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Splenic and portal venous flow associated with frailty and sarcopenia in older outpatients with cardiovascular disease

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Abstract

Background Older patients with cardiovascular disease often experience frailty and sarcopenia. We evaluated whether a reduced blood flow in the splenic and portal vein is associated with frailty and sarcopenia in older patients with cardiovascular disease.

Methods Blood flow in the splenic and portal vein was evaluated using EPIQ7 (Philips) in older patients (aged ≥ 65 years, 123 patients) with cardiovascular disease, who visited the frailty outpatient clinic. Frailty was assessed using the Japanese version of Cardiovascular Health Study (J-CHS) criteria and the Kihon Checklist (KCL), while sarcopenia was assessed using the Asian Working Group of Sarcopenia 2019 criteria.

Results The mean age of the patients was 81.6 ± 6.6 years (42.3% female). Frailty was observed in 34.2% of patients using the J-CHS criteria and 36.9% using the KCL criteria, while severe sarcopenia was identified in 20.2% of patients. In the KCL criteria, the splenic venous flow decreased with the severity of frailty (248.3 ± 148.4, 202.1 ± 177.9, 139.2 ± 81.1 mL/min, $P = 0.007$), Additionally, the splenic venous flow was significantly lower in frail patients than in robust patients ($P = 0.006$). This association remained significant even after adjusting for confounding factors such as age, sex, body mass index, habitual drinking, smoking history, diabetes, dyslipidemia, hypertension, systolic blood pressure, atrial fibrillation, heart failure, and history of stroke ($P = 0.039$). In a parallel analysis, the splenic venous flow was remarkably decreased in patients with sarcopenia (232.0 ± 172.8 vs. 145.0 ± 91.9 mL/min, $P = 0.003$); however, no significant relationship was found between the severity of frailty and splenic venous flow according to the J-CHS criteria ($P = 0.159$). Among the J-CHS criteria sub-items, the splenic venous flow was decreased in patients with a decreased appendicular skeletal muscle index (ASMI) (332.9 ± 41.6 vs. 98.5 ± 43.5 mL/min, $P = 0.005$); however, there was no significant difference in the splenic venous flow between patients with and without decreased walking speed ($P = 0.064$) or reduced grip strength ($P = 0.369$). The portal venous flow was not significantly associated with frailty or sarcopenia.

Conclusion In older patients with cardiovascular disease, a decreased splenic venous flow was observed in those with frailty by the KCL criteria, those with sarcopenia, and those with a decreased ASMI.

Keyword Splenic venous flow, Frailty, Sarcopenia, Appendicular skeletal muscle index

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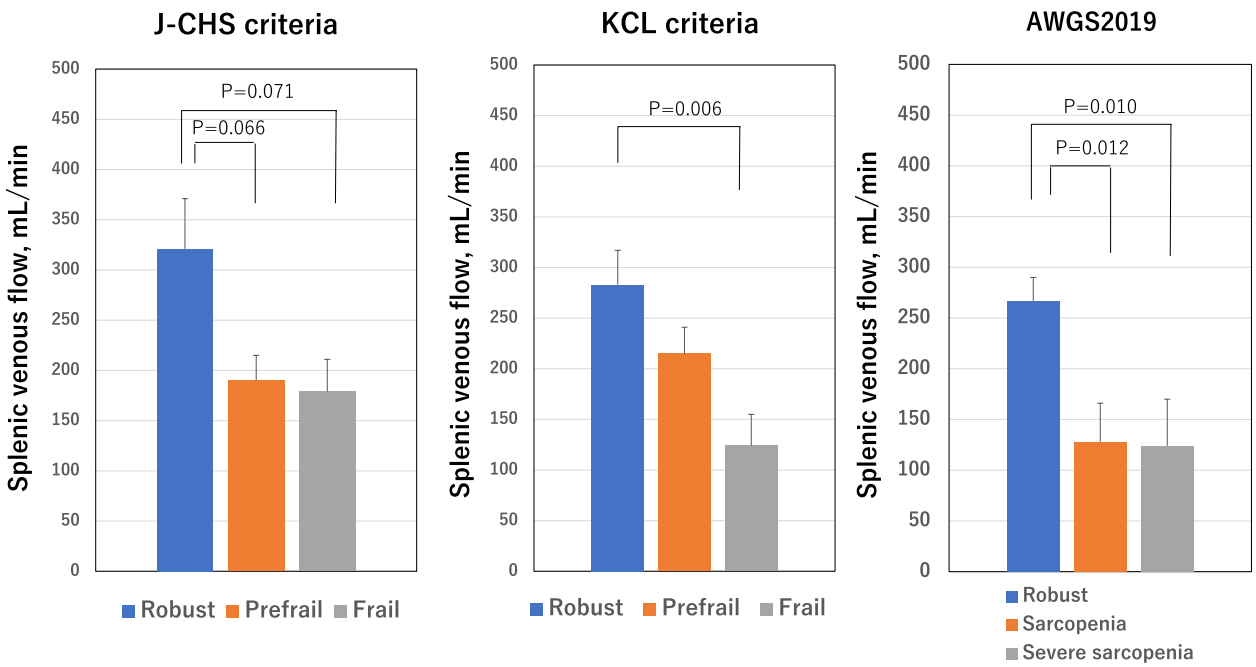

Fig. 1 Difference in the splenic venous flow in patients stratified by frailty using the Japanese version of the Cardiovascular Health Study (J-CHS) criteria, frailty using the Kihon Checklist (KCL) criteria, and sarcopenia using the Asian Working Groups of Sarcopenia (AWGS) 2019 criteria. P-values were calculated using analysis of covariance and Bonferroni test in the adjusted model for age, sex, body mass index, hypertension, diabetes, dyslipidemia, alcohol consumption, smoking status, SBP at echo, atrial fibrillation, heart failure, and history of stroke

Introduction

Patients with congestive heart failure have a higher prevalence of sarcopenia, compared to healthy people of the same age [1, 2]. In a meta-analysis, the prevalence of sarcopenia was reported to be 55% for hospitalized patients with heart failure and 26% for ambulatory patients [3]. Patients with heart failure and frailty were associated with an increased risk of mortality [4], and those with sarcopenia had a 1.64-fold higher risk of poor prognosis [5]. Frailty and sarcopenia may result from an abnormal energy metabolism coupled with mitochondrial dysfunction [6]. Catabolic responses in the diaphragm and quadriceps muscles have been observed [7]. Increased catabolic stress in the skeletal muscle results in insulin resistance [8]. Furthermore, malnutrition could be attributed to inflammatory cytokines [9], which are known to contribute to anorexia [10]. Sarcopenia in congestive heart failure may ultimately progress to cachexia, which is associated with an extremely poor prognosis [2, 11]. Frailty and sarcopenia are prevalent in older people with cardiovascular disease before the development of heart failure [12]. Left ventricular hypertrophy, reduced left ventricular (LV) longitudinal strain, and greater left atrial volume index on echocardiography were associated with an increased risk of frailty [13].

The blood flow of visceral organs could have an important role in the pathogenesis of malnutrition (cachexia), frailty, and sarcopenia in patients with cardiovascular diseases. A higher portal vein congestive index has been observed in patients with heart failure [14]. The spleen may play a role in the pathogenesis of malnutrition as lymphocyte count is a marker of nutritional status [15]. Recently, blood flow in the portal and splenic veins has been easily evaluated using echo sonography.

This study aimed to evaluate whether parameters assessed using abdominal sonography, such as portal and splenic venous flow are associated with frailty and sarcopenia in patients with cardiovascular diseases such as hypertension, atrial fibrillation, and heart failure.

Methods

Participants

We consecutively enrolled older patients with cardiometabolic diseases at a frail outpatient clinic between July 2015 and December 2023 [16]. The detailed protocol has been previously described [16]. The flowchart of patients in this study is shown in Supplemental Fig. 1. In the present study, we analyzed data from 123 participants who agreed to undergo both cardiac and abdominal echography for evaluation of cardiovascular disease. We excluded those with duplication, withdrawal of informed consent, and age < 65 years.

Evaluation of frailty and sarcopenia

The detailed methods used to measure the appendicular skeletal muscle index (ASMI), grip strength, and walking speed and the diagnostic criteria for sarcopenia and frailty have been previously described [16]. Patients were diagnosed with sarcopenia if they had weak handgrip strength (< 28 kg for men and < 18 kg for women) or slow walking speed (< 1.0 m/s) in addition to a low ASMI (< 7.0 kg/m^2 for men and < 5.7 kg/m^2 for women measured by the bioimpedance method), according to the latest diagnostic criteria for sarcopenia, as defined by the Asian Working Group for Sarcopenia 2019 [17]. Frailty was diagnosed using the modified Japanese version of the Cardiovascular Health Study (J-CHS) criteria [16, 18, 19] and the Kihon Checklist (KCL) criteria [20–22], developed by the Ministry of Health, Labour, and Welfare of the Japanese government to screen older frail groups. KCL comprises 25 items that evaluate the activities of daily living and physical function and nutrition, oral health, social withdrawal, cognition, and depression, and individuals with scores ≥ 8 are diagnosed with frailty. Nutritional controlling status (CONUT) score was evaluated using lymphocyte count, serum albumin, and total cholesterol level [15].

Abdominal echo sonography

Abdominal echography was performed using EPIQ (Phillips, Amsterdam, Netherlands) with a 3.5-MHz convex probe. Patients were instructed to visit the hospital for the measurement in a fasting state. The portal venous flow was measured at the hepatic inflow tract (Supplemental Figure S2). The portal venous congestion index was calculated as the ratio between the cross-sectional area (cm^2) and the blood flow velocity (cm/s) of the portal vein, as determined by a Doppler system [23]. The splenic venous flow was measured anterior to the pancreas (Supplemental Figure S3). The spleen index was calculated as spleen long axis distance (cm) × short axis distance (cm) [24]. The S/P ratio was calculated as the splenic venous flow divided by the portal venous flow. To assess reproducibility, splenic and portal venous blood flow measurements were performed on five patients by three technicians (M.K., S.K., and H.O.) in a blinded manner, and the differences in measurements among the technicians were then evaluated. Interobserver differences of portal and splenic venous flows were 357.4 ± 243.6 mL/min and 114.0 ± 68.1 mL/min, respectively.

Echocardiography

Echocardiography was conducted at the time of abdominal echo using Vivid E9 or E95 (GE Medical, USA). LV stroke volume was measured using pulse wave form at the LV outflow in the apical three-chamber view and diameter in the parasternal long axis view. LV ejection fraction was measured using modified Simpson's method in the apical four- and two-chamber views. Inferior vena cava (IVC) diameter was measured in the subxiphoid view at end-inspiration and end-expiration. Trans-mitral E and A wave velocities were measured in the apical three-chamber view; septal e′ wave of the mitral valve tissue Doppler image was measured and septal E/e′ was calculated for the evaluation of LV diastolic function.

Statistical analysis

Data are presented as mean ± standard deviation or percentage. Differences in patients' characteristics among severity of frailty using the J-CHS and KCL criteria and sarcopenia by Asian Working Group of Sarcopenia 2019 (AWGS2019) were evaluated using analysis of variance for continuous variables and chi-square analysis for dichotomous variables. The intergroup difference was assessed using Tukey's test. After adjusting for covariates of age, sex, body mass index (BMI), regular alcohol consumption, smoking status, hypertension, diabetes, dyslipidemia, atrial fibrillation, heart failure, and history of stroke, differences in the parameters from abdominal echography among severity of frailty by J-CHS and KCL criteria and sarcopenia was assessed using analysis of covariance, and the intergroup difference was evaluated using the Bonferroni test.

Linear relationships between the splenic venous flow and both the KCL score and ASMI were evaluated using Pearson's correlation coefficients (continuous variables). Stepwise multiple linear regression analysis was conducted to exclude the effects of the following confounding factors: age, sex, BMI, regular alcohol consumption habits, smoking status, diabetes mellitus, dyslipidemia, atrial fibrillation, heart failure, and history of stroke.

The odds ratios (ORs) for frailty by the J-CHS criteria, frailty by the KCL criteria, and sarcopenia associated with the splenic venous flow (as a continuous variable) were evaluated using univariate and multivariate logistic regression analyses, adjusted for age, sex, BMI, regular alcohol consumption, smoking status, diabetes mellitus, dyslipidemia, atrial fibrillation, heart failure, and history of stroke.

Linear relationships between the splenic venous flow and age, BMI, left ventricular stroke volume, and inferior vena cava diameter at the end-inspiratory phase were shown in scatter plots and evaluated using Pearson's correlation coefficients.

Statistical significance was set at $P < 0.05$. The statistical software IBM SPSS (version 25.0; Chicago, IL, USA) was used for all analyses.

Table 1 Characteristics of patients ($N = 123$)

Age, years	81.6	±	6.6
Men, %	42.3		
BMI, kg/m^2	23.8	±	4.0
Clinic SBP, mmHg	133.1	±	17.5
Clinic DBP, mmHg	72.2	±	11.3
Clinic pulse rate, bpm	76.8	±	13.9
SBP at echo, mmHg	133.1	±	19.9
DBP at echo, mmHg	71.3	±	13.6
Pulse rate at echo, bpm	64.0	±	10.2
Heart failure, %	20.3		
Atrial fibrillation, %	30.1		
Stroke, %	13.0		
Regular alcohol drinking habit, %	10.0		
Smokers			
Past, %	35.5		
Current, %	5.5		
Dyslipidemia, %	70.5		
Diabetes, %	14.9		
HbA1c 5.7–6.5%, %	47.9		
HbA1c ≥ 6.5%, %	24.4		
Hypertension, %	88.7		
Portal vein peak velocity, cm/s	35.6	±	15.2
Portal vein mean velocity, cm/s	23.7	±	10.7
Portal vein diameter, mm	7.6	±	2.0
Portal venous flow, mL/min	714.2	±	623.2
Portal vein congestion index	0.48	±	0.26
Spleen long axis, mm	76.3	±	12.7
Spleen short axis, mm	28.7	±	5.6
Splenic index	17.9	±	5.9
Spleen vein peak velocity, cm/s	33.5	±	10.6
Spleen vein men velocity, cm/s	20.5	±	7.6
Splenic vein diameter, mm	4.2	±	1.3
Estimated splenic venous flow, mL/min	189	±	146

Data are shown as mean ± standard deviation or percentage

BMI Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure

Results

Participants

The participants' mean age was 81.6 ± 6.36 years (male, 42.3%). The patients' characteristics are presented in Table 1. The percentages of patients with hypertension, atrial fibrillation, heart failure, and a history of stroke were 88.7%, 30.1%, 20.3%, and 13.0%, respectively.

Patient characteristics stratified by frailty according to the J-CHS and KCL criteria and sarcopenia using AWGS2019 are presented in Supplemental Tables S1, S2, and S3. The splenic venous flow was significantly reduced with increasing frailty severity based on the KCL criteria ($P = 0.007$) and sarcopenia ($P = 0.012$). The S/P ratio was significantly different across severity of frailty according to the J-CHS criteria ($P = 0.006$), and the splenic index was significantly lower across severity of sarcopenia ($P = 0.039$). Even after adjusting for confounding factors of age, sex, BMI, hypertension, diabetes, dyslipidemia, atrial fibrillation, heart failure, and history of stroke, the splenic venous flow was significantly reduced in patients with frailty by KCL ($P = 0.006$) and in those with sarcopenia ($P = 0.010$) (Fig. 1).

Patient characteristics stratified by high or low ASMI, gait speed, and handgrip strength are presented in Supplemental Tables S4, S5, and S6. Even after adjusting for the confounding factors, the splenic venous flow was significantly reduced in patients with a low ASMI ($P = 0.007$) (Fig. 2). The S/P ratio was significantly reduced in patients with frailty according to the J-CHS criteria ($P = 0.021$) (Supplemental Figure S4), and the splenic index was significantly reduced in those with a low ASMI ($P = 0.048$) (Supplemental Figure S5).

Linear relationship of the splenic venous flow to the KCL score and ASMI

In the stepwise linear regression analysis that included age, sex, BMI, hypertension, diabetes, dyslipidemia, atrial fibrillation, heart failure, history of stroke, and splenic venous flow as explanatory factors, splenic venous flow was significantly related to KCL score ($P = 0.014$) independently of age. In a parallel analysis, the splenic venous flow was significantly related to the ASMI ($P = 0.014$), independently of sex, BMI, and age (Table 2).

ORs for frailty and sarcopenia are associated with the splenic venous flow

In the logistic regression analysis, the splenic venous flow was associated with risk of frailty according to the KCL criteria (OR, 0.993 per 1 mL/min increase; 95% CI, 0.988–0.998; $P = 0.008$), sarcopenia according to AWGS2019 (OR, 0.991 per 1 mL/min increase; 95% CI, 0.985–0.997; $P = 0.004$), and a low ASMI (OR = 0.994 per 1 mL/min increase; 95% CI, 0.990–0.999; $P = 0.009$) (Table 3).

Cardiac and neuroinflammatory factors are related to the splenic venous flow

In the scatter plots, the splenic venous flow was significantly related to LV stroke volume and inferior vena cava diameter at end-inspiratory time (Fig. 3). However, the splenic venous flow was not significantly related to neutrophil cell count (r = −0.021, $P = 0.826$), lymphocyte count (r = 0.125, $P = 0.190$) or the neutrophil to lymphocyte counts ratio (NLR) (r = −0.099, $P = 0.297$) (Supplemental Figure S6).

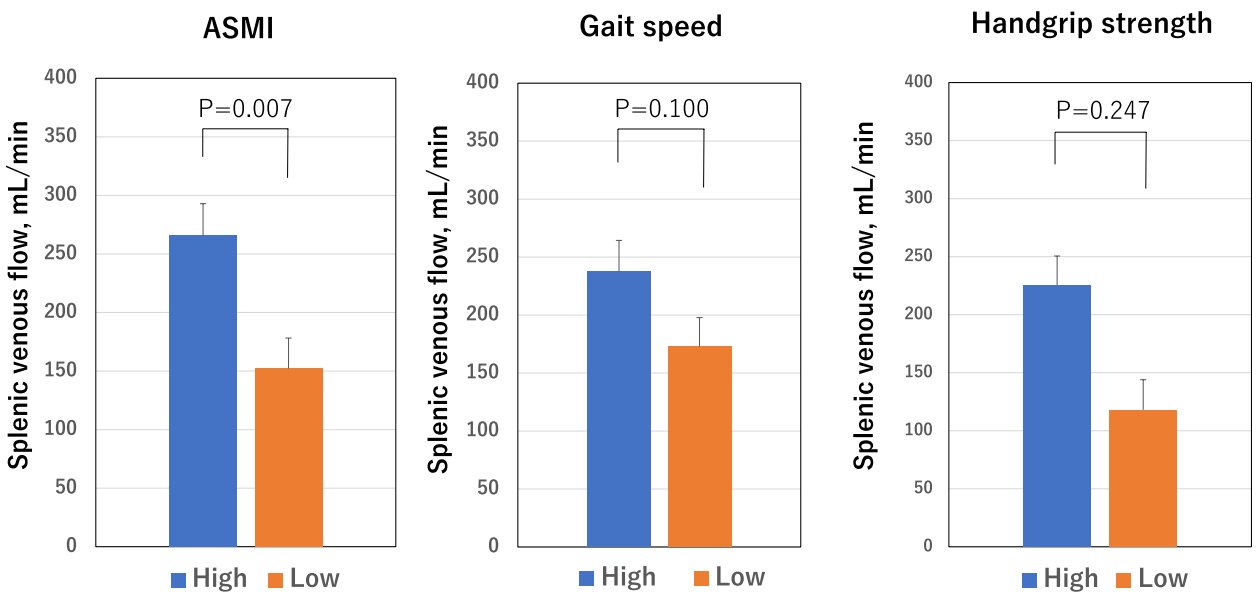

Fig. 2 Difference in the splenic venous flow in patients stratified by the appendicular skeletal muscle index (ASMI), handgrip strength, and gait speed. P-values were calculated using ANCOVA and Bonferroni test in the adjusted model for age, sex, BMI, hypertension, diabetes, dyslipidemia, alcohol consumption, smoking status, SBP at echo, atrial fibrillation, heart failure, and history of stroke

Table 2 Stepwise linear regression analysis for KCL score and ASMI

	B	SE	P
Model for KCL score			
Age, years	0.268	0.058	< 0.001
Estimated splenic venous flow, mL/min	− 0.006	0.002	0.014
Model for ASMI			
Sex, women = 0, men = 1	1.410	0.147	< 0.001
BMI, kg/m^2	0.155	0.017	< 0.001
Estimated splenic venous flow, mL/min	0.001	0.000455	0.014
Age, years	− 0.025	0.012	0.033

Explanatory variables were age, sex, BMI, SBP at echo, regular alcohol drinking habit, smoking status, dyslipidemia, diabetes, hypertension, atrial fibrillation, heart failure, history of stroke, and estimated splenic venous flow

Table 3 Multivariate logistic regression analysis for frailty and sarcopenia associated with estimated splenic venous flow

	OR	LCI	UCI	P
Model for frailty by J-CHS criteria with estimated splenic venous flow, mL/min				
Univariate	0.999	0.996	1.002	0.554
Multivariate-adjusted model	0.999	0.995	1.002	0.448
Model for frailty by KCL criteria with estimated splenic venous flow, mL/min				
Univariate	0.996	0.992	1.000	0.028
Multivariate-adjusted model	0.993	0.988	0.998	0.008
Model for sarcopenia by AWGS2019 with estimated splenic venous flow, mL/min				
Univariate	0.994	0.990	0.998	0.005
Multivariate-adjusted model	0.991	0.985	0.997	0.004
Model for low ASMI with estimated splenic venous flow, mL/min				
Univariate	0.997	0.994	0.9999	0.043
Multivariate-adjusted model	0.994	0.990	0.999	0.009
Model for low handgrip strength with estimated splenic venous flow, mL/min				
Univariate	0.999	0.996	1.001	0.367
Multivariate-adjusted model	0.998	0.995	1.001	0.250
Model for slow gait speed with estimated splenic venous flow, mL/min				
Univariate	0.997	0.994	1.000	0.057
Multivariate-adjusted model	0.997	0.993	1.000	0.077

OR odds ratio, *LCI* 95% lower confidence interval, *UCI* 95% upper confidence interval, *J-CHS criteria* Japanese version Cardiovascular Health Study criteria, *KCL* Kihon check list, *ASMI* appendicular skeletal muscle index. Age, sex BMI, SBP at echo, regular alcohol drinking habit, smoking status, dyslipidemia, diabetes, hypertension, atrial fibrillation, heart failure, and history of stroke were included in the multivariate-adjusted model

Analysis of portal venous flow

There was no significant difference in portal venous flow across severity of frailty and sarcopenia (Supplemental Tables S1, S2, S3, S5, and S6); however, in patients with a lower ASMI, the portal vein diameter was significantly smaller (8.2 ± 2.2 vs. 7.1 ± 1.8 mm, $P = 0.005$) and the portal congestive index was also smaller (0.57 ± 0.30 vs. 0.42 ± 0.22, $P = 0.004$) than those with a higher ASMI (Supplemental Table S4). The portal vein flow was significantly related to the A wave velocity of the trans-mitral flow (r = 0.234, $P = 0.036$). Additionally, the portal vein flow was significantly related to the CONUT score (Spearman's r= − 0.211, $P = 0.037$). The portal vein congestion

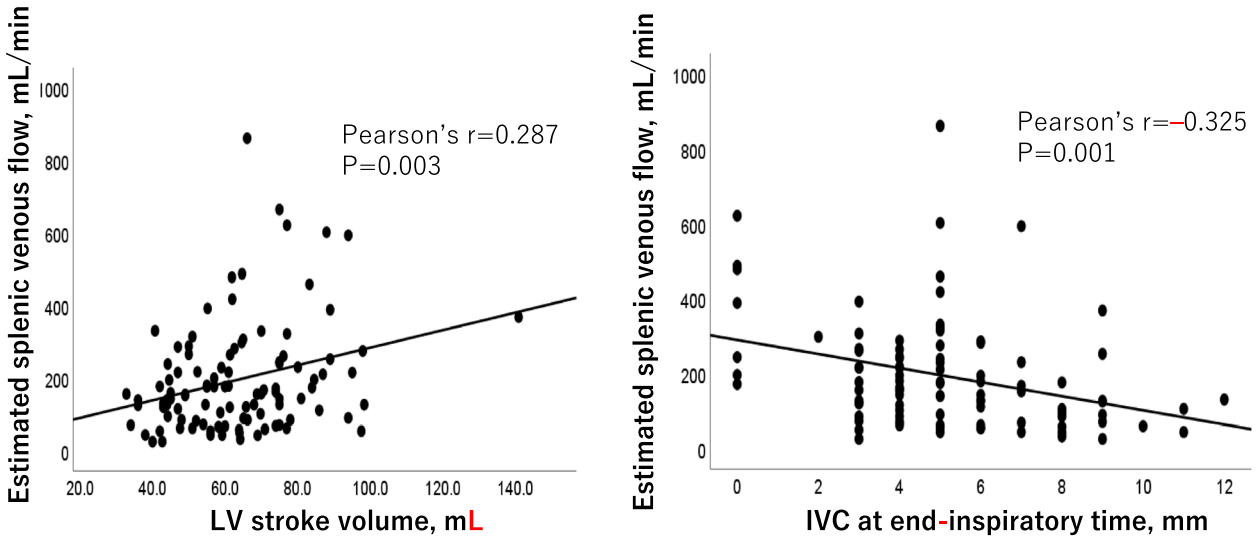

Fig. 3 Scatter plots of the splenic venous flow in relation to the left ventricular stroke volume and to the inferior vena cava diameter at end-inspiratory time. P-values were calculated using Pearson's correlation coefficients

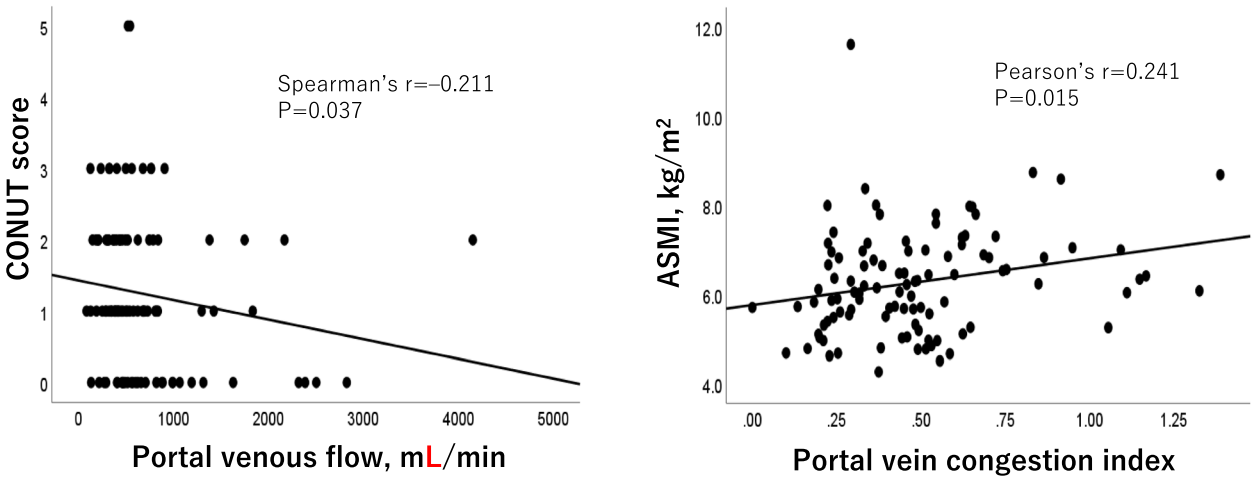

Fig. 4 Scatter plots of the CONUT score in relation to the portal venous flow, and that of the ASMI to the portal vein congestive index. *P*-values were calculated using Spearman's correlation coefficients between the portal venous flow and CONUT score, and Pearson's correlation coefficients between the portal vein congestive index and ASMI

index was significantly related to the ASMI (r = 0.241, *P* = 0.015) (Fig. 4).

Discussion

The splenic venous flow was significantly reduced in patients with frailty using the KCL criteria, sarcopenia by AWGS2019, a low ASMI, and low handgrip strength and tended to reduce in those with frailty using the J-CHS criteria. The reduction of the splenic venous flow was related to a lower left ventricular stroke volume in the heart and a larger IVC at the end-inspiratory phase. To our knowledge, this is the first study to show that the splenic venous flow is reduced in patients with sarcopenia and frailty in older patients with cardiovascular diseases such as hypertension, atrial fibrillation, and/or heart failure. Muscle wasting continuum, from sarcopenia to cachexia, can be observed in cardiovascular disease with the aging process and reduced cardiac function [11], and this may be associated with a reduced blood flow in visceral organs.

In the present study, possible mechanisms of the reduced splenic flow causing frailty and sarcopenia remain unclear. Increased splenic metabolic activity, detected by ^{18}F-fluorodeoxyglucose (^{18}FDG)–positron

emission tomography imaging, after acute coronary syndrome, has been associated with proinflammatory remodeling of circulating leukocytes and the metabolic activity of the spleen, which independently predict the risk of subsequent cardiovascular disease events, suggesting the existence of a cardio–splenic axis [25]. Furthermore, shear wave imaging of the spleen has been reported to be useful for stratifying the prognosis of patients with heart failure [26]. Splenocytes (presumably splenic monocytes and dendritic cells) could promote immune-mediated injurious responses in the failing heart and retain this memory upon adoptive transfer [27]. The neuroimmune axis of cardiovascular control may include both the heart and spleen [28]. A decreased lymphocyte count is included in the CONUT score [15], which has been associated with an increased mortality in patients with heart failure [29]. A decreased splenic venous flow related to a lower left ventricular stroke volume in the heart might be a cause of frailty and sarcopenia, leading to malnutrition. The CONUT score was significantly related to the portal venous flow, but not to the splenic venous flow. Moreover, relationship between NLR and the splenic venous flow did not reach to statistical significance in the present study, while NLR was associated with an increased risk of mortality in patients with cardiovascular diseases [30].

The portal venous flow has been reported to be related to nutritional scores and glucose uptake in the muscles [31], and progressively declines with worsening cardiac function [32]. Increased portal congestion and intestinal edema have been observed in patients with severe heart failure, especially those with impaired right-sided cardiac function [14]. In the present study, the difference in the association between frailty and sarcopenia and the portal and splenic vein was unclear. The S/P ratio was significantly reduced in patients with prefrailty using the J-CHS criteria, but not in those with frailty, compared to those who were robust.

Frailty and sarcopenia could be associated with factors other than cardiovascular diseases, such as pain [33] and cognitive impairment [34], but splenic venous flow was not significantly related to cognitive function scores or pain in the present study (data not shown). Patients with prediabetes and diabetes have been reported to have an increased risk of frailty [35]. In the present study, patients with a low ASMI had a lower prevalence of HbA1c level being $\geq$6.5% (Supplemental Table S4), suggesting that decreased skeletal muscle was associated with uncontrolled diabetes.

Study limitations

The causal relationship between the reduced splenic flow and frailty/sarcopenia is unclear from this study because of the cross-sectional analysis. The splenic vein diameter was smaller in patients with a small body size. Further research is required to explore whether a reduced splenic flow could be a risk factor for developing sarcopenia and frailty. Moreover, this study's sample size was relatively small, and these results should be validated in a large sample size.

Conclusion

In older patients with cardiovascular diseases such as hypertension, atrial fibrillation, and/or heart failure, the splenic venous flow was significantly reduced in patients with frailty using the KCL criteria, sarcopenia using the AWGS2019, a low ASMI, and low handgrip strength, and tended to be reduced in those with frailty as evaluated by the J-CHS criteria. A reduction of the splenic venous flow was related to a lower left ventricular stroke volume in the heart and a larger IVC at the end-inspiratory phase. These results suggest that reduced blood flow to a visceral organ could play a role in the pathogenesis of frailty and sarcopenia in older patients with cardiovascular diseases.

Abbreviations

J-CHS	The Japanese version of Cardiovascular Health Study
KCL	The Kihon Checklist
ASMI	Appendicular skeletal muscle index
LV	Left ventricular
CONUT	Nutritional controlling status
IVC	Inferior vena cava
AWGS2019	Asian Working Group of Sarcopenia 2019
BMI	Body mass index
ORs	Odds ratios

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05973-y.

Supplementary Material 1.

Acknowledgements

None.

Authors' contributions

J Ishikawa had full access to all the data in this study. J Ishikawa was responsible for the accuracy of the data analysis. Concept and design: J Ishikawa. Data acquisition: Keisho Kobayashi, Kana Takani, Teppei Maeda, Masuyo Kawano, and Masaru Kiyomizu. Analysis and interpretation: J Ishikawa. Drafting of the manuscript: J Ishikawa and Shutaro Futami. Critical revisions: All authors. Statistical analysis: J Ishikawa.

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Data availability
The data that support the findings of this study are not openly available and may be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Tokyo Metropolitan Geriatric Hospital (R15-20, 19–03). All the participants provided written informed consent. This study adhered to the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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