged heart transplant recipients at 5 years after surgery.[19] Similarly, in this report, we found that older DT LVAD patients had less depression than younger patients after implant. Older age was also related to enhanced (emotional) quality of life in heart transplant candidates.[30]

Reports from other chronic illness populations having undergone invasive device therapy also provide support for some of our findings. Older heart failure patients who underwent cardiac resynchronization therapy derived similar HRQOL benefits as younger patients, for as long as 2 years.[31,32] Older patients with end-stage renal disease who underwent peritoneal dialysis or hemodialysis also reported HRQOL to be better than or similar to that of younger age groups.[33–35] When domains were examined, older dialysis patients were more challenged by physical problems, but mental health was similar to or better than that reported by younger patients.[33,34] The finding of more physical problems in older dialysis patients differed from

Table 4 Change in VAS Scores by Age: Pre- vs 12 Months Post-implant

	<60 years		60–69 years		70+ years	
	n	Percent	*n*	Percent	*n*	Percent
No change or decline						
>10 units worse	10	8.1%	8	5.6%	8	4.8%
>1–10 units worse	5	4.0%	9	6.3%	8	4.8%
No change	5	4.0%	9	6.3%	5	3.0%
Improvement						
1–10 units better	13	10.5%	10	6.9%	22	13.1%
11–20 units better[a]	14	11.3%	18	12.5%	27	16.1%
21–30 units better[a]	14	11.3%	13	9.0%	18	10.8%
31–40 units better[a]	14	11.3%	16	11.1%	17	10.2%
41–50 units better[a]	6	4.8%	17	11.8%	17	10.2%
51–60 units better[a]	12	9.7%	10	6.9%	14	8.4%
61–70 units better[a]	10	8.1%	14	9.7%	11	6.6%
71+ units better[a]	21	16.9%	20	13.9%	20	12.0%
Totals	124	100.0%	144	100.0%	167	100.0%

VAS, visual analog score. *P*(overall) = 0.76.
[a]Minimally important difference.

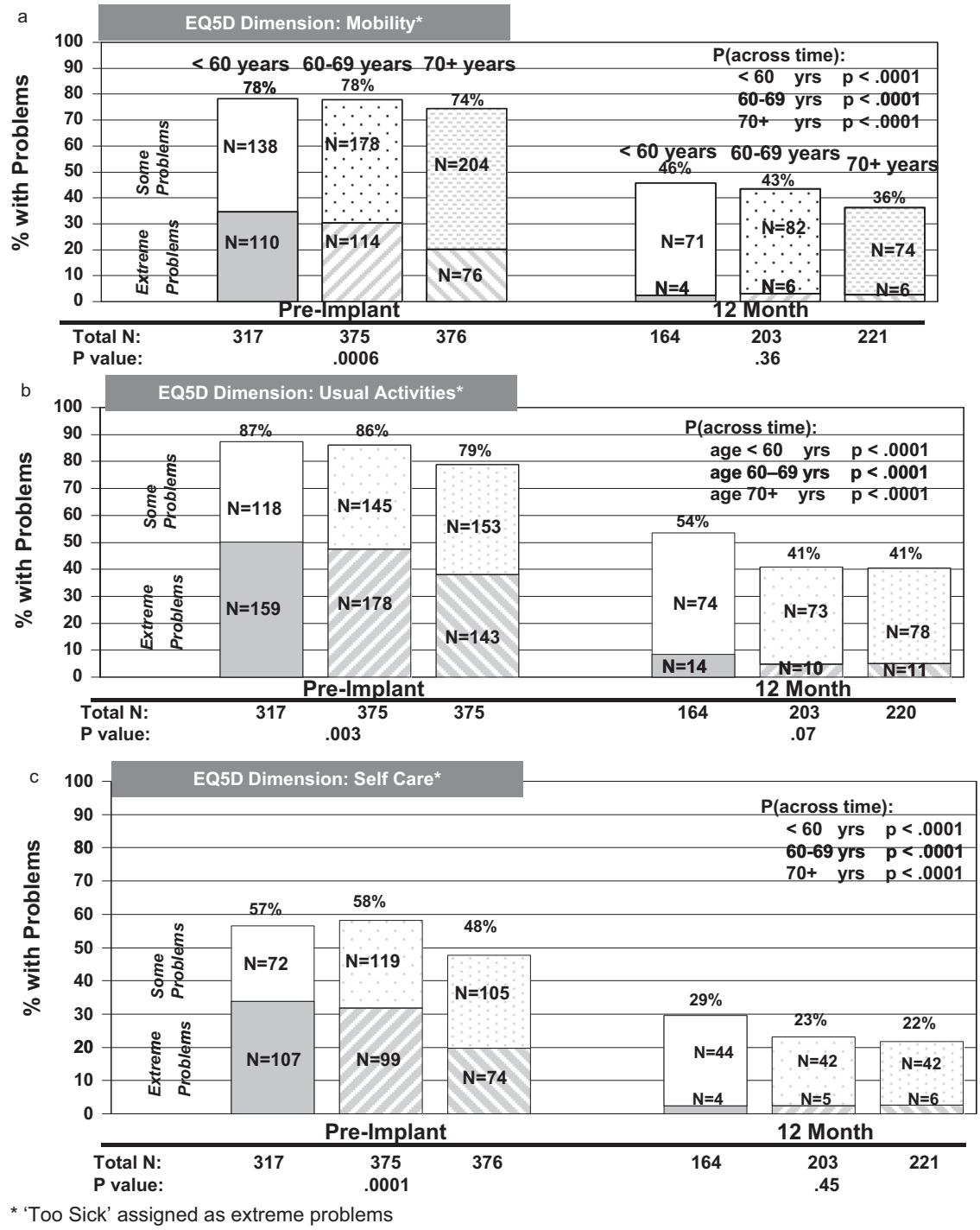


Figure 2 EQ-5D physical function/activities of daily living dimensions by age group.

our findings, wherein the frequency of physical problems was similar among the age groups after implant, which may be explained by elderly DT MCS patients having a lower risk profile than younger patients.[8]

The relationship between hospital re-admission and HRQOL deserves comment. Our finding that rehospitalization was associated with less improvement in HRQOL from pre-implant to after DT LVAD implant may be due to frequency of readmissions. Rates of hospital re-admission during the first year after LVAD implant are 65% (e.g., due to gastrointestinal bleeding, cardiac-related causes, infection, stroke and renal failure).[36,37]

We also found that less improvement in the VAS score from pre-implant to 1 year post-implant was related to having a higher VAS score before implant. This may be a ceiling effect (i.e., inability to discriminate between comparatively good health states),[25] but it is also logical and supported by our previous report from INTERMACS, wherein we found that patients with higher INTERMACS profiles (and higher HRQOL) had less change in HRQOL than patients with lower INTERMACS profiles (and lower HRQOL) before implant.[38] Similar findings have been reported in the cardiac surgery literature.[39]

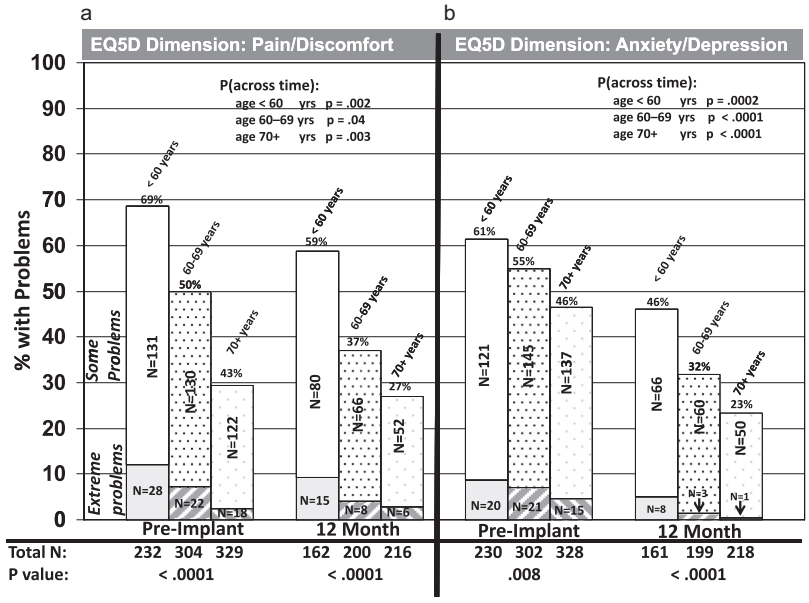


Figure 3 EQ-5E pain/emotions dimensions by age group.

Our study has limitations. We collected HRQOL data using a brief, generic HRQOL survey, which may have been less responsive in this population of patients, because it is not disease- and/or treatment-specific. Reduced instrument completion before and after LVAD implantation may have limited the generalizability of our findings. To address this issue, we used a strategy of post hoc assignment of scores for patients who were too sick to respond. Also, only variables available in the registry were used to build models; other variables (e.g., socioeconomic factors and family support), not collected in the registry, may have explained variance in HRQOL. Notably, educational level, which is a commonly used proxy for socioeconomic status, was included in our modeling. Finally, survivorship bias in our cohort may have contributed to overly optimistic findings. However, there was no difference in survival by age group.

In conclusion, overall HRQOL improves similarly over time for all age groups after DT LVAD implantation, although older patients have better HRQOL than younger patients before and after implant. Hospitalization after implant is a major factor associated with less improvement in HRQOL from before to 1 year after implant. These findings add to the body of evidence by which clinicians can educate and inform patients considering VADs as a treatment option, as well as for tailoring care for patients of all ages who are living with VADs.

Disclosure statement

J.S. owns the copyright to the Kansas City Cardiomyopathy Questionnaire. He currently serves as a consultant to the scientific advisory boards of UnitedHealthcare, Amgen and Novartis. E.C.M. is a consultant and speaker for HeartWare, Inc. The remaining

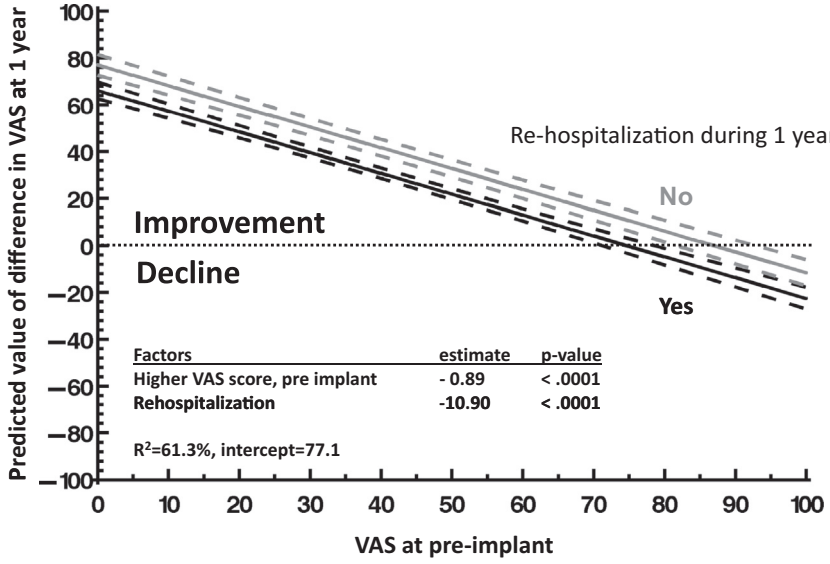


Figure 4 Factors associated with change in HRQOL (VAS score) ($n = 435$).

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