ORIGINAL ARTICLE

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Is pectoralis muscle index a risk factor for mortality in left ventricular assist device patients?

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SUMMARY

OBJECTIVE: We aimed to investigate whether sarcopenia measured from pectoralis muscles is a risk factor for long-term mortality in left ventricular assist device patients.

METHODS: Patients aged >18 years implanted with a left ventricular assist device in a single center between 2013 and 2019 were retrospectively included. Patients without a thoracic computed tomography scan performed within 3 months of left ventricular assist device implantation and without computed tomography scans appropriate for pectoralis muscle measurement were excluded. Pectoralis muscle measurements were made on thoracic computed tomography slices, and pectoralis muscle indices were calculated for each patient. Sarcopenia was defined as being in the gender-specific lowest tertile of pectoralis muscle index. Survival was compared between patients with and without sarcopenia.

RESULTS: The study was conducted on 64 left ventricular assist device patients who met the inclusion criteria. Notably, 21 (32.8%) of the study patients were sarcopenic. Diabetes mellitus and sarcopenia were more common in patients with 2-year mortality in our cohort. Patients with sarcopenia had a worse 2-year survival (p<0.001). Sarcopenia had an adjusted hazard ratio of 4.04 (95% confidence interval (CI) 1.36–12.02, p=0.012), while diabetes mellitus was associated with an adjusted hazard ratio of 3.14 (95%CI 1.17–8.39, p=0.023).

CONCLUSION: Sarcopenia defined by low pectoralis muscle index increases the risk for 2-year mortality in left ventricular assist device patients.

KEYWORDS: Ventricular assist device. Sarcopenia. Heart failure. Survival.

INTRODUCTION

With the continuing shortage of heart donors, left ventricular assist devices (LVADs) are increasingly implanted for end-stage heart failure (HF) patients[1]. Appropriate patient selection and greater operative experience have resulted in up to 80% 1-year survival on LVADs[2]. While the operative risk of LVAD implantation is better understood, factors that influence long-term success are less elucidated.

Frailty is an age-related vulnerability that limits a patient's capacity against disease, injury, or a procedure. It is a significant prognostic factor for HF patients who face a greater risk of frailty due to cardiopulmonary failure and their coexisting comorbidities[3]. In LVAD patients, frailty negatively impacts long-term survival with a 1.11 to 3-fold increase in overall mortality[4-6]. Widely used risk scores in current use, such as the Heartmate 2 risk score, take demographic, echocardiographic, laboratory, and catheterization data into account but do not incorporate frailty[7].

Sarcopenia is one component of frailty that encompasses muscle strength and muscle quantity. Sarcopenia is more prevalent in HF patients than in healthy subjects in the same age group and impacts survival[8,9]. Low handgrip strength was associated with worse outcomes in HF patients implanted with an LVAD[10]. The definition of sarcopenia varies with many methods used in literature to measure sarcopenia, including muscle quantity, quality, and strength.

While other measurements of sarcopenia are valuable, in clinical practice, thoracic computed tomography (CT) is the most routinely performed preoperative assessment that can quantify sarcopenia in LVAD patients. This study aimed to investigate whether sarcopenia measured from pectoralis muscles is a risk factor for long-term mortality in LVAD patients.

METHODS

Approval was obtained from the institutional academic board (28001928.01.01) and the associated ethics committee (HNHEAH-KAEK 2021/264-3391) for this study. Patients aged >18 years implanted with an LVAD in a single center between 2013 and 2019 were retrospectively included. All operations

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were performed by a single, dedicated HF and transplant team. Patients implanted with a bridge-to-transplant indication or a bridge-to-destination indication were included. Patients without a thoracic CT scan performed <3 months of LVAD implantation and without CT scans appropriate for pectoralis muscle measurement were excluded. Patient demographics, laboratory results before surgery, echocardiographic data, and indication for transplant, survival data, and causes of death were recorded. The outcome of interest was 2-year survival.

Measurement of muscle mass

All CT images recorded as 3 mm slices with a Toshiba Aquilion 64 device were evaluated by a single radiologist experienced in cardiac and thoracic pathologies and blinded to the patient information. Pectoralis muscle measurements were made on a single axial slice immediately above the aortic arch using the Vitrea (Canon Medical Informatics, Minnesota, USA) postprocessing software. CT scans were performed with the upper extremities at full extension in the neutral position. Patients were excluded if scans were performed without arms at extension or if a defibrillator prevented measurement of the muscle quantity. Left and right pectoralis muscle areas were measured in cm^2 with the postprocessing software. The two areas were averaged and divided by the square of the patient's height in meters, standardizing a pectoralis muscle index (PMI) (cm^2/m^2) for each patient.

Definition of sarcopenia

Tertiles were calculated for PMI separately for female and male patients. Sarcopenia was defined as being in the gender-specific lowest tertile of PMI. Gender-specific tertile method is the most frequently used method for defining sarcopenia groups in the literature[11-13]. We grouped patients into two with patients in the lowest tertile as sarcopenic and in the mid and high tertiles as nonsarcopenic.

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY). Nominal variables are presented as numbers and percentages, and continuous variables are presented as mean and standard deviation. Groups were compared using the chi-squared test or Fisher's exact test for nominal variables, the Student's t-test for continuous variables with normal distribution, and the Mann-Whitney U test for continuous variables without normal distribution. Survival of patients with and without sarcopenia was analyzed using Kaplan-Meier curves, log-rank test, and Cox regression analysis. The level of statistical significance was set at $p<0.05$.

RESULTS

During the study period, 79 patients were implanted with an isolated LVAD. Three patients aged <18 years, eight patients without recent preoperative CTs, and four patients whose CTs were not suitable for pectoralis muscle measurement were excluded. The study was conducted on 64 LVAD patients.

The mean age of the study patients was 50.2±8.7 years, and 9 (14.9%) were female. Notably, 21 (32.8%) of our LVAD patients were sarcopenic. Sarcopenic LVAD patients were less likely to have hyperlipidemia (4.8% vs. 30.2%, p=0.021) and had higher bilirubin (2.43±4.68 vs. 1.42±3.2, p=0.012) and lower blood urea nitrogen levels (21.7±10.9 vs. 26.2±11.9, p=0.044). Other baseline characteristics were similar between sarcopenic and nonsarcopenic patients.

Overall, 1-year mortality was 26.6% and 2-year mortality was 34.4%. The causes of death for the 22 patients with 2-year mortality were cerebrovascular events for 10 patients, right HF for 5 patients, infectious causes for 3 patients, pump thrombosis for 2 patients, mesenteric ischemia for 1 patient, and acute graft failure after heart transplant for 1 patient. At univariate analysis, diabetes mellitus and sarcopenia were associated with 2-year mortality in our cohort. Male and female patients with 2-year mortality had lower pectoralis muscle indices. Other baseline parameters or type of implanted device did not differ in patients with and without mortality (Table 1).

The effect of sarcopenia on 2-year mortality was assessed. The Kaplan-Meier curves were plotted for patients with and without sarcopenia (Figure 1). The 2-year mortality was 25.6% for nonsarcopenic patients and 52.4% for sarcopenic patients. The survival distributions for the two groups were significantly different (p<0.001). A Cox regression model was created with parameters significant at univariate analysis and Interagency Registry for Mechanically Assisted Circulatory Support profile to assess the effect of sarcopenia on 2-year mortality. The results of the analysis are given in Table 2. Sarcopenia had an adjusted hazard ratio (HR) of 4.04 (95% confidence interval (CI) 1.36–12.02, p=0.012), while diabetes mellitus was associated with an HR of 3.14 (95%CI 1.17–8.39, p=0.023). The model with PMI instead of sarcopenia showed an increase of 1 unit in PMI to be protective with an HR of 0.379. (95%CI 0.214–9.670, p=0.001).

DISCUSSION

Our study demonstrated that sarcopenia measured by PMI is a useful risk factor for long-term mortality in LVAD patients. PMI can be readily measured from CT images routinely captured during preoperative assessment of LVAD patients and be used to assess long-term mortality in LVAD patients.

Table 1. Baseline factors in patients with and without 2-year mortality.

	2-Year Mortality (-) (n=42)	2-Year Mortality (+) (n=22)	p-value
Age	51.4±8.1	47.9±9.5	0.165
Female Gender (%)	5 (11.9)	4 (18.2)	0.480
Body Mass Index (kg/m^2)	26.84±4.76	26.77±4.53	0.972
Diabetes Mellitus (%)	10 (23.8)	11 (50.0)	**0.034**
Hypertension (%)	14 (33.3)	6 (27.3)	0.619
Hyperlipidemia (%)	9 (21.4)	5 (22.7)	1.000
Creatinine (mg/dL)	1.05±0.39	1.18±0.41	0.157
Pro-BNP (pg/mL)	1069.4±1028.8	1065.5±1074.0	0.966
Albumin (g/dL)	3.56±0.69	3.37±1.06	0.904
Bilirubin (mg/dL)	1.10±0.64	2.98±6.24	0.511
INR	1.32±0.37	1.29±0.35	0.955
Na (mEq/L)	136.4±4.3	135.5±2.8	0.352
K (mEq/L)	4.2±0.5	4.2±0.6	0.659
BUN (mg/dL)	25.2±12.0	23.8±11.2	0.821
Platelet (1000/μL)	219.0±68.9	222.5±83.6	0.858
Hemoglobin (g/dL)	12.6±3.8	11.6±2.3	0.392
ALT (IU/L)	29.4±20.5	22.1±13.6	0.211
AST (IU/L)	25.2±11.9	25.8±19.2	0.772
PVR (Wood)	2.97±1.26	3.24±1.39	0.327
TAPSE	16.6±3.2	16.9±4.4	0.837
Aortic Insufficiency			
None (%)	35 (83.3)	20 (90.9)	0.707
Mild (%)	7 (16.7)	2 (9.1)	
Previous Sternotomy (%)	1 (2.4)	1 (4.5)	1.000
Etiology			
Dilated CMP (%)	23 (54.8)	9 (40.9)	0.292
Ischemic CMP (%)	19 (45.2)	13 (59.1)	
Indication			
BTT (%)	10 (23.8)	9 (40.9)	0.155
Destination (%)	32 (76.2)	13 (59.1)	
Sarcopenia (%)	11 (25.6)	11 (52.4)	**0.034**
Pectoralis Index (cm^2/m^2)			
Men	4.62±1.26	4.05±0.68	**0.033**
Women	4.84±1.29	2.85±0.59	**0.026**
INTERMACS			
1 (%)	4 (9.5)	1 (4.5)	0.518
2 (%)	2 (4.8)	2 (9.1)	
3 (%)	15 (35.7)	4 (18.2)	
4 (%)	18 (42.9)	13 (59.1)	
5 (%)	3 (7.1)	2 (9.1)	
Implanted Device			
Heartware (%)	8 (19.0)	7 (31.8)	0.576
Heartmate 2 (%)	18 (42.9)	7 (31.8)	
Heartmate 3 (%)	15 (35.7)	8 (36.4)	
Heart Asist 5 (%)	1 (2.4)	0 (0)	

Pro-BNP: pro-brain natriuretic peptide; INR: international normalized ratio; BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase pulmonary vascular resistance; TAPSE: tricuspid annular plane systolic excursion; CMP: cardiomyopathy; BTT: bridge to transplant. Numbers in bold emphasize statistical significance.

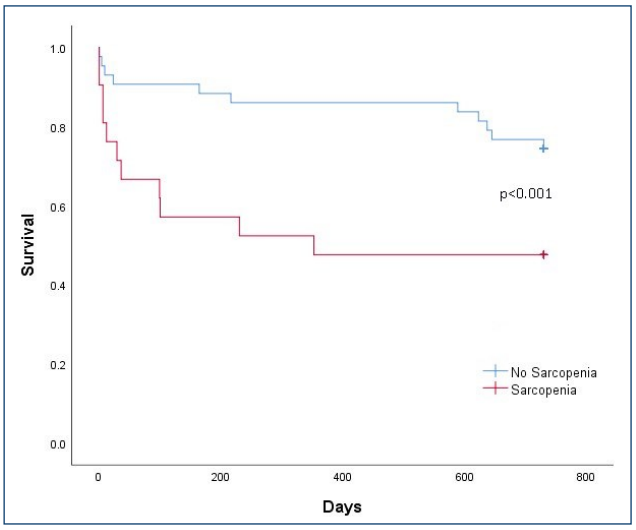

Figure 1. Kaplan-Meier curves of LVADs patients with and without sarcopenia

Table 2. Cox regression model for 2-year mortality.

		Hazard Ratio (95%CI)
Sarcopenia	**0.012**	4.041 (1.358–12.020)
Diabetes Mellitus	**0.023**	3.136 (1.172–8.393)
INTERMACS		
1	0.943	0.914 (0.075–11.058)
2	0.195	3.997 (0.491–32.517)
3	0.462	0.526 (0.095–2.915)
4	0.815	1.200 (0.261–5.527)
5 (reference)	0.314	
Bilirubin	0.490	1.033 (0.942–1.134)
Hyperlipidemia	0.645	1.327 (0.398–4.425)
Blood Urea Nitrogen	0.755	1.007 (0.962–1.055)

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support. The significant p values are given in bold.

There are several risk scores valuable in assessing operative risk in LVAD patients. These scores have their own shortcomings, such as the destination therapy score being developed before the era of continuous flow assist devices and the Heartmate 2 score lacking external validity[14]. These scores serve to identify operative risk but fall short of identifying patients who can benefit from LVAD therapy in the long term[15]. Other risk models have been developed for long-term mortality after LVAD implantation. The Penn-Columbia risk score considers age, creatinine, bilirubin, body mass index (BMI), right ventricular dysfunction, and aortic insufficiency for 1-year survival[16]. Similarly, other risk models for 1-year mortality have found age, renal function, low hemoglobin, and destination therapy, besides several other hemodynamic and patient factors, to be predictive of 1- and 2-year survival[17,18]. No current model for LVAD survival has incorporated frailty or sarcopenia. A major reason for this is that this patient group is not able to perform frailty tests that can comprehensively evaluate sarcopenia. Radiological measurements of muscle quantity or quality can be better suited for this patient population.

Sarcopenia is used as a marker of biological aging and has been shown to have prognostic value in HF[19]. Myofibrillar wasting in the skeletal muscles exacerbates exercise intolerance and ventilatory insufficiency, lowering the patient's overall functional status, which can explain the association with surgical and long-term mortality in LVAD patients with lowered muscle mass[20]. It is speculated that as the patient's HF contributes to frailty, successful LVAD therapy may revert a component of the patient's frail status[21]. One study has shown frailty in LVAD patients to be reversible to a certain extent, and higher quality of life and a better baseline glomerular filtration rate were associated with improved frailty scores[22]. Data on postoperative PMI were not available for our study patients, and future studies with muscle quality and quantity measures after long-term LVAD therapy can provide more information on the reversibility of sarcopenia with LVADs and the benefits of interventions on sarcopenia before surgery on survival.

Definitions of sarcopenia vary and include physical performance (gait speed), muscle strength, muscle quality (fat infiltration), or muscle quantity[9]. PMI is readily available in most LVAD patients, and most patients are unable to complete performance-based frailty tests, which in itself is associated with worse HF and worse long-term LVAD outcomes[23]. A high BMI can mask muscle wasting or early muscle changes that precede cardiac cachexia, and radiological measurements are more valuable in the precise detection of early sarcopenia[24]. Muscle quantity measurements can aptly capture the risk in this patient group that is too ill to perform frailty tests and have prognostic value. Pectoralis muscle quantity was found to be a stronger indicator of mortality than other traditional risk factors[25]. In our study patients, sarcopenia and diabetes affected long-term survival, and sarcopenia was the factor with the highest HR.

There are certain limitations to our study. The study design is single center and retrospective. The outcome of interest was all-cause mortality, and conclusions cannot be generalized to specific causes of mortality. Different definitions of sarcopenia can make external validation difficult; however, we have categorized our patients with the lowest tertile definition that is frequently used in the literature. While all implanted devices

are continuous flow LVADs, four different devices were used in our institution during the study period.

CONCLUSION

Sarcopenia, defined by low PMI, increases the risk for 2-year mortality in LVAD patients. Methods that best quantify sarcopenia in end-stage HF patients should be studied, as well as the benefits of preoperative reversal of sarcopenia.

AUTHORS' CONTRIBUTION

SBE: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. **HB:** Data curation, Investigation, Methodology, Writing – original draft. **MB**: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **MS:** Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **ŞA:** Conceptualization, Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing.

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