ORIGINAL ARTICLE

Muscle wasting diseases has two distinct trajectories on the 3-dimensional age-BMI-peak VO_2 scatterplot

Masamitsu Sugie[1,2], Kazumasa Harada[1,2], Tetsuya Takahashi[2,3], Marina Nara[2,4], Teruyuki Koyama[5], Hajime Fujimoto[1], Shunei Kyo[6], Hideki Ito[7]

1 Department of Cardiology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015 Japan; **2** Department of Geriatric Health promotion center, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015 Japan; **3** Department of Rehabilitation, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan; **4** Japanese Association for Healthy Life Expectancy, 2-11-4-203 Shibuya, Shibuya-ku, Tokyo 150-0002, Japan; **5** Department of Rehabilitation, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015 Japan; **6** Department of Cardiac Surgery, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015 Japan; **7** Department of Diabetes, Metabolism and Endocrinology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015 Japan

Abstract

Aims: Frailty and sarcopenia are age-related morbid states, and a low body mass index (BMI) is a characteristic of frailty and cachexia. However, no common index for assessing these three muscle wasting states is available, making it difficult to understand the relationship among them. Peak oxygen uptake (peak VO_2), an index of life expectancy, may be a useful common index. Therefore, this study aimed to investigate the relationship among sarcopenia, frailty, and cachexia using age, BMI, and peak VO_2.

Methods and Results: Participants were 175 Japanese community dwelling older adults (58 men, 117 women; 77.6 years). We assessed biochemical, physiological, and physical factors, and symptoms associated with frailty, and cachexia. Peak VO_2 was assessed with a cardiopulmonary exercise test. Participants were classified into five groups: robust, pre-frail, frail, sarcopenia, and cachexia. We compared the groups by age, BMI, and peakVO_2 with average values and 95% confidence intervals (CIs). 17% (n=30) of participants were classified as robust, 40% (n=70) as pre-frail, 12% (n=21) as sarcopenia, 25% (n=44) as frail, and 6% (n=10) as cachexia. Significant differences were found in age (robust vs. frail, pre-frail vs. frail), BMI (robust vs. cachexia, pre-frail vs. cachexia, frail vs. cachexia), and peak VO_2 (robust vs. frail, robust vs. cachexia, pre-frail vs. cachexia) with average values and 95% CIs. Three dimensions among age, BMI and peak VO_2 revealed two trajectories (from robust to frailty via pre-frailty, and from robust to cachexia via sarcopenia) among muscle wasting diseases.

Conclusions: This study revealed two trajectories among muscle wasting diseases.

Address for correspondence: Masamitsu Sugie; Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015 Japan; Tel.: +81-3-3964-1141; Fax +81-3-3964-1982, E-mail: masamitsu_sugie@tmghig.jp

Keywords: Frailty, Sarcopenia, Cachexia, Peak oxygen uptake, Prevalence, Overlapping status.

Received 02 June 2018 **Accepted** 02 August 2018

Introduction

Sarcopenia (1), frailty (2), and cachexia (3) are muscle wasting states that receive much attention in super aging societies. Previous reports indicated that sarcopenia prior to frailty, furthermore, indicated that sarcopenia may be one of a component of frailty (2) (4). Similarly, previous reports indicated that sarcopenia and cachexia are overlapping each other, furthermore, indicated that cachexia may be one of a component of sarcopenia (5) (6) (7) (8). Although these three morbid states are related, the exact relationship among them remains unknown. Reasons for this include: each state has a different definition (1-3); hand grip strength is a common parameter in these definitions, with the cut-off value for hand grip strength in sarcopenia often applied to frailty and cachexia; frailty and sarcopenia are age-related morbid states whereas cachexia is not; and body weight loss is characteristic of frailty and cachexia, but not of sarcopenia. Therefore, despite two common indices (i.e., age and body weight loss) for frailty and sarcopenia, frailty and cachexia, a lack of common useful indicators for the three states creates difficulty in understanding their relationship.

Peak oxygen uptake (peak VO_2) is known as an index of life expectancy (9) and a component of the cycle of frailty (2). As sarcopenia, frailty, and cachexia are associated with mortality (2) (10) (11), we considered peak VO_2 as a common useful indicator to understand the relationship among the three states.

We hypothesized that age, body mass index (BMI), and peak VO_2 may be useful indices to understand the relationship among sarcopenia, frailty, and cachexia. Developing understanding of this area is clinically important; therefore, this study aimed to investigate the relationship among sarcopenia, frailty, and cachexia using age, BMI, and peak VO_2, in Japanese community dwelling older adults.

Methods

Participants

Participants were 175 community dwelling older adults aged 65 years or over (58 men and 117 women) who lived in the Tokyo metropolitan area. Participants' mean age was 77.6 years (range 65–97 years). None of the participants were currently hospitalized, but all were receiving outpatient treatment at the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology. Exclusion criteria were: age younger than 65 years, impaired vision, impaired hearing, musculoskeletal impairments that might interfere with the ability to perform the exercise test, and a clinically unstable condition. Potential participants who performed habitual exercise training were also excluded from the study. Habitual exercise training is defined as the performance of repetitive activity more than three times a week for the purpose of improving and/or maintaining physical performance such as aerobic training (i.e. walking, swimming), resistance training, and/or a combination of these methods (i.e. cycling). All willing participants were assigned to the study after application of the exclusion criteria. Participants' clinical characteristics are summarized in Table 1 and 2.

Laboratory investigations

Fasting blood samples for all participants were drawn from a large antecubital vein to determine hemoglobin, serum albumin, and high-sensitivity C-reactive protein (hs-CRP). Hemoglobin levels were analyzed using Sysmex XE-5000 (Sysmex Corporation, Hyogo, Japan). Serum albumin levels were analyzed using the bromocresol purple assay (Shino-Test Corporation, Tokyo, Japan), and hs-CRP levels were analyzed using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken Corporation, Tokyo, Japan).

Skeletal muscle mass index (SMI), body mass index (BMI), and total body fat mass index

Appendicular skeletal muscle mass was measured using total body dual-energy X-ray absorptiometry (DEXA, Lunar iDXA, GE Healthcare, Tokyo, Japan). Appendicular skeletal muscle mass was considered the sum of the muscle mass of the four limbs, which was divided by height in meters squared to give the SMI (kg/m^2). Total body fat mass index was measured using total body dual-energy X-ray absorptiometry. The sum of the total fat mass index was calculated as total fat mass index divided by height in meters squared (kg/m^2). BMI was calculated as body weight divided by height in meters squared (kg/m^2).

Evaluation of physical performance

To test usual walking speed (m/s), we asked participants to walk along a straight 11-m walkway on a flat floor, once, at their usual speed. Walking speed was measured over a 5-m distance between markers placed 3 and 8 m from the start of the walkway. Two trials were conducted per participant, with the shorter time used in the analyses. Hand grip strength (HGS) is a valid indicator of overall muscle strength, and it is a particularly useful indicator of upper-extremity strength. HGS was assessed two times on each hand alternately using a Smedley-type JAMAR hand dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). The highest value was used in the analyses. All physical performance parameters for each participant were assessed by trained research assistants.

Assessment of robust, pre-frailty, frailty, sarcopenia, and cachexia

Frailty and pre-frailty were evaluated with the Japanese version of Cardiovascular Health Study (J-CHS) criteria (12). Sarcopenia was evaluated with the Asian Working Group for Sarcopenia (AWGS) criteria (13). Cachexia was evaluated according to "Cachexia: A new definition", except interleukin-6 (3).

AWGS criteria indicate the threshold for the SMI in sarcopenia is 7.0 kg/m^2 for men and 5.4 kg/m^2 for women, and that for hand grip strength is 26 kg for men and 18 kg for women and that for usual walking speed is 0.8 m/s (13). J-CHS criteria indicate the threshold for usual walking speed in frailty is 1.0 m/s, and that for hand grip strength is 26 kg for men and 18 kg for women (12). Cachexia criteria indicate that hand grip strength thresholds are 26 kg for men and 18 kg for women, and the SMI threshold is 7.0 kg/m^2 for men and 5.4 kg/m^2 for women (13). According to the definition of cachexia (3), the thresholds of C-reactive protein, hemoglobin, and serum albumin are 0.5mg/dl, 12g/dl, and 3.2g/dl, respectively.

All participants completed a questionnaire that covered fatigability, anorexia, and low physical activity in daily life to assess status relating to frailty and cachexia. Participants were classified into robust, pre-frail, frail, sarcopenia, or cachexia groups using the following method. First, we counted the number of participants with cachexia. After excluding those with cachexia, we counted the number of participants with frailty. Next, after excluding those with cachexia and frailty, we counted the number of participants with sarcopenia, according to the report "From sarcopenia

to frailty" by Morley et al. (4). After excluding participants with cachexia, frailty, and sarcopenia, we counted the number of participants who were pre-frail. Finally, after excluding those with cachexia, frailty, sarcopenia, and pre-frailty, the remaining participants were considered robust. The clinical characteristics of the five groups are summarized in Tables 1 and 2. To assess the overlapping status, we investigated whether each group are also classified to robust, pre-frailty, sarcopenia, frailty and cachexia. Table 3 shows the number of participants in each group with overlapping status.

Cardiopulmonary exercise test (CPET)

All participants underwent a symptom-limited bicycle ergometer CPET using an upright, electromagnetically braked cycle ergometer (Aerobike Strength Ergo-8, Mitsubishi Electronic, Tokyo, Japan), a metabolic analyzer (Aeromonitor AE-310S, Minato Medical Science, Osaka, Japan), and an electrocardiogram (Stress test system ML-9000, Fukuda Denshi, Tokyo, Japan). The CPET began with a 3-min rest on the ergometer, followed by a 4-min warm-up at 0 watt and 60 rpm. During the exercise test, the load was increased incrementally by 15 watts per min. CPET parameters were measured from the beginning of the initial rest on the cycle ergometer until the end of the exercise session.

The CPET was terminated on the participant's request, if abnormal physiologic responses occurred (14), or if a participant was unable to continue to perform the pedaling exercise correctly. Oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation, tidal volume, and respiration frequency were smoothed with an 8-breath moving average. Peak VO_2 was defined as the highest VO_2 value obtained during the last minute of the CPET. When the respiratory exchange ratio (VCO_2/VO_2) was less than 1.0 at peak exercise, the test was considered insufficient because of the participant's poor effort, and those peak exercise data were not used in the analyses. In this study, we explored peak VO_2 (ml/min) but not peak VO_2/weight (ml/min/kg), because we combined BMI (and age) with peak VO_2 to investigate the relationship among sarcopenia, frailty, and cachexia.

Statistical analyses

A sample size of 140 participants was calculated for 80% power, $\alpha = 0.05$, and an anticipated effect size of 0.30 using sample size software (G*Power 3.1.9.2., Germany). One-way analysis of variance (ANOVA) and chi-square tests were performed to compare the characteristics of participants in the five groups. All statistical analyses were performed with SPSS Version 22 (IBM Japan, Tokyo, Japan). Significance was set at $p<0.05$ for all tests.

Ethical considerations

This study was approved by the Ethics Committee of the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology (Authorization Number: 240301), and conformed to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent before data collection.

Results

Table 1 shows the comparison of biochemical, physiological, and physical assessments for the five groups (robust, pre-frail, sarcopenia, frail, and cachexia) using one-way ANOVA. Of the 175 community dwelling older adults, 17% (n=30) were robust, 40% (n=70) were pre-frail, 12% (n=21) were sarcopenia, 25% (n=44) had frail, and 6% (n=10) had cachexia. Significant differences were seen in age (years) between the robust and frail groups (75.4±5.7 vs. 80.6±6.7), and the pre-frail and frail groups (77.2±6.3 vs. 80.6±6.7). Significant differences were seen in BMI (kg/m^2) between the robust and cachexia groups (23.6±3.5 vs. 18.2±1.1), the pre-frail and cachexia groups (23.4±3.3 vs. 18.2±1.1), and the frail and cachexia groups (23.2±3.5 vs. 18.2±1.1). There were significant differences in peak VO_2 (ml/min) between the robust and frail groups (1065.0±244.5 vs. 788.3±262.5), the robust and cachexia groups (1065.0±244.5 vs. 667.0±306.4), and the pre-frail and cachexia groups (927.9±301.8 vs. 667.0±306.4). In addition, significant differences were seen in SMI (kg/m^2) between the robust and sarcopenia groups (6.4±0.8 vs. 5.4±0.8), the pre-frail and sarcopenia groups (6.3±0.8 vs. 5.4±0.8), the frail and sarcopenia groups (6.3±0.9 vs. 5.4±0.8), the robust and cachexia groups (6.4±0.8 vs. 5.4±0.6), the pre-frail and cachexia groups (6.3±0.8 vs. 5.4±0.6), and the frailty and cachexia groups (6.3±0.9 vs. 5.4±0.6). There were also significant differences in total body fat mass index between robust and cachexia (8.0±2.7 vs. 3.9±1.0), pre-frailty and cachexia (7.6±2.4 vs. 3.9±1.0), sarcopenia and cachexia (7.0±2.6 vs. 3.9±1.0), and frailty and cachexia (7.5±2.9 vs. 3.9±1.0). There were also significant differences in usual walking speed (m/s) between the robust and frail groups (1.2±0.1 vs. 0.8±0.2), the pre-frail and frail groups (1.0±0.2 vs. 0.8±0.2), and the sarcopenia and frail groups (1.0±0.2 vs. 0.8±0.2). Significant differences were seen in peak VO_2/heart rate between robust and cachexia, and pre-frailty and cachexia, and seen in VE/VCO_2 slope between robust and cachexia, pre-frailty and cachexia, and frail and cachexia.

Table 2 shows the comparisons with the comorbidities among robust, pre-frail, sarcopenia, frail and cachexia participants using chi-square tests. Significant differences were seen in sex and prevalence of hypertension, chronic heart failure, chronic

obstructive pulmonary disease, chronic kidney disease, cancer, fatigability, low physical activity, and anorexia.

Table 3 shows the number of participants with overlapping muscle wasting states based on the original definitions. Of 10 participants in the cachexia group, two were also classified as sarcopenia and pre-frail, one as frail, and seven as sarcopenia and frail. Of the 44 participants in the frail group, 32 were also classified as frail and 12 as sarcopenia. All 21 participants in the sarcopenia group were classified with overlapping pre-frailty. Of all participants (n=175), the prevalence rates of overlapping states were 17% (n=30) for robust, 53% (n=93) for pre-frailty, 24% (n=42) for sarcopenia, 30% (n=52) for frailty, and 6% (n=10) for cachexia.

Figure 1 shows the relationship between age and peak VO_2 (Figure 1A), BMI and peak VO_2 (Figure 1B), and age and BMI (Figure 1C) among the five groups, with average values and 95% confidence intervals (CIs). The average values and 95% CIs for age, BMI, and peak VO_2 were: robust group, age 75.4 years (73.4–77.7 years), BMI 23.6 kg/m^2 (22.4–25.0 kg/m^2), and peak VO_2 1065.0 ml/min (965.3–1146.1 ml/min); pre-frail group, age 77.2 years (75.7–78.7 years), BMI 23.4 kg/m^2 (22.6–24.1 kg/m^2), and peak VO_2 927.9 ml/min (856.0–999.9 ml/min); sarcopenia group, age 76.3 years (73.7–78.9 years), BMI 21.2 kg/m^2 (19.6–22.8 kg/m^2), and peak VO_2 868.2 ml/min (772.6–963.9 ml/min); frail group, age 80.6 years (78.5–82.6 years), BMI 23.2 kg/m^2 (22.2–24.3 kg/m^2), and peak VO_2 788.3 ml/min (708.4–868.1 ml/min); and the cachexia group, age 76.6 years (72.4–80.8 years), BMI 18.2 kg/m^2 (17.4–19.0 kg/m^2), and peak VO_2 667.0 ml/min (447.9–886.2 ml/min).

Figure 2 shows the relationship for age, BMI, and peak VO_2 in the five groups in three dimensions using gnuplot software (ver.5.2 patch level 0). The average points for age, BMI, and peak VO_2 (the same as in Figure 1) are plotted for the robust, pre-frail, sarcopenia, frail, and cachexia groups.

Table 1. Characteristics of participants and comparison with the biochemical, physiological, physical assessment among robust, pre-frailty, sarcopenia, frailty and cachexia using with one-way ANOVA

	All (175)			Robust (30)			Pre-frailty (70)			Sarcopenia (21)			Frailty (44)			Cachexia (10)			
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	
age (years)	77.6	±	6.4	75.4	±	5.7	77.2	±	6.3	76.3	±	5.6	80.6	±	6.7 [a,b]	76.6	±	5.9	
Height (cm)	153.9	±	8.8	156.1	±	7.8	153.2	±	7.7	156.4	±	9.2	151.4	±	9.6	158.2	±	11.1	
Body weight (kg)	54.2	±	10.0	57.5	±	9.1	55.0	±	9.7	52.3	±	11.6	53.3	±	9.9	45.7	±	7.3	[a,b]
Body mass index (kg/m^2)	22.8	±	3.5	23.6	±	3.5	23.4	±	3.3	21.2	±	3.5	23.2	±	3.5	18.2	±	1.1	[a,b,d]
Hemoglobin (g/dl)	12.8	±	1.4	13.3	±	1.7	12.8	±	1.2	13.1	±	1.3	12.5	±	1.4	12.3	±	1.9	
Serum albumin (g/dl)	4.0	±	0.4	4.0	±	0.3	4.0	±	0.5	3.9	±	0.3	4.0	±	0.3	3.7	±	0.4	
High-sensitivity C-reactive protein (mg/dl)	0.1	±	0.2	0.1	±	0.1	0.1	±	0.1	0.2	±	0.4	0.2	±	0.3	0.2	±	0.2	
Skeletal muscle mass index (kg/m^2)	6.2	±	0.9	6.4	±	0.8	6.3	±	0.8	5.4	±	0.8 [a,b]	6.3	±	0.9 [c]	5.4	±	0.6	[a,b,d]
Total body fat mass index (kg/m2)	7.3	±	2.7	8.0	±	2.7	7.6	±	2.4	7.0	±	2.6	7.5	±	2.9	3.9	±	1.0	[a,b,c,d]
Hand grip strength (kg)	20.0	±	6.6	24.0	±	5.9	20.1	±	6.5 [a]	17.6	±	5.6 [a]	18.6	±	6.8 [a]	18.7	±	5.9	
Usual walking speed (m/s)	0.9	±	0.2	1.2	±	0.1	1.0	±	0.2 [a]	1.0	±	0.2 [a]	0.8	±	0.2 [a,b,c]	0.8	±	0.3	[a]
peak VO_2(ml/min)	895.3	±	290.7	1065.0	±	244.5	927.9	±	301.8	868.2	±	210.2	788.3	±	262.5 [a]	667.0	±	306.4	[a,b]
peak VO_2/weight (ml/min/kg)	16.4	±	4.4	18.7	±	4.0	16.7	±	4.5	16.9	±	3.6	14.7	±	4.1 [a]	14.3	±	5.0	[a]
peak heart rate (bpm)	122.8	±	22.3	132.3	±	18.8	121.4	±	23.3	130.3	±	18.7	144.6	±	20.8 [a]	123.2	±	27.1	
peak VO_2/heart rate (ml/beat)	7.3	±	2.2	8.1	±	1.7	7.6	±	2.2	6.8	±	1.8	6.9	±	2.3	5.3	±	1.9	[a,b]
peak watts	68.4	±	25.5	85.4	±	21.5	71.0	±	24.4 [a]	67.4	±	18.9	56.6	±	25.1 [a,b]	51.7	±	25.7	[a]
peak metabolic equivalent	4.7	±	1.3	5.3	±	1.2	4.8	±	1.4	4.8	±	1.0	4.2	±	1.2 [a]	4.1	±	1.4	[a]
$\Delta VO_2/\Delta LOAD$ (ml/watt)	8.6	±	2.5	9.3	±	2.0	8.8	±	2.8	8.7	±	2.4	8.0	±	2.4	7.6	±	1.9	
VE/VCO_2 slope	34.1	±	9.6	32.1	±	8.3	32.7	±	8.1	35.8	±	10.0	34.8	±	10.1	45.4	±	15.6	[a,b,d]

VO_2: oxygen uptake, VE/ VCO_2 slope, minute ventilation vs. carbon dioxide output slope.

one-way ANOVA ($p<0.05$) : a: vs Robust, b: vs Pre-frailty, c: vs Sarcopenia, d: vs Frailty

Table 2. Comparison with the comorbidity among robust, pre-frailty, sarcopenia, frailty and cachexia using with chi-squared test

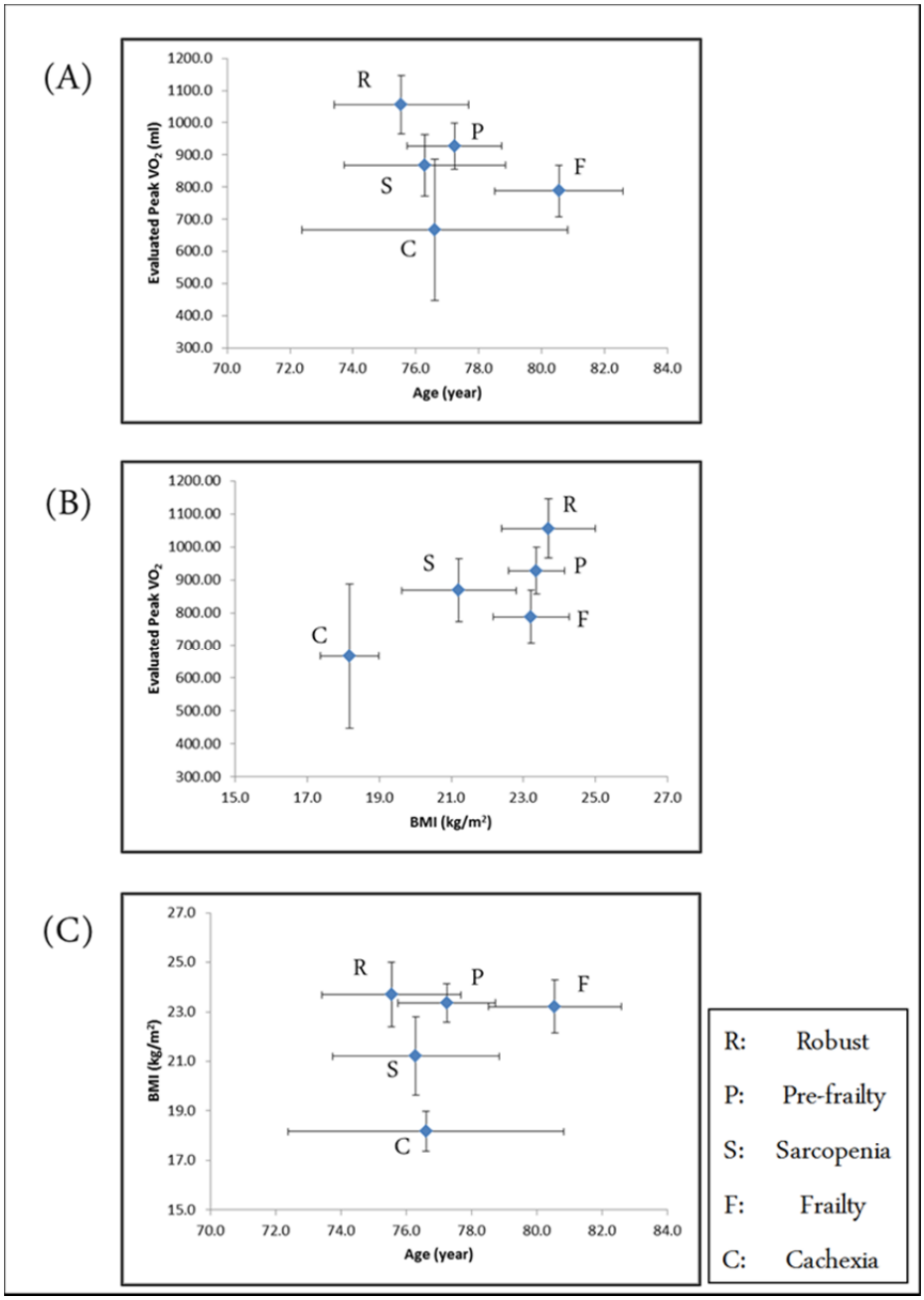
		All	Robust	Pre-frailty	Sarcopenia	Frailty	Cachexia	χ^2	p
	n	175	30	70	21	44	10		
Sex	Male	58	8	18	9	16	7	9.5	<0.05
	Female	117	22	52	12	28	3		
Hypertension	-	76	12	30	14	13	7	9.7	<0.05
	+	99	18	40	7	31	3		
Diabetes mellitus	-	140	26	55	19	35	5	7.6	0.11
	+	35	4	15	2	9	5		
Dyslipidemia	-	116	24	43	13	27	9	6.2	0.18
	+	59	6	27	8	17	1		
Atrial fibrillation	-	159	26	65	20	40	8	3.1	0.53
	+	16	4	5	1	4	2		
Coronary artery disease	-	138	26	52	19	35	6	5.3	0.26
	+	37	4	18	2	9	4		
Post-cardiac operation	-	163	29	67	17	41	9	6.1	0.2
	+	12	1	3	4	3	1		
Osteoporosis	-	168	29	68	20	42	9	1.1	0.9
	+	7	1	2	1	2	1		
Lumbar canal stenosis	-	163	29	67	19	39	9	2.7	0.61
	+	12	1	3	2	5	1		
Knee osteoarthritis	-	160	27	62	20	41	10	2.1	0.72
	+	15	3	8	1	3	0		
Dementia	-	170	28	70	20	42	10	4.3	0.36
	+	5	2	0	1	2	0		
Chronic heart failure	-	158	29	62	20	43	4	33.4	<0.001
	+	17	1	8	1	1	6		
Cerebral infarction	-	159	29	64	18	39	9	2.4	0.67
	+	16	1	6	3	5	1		
COPD	-	171	29	70	20	44	8	16.3	<0.001
	+	4	1	0	1	0	2		
Chronic kidney disease	-	169	30	68	21	43	7	21.8	<0.001
	+	6	0	2	0	1	3		
Cancer	-	160	28	64	20	42	6	13.9	<0.01
	+	15	2	6	1	2	4		
Fatigability	-	124	30	54	20	16	4	49.7	<0.001
	+	51	0	16	1	28	6		
Low physical activity	-	122	30	52	19	17	4	42.3	<0.001
	+	53	0	18	2	27	6		
Anorexia	-	132	26	63	14	27	2	32.2	<0.001
	+	43	4	7	7	17	8		

COPD: Chronic Obstructive Pulmonary Disease

Table 3. Overlapped the number of muscle wasting diseases

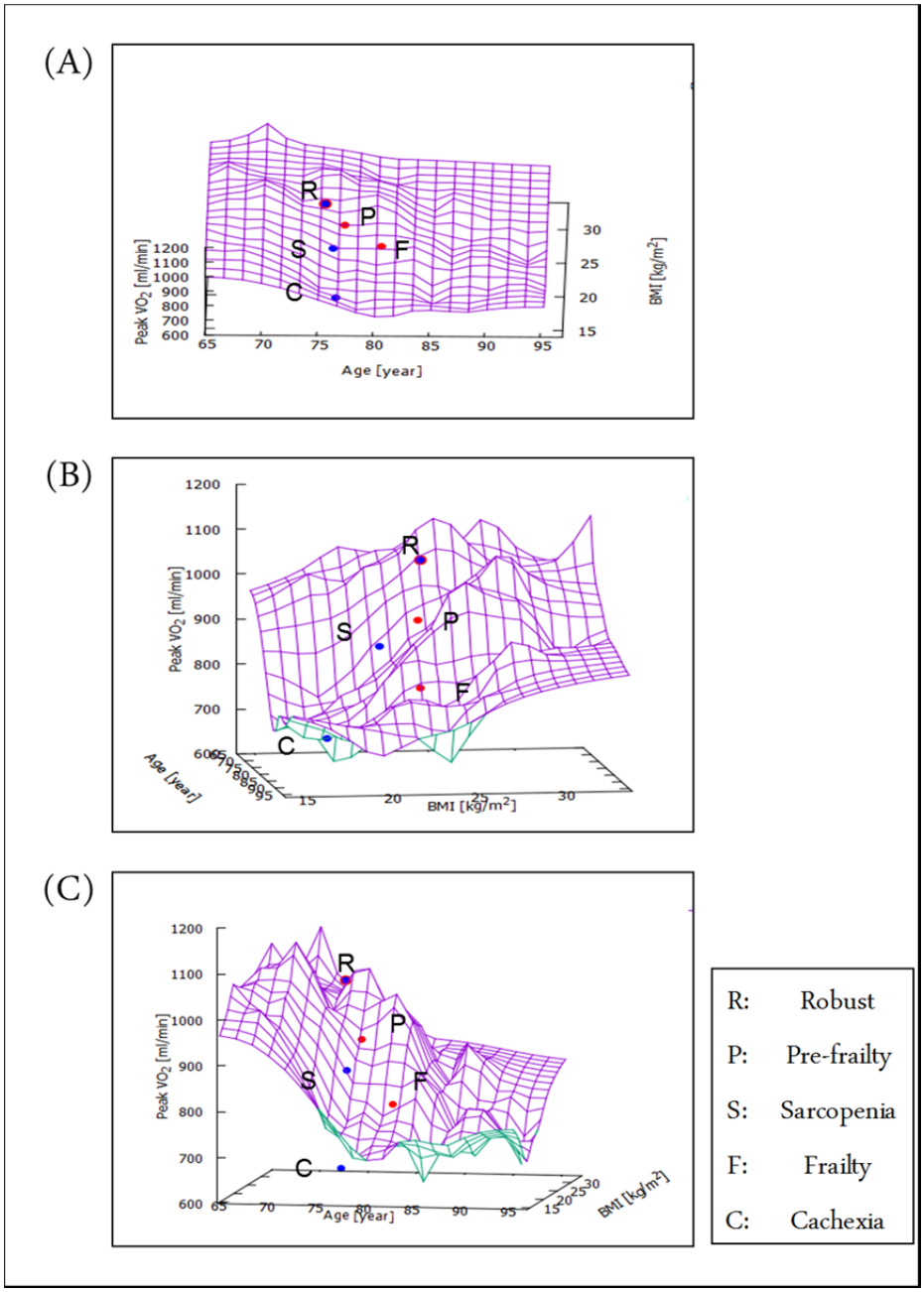
The comorbid status of muscle wasting disease	Robust n=30	Pre-frailty n=70	Sarcopenia n=21	Frailty n=44	Cachexia n=10
Robust	30				
pre-frailty		70			
Sarcopenia			0		
Sarcopenia + pre-frailty			21		
Frailty				32	
Frailty + Sarcopenia				12	
Cachexia					0
Cachexia + pre-frailty					0
Cachexia + sarcopenia					0
Cachexia + sarcopenia + pre-frailty					2
Cachexia + frailty					1
Cachexia + frailty + sarcopenia					7

Fig. 1



The relationship between peak oxygen uptake (VO_2) and age is shown in Figure 1A, peak VO_2 and body mass index (BMI) in Figure 1B, and BMI and age in Figure 1C. The average values and 95% confidence intervals for age, BMI, and peak VO_2 among the robust, pre-frail, sarcopenia, frail, and cachexia groups were as follows. Robust: age 75.4 years (73.4–77.7 years), BMI 23.6 kg/m^2 (22.4–25.0 kg/m^2), peak VO_2 1065.0 ml/min (965.3–1146.1ml/min). Pre-frailty: age 77.2 years (75.7–78.7 years), BMI 23.4 kg/m^2 (22.6–24.1 kg/m^2), peak VO_2 927.9 ml/min (856.0–999.9 ml/min). Sarcopenia: age 76.3 years (73.7–78.9 years), BMI 21.2 kg/m^2 (19.6–22.8 kg/m^2), peak VO_2 868.2 ml/min (772.6–963.9 ml/min). Frailty: age 80.6 years (78.5–82.6 years), BMI 23.2 kg/m^2 (22.2–24.3 kg/m^2), peak VO_2 788.3 ml/min (708.4–868.1 ml/min). Cachexia: age 76.6 years (72.4–80.8 years), BMI 18.2 kg/m^2 (17.4–19.0 kg/m^2), peak VO_2 667.0 ml/min (447.9–886.2 ml/min).

Fig. 2



The relationship among age and body mass index (BMI) and peak oxygen uptake (VO_2) is shown in three dimensions: A is the view from the top, B is a front view with BMI on the horizontal axis, and C is a front view with age on the horizontal axis. The average points for age, BMI, and peakVO_2 are plotted for the robust, pre-frailty, sarcopenia, frailty, and cachexia groups. The average points for age, BMI, and peakVO_2 are as follows. Robust: age 75.4 years, BMI 23.6 kg/m^2, peak VO_2 1065.0 ml/min. Pre-frailty: age 77.2 years, BMI 23.4 kg/m^2, peak VO_2 927.9 ml/min. Sarcopenia: age 76.3 years, BMI 21.2 kg/m^2, peak VO_2 868.2 ml/min. Frailty: age 80.6 years, BMI 23.2 kg/m^2, peak VO_2 788.3 ml/min. Cachexia: age 76.6 years, BMI 18.2 kg/m^2, peak VO_2 667.0 ml/min.

Discussion

Our study using data from community dwelling older adults aged 65 years or over who lived in the Tokyo metropolitan area showed the prevalence of robust was 17%, pre-frailty was 40%, sarcopenia was 12%, frailty was 25%, and cachexia was 6%. A previous study reported the prevalence of robust was 44.4%, pre-frailty was 48.1%, and frailty was 7.4% (15). Similarly, the prevalence of sarcopenia in Japan was previously reported as 2.5%–28.0% in males and 2.3%–11.7% in females (16), and that of cachexia was 0.5%–1.0% (17). However, from the perspective of overlapping states, we showed the prevalence of robust was 17% (n=30), pre-frailty was 53% (n=93), sarcopenia was 24% (n=42), frailty was 30% (n=52), and cachexia was 6% (n=10). Our study involving geriatric clinic outpatients showed a high prevalence of these muscle wasting states, especially for frailty and cachexia, and a low prevalence of robust older adults. Konishi et al. reported that using the same cachexia definition in Japan as used in Western countries leads to gross overestimation of the prevalence of cachexia because of lower BMI and body weight (18). Although this study is not representative of community dwelling older adults, it is representative of community dwelling older adults with chronic disease(s) in the Tokyo metropolitan area in Japan.

This study aimed to show the relationship among three muscle wasting states. We found that peak VO_2 is one of the useful indicators for sarcopenia, frailty, and cachexia (including robust and pre-frail older adults). The relationships between peak VO_2 and age (Figure 1A), peak VO_2 and BMI (Figure 1B), and BMI and age (Figure 1C) may be useful in understanding the relation among these muscle wasting states.

Interestingly, Figures 1A–C suggests there are two trajectories from robust; one is “from robust to frailty via pre-frailty” (i.e. aging-based trajectory), and the other is “from robust to cachexia via sarcopenia” (disease-based trajectory). Furthermore, interestingly, these two trajectories shows the significant difference between sarcopenia which is in the aging-based trajectory, as 12 among all of 44 frail participants, and sarcopenia which is in the disease-based trajectory, as all of 21 sarcopenia participants (Table 3, Figure 1 A-C). Although, Muscaritoli M et al reported that cachexia-related sarcopenia must be distinguished from age-related sarcopenia (6), it is difficult to distinguish in clinical practice, so far. This result might indicate that sarcopenia in the aging-based trajectory corresponds to age-related sarcopenia, and sarcopenia in the disease-based trajectory corresponds to cachexia-related sarcopenia. Additionally, this result might be indicated that the prevalence of age-related sarcopenia and cachexia-related sarcopenia among community dwelling older adults are 6.9% and 12.0%. After clarifying the relationship among these three muscle wasting states using two dimensions, we showed three dimensions with age, BMI and peak VO_2, to understand the relation, more easily, among these three muscle wasting states (Figure 2A–C). This three-dimensional scatter plot showed a “valley of aging” and two cliffs toward this valley (i.e. aging- and disease-based trajectories), in this cross-sectional study (Figures 2A–C). One shows slowly decreasing peak VO_2, while maintaining BMI along with aging (aging-based trajectory). The other shows rapidly decreasing peak VO_2 and BMI, regardless of aging (disease-based trajectory).

Additionally, based on Table 3, it might be indicated that there are no sarcopenia which does not co-exist with pre-frailty, and no cachexia which does not co-exist with pre-frailty and/or frailty, in the disease-based trajectory. Therefore, it may be reasonable to understand that there are three layers : robust layer (age 75.4±5.7 years, BMI 23.6±3.5 kg/m^2, peak VO_2 1065.0±244.5 ml/min), pre-frailty layer (age 77.2±6.3 years, BMI 23.4±3.3 kg/m^2, peak VO_2 927.9±301.8 ml/min), and frailty layer (age 80.6±6.7 years, BMI 23.2±3.5 kg/m^2, peak VO_2 788.3±262.5 ml/min), and despite younger age compared with those who were pre-frail and frail, status falling to the pre-frailty layer may be considered cachexia-related sarcopenia; similarly, status falling to the pre-frailty to the frailty layer may be considered cachexia.

This study showed that age, BMI, and peakVO_2 were useful measures, although evaluating peakVO_2 among older adults is sometimes challenging. We previously reported a novel method of predicting peakVO_2 with relatively high quality using the following formula compared with evaluated peak VO_2 ($r=0.74$, $p<0.001$) (19): predicted peak VO_2 = (114.5 × SMI [kg/m^2]) + (7.4 × hand grip strength [kg]) + (352.3 × usual walking speed [m/s]) + (8.7 × the score of the Japanese version of the Montreal Cognitive Assessment) + (31.7 × hemoglobin [g/dl]) − 893.6. Therefore, it may be useful and helpful for clinicians to determine the status of patients using age, BMI, and this formula to predict peak VO_2.

This study had several limitations. We did not evaluate interleukin-6, which is an important parameter for cachexia. A larger sample is needed to understand the prevalence of these three muscle wasting states based on community-dwelling people, rather than clinical outpatients. In addition, a larger sample is needed to understand prevalence rates by sex, and to investigate the prevalence of sarcopenic obesity. Although, this study shows the potential usefulness of SMI as an alternative for BMI, the sample size was small because it needs divide into both of sex. In future, it needs to investigate whether age, BMI, and peak VO_2 could be useful to understand the relationship among sarcopenia, frailty, and cachexia in other ethnicities. Additionally, it needs to investigate the change of these states with nutritional intervention and/or exercise intervention, as longitudinal study. Finally, the participants of this study were based on

hospital sample, and based on chronic disease(s); therefore, there is a limitation to applicate to general elderly population.

In conclusion, this cross-sectional, a pilot study showed the relationship among these muscle wasting states, and the two distinct trajectories among these muscle wasting states on the 3-dimensional age-BMI-peak VO_2 scatterplot.

Acknowledgement

We thank Muneyuki Kagaya for creating the three-dimensional figure using gnuplot software (ver. 5.2 patch level 0). We thank Bonnie Lynch, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. The authors confirm that they have complied with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle Clinical Reports (20).

Author contributions

Masamitsu Sugie, Tetsuya Takahashi, and Marina Nara contributed to acquisition of data and performed the statistical analysis. Kazumasa Harada, Teruyuki Koyama, Hajime Fujimoto, Shunei Kyo, and Hideki Ito contributed to the interpretation of the data. Masamitsu Sugie, Kazumasa Harada, Tetsuya Takahashi, and Marina Nara wrote each draft of the manuscript. All authors critically reviewed and significantly contributed to the intellectual content of the manuscript. All authors agreed on the final content of the manuscript.

Funding

This study had no sponsor.

Declaration of conflicts of interest

Masamitsu Sugie has no conflicts of interest to declare.
Kazumasa Harada has no conflicts of interest to declare.
Tetsuya Takahashi has no conflicts of interest to declare.
Marina Nara has no conflicts of interest to declare.
Teruyuki Koyama has no conflicts of interest to declare.
Hajime Fujimoto has no conflicts of interest to declare.
Shunei Kyo has no conflicts of interest to declare.
Hideki Ito has no conflicts of interest to declare.

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