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Interaction of Skeletal and Left Ventricular Mass in Older Adults with Low Muscle Performance

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Interaction of Skeletal and Left Ventricular Mass in older adults with low muscle performance

Running Title: Left ventricular mass and Sarcopenia

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IMPACT STATEMENT

Older patients with low skeletal muscle mass and physical performance are unique population at high risk of cardiovascular events. We demonstrated for the first time, in this specific population with low

multimorbidity, that left ventricular muscle mass and skeletal muscle mass were positively correlated independently of cardiac output, haemoglobin and body mass index. These findings underline the future need of evaluating and monitoring in parallel left ventricular mass and skeletal muscle mass after proactive interventions including nutrition counseling and resistance exercise. We certify that this work is confirmatory of recent novel clinical research. (Keng et al, JAGS 2019;67:2568-2573).

For Review Only

ABSTRACT

BACKGROUND: It was recently hypothesized the existence of “cardiac-skeletal muscle axis”. However, the relationship between skeletal muscle mass (SMM) and left ventricular mass (LVM) has never been investigated in the specific group of older individuals with low skeletal mass and physical performance.

We tested this hypothesis in the SPRINT-T (Sarcopenia and Physical Frailty IN older people: multicomponent Treatment strategies Trial) population using LVM as independent variable and SMM as dependent variable.

METHODS: SMM was assessed by DEXA-scan and expressed as Appendicular Muscle Mass (ALM), LVM was estimated through echocardiography. Low ALM was defined according to Foundation for the National Institutes of Health Sarcopenia Project (FNIH) criteria, and Short Physical Performance Battery (SPPB) was used to assess physical performance.

RESULTS: The population consisted of 100 persons (33 men and 67 women), aged ≥ 70 years (mean age 79 ± 5) with low ALM and SPPB ranged between 3 and 9 suggestive of physical frailty. Charlson Comorbidity Index median score was 0. Mean values of LVM were 193 ± 67 (g), indexed LVM to body surface area (LVM/BSA) 112 ± 33 (g/m²), and Cardiac Output (CO) 65 ± 19 (l/min). ALM was strongly and positively correlated with LVM ($r=0.54602$, $p<.0001$), LVM/BSA ($r=0.30761$, $p<0.002$), CO ($r=0.49621$, $p<.0001$), BMI ($r=0.52461$, $p<.0001$), sex ($r=0.77$, $p<0.001$), fat mass ($r=0.38977$, $p<0.0001$) and Hb ($r=0.26001$, $p<0.01$). In the multivariate analysis, LVM (β 0.019 ± 0.005 ; $p<0.0001$), CO (β 0.038 ± 0.016 ; $p=0.019$), BMI (β 0.286 ± 0.051 ; $p<0.0001$) and Hb (β 0.544 ± 0.175 ; $p=0.0025$) remained associated to ALM.

CONCLUSIONS: In a sample of older persons with low muscle mass and physical performance, LVM was positively and significantly correlated with ALM, independently from blood pressure, physical activity, and other potential confounders. Future studies are needed to address the effect of interventions targeting LVM and SMM.

Key words: skeletal muscle mass; left ventricular mass; low physical performance; SPRINTT study.

For Review Only

INTRODUCTION

Sarcopenia is considered a primarily age-dependent condition, frequently overlapped with physical frailty,¹ a geriatric syndrome characterized by reduced homeostatic reserve. Both these conditions expose the subject to an increased risk of adverse events, including impaired physical function and disability.²

Changes in skeletal muscle mass (SMM) have been associated with cardiovascular diseases.³⁻⁶ In particular, in patients with heart failure, either with reduced or preserved ejection fraction, a loss of SMM contributes to the onset of fatigue and exercise intolerance. Observational studies have also evaluated the relationship between frailty and cardiac function and cardiovascular diseases.⁷⁻¹⁰ Patients with physical frailty have a higher prevalence of cardiovascular diseases such as myocardial infarction, angina, and congestive heart failure than well-performing patients.¹⁰ Furthermore, in those patients without a history of cardiovascular disease, frailty was associated with subclinical heart disease i.e., left ventricular hypertrophy (LVH), which is considered a form of preclinical organ damage associated with systolic and diastolic dysfunction.⁷⁻⁹

Moreover, it has been demonstrated that, after bed rest or inactivity - well-known risk factors for sarcopenia and physical impairment - cardiac atrophy occurs in both men and women suggesting a common regulation of heart and muscle mass.¹¹⁻¹³

All these data suggest the utmost important interaction of sarcopenia with cardiac mass during aging. The existence of *cardiac- muscle axis* has been recently hypothesized in older Singapore subjects where a positive and significant relationship was found between skeletal and cardiac ventricular mass.¹⁴ Additionally, although low skeletal muscle mass is considered the other side of the coin, physical impairment,² the combination of these conditions is not routinely assessed during daily clinical practice. Given the unique opportunity to assess a selected cohort of participants enrolled because of low ALM and score of SPPB in the range between 3 and 9 (proxy of physical frailty), we explored the relationship between LVM (independent variable) and SMM (dependent variable) in a group of individuals with these characteristics.

METHODS

Data are from an ancillary study of the Sarcopenia and Physical Frailty IN older people: multi-component Treatment strategies (SPRINT-T) project,¹⁵ a randomized control trial conducted in frail, sarcopenic older subjects aged 70 years and older, to demonstrate the effectiveness of a multicomponent (MCI) intervention based on physical activity, nutritional and technological intervention versus a healthy aging lifestyle education (HALE) program for the prevention of mobility disability.

Inclusion and Exclusion criteria for the Study were detailed elsewhere:¹⁶

- Men and women aged ≥ 70 years;
- SPPB score between 3 (included) and 9 (included);
- Ability to complete the 400-m walk test within 15 min without sitting down, help from another person, use of a walker, or stopping for more than 1 minute at a time;
- Presence of low muscle mass according to results from a Dual Energy X-Ray Absorptiometry (DEXA) scan. In agreement with the FNIIH report 32, low muscle mass will be defined as: Body mass index-adjusted appendicular lean mass (ALM; i.e., the sum of lean mass from both arms and legs): <0.789 in men, and <0.512 in women, OR ii. ALM <19.75 kg in men and <15.02 kg in women;
- Willingness to be randomised to either intervention group and to follow the study protocol.

Exclusion criteria:

- Unable or unwilling to provide informed consent or accept randomisation to either study group;
- Plans to relocate out of the study area within the next 2 years or plans to be out of the study area for more than 6 consecutive weeks in the next year;
- Residence in long-term care;
- Household member enrolled in the study;

- Current diagnosis of schizophrenia, other psychotic or bipolar disorder. Depression is not an exclusion criterion;
- Consumption of more than 14 alcoholic drinks per week;
- Difficulty communicating with the study personnel due to speech, language, or (noncorrected) hearing problems;
- Mini Mental State Examination (MMSE) lower than 24/30;
- Severe osteoarthritis (e.g., awaiting joint replacement) that would interfere with the ability to participate fully in either study arm;
- Cancer requiring treatment in the past 3 years, except for non-melanoma skin cancers or cancers that have an excellent prognosis (e.g., early stage breast or prostate cancer);
- Lung disease requiring regular use of supplemental oxygen;
- Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents;
- Severe cardiovascular disease (including New York Heart Association [NYHA] class III or IV. The investigators of the Parma SPRINT-T¹⁵⁻¹⁶ site added, at the enrolment of participants, a complete cardiac assessment including clinical evaluation with 12-lead resting Electrocardiogram (ECG) and conventional and Doppler Tissue Echocardiographic (DTE) examination as part of the ancillary protocol to the enrolment of participants.

This ancillary study was submitted to SPRINT-T Scientific Committee and accepted by the Managing Entity, and subsequently approved by AVEN Local ethics committee (*Protocol n.10872*). Written informed consent was obtained from the participants.

One hundred subjects from those enrolled in the SPRINT-T study in the Frailty Clinic of the University-Hospital of Parma site were selected. Blood pressure (BP) and heart rate (HR) (OMRON 705 IT) were assessed with three consecutive measurements, the data of which were averaged.

Level of physical activity (PA) was assessed by a questionnaire that included detailed information on type, intensity and duration of physical activity.¹⁷

Whole-body DEXA scans were used to estimate SMM as ALM, and sarcopenia was defined according to the recommendation of the FNIH (ALM/BMI <0.789 in men and <0.512 in women; and/or crude ALM <19.75 Kg in men and <15.02 Kg in women).¹⁸ Fat mass (FM) was also derived from DEXA and expressed in Kg.

Physical Frailty was assessed by SPPB, a battery of three tests with a score in the range between 3 and 9, and this was considered one of the eligibility criteria. Participants in the SPRINT-T trial needed to have sufficient cognitive abilities measured using MMSE, and those participants with MMSE > 24 were included in the study.¹⁹

Charlson Comorbidity Index (CCI) was used to assess multimorbidity, the median score of CCI was estimated according to Charlson et al.²⁰

M-mode, two-dimensional, and Doppler ECHO were performed by an ultrasonography-experienced cardiologist (GP), using a commercially available, multi-hertz sector, 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior (PWT) left ventricular (LV) wall thicknesses, systolic and diastolic (EDD) diameters and volumes, absolute LVM and indexed to body surface area (LVM/BSA) were calculated as previously described.²¹ LVH was defined as LVM/BSA of $>95\text{g}/\text{m}^2$ in women and $>115\text{g}/\text{m}^2$ in men.²² Relative wall thickness (RWT) was calculated as: $(\text{SWT}+\text{PWT})/\text{EDD}$, using the 0.42 cut-off to define eccentric (≤ 0.42) or concentric (>0.42) remodelling.²² Simpson's biplane rule-based end-diastolic (EDV) and systolic (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS) was: $[(\text{EDV} - \text{ESV})/\text{EDV}] \times 100$. Cardiac output was derived by the formula: $\text{EDV}-\text{ESV}$.

Mitral inflow pattern was analysed from apical 4-chamber view, and E and A wave and their ratio were considered as peak flow velocity (pv) and time velocity integral (tvi), in order to evaluate the conventional diastolic function. From the same projection, DTE analysis was performed at lateral site and postero-septum of mitral annulus to assess myocardial systolic (S) and diastolic (E', A') waves of LV. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/E' ratio) was calculated for the estimation of LV filling pressure.

DEXA scan and cardiological assessment were performed at baseline, within a temporal window of 30 days.

Data are reported as means±SD or numbers and percentage. Factors statistically correlated with ALM, proxy of SMM, were identified using age- and sex-adjusted partial correlation coefficient and Spearman partial rank–order correlation coefficients, as appropriate. Parsimonious models obtained by backward selection from initial fully adjusted models, including age, BMI, systolic BP (SBP), HR, LVM, CO, level of PA, Hb, MMSE and beta-blockers or ACE-inhibitors/angiotensin receptor blockers, were used to identify independent factors of ALM. Sex was not included in the model because the collinearity between LVM and sex ($R=0.51$, $p<0.0001$). A 2-tailed p value <0.05 was considered as statistically significant. SAS 8.2 statistical package was used for all analyses (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Table 1 shows the main characteristics of the study population: 67 were women and 33 men (mean age was 79 ± 5 years). The mean BMI was 27.6 Kg/m² with one third of the sample having BMI value >30 Kg/m². CCI median score was 0, without significant differences between men and women. The mean SBP value was 138 ± 18 mmHg and 70% had a history of hypertension; 12% had coronary artery disease, and 3% had significant cardiac valve disease. No sign of heart failure was detected in any of the patients. With regard to the other comorbidities of the sample, thyroid diseases were reported in 20% and diabetes mellitus in 9%. Forty-one percent of the participants were chronically on β -blockers, 32% on ACE-inhibitors, and 21% on Angiotensin II Receptor Blockers (ARB). Mean values of ALM crude and ALM/BMI and indexed by BMI and SPPB were consistent with the eligibility criteria adopted in SPRINT-T for defining a sarcopenic and physically frail population (Table 1).

The thicknesses of SWT and PW and the LV cavity size, as assessed by diameters and volumes, were in the normal range with males exhibiting greater LV thicknesses and dimensions compared

with females (Supplementary Table). Both LVM and LVM/BSA were higher in men and women, especially in older and hypertensive subjects with a tendency to a geometric remodelling, as evaluated by RWT in both groups (Supplementary Table).

LV systolic function, assessed by EF and FS, was in the normal range as well as CO in the total population, with females showing significantly lower CO and higher EF compared to the male group (Supplementary Table). The mitral inflow pattern showed significant reduction of the E/A ratios in these patients, suggesting an impaired relaxation, confirmed by a lower E' wave from DTE-analysis, which also demonstrated a reduction of S wave without significant differences between the male and female groups (Supplementary Table). E/E' excluded an increased LV filling pressure in our cohort.

ALM was strongly and positively correlated with LVM ($r=0.54602$, $p<.0001$), LVM/BSA ($r=0.30761$, $p<0.002$), CO ($r=0.49621$, $p<.0001$), but also with other structural cardiac parameters such as LV thicknesses, diameters, and volumes (Table 2). In addition, factors associated to ALM included BMI ($r=0.52461$, $p<.0001$), sex ($r=0.77$, $p<0.001$), FM ($r=0.38977$, $p<0.0001$) and Hb ($r=0.26001$, $p<0.01$) (Table 2). A negative association was detected between ALM and EF ($r=-0.30$, $p<.0001$) and FS ($r=-0.27$, $p<.001$), whilst no significant correlation was found with S wave and all diastolic parameters (E/A, E' wave and E/E'). Multivariate analysis confirmed as factors independently associated to ALM, only LVM (β 0.019 ± 0.005 ; $p<0.0001$), CO (β 0.038 ± 0.016 ; $p=0.019$), BMI (β 0.286 ± 0.051 ; $p<0.0001$) and Hb (β 0.544 ± 0.175 ; $p=0.0025$) (Table 3). Age, SBP, HR, levels of PA, pharmacological therapy, and MMSE were not significantly associated with ALM.

DISCUSSION

Main results of the present study are the significant correlations between ALM, proxy of SMM, and LVM in older adults with low skeletal muscle mass and physical performance, independently by confounders. ALM was also associated with cardiac output, independently of LVM.

This relationship is not surprising. Sarcopenia shares with cardiovascular disease risk factors, such as age, sedentary lifestyle, obesity, insulin resistance, and metabolic syndrome.^{23,24} Sarcopenia is also associated with an increased risk of cardiovascular diseases, as reported by the KNHANES survey.²⁵

Recent studies have also shown that sarcopenia is strictly and independently associated with PWV and intima-media thickness, all risk factors of cardiovascular disease.²⁶

The link between the cardiac disease and SMM is well-established in heart failure patients who develop secondary sarcopenia due to heart disease.³⁻⁶ Reduced blood oxygenation, physical inactivity and associated increase of inflammatory markers, may induce damage in SMM and cardiac muscle mass.³⁻⁶

There are indeed few studies on the relationship between skeletal muscle disease, sarcopenia, and cardiac structure and function. We studied this relationship in a specific population of older persons selected because of low muscle mass and physical performance. Interestingly, we found a strong positive association between ALM and LVM and CO (functional and hemodynamic parameter), also independently of LVM (structural cardiac parameter) -i.e. more skeletal mass, more LVM and CO. Our data are consistent with Keng et coworkers who recently demonstrated, among a study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting the presence of cardio-sarcopenia syndrome.¹⁴ We confirmed this concept here in a different more characterized population (European vs Asian) of older individuals using a more robust technique of DEXA (instead of bioimpedance) to assess body composition.

These results are not in agreement with those presented in two previous studies.^{27,28} The first study, conducted in a population of Koreans with an average age of 58 years enrolled in an

epidemiological study, showed that high visceral adiposity and low skeletal muscle mass were independent predictors of LVM.²⁷ However, the participants of this study were not classified according to sarcopenic status and were relatively young.

The second study, realized in a very large cohort of Korean adults (n=67,106), showed an increased prevalence of both diastolic dysfunction and LVH in the lowest skeletal muscle mass quartile.²⁸ In our cohort, ALM was positively correlated with LVM, and did not correlate with all diastolic indexes such as E/A, E' wave and E/E'. The different results can be explained by the fact that in the Korean study²⁸, 70.7% of population attributed to Q1 group were obese (vs 39.0%, 20.7 and 7.1 in Q2, Q3 and Q4 respectively) with a higher proportion of hypertensive (23.1% vs 14.8, 11.6 and 7.7 in Q2, Q3 and Q4 respectively) and diabetic (8.4% vs 5.5, 3.8 and 2.5 in Q2, Q3 and Q4 respectively), well known factors that potentially influence negatively the diastolic function.

Our study is also different from the studies aforementioned for many reasons: the age of the population, ethnicity (Caucasian vs. Asian), and the homogeneity of our sample population, which included only older subjects with low SMM and physical performance.

We should also consider that high LVM is traditionally viewed as clinically unfavourable phenomenon and LVH in hypertensive pathology is associated with greater CV risk and poorer prognosis.²⁹ The higher incidence of CV, mainly coronary LVH-related events, is justified by the imbalance between increased consumption and insufficient O₂ intake available for increased demand. Conversely, it should be also underlined the potential role of LVH as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart or pathological LVH occurring with the hypertensive heart or aortic stenosis.^{30,31}

While physiological LVH allows an increase in cardiac output during sports performance, the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load.³⁰ Pathological LVH, in contrast to the physiological one, is associated with both diastolic and

systolic dysfunction, which can be highlighted not with conventional functional indices, such as EF and FS, but with more sophisticated techniques such as DTE and Strain.^{32,33}

Consistently, in our study ALM positively correlated with CO and this relationship was also maintained in the multivariate analysis, including LVM as covariate. We cannot exclude that the relationship between exposure and outcome (LVM and SMM) could have been influenced by multimorbidity. In our study sample, there were patients who had heart disease such as CAD, cardiac valve disease, as well as chronic conditions such as hypertension, COPD and thyroid disease. In total, these conditions may account for at least 40% of the study sample. In particular, the increased systolic BP and the high prevalence of hypertensive subjects (70%), could have contributed to increase LV mass; however, this hypothesis was not confirmed in the multivariate analysis.

Moreover, to better clarify the role of multimorbidity, we calculated crude CCI whose median score of 0 (not surprising given the strict exclusion criteria aforementioned), we evaluated the relationship between CCI and ALM, and the role of CCI in the association between ALM and LVM in the multivariate analysis. CCI was not a significant predictor of ALM ($r=-0.12$, $p=0.22$) and the introduction of CCI in the Backward Analysis did not change the significant relationship between ALM and LVM. Basing on this data, we can assume that multimorbidity had not a relevant impact in this specific sample.

We should acknowledge that our study has two main limitations including the limited number of subjects enrolled and the cross-sectional nature of this study that does not allow drawing conclusions about the nature of the relationship. Moreover, given the strict inclusion criteria and the cohort precisely defined features, the generalization of results for the entire population of the community of older adults deserves further investigation. Additionally, given the collinearity between sex and LVM, we cannot exclude an independent role of sex in determining ALM values. This should be verified in separate groups of males and females with a wider range of ALM values. The relatively low simple size of our group and the narrow dispersion of ALM in both

males and females cannot permit such an analysis and therefore it should be considered as a major limitation of the study.

However, these limitations are offset by important strengths. This is the first time a study investigates the relationship between ALM and LVM in a homogeneous group of both low muscle mass and physical performance. Furthermore, the echocardiographic examinations were performed by a single, experienced operator to limit the variability of the calculation of the LVM - a measure that is affected by both the quality of the images and the experience of the operator.

In conclusion, the present study is the first one that demonstrates a highly significant and positive relationship between ALM and LVM in a cohort of older adults with low muscle mass and physical performance. Our novel findings emphasize the need of studying skeletal and heart in tandem to better address the complexity of aging process.

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Conflicts of interest: None declared

Author contributions: GP, FL and MM contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. GP performed all echocardiographic examinations and drafted the manuscript. All authors critically revised the manuscript and gave final approval.

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FIGURE LEGEND

Figure 1 is depicting the correlation between crude value of ALM and LVM (age- and sex-adjusted model).

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1 **Table 1. Characteristics of CARDIO-SPRINTT population (N=100):**

VARIABLE	Total	Female	Male
Age (years)	79 ± 5	79 ± 5	80 ± 5
Female n, (%)	67 (67)	67	33
BMI (Kg/m ²)	27.6 ± 5.1	27.5 ± 5.5	28.0 ± 4.3
Height (cm)	159 ± 8	155 ± 6	167 ± 7
Weight (Kg)	70 ± 15	65 ± 18	79 ± 13
HR (bpm)	66 ± 11	67 ± 12	65 ± 6
SBP (mmHg)	138 ± 18	138 ± 17	140 ± 20
DBP (mmHg)	80 ± 9	80 ± 9	79 ± 9
24h-SBP (mmHg)	129 ± 13	128 ± 10	130 ± 16
Hb (g/dl)	13.3 ± 1.4	13.0 ± 1.1	14.0 ± 1.9
Smoking n, (%)	8 (8)	4 (6)	4 (12)
Hypertension n, (%)	70 (70)	47 (70)	23 (70)
CAD n, (%)	12 (12)	3(4)	9 (27)
Cardiac valve disease n, (%)	3 (3)	3 (4)	-
COPD n, (%)	9 (9)	3 (4)	6 (18)
Diabetes mellitus	9 (9)	6 (9)	3 (9)
Obesity	30 (30)	20 (30)	10 (30)
Charlson Comorbidity Index, median , IQR	0 [0-1]	0[0-1]	1 [0-2]
Thyroid disease	20 (20)	19 (28)	1 (3)
Beta-Blockers n, (%)	41 (41)	26 (39)	15 (45)
Ace-Inhibitors n, (%)	32 (32)	21 (31)	11 (33)
ARB	21 (21)	14 (21)	7 (21)
ALM (Kg)	17.22 ± 3.73	15.23 ± 2.05	21.28 ± 3.02
ALM/BMI	0.62 ± 0.12	0.56 ± 0.08	0.76 ± 0.07
FM (Kg)	2.57 ± 0.85	2.53 ± 0.84	2.67 ± 0.86
SPPB	7.06 ± 1.2	7.15 ± 0.1	6.88 ± 1.56
MMSE	27.9 ± 1.7	27.9 ± 1.6	28.0 ± 1.8

2 Data are expressed as mean ± standard deviation or number of subjects with corresponding
3 percentage [or Median and Interquartile Range \(IQR\)](#). ALM, appendicular lean mass; ALM/BMI,
4 indexed appendicular lean mass; ARB, angiotensin receptor blocker; BMI, body mass index; CAD,
5 coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood
6 pressure; FM, Trunk Fat Mass; Hb, haemoglobin; HR, heart rate; MMSE, Mini Mental State
7 Examination; SBP, systolic blood pressure; SPPB, short physical performance battery.

1 **Table 2. Factors related to Appendicular Lean Mass in All Subjects.**

Variable	Pearson's correlation r, (p-value)
<i>Clinical data</i>	
FM	0.39 (<0.001)
Age	-0.06 (0.23)
Sex	0.77 (<0.001)
BMI	0.52 (<0.001)
BSA	0.89 (<0.001)
SBP	-0.01 (0.21)
Hb	0.26 (<0.01)
SPPB	-0.06 (0.18)
HR	-0.10 (0.30)
MMSE	0.14 (0.15)
Ace-inhibitors	0.04 (0.72)*
B-blockers	0.24 (0.01)*
ARB	0.03 (0.70) *
Charlson Comorbidity Index	-0.12 (0.22)
<i>Structural LV data</i>	
LVM	0.55 (<0.001)
LVM/BSA	0.31 (0.002)
ESV	0.47 (<0.001)
EDV	0.54 (<0.001)
EDD	0.46(<0.001)
ESD	0.47 (<0.001)
SWT	0.35 (<0.001)
PW	0.34 (<0.001)
<i>Functional LV data</i>	
CO	0.50 (<0.001)
EF	-0.30 (<0.01)
FS	-0.27 (<0.01)
E/A pv	0.02 (0.32)
E/A tvi	0.13 (0.62)
DTE S pv sept.	0.11 (0.18)
DTE S pv lat.	-0.15 (0.25)
DTE E' pv sept.	0.08(0.22)
DTE E'pv lat.	-0.01 (0.27)
E/E'	-0.23 (0.70)

Footnotes: ARB, angiotensin receptor blocker; BMI: body mass index; BSA, body surface area; CO, cardiac output; DTE, Doppler tissue echocardiography; A', end-diastolic myocardial wave; E', proto-diastolic myocardial wave; S, systolic myocardial wave; pv, peak velocity; tvi, time velocity integral; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FS, fractional shortening; LVM, left ventricular mass; ; MMSE, Mini Mental State Examination ; PW, posterior wall thickness; RWT, relative wall thickness; SWT, septal wall thickness;

2 * using logistic regression analysis

1 **Table 3. Factors independently related to Appendicular Lean Mass.**

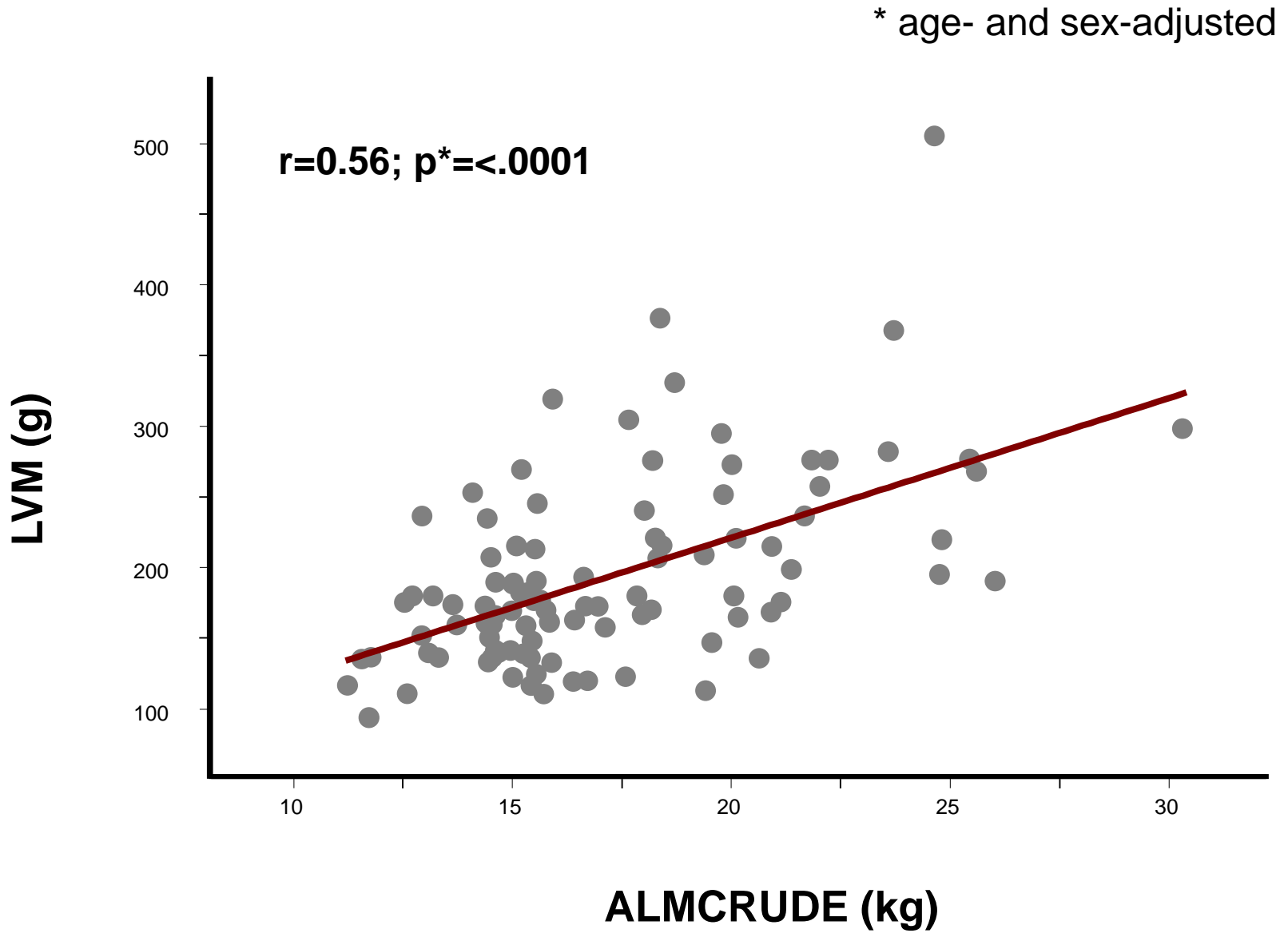
VARIABLE	$\beta \pm SE$	p-value
LVM	0.019 \pm 0.005	<0.0001
CO	0.038 \pm 0.016	0.019
BMI	0.286 \pm 0.051	<0.0001
Haemoglobin	0.544 \pm 0.175	0.0025

2 The full model obtained by Backward regression analysis included age, heart rate, Mini

3 Mental State Examination, Systolic Blood Pressure; Ace-inhibitors, betablockers, Mean level

4 of Physical Activity from 40 to 60 years old, **Charlson Comorbidity Index**.

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1 **Supplementary Table S1. Left ventricular structural and functional data in**
 2 **CARDIO-SPRINTT Population (N=100)**

3

Variable	Total	Female	Male
EDD (mm)	46.6 ± 6.3	45.0 ± 5.4	49.9 ± 6.8
ESD (mm)	27.8 ± 6.2	26.2 ± 3.9	30.9 ± 8.5
SWT (mm)	9.7 ± 1.5	9.2 ± 1.2	10.6 ± 1.6
PW (mm)	9.3 ± 1.5	8.9 ± 1.3	10.0 ± 1.7
EDV (ml)	95 ± 31	87 ± 22	112 ± 40
ESV (ml)	30 ± 15.9	26 ± 8	38 ± 24
LVM (g)	193 ± 67	169 ± 45	241 ± 79
LVM/BSA	112 ± 33	104 ± 26	128 ± 39
LVH (%)	54 (54)	33 (58)	21 (64)
RWT	0.41 ± 0.07	0.41 ± 0.07	0.41 ± 0.06
FS (%)	40 ± 8	42 ± 6	39 ± 10
EF (%)	69 ± 7	70 ± 5	66 ± 10
CO (ml)	65 ± 19	61 ± 17	74 ± 21
Mitral E pv (cm/sec)	59 ± 17	60.1 ± 17	55.2 ± 15
Mitral E tvi (cm)	10.5 ± 3.1	10.5 ± 3.0	10.6 ± 3.4
Mitral A pv (cm/sec)	82 ± 19	84 ± 20	78 ± 16
Mitral A tvi (cm)	9.4 ± 2.7	9.8 ± 2.8	8.8 ± 2.5
Mitral E/Apv (cm/sec)	0.75 ± 0.35	0.76 ± 0.40	0.72 ± 0.21
Mitral E/A tvi (cm)	1.25 ± 0.93	1.15 ± 0.47	1.46 ± 1.49
DTE S pv (cm/sec)	8.12 ± 2.04	8.30 ± 1.90	7.77 ± 2.28
DTE S tvi (cm)	1.61 ± 0.35	1.65 ± 0.34	1.54 ± 0.37
DTE E' pv (cm/sec)	6.93 ± 2.14	7.11 ± 2.22	6.56 ± 1.97
DTE E' tvi (cm)	0.91 ± 0.14	0.88 ± 0.79	0.98 ± 1.63
DTE A' pv (cm/sec)	11.55 ± 2.93	11.34 ± 2.89	11.98 ± 2.99
DTE A' tvi (cm)	0.93 ± 0.23	0.92 ± 0.23	0.95 ± 0.24
DTE E'/A' pv	0.65 ± 0.37	0.69 ± 0.42	0.58 ± 0.22
DTE E'/A' tvi	1.01 ± 1.04	1.02 ± 0.94	0.99 ± 1.24
E/E'	9.9 ± 4.2	10.1 ± 4.4	9.5 ± 3.9

4 Data are expressed as mean ± standard deviation. BSA, body surface area; CO, cardiac output;
 5 DTE, doppler tissue echocardiography; A', end-diastolic myocardial wave; E', proto-diastolic
 6 myocardial wave; S, systolic myocardial wave; pv, peak velocity; tvi, time velocity integral;
 7 EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-
 8 systolic diameter; ESV, end-systolic volume; FS, fractional shortening; LVH, left ventricular
 9 hypertrophy; LVM, left ventricular mass; ; PW, posterior wall thickness; RWT, relative wall
 10 thickness; SWT, septal wall thickness. Values from DTE analysis are the mean of septal and
 11 lateral walls.

1 **Relationship between Interaction of sSkeletal and LLeft Vventricular Mmass in**
 2 **older adults with low physiealmuscle performance skeletal mass and left**
 3 **ventricular mass in sarcopenic and frail older adults.**

4 **Running Title: Left ventricular mass and Sarcopenia**

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29 *Word count abstract: 2889215; –Word count text: 279529255; Tables: 43; Figure: 1.*

30 **IMPACT STATEMENT**

31 ~~Frail and sarcopenic~~ Older patients ~~with~~ low skeletal muscle mass and physical performance are unique
32 population at high risk of cardiovascular events. We demonstrated for the first time, in ~~–this specific~~
33 ~~population with low multimorbidity, older frail and sarcopenic patients,~~ ~~t~~ that left ventricular muscle mass
34 and skeletal muscle mass were positively correlated independently of cardiac output, haemoglobin and body
35 mass index. These findings underline the ~~future~~ need of evaluating ~~and monitoring~~ in parallel left ventricular
36 mass and skeletal muscle mass ~~and in the future their changes~~ after proactive interventions including
37 nutrition counseling and ~~–~~resistance exercise. We certify that this work is ~~–~~confirmatory of recent novel
38 clinical research. (Keng et al, JAGS 2019;67:2568-2573).

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57 **ABSTRACT**

58 **BACKGROUND:** It was recently hypothesized the existence of “cardiac-skeletal muscle axis”.
59 However, the~~No study has fully addressed the~~ relationship between skeletal muscle mass (SMM)
60 and left ventricular mass (LVM) -has never been investigated in the specific group of of sarcopenic
61 and frail older individuals with low skeletal mass and physical performances~~sarcopenic and frail~~
62 older persons.

63 We tested this hypothesis in the SPRINT-T (Sarcopenia and Physical Frailty IN older people:
64 multicomponent Treatment strategies Trial) population using ~~The aim of the present study was to~~
65 evaluate the existence of “cardiac-skeletal muscle axis” assessing the relationship between LVM as
66 (independent variable) and SMM as dependent variable~~in the SPRINT-T (Sarcopenia and Physical~~
67 Frailty IN older people: multicomponent Treatment strategies Trial) population.

68 **METHODS:** ~~The population consisted of 100 persons (33 men and 67 women), aged ≥ 70 years.~~
69 SMM was assessed by DEXA-scan and expressed as Appendicular Muscle Mass (ALM), LVM was
70 estimated through echocardiography. Low ALM Sarcopenia was defined according to Foundation
71 for the National Institutes of Health Sarcopenia Project (FNIH) criteria, and Short Physical
72 Performance Battery (SPPB) was used to assess physical performance~~physical frailty basing on~~
73 Short Physical Performance Battery (SPPB).

74 **RESULTS:** The population consisted of 100 persons (33 men and 67 women), aged ≥ 70 years
75 (mean age 79 ± 5) with low ALM and SPPB ranged between 3 and 9 suggestive of physical frailty.
76 Charlson Comorbidity Index median score was 0. Mean values of LVM were 193 ± 67 (g), indexed

77 LVM to body surface area (LVM/BSA) 112±33 (g/m²), and Cardiac Output (CO) 65±19 (l/min).
78 Females showed significantly lower CO and higher ejection fraction (EF) compared to the male
79 group. ALM was strongly and positively correlated with LVM ($r=0.54602$, $p<.0001$), LVM/BSA
80 ($r=0.30761$, $p<0.002$), CO ($r=0.49621$, $p<.0001$), BMI ($r=0.52461$, $p<.0001$), sex ($r=0.77$, $p<0.001$),
81 fat mass ($r=0.38977$, $p<0.0001$) and Hb ($r=0.26001$, $p<0.01$). ~~The population consisted of 100~~
82 ~~persons (33 men and 67 women), aged ≥ 70 years with low ALM and SPPB ranged between 3 and 9~~
83 ~~suggestive of physical frailty. Mean values of LVM were 193 ± 67 (g), indexed LVM to body~~
84 ~~surface area (LVM/BSA) 112 ± 33 (g/m²), and Cardiac Output (CO) 65 ± 19 (l/min). Females~~
85 ~~showed significantly lower CO and higher EF compared to the male group. ALM was strongly and~~
86 ~~positively correlated with LVM ($r=0.54602$, $p<.0001$), LVM/BSA ($r=0.30761$, $p<0.002$), CO~~
87 ~~($r=0.49621$, $p<.0001$), BMI ($r=0.52461$, $p<.0001$), sex ($r=0.77$, $p<0.001$), FM ($r=0.38977$,~~
88 ~~$p<0.0001$) and Hb ($r=0.26001$, $p<0.01$).~~ In the multivariate analysis, LVM (β 0.019±0.005;
89 $p<0.0001$), CO (β 0.038±0.016; $p=0.019$), BMI (β 0.286±-0.051; $p <0.0001$) and Hb (β 0.544 ±
90 0.175; $p=0.0025$) remained associated to ALM.

91 **CONCLUSIONS:** In a sample of older persons with low muscle mass and physical performance
92 sarcopenia and physical frailty, LVM was positively and significantly correlated with ALM,
93 independently from blood pressure, physical activity, and other potential confounders. Future
94 studies are needed to address the effect of interventions targeting LVM and SMM.

95

96 **Key words:** skeletal muscle mass; left ventricular mass; low physical performance
97 sarcopenia; frailty; SPRINTT study.

98 INTRODUCTION

99 ~~Current understanding between skeletal muscle mass and the heart is confined to literature that~~
100 ~~describes alterations in skeletal muscle mass (SMM) and cardiovascular diseases.¹⁻⁴ In particular, in~~
101 ~~patients with heart failure, either with a reduced or preserved ejection fraction, a loss of SMM~~
102 ~~contributes to the onset of fatigue and exercise intolerance. However, much less is known about the~~
103 ~~relationship between skeletal mass deficit, i.e., sarcopenia, and cardiac function and structure.~~

104 ~~Sarcopenia is considered a primarily age-dependent condition, characterized by the loss of SMM~~
105 ~~and strength.~~ Sarcopenia is considered a primarily age-dependent condition, frequently overlapped
106 with physical frailty.⁵¹ ~~The aforementioned condition is closely related to a level of physical~~
107 ~~impairment that can lead to disability. The flip side of this assertion is physical frailty,~~ a geriatric
108 syndrome characterized by reduced homeostatic reserve. Both these ~~This conditions~~ exposes the
109 subject to an increased risk of adverse negative events, ~~including and, as with sarcopenia, the risk~~
110 ~~of impaired physical function impairment and disability.~~⁶²

111 Changes in skeletal muscle mass (SMM) have been associated with cardiovascular diseases.^{1-4,3-6} In
112 particular, in patients with heart failure, either with reduced or preserved ejection fraction, a loss of
113 SMM contributes to the onset of fatigue and exercise intolerance. ~~Observational studies have also~~
114 ~~evaluated the relationship between frailty and cardiac function and cardiovascular diseases.~~⁷⁻¹⁰

115 Patients with physical frailty have a higher prevalence of cardiovascular diseases such as myocardial
116 infarction, angina, and congestive heart failure than well-performing patients.¹⁰ Furthermore, in
117 those patients without a history of cardiovascular disease, frailty was associated with subclinical
118 heart disease i.e., left ventricular hypertrophy (LVH), which is considered a form of preclinical
119 organ damage associated with systolic and diastolic dysfunction.⁷⁻⁹ ~~These data support the~~
120 ~~hypothesis that cardiovascular dysfunction plays an important role in the development of frailty and~~
121 ~~suggests the importance of a cardiac evaluation in frail subjects.~~

122 Moreover, it has been demonstrated that, after bed rest or inactivity - well-known risk factors for
123 sarcopenia and physical impairment and physical frailty- cardiac atrophy occurs in both men and
124 women suggesting a common regulation of heart and muscle mass.¹¹⁻¹³

125 All these data suggest Given the burden of physical disability with aging, the utmost important
126 interaction of the identification of factors contributing to the development of sarcopenia and
127 physical frailty with cardiac mass during aging is of utmost importance. The existence of cardiac-
128 muscle axis has been recently hypothesized in older- Singapore Korean subjects where a se-positive
129 and significant relationship was found between skeletal and cardiac ventricular mass.¹⁴⁻²⁸ Keng
130 (ref). However this association was not independent of confounders frequently encountered in the
131 real multimorbid determinants could influence not only the risk of disability but also affects heart
132 structure and function and, as a consequence, the patients cardiovascular prognosis. Additionally,
133 although low skeletal muscle mass is considered the other side of the coin, physical impairment
134 physical frailty coin,² the combination of these conditions is not routinely assessed during daily
135 clinical practice.

136 ==

137 However, Given the unique opportunity to assess a selected cohort of participants enrolled because
138 of low ALM and score of SPPB short physical performance battery in the range between 3 and 9
139 (proxy of physical frailty), we However, since no study has specifically explored the relationship
140 between left ventricular mass (LVM; (independent variable) and SMM (dependent variable) in a
141 group of individuals with these characteristics older people with sarcopenia and physical frailty, we
142 tested this hypothesis in a group of individuals with these characteristics.

143

144

145 METHODS

146 Data are from an ancillary study of the Sarcopenia and Physical fRailty IN older people: multi-
147 component Treatment strategies (SPRINT-T) project,¹⁴⁵ –a randomized control trial conducted in
148 frail, sarcopenic older subjects aged 70 years and older, to demonstrate the effectiveness of a
149 multicomponent (MCI) intervention based on physical activity, nutritional and technological
150 intervention versus a healthy aging lifestyle education (HALE) program for the prevention of
151 mobility disability.

152 Inclusion and Exclusion criteria for the Study were detailed elsewhere:¹⁶⁻

153 -Men and women aged \geq -70 years;

154 -~~Short Physical Performance Battery (SPPB)~~ score between 3 (included) and 9 (included);

155 -Ability to complete the 400-m walk test within 15 min without sitting down, help from another
156 person, use of a walker, or stopping for more than 1 minute at a time;

157 -Presence of low muscle mass according to results from a Dual Energy X-Ray Absorptiometry
158 (DEXA) scan. In agreement with the ~~Foundation for the National Institutes of Health Sarcopenia
159 Project (FNIH)~~ report 32, low muscle mass will be defined as: Body mass index-adjusted
160 appendicular lean mass (AaLM; i.e., the sum of lean mass from both arms and legs): <0.789 in men,
161 and <0.512 in women, OR ii. aALM <19.75 kg in men and <15.02 kg in women;

162 -Willingness to be randomised to either intervention group and to follow the study protocol.

163 Exclusion criteria:

164 -Unable or unwilling to provide informed consent or accept randomisation to either study group;

165 -Plans to relocate out of the study area within the next 2 years or plans to be out of the study area for
166 more than 6 consecutive weeks in the next year;

167 -Residence in long-term care;

168 -Household member enrolled in the study;

169 -Current diagnosis of schizophrenia, other psychotic or bipolar disorder. Depression is not an
170 exclusion criterion;

171 -Consumption of more than 14 alcoholic drinks per week;

172 -Difficulty communicating with the study personnel due to speech, language, or (noncorrected)
173 hearing problems;

174 -Mini Mental State Examination (MMSE) lower than 24/30;

175 -Severe osteoarthritis (e.g., awaiting joint replacement) that would interfere with the ability to
176 participate fully in either study arm;

177 -Cancer requiring treatment in the past 3 years, except for non-melanoma skin cancers or cancers
178 that have an excellent prognosis (e.g., early stage breast or prostate cancer);

179 -Lung disease requiring regular use of supplemental oxygen;

180 -Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents;

181 -Severe cardiovascular disease (including New York Heart Association [NYHA] class III or IV.

182 The investigators of the Parma SPRINT-T⁻¹⁴⁵⁻¹⁵⁶ site added, at the enrolment of participants, a
183 complete cardiac assessment including clinical evaluation with 12-lead resting Electrocardiogram
184 (ECG) and conventional and Doppler Tissue Echocardiographic (DTE) examination as part of the
185 ancillary protocol to the enrolment of participants.

186 This ancillary study was submitted to SPRINT-T Scientific Committee and accepted by the
187 Managing Entity, and subsequently approved by AVEN Local ethics committee (*Protocol n.10872*).

188 Written informed consent was obtained from the participants.

189 One hundred subjects from those enrolled in the SPRINT-T study in the Frailty Clinic of the
190 University-Hospital of Parma site were selected. Blood pressure (BP) and heart rate (HR) (OMRON
191 705 IT) were assessed with three consecutive measurements, the data of which were averaged.

192 Level of physical activity (PA) was assessed by a questionnaire that included detailed information
193 on type, intensity and duration of physical activity.⁻¹⁶⁷

194 Whole-body ~~dual energy X-ray absorptiometry~~ (DEXA) scans were used to estimate SMM as
195 ~~Appendicular Lean Muscle Mass~~ (ALM), and sarcopenia was defined according to the
196 recommendation of the ~~Foundation for the National Institutes of Health~~ (FNIH) (ALM/BMI <0.789

197 in men and <0.512 in women; and/or crude ALM <19.75 Kg in men and <15.02 Kg in women).¹⁷⁸

198 Fat mass (FM) was also derived from DEXA and expressed in Kg.

199 Physical Frailty was assessed by ~~Short Physical Performance Battery (SPPB)~~, a battery of three
200 tests with a score in the range between 3 and 9, and this was considered one of the eligibility
201 criteria. Participants in the SPRINT-T trial needed to have sufficient cognitive abilities measured
202 using ~~Mini Mental State Examination test (MMSE)~~, and those participants with MMSE > 24 were
203 included in the study.¹⁹⁸

204 Charlson Comorbidity Index (CCI) Mean score was used to assess multimorbidity, the median score
205 of CCI was estimated according to Charlson et al..²⁰

206 M-mode, two-dimensional, and Doppler ECHO were performed by an ultrasonography-experienced
207 cardiologist (GP), using a commercially available, multi-hertz sector, 2-4 MHz probe-equipped
208 machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior (PWT)
209 left ventricular (LV) wall thicknesses, systolic and diastolic (EDD) diameters and volumes, absolute
210 LVM and indexed to body surface area (LVM/BSA) were calculated as previously described.¹⁹²¹

211 LVH was defined as LVM/BSA of $>95\text{g}/\text{m}^2$ in women and $>115\text{g}/\text{m}^2$ in men.²²⁰ -Relative wall
212 thickness (RWT) was calculated as: $(\text{SWT}+\text{PWT})/\text{EDD}$, using the 0.42 cut-off to define eccentric
213 (≤ 0.42) or concentric (>0.42) remodelling.²²⁰ Simpson's biplane rule-based end-diastolic (EDV)
214 and systolic (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening
215 (FS) was: $[(\text{EDV} - \text{ESV})/\text{EDV}] \times 100$. Cardiac output was derived by the formula: $\text{EDV}-\text{ESV}$.

216 Mitral inflow pattern was analysed from apical 4-chamber view, and E and A wave and their ratio
217 were considered as peak flow velocity (pv) and time velocity integral (tvi), in order to evaluate the
218 conventional diastolic function. From the same projection, DTE analysis was performed at lateral
219 site and postero-septum of mitral annulus to assess myocardial systolic (S) and diastolic (E', A')
220 waves of LV. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus
221 velocity (E/E' ratio) was calculated for the estimation of LV filling pressure.

222 DEXA scan and cardiological assessment were performed at baseline, within a temporal window of
223 30 days.

224 Data are reported as means \pm SD or numbers and percentage. Factors statistically correlated with
225 ALM, proxy of SMM, were identified using age- and sex-adjusted partial correlation coefficient
226 and Spearman partial rank-order correlation coefficients, as appropriate. Parsimonious models
227 obtained by backward selection from initial fully adjusted models, including age, BMI, systolic BP
228 (SBP), HR, LVM, CO, level of physical activity PA, Hb, MMSE and beta-blockers or ACE-
229 inhibitors/angiotensin receptor blockers, were used to identify independent factors of ALM. Sex
230 was not included in the model because the collinearity between LVM and sex ($R=0.51$, $p<0.0001$).
231 A 2-tailed p value <0.05 was considered as statistically significant. SAS 8.2 statistical package was
232 used for all analyses (SAS Institute, Inc., Cary, NC, USA).

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235 RESULTS

236 Table 1 shows the main characteristics of the study population: 67 were women and 33 men (mean
237 age was 79 ± 5 years). The mean BMI was ~~higher than~~ 27.6 Kg/m^2 with one third of the sample
238 having BMI value >30 Kg/m^2 . CCI median score was 0, without significant differences between
239 men and women. The mean SBP value was 138 ± 18 mmHg ~~high normal~~ and 70% had a history of
240 hypertension; 12% had coronary artery disease, and 3% had significant cardiac valve disease. No
241 sign of heart failure was detected in any of the patients. With regard to the other comorbidities of
242 the sample, thyroid diseases were reported in 20% and diabetes mellitus in 9%. Forty-one percent
243 of the participants were chronically on β -blockers, 32% on ACE-inhibitors, and 21% on
244 Angiotensin II Receptor Blockers (ARB). Mean values of ALM crude and ALM/BMI and indexed
245 by BMI and SPPB were consistent with the eligibility criteria adopted in SPRINT-T for defining a
246 sarcopenic and physically frail population (Table 1).

247 The thicknesses of SWT and PW and the LV cavity size, as assessed by diameters and volumes,
248 were in the normal range with males exhibiting greater LV thicknesses and dimensions compared
249 with females ([Supplementary Table 2](#)). Both LVM and LVM/BSA were higher in men and
250 women, especially in older and hypertensive subjects with a tendency to a geometric remodelling,
251 as evaluated by RWT in both groups ([Supplementary Table 2](#)).

252 LV systolic function, assessed by EF and FS, was in the normal range as well as CO in the total
253 population, with females showing significantly lower CO and higher EF compared to the male
254 group ([Supplementary Table 2](#)). The mitral inflow pattern showed significant reduction of the E/A
255 ratios in these patients, suggesting an impaired relaxation, –confirmed by a lower E' wave from
256 DTE-analysis–, which also demonstrated a reduction of S wave without significant differences
257 between the male and female groups ([Supplementary Table 2](#)). E/E' excluded an increased LV
258 filling pressure in our cohort.

259 ALM was strongly and positively correlated with LVM ($r=0.54602$, $p<.0001$), LVM/BSA
260 ($r=0.30761$, $p<0.002$), CO ($r=0.49621$, $p<.0001$), but also with other structural cardiac parameters
261 such as LV thicknesses, diameters, and volumes (Table [23](#)). In addition, factors associated to ALM
262 included BMI ($r=0.52461$, $p<.0001$), sex ($r=0.77$, $p<0.001$), FM ($r=0.38977$, $p<0.0001$) and Hb
263 ($r=0.26001$, $p<0.01$) (Table [23](#)). A negative association was detected between ALM and EF ($r=-$
264 0.30 , $p<.0001$) and FS ($r=-0.27$, $p<.001$), whilst no significant correlation was found with S wave
265 and all diastolic parameters (E/A, E' wave and E/E'). Multivariate analysis confirmed as factors
266 independently associated to ALM, only LVM (β 0.019 ± 0.005 ; $p<0.0001$), CO (β 0.038 ± 0.016 ;
267 $p=0.019$), BMI (β 0.286 ± 0.051 ; $p<0.0001$) and Hb (β 0.544 ± 0.175 ; $p=0.0025$) (Table [34](#)). Age,
268 SBP, HR, levels of physical activity PA, pharmacological therapy, and MMSE were not
269 significantly associated with ALM.

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279 DISCUSSION

280 Main results of the present study are the significant correlations between ALM, proxy of SMM, and
281 LVM in ~~frail and sarcopenic~~ older adults with low skeletal muscle mass and physical performance,
282 independently by confounders. ALM was also associated with cardiac output, independently of
283 LVM.

284 This relationship is not surprising. S~~Both sarcopenia and cardiovascular disease shares with~~
285 cardiovascular disease ~~common~~ risk factors, such as age, sedentary lifestyle, obesity, insulin
286 resistance, and metabolic syndrome.^{213,224} ~~Sarcopenia is also associated with an increased risk of~~
287 ~~cardiovascular diseases, as reported by the KNHANES survey.~~²⁵³

288 Recent studies have also shown that sarcopenia is strictly and independently associated with
289 ~~indicators of atherosclerosis (such as stiffness, PWV and intima-media thickness, alls) that are~~ risk
290 factors of cardiovascular disease.²⁴⁶ ~~Our results suggest that both cardiac and skeletal muscle are~~
291 ~~associated and potentially share the same contributors.~~

292 The link between the cardiac disease and SMM is well-established in heart failure patients who
293 develop secondary sarcopenia due to heart disease.³⁻⁶¹⁻⁴ ~~In this context, the SMM loss can be~~
294 ~~attributed to R~~reduced blood oxygenation, physical inactivity and associated increase of
295 inflammatory markers, ~~may induce damage in that can damage both~~ SMM and cardiac muscle
296 mass.³⁻⁶¹⁻⁴

297 ~~Morphological, histological, biochemical, metabolic and energetic analyses, conducted on muscle~~
298 ~~biopsies, electromyography, spectroscopy and magnetic resonance imaging have shown that in~~

299 ~~chronic heart failure the early onset of fatigue and intolerance to exercise was attributable to a shift~~
300 ~~from an aerobic to anaerobic metabolism at the muscle level.~~

301 There are indeed few studies on the relationship between skeletal muscle disease, sarcopenia, and
302 cardiac structure and function. We studied this relationship in a specific population ~~off frail and~~
303 ~~sarcopenic~~ older persons selected because of low muscle mass and physical performance.

304 Interestingly, we found a strong positive association between ALM and LVM and CO (functional
305 and hemodynamic parameter), also independently of LVM (structural cardiac parameter) -i.e. more
306 skeletal mass, more LVM and CO.

307 Our data are consistent with Keng et coworkers ~~that~~who recently demonstrated, among a large
308 study sample of Asian older adults without cardiovascular disease, that sarcopenic participants
309 (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting
310 the presence of cardio-sarcopenia syndrome.²¹⁴⁷ We confirmed this concept here in a different more
311 characterized population (European vs Asian) of older ~~sarcopenic and physical frail~~ individuals
312 using a ~~Importantly, a~~ more robust technique of DEXA (instead of bioimpedance) was used in our
313 study to assess body composition.

314 These results are not in agreement with those presented in two previous studies.^{275,268} -The first
315 study, conducted in a population of Koreans with an average age of 58 years enrolled in an
316 epidemiological study, showed that high visceral adiposity and low skeletal muscle mass were
317 independent predictors of LVM.²⁵⁷ -However, the participants of this study were not classified
318 according to sarcopenic status and were relatively young.

319 The second study, realized in a very large cohort of Korean adults (n=67,106), showed an increased
320 prevalence of both diastolic dysfunction and LVH in the lowest skeletal muscle mass quartile.²⁶⁸ -In
321 our cohort, ALM was positively correlated with LVM, and did not correlate with all diastolic
322 indexes such as E/A, E' wave and E/E'. The different results can be explained by the fact that
323 However, in the Korean study²⁸⁶, -70.7% of population attributed to Q1 group were obese (vs
324 39.0%, 20.7 and 7.1 in Q2, Q3 and Q4 respectively) with a higher proportion of hypertensive

325 (23.1% vs 14.8, 11.6 and 7.7 in Q2, Q3 and Q4 respectively) and diabetic (8.4% vs 5.5, 3.8 and 2.5
326 in Q2, Q3 and Q4 respectively), – well known factors that potentially influence negatively the
327 diastolic function. – ~~These data can justify the different results between our and Korean study.~~

328 ~~However,~~ Our study is also different from the studies aforementioned ~~previous studies~~ for many
329 reasons: the age of the population, ethnicity (Caucasian vs. Asian), and the homogeneity of our
330 sample population, which included only ~~frail and sarcopenic~~ older subjects with low SMM and
331 physical performance.

332 ~~Keng et coworkers recently demonstrated, among a large study sample of Asian older adults~~
333 ~~without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV~~
334 ~~cavity size and mass than not sarcopenic, suggesting the presence of cardio-sarcopenia syndrome.²⁷~~

335 ~~We confirmed this concept here in a different more characterized population (European vs Asian) of~~
336 ~~older sarcopenic and physical frail individuals. Importantly, a more robust technique of DXA~~
337 ~~(instead of bioimpedance) was used in our study to assess body composition.~~

338 We should also consider that hHigh ~~The positive relationship between ALM and LVM is~~
339 traditionally can be viewed as clinically unfavourable ~~phenomenon.~~ ~~This datum is somewhat of a~~
340 ~~paradox because it is well known that~~ and LVH in hypertensive pathology is associated with
341 ~~implies~~ greater CV risk and poorer prognosis.^{29,28} ~~—The higher incidence of CV, mainly coronary~~
342 ~~events due to LVH-related events,~~ is justified by the imbalance between increased consumption and
343 insufficient O2 intake available for ~~due to~~ increased demand.

344
345 Conversely, ~~However,~~ it should be also underlined the potential role of ~~LVH should be interpreted~~
346 ~~not only as an energy expenditure but also considered~~ as a secondary compensatory mechanism
347 adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the
348 athlete, i.e., the athlete's heart, ~~induced by regular exercise,~~ or pathological LVH ~~secondary to CV~~

349 ~~diseases, such as what occurings~~ with the hypertensive heart or ~~in cases of~~ aortic
350 stenosis.^{2929,30030,31}

351 While pPhysiological LVH allows an increase in cardiac output during sports performance, ~~while~~
352 the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased
353 after-load.³⁰~~Therefore, pathological LVH is a positive functional adaptation mechanism in which~~
354 ~~the heart reshapes itself into a condition capable of normalizing stress and maintaining stroke~~
355 ~~volume.~~²⁹³⁰

356 ~~It is also well known that~~ Ppathological LVH, in contrast to the physiological one, is associated
357 with both diastolic and systolic dysfunction, which can be highlighted not with conventional
358 functional indices, such as EF and FS, but with more sophisticated techniques such as DTE and
359 Strain.^{3121,3223}

360 Consistently, in our study, ALM positively correlated with ~~CO~~cardiac output, and this relationship
361 was also ~~maintained~~confirmed in by the multivariate analysis, including LVM as covariate. ~~We~~
362 ~~cannot exclude that the relationship between exposure and outcome (LVM and SMM) could have~~
363 ~~been influenced by -multimorbidity. In our study sample, there were patients who had heart disease~~
364 ~~such as CAD, cardiac valve disease, as well as chronic conditions such as hypertension, COPD and~~
365 ~~thyroid disease. In total, these conditions may account for at least 40% of the study sample. In~~
366 ~~particular, the increased systolic BP and the high prevalence of hypertensive subjects (70%), could~~
367 ~~have contributed to increase LV mass; however, this hypothesis was not confirmed in the~~
368 ~~multivariate analysis.~~

369 Moreover, to better clarify the role of multimorbidity, we calculated- crude ~~Charlson Comorbidity~~
370 ~~Index~~CCI whose median score of 0 (not surprising ~~-given the stricted exclusion criteria~~
371 ~~aforementioned), we evaluated the relationship between CCI and ALM, and the role of CCI in the~~
372 ~~association between ALM and LVM in the multivariate analysis.~~

373 ~~CCI median score~~enbasing on these data, ~~w~~moCCIALMCCI-CCI was not a significant predictor of
374 ~~ALM (r=-0.12, p=0.22) -and -the introduction of~~ ~~Charlson Comorbidity Index~~CCI in the Backward

375 Analysis did not change the significant relationship between -ALM and LVM. Basing on this data,
376 we can assume that multimorbidity had not a relevant impact in this specific sample.

377 ~~Skeletal muscle and heart muscle have many points in common. Both are streaky and composed of~~
378 ~~sarcoma units, albeit with different characteristics and functions. They have the same embryonic~~
379 ~~origin, both derived from mesoderm; the heart shares with SMM a large number of genes, mainly~~
380 ~~those regulating the transcription of contractile and mitochondrial proteins.^{343,345} The high number~~
381 ~~of mitochondria, an expression of high oxidative capacity, testifies to a predominantly aerobic~~
382 ~~metabolism of these two organs.³⁵⁴~~

383 ~~The size of these organs depends on anthropometric characteristics (height, weight and body~~
384 ~~surface), sex, genetic makeup, and ethnicity.^{19, 35-38} The most cardiac and muscular hypertrophy~~
385 ~~among people of African ethnicity vs. Caucasian ethnicity are examples.³⁶⁻³⁹ However, SMM is the~~
386 ~~force of gravity, while the heart is governed by blood pressure.⁴⁰~~

387 ~~The main strength of this study is the homogeneous sample of frail and sarcopenic older persons~~
388 ~~enrolled in the study. Furthermore, the echocardiographic examinations were performed by a single,~~
389 ~~experienced operator to limit the variability of the calculation of the LVM -- a measure that is~~
390 ~~affected by both the quality of the images and the experience of the operator.~~

391 We should acknowledge that our study has two main limitations including may be the limited
392 number of subjects enrolled and the cross-sectional nature of this study that does not allow to
393 drawdrawingown conclusions about the nature of the relationship. Moreover, given the strict
394 inclusion criteria and the cohort precisely defined features, the generalization of results for the
395 entire population of the community of older adults deserves further investigation. Additionally,
396 given the collinearity between sex and LVM, we cannot exclude an independent role of sex in
397 determining ALM values. This should be verified in separate groups of males and females with a
398 wider range of ALM values. The relatively low simple size of our group and the narrow dispersion
399 of ALM in both males and females cannot permit such an analysis and therefore it should be
400 considered as a major limitation of the study.

401 However, ~~these limitations are offset by important strengths. to our knowledge, T~~this is the first
402 time a study investigates the relationship between ALM and LVM in a homogeneous group of both
403 low frail and sarcopenic older people. muscle mass and physical performance. Furthermore, the
404 echocardiographic examinations were performed by a single, experienced operator to limit the
405 variability of the calculation of the LVM - a measure that is affected by both the quality of the
406 images and the experience of the operator.

407 Moreover, ~~given the strict inclusion criteria and the cohort precisely defined features, the~~
408 ~~generalization of results for the entire population of the community of older adults deserves~~
409 ~~further investigation.~~

410 Since there was collinearity between sex and LVM, we cannot exclude an independent role of sex
411 in determining ALM values. This should be verified in separate groups of males and females with
412 a wider range of ALM values. The relatively low sample size of our group and the narrow
413 dispersion of ALM in both males and females cannot permit such an analysis and therefore it
414 should be considered as a major limitation of the study.

415 The increased systolic BP and the high prevalence of hypertensive subjects (70%), related to CV
416 aging process, could have contributed to increase LV mass; however, SBP did not influence the
417 relationship between ALM and LVM in the multivariate analysis.

418 In our study we could not demonstrate the existence of other mechanisms to explain the relationship
419 between the muscle heart and SMM. It is well known that SMM has paracrine and endocrine
420 activity that releases modulators for the heart but also for the brain, liver, pancreas, bone and fatty
421 tissue.⁴¹ However, we did not have data on follistatin like 1 (TSTL1), apelin, musclin, fibroblast
422 growth factor 21 (FGF-21), factors released by SMM and exerting beneficial effects on CV system
423 in terms of cardioprotection, vascularization, and optimization of blood pressure.⁴²

424 The available biobank of SPRINT-T will allow to measure biomarkers and to perform future
425 analyses to test these interesting hypotheses.

426 In conclusion, the present study is the first one that demonstrates a highly significant and positive
427 relationship between ALM and LVM in a ~~frail and sarcopenic cohort of~~ cohort of older adults with
428 low muscle mass and physical performance. Our novel findings -emphasize the need of studying
429 skeletal and heart in tandem -to better address -the -complexity of aging process.

430

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439 all echocardiographic examinations and drafted the manuscript. All authors critically revised the
440 manuscript and gave final approval.

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444

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584 Figure 1 is depicting the correlation between crude value of ALM and LVM (age- and sex-adjusted
585 model).

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588 42.