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Changes in the Quality of Life of Patients with Left Ventricular Assist Device and their Caregivers in Japan: Retrospective Observational Study

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Left ventricular assist devices (LVAD) improve quality of life (QOL) in many patients with end-stage severe heart failure, but not in some patients. In addition, the burden on caregivers is expected to increase after LVAD patients are discharged. Our study aimed to investigate the impact of LVAD on the QOL of patients and caregivers. Thirty-two LVAD patients were assessed for changes in QOL, mental status, and activity level using the Euro QOL (EQ-5D-5L), Short Form 12 (SF-12), Minnesota Living with Heart Failure Questionnaire, Hospital Anxiety and Depression Scale (HADS), and Frenchay Activities Index. Twenty-four caregivers were assessed for changes in QOL, mental status, and burden of care using the EQ-5D-5L, SF-12, HADS, and Burden Index of Caregiver (BIC-11). The LVAD patients and caregivers responded contemporaneously regarding two points: pre-and post-LVAD. Patients' physical and mental QOL was significantly improved, but not social QOL and activity level. Caregivers' QOL and burden of care did not change, and anxiety was reduced ($p = 0.028$). The patients were divided into two groups based on whether EQ-5D-5L was improved: twelve patients in the unimproved group (UG) and twenty patients in the improved group (IG). In the UG, 50% had LVAD-related strokes ($p = 0.001$, IG: 0%), and their social QOL decreased ($p = 0.023$). The activity levels improved in the IG. Multi-dimensional analyses on the QOL in LVAD patients yielded mixed results. Anticipated benefits derived from LVAD therapy may be limited by LVAD-related complications such as stroke that negatively impacts on the QOL.

Keywords: caregivers; heart failure; left ventricular assist device; quality of life; stroke
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Introduction

Treatment with a continuous-flow left ventricular assist device (LVAD) in patients with advanced heart failure significantly improved the probability of survival, quality of life (QOL), and functional capacity (Slaughter et al. 2009; Rogers et al. 2010; Maciver and Ross 2012). In Japan, Kato et al. (2015) reported that implantation of an LVAD improves patients' QOL more than an extracorporeal LVAD. Despite experiencing more frequent adverse events, such as bleeding, driveline infection, pump thrombosis, stroke, and worsening heart failure, LVAD patients have improved QOL and depression (Estep et al. 2015). While LVAD often improves survival and QOL, one-third of high-acuity patients experience a poor global outcome (comprising death, poor QOL, recurrent heart failure, or severe stroke) over the year post-LVAD (Fendler et al. 2017). Furthermore, LVAD patients experience role changes, changes in their interpersonal relationships, and a lack of independence and control over their life (Casida et al.

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2011); their emotional distress may remain high (Modica et al. 2015). Adams and Wrightson (2018) reported that LVAD patients were not aware of all the social, physical, and mental challenges that would lie ahead after implantation.

In Japan, the number of LVAD patients has been rapidly increasing since 2011, as implantation is now covered by health insurance as a bridge to transplantation (BTT). However, the number of heart transplant procedures remains low by international standards, and the mean waiting period exceeded 1,150 days at the end of June 2016 (Fukushima et al. 2017). After LVAD patients are discharged from the hospital, their families and community members must provide home care, risk management, device management, exercise therapy, psychological support, and support for reintegration into society, which are traditionally provided in the hospital. In Japan, there are severe restrictions on LVAD patients and their caregivers, such as the need for caregivers to always be within hearing range of LVAD alarms, which may cause new problems for patients and caregivers in the absence of a social support system. The objectives of our study were to investigate the changes in the QOL of patients and caregivers before and after LVAD implantation and to identify the factors that reduce the patients' QOL, in order to develop a better support system in near future.

Materials and Methods

Study population and design

This paper reports on a retrospective observational study within a single institution in which adults with advanced heart failure underwent LVAD implantation. LVAD implantation was performed in patients with end-stage severe heart failure (NYHA III-IV) whose symptoms progressed despite adequate standard treatment as recommended in the guidelines. Patients who underwent LVAD implantation at Tohoku University Hospital in Miyagi, Japan, until July 2019, discharged at least once by October 2019, and inpatients or outpatients of the Department of Cardiovascular Surgery at Tohoku University Hospital, between February 2019 and October 2019, were recruited. Patients who died, received a heart transplant, removed LVAD, or transferred follow-up care to another institution before February 2019 were excluded, and foreigners were also excluded because of linguistic and cultural backgrounds. Caregivers could consent to participate in the study only if the LVAD patients had consented to participate in the outpatient clinic, and we excluded those who were not the primary caregivers living with patients. The study population and design are illustrated in Figs. 1 and 2.

Nieuwkerk et al. (2007) reported that a method for measuring change in QOL incorporating a retrospective baseline-measurement is a more valid measurement of change in QOL than a conventional prospective method. In this study, the patients and caregivers were asked to complete two sets of questionnaires. They responded contemporaneously regarding two points in time: the preoperative and postoperative conditions. For their preoperative state, they responded by recalling their status just before the surgery, and for their postoperative state, they responded about their current status. The same doctor explained how to answer the questionnaire so that there would be no difference depending on the method of explanation. The questionnaire was administered to LVAD patients and caregivers who visited the outpatient clinic or LVAD patients who were hospitalized in the Department of Cardiovascular Surgery at Tohoku University Hospital between February 2019 and October 2019. The questionnaires were returned on the same day or at the next outpatient visit.

Lawson et al. (2020) reported that agreement between prospective and retrospective measurements was substantial for the Euro-QoL 5 Dimensions 5 Levels (EQ-5D-5L) index score at an individual level. The patients were divided into the improved group (IG) and unimproved group (UG) based on whether the EQ-5D-5L index score was improved or not after LVAD. Based on the study by McClure et al. (2017), the minimal important difference in the Japanese EQ-5D-5L index score is estimated to be 0.044 ± 0.004. IG was defined as the group in which the difference in EQ-5D-5L index score before and after LVAD was greater than the minimal important difference ($> 0.044 + 0.004$), while UG was defined as the group in which it was less than the minimal important difference ($\leq 0.044 + 0.004$). The groups were compared for differences in background factors, current status, and elements of the questionnaire (QOL, anxiety/depression, and activity). Their views regarding their preimplantation state in comparison to their current state were surveyed.

In addition, the caregivers were also asked to complete the patients' current QOL using EQ-5D-5L, as estimated by them, to examine the correlation between the patients' QOL perceived by the caregivers and the patients' own perceptions.

Measures

Patient background: The patients' age, sex, duration of LVAD implantation, primary disease, medical history, reason for LVAD (BTT or destination therapy), LVAD model, preoperative and postoperative state, primary caregiver, place of residence, complications, total number of days of hospitalization after LVAD implantation, and frequency of hospitalization following LVAD implantation were obtained through review of the medical records.

Caregivers' information: Data regarding caregivers' age, sex, and relationship to the patients were obtained through review of the medical records and interviews.

QOL: The patients and caregivers' QOL was measured using the EuroQoL-5 Dimension-5 Level (EQ-5D-5L) questionnaire (EuroQol Group 1990; Tsuchiya et al. 2002; Shiroiwa et al. 2016) and the 12-Item Short Form Health Survey (SF-12) (Fukuhara and Suzukamo 2004, 2015) as the comprehensive scales. SF-12 is compatible with SF36,

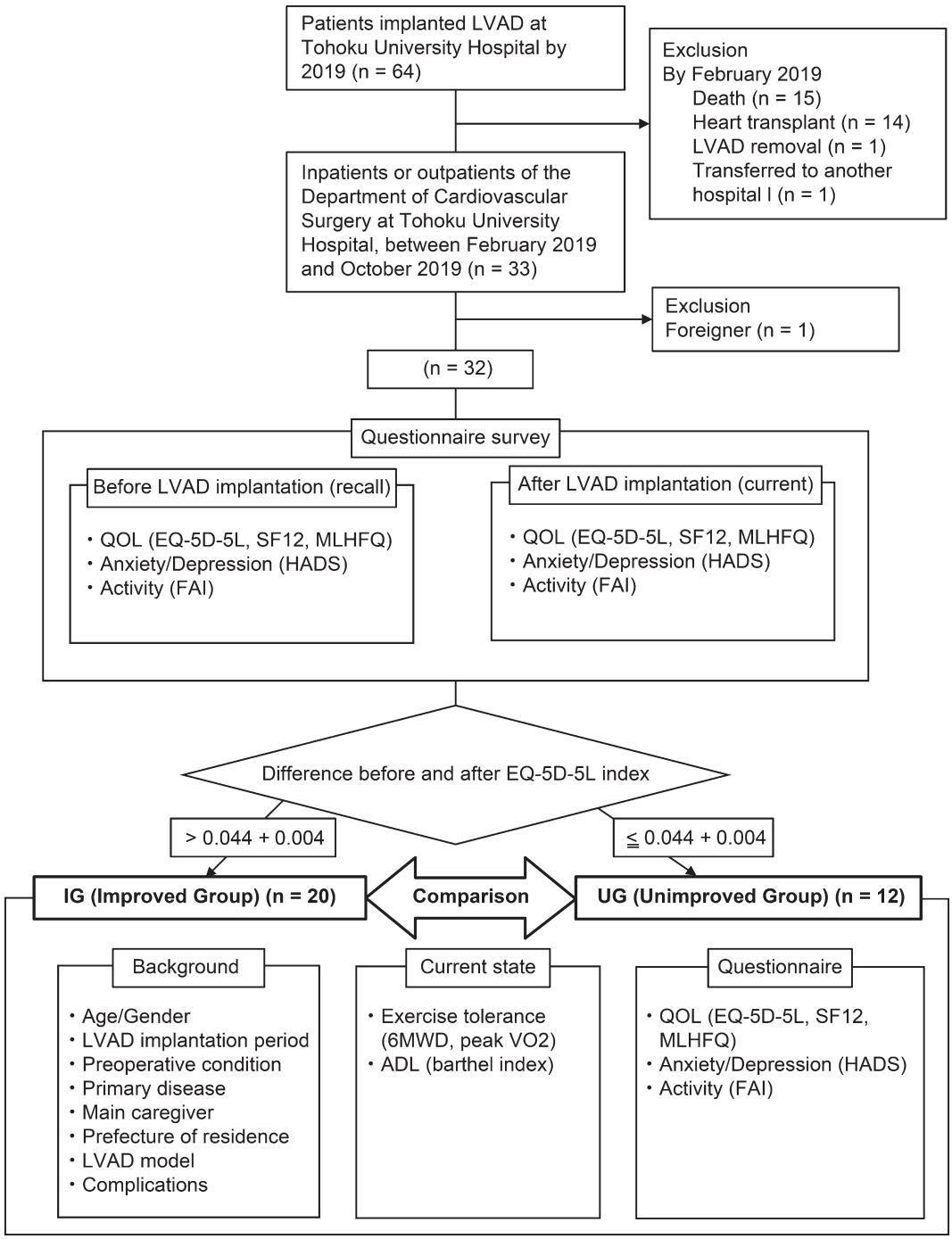

Fig. 1. Study flow chart of patients.
LVAD, left ventricular assist devices; QOL, quality of life; EQ-5D-5L, Euro-QOL 5 Dimensions 5 Levels; SF12, 12-Item Short Form Health Survey; MLHFQ, Minnesota Living with Heart Failure Questionnaire; HADS, Hospital Anxiety and Depression Scale; FAI, Frenchay Activities Index; 6MWD, 6-minute walk distance; ADL, Activities of daily living.

and the physical health component summary score (PCS), mental health component summary score (MCS), and role/social component summary score (RCS) were measured using the Japanese norm-based scoring method. Furthermore, we used the Minnesota Living with Heart Failure Questionnaire (MLHFQ) as the disease-specific scale (Rector 1987; Rector and Cohn 1992).

Symptoms of depression and anxiety: Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983; Kitamura 1993)

Activity: The activity of patients was measured using the simplified Japanese version of the Frenchay Activities Index (FAI) (Holbrook and Skilbeck 1983), the revised self-

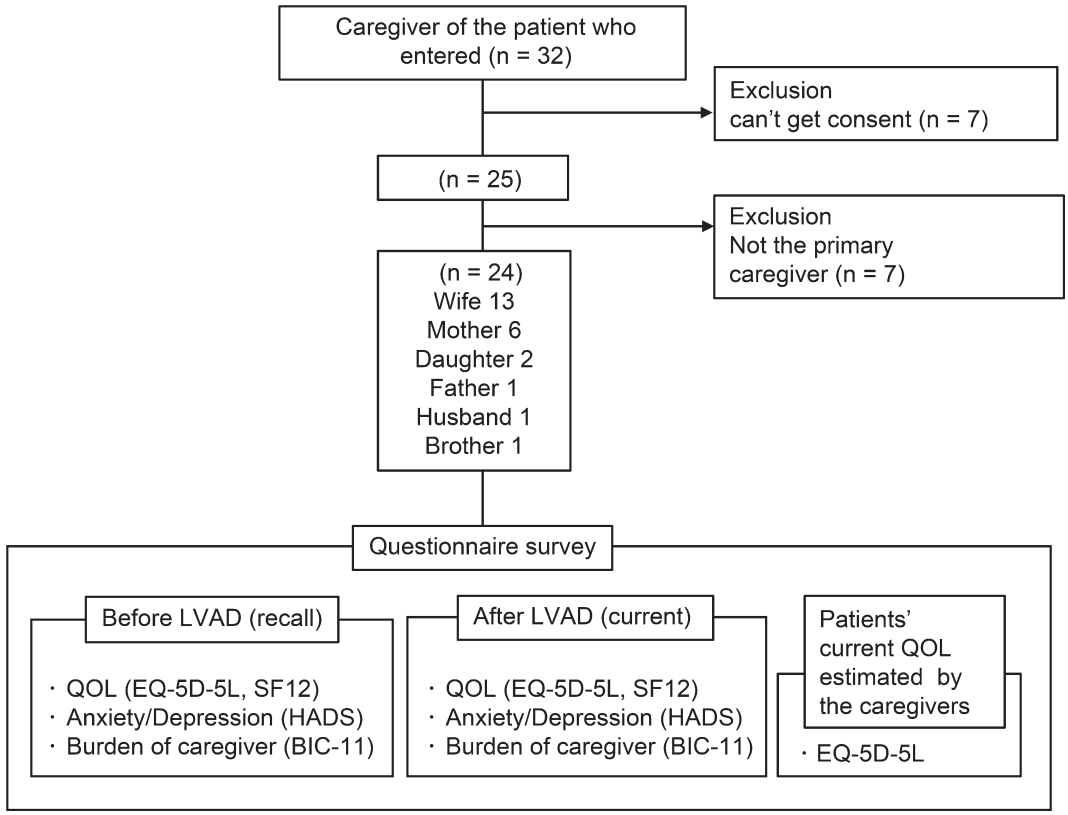

Fig. 2. Study flow chart of caregiver.
LVAD, left ventricular assist devices; QOL, quality of life; EQ-5D-5L, Euro-QOL 5 Dimensions 5 Levels; SF12, 12-Item Short Form Health Survey; HADS, Hospital Anxiety and Depression Scale; BIC-11, burden index of the caregiver-11.

rating FAI (Suenaga et al. 2000).

Present status: Activities of daily living of the patients were measured using the Barthel Index (BI) (Mahoney and Barthel 1965). Exercise tolerance of patients was measured using the peak oxygen uptake (peak VO2) based on the cardiopulmonary exercise test and 6-minute walk distance (6 MWD). The value obtained within one year from the time of responding to the questionnaire was used as the present status (after LVAD).

Burden of caregivers: Caregivers' burden was measured using the burden index of the caregiver (BIC-11) (Miyashita et al. 2006).

Statistical processing

Data are expressed as median (25^{th} quartile-75^{th} quartile) or number (%). To compare the two groups, the Mann-Whitney test was used for continuous variables and Fisher's test was used for categorical variables. For changes over time, the Wilcoxon signed-rank test was used. The correlation between the QOL perceived by the patient and caregiver was determined using Spearman's correlation measure. All statistical analyses were performed using SPSS software (version 21; SPSS Inc., Armonk, NY, USA). For the significance level of all data, a p-value of less than 5% was considered significant.

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki. The patients and caregivers were informed orally and in writing, and they provided written consent for data collection. The study was approved by the Medical Ethics Committee of Tohoku University Hospital (approval number 2018-1-799, approval date January 28, 2019).

Results

There were 64 patients with advanced heart failure who received continuous-flow LVAD at Tohoku University Hospital in Miyagi, Japan, through February 2019. Fifteen patients who died, 14 patients who received heart transplants, 1 patient who removed LVAD, 1 patient who transferred follow-up care to another institution, and 1 patient who was a foreigner, were excluded. Thus, 32 patients were included in the final analysis and all of them consented to respond to the questionnaire (response ratio: 100%). There were 20 (63%) patients in the IG and 12 (38%) patients in the UG.

There were 25 caregivers who consented to participate in the study, and one caregiver who did not live with the patient was excluded. Our final analytic cohort comprised 24 caregivers that responded to the questionnaire (response ratio: 78.1%). The median age of caregivers was 52 (47-57)

years, most of them were female (87.5%), and almost half of the caregivers were spouses of the patients (58%).

Responses to the questionnaire by patients and caregivers

The patient characteristics are summarized in Table 1. The median age was 48 (37-56), and 75% of the patients were male. The most common primary disease was idiopathic dilated cardiomyopathy (iDCM; n = 17, 53%). The number of days from LVAD implantation to questionnaire response was 1,003 days (minimum, 88 days; maximum, 1,798 days).

The comparison of questionnaire scores before and after LVAD implantation of the patients and caregivers are presented in Table 2. The patients showed improvement after LVAD implantation in the EQ-5D-5L, MLHFQ, PCS, and MCS scores of SF-12 (except RCS) and HADS (Table 2). On the other hand, there was no improvement in the RCS of SF-12 [before LVAD: 38.7 (15.7-46.3) vs. after LVAD 29.4 (19.9-41.0), p = 0.395] and FAI [before LVAD: 11.0 (3.8-20.0) vs. after LVAD: 14.5 (8.8-20.3), p = 0.108].

The caregivers' QOL revealed no change in many indices after LVAD implantation; however, total and anxiety indicators improved in the HADS [before LVAD 15.0 (9.8-21.3) vs. after LVAD: 13.0 (7.0-17.0), p = 0.041] [before LVAD: 8.0 (6.0-11.3) vs. after LVAD: 6.5 (4.0-9.0), p = 0.028]. The burden of caregivers did not worsen after LVAD implantation in the BIC-11 [before LVAD: 9.0 (4.0-13.0) vs. after LVAD: 7.5 (2.0-11.0), p = 0.118].

Table 1. Characteristics of the patients.

Characteristics		
Age (years)	48 (37-56)	
Sex		
Male	24	75%
Female	8	25%
Days after LVAD implantation	1,003 (531-1,272)	
Number of hospitalization after LVAD implantation	4.0 (2.0-6.3)	
Primary disease		
iDCM	17	53%
dHCM	5	16%
ICM	3	9%
Congenital heart disease	2	6%
Drug-induced cardiomyopathy	1	3%
Muscular dystrophy	2	6%
Heart sarcoidosis	1	3%
MELAS	1	3%
Device strategy		
BTT	27	84%
DT	5	16%
LVAD model		
HeartMate®II	17	53%
Jarvik 2000®	7	22%
EVAHEART®	7	22%
HVAD™	1	3%
Preoperative state		
EF (%)	18.5 (15.0-22.3)	
BNP (pg/μl)	942 (471-1,844)	
Extracorporeal VAD	5	16%
IABP	2	6%
CRT-D/ICD/PM	13	41%

Data are expressed as median (25th quartile-75th quartile) or number (%).
LVAD, left ventricular assist devices; DCM, idiopathic dilated cardiomyopathy; dHCM, dilated phase hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes syndrome; BTT, bridge to transplant; DT, destination therapy; EF, ejection fraction; BNP, B-type natriuretic peptide; VAD, ventricular assist device; IABP, intra-aortic balloon pumping; CRT, cardiac resynchronization therapy; D, defibrillator; ICD, implantable cardioverter defibrillator; PM, pacemaker.

Table 2. Comparison of questionnaire between pre and post left ventricular assist devices (LVAD) in patients and caregivers.

	Patients (n = 32)			Caregivers (n = 24)		
	before LVAD	after LVAD	p	before LVAD	after LVAD	p
EQ-5D-5L						
EQ-VAS	45.0 (18.8-80.0)	76.5 (60.0-80.0)	0.001**	80 (65.0-90.0)	80.0 (75.0-86.3)	0.222
EQ-index	0.59 (0.16-0.84)	0.77 (0.61-0.90)	0.008**	0.84 (0.71-1.00)	0.87 (0.77-1.00)	0.326
SF-12						
PCS	22.8 (15.6-35.9)	37.7 (29.1-49.9)	0.017*	61.1 (48.2-64.1)	53.7 (50.5-59.6)	0.475
MCS	48.6 (40.9-57.2)	56.9 (52.4-64.5)	0.001**	48.0 (41.1-52.3)	50.7 (42.7-56.3)	0.100
RCS	38.7 (15.7-46.3)	29.4 (19.9-41.0)	0.395	39.0 (32.7-45.9)	44.4 (38.2-50.0)	0.083
MLHFQ	73.5 (39.5-87.8)	41.5 (22.5-57.0)	0.003**			
HADS						
Total	18.5 (8.0-27.3)	9.0 (7.0-16.0)	0.001**	15.0 (9.8-21.3)	13.0 (7.0-17.0)	0.041*
Anxiety	8.5 (4.0-14.3)	4.0 (3.8-7.3)	< 0.001***	8.0 (6.0-11.3)	6.5 (4.0-9.0)	0.028*
Depression	10.0 (4.0-13.0)	5.5 (3.0-8.3)	0.003**	7.0 (4.8-10.3)	6.0 (4.8-8.3)	0.129
FAI	11.0 (3.8-20.0)	14.5 (8.8-20.3)	0.108			
BIC-11 (total)				9.0 (4.0-13.0)	7.5 (2.0-11.0)	0.118

Data are expressed as median (25th quartile-75th quartile). *p < 0.05, **p < 0.01, ***p < 0.001.
EQ-5D-5L, Euro-QOL 5 Dimensions 5 Levels; EQ-VAS, EQ-5D-5L visual analogue scale; EQ-Index, EQ-5D-5L index score; SF-12, The 12-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; RCS, Role Component Summary; MLHFQ, Minnesota Living with Heart Failure Questionnaire; HADS, Hospital Anxiety and Depression Scale; FAI, Frenchay Activities Index; BIC-11, Burden Index of Caregiver.
EQ-5D-5L, SF-12, MLHFQ as quality of life (QOL), HADS as an indicator of depression and anxiety, FAI as an indicator of patient activity, and BIC as a burden on the caregiver.
Patients showed an improvement after LVAD in EQ-5D-5L, MLHFQ, PCS, and MCS scores of the SF-12 (except RCS) and HADS. On the other hand, there was no improvement in the RCS of SF-12 and FAI.
Caregivers' QOL revealed no change in many indices after LVAD implantation; however, total and anxiety indicators improved in the HADS. The caregivers' sense of caregiving burden did not worsen after LVAD implantation in the BIC-11.

Intergroup comparison of the IG and UG

There were 20 patients in the IG and 12 in the UG. A comparison of the background and current states between IG and UG is presented in Table 3. Stroke as a complication after LVAD was more common in the UG (n = 5, 42%) than in the IG (n = 0.0%) (p = 0.004). When one case of cerebellar hemorrhage caused by an extracorporeal LVAD prior to LVAD implantation was included, the rate of LVAD-related stroke was 50% (n = 6) in the UG (p = 0.001). There were no differences between the other background and current states.

The questionnaire

A comparison of the questionnaire between the IG and UG is presented in Fig. 3. After the implantation, there was no difference in activity between the IG and the UG, and there was no difference in PCS, MCS, and RCS of SF-12 and HADS, but MLHFQ scores were worse in the UG [UG: 54.5 (44.3-65.3) vs. IG: 32.5 (14.8-46.0), p = 0.029].

In contrast, before LVAD implantation, there was no difference in FAI, but PCS, MCS, and RCS of SF-12, MLHFQ, and HADS were better in the UG than in the IG. This demonstrates that before implantation, many patients who felt good about their QOL and emotions were in the UG.

Furthermore, on comparing before and after LVAD implantation, the patients in the IG showed an improvement after LVAD implantation in PCS, MCS of SF-12 (except RCS), HADS, and FAI. The patients in the UG had better PCS, MCS, and RCS of SF-12 and HADS before implantation than those in the IG, and there was no improvement after implantation. Additionally, RCS decreased after implantation in the UG [before: 42.9 (39.5-48.6) vs. after: 28.1 (17.7-36.9), p = 0.023], and the activity level did not change after LVAD implantation.

The correlation between patient QOL as estimated by the caregiver and the patient's actual QOL

Upon examining the relationship between the patients' QOL as perceived by the caregiver and QOL evaluated by the patients themselves, a positive correlation was found between them in terms of EQ-VAS but not in the EQ-5D-5L index (r = 0.492, p = 0.020 and r = 0.397, p = 0.061, respectively).

Table 3. Comparison of background and current state between the improved group (IG) and the unimproved group (UG).

	IG (n = 20)		UG (n = 12)		p
Age, years	49 (34-57)		48 (43-54)		N.S.
Male	14	70%	10	83%	N.S.
Days after LVAD, days	949 (629-1,217)		1,123 (524-1,605)		N.S.
Before LVAD condition					
EF (%)	18.5 (15.0-21.8)		18.5 (14.8-22.3)		N.S.
BNP (pg/μl)	953 (421-1,660)		860 (556-1,933)		N.S.
Primary disease					
iDCM	11	55%	5	42%	N.S.
dHCM	5	25%	0	0%	N.S.
ICM	1	5%	3	25%	N.S.
Congenital heart disease	1	5%	1	8%	N.S.
Drug-induced cardiomyopathy	1	5%	0	0%	N.S.
Muscular dystrophy	1	5%	1	8%	N.S.
MELAS	0	0%	1	8%	N.S.
Heart sarcoidosis	0	0%	1	8%	N.S.
Device strategy					
BTT	16	80%	11	92%	N.S.
DT	4	20%	1	8%	N.S.
Primary caregiver					
Wife	10	50%	7	58%	N.S.
Mother	7	35%	3	25%	N.S.
Daughter	1	5%	1	8%	N.S.
Husband	1	5%	0	0%	N.S.
Father	0	0%	1	8%	N.S.
Brother	1	5%	0	0%	N.S.
Place of residence					
Aomori	2	10%	0	0%	N.S.
Iwate	3	15%	2	17%	N.S.
Akita	5	25%	2	17%	N.S.
Miyagi	7	35%	4	33%	N.S.
Yamagata	2	10%	2	17%	N.S.
Fukushima	1	5%	2	17%	N.S.
LVAD model					
HeartMate®II	12	60%	5	42%	N.S.
Jarvik 2000®	4	20%	3	25%	N.S.
EVAHEART®	3	15%	4	33%	N.S.
HVAD™	1	5%	0	0%	N.S.
Complications					
Stroke	0	0%	5	42%	0.004**
Cerebral infarction			3	25%	
Cerebral hemorrhage			2	17%	
NOMI	1	5%	2	17%	N.S.
AVR	2	10%	0	0%	N.S.
Hospitalization of driveline infection	5	25%	5	42%	N.S.
Replacement of LVAD, times	4	20%	2	17%	N.S.
Days to discharge after LVAD, days	90 (65-116)		98 (72-120)		N.S.
Number of hospitalization after LVAD, times	4.0 (3.0-6.0)		5.5 (2.0-7.3)		N.S.
Days of hospitalization after LVAD, days	196 (98-298)		259 (184-462)		N.S.
Current state					
Barthel index	100 (100-100)		100 (97.5-100)		N.S.
6MWD (m)	492 (441-582)		440 (402-524)		N.S.
exercise capacity (METs)	4.3 (3.3-4.5)		3.3 (2.7-3.8)		N.S.

Data are expressed as median (25th quartile-75th quartile) or number (%). **p < 0.01.
Stroke complications were as high as 0% in the improved group and 42% in the unimproved group.
LVAD, left ventricular assist devices; N.S., not significant; EF, ejection fraction; BNP, B-type natriuretic peptide; iDCM, idiopathic dilated cardiomyopathy; dHCM, dilated phase hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome; BTT, bridge to transplant; DT, destination therapy; NOMI, nonocclusive mesenteric ischemia; AVR, aortic valve replacement; 6MWD, 6-minute walk distance.

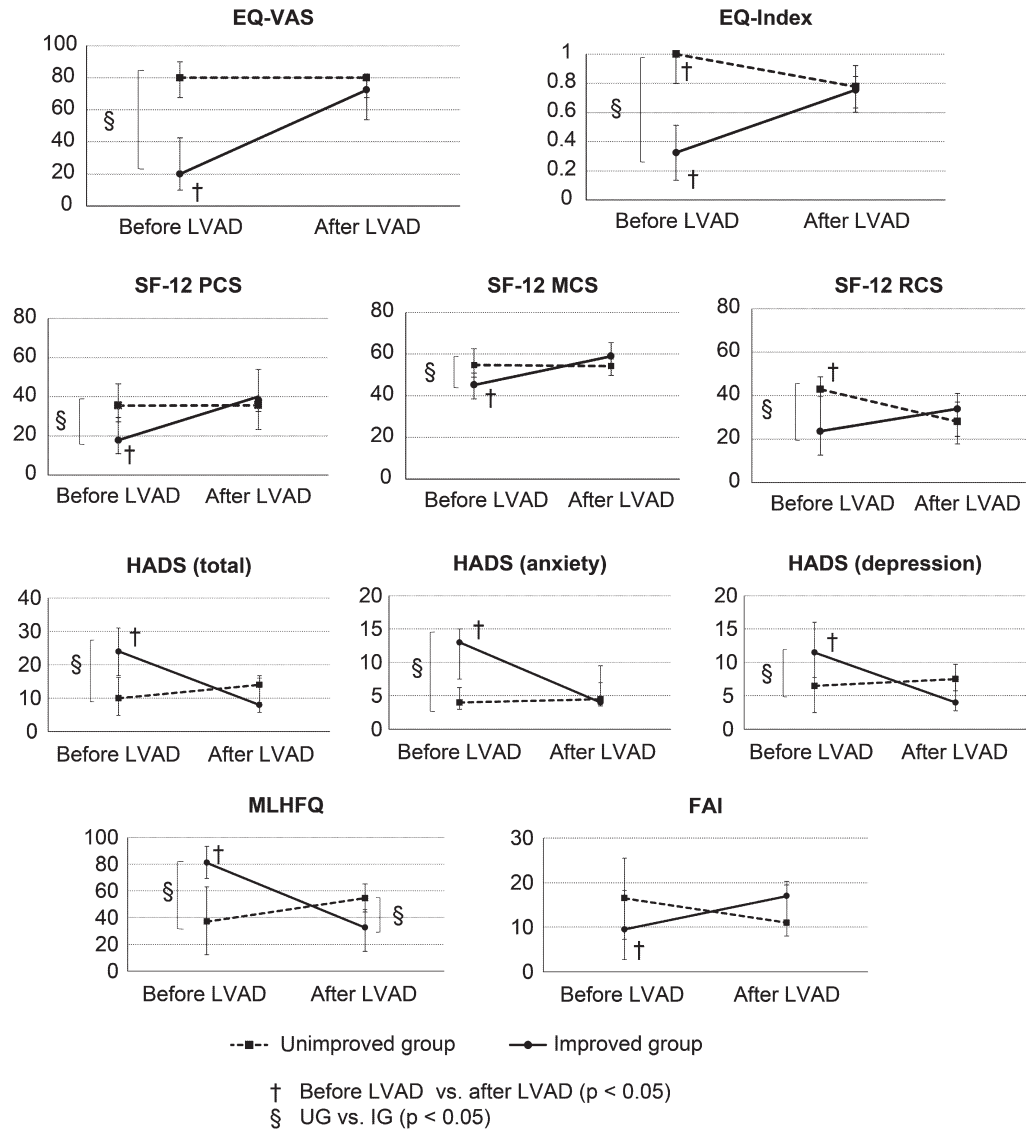

Fig. 3. Comparison of Questionnaire score between the improved group (IG) and the unimproved group (UG).
In the comparison between IG and UG, the only difference after left ventricular assist devices (LVAD) was in the Minnesota Living with Heart Failure Questionnaire (MLHFQ). On the other hand, before the LVAD, there was no difference in activity level, but other items were better in the UG than in the IG.
In the comparison between before and after the LVAD, the role/social component summary score (RCS) did not change in the IG, but improved in other items. On the other hand, in the UG, the RCS worsened and there was no improvement in other items.
EQ-VAS, EQ-5D-5L visual analogue scale; EQ-Index, EQ-5D-5L index score; SF12, 12-Item Short Form Health Survey; PCS, physical health component summary score; MCS, mental health component summary score; HADS, Hospital Anxiety and Depression Scale; FAI, Frenchay Activities Index.

Discussion

The major findings of this study were that the QOL of patients with LVAD may not improve due to complications, limitation of activity, and reduced social roles. Using the EQ-5D-5L index score to evaluate changes and comparatively examine the IG and UG, it was found that, of the patients in the UG, 50% had LVAD-related strokes, and social QOL decreased after implantation. The activity levels improved in the IG. The caregivers' QOL was unchanged, but their anxiety was reduced.

The results of this study agree with those of previous studies, that the MLHFQ scores decreased, indicating an improvement in QOL in patients with LVAD (Slaughter et al. 2009; Rogers et al. 2010). In Japan, Kato et al. (2015) reported that after LVAD implantation, QOL significantly improved (MLHFQ, mental and physical QOL of SF-8). The present study showed that social QOL and level of activity did not improve after LVAD implantation, suggesting that the social participation and activities of LVAD patients are limited. Under existing circumstances in Japan, LVAD in patients will not lead to an improvement in social

roles since patients need to be accompanied by their caregivers (mostly primary caregivers), who have learned how to manage the LVAD, because complications and mechanical malfunctions can occur. This potentially disturbs the work and leisure activities of patients with LVAD, even if their symptoms of heart failure have improved. In the present study, the proportion of non-workers aged < 65 years was high (59%), and even after returning to work, 17% of them were able to work for ≥ 30 hours per week. Considering that the number of patients with LVAD will increase in the future, it is necessary to improve the awareness and understanding of LVAD in the workplace and among the general public. It is desirable that social support systems be strengthened, such as going out with supporters and visiting nursing staff trained in the devices so that patients are not restricted in their activities with family members living with them.

A recent study showed that some patients experienced a poor global outcome (including death, poor QOL, recurrent heart failure, or severe stroke) after LVAD (Fendler et al. 2017). Our findings extend prior insights into poor global outcomes. Half of the UG patients had an LVAD-related stroke, including one patient with a history of cerebral hemorrhage and extracorporeal LVAD, compared to 0% in the IG. The breakdown of strokes was cerebral hemorrhage in three cases and cerebral infarction in three cases. Of the three cases of cerebral hemorrhage, two had a slightly high prothrombin time international standard ratio (PT-INR) of 3.4 and 3.7 before the onset of stroke, which may have caused the stroke, and one had a PT-INR of 2.55 before the onset of stroke, which was in the optimal range and was considered to be cerebral hemorrhage due to primary disease (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome; MELAS). All three cases of cerebral infarction were thought to have an embolic mechanism. In Japan, the prognosis of patients with an LVAD at 1 year is ≥ 90%, which is better than that reported overseas; however, it has been suggested that the incidence of neurologic dysfunction at 1 year after implantation is approximately 30%, which might be higher than the incidence overseas (Kirklin et al. 2017; Nakatani et al. 2017; de By et al. 2018). The risk factors for neurologic dysfunction in LVAD patients are multifactorial, including high mean arterial pressure, infection, device thrombotic treatment (Kislitsina et al. 2018), and no standard treatment to prevent neurologic dysfunction has been established. It has been reported that when neurologic dysfunction occurs, various functional impairments are associated with markedly low QOL (Baumann et al. 2014). Exercise therapy for chronic stroke survivors in the community, such as treadmill training, gait training, and leg muscle strengthening exercises, not only improved gait function (Ada et al. 2003), but also improved activity level and QOL (Teixeira-Salmela et al. 1999). Therefore, a physical activity and exercise program combining aerobic exercise with resistance exercise is recommended for stroke survivors (Billinger et al. 2014; Regan et al. 2019; Luo et al. 2020; Pogrebnoy and Dennett 2020). When stroke occurs in LVAD patients and results in decreased activity, ongoing community-based cardiac rehabilitation is necessary to manage complications and maintain activity levels.

The reason for the lack of improvement in QOL in the UG may be that many patients in the UG have worsening physical function due to progression of the primary disease or complications. In the UG, there were 6 patients with VAD-related strokes, 1 patient with worsening heart failure symptoms due to progression of muscular dystrophy, and 2 patients with nonocclusive mesenteric ischemia and subsequent colostomy.

The present study showed better QOL, anxiety, and depression before implantation in the UG than in the IG. Kitko et al. (2016) reported that the patients' perceived expectations of QOL improvement were not met after LVAD implantation. In the present study, the patients were asked to recall their pre-LVAD status along with their current status, so those whose QOL deteriorated after implantation may have responded better to the pre-LVAD status than they actually did because of recall bias. Before implantation, some patients lacked decisional capacity due to poor health, and therefore, it is important for medical staff to share information with patients who are expected to implant LVAD and their caregivers from an early stage, including changes in life and QOL due to complications.

The present study showed that the patients in the IG exhibited an improvement in the level of activity, QOL, and anxiety and depression after implantation; however, in the UG, there was no change in the level of activity, whereas QOL, anxiety, and depression did not improve. An improvement in the level of activity may contribute to QOL, anxiety, and depression. It has been reported that, compared to patients with severe heart failure, patients with LVAD have higher exercise tolerance and physical activity levels; however, the levels remain lower than those predicted by age, and do not improve to the same extent as in heart transplant patients (Jakovljevic et al. 2010; Kugler et al. 2011; Dunlay et al. 2014; Jung and Gustafsson 2015; Schmidt et al. 2018; Moreno-Suarez et al. 2020). It has been reported that cardiac rehabilitation significantly improves the QOL, muscle strength of the legs, and exercise tolerance in patients with LVAD, and it is important for LVAD patients to improve QOL, anxiety, and depression to maintain activity levels, continuing cardiac rehabilitation with appropriate load volume after discharge. At Tohoku University Hospital, physical therapists intervened in all cases after LVAD implantation as cardiac rehabilitation under the prescription of physicians. However, for patients whose activity level may decrease after discharge from the hospital, a system to continuously maintain physical activity levels is necessary, such as introduction of home rehabilitation.

A previous study of the caregiver of LVAD patients in Japan reported that LVAD implantation improves caregiv-

ers' mental QOL, but it is still lower than in the general population (Kato et al. 2018). In the present study, while there was no change before and after implantation in terms of the caregiver's physical, mental, and social QOL, and burden of care, there was an improvement in anxiety. Although LVAD implantation did not affect the caregivers enough to improve their QOL, it reduced their anxiety, which was likely attributed to the improvement in the patients' heart failure symptoms and improvement their QOL. In addition, in our hospital, the patients and caregivers can contact to the hospital staff at any time if something happens, and this was likely contributed to the reduction of caregivers' anxiety and maintenance of QOL.

In addition, the present study found that even for caregivers, who are the closest to the patients, the patients' QOL perceived by the caregivers did not always match the patients' perceptions. Previous studies on ventilator-assisted patients with Duchenne muscular dystrophy have reported that medical staff significantly underestimated patients' life satisfaction and overestimated patients' hardships associated with ventilator dependence (Bach et al. 1991). It should be noted that the patients' perception of QOL and the patients' QOL estimated by caregivers and medical staff may not be the same.

This study has some limitations. First, the small single-center sample limits the generalizability of the present findings. Second, since more strict rules have been applied to LVAD patients and their caregiver in our country than those in U.S.A., QOL in LVAD patients and caregiver burden should not be the same between these two countries. The burden of care unique to Japan needs to be examined. Third, the QOL before LVAD implantation was evaluated retrospectively, which involves a patient's recall bias and may not be accurate. Forth, since the preoperative QOL score is greatly influenced by the patients' preoperative condition, a more detailed assessment of the preoperative condition was needed. Fifth, there are no data on the caregivers of hospitalized patients, therefore, the changes in caregivers may not have been fully assessed. In addition, the incidence of neurological dysfunction has decreased in recent years due to improvements in devices. It is necessary to re-evaluate the results after several years and examine the results.

In conclusion, multi-dimensional analyses on the QOL in LVAD patients yielded mixed results. Anticipated benefits derived from LVAD therapy may be limited by LVAD-related complications such as stroke that negatively impacts on the QOL. It is essential to strengthen the social support system to improve the social roles and activities of patients after discharge.

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Conflict of Interest

The authors declare no conflict of interest.

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