ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 732–737
Published online 11 October 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14195

SHORT COMMUNICATION

Prognostic impact of upper and lower extremity muscle mass in heart failure

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Abstract

Aims Reduced skeletal muscle mass is a major component of sarcopenia, associated with impaired exercise capacity and poor prognosis in patients with heart failure (HF). Measurement of skeletal muscle mass by dual-energy X-ray absorptiometry may be affected by fluid retention, typically in the patients' lower extremities. The aim of the present study was to elucidate the association between upper and lower extremity skeletal muscle mass (USM and LSM) and all-cause mortality in hospitalized patients with HF, after discharge.

Methods This was a single-centre observational cohort study of 418 patients (59% were men) admitted with a diagnosis of HF (71 ± 13 years), with a left ventricular ejection fraction of 39 ± 16%. USM and LSM were measured by dual-energy X-ray absorptiometry with patients in a stable state after decongestion therapy.

Results The USM and LSM were 5.29 ± 1.18 and 13.78 ± 3.20 kg for men and 3.37 ± 0.68 and 9.19 ± 1.80 kg for women. A positive correlation was obtained between USM and LSM with mid-upper arm circumference (r = 0.684, $P < 0.001$) and calf circumference (r = 0.822, $P < 0.001$), respectively. During a median follow-up of 37 months, 92 (22.0%) of the 418 patients died. A Kaplan–Meier analysis revealed that sex-specific quartiles of USM/height^2 and LSM/height^2 were associated with all-cause mortality (both $P < 0.001$ by the log-rank test). In Cox models adjusted by age, sex, creatinine, haemoglobin, NYHA class, and height^2, the hazard ratio with 95% confidence intervals for all-cause mortality was 0.557 [0.393–0.783] ($P < 0.001$) for USM per 1 kg, and 0.783 [0.689–0.891] ($P < 0.001$) for LSM per 1 kg. The receiver-operator-characteristic curve analysis showed a comparable area under the curve between the USM/height^2 and LSM/height^2 (0.557 vs. 0.568, P = 0.562) in predicting all-cause mortality. The ratio of USM to LSM was significantly lower in 37 patients with residual leg oedema than in the 360 patients without oedema (36.1% vs. 38.1%, P = 0.004), suggesting the influence of oedema on measured LSM.

Conclusions Both USM and LSM had a prognostic implication on mortality after discharge in HF, even though LSM may have been affected by leg oedema. These findings indicate that clinicians should not ignore a patient's USM or LSM in the prognostication of patients with HF.

Keywords Skeletal muscle; Sarcopenia; Heart failure

Received: 22 February 2022; Revised: 10 September 2022; Accepted: 2 October 2022
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Background

Abnormalities in the quantity and quality of skeletal muscle have been discussed with regard to sarcopenia, cachexia, frailty, and malnutrition and are closely related to impaired exercise tolerance and poor outcomes in patients with heart failure (HF).[1–5] Measurement of skeletal muscle mass by dual-energy X-ray absorptiometry (DXA) can be affected by

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fluid retention,[6] typically in patients' lower extremities.[7] However, no previous reports have examined the prognostic implications of upper and lower extremity skeletal muscle mass (USM and LSM) separately.

Aims

We hypothesized that both USM and LSM have a prognostic impact in HF. The purpose of the present study was to elucidate the association between upper/lower skeletal muscle mass and all-cause mortality in hospitalized patients with HF, after discharge.

Methods

We retrospectively analysed data in a single-centre observational cohort study of patients with HF.[2] The detailed study design has been described elsewhere.[2] Briefly, the inclusion criteria were patients with a diagnosis of HF based on Framingham criteria[7] and those who had undergone DXA during hospitalization. The exclusion criteria were patients with incomplete data (n = 1) and who died during hospitalization (n = 3). Informed consent was obtained from each patient. Our institutional ethics board approved the study, which was in line with ethical standards laid down in the 1964 Declaration of Helsinki. Blood examinations were performed at discharge. Echocardiography was performed during

Table 1 Characteristics of patients according to sex

	Missing data	All	Male	Female
N		418	247	171
Age (years)	0	71 (13)	68 (14)	76 (10)
Body mass index (kg/m^2)	0	22.1 (4.6)	22.6 (4.5)	21.6 (4.6)
Readmission	0	27.8%	27.1%	28.7%
Co-morbidity				
Hypertension	0	75.1%	76.5%	73.1%
Diabetes	0	36.6%	37.3%	35.7%
Coronary artery disease	0	39.0%	43.7%	32.2%
Atrial fibrillation	0	35.4%	32.8%	39.2%
Severe valvular disease	0	32.8%	29.2%	38.0%
COPD	0	5.3%	7.7%	1.8%
Stroke	0	8.6%	9.3%	7.6%
Malignancy	0	8.9%	9.7%	7.6%
Status at discharge				
NYHA class	0			
≤2		83.7%	88.7%	76.6%
3		15.8%	10.5%	23.4%
4		0.5%	0.8%	0.0%
Systolic blood pressure (mmHg)	1	110 (17)	111 (18)	110 (17)
Laboratory findings at discharge				
Haemoglobin (g/dL)	0	12.0 (2.2)	12.5 (2.2)	11.3 (2.0)
Creatinine (mg/dL)	0	1.39 (1.04)	1.50 (1.14)	1.24 (0.84)
Estimated GFR (mL/min/1.73 m^2)	0	46 (19)	48 (19)	42 (17)
Albumin (g/dL)	1	3.62 (0.53)	3.65 (0.54)	3.57 (0.51)
BNP, median (pg/mL)	0	240 [132–417]	230 [116–408]	247 [149–460]
Medication at discharge				
Beta-blocker	1	72.7%	76.9%	66.5%
ACE inhibitor/ARB	0	81.8%	85.4%	76.6%
Loop diuretics	0	78.7%	76.5%	81.9%
MRA	0	59.6%	61.5%	56.7%
LVEF (%)	0	39 (16)	37 (16)	43 (16)
HFrEF		53.8%	59.5%	45.6%
HFmrEF		15.6%	17.0%	13.5%
HFpEF		30.6%	23.5%	40.9%
Body composition	0			
ASM/height^2 (kg/m^2)		6.35 (1.28)	6.88 (1.23)	5.59 (0.92)
USM (kg)		4.51 (1.38)	5.29 (1.18)	3.37 (0.68)
USM/height^2 (kg/m^2)		1.74 (0.37)	1.91 (0.34)	1.50 (0.27)
LSM (kg)		11.90 (3.54)	13.78 (3.20)	9.19 (1.80)
LSM/height^2 (kg/m^2)		4.61 (0.95)	4.97 (0.93)	4.09 (0.69)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASM, appendicular skeletal muscle mass; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LSM, lower extremity skeletal muscle mass; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; USM, upper extremity skeletal muscle mass.
Values presented as frequency (%), mean (standard deviation), or median [interquartile range].

DOI: 10.1002/ehf2.14195

Table 2 Characteristics of patients according to upper/lower extremity skeletal muscle mass by sex-specific medians

			USM/height^2			LSM/height^2		
	Missing data	All	Below median	Above median	*P*	Below median	Above median	*P*
N		418	208	210		208	210	
Age (years)	0	71 (13)	74 (10)	68 (14)	<0.001	74 (10)	68 (14)	<0.001
Body mass index (kg/m^2)	0	22.1 (4.6)	19.6 (2.7)	24.6 (4.7)	<0.001	19.6 (2.8)	24.7 (4.6)	<0.001
Readmission	0	27.8%	28.4%	27.1%	0.827	29.8%	25.7%	0.383
Co-morbidity								
Hypertension	0	75.1%	69.7%	80.5%	0.013	70.2%	80.0%	0.024
Diabetes	0	36.6%	30.3%	42.9%	0.008	35.1%	38.1%	0.544
Coronary artery disease	0	39.0%	37.5%	40.5%	0.549	39.9%	38.1%	0.764
Atrial fibrillation	0	35.4%	39.4%	31.4%	0.102	35.1%	35.7%	0.919
Severe valvular disease	0	32.8%	37.5%	28.1%	0.048	35.1%	30.5%	0.349
COPD	0	5.3%	6.3%	4.3%	0.390	5.8%	4.8%	0.668
Stroke	0	8.6%	11.1%	6.2%	0.083	10.1%	7.1%	0.300
Malignancy	0	8.9%	11.5%	6.2%	0.060	12.5%	5.2%	0.010
Status at discharge								
NYHA class	0				0.011			0.011
≤2		83.7%	78.9%	88.6%		78.9%	88.6%	
3		15.8%	20.2%	11.4%		20.2%	11.4%	
4		0.5%	1.0%	0.0%		1.0%	0.0%	
Systolic blood pressure (mmHg)	1	110 (17)	108 (18)	113 (17)	0.001	108 (18)	112 (16)	0.013
Laboratory findings at discharge								
Haemoglobin (g/dL)	0	12.0 (2.2)	11.6 (2.0)	12.3 (2.3)	0.001	11.7 (2.1)	12.3 (2.3)	0.002
Creatinine (mg/dL)	0	1.39 (1.04)	1.39 (0.87)	1.40 (1.18)	0.944	1.32 (0.69)	1.46 (1.29)	0.172
Estimated GFR (mL/min/1.73 m^2)	0	46 (19)	44 (17)	47 (20)	0.048	45 (18)	46 (19)	0.512
Albumin (g/dL)	1	3.62 (0.53)	3.60 (0.50)	3.64 (0.55)	0.385	3.55 (0.49)	3.69 (0.56)	0.007
BNP, median (pg/mL)	0	240 [132–417]	277 [162–506]	212 [103–365]	<0.001	277 [153–510]	213 [112–366]	<0.001
Medication at discharge								
Beta-blocker	1	72.7%	71.2%	74.2%	0.511	73.6%	71.8%	0.742
ACE inhibitor/ARB	0	81.8%	76.4%	87.1%	0.005	77.4%	86.2%	0.023
Loop diuretics	0	78.7%	78.9%	78.6%	1.000	80.8%	76.7%	0.340
MRA	0	59.6%	60.1%	59.1%	0.843	61.5%	57.6%	0.427
LVEF (%)	0	39 (16)	39 (16)	40 (16)	0.615	37 (16)	41 (17)	0.024
HFrEF		53.8%	54.8%	52.9%	0.716	58.2%	49.5%	0.109
HFmrEF		15.6%	16.4%	14.8%		15.9%	15.2%	
HFpEF		30.6%	28.9%	32.4%		26.0%	35.2%	

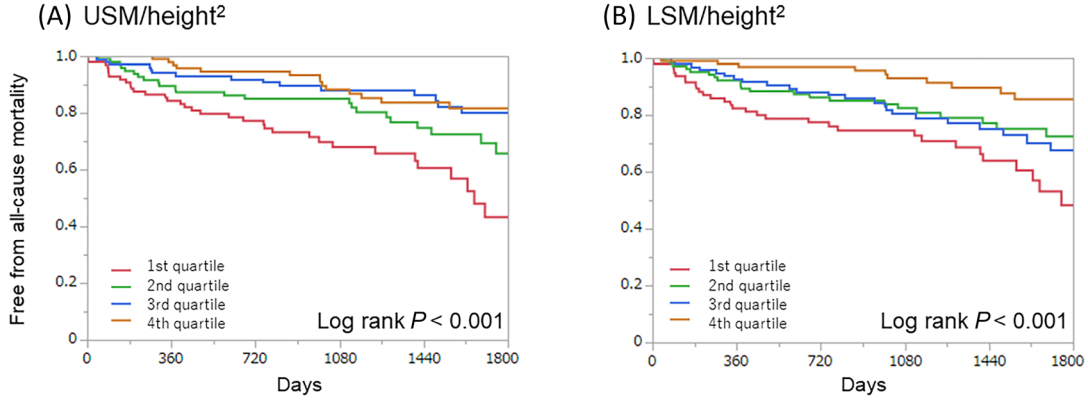
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASM, appendicular skeletal muscle mass; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LSM, lower extremity skeletal muscle mass; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; USM, upper extremity skeletal muscle mass.
Values presented as frequency (%), mean (standard deviation), or median [interquartile range].

hospitalization. Measurement of muscle mass was performed using a DXA scan (Discovery, Hologic Japan Inc., Tokyo, Japan) with patients in a stable state after decongestion therapy. USM and LSM were defined as the sum of muscle mass in the upper and lower extremities, respectively. Data regarding the presence or absence of leg oedema and mortality after discharge were obtained from a review of the medical records of the hospital and form information sent from the referring hospital/clinic. The Student's *t*-test or Mann–Whitney test for continuous variables and $\chi 2$ tests or Fisher's exact test for categorical variables were employed for comparing the groups, as appropriate. A Pearson coefficient was calculated between the two continuous variables. Multivariate linear regression analysis with the ratio of upper to lower extremity muscle mass as a dependent variable was performed. The Kaplan–Meier time-to-event curves using the log-rank test were computed according to muscle mass. Cox proportional hazards models were adjusted by the same prognostic factors in HF as in the main study[2] (i.e. age, sex, creatinine, haemoglobin, NHYA class, and height squared) to investigate the association between muscle mass and all-cause mortality. To compare the association with all-cause mortality, receiver-operator-characteristic curve analysis was performed, and the area under the curve was assessed using DeLong's method. All statistical tests were two-tailed, and a P value < 0.05 was considered statistically significant. Analyses were carried out using JMP Pro software 16 (SAS Institute Japan Inc., Tokyo, Japan).

Results

The study cohort consisted of 418 patients with 59.1% males, and the mean age was 71 ± 13 years. The baseline characteristics of the study population and the results from DXA are shown separately by sex and higher/lower USM and LSM using sex-specific medians in *Tables 1 and 2*. The median length of stay was 18 days (interquartile range, 14–27), and patients underwent DXA a median of 6 days (interquartile range, 1–12) before discharge. USM and LSM were 5.29 ± 1.18 and 13.78 ± 3.20 kg for men and 3.37 ± 0.68 and 9.19 ± 1.80 kg for women. Mid-upper arm and calf circumference was measured after November 2016 in 44 patients, showing a positive correlation to USM (r = 0.684, $P < 0.001$) and LSM (r = 0.822, $P < 0.001$), respectively. The ratio of USM to LSM was 38.0% in the overall cohort. At discharge, leg oedema remained in 37 of the 397 (9.3%) patients and was not documented in 21 patients. The ratio of USM to LSM was significantly lower in patients with residual leg oedema than in those with no oedema at discharge (36.1 vs. 38.1%, $P = 0.004$). In the multivariate linear regression analysis, the presence of residual leg oedema was associated with a lower ratio of USM to LSM after adjustment for age and sex (standardized beta = −0.112, $P = 0.025$). During the median follow-up of 37.0 months, 92 (22.0%) patients died. In the Kaplan–Meier analysis, there was a significant difference in all-cause mortality among the sex-specific quartiles of USM and LSM indexed by height squared (both $P < 0.001$;

Figure 1 Kaplan–Meier estimates of the cumulative incidence of all-cause mortality according to quartiles of USM/height^2 and LSM/height^2. Kaplan–Meier curve according to quartiles of USM/height^2 (A) and LSM/height^2 (B) for all-cause mortality. LSM, lower extremity skeletal muscle mass; USM, upper extremity skeletal muscle mass.



Survival					
1st quartile		84.3%	77.2%	68.0%	60.6%
2nd quartile		89.5%	85.1%	85.1%	74.7%
3rd quartile		94.2%	92.1%	88.3%	86.3%
4th quartile		97.9%	94.7%	88.3%	83.7%
At Risk					
1st quartile	104	77	59	36	22
2nd quartile	104	85	74	58	37
3rd quartile	108	96	80	61	45
4th quartile	102	93	80	66	48

Survival					
1st quartile		82.4%	77.4%	74.5%	63.9%
2nd quartile		92.3%	86.2%	82.4%	77.1%
3rd quartile		92.8%	88.3%	80.5%	75.3%
4th quartile		98.0%	97.0%	93.0%	89.6%
At Risk					
1st quartile	101	71	58	42	25
2nd quartile	107	96	77	59	41
3rd quartile	106	88	76	56	39
4th quartile	104	96	82	64	48

Figure 1). In the multivariate Cox models, the hazard ratio for all-cause mortality was 0.557 [0.393–0.783] ($P < 0.001$) for 1 kg increase of USM and 0.783 [0.689–0.891] ($P < 0.001$) for 1 kg increase of LSM. The receiver-operator-characteristic curve analysis showed a comparable area under the curve between USM/height^2 and LSM/height^2 (0.557 vs. 0.568, $P = 0.562$) in predicting all-cause mortality.

Conclusions

The principal findings of the study were as follows: (i) Both USM and LSM were associated with all-cause mortality in the Kaplan–Meier analyses; (ii) multivariate analysis revealed that both USM and LSM were associated with all-cause mortality even after adjustment for multiple known prognostic factors in HF; and (iii) LSM was relatively higher than USM in patients with residual leg oedema.

The mechanisms associated with muscle mass and mortality have already been discussed in our previous study,[2] some of which (i.e. a beneficial 'myokine' or a good cardiorespiratory fitness in patients with a large muscle mass) may be common to USM and LSM. Given a potential benefit from adding upper extremity muscle interventions to lower extremity muscle interventions,[8] it may be meaningful to assess upper and lower extremity muscle masses separately. The difference in the radio of USM to LSM in patients with and without residual leg oedema may be indirect evidence that the LSM measured by DXA was overestimated due to fluid retention in the lower extremities. In patients with cirrhosis, USM is a better prognostic marker than appendicular skeletal muscle mass.[9] There are some limitations to this research, including a retrospective observational study design that may lead to sampling bias and a lack of data regarding muscle function, which is a major component of a diagnosis of sarcopenia.[10]

In conclusion, this study showed that in hospitalized patients with HF, both USM and LSM were associated with all-cause mortality after discharge. These findings are a caution that clinicians should not ignore a patient's USM or LSM in the prognostication of patients with HF.

Conflict of interest

K. Tamura has received lecture fees from Daiichi-Sankyo, Mochida, Kyowa-hakko Kirin, Pfizer, Boehringer Ingelheim Japan, and Dainippon-Sumitomo. His institution has received a research grant from Daiichi-Sankyo, Takeda, Mochida, Kyowa-hakko Kirin, Pfizer, Novartis, Dainippon-Sumitomo, AstraZeneca, Ono Pharmaceutical, Tsumura, Kaneka, and Oriental Yeast. K. Kimura has received lecture fees from Astrazeneca, Toa Eiyo Ltd., MSD, Bayer, and Daiichi-Sankyo. His institution has received a research grant from MSD, Daiichi-Sankyo, Ono Pharmaceutical, Phizer, Bayer, Takeda, Boehringer Ingelheim Japan, Tanabe Mitsubishi, and Astellas Pharma. Masaaki Konishi, Eiichi Akiyama, Yasushi Matsuzawa, Ryosuke Sato, Shinnosuke Kikuchi, Hidefumi Nakahashi, Kozo Okada, Noriaki Iwahashi, Masami Kosuge, Toshiaki Ebina, Kiyoshi Hibi, and Toshihiro Misumi declare that they have no conflicts of interest.

Funding

This study was supported by the Grant-in-Aid for Young Scientist (B) 19K16986 (M.K.).

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