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Relationship between the serum GDF-15 concentration and muscle function in female patients receiving aortic valve replacement (TAVR, SAVR): Comparison with healthy elderly female subjects

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ABSTRACT

Purpose: Sarcopenia is closely associated with postoperative prognosis in patients undergoing cardiovascular surgery. Growth differentiation factor (GDF)-15 is involved in the pathogenesis of cardiovascular disease. We examined the relationship between the serum GDF-15 concentration and muscle function in patients receiving aortic valve replacement and healthy elderly subjects.

Methods: Forty-three female patients undergoing aortic valve surgery (79.9 ± 6.4 years; transcatheter aortic valve replacement [TAVR] n = 19, conventional surgical aortic valve replacement [SAVR] n = 24) and 64 healthy elderly female subjects (75.9 ± 6.1 years) were included. Walking speed, grip strength, and skeletal muscle mass index (SMI) by a multifrequency bioelectrical impedance analyzer were measured to determine the presence of sarcopenia. Preoperative serum GDF-15 concentration was measured by enzyme-linked immunosorbent assay.

Results: The GDF-15 level was higher in patients receiving aortic valve replacement than in healthy elderly subjects (aortic valve replacement: 1624 ± 1186 pg/mL vs. healthy: 955 ± 368 pg/mL, $p < 0.001$). Multivariate linear regression analysis showed that the serum GDF-15 level determined grip strength independently of the high-sensitivity C-reactive protein level and eGFR, even after adjusting for age ($\beta = -0.318$, $p = 0.025$). Sarcopenia was found in 12.5% of healthy elderly subjects, 83.3% of patients with TAVR, and 64.3% of patients with SAVR. The GDF-15 concentration that defined sarcopenia was 1109 pg/mL in subjects including patients receiving aortic valve replacement.

Conclusions: The preoperative serum GDF-15 concentration, which was higher in female patients receiving aortic valve replacement than in healthy elderly subjects, may be a serum marker of sarcopenia.

Abbreviations: GDF, growth differentiation factor; TAVR, transcatheter aortic valve replacement; SAVR, conventional surgical aortic valve replacement; SMI, skeletal muscle mass index; ROC, receiver-operating characteristics; eGFR, estimated glomerular filtration rate; AS, aortic stenosis; CHF, chronic heart failure; VO_2, oxygen uptake; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; TGF, transforming growth factor; hsCRP, high-sensitive C-reactive protein; ELISA, enzyme-linked immunosorbent assay; AWGS, Asian Working Group for Sarcopenia; ANOVA, analysis of variance; CFS, Clinical Frailty Scale; PAH, pulmonary arterial hypertension; BNP, brain natriuretic peptide; GH, growth hormone; TAK1, TGFβ-activated kinase 1.

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1. Introduction

With the coming of a super-aging society, age-related muscle loss (sarcopenia in the narrow sense) has become a serious problem, while the heart failure pandemic has arrived [1]. The incidence of aortic stenosis (AS) has been increasing in elderly patients, and transcatheter aortic valve replacement (TAVR) has become a popular therapeutic choice for AS management [2,3]. In addition, frailty and heart failure are closely related [4], and muscle loss (sarcopenia in the broad sense) occurs due to cachexia caused by heart failure and other diseases. In a study that evaluated sarcopenia in patients with chronic heart failure (CHF), sarcopenia was an independent determinant of low peak oxygen uptake (VO_2) on multivariate analysis, even after adjustment for age, gender, New York Heart Association (NYHA) class, hemoglobin level, left ventricular ejection fraction (LVEF), 6-minute walk distance, and number of comorbidities [5]. Thus, the evaluation of sarcopenia may also be important for patients receiving aortic valve replacement including TAVR.

Growth differentiation factor (GDF)-15 is a stress-responsive member of the transforming growth factor (TGF)-β cytokine superfamily. Sarcopenia involves both attenuated muscle growth promotion and enhanced muscle growth inhibition, and biomarkers of muscle growth inhibition include myostatin and GDF-15 [6]. Plasma myostatin levels are increased in patients with heart failure compared to healthy subjects [7]. Also, in patients with severe AS, the level of GDF-11, but not myostatin, was elevated in frail patients and associated with prognosis [8]. In addition, results of a randomized placebo-controlled trial of bimagrumab, the myostatin / activin type II receptor antibody, in elderly sarcopenic patients failed to show improvement in physical function [9]. Thus, the relationship between biomarkers of muscle growth inhibition and sarcopenia in patients with heart disease including AS remains unclear.

Although biomarkers for sarcopenia are needed, no study has investigated the association of the serum GDF-15 level with sarcopenia in subjects including patients undergoing aortic valve replacement. The present study was aimed to clarify the association between the preoperative serum GDF-15 concentration, and walking speed, grip strength and skeletal muscle mass index (SMI) in female subjects including patients undergoing aortic valve replacement (TAVR, conventional surgical aortic valve replacement [SAVR]).

2. Methods

2.1. Participants

Forty-three female patients receiving aortic valve replacement (mean age, 79.9 ± 6.4 years) and sixty-four healthy elderly female subjects (mean age, 75.9 ± 6.1 years) participated in this study. Nineteen patients underwent TAVR, and 24 underwent SAVR.

Patients undergoing aortic valve replacement (TAVR, SAVR) at Dokkyo Medical Hospital were included in this study. In patients undergoing TAVR, two patients were in NYHA class 1, nine were in NYHA class 2, and eight were in NYHA class 3. In patients undergoing SAVR, six patients were in NYHA class 1, twelve were in NYHA class 2, and six were in NYHA class 3. Some patients undergoing aortic valve replacement were receiving medical treatment as shown in Table 1. Standard echocardiographic imaging was performed for the evaluation of LVEF in patients receiving aortic valve replacement. Healthy subjects lived in Yokohama and Yokosuka city and regularly attended the exercise class offered at Kanagawa University of Human Services. We asked 75 of those participants to cooperate. However, since only seven of them were males, we focused on females. All healthy subjects had no severe disease, but some were receiving medical treatment including antihypertensive drugs (n = 9) and cholesterol-lowering drugs (n = 2). The Ethics Committees of Dokkyo Medical University (approval number: 27077) and Kanagawa University of Human Services (approval number: 7–20-37) approved the study protocol, and the study was conducted according to the Declaration of Helsinki. All patients and healthy subjects were informed of the methods, procedures, and risks, and signed an informed consent document before participation.

Table 1
Patient Characteristics.

Patients, Number	TAVR, 19	SAVR, 24
Risk factors, number		
Hypertension (HT), n (%)	7 (37)	20 (83)
Diabetes (DM), n (%)	1 (5)	5 (21)
Dyslipidemia (Dlp), n (%)	4 (21)	12 (50)
Smoking, n (%)	0 (0)	4 (17)
CKD, n (%)	6 (32)	7 (29)
Hemodialysis (HD), n (%)	0 (0)	4 (17)
Previous cardiac surgery, n (%)	1 (5)	0 (0)
NYHA classification	2.3 ± 0.7	2.0 ± 0.7
Drugs, number		
β-blockers, n (%)	3 (16)	6 (25)
Ca-blockers, n (%)	1 (5)	7 (29)
ACE-I/ARB, n (%)	3 (16)	9 (38)
Diuretics, n (%)	3 (16)	5 (21)
Statins, n (%)	3 (16)	6 (25)
Oral antidiabetic drugs, n (%)	1 (5)	4 (17)
Preoperative data		
Hb, g/dL	10.6 ± 1.4	11.8 ± 1.6
Alb, g/dL	3.7 ± 0.6	4.0 ± 0.6
HbA1c, %	5.8 ± 0.5	5.8 ± 0.6
BNP, pg/mL	438 ± 589	304 ± 349
LVEF, %	58.2 ± 10.9	61.9 ± 11.7

The values shown are mean ± SD. TAVR, transcatheter aortic valve replacement; SAVR, conventional surgical aortic valve replacement; CKD, chronic kidney disease; NYHA, New York Heart Association; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Hb, hemoglobin; Alb, albumin; HbA1c, hemoglobin A1c; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

Preoperative blood samples were obtained in tubes containing sodium EDTA and polystyrene tubes without an anticoagulant. Plasma was immediately separated by centrifugation at 3000 rpm at 4℃ for 10 min, and serum was collected by centrifugation at 1000 rpm at room temperature for 10 min. Brain natriuretic peptide (BNP), creatinine, hemoglobin (Hb), albumin (Alb), and estimated glomerular filtration rate (eGFR) were measured before the operation. Creatinine and estimated glomerular filtration rate (eGFR) were measured before surgery in patients and in healthy subjects. Levels of the inflammatory marker, high-sensitive C-reactive protein (hsCRP), were measured with a latex-enhanced nephelometric immunoassay (N Latex CRP II and N Latex SAA, Dade Behring Ltd., Tokyo, Japan).

To measure the GDF-15 level, we collected blood samples in pyrogen-free tubes without EDTA on the morning of cardiovascular surgery in patients and on the morning of health measurements in healthy subjects. The serum was stored in aliquots at −80℃ for all enzyme-linked immunosorbent assays (ELISAs).

2.2. Enzyme-linked immunosorbent assay (ELISA)

Serum GDF-15 concentrations were measured by ELISA with the Human Quantikine ELISA Kit (DGD150 for GDF-15, R&D Systems, Minneapolis, MN, USA) as previously described [10]. The detection threshold of GDF-15 was 2.0 pg/mL.

2.3. Bioelectrical impedance analyzer (BIA) measurements

Body composition was measured with a multi-frequency bioelectrical impedance analyzer (BIA; InBody S10 Biospace, Biospace Co. Ltd., Korea/Model JMW 140) while the patient was in a supine position, as previously described [11,12]. SMI was calculated with the following equation:

SMI (kg/m^2) = skeletal muscle mass (kg) /{body height (m)} ^{2}.

Hand-grip strength for the right hand was measured twice, and the higher value was adopted. Walking speed was measured as the time needed to walk 10 m twice (for healthy people), and the higher value was adopted, and as the time needed to walk 4 m (for patients with valvular heart disease). The evaluation of sarcopenia was based on the Asian Working Group for Sarcopenia (AWGS) criteria (Grip strength < 18 kgf or walking speed < 1.0 m/s, and SMI < 5.7 kg / m^2) only in females.

We also evaluated 30-day mortality and 30-day morbidity. Morbidity was defined as follows: renal failure (requiring new hemodialysis), permanent stroke, prolonged ventilation (greater than 48 h), deep sternal wound infection, and re-operation.

2.4. Statistical analysis

Measurement values are shown as mean ± SD. After testing for normality (Shapiro-Wilk test or Kolmogorov-Smirnov test), we compared the mean values among the three groups with one way-analysis of variance (ANOVA) in the case of normally distributed parameters or with the Kruskal-Wallis test in the case of non-normally distributed parameters. As for the serum GDF-15 level, the comparison between patients receiving aortic valve replacement and healthy elderly subjects was carried out with the Mann-Whitney-*U* test. Associations among parameters were evaluated with Pearson or Spearman correlation coefficients. Multivariate linear regression analysis with walking speed, grip strength, or SMI as the dependent variable was performed to determine independent factors (serum GDF-15 level, hsCRP or eGFR). An ROC curve was plotted to identify an optimal cutoff level of the GDF-15 concentration to detect sarcopenia. All statistical analyses were performed with SPSS version 28 for Windows (IBM Corp., New York, USA). A *p* value of 0.05 was regarded as significant.

3. Results

Table 2 shows a comparison of various parameters among female patients undergoing TAVR and SAVR, and healthy elderly females. Age was significantly higher in patients receiving TAVR than in patients receiving SAVR and in healthy elderly subjects.

Walking speed was significantly decreased in patients receiving TAVR and SAVR compared with that in healthy elderly subjects. Grip strength was also lower in patients receiving TAVR and SAVR than in healthy elderly subjects. Furthermore, SMI was lower in patients undergoing TAVR and SAVR than in healthy elderly subjects (SMI; TAVR: 5.14 ± 0.51, SAVR: 5.42 ± 0.65 vs. healthy: 6.04 ± 0.61 kg/m^2, p < 0.001, p < 0.01, respectively). Sarcopenia was found in 83.3% of patients receiving TAVR, 64.3% of those receiving SAVR, and 12.5% of healthy elderly subjects.

The GDF-15 level was higher in patients receiving aortic valve replacement (TAVR and SAVR) than in healthy elderly subjects (aortic valve replacement: 1624 ± 1186 vs. healthy: 955 ± 368 pg/mL, p < 0.001). It was also significantly higher in patients receiving TAVR than in healthy elderly subjects (TAVR: 1593 ± 803 vs. healthy: 955 ± 368 pg/mL, p = 0.001) as shown in Table 2. These results suggested that the GDF-15 level was higher in patients receiving aortic valve replacement, especially those receiving TAVR, than in healthy elderly subjects. eGFR and hsCRP levels were not significantly different among the three groups.

Table 3 shows correlations between the serum GDF-15 concentration and various parameters in patients receiving aortic valve replacement and healthy elderly subjects. The serum GDF-15 level was negatively correlated with walking speed and eGFR, but positively correlated with age in patients receiving aortic valve replacement (Fig. 1, walking speed: r = -0.624, p = 0.001). The GDF-15 level was also negatively correlated with grip strength and SMI in patients undergoing aortic valve replacement.

The serum GDF-15 level was negatively correlated with walking speed and eGFR, but positively correlated with age in elderly healthy subjects (Fig. 2, walking speed: r = -0.396, p = 0.001). The GDF-15 level did not significantly correlate with grip strength and SMI in healthy elderly subjects.

Multivariate linear regression analysis with walking speed, grip strength, or SMI as the dependent variable was performed to identify independent factors (serum GDF-15 level, hsCRP level, and eGFR) as shown in Table 4. In unadjusted multivariate regression analysis, walking speed, grip strength and SMI were significantly associated with the serum GDF-15 level (walking speed: β = -0.483, p < 0.001; grip strength: β = -0.539, p < 0.001; SMI: β = -0.498, p < 0.001. In a multivariate regression analysis that adjusted for age, grip strength remained significantly associated with the serum GDF-15 level (β = -0.318, p = 0.025).

An ROC curve was plotted to identify the optimal cutoff level of GDF-15 for detecting sarcopenia, as shown in Fig. 3. To generate the ROC curve, different GDF-15 levels were used to predict sarcopenia with true positives (sensitivity) on the vertical axis and false positives (1 -

Table 2
Comparison of various parameters between female patients receiving aortic valve replacement and healthy elderly female subjects.

	Patients receiving aortic valve replacement		Healthy elderly subjects (n = 64)	p value (among the three groups)
	TAVR (n = 19)	SAVR (n = 24)		
Age, years	84.8 ± 3.6$^{***, ‡‡‡}$	76.0 ± 5.3	75.9 ± 6.1	<0.001
Grip strength, kgf	16.0 ± 3.9***	16.5 ± 5.5***	22.6 ± 4.3	<0.001
Walking speed, m/s	0.69 ± 0.25***	0.82 ± 0.33***	1.42 ± 0.32	<0.001
SMI, kg/m^2	5.14 ± 0.51***	5.42 ± 0.65**	6.04 ± 0.61	<0.001
eGFR, mL/min/1.73 m^2	59.9 ± 16.8	58.7 ± 28.6	67.4 ± 13.4	0.193
hsCRP, mg/L	0.10 ± 0.13	0.46 ± 0.84	0.11 ± 0.26	0.042
GDF-15, pg/mL	1593 ± 803**	1649 ± 1436	955 ± 368	0.001

Data show mean ± standard deviation. ** p < 0.01, *** p < 0.001 vs. healthy elderly subjects, ‡‡‡ p < 0.001 vs. SAVR. TAVR, transcatheter aortic valve replacement; SAVR, conventional surgical aortic valve replacement; SMI, skeletal muscle mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitive C reactive protein; GDF, growth differentiation factor.

Table 3
Correlations between serum GDF-15 concentration and various parameters in female patients receiving aortic valve replacement (TAVR, SAVR) and healthy elderly female subjects.

	Patients receiving aortic valve replacement (n = 43)	Healthy elderly subjects (n = 64)
	GDF-15	GDF-15
Age	0.357 (0.019)*	0.541 (<0.001)***
Grip strength	−0.614 (<0.001)***	−0.186 (0.142)
Walking speed	−0.624 (0.001)**	−0.396 (0.001)**
SMI	−0.561 (0.003)**	−0.158 (0.212)
eGFR	−0.753 (<0.001)***	−0.518 (<0.001)***
hsCRP	0.115 (0.478)	0.123 (0.331)
BNP	0.280 (0.094)	–
LVEF	−0.532 (0.002)**	–

Data show r value (p value). * p < 0.05, ** p < 0.01, *** p < 0.001. GDF, growth differentiation factor; SMI, skeletal muscle mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitive C reactive protein; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

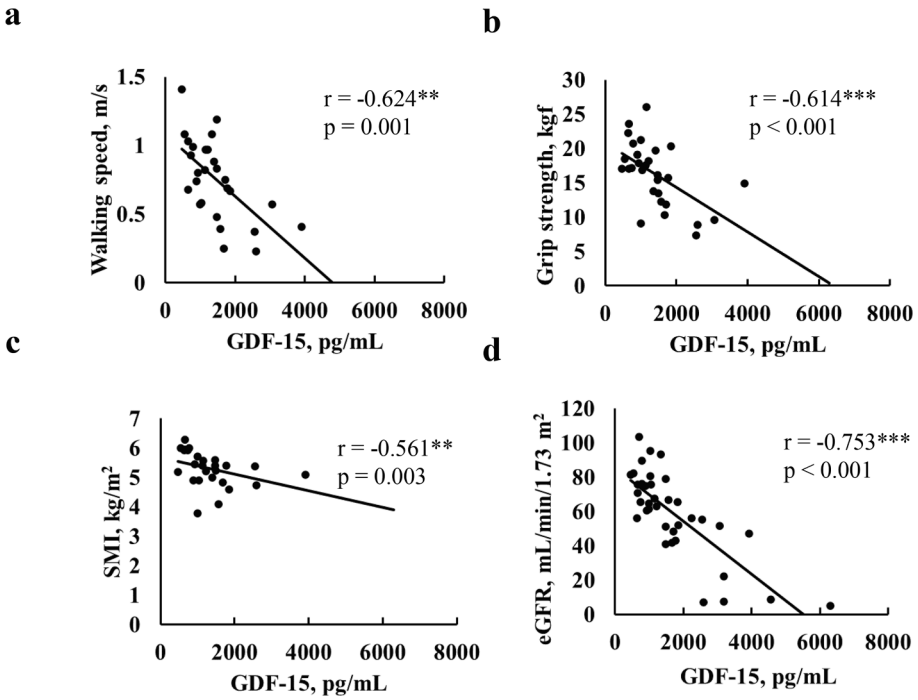


Fig. 1. Correlations between the preoperative GDF-15 level and clinical data in female patients receiving aortic valve replacement. Correlations between the preoperative GDF-15 level and walking speed (a), grip strength (b), SMI (c), and eGFR (d).

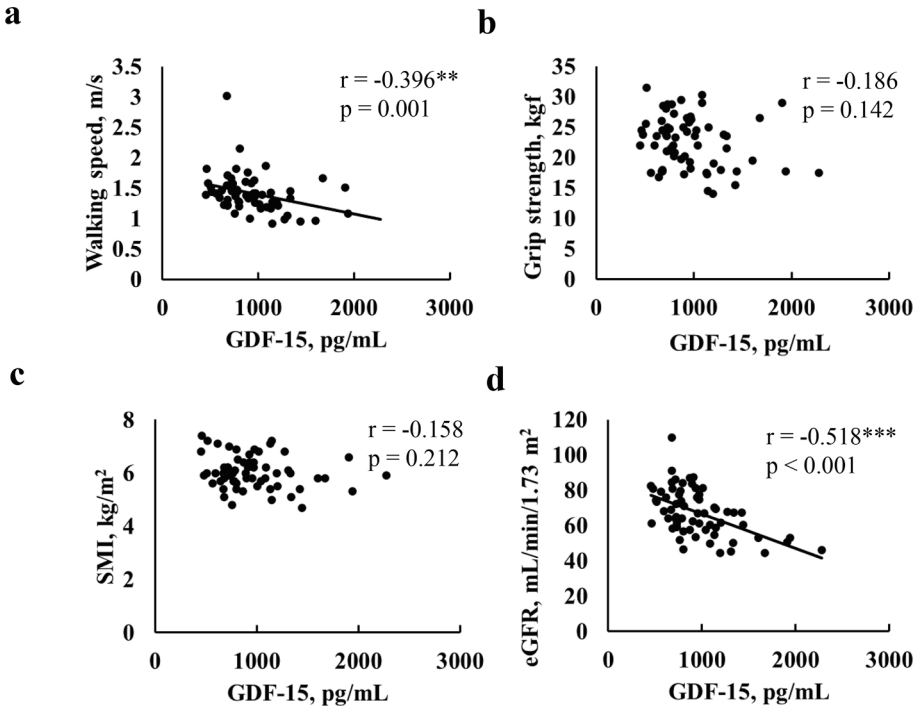


Fig. 2. Correlations between the preoperative GDF-15 level and clinical data in healthy elderly female subjects. Correlations between the preoperative GDF-15 level and walking speed (a), grip strength (b), SMI (c), and eGFR (d).

specificity) on the horizontal axis. The area under the curve (AUC) for GDF-15 was 77.2%. Sensitivity and specificity were 70.4% and 81.0%, respectively, for GDF-15. The optimal cutoff value was 1109 pg/mL.

We evaluated the 30-day short-term mortality and morbidity. As shown in Supplementary Table 1, the 30-day mortality and morbidity in patients undergoing TAVR and SAVR was 0 patients (0%) and 3 patients (13%), respectively.

4. Discussion

In this study, the GDF-15 level was higher in patients receiving aortic valve replacement (TAVR and SAVR) than in healthy elderly subjects. We also found that the GDF-15 level was associated with walking speed, both in patients undergoing aortic valve replacement and in healthy elderly subjects. Multivariate regression analysis showed that the serum

Table 4
Multivariate analysis to determine walking speed, grip strength and SMI in all subjects (female patients receiving aortic valve replacement and healthy elderly female subjects).

A: Multivariate linear regression analysis of walking speed and clinical data		
Dependent variable: walking speed		
	Model 1	Model 2
Independent variable	β value (p)	β value (p)
GDF-15 (log)	−0.483*** (<0.001)	−0.212 (0.107)
hsCRP (log)	−0.038 (0.676)	−0.062 (0.468)
eGFR	0.139 (0.204)	0.178 (0.087)
B: Multivariate linear regression analysis of grip strength and clinical data		
Dependent variable: grip strength		
	Model 1	Model 2
Independent variable	β value (p)	β value (p)
GDF-15 (log)	−0.539*** (<0.001)	−0.318* (0.025)
hsCRP (log)	−0.161 (0.089)	−0.186* (0.044)
eGFR	−0.154 (0.177)	−0.120 (0.281)
C: Multivariate linear regression analysis of SMI and clinical data		
Dependent variable: SMI		
	Model 1	Model 2
Independent variable	β value (p)	β value (p)
GDF-15 (log)	−0.498*** (<0.001)	−0.240 (0.113)
hsCRP (log)	−0.013 (0.896)	−0.049 (0.618)
eGFR	−0.197 (0.118)	−0.147 (0.226)

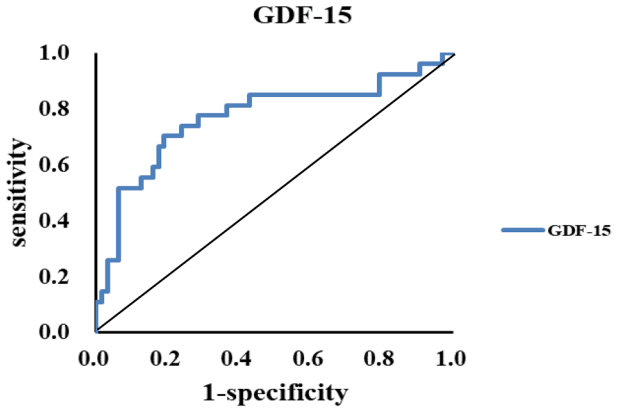
* $p < 0.05$, *** $p < 0.001$. Model 1, unadjusted; Model 2, adjusted by age. SMI, skeletal muscle mass index, GDF, growth differentiation factor; hsCRP, high-sensitive C reactive protein; eGFR, estimated glomerular filtration rate.

GDF-15 level was an independent parameter to determine walking speed, grip strength and SMI. The GDF-15 concentration that defines sarcopenia was 1109 pg/mL in subjects including patients receiving aortic valve replacement. Thus, GDF-15 may be a biomarker of sarcopenia in female subjects including patients receiving aortic valve replacement.

A Japanese multicenter registry study investigated the prognostic value of the Clinical Frailty Scale (CFS) in patients who underwent TAVR [13]. That study showed that the CFS had a significant correlation with both walking speed and grip strength, and in multivariate regression analysis, the CFS was an independent predictive factor for increased late cumulative mortality risk. The present study showed that in multivariate regression analysis, the serum GDF-15 level was an independent predictive factor for grip strength, even after adjusting for age in female subjects including patients receiving TAVR and SAVR. Thus, these findings might suggest that the serum GDF-15 concentration is a biomarker of lower grip strength, and then sarcopenia in elderly subjects including patients receiving aortic valve replacement.

The present study revealed that the optimal GDF-15 cutoff level for detecting sarcopenia was 1109 pg/mL in female subjects including patients receiving aortic valve replacement. A prior study showed that the GDF-15 level was inversely correlated with the cross-sectional area of the rectus femoris, and GDF-15 levels lower than 564 pg/mL predicted preserved quadriceps maximal muscle strength with sensitivity and specificity more than 80% in patients with pulmonary arterial hypertension (PAH) [14].

In a study where blood GDF-15 levels were determined in patients with CHF with a median LVEF of 32%, the median GDF-15 level was 1949 pg/mL, and 74.9% of the patients had GDF-15 levels higher than 1200 pg/mL [15], which was the upper limit of normal for the healthy elderly patients in the present study. That study also demonstrated that GDF-15 levels were closely related to NYHA functional class and N-terminal pro-brain natriuretic peptide (NT-pro BNP) levels, and the risk of death during follow-up increased with increasing quartile of GDF-15 level ($p < 0.001$). After adjusting for clinical data and established biomarkers of adverse outcome, including NT-pro BNP, renal dysfunction, anemia, and hyperuricemia, the GDF-15 level remained an independent determinant of death. Also, in another study examining community-dwelling older adults, the GDF-15 level was a robust predictor of all-cause, cardiovascular, and non-cardiovascular mortality in a model adjusted for traditional cardiovascular disease risk factors [16]. That study showed that participants in the highest quartile for both GDF-15 and NT-pro BNP levels had an incremental risk of death compared to those with an elevated NT-pro BNP level alone (HR 1.5, $p = 0.01$). Thus, the GDF-15 level may add prognostic information to traditional risk factors and biomarkers such as the NT-pro BNP level in both patients with CHF and community-dwelling older adults. In the present study, there was also negative correlation between plasma GDF-15 levels and LVEF, but not BNP, in patients receiving aortic valve replacement. Also, there were negative correlation between serum GDF-15 level and SMI in patients with mitral valve repair or replacement as well as those with aortic valve replacement (Supplementary Table 2). These results suggested that plasma GDF-15 level may be a biomarker for patients with heart failure of various cause rather than those with aortic stenosis. We evaluated the 30-day short-term mortality and morbidity. It was 0 patients (0%) and 3 patients (13%) in patients undergoing TAVR and SAVR, respectively. Thus, we could not evaluate that the GDF-15 level may add prognostic information to the short-term mortality and morbidity due to a small number of patients. However, the present study



	AUC	standard error	*P*-value	sensitivity	specificity	cut-off value
GDF-15 (pg/mL)	0.772	0.061	<0.001	0.704	0.81	1109

Fig. 3. An ROC curve to identify the optimal GDF-15 cutoff level for detecting sarcopenia in female patients receiving aortic valve replacement and healthy elderly female subjects. To generate the ROC curve, different GDF-15 levels were used to predict sarcopenia with true positives (sensitivity) on the vertical axis and false positives (1 – specificity) on the horizontal axis.

suggests that this prognostic information from the GDF-15 level may be linked to sarcopenia.

GDF-15 is a stress-sensitive blood factor that regulates whole-body energy balance. In one animal study of mice injected daily with GDF-15, GDF-15 acted on the liver to inhibit growth hormone (GH) signaling and body growth [17]. The study furthermore demonstrated that blocking cardiomyocyte production of GDF-15 normalized the circulating GDF-15 level and restored liver GH signaling. Thus, GDF-15 may be a cardiac hormone that regulates body growth in children with heart disease. In addition, in a study using an animal model of PAH, GDF-15 stimulated increased phosphorylation of TGF β-activated kinase 1 (TAK1) [14]. That study showed that inhibition of TAK1 increased muscle fiber diameter and decreased blood GDF-15 levels in rats that responded to treatment, suggesting that circulating GDF-15 was a biomarker of muscle loss in PAH that is responsive to treatment. To summarize the above, the blood GDF-15 level may be a biomarker of body growth inhibition or muscle loss in patients with heart diseases. The present study has shown that serum GDF-15 levels increased in patients receiving aortic valve replacement compared to those in healthy elderly subjects. It also showed that serum GDF-15 levels had a significant negative correlation with walking speed, grip strength and SMI independently of hsCRP levels and eGFR in subjects including patients receiving aortic valve replacement, which are in agreement with the findings of those past studies.

The present study has several limitations. Only females were considered, so it is unclear if this result is applicable to males. Also, since there was no prior statistical planning and the number of subjects was small, a larger study with prior statistical planning is needed. Furthermore, the ROC analysis of the present study included both healthy subjects as well as patients who were to undergo aortic valve replacement. To identify sarcopenia in those with aortic valve replacement, the analysis should be performed in those patients only, but we did not have enough patients in patients with aortic valve replacement. Lastly, further studies using a large number of patients are required to clarify whether GDF-15 level may add prognostic information such as the short-term mortality and morbidity in patients receiving aortic valve replacement.

In conclusion, the present study showed that the preoperative serum GDF-15 concentration was higher in patients receiving aortic valve replacement than in healthy elderly subjects. Also, in multivariate regression analysis, the serum GDF-15 level was an independent predictive factor for grip strength, even after adjusting for age in female subjects including patients receiving aortic valve replacement. Thus, the preoperative serum GDF-15 level might be a biomarker of lower grip strength, and then sarcopenia in elderly subjects including patients receiving aortic valve replacement.

Financial disclosure

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CRediT authorship contribution statement

Taira Fukuda: Conceptualization, Formal analysis, Funding acquisition. **Toshiaki Nakajima:** Data curation, Funding acquisition. **Hiroko Yazawa:** Resources. **Suguru Hirose:** Resources. **Jun Yokomachi:** Resources. **Takashi Kato:** Resources. **Riichi Nishikawa:** Resources. **Nobuo Koshiji:** Resources. **Michiaki Tokura:** Resources. **Takahisa Nasuno:** Resources. **Setsu Nishino:** Resources. **Syotaro Obi:** Resources. **Ikuko Shibasaki:** Resources. **Tomoaki Kanaya:** Resources. **Fumitaka Nakamura:** Supervision. **Hirotsugu Fukuda:** Supervision. **Shichiro Abe:** Resources. **Masashi Sakuma:** Resources. **Shigeru Toyoda:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101032.

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