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ORIGINAL ARTICLE
Exercise Physiology

Composite Biomarkers for Assessing Frailty Status in Stable Older Adults With Cardiovascular Disease

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Background: The relationship between frailty status and laboratory measurements in cardiovascular disease (CVD) remains unclear. We investigated which laboratory measurements indicated frailty in stable older CVD patients.

Methods and Results: One-hundred thirty-eight stable older CVD patients were evaluated by laboratory measurements, with frailty assessed using the Kihon Checklist (KCL). Laboratory measurements were compared between frail and non-frail groups. Across the entire cohort, mean age was 81.7 years, mean left ventricular ejection fraction was 57.8%, and mean plasma B-type natriuretic peptide was 182 pg/mL. KCL scores were used to divide patients into non-frail (n=43; KCL <8) and frail (n=95; KCL ≥8) groups. Serum iron was significantly lower in the frail than non-frail group (mean [±SD] 61.2±30.3 vs. 89.5±26.1 μg/dL, respectively; P<0.001). Blood urea nitrogen (BUN; 27.3±16.5 vs. 19.7±8.2 mg/dL; P=0.013) and C-reactive protein (CRP; 1.05±1.99 vs. 0.15±0.21 mg/dL; P=0.004) were significantly higher in the frail than non-frail group. Multivariate analysis revealed that serum iron, CRP, and BUN were significant independent predictors of frailty (β=–0.069, 0.917, and 0.086, respectively).

Conclusions: Frailty status was significantly associated with iron, CRP, and BUN in stable older CVD patients. Composite biomarkers (inflammation, iron deficiency, and renal perfusion) may be useful for assessing frailty in these patients.

Key Words: Biomarker; Cardiovascular disease; Frailty; Inflammation; Older adult

Frailty is an important concept in geriatric medicine, and understanding its etiology has become a fundamental aspiration of many researchers in the field of aging.[1] Frailty is an aging-associated syndrome that produces subclinical dysfunction across multiple organ systems, leading to increased risk of mortality.[2] Between 25% and 50% of patients with cardiovascular disease (CVD) are frail.[3] Moreover, according to a systematic review, the prevalence of frailty in heart failure (HF) ranges from 18% to 54%.[4,5]

The development of frailty is linked to various conditions, such as chronic inflammation and changes in the immune and endocrine systems,[6,7] and is associated with an increased risk of death.[8] CVD, including HF, is the leading cause of morbidity in frail patients.[9,10] The Kihon Checklist (KCL) was developed by the Japanese Ministry of Health, Labour and Welfare to identify older people with frailty in need of care; it is a reliable tool for predicting general frailty in the elderly.[11]

Biomarkers identified through the implementation of multivariate strategies may be used to support the detection of frailty. The progression of these biomarkers can be tracked over time or in response to interventions, and reveals the onset of complications, such as mobility disability, at a very early stage.[12] Therefore, there is an increasing need to identify and validate robust biomarkers for frailty. Inflammation, as indicated, for example, by serum concentrations of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α, has been implicated in the pathogenesis of both frailty[12] and HF,[13] although the pathophysiology of both disorders is complex and includes multiple deranged pathways that require further elucidation. However, the importance of general laboratory measurements in assessing frailty in older adults with CVD remains unclear. Therefore, the aim of this study was to evaluate which laboratory measurements indicate frailty in stable older adults with CVD.

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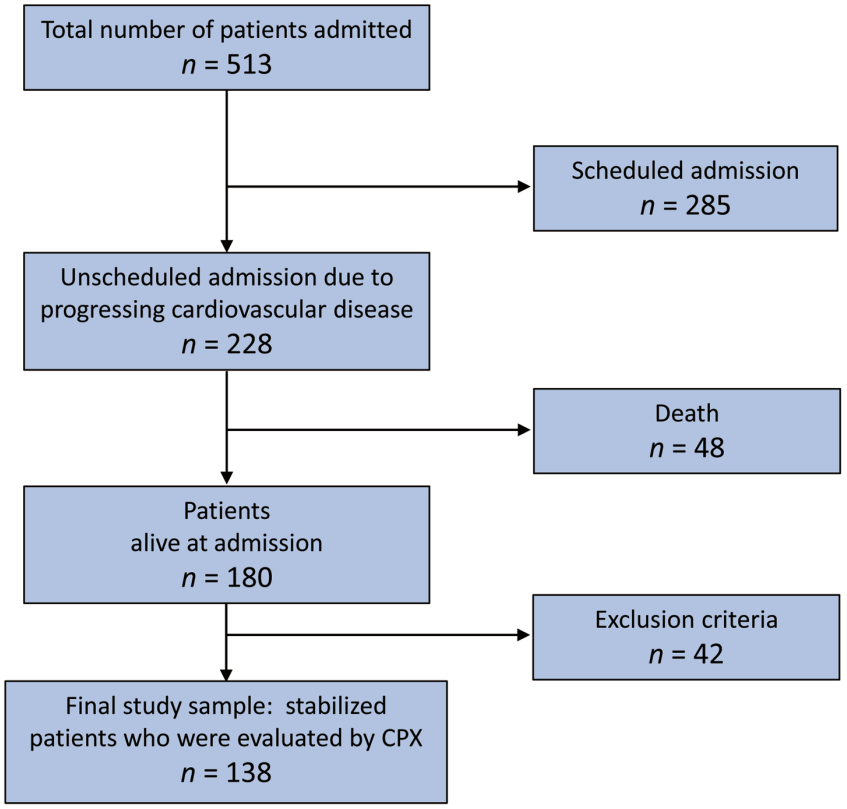

Figure 1. Study flowchart for the present analysis. Of the 228 patients with an unscheduled admission due to progressing cardiovascular disease to the Cardiology Department of the National Center of Geriatrics and Gerontology, Japan, between August 2016 and December 2019, 138 were included in the present study. CPX, cardiopulmonary exercise.

Methods

Study Population

We conducted a cross-sectional study of patients who were admitted to the Cardiology Department of the National Center of Geriatrics and Gerontology, Japan, between August 2016 and December 2019. The study population consisted of 138 patients with CVD who were at least 65 years old and were able to perform cardiopulmonary exercise testing, undergo laboratory measurements, echocardiography, and a physical function evaluation, and complete questionnaires. These assessments were performed after the patients had been medically stabilized.

The inclusion criteria were structural heart disease consisting of coronary artery disease (having experienced angina pectoris or myocardial infarction, with or without a history of revascularization procedures), symptomatic HF (including conditions such as non-ischemic cardiomyopathy, ischemia, tachycardia, bradycardia, valvular disease, and hypertension), and others (see below). Non-ischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial, or congenital heart disease. Tachycardia and bradycardia included atrial, supraventricular, and ventricular arrhythmias, sick sinus syndrome, and atrioventricular block in the absence of structural heart disease. Valvular heart disease was diagnosed on the basis of hemodynamic or echocardiographic findings or a history of valvular or congenital cardiac surgery. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a history of treatment for hypertension. Included in the "others" category were aortic disease, peripheral artery disease, and other vascular diseases. HF was defined as pulmonary venous congestion or edema on chest X-ray plus any symptoms (e.g., dyspnea, ankle swelling, peripheral edema, or fatigue).

Exclusion criteria were severe respiratory dysfunction (those receiving long-term oxygen therapy for respiratory disease), liver dysfunction (Child-Pugh Class C), stroke, renal dysfunction (albuminuria and glomerular filtration rate category G5), malignant tumors carrying a prognosis of <1 year, difficulty walking 10 m even with a walking aid, a Mini-Mental State Examination score <18, and living in a nursing care facility before admission.

Only patients who were stable after admission were enrolled in the study (**Figure 1**). Of 228 patients with unscheduled hospital admittance due to worsening CVD, 138 were included in the final analysis.

Study Protocol

Physical examination, laboratory measurements, cardiopulmonary exercise testing, and the KCL questionnaire were applied within 3 days of study enrollment. All patients were in a stable condition at the time of testing. The study protocol complied with the Declaration of Helsinki, and written informed consent was obtained from each subject. The Ethics and Conflict of Interest Committee of the National Center for Geriatric and Gerontology approved the study (Approval no. 1272).

KCL

The KCL was developed by the Japanese Ministry of Health,

No.	Questions	Answer	
1	Do you go out by bus or train by yourself?	□0. YES	□1. NO
2	Do you go shopping to buy daily necessities by yourself?	□0. YES	□1. NO
3	Do you manage your own deposits and savings at the bank?	□0. YES	□1. NO
4	Do you sometimes visit your friends?	□0. YES	□1. NO
5	Do you turn to your family or friends for advice?	□0. YES	□1. NO
6	Do you normally climb stairs without using handrail or wall for support?	□0. YES	□1. NO
7	Do you normally stand up from a chair without any aids?	□0. YES	□1. NO
8	Do you normally walk continuously for 15 minutes?	□0. YES	□1. NO
9	Have you experienced a fall in the past year?	□1. YES	□0. NO
10	Do you have a fear of falling while walking?	□1. YES	□0. NO
11	Have you lost 2kg or more in the past 6 months?	□1. YES	□0. NO
12	Height: cm, Weight: kg, BMI: kg/m^2 If BMI is less than 18.5, this item is scored.	□1. YES	□0. NO
13	Do you have any difficulties eating tough foods compared to 6 months ago?	□1. YES	□0. NO
14	Have you choked on your tea or soup recently?	□1. YES	□0. NO
15	Do you often experience having a dry mouth?	□1. YES	□0. NO
16	Do you go out at least once a week?	□0. YES	□1. NO
17	Do you go out less frequently compared to last year?	□1. YES	□0. NO
18	Do your family or your friends point out your memory loss? e.g."You ask the same question over and over again."	□1. YES	□0. NO
19	Do you make a call by looking up phone numbers?	□0. YES	□1. NO
20	Do you find yourself not knowing today's date?	□1. YES	□0. NO
21	In the last 2 weeks have you felt a lack of fulfillment in your daily life?	□1. YES	□0. NO
22	In the last 2 weeks have you felt a lack of joy when doing the things you used to enjoy?	□1. YES	□0. NO
23	In the last 2 weeks have you felt difficulty in doing what you could do easily before?	□1. YES	□0. NO
24	In the last 2 weeks have you felt helpless?	□1. YES	□0. NO
25	In the last 2 weeks have you felt tired without a reason?	□1. YES	□0. NO

Figure 2. Kihon checklist. BMI, body mass index.

Labor and Welfare to identify older people in need of care and is a reliable tool for predicting general frailty in older adults. The KCL is a 25-item self-administered questionnaire (**Figure 2**). It comprises 7 categories of questions that assess instrumental activities of daily living, physical function, nutritional status, oral function, social activities of daily living, cognitive function, and depressive mood. Thus, the KCL comprehensively examines the social, psychological, and physical aspects of frailty.[14–16] The questions require simple yes/no answers, which are scored as either 1 or 0, depending on the question. The sum of the indices ranges from 0 (non-frail) to 25 (severe frailty); a higher score indicates worse functioning. KCL scores of 0–3 are classified as robust, scores of 4–7 are classified as pre-frail, and scores ≥8 are classified as frail.[14] In the present study, patients were allocated to non-frail (KCL <8; n=43) and frail (KCL ≥8; n=95) groups on the basis of the KCL score.

Statistical Analysis

Data are presented as the mean±SD, unless stated otherwise. Variables were compared between CVD patients with and without frailty using Student's t-test for unpaired data. The Chi-squared test was used to assess the significance of differences between dichotomous variables. Spearman's rank and Pearson's correlation coefficients were used to assess the relationships between KCL score and laboratory measurements. Multivariate linear regression analyses were used to identify factors that were independently associated with KCL score; the multivariate model included all baseline variables that had a significant correlation with KCL score in the Pearson's correlation. All analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Two-sided $P<0.05$ was considered statistically significant.

Results

Patient Characteristics

Baseline clinical characteristics of the patients are presented in **Table 1**. In all, 138 consecutive older adult patients with CVD (78 (57%) men; mean age 81.7±6.6

Table 1. Baseline Characteristics of the Study Population (n=138)	
Age (years)	81.7±6.6
Male sex	78 (57)
BMI (kg/m^2)	22.1±4.1
Atrial fibrillation	44 (32)
KCL	10.7±5.7
No. robust/pre-frail/frail	12/31/95
Resting SBP (mmHg)	136±22
Resting HR (beats/min)	72±12
Underlying disease	
Heart failure	126 (91)
Cardiomyopathy	25 (18)
Ischemic heart disease	28 (20)
Hypertension	12 (9)
Tachycardia-induced	23 (17)
Valve	21 (15)
Bradycardia	11 (8)
Other	6 (4)
Post-PCI or -CABG	12 (9)
Medication	
Diuretics	76 (55)
Tolvaptan	30 (22)
ACE-I/ARB	50 (36)
β-blockers	43 (31)
Spironolactone	33 (24)
Anticoagulant	52 (38)
Clinical data	
LVEF (%)	57.8±14.3
BNP (pg/mL)	182 [42–272]
eGFR (mL/min/1.73 m^2)	50±19
Hb (mg/dL)	12.1±2.0
TP (g/dL)	6.87±0.63
Albumin (g/dL)	3.75±0.52
TC (mg/dL)	175±36

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range], or n (%). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, heart rate; KCL, Kihon Checklist; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TC, total cholesterol; TP, total protein

years) were enrolled in the study. At the time of enrollment, all patients were stable and on optimal pharmacological therapy according to current guidelines for the treatment of CVD.[17,18] The median plasma B-type natriuretic peptide (BNP) concentration was 182 pg/mL (interquartile range 42–272 pg/mL) and the mean left ventricular ejection fraction (LVEF) was 57.8±14.3%. On the basis of KCL scores, 68.4% of patients were frail (mean KCL score for all patients 10.7±5.7).

Comparisons of Non-Frail and Frail Patients

Subjects were allocated to 1 of 2 groups based on the absence (n=43) or presence (n=95) of frailty (**Table 2**). Age was significantly higher in the frail than non-frail group (P=0.019). Similarly, plasma BNP concentrations were significantly higher in the frail than non-frail group (P=0.038); however, the estimated glomerular filtration rate (eGFR) was comparable in both groups. Serum iron concentrations were significantly lower in the frail than non-frail group (61.2±30.3 vs. 89.5±26.1 μg/dL, respectively; P<0.001). Blood urea nitrogen (BUN) was significantly higher in the frail than non-frail group (27.3±16.5 vs. 19.7±8.2 mg/dL, respectively; P=0.013), as was serum CRP (1.05±1.99 vs. 0.15±0.21 mg/dL, respectively; P=0.004).

Correlations Between Biomarkers and Frailty

The KCL score was significantly associated with hemoglobin, albumin, BUN, iron, CRP, eGFR, and BNP in the Spearman's rank and Pearson's correlation analyses (**Table 3**). We then analyzed these significantly associated parameters for KCL score in multivariate analyses and found that serum iron and CRP concentrations and BUN were significant independent predictors of frailty (β=−0.069, 0.917, and 0.086, respectively; **Table 3**).

Discussion

The main aim of the present study was to elucidate the relationship between general biomarkers and frailty in older adults with CVD. Here, we report for the first time that serum iron and CRP and BUN concentrations are strongly associated with the presence of frailty in older adults with CVD. Frail patients scored significantly more poorly than non-frail patients on these items related to nutrition, inflammation, and protein catabolism. However, the frail group had people on a gradual scale from mild to severe frailty. In fact, the KCL scoring system runs from 0 to 25 points. Therefore, we thought it may be more important data-wise to correlate the baseline characteristics with the KCL score. Furthermore, we wanted to show which laboratory data contributed to the KCL scores. Among the blood biomarkers, iron, CRP, and BUN were regulatory factors independent of the deterioration of KCL in older adults with CVD.

Iron

Aging-related comorbidities are an emerging problem in patients with CVD. Among them, iron deficiency is an important therapeutic target regardless of the concomitant hemoglobin level.[19] A recent study confirmed the relationship between reduced iron concentration and the occurrence of frailty syndrome.[20] Iron deficiency affects up to 50% of CVD patients, and its association with poor quality of life, impaired exercise tolerance, and increased mortality rates has been widely established.[21] Current European Society of Cardiology Guidelines for CVD recommend a diagnostic workup for iron deficiency in all CVD patients.[22] Iron deficiency has detrimental effects in patients with coronary artery disease, HF, or pulmonary hypertension, and possibly in patients undergoing cardiac surgery.[23] Perturbations of iron metabolism resulting in changes in iron status are observed in a variety of age-related medical conditions, including kidney disease, cancer, CVD, and neurodegenerative diseases.[19]

BUN

The kidneys play an important role in the initiation and progression of CVD, and approximately one-third of patients with CVD show some degree of renal dysfunction.[24] BUN is an independent predictor of long-term mortality in older, medically stable veterans.[25] Elevated BUN may

Table 2. Comparisons of Non-Frail and Frail Groups

	Non-frail group (KCL <8; n=43)	Frail group (KCL ≥8; n=95)	P value
Age (years)	79.1±7.6	83.1±6.1	0.019
Sex (male/female)	25/18	53/42	0.724
BMI (kg/m^2)	24.1±3.6	21.0±3.3	0.001
Diuretics	17 (39)	61 (64)	0.056
Tolvaptan	9 (22)	22 (23)	0.878
ACE-I/ARBs	22 (52)	41 (43)	0.539
β-blockers	9 (22)	30 (32)	0.877
Spironolactone	9 (22)	22 (23)	0.878
Anticoagulants	17 (39)	36 (38)	0.948
Clinical data			
LVEF (%)	62.1±9.4	55.7±15.9	0.082
E/e'	15.1±7.2	16.1±6.7	0.534
LAD (mm)	40.7±8.3	39.1±6.0	0.402
WBC (/mm^3)	57.3±16.3	59±22.4	0.741
Hb (g/dL)	13.3±1.9	11.5±1.9	0.001
Plt (g/dL)	20.4±5.1	20.1±7.3	0.87
TP (g/dL)	7.2±0.5	6.7±0.6	0.547
Albumin (g/dL)	4.0±0.3	3.6±0.6	<0.001
AST (IU/L)	22±4.3	23.5±18.2	0.705
ALT (IU/L)	21.7±11.2	20.7±40.3	0.906
LDH (IU/L)	205.1±35	204.5±58.5	0.963
BUN (mg/dL)	19.7±8.2	27.3±16.5	0.013
Cr (mg/dL)	0.9±0.2	1.3±0.7	0.004
TC (mg/dL)	186±32	173±37	0.164
TG (mg/dL)	127.2±58.9	119.3±67.8	0.637
Fe (μg/dL)	89.5±26.1	61.2±30.3	<0.001
CRP (mg/dL)	0.15±0.21	1.05±1.99	0.004
HbA1c (%)	6.1±0.4	6.2±0.8	0.602
BNP (pg/mL)	123.4±143.6	221.9±194.6	0.038
eGFR (mL/min/1.73 m^2)	56.4±14.1	47.7±23	0.101

Unless indicated otherwise, data are given as the mean±SD or n (%). ALT, aspartate aminotransferase; AST, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; E/e', ratio of early transmitral flow velocity to early diastolic mitral annular velocity; Fe, iron; LAD, left atrial dimension; LDH, lactate dehydrogenase; Plt, platelets; TG, triglycerides; WBC, white blood cell count. Other abbreviations as in Table 1.

reflect poor global health status, rather than solely being an indicator of the severity of acute illness or unstable chronic disease.[25]

Silverberg et al first described the term "cardiorenal anemia syndrome".[26] This term has been widely used in recent years, now that we understand the importance of the associations among HF, renal failure, and anemia. High BUN has a negative effect on patient survival and reflects the extent of catabolism. In the acute phase of a critically illness, this catabolism may be beneficial, providing amino acids for hepatic gluconeogenesis and for the synthesis of proteins involved in immune functions, but persistent hypercatabolism in critically ill patients results in decreased immune function, which leads to increased mortality.[27] In addition, Kameda et al reported that metabolite profiles efficiently distinguish frailty from non-frailty.[28] Oxidative stress resulting from diminished antioxidant levels could be a key vulnerability for the pathogenesis of frailty, exacerbating illnesses related to human aging.[28] Therefore, BUN is considered an integral marker of tissue necrosis, protein catabolism, and renal perfusion.

CRP

In older adults, there is a significant association between elevated levels of high-sensitivity CRP and the development of HF.[29,30] In addition, aging has been associated with an increase in inflammatory biomarkers.[31] Increased serum CRP concentrations are positively associated with increased severity of frailty in people aged >75 years, and increasing frailty is also associated with increasing TNF-α and IL-6 levels.[32] Here, we chose to perform only those standard laboratory measurements that are used for health insurance purposes, so we did not check TNF-α and IL-6 levels. However, even in the absence of clinical signs, CRP may be useful in detecting frailty in older adult patients with CVD.

BNP

In patients with chronic HF, the BNP concentration provides powerful prognostic information regarding survival and deterioration of functional status.[33] In the Valsartan Heart Failure Trial, patients with the greatest rise in BNP concentrations despite therapy had the highest rates of morbidity and mortality.[34] Notably, in the present study

Table 3. Correlation and Multivariate Linear Regression Analyses for KCL Scores

Laboratory measurement	Spearman		Pearson		Multivariate	
	ρ	P value	r	P value	β (95% CI)	P value
WBC	−0.020	0.872	−0.079	0.514		
Hb	−0.337	0.004	−0.317	0.008	−0.137 (−0.891, 0.616)	0.716
Plt	−0.163	0.179	−0.053	0.661		
Albumin	−0.435	<0.001	−0.461	<0.001	−2.250 (−5.060, 0.558)	0.112
AST	−0.151	0.213	−0.089	0.464		
ALT	−0.162	0.193	−0.036	0.766		
LDH	−0.077	0.524	−0.055	0.649		
BUN	0.256	0.032	0.351	0.003	0.086 (0.006, 0.166)	0.036
Cr	0.211	0.079	0.245	0.041		
TC	−0.176	0.145	−0.144	0.236		
LDL-C	−0.214	0.082	−0.191	0.121		
TG	−0.237	0.053	−0.190	0.045		
Fe	−0.435	<0.001	−0.441	<0.001	−0.069 (−0.107, −0.031)	0.001
CRP	0.428	<0.001	0.431	0.001	0.917 (0.226, 1.608)	0.010
eGFR	−0.321	0.007	−0.280	0.041	−1.472 (−4.522, 1.579)	0.338
HbA1c	0.007	0.957	0.114	0.350		
BNP	0.334	0.005	0.291	0.015	0.002 (−0.005, 0.010)	0.537

ρ, Spearman's rank correlation coefficient; r, Pearson's correlation coefficient; β, multiple regression coefficient; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol. Other abbreviations as in Tables 1,2.

we found that serum iron and CRP concentrations and BUN were superior to BNP concentrations for the diagnosis of frailty in older adults with stable CVD. Ninety-one per cent of our 138 patients were admitted because of worsening HF. Even in patients in a stable condition after medical treatment, BNP is supposed to indicate disease severity or prognosis in HF. However, although BNP was significantly correlated with KCL, it was not a significant independent predictor of frailty according to the KCL in older adult patients with CVD. In assessing frailty, we need to pay attention to the evaluation of laboratory items other than powerful conventional prognostic markers, such as BNP, in the elderly CVD population.

Frailty and CVD

Frailty is a multidimensional syndrome based on an aggregate susceptibility to adverse health outcomes due to age- and disease-related deficits that accumulate across multiple domains.[35,36] It is also associated with mortality.[37] Several tools have been developed for assessing frailty, but there is no international standard measurement. The KCL, a self-administered questionnaire, is considered useful for frailty screening in older adult populations.[14] KCL scores are significantly correlated with Fried's frailty phenotype values.[14]

The mean age of the patients in this study was 81.7 years, and many were frail (68.5% had KCL scores ≥8). The mean BNP concentration once the patients had been stabilized after appropriate medical therapy during admission was 182pg/mL. In addition, the frail CVD patients were significantly older and had a significantly lower body mass index than those who were not frail, in accordance with the general concept of frailty.[2,9] However, echocardiogram parameters, such as LVEF and left arterial dimension, did not differ between the 2 groups. In the case of LVEF, this finding is not surprising given that approximately half of all patients with HF have preserved ejection fraction.[38] This population likely well represents those patients currently admitted to Japanese hospitals with worsening CVD; the numbers of older adults with CVD are likely increasing because of the recent decline in the birthrate and aging of the population. Therefore, our study focused on evaluating the clinical usefulness of common biomarkers for detecting frailty as determined by the KCL in the increasing Japanese population of stable older adult patients with CVD.

One of the reasons why composite biomarkers are useful for assessing frailty is multimorbidity, which is common in older adults. The strong association of multimorbidity with age is well recognized, but, because of the variations mentioned above, further research is needed to develop accurate composite markers that take these multimorbidities into account.

Clinical Implications

Laboratory measurements are commonly evaluated in daily practice because they are inexpensive, repeatable, and non-invasive tests. In the present study, we did not include specialized items relevant to frailty, such as IL-6 and TNF-α, in the laboratory measurements because we wanted to test only those biomarkers used in general assessments. To the best of our knowledge, the present study is the first to have investigated the ability of these standard laboratory measurements to detect frailty in older adults with stable CVD. The primary goals of CVD therapy are to improve quality of life and extend survival. The recognition of frailty within the medical community has created the need for diagnostic tests to determine when a patient's physical ability has deteriorated.

Study Limitations

The present study was a single-center study with a small sample size. Moreover, we did not assess repeated measures over time or follow the incidence of cardiac events in the enrolled patients. We did not check ferritin levels, which are associated with iron levels. Nor did we check

IL-6 and TNF-α levels, which are also related to frailty. We also did not assess changes in the trajectory of exercise capacity or frailty due to medical intervention or cardiac rehabilitation.

Conclusions

Frailty status was significantly associated with serum iron and CRP concentrations and BUN in stable older adults with CVD. Composite biomarkers for inflammation, iron deficiency, and renal perfusion may be useful for assessing frailty in stable older adults with CVD.

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Disclosures

T.M. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to disclose.

Author Contributions

A.H., A.S., I.K., T.M., and H.A. supervised the research and prepared the text. K.H. and K.S. evaluated frailty. A.H., K.N., M.K., N.S., and A.S. evaluated patients. All authors reviewed the text and agree with the paper's publication.

IRB Information

The present study was approved by the Ethics and Conflict of Interest Committee of the National Center for Geriatric and Gerontology (Reference no. 1272).

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