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Original article

Knee extensor muscle strength and index of renal function associated with an exercise capacity of 5 metabolic equivalents in male chronic heart failure patients with chronic kidney disease

Running title: *Exercise Capacity in Patients with Heart Failure*

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Abstract

Background The goal of the present study was to determine knee extensor muscle strength (KEMS) and degree of renal dysfunction associated with an exercise capacity of ≥ 5 metabolic equivalents (METs) in male chronic heart failure (CHF) patients with chronic kidney disease (CKD).

5 *Methods* In this cross-sectional study of 75 male CHF patients with CKD (65.3 ± 11.6 years), we measured clinical characteristics, peak $\dot{V}O_2$, estimated glomerular filtration rate (eGFR), and KEMS. Patients were divided into two groups by exercise capacity: ≥ 5 METs group ($n = 41$) and < 5 METs group ($n = 34$). Cutoff values for KEMS and eGFR resulting in an exercise capacity of ≥ 5 METs were selected with ROC curves. Patients were divided into four groups according to cutoff values, and numbers of patients attaining an exercise capacity of ≥ 5 METs were compared between groups.

10 *Results* Age was significantly higher although eGFR, Hb, and KEMS were lower in the < 5 METs versus ≥ 5 METs group ($P < 0.001$). Multiple logistic regression analysis revealed a positive significant relation between KEMS and eGFR and exercise capacity of ≥ 5 METs. Exercise capacity of ≥ 5 METs was associated with KEMS of approximately 1.69 Nm/kg and an eGFR of 45.7 mL/min/1.73 m². The number of patients attaining an exercise capacity of ≥ 5 METs in the patients who did not reach both cutoff values was significantly lower than that in any other patients ($P < 0.001$).

Conclusion KEMS and eGFR may be useful indices for predicting attainment of exercise capacity of ≥ 5 METs in male

CHF patients with CKD.

Keywords: Exercise capacity, Chronic heart failure, Chronic kidney disease, Knee extensor muscle strength

Introduction

Exercise capacity is a potent predictor of risk in patients with chronic heart failure (CHF) [1]. Previous studies have suggested that people with an exercise capacity of <5 metabolic equivalents (METs) are classified as patients with cardiac disease who are considered to be at high risk for death and to have low ability to perform activities of daily living [1, 2]. We sometimes experience CHF patients in whom it is difficult to evaluate exercise capacity with cardiopulmonary exercise tolerance testing (CPETT) because of their decreased physical function. In addition, there are a number of CHF patients with concomitant chronic kidney disease (CKD), which is an independent risk factor for prognostic decline [3, 4].

Clyne et al. [5] suggested a relation between glomerular filtration rate (GFR) and exercise capacity, and decreased renal function is one factor that can cause a decrease in exercise capacity. We previously reported that exercise capacity of CHF patients with CKD was independently related to knee extensor muscle strength and estimated GFR (eGFR) [6]. However, it is not clear whether the decrease in exercise capacity in male CHF patients with CKD can be predicted on the basis of knee extensor muscle strength and renal function.

We hypothesized that knee extensor muscle strength and eGFR as the index of renal function might predict whether exercise capacity in male CHF patients with CKD reaches 5 METs, and we investigated both the levels of knee extensor

muscle strength and renal function required to attain an exercise capacity of ≥ 5 METs and their prognostic usefulness.

The purpose of the present study was to determine 1) knee extensor muscle strength and the eGFR level, as the index of renal function, required to attain an exercise capacity of ≥ 5 METs and 2) whether combined use of these measures is beneficial in predicting exercise capacity in male CHF patients with CKD.

5

Material and methods

Study design and patients

The present study was a cross-sectional study comprising 86 consecutive CHF outpatients with CKD who visited St.

Marianna University School of Medicine Hospital from January 2003 to December 2010 for evaluation of exercise capacity

10 by CPETT. All patients in this study were diagnosed as having CHF, which was defined on the basis of symptoms such as

dyspnea and fatigue that can occur at rest or during physical activity based on the New York Heart Association (NYHA)

functional class definitions and a brain natriuretic peptide (BNP) concentration of >18.4 pg/ mL. All patients underwent

CPETT from 3 to 6 months after hospital discharge. Exclusion criteria were female sex, eGFR of ≥ 60 mL/min/1.73 m²,

appearance of ischemic change or lethal arrhythmias on the electrocardiogram (ECG) during CPETT, respiratory exchange

ratio (RER) at the end of load of <1.15 , and myelodysplastic syndrome or hemodialysis [7].

Eleven patients were excluded resulting in a study population of 75 patients. The present study was approved by the St. Marianna University School of Medicine institutional committee on human research (Approval Number: 340). All patients gave their written informed consent for participation in this study.

5

Patient population

Age, height, weight, body mass index (BMI), NYHA functional class, etiology of CHF, and medications were investigated from the patients' clinical records. The BMI was calculated as the weight in kilograms divided by the square of the height in meters. The eGFR and blood hemoglobin (Hb) levels were also measured. All indices were determined or measured on the

10 day of CPETT or as close as possible to that day. The eGFR was estimated from the serum creatinine level, age, and sex by

using the formula recommended by the Japanese Society of Nephrology [8]. A cardiologist assessed cardiac function by

ultrasound measurement of left ventricular ejection fraction (LVEF) and disease severity by brain natriuretic peptide (BNP)

concentration. All patients underwent standard M-mode echocardiography (Apio; Toshiba, Tokyo, Japan) with a 3.5-MHz

transducer in the parasternal long-axis view to obtain the LVEF. A blood sample for measurement of BNP was drawn from a

cubital vein of each patient after 15 minutes of rest in the supine position before CPETT. Blood samples were immediately immersed in ice and centrifuged at 3000 rpm for 10 minutes at 4°C. The plasma was stored at -70°C, and BNP was measured by radioimmunoassay within 1 week of sampling [9].

5 Physiological outcome measurements

Peak oxygen consumption (peak $\dot{V}O_2$)

All 75 patients underwent CPETT via a ramp cycle ergometer protocol on a CORIVAL 400 ergometer (Lode Co., Groningen, The Netherlands). Symptom-limited exercise testing consisted of an initial 3-minute rest period on the cycle ergometer,

3-minute warm-up at a load of 10 or 20 W, and full exercise with application of a linear increase in load of 1 W every 6

10 seconds. A 12-lead ECG was monitored continuously throughout CPETT, and heart rate was determined from the R-R

interval of the ECG (ML-5000; Fukuda Denshi Co., Tokyo, Japan). Peak $\dot{V}O_2$, relation between minute ventilation and

carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$ slope), and RER were measured throughout the exercise period with an AE-300S aero

monitor (Minato Ikagaku Co., Tokyo, Japan) and calculated on a personal computer. Measurements made from expired gases

were used as indices of cardiovascular dynamics during exercise. Exercise capacity was calculated following measurement of

peak $\dot{V}O_2$. The endpoint of exercise testing was determined according to the criteria of the American College of Sports

Medicine [7] and included leg fatigue, shortness of breath, or $RER > 1.15$. After the end of load and a 3-minute cool-down

period, we collected expired gases for analysis for an additional 5 minutes with the patient in the seated position. METs for

each patient were calculated as follows: $METs = \text{peak } \dot{V}O_2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} / 3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

5

Knee extensor muscle strength

We measured knee extensor muscular strength as the index of lower limb muscular strength with the Biodex System 2

isokinetic dynamometer (Biodex Medical Systems, Inc., New York, NY). Testing was performed for a maximum of five

repetitions for knee extensors at isokinetic speeds of 60 degrees/sec [9]. Isokinetic test results were analyzed with the Biodex

10 System 2 software. We measured the knee extensor muscular strength peak torque per bodyweight value of both knees. After

measurement, the index of knee extensor muscle strength was calculated by averaging the highest value of the right- plus

left-side knee extensor strength / 2 (Nm/kg) [9].

Statistical analysis

Results are expressed as median (interquartile range) or mean $\pm$ SD, as appropriate. After CPETT, we divided the patients into two groups according to exercise capacity: ≥ 5 METs group ($n = 41$) and < 5 METs group ($n = 34$). The χ^2 test was used to analyze differences between these two groups in NYHA functional class, etiology of CHF, and medications, and the Mann-Whitney U test was used for all other variables.

5 Multiple logistic regression analysis was performed with exercise capacity of ≥ 5 METs as the dependent variable, and age, eGFR, Hb, BNP, and knee extensor muscle strength as the independent variables [10]. A previous study suggested a relation between NYHA functional class and exercise capacity such that exercise capacity assessed by the CPETT index of peak $\dot{V}O_2$ decreases as NYHA class increases [11]. Thus, NYHA functional class was not adopted as the independent variable.

10 Receiver operating characteristic (ROC) analysis was used to assess whether the patients could attain an exercise capacity of ≥ 5 METs on the basis of knee extensor muscle strength and eGFR values. The cutoff values that yielded the highest combined sensitivity and specificity were used to obtain the positive and negative predictive values of the significant predictors.

We then divided the patients into four groups according to cutoff values of knee extensor muscle strength (1.69 Nm/kg)

and eGFR (45.7 mL/min/1.73 m²) to determine the necessity of meeting either or both of the cutoff values to attain an exercise capacity of at least 5 METs. Group I comprised patients in whom both indices were greater than the cutoff values; group II comprised patients in whom only knee extensor muscle strength was greater than the cutoff value; group III comprised patients in whom only eGFR was greater than the cutoff value; and group IV comprised patients in whom both indices were less than the cutoff values. The χ^2 test was used to test for differences between groups I-IV in terms of the number of patients in each group who attained an exercise capacity of ≥ 5 METs.

In all analyses, statistical significance was established if the *P* value was <0.05 . All analyses were performed using IBM SPSS 12 statistical software (IBM SPSS Japan, Inc., Tokyo, Japan).

10 Results

Clinical characteristics

Clinical characteristics and functional variables in all patients are summarized in Table 1. BMI, LVEF, etiology of CHF, and medications were not significantly different between both groups. BNP in the ≥ 5 METs group tended to be lower than that in the <5 METs group. The median peak $\dot{V}O_2$ was significantly higher in the ≥ 5 METs group than in the <5 METs group. Age

($P = 0.003$) was significantly higher although eGFR, Hb, and knee extensor muscle strength were significantly lower in the <5 METs versus ≥ 5 METs group (all, $P < 0.001$). NYHA functional class differed significantly between the two groups ($P < 0.001$), with the data showing a tendency for CHF to be more severe in the <5 METs group.

5 Determinants of exercise capacity of 5 METs

Multiple logistic regression models revealed a significant relation between an exercise capacity of ≥ 5 METs and knee extensor muscle strength and eGFR (Table 2). The odds ratio of the knee extensor muscle strength was 98.42 (95% confidence interval [CI]: 7.37-1314.41) and that of eGFR was 1.07 (95% CI: 1.00-1.14) for an exercise capacity of ≥ 5 METs.

10 Cutoff values of knee extensor muscle strength and eGFR associated with an exercise capacity of ≥ 5 METs

The sensitivities of cutoff values of knee extensor muscle strength and eGFR required to attain an exercise capacity of ≥ 5 METs were calculated and used to construct ROC curves (Figures 1, 2). Using ROC analysis, we identified a cutoff value for knee extensor muscle strength of 1.69 Nm/kg, with a sensitivity of 78.0%, specificity of 82.4%, and area under the curve (AUC) value of 0.86 (95% CI: 0.77-0.94, $P < 0.001$). The cutoff value identified for eGFR was 45.7 mL/min/1.73 m², with a

sensitivity of 76.2%, specificity of 66.7%, and AUC value of 0.77 (95% CI: 0.66-0.87, $P < 0.001$).

Relation between knee extensor muscle strength, eGFR, and exercise capacity of 5 METs

A scattergram showing the relation between knee extensor muscle strength and eGFR in groups I-IV is presented in Figure 3.

5 The number of patients in each group who attained an exercise capacity of ≥ 5 METs was 24 in group I, 8 in group II, 8 in group III, and 1 in group IV. The number of patients attaining an exercise capacity of ≥ 5 METs in group I was higher than that in groups III and IV (both, $P < 0.001$) but was not significantly different from that in group II ($P = 0.67$). However, the number of patients attaining an exercise capacity of ≥ 5 METs in group IV was significantly lower than that in each of the other 3 groups ($P < 0.001$).

10

Discussion

The present study showed that knee extensor muscle strength and eGFR level were significantly lower in patients with an exercise capacity of < 5 METs, and the cutoff values for knee extensor muscle strength and eGFR in male CHF patients with CKD attaining an exercise capacity of ≥ 5 METs were 1.69 Nm/kg and 45.7 mL/min/1.73 m², respectively. Furthermore, the

number of patients attaining an exercise capacity of ≥ 5 METs was significantly higher in the patients who reached the cutoff values for both variables and significantly lower in the patients who did not reach both cutoff values.

Age was higher although the values of Hb, eGFR, and knee extensor muscle strength were lower in the <5 METs group versus the ≥ 5 METs group in male CHF patients with CKD, and NYHA functional class tended to be more severe in the <5

5 METs group. Erythropoietin production decreases as renal function decreases and is known to cause anemia of CKD [12]. We

thought that the decline in Hb level was affected by renal function because of the significant difference between both groups

in renal function in this study. Izawa et al. [11] reported that values of muscle strength decrease as NYHA functional class

increases. Therefore, we surmised that knee extensor muscle strength decreased due to the influence of the severity of CHF. It

was also previously reported that lower extremity muscle strength is lower in predialysis CKD patients than in healthy people

10 of the same age [13, 14]. There are several causes of low muscle strength in CKD patients, such as malnutrition, insufficient

protein intake, catabolism, and increased inflammation [15]. However, the specific relation between knee extensor muscle

strength and renal function in the present study was not clear because we did not investigate the causes of low values of these

indices.

In the present study, a positive significant relation between knee extensor muscle strength and eGFR and the ability to

predict an exercise capacity of ≥ 5 METs was revealed by multiple logistic regression analysis. There are several reports that exercise capacity is related to knee extensor muscle strength in CHF patients [16-18]. In addition, Clyne et al. [5] reported a positive correlation between GFR and exercise capacity, and we previously reported that knee extensor muscle strength and eGFR are important factors in predicting exercise capacity in HF patients with CKD [6]. GFR as an index of renal function is known to decrease with aging [19]. Therefore, we predicted that the results of the present study would be similar to those of these previous studies, and our results suggested that exercise capacity may be related to knee extensor muscle strength [11] and eGFR [5] in male CHF patients with CKD.

An exercise capacity of ≥ 5 METs in male CHF patients with CKD was equivalent to approximately 1.69 Nm/kg of knee extensor strength and an eGFR of 45.7 mL/min/1.73 m². Manini et al. [20] reported that in healthy men aged 70-79 years, the cutoff value defining low risk of severe mobility limitation corresponds to more than 1.71 Nm/kg of knee extensor muscle strength. Izawa et al. [9] also suggested that an exercise capacity of ≥ 5 METs in male HF patients is equivalent to 1.70 Nm/kg of knee extensor muscle strength. The cutoff value for knee extensor muscle strength in the present study was almost equal to those of these two previous studies. Therefore, we thought that the cutoff value for knee extensor muscle strength determined in the present study was suitable for use with male CHF patients with CKD.

Hillege et al. [3] suggested that patients with a GFR of <44 mL/min/1.73 m² have 2.85 times the risk of mortality as compared with patients with a GFR of >76 mL/min/1.73 m². To our knowledge, there are no reports that have determined the renal function levels associated with different levels of exercise capacity, but the cutoff value for eGFR in this study was similar to the levels that predict prognosis of or decrease in exercise capacity in previous studies [3, 5]. The cutoff value of eGFR in the present study may be useful to predict attainment of an exercise capacity of at least 5 METs in older-aged male patients with CHF and CKD.

When we compared the number of patients who attained an exercise capacity of ≥ 5 METs in the four groups on the basis of the cutoff values in the present study, the rate was highest in the patients who exceeded both cutoff values and was lower in the patients who could not meet one of the two cutoff values. Thus, we suggest that the cutoff values for knee extensor muscle strength and eGFR in the present study may be useful to predict attainment of an exercise capacity of at least 5 METs in male CHF patients with CKD. Especially, when patients cannot meet both cutoff values, the possibility that they will have an exercise capacity of <5 METs is very high, suggesting that these cutoff values may be useful when considering risk for exercise or to discover patients with low physical function. However, it is difficult to predict an exercise capacity of ≥ 5 METs on the basis of either knee extensor muscle strength or eGFR alone. Especially, prediction only on the basis of eGFR is

difficult because the AUC value of eGFR was not high in the ROC analysis in the present study.

This study has several limitations. First, eGFR was used as the index of renal function. eGFR, which can be estimated from creatinine level, age, and sex, is a useful index. However, because creatinine is influenced by muscle mass, eGFR may

have been affected by this influence in the study patients. Second, the patients were all male CHF patients with CKD who

5 could undergo CPETT. It is unknown whether the cutoff values determined in this study can be applied to women or to CHF patients without CKD. Finally, because of the small sample size and cross-sectional design of this study, a longitudinal study would be required in the future.

CONCLUSION

An exercise capacity of ≥ 5 METs in male CHF patients with CKD was associated with a knee extensor strength of

10 approximately 1.69 Nm/kg and eGFR level of 45.7 mL/min/1.73 m². Knee extensor muscle strength and eGFR may be useful indices for predicting attainment of an exercise capacity of ≥ 5 METs in such patients. Values for these indices that are either above or below these cutoff values may allow prediction of an exercise capacity of ≥ 5 METS or < 5 METS, respectively, in spite of not performing CPETT in male CHF patients with CKD.

CONFLICT OF INTEREST

All authors declare no conflicts of interest in relation to the work reported in this manuscript.

REFERENCES

1. Myers J. Exercise capacity and prognosis in chronic heart failure. *Circulation*. 2009;119:3165-7.
2. Morey MC, Pieper CF, Cornoni-Huntley J. Physical fitness and functional limitations in community-dwelling older adults. *Med Sci Sports Exerc*. 1998;30:715–23.
- 5 3. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation*. 2000;102:203–10.
4. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J; ADHERE Scientific Advisory Committee and Investigators. High prevalence of dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Cardiac Fail*. 2007;13:422–30.
- 10 5. Clyne N, Jogestrand T, Lins LE, Pehrsson SK. Progressive decline in renal function induces a gradual decrease in total hemoglobin and exercise capacity. *Nephron*. 1994;67:322–6.
6. Hotta C, Hiraki K, Watanabe S, Izawa KP, Yasuda T, Osada N, et al. Determinants of exercise capacity in chronic heart failure patients with chronic kidney disease. *Rigakuryouhougaku*. 2011;38:436–41. (in Japanese)

7. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. In: Johnson EP, ed. *Clinical Exercise Testing*. 6th ed. Baltimore: Williams & Wilkins; 2000: 91–114.
8. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–92.
- 5 9. Izawa KP, Watanabe S, Oka K, Hiraki K, Morio Y, Kasahara Y, et al. Upper and lower extremity muscle strength levels associated with an exercise capacity of 5 metabolic equivalents in male patients with heart failure. *J Cardiopulm Rehabil Prev*. 2012;32:85–91.
- 10 10. Suzukawa M, Shimada H, Tamura M, Suzuki T, Inoue N. The relationship between the subjective risk rating of specific tasks and falls in frail elderly people. *J Phys Ther Sci*. 2011;23:425-9.
- 10 11. Izawa KP, Watanabe S, Yokoyama H, Hiraki K, Morio Y, Oka K, et al. Muscle strength in relation to disease severity in patients with congestive heart failure. *Am J Phys Med Rehabil*. 2007;86:893–900.
12. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med*. 2002;162:1401–8.
13. Padilla J, Krasnoff J, Da Silva M, Hsu CY, Frassetto L, Johansen KL, et al. Physical functioning in patients with chronic

kidney disease. *J Nephrol.* 2008;21:550–9.

14. Heiwe S, Tollbäck A, Clyne N. Twelve weeks of exercise training increases muscle function and walking capacity in elderly predialysis patients and healthy subjects. *Nephron.* 2001;88:48–56.

15. Patel DR, Raj VM, Torres A. Chronic kidney disease, exercise, and sports in children, adolescents, and adults. *Phys Sportsmed.* 2009;37:1–9.

16. Harrington D, Anker SD, Chua TP, Webb-Peploe KM, Ponikowski PP, Poole-Wilson PA, et al. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. *J Am Coll Cardiol.* 1997;30:1758–64.

17. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the

- European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil.* 2010;17:1–17.

18. Massie BM, Simonini A, Sahgal P, Wells L, Dudley GA. Relation of systemic and local muscle exercise capacity to skeletal muscle characteristics in men with congestive heart failure. *J Am Cardiol.* 1996;27:140–5.

19. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest.* 1950;29:496–507.

20. Manini TM, Visser M, Won-Park S, Patel KV, Strotmeyer ES, Chen H, et al. Knee extension strength cutpoints for maintaining mobility. *J Am Geriatr Soc.* 2007;55:451–7.

FIGURE LEGENDS

Fig. 1 Cutoff point for knee extensor strength by receiver operating characteristic analysis of exercise capacity of ≥ 5

metabolic equivalents in all patients. *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the curve,

CI confidence interval

5

Fig. 2 Cutoff point for estimated glomerular filtration rate by receiver operating characteristic analysis of exercise capacity

of ≥ 5 metabolic equivalents in all patients. *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the

curve, *CI* confidence interval

10 **Fig. 3** Scattergram showing the relation between knee extensor strength and eGFR. Cutoff values are 1.69 Nm/kg for knee

extensor muscle strength and 45.7 mL/min/1.73 m² for eGFR. Boxes in the four corners of the scattergram show the number

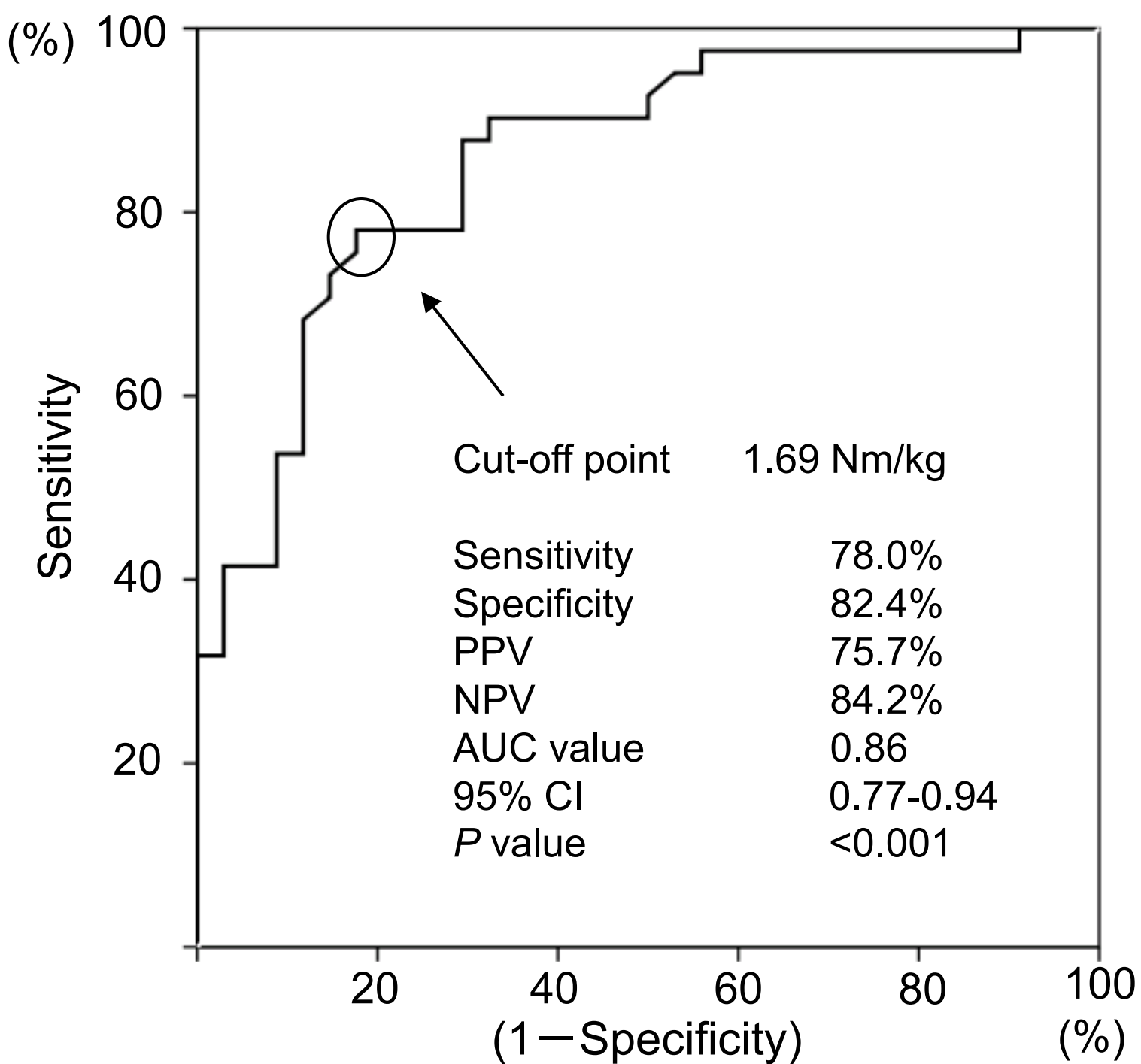
of patients who attained an exercise capacity of ≥ 5 METs on the basis of meeting the cutoff values of the two indices. Group I:

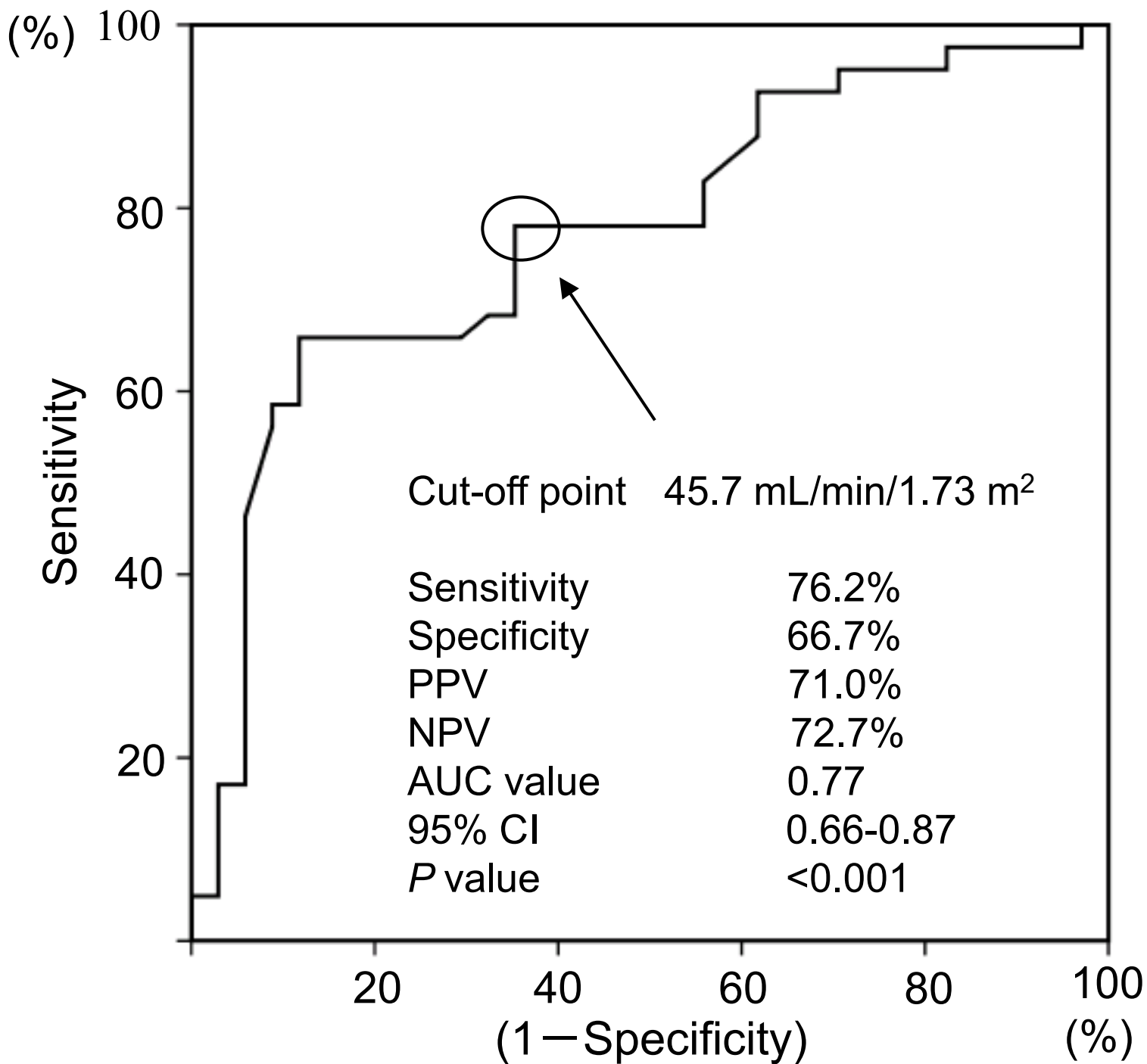
Values of both indices were greater than the cutoff values in 24 of 28 patients. Group II: The value for knee extensor muscle

strength only was greater than the cutoff value in 8 of 10 patients. Group III: The value for eGFR only was greater than the

cutoff value in 8 of 16 patients. Group IV: The values for both indices were less than the cutoff values in 20 of 21 patients.

eGFR estimated glomerular filtration rate, *METs* metabolic equivalents





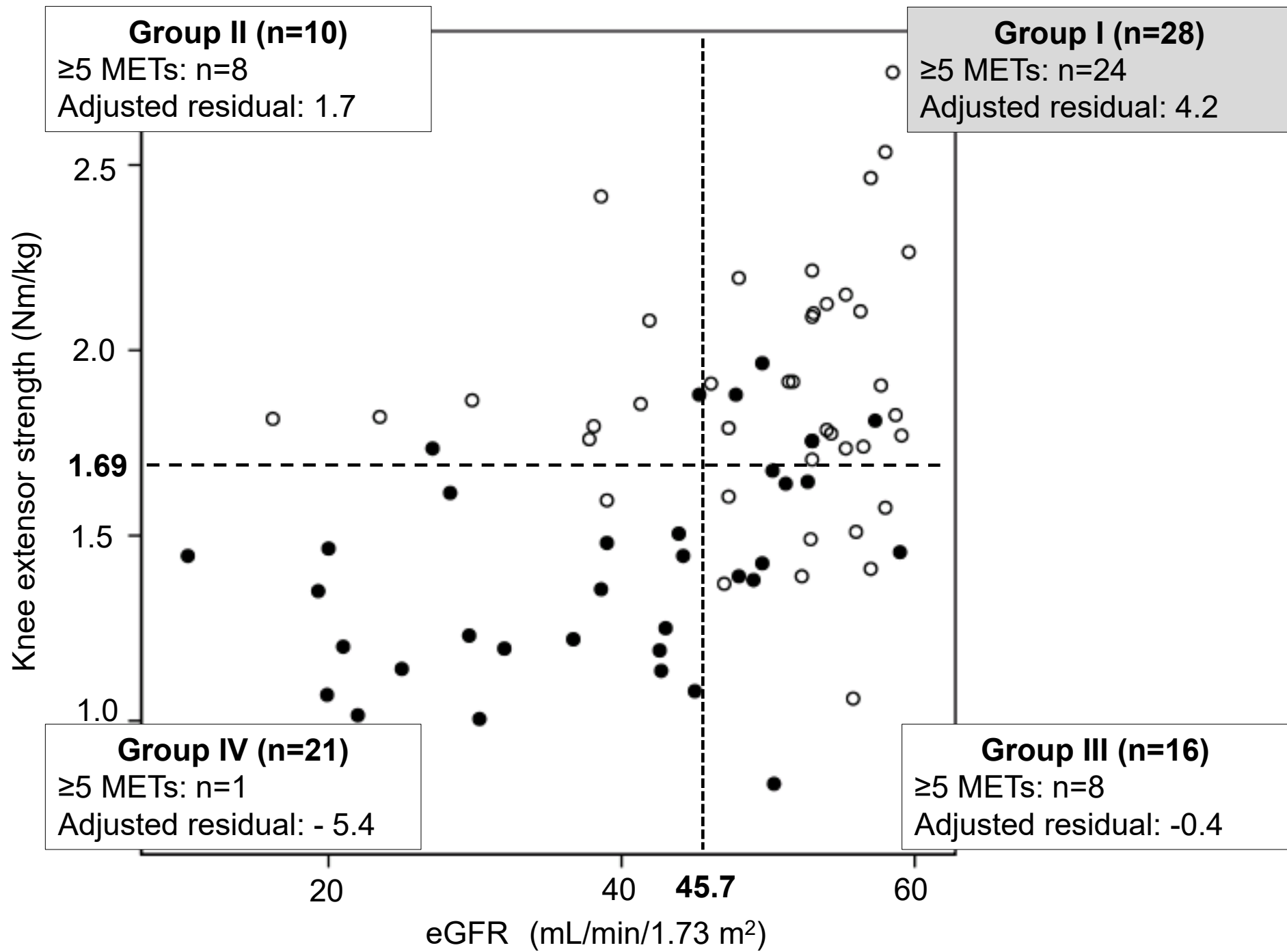


Table 1. Clinical characteristics of the patients

	All (<i>n</i> = 75)	≥5 METs group (<i>n</i> = 41)	<5 METs group (<i>n</i> = 34)	<i>P</i> value
Age (y)	65.3 ± 11.6	60.1 ± 12.1	70.0 ± 9.2	0.003
BMI (kg/m ²)	24.0 ± 3.6	24.9 ± 3.7	23.3 ± 3.5	0.13
eGFR (mL/min/1.73 m ²)	48.0 (40.3-55.7)	54.0 (50.7-57.3)	43.0 (32.7-53.4)	<0.001
Hb (g/dL)	13.1 ± 1.7	13.9 ± 1.1	12.4 ± 1.8	<0.001
BNP (pg/mL)	138.0 (20.8-255.3)	99.9 (19.6-258.6)	185.3 (82.1-288.5)	0.05
LVEF (%)	39.0 ± 15.6	41.4 ± 17.1	36.0 ± 13.7	0.19
NYHA class (I, II, III)	28/35/12	25/15/1	3/20/11	<0.001
Etiology (n)				
Previous MI	21	8	13	0.06
CABG/VR	21	12	9	0.50
Hypertension	5	3	2	0.59
Cardiomyopathy	28	18	10	0.15
Medications (n)				
β-Blockers	42	21	21	0.25
Diuretic	57	30	27	0.36
ACEI	26	13	13	0.36
ARB	28	15	13	0.54
Knee extensor muscle strength (Nm/kg)	1.66 ± 0.39	1.88 ± 0.35	1.41 ± 0.29	<0.001

eGFR and BNP data are median (interquartile range); other data are mean ± SD. The χ^2 test was used to analyze differences between these two groups for NYHA functional class, etiology of CHF, and medications, and the Mann-Whitney U test was used for all other variables. *METs* metabolic equivalents, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *MI* myocardial infarction, *CABG* coronary artery bypass graft, *VR* valve replacement, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker

Table 2. Logistic regression analysis for prediction of an exercise capacity of ≥ 5 METs

	<i>P</i> value	OR (95% CI)
Age	0.60	
eGFR	0.04	1.07 (1.00-1.14)
Hb	0.66	
BNP	0.20	
Knee extensor muscle strength	0.001	98.42 (7.37-1314.41)

METs metabolic equivalents, *OR* odds ratio, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *Hb*, hemoglobin, *BNP*, brain natriuretic peptide.