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Original Article

Non-dominant handgrip strength is associated with higher cardiorespiratory endurance and elevated NT-proBNP concentrations in ambulatory male adult outpatients with stable HFrEF

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Abstract

Understanding the significance of handgrip strength is essential for identifying frailty in heart failure patients. The aim of this study was to identify the association between handgrip strength and cardiorespiratory endurance while highlighting the importance of the musculoskeletal system in cardiac rehabilitation for patients with heart failure. An observational cross-sectional study was conducted at Harapan Kita Hospital, Jakarta, Indonesia, from April 2022 to April 2023, among patients with heart failure with reduced ejection fraction (HFrEF) attributed to cardiomyopathy or coronary artery disease. Patients were classified by a 6-minute walk test (6MWT) distance into <400 meters (low endurance) or ≥400 meters (high endurance). The short physical performance battery (SPPB), handgrip strength, ultrasonographic forearm muscle thickness, left ventricle ejection fraction, tricuspid annular plane systolic excursion, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured. Results indicated significant differences in non-dominant handgrip strength, gait speed, and sit-to-stand SPPB scores between patients achieving a 6MWT distance of ≥400 meters and those below this threshold, with values of 31.11±6.88 kg vs 27.66±6.66 kg (p=0.049), 0.52±0.08 m/s vs 0.61±0.13 m/s (p=0.001), and 10.71±2.47 seconds vs 12.85±4.11 seconds (p=0.014), respectively. Stronger non-dominant handgrip strength (>30 kg) was associated with higher endurance (odds ratio (OR): 3.80; 95%CI: 1.35–10.67; p=0.010) and thicker forearm muscles (>1.9 cm) as measured by ultrasonography (AUC: 0.713; 95%CI: 0.585–0.840, p=0.001). In conclusion, a cut-off of ≤30 kg for non-dominant handgrip strength could effectively stratify the male patients into a lower endurance group (6MWT ≤400 meters), which is associated with elevated NT-proBNP levels and reduced forearm muscle thickness.

Keywords: Heart failure reduced ejection fraction, cardiac rehabilitation, non-dominant handgrip strength, musculoskeletal system, LVEF

Introduction

Heart failure with reduced ejection fraction (HFrEF) patients commonly experience low cardiorespiratory endurance and extremity edema, leading to immobility and reduced quality of

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life [1,2]. Frailty is frequently coexistent in heart failure patients, including younger individuals [3,4]. The coexistence of frailty and heart failure is associated with a worse prognosis, as both conditions affect multiple extracardiac organs, highlighting a multi-organ disorder that warrants early identification to improve functional outcomes [5,6].

Cardiac rehabilitation is recognized as the fifth pillar of heart failure management, alongside four key medications: beta blockers, angiotensin receptor-neprilysin inhibitors (ARNi), calcium channel blockers (CCB), and sodium-glucose co-transporter-2 inhibitors (SGLT2i) [7]. Cardiac rehabilitation encompasses a holistic program—including exercise, psychological support, group sessions, and dietary consultation—that has demonstrated efficacy in enhancing cardiovascular endurance, improving musculoskeletal health, and reducing systemic inflammation in heart failure patients [8-10]. Recent guidelines highlight resistance training as essential for sustaining cardiovascular endurance [11,12], yet resistance training remains underutilized, with limited research on targeted exercise prescriptions in heart failure care [13].

Handgrip strength is used to assess frailty, though it is infrequently measured in heart failure patients [14,15]. Various handgrip strength thresholds have been established; however, most research has focused on older adults (aged >65 years) [14,16,17]. Fried *et al.* initially proposed thresholds adjusted for body mass index (BMI), with ≤29 kg for normal-weight males [18], while Ishiyama *et al.* identified <21.9 kg for hospitalized male patients with HfrEF [19]. Previous studies have demonstrated that handgrip strength correlates with physical activity levels, nutritional status, and muscle quality; however, not all studies are heart failure-specific [15,16,20]. Therefore, understanding the significance of handgrip strength is essential for identifying frailty in heart failure patients.

The musculoskeletal system adversely affects the ability to perform adequate cardiorespiratory exercise testing, as indicated by six-minute walk test (6MWT) results [5,21]. A study found that handgrip strength is inversely correlated with the extracellular water (ECW) to intracellular water (ICW) ratio in octogenarian patients with heart failure [21]. An increased ECW/ICW ratio indicates a loss of muscle mass, as intracellular water reflects muscle cell mass while extracellular water represents interstitial fluid [21]. Low handgrip strength values are typically associated with weaker muscles, particularly in frail individuals [4,22,23]. Previous studies failed to specify which hand was used during handgrip strength measurement, leaving the potential impact of the less-trained non-dominant hand unexplored [4,14]. The aim of this study was to identify the association between handgrip strength and cardiorespiratory endurance while highlighting the importance of the musculoskeletal system in cardiac rehabilitation for patients with heart failure.

Methods

Study design and setting

An observational cross-sectional study was conducted at Harapan Kita Hospital, Jakarta, Indonesia, from April 2022 to April 2023, included patients undergoing cardiac rehabilitation, with HFrEF as the primary diagnosis due to cardiomyopathy or coronary artery disease. The present study assessed frailty in male subjects using the European Working Group on Sarcopenia in Older People (EWGSOP) criteria, which included reduced handgrip strength and slow walking speed [24]. Patients were classified by a 6MWT distance of <400 meters (low endurance) or ≥400 meters (high endurance). Assessments included the short physical performance battery (SPPB), handgrip strength, ultrasonographic forearm muscle thickness, left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

Sample size, sampling method, and patient criteria

Consecutive sampling was employed. Sample size was calculated using a formula for two-proportion comparison based on Blanquet *et al.* [25], resulting in a minimum initial size of 56, which was increased to 65 participants to accommodate a 15% dropout rate. Inclusion criteria included patients aged 18 to 65 years diagnosed with chronic HFrEF by the attending cardiologist and who had been hemodynamically stable for at least one week after the last hospital admission. Patients were required to be self-ambulatory and free from debilitating pain or neuro-

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musculoskeletal conditions affecting gait. According to a prior study [26], patients were expected to achieve at least 240 meters in the six-minute walk distance (6MWD) to reduce the risk of major adverse cardiovascular events in HFrEF patients. Exclusion criteria comprised refusal to participate and the presence of severe valvular or congenital heart disease. Patients with missing data in any component of the 6MWT, SPPB, handgrip strength, ultrasonographic measurement of forearm muscle thickness, LVEF, TAPSE, or NT-proBNP levels were considered dropouts.

Transthoracic echocardiography measurements

Transthoracic echocardiography was performed in accordance with the guidelines established by the American Society of Echocardiography [27]. LVEF was calculated by quantifying the percentage of blood volume ejected from the left ventricle during systole, with the probe positioned in the left parasternal or apical region. The apical 4-chamber and 2-chamber views were used to visualize left ventricle volumes. Simpson's biplane method was employed for calculating LVEF, which estimates left ventricular volumes at both end-diastole and end-systole, reported as a percentage (%). HFrEF is defined by impaired left ventricular systolic function, with an LVEF of ≤40% serving as the diagnostic threshold [28]. Additionally, right ventricular function was assessed using TAPSE by evaluating the longitudinal displacement of the tricuspid valve annulus during systole [27]. TAPSE was assessed in the apical 4-chamber view, with alignment to capture the right ventricular free wall and tricuspid annulus. M-mode echocardiography was then used to measure the distance of annular excursion, reported in millimeters (mm). A TAPSE of 1.6 cm or more is considered normal, while lower values indicate right ventricular systolic dysfunction.

Ultrasonography measurements

Musculoskeletal measurements were conducted using the ultrasonography method, as described in previous studies on sarcopenia, which identified ulnar muscle thickness as a superior determinant [22,23]. A 7.5 MHz ultrasonography linear probe was gently placed on the anterior surface of the forearm, utilizing minimal pressure and adequate gel to capture cross-sectional images of individual muscles [22,23,29]. Forearm muscle thickness was assessed by measuring the distance from the subcutaneous fat layer to the muscle-bone interface of the ulna, reflecting the combined thickness of both the superficial and deep flexor digitorum muscles, reported in centimeter (cm) [22,23]. Radiological images were verified by radiologists with expertise in the field.

NT-proBNP level measurement

Patients were instructed to fast for eight hours prior to venous blood collection. Venipuncture was performed on the median cubital vein or another accessible site on the arm. A total of 5 mL of blood was collected by an experienced laboratory analyst. Blood samples were left undisturbed at room temperature for 15–30 minutes to allow clot formation. Following clotting, samples were centrifuged at 1,500–2,000 g for 10–15 minutes to achieve serum separation, after which the serum was transferred to a new, labeled storage tube. Prior to analysis, blood samples were checked for hemolysis, lipemia, and icterus; any sample exhibiting these conditions was excluded. Analysis was performed as soon as possible after collection. Electrochemical Luminescence Automatic Immunoassay (ECLIA) System and Roche Elecsys® NT-proBNP assay kit (Roche Diagnostics, Mannheim, Germany) were utilized. NT-proBNP levels were quantified in picograms per milliliter (pg/mL).

Assessment of musculoskeletal endurance and strength with SPPB

Three primary components of the physical examination were conducted to assess both endurance and strength for each patient. First, an assessment was performed to ensure patient safety and stability during walking, utilizing the SPPB, which includes evaluations of balance, four-meter gait speed, and the five-times sit-to-stand test, as previously described [4,5]. An initial assessment of standing balance was performed by instructing patients to maintain various stances for 10 seconds. The first position required standing with both feet close together [4]. The second position involved placing one heel adjacent to the toes of the opposite foot, simulating a semi-tandem stance [4]. The final position entailed a full tandem stance, with one heel positioned in front of the other foot [4]. Patients who successfully maintained the semi-tandem stance were permitted to proceed to the next assessment, the four-meter gait speed test [4]. This test was conducted on a 6-meter track marked by cones at each end, where patients were instructed to traverse the distance as quickly as possible, with the time taken for the middle four meters recorded [4]. The final assessment involved the five-times sit-to-stand test, during which patients were instructed to sit in a chair and stand repeatedly five times, with the entire duration measured and recorded [4,30]. Each measurement was taken in seconds to enhance accuracy, in addition to utilizing the standardized 12-point SPPB scoring system, where a maximum of 4 points is assigned to each component. A total composite score below 9 was considered indicative of frailty [4,5,30].

Assessment of handgrip strength

Handgrip strength was assessed using a Camry electronic hand dynamometer model EH101 (Zhongshan Camry Electronic Co. Ltd., Zhongshan, China) [31]. The results from the device indicate the maximum force exerted during the handgrip test, measured in kilograms (kg). Assessment was taken from both hands. Hand dominance was determined by asking each patient which hand was used for proficient tasks such as writing, holding utensils, brushing teeth, and throwing. Validity investigations comparing this device to the gold standard Jamar Handgrip Dynamometer have been published, involving three trials to obtain the highest value and minimize bias [31]. Various cut-off values have been published [18,19,30, 32-34], and the present study aims to compare them to endurance groups and ultrasonography muscle thickness [22,23]. After establishing the cut-off value from receiver operating characteristic (ROC) analysis in the present study, patients with handgrip strength below this threshold were categorized as the weaker group, while those exceeding the cut-off were classified as the stronger group.

Six-minute walk test

Following the completion of the SPPB and handgrip strength assessments, patients were eligible to proceed with the 6MWT after a 15-minute rest. The test took place on a 30-meter linear track [35]. Standardized instructions from the American Thoracic Society (ATS) were employed to minimize encouragement bias, and the distance covered was recorded in meters [35]. Heart rate was measured before and immediately after the 6MWT test using a pulse oximeter, while the patient remained standing. A cut-off distance of 400 meters, as described by Aida *et al.* [19]. Patients were classified by a 6MWT distance of <400 meters (low endurance) or ≥400 meters (high endurance) [19]. This distance correlates to a predicted VO_2 max of approximately 15.98 mL/kg/min, or 4.6 metabolic equivalents (METs), using the Cahalin formula for patients with HFrEF [35].

Study variables

Patient demographic data, including age (years) and BMI (kg/m^2), were retrieved from medical records. Baseline and post-6MWT heart rates were measured before and after the 6MWT using a pulse oximeter and reported in beats per minute (bpm). 6MWT was performed, and patients were subsequently classified by a 6MWT distance of <400 meters (low endurance) or ≥400 meters (high endurance). Handgrip strength was assessed for both dominant and non-dominant hands using a hand dynamometer, with results recorded in kilograms (kg). Physical performance parameters, including full tandem balance (seconds), four-meter gait time (seconds), gait speed (m/s), and the five-times sit-to-stand test (seconds), were measured using SPPB, and the final score was presented as the SPPB composite score. Forearm muscle thickness for each side was measured by ultrasound and reported in centimeters (cm), while LVEF and TAPSE were assessed via transthoracic echocardiography, with LVEF presented as a percentage (%) and TAPSE as millimeters (mm). NT-proBNP levels were measured using an ECLIA immunoassay system and reported in picograms per milliliter (pg/mL).

Statistical analysis

Statistical analyses were performed using SPSS version 29.0 (IBM SPSS, Chicago, Illinois, USA), with $p \leq 0.05$ considered statistically significant. Kolmogorov-Smirnov test was employed to assess data distribution. Continuous variables were presented as mean±standard deviation (SD) (for normally distributed data) or median with minimum and maximum values (for non-normally distributed data), while categorical variables were expressed as proportions. The association between cardiorespiratory endurance groups was evaluated using an independent Student's t-test (for normally distributed data) and Mann-Whitney U test (for non-normally distributed data). Handgrip strength cut-offs were compared with cardiorespiratory endurance levels using Chi-square or Fisher's exact test, followed by ROC analysis for forearm muscle thickness cut-offs. Factors correlated with NT-proBNP levels were assessed using Pearson correlation (for normally distributed data) and Spearman correlation analysis (for non-normally distributed data).

Results

Patient characteristics

The present study initially included 109 patients with HFrEF. Fourteen patients were excluded due to severe valvular disorders, 16 due to antalgic gait from neuromusculoskeletal conditions, and 14 due to missing handgrip data. Ultimately, 65 patients met the inclusion and exclusion criteria (**Figure 1**).

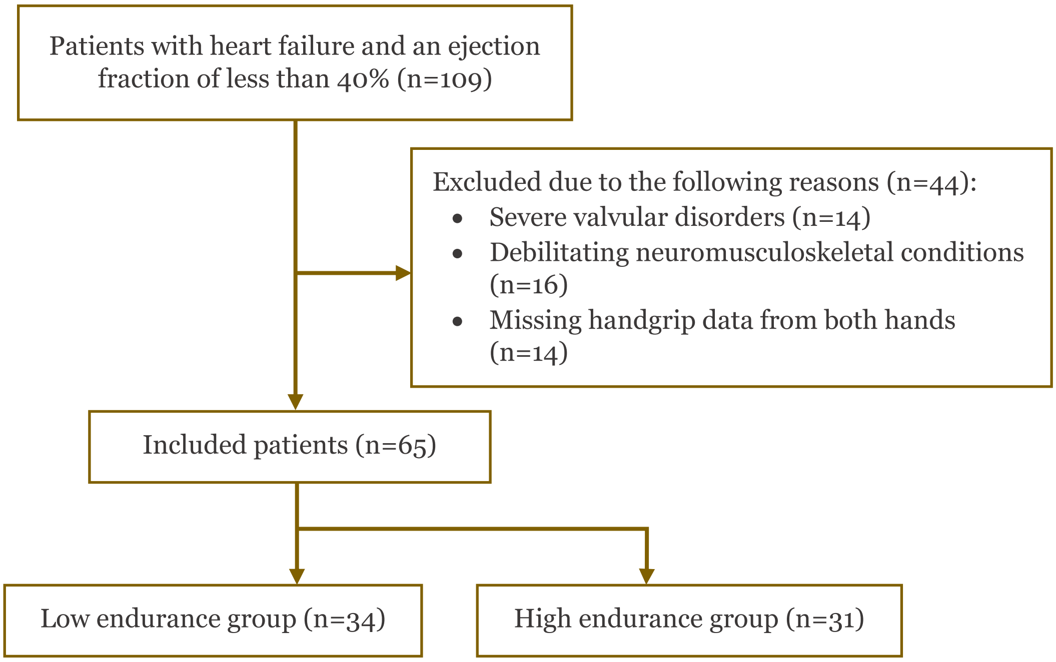

Figure 1. Recruitment flowchart of patients for the present study.

The median age was 56 years (42–65 years), with a mean BMI of 25.71±4.55 kg/m², indicating a slightly overweight population. Echocardiographic assessments showed an LVEF of 27.08±7.07% and a TAPSE of 17.17±6.27 mm. The overall distance achieved in 6MWT was 394.98±73.02 m, with baseline and post-test heart rates of 77.80±13.03 bpm and 100.22±15.52 bpm, respectively (**Table 1**).

Three patients (4.62%) scored below 9 on the SPPB and were classified as frail, with a median score of 11 (7–12 years). All patients remained balance for over 10 seconds in the side-by-side and semi-tandem stances, while the mean duration for the full tandem stance was 8.76±2.00 seconds. Musculoskeletal strength, assessed by SPPB, showed a maximum score of 4 for two components contributing to the composite score. The average walking speed was 0.57±0.12 m/s, and the time to complete five sit-to-stand repetitions was 11.83±3.57 seconds. Handgrip strength was higher in the non-dominant hand (29.31±7.14 kg) than in the dominant hand (27.49±6.92 kg), while forearm muscle thickness was greater in the dominant arm (2.24±0.64 cm) compared to the non-dominant arm (2.13±0.63 cm). The mean NT-proBNP level was 814 pg/mL, ranging from 12 to 10,621 pg/mL (**Table 1**).

Table 1. Characteristics of the included patients (n=65)

Variables	Mean±SD
Age (years), median (min-max)	56 (42–65)
Body mass index (kg/m²)	25.71±4.55
6MWT distance (m)	394.98±73.02
Baseline heart rate (bpm)	77.80±13.03
Post-6MWT heart rate (bpm)	100.22±15.52
Full tandem balance (seconds)	8.76±2.00
Four-meter gait (seconds)	2.26±0.47
Gait speed (m/s)	0.57±0.12
Five-times sit to stand (seconds)	11.83±3.57
SPPB composite score, median (min-max)	11 (7–12)
Frail (SPPB <9), n (%)	3 (4.62)
Dominant handgrip strength (kg)	27.49±6.92
Non-dominant handgrip strength (kg)	29.31±7.14
Dominant side forearm muscle thickness (cm)	2.24±0.64
Non-dominant side forearm muscle thickness (cm)	2.13±0.63
Left ventricle ejection fraction (%)	27.08±7.07
Tricuspid annular plane systolic excursion (TAPSE) (mm)	17.17±6.27
NT-proBNP (pg/mL), median (min-max)	814 (12–10,621)

6MWT: 6-minute walking test; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SD: standard deviation; SPPB: short physical performance battery.

Comparative analysis of patient characteristics based on 6MWT endurance classifications

Categorizations based on the 6MWT distance indicated that 34 patients (52.31%) achieved distances below 400 meters, while 31 patients (47.69%) exceeded this threshold (**Table 2**). The lower endurance group had a median age of 56 years and a BMI above 25 kg/m², whereas the higher endurance group had a median age of 57 years and a leaner BMI of 24.97±3.93 kg/m². The lower cardiorespiratory capacity group covered 343.27±34.70 m during the 6MWT, while the higher endurance group achieved 451.71±60.41 m. Post-6MWT heart rates were 95.50±13.77 bpm in the lower endurance group and 105.39±15.88 bpm in the higher endurance group. Significant differences in SPPB scores were observed, with a slower gait speed of 0.61±0.13 m/s in the lower endurance group compared to 0.52±0.08 m/s in the higher endurance group. The time for five repetitions of sit-to-stand was also significantly different, with the lower endurance group taking 12.85±4.11 seconds versus 10.71±2.47 seconds for the higher endurance group. No patients in the higher endurance group were classified as frail, with a median SPPB composite score of 11, while three patients in the lower endurance group scored below 9, resulting in a median score of 10.

Upper extremity examinations indicated that the dominant hand was stronger, while the non-dominant hand had thicker muscle mass. The non-dominant handgrip dynamometry showed a significant difference between groups, with the lower endurance group measuring 27.66±6.66 kg, significantly lower than the higher endurance group at 31.11±6.88 kg (p=0.049). Forearm muscle thickness differed between groups but was not statistically significant.

NT-proBNP and echocardiographic parameters (LVEF and TAPSE) did not reveal significant differences. The LVEF averaged 27.12±7.27%, consistently below 30%, while the TAPSE had a combined mean of 16.85±6.30 mm. Although the median NT-proBNP level was lower in the higher endurance group at 702 pg/mL (12–10,621 pg/mL), this difference was not statistically significant (p=0.250).

Table 2. Comparative analysis of patient characteristics based on six-minute walking test (6MWT) endurance classifications

Variable	6MWT <400 m (n=34)	6MWT ≥400 m (n=31)	p-value
	Mean±SD	Mean±SD	
Age (years), median (min-max)	56 (42–65)	57 (42–65)	0.843[a]
Body mass index (kg/m²)	26.39±5.01	24.97±3.93	0.210[b]
6MWT distance (m)	343.27±35.28	451.71±60.41	<0.001[b*]
Baseline heart rate (bpm)	77.56±11.22	78.07±14.95	0.877[b]
Post-6MWT heart rate (bpm)	95.50±13.77	105.39±15.88	0.010[b*]
Full tandem balance (seconds)	10 (2–10)	10 (1.81–10)	0.572[b]
Four-meter gait (seconds)	2.43±0.52	2.07±0.32	0.001[b*]

Variable	6MWT <400 m (n=34)	6MWT ≥400 m (n=31)	p-value
	Mean±SD	Mean±SD	
Gait speed (m/s)	0.61±0.13	0.52±0.08	0.001[b*]
Five-times sit to stand (seconds)	12.85±4.11	10.71±2.47	0.014[b*]
SPPB composite score, median (min-max)	10 (7–12)	11 (9–12)	0.086[a]
Frail (SPPB<9), n (%)	3 (8.82)	0 (0.00)	0.240[c]
Dominant handgrip strength (kg)	25.96±7.23	29.16±6.46	0.062[b]
Non-dominant handgrip strength (kg)	27.66±6.66	31.11±6.88	0.049[b*]
Dominant side forearm muscle thickness (cm)	2.21±0.60	2.28±0.69	0.700[b]
Non-dominant side forearm muscle thickness (cm)	2.12±0.62	2.12±0.62	0.881[b]
Left ventricular ejection fraction (%)	26.21±7.21	28.03±6.90	0.302[b]
TAPSE (mm)	16.32±5.95	18.10±6.59	0.257[b]
NT-proBNP (pg/mL), median (min-max)	1,026.50 (96–8,653)	702 (12–10,621)	0.250[a]

6MWT: 6-minute walking test; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SD: standard deviation; SPPB: short physical performance battery; TAPSE: tricuspid annular plane systolic excursion
[a] Analyzed using Mann-Whitney U test
[b] Analyzed using independent Student's t-test
[c] Analyzed using Fisher's exact test
[*]Statistically significant at $p \leq 0.05$

Association of handgrip strength cut-offs with cardiorespiratory endurance

Several handgrip cut-offs from prior studies have been cross-tabulated with the endurance group of patients [18,19,30,32-34]. A significant association was observed only with the non-dominant handgrip at the 30 kg cut-off, yielding an odds ratio (OR) of 3.800 (95%CI: 1.353–110.673; *p*=0.010), which was not replicated for the dominant hand. Few patients exceeded the higher cut-off of 39.5 kg, making this cut-off seemed to be inapplicable to our population. Other cut-offs failed to achieve statistical significance, though a trend indicated that stronger grips in either hand were associated with higher endurance profiles (**Table 3**).

Table 3. Association of handgrip strength cut-offs with cardiorespiratory endurance

Authors	Measurements	6MWT <400 m (n=34)	6MWT ≥400 m (n=31)	OR (95%CI)	p-value[a]
		n (%)	n (%)		
Aida *et al.* [19]	Non-dominant HGS ≥21.9 kg	26 (76.47)	28 (90.32)	2.87 (0.68–12.00)	0.137[a]
	Dominant HGS ≥21.9 kg	22 (64.71)	26 (83.87)	2.83 (0.86–9.30)	0.079[a]
Chung *et al.* [34]	Non-dominant HGS ≥25% BW	33 (97.06)	31 (100)	N/A	0.523[b]
	Dominant HGS ≥25% BW	29 (85.29)	31 (100)	N/A	0.054[b]
Yamamoto *et al.* [30]	Non-dominant HGS ≥25.5 kg	24 (70.59)	26 (83.87)	2.167 (0.64–7.52)	0.204[a]
	Dominant HGS ≥25.5 kg	18 (52.94)	21 (67.74)	1.867 (0.680–5.12)	0.224[a]
Yamada *et al.* [33]	Non-dominant HGS ≥30 kg	10 (29.42)	19 (61.29)	3.800 (1.35–10.67)	0.010[a*]
	Dominant HGS ≥30 kg	12 (35.29)	15 (48.39)	1.719 (0.63–4.65)	0.285[a]
Lam *et al.* [36]	Non-dominant HGS ≥39.5 kg	2 (5.88)	3 (9.68)	1.714 (0.26–11.01)	0.566[a]
	Dominant HGS ≥39.5 kg	0 (0)	2 (6.45)	N/A	0.224[b]

6MWT: 6-minute walking test; CI: confidence interval; HGS: handgrip strength; N/A: not available; OR: odds ratio
[a] Analyzed using the Chi-squared test
[b] Analyzed using the Fisher's exact test
[*]Statistically significant at $p \leq 0.05$

Association between non-dominant handgrip strength and the 30 kg cut-off

A significant difference was observed in non-dominant handgrip strength between groups: 36 patients (55.39%) in the weaker group (≤30 kg) had an average strength of 24.45±4.84 kg, while the stronger group achieved 35.33±4.39 kg (*p*<0.001). The 6MWT distance, gait speed, and five-times sit-to-stand test also showed significance, with the weaker group averaging 12.78±3.86 seconds, compared to 10.66±2.81 seconds in the stronger group (*p*=0.038). Ultrasonographic forearm muscle thickness differed significantly, with the weaker group measuring 1.99±0.64 cm versus 2.29±0.58 cm in the stronger group (*p*=0.028). ROC analysis revealed significant cut-offs at 1.8 cm, 1.9 cm, and 2.0 cm (*p*=0.014, 0.001, and 0.030, respectively), with the 1.9 cm cut-off having the highest area under the curve (AUC) at 0.713 (95%CI: 0.585–0.840). NT-proBNP levels were also significantly higher in the lower strength group, with a median of 1,189.50 pg/mL (238–10,621 pg/mL) compared to 493 pg/mL (12–6,923 pg/mL) in the stronger group (*p*=0.001) (**Table 4**).

Table 4. Association between non-dominant handgrip strength and the 30 kg cut-off

Variables	Non-dominant HGS <30 kg (n=36)	Non-dominant HGS ≥30 kg (n=29)	AUC (95%CI)	*p*-value
	Mean±SD	Mean±SD		
Age (years), median (min-max)	56 (42–65)	57 (44–65)		0.667[a]
Body mass index (kg/m²)	25.52±4.54	25.94±4.62		0.707[b]
6MWT distance (m)	373.06±56.62	422.21±82.43		0.006[b*]
Baseline heart rate (bpm)	10 (1.81–10)	9.46 (2–10)		0.459[a]
Post-6MWT heart rate (bpm)	2.39±0.55	2.10±0.29		0.010[b*]
Full tandem balance (seconds)	0.60±0.14	0.53±0.74		0.010[b*]
Four-meter gait (seconds)	12.78±3.86	10.66±2.81		0.016[b*]
Gait speed (m/s)	10 (8–12)	11 (7–12)		0.090[a]
Five-times sit to stand (seconds), n (%)	1 (2.78)	2 (6.90)		0.582[c]
Non-dominant HGS (kg)	24.45±4.84	35.33±4.39		<0.001[b*]
Non-dominant side forearm muscle thickness (cm)	1.99±0.64	2.29±0.58		0.028[b*]
≤1.8 cm, n (%)	13 (36.11)	3 (10.34)	0.67 (0.53–0.81)	0.014[d*]
≤1.9 cm, n (%)	21 (58.33)	5 (17.24)	0.71 (0.58–0.84)	0.001[d*]
≤2.0 cm, n (%)	23 (63.89)	9 (31.03)	0.66 (0.52–0.79)	0.017[d*]
≤2.1 cm, n (%)	26 (72.22)	15 (51.72)	0.574(0.42–0.72)	0.329[d]
NT-proBNP (pg/mL), median (min-max)	1,189.50 (238–10,621)	493 (12–6,923)		0.001[a*]

6MWT: 6-minute walking test; AUC: area under the curve; CI: confidence interval; HGS: handgrip strength; NT-proBNP: N-terminal pro-B-type natriuretic peptide
[a] Analyzed using Mann-Whitney U test
[b] Analyzed using independent Student's t-test
[c] Analyzed using Fisher's exact test
[d] Analyzed using receiver operating characteristic (ROC) curve analysis
[*]Statistically significant at $p \leq 0.05$

Factors correlated with NT-proBNP levels

Handgrip strength showed statistical significance with moderate inverse correlations: r=-0.486 (p<0.001) for the dominant hand and r=-0.455 (p<0.001) for the non-dominant hand. The sit-to-stand values correlated mildly with NT-proBNP, yielding r=0.327 (p=0.008). No significant correlations were found between NT-proBNP and LVEF, muscle thickness, 6MWT distance, or components of the SPPB.

Table 5. Factors correlated with NT-proBNP levels

Variables	Correlation coefficient (*r*)	*p*-value[a]
Age (years)	0.040	0.753
6-minute walking test distance (6MWT) (meter)	-0.249	0.045
Full tandem balance (seconds)	0.021	0.868
Four-meter gait (seconds)	0.228	0.068
Gait speed (m/s)	0.234	0.061
Five-times sit to stand (seconds), n (%)	0.327	0.008[*]
Dominant handgrip strength (kg)	-0.486	<0.001[*]
Non-dominant handgrip strength (kg)	-0.507	<0.001[*]
Dominant side forearm muscle thickness (cm)	-0.094	0.458
Non-dominant side forearm muscle thickness (cm)	-0.175	0.163
Left ventricular ejection fraction (%)	-0.190	0.130

[a] Analyzed using Spearman's correlation
[*] Statistically significant at $p \leq 0.05$

Discussion

Key findings from the present study include establishing a 400-meter cut-off for the 6MWT distance, a 30 kg cut-off for non-dominant handgrip strength, and a 1.9 cm cut-off for non-dominant forearm muscle thickness in adult male patients with HFrEF. The 400-meter cut-off distinguished cardiorespiratory functional capacities, specifically sit-to-stand speed, gait speed, and handgrip strength. Although a 400-meter cut-off may initially seem high for heart failure patients, it aligns well with prior studies, particularly in younger heart failure patients [19]. The non-dominant handgrip strength finding suggests that those with grip strength exceeding 30 kg may demonstrate better endurance, greater muscle mass, and lower NT-proBNP concentrations than those with weaker grip strength.

The present study recruited outpatient adults with HFrEF comprising younger patients compared to similar studies, which predominantly included patients over 65 years of age [14,21,37]. Consequently, prior studies reported lower 6MWT distances, while the present study had a median age of 56 years (42–65 years) [14,21,37,38]. Previous studies primarily enrolled inpatients with heart failure, who often experiencing hemodynamic instability, which likely affected 6MWT results [5,39]. Notably, in the present study, only three patients (4.62%) met the frailty threshold (<9) due to limitations in balance and sit-to-stand speed. However, using the latest cardiovascular frailty criteria, all patients in the present study were classified as non-frail (SPPB score ≥5), suggesting that younger adult outpatients with HFrEF may exhibit distinct endurance profiles, potentially attributable to differences in musculoskeletal characteristics compared to older populations [40,41].

The present study found a significant difference in non-dominant handgrip strength between endurance groups. This highlights the importance of hand dominance in assessing handgrip strength's relationship with endurance, suggesting potential biomechanical or physiological differences impacting skeletal muscle strength [22]. Muscle strength is influenced by five primary components: muscle size, muscle shape, insertion site, torque curve, and neuromuscular factors [42,43]. Of these, handgrip strength between patients recruits similar muscles—the finger flexors and wrist extensors—with consistent shape, insertion site, and torque curve, leaving neuromuscular factors and muscle size as primary determinants [43]. Resistance training has been shown to enhance muscle strength by increasing neuron firing rates and muscle fiber recruitment [12,42]. The non-dominant hand exemplifies an untrained muscle group, where strength improvements may indicate broader musculoskeletal health [22,42].

The present study measured anterior forearm muscle size, revealing that the 30 kg cut-off effectively distinguished the endurance group, correlating with muscle thickness above 1.9 cm and an acceptable AUC (0.713; p=0.001), findings reproducible only in the non-dominant hand. This suggests that trained muscles in patients with HFeEF may differ from untrained muscles, which appear more vulnerable to deconditioning [43,44]. Further research is warranted to refine assessment methods for trained muscles, particularly in active ambulatory heart failure patients.

Further analysis demonstrated a significant inverse correlation between NT-proBNP levels and handgrip strength (r=-0.507, p<0.001 for the non-dominant hand; r=-0.486, p<0.001 for the dominant hand), along with a significant difference within the 30 kg non-dominant handgrip strength cut-off group (p=0.001). While prior studies have indicated that NT-proBNP levels are influenced by muscle quality, the present study is the first to analyze handgrip dynamometry as a simple physical examination in patients with HFrEF, rather than relying on dual X-ray absorptiometry (DXA) [16,17]. In a multi-ethnic study of atherosclerosis (MESA) cohort, DXA assessed overall muscle quality (area and density) and found that muscle density is inversely correlated with NT-proBNP levels, although the patients were initially free of cardiovascular disease at baseline [16]. Another study noted an inverse correlation between handgrip strength and NT-proBNP in heart failure subjects; however, it did not establish specific cut-offs or consider hand dominance [17]. The relationship between muscle strength and NT-proBNP remains unclear, but it is plausible that recurrent training enhances neuromuscular contraction, leading to increased peripheral angiogenesis and subsequently lowered NT-proBNP levels [12].

Moreover, faster gait speed, higher SPPB values, and greater 6MWT distances correlate with improved cardiorespiratory endurance, potentially reflecting lower NT-proBNP levels in trained patients with HFrEF [9]. The present study findings suggest that handgrip strength is essential for assessing endurance and NT-proBNP levels in patients with HFrEF, as supported by previous studies [5,9,16]. Further research is needed to explore this correlation in multi-ethnic populations.

The present study findings hold significant implications for exercise prescription and rehabilitation strategies for patients with heart failure, tailored to accommodate varying levels of strength and endurance. However, several limitations were identified in the present study. First, the inclusion of only male patients reflects the male majority within the local heart failure population, potentially limiting the generalizability of the results to female patients [38]. Second, the modest sample size, while showing a moderate correlation with NT-proBNP, may lead to disparities in achieving the AUC, suggesting that a larger sample size could enhance the robustness of the present study findings. Lastly, the mechanism linking handgrip strength and NT-proBNP remains unexplored and may be due to enhanced peripheral vascularization rather than muscle size. Previous studies have indicated that flow-mediated dilation may be a promising biomarker for profiling deconditioned extremities in patients with heart failure [45,46]. Future research should investigate these mechanisms by analyzing flow-mediated dilation in ambulatory patients with HFrEF to confirm vascularization profiles in non-dominant extremities.

Conclusion

Ambulatory patients with HFrEF may benefit from measuring non-dominant handgrip strength to classify endurance levels for precise exercise prescription and to reflect systemic NT-proBNP levels. A cut-off of ≤30 kg for non-dominant handgrip strength effectively stratifies male patients into a lower endurance group (6MWT ≤400 meters), which is associated with elevated NT-proBNP levels and reduced forearm muscle thickness.

Ethics approval

Protocol of the present study was reviewed and approved by Ethical Committee for Health Research, Harapan Kita Hospital, Jakarta, Indonesia (Approval Number: DP.04.03/KEP238/EC105/2023).

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Competing interests

Hajime Katsukawa receives a full-time salary as chair from the Japanese Society for Early Mobilization, a nonprofit organization. All the other authors declare that there are no conflicts of interest to disclose.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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References

1. Ravera A, Santema BT, Sama IE, *et al.* Quality of life in men and women with heart failure: Association with outcome, and comparison between the Kansas City Cardiomyopathy Questionnaire and the EuroQol 5 dimensions questionnaire. Eur J Heart Fail 2021;23:567-577.

2. Bozkurt B, Fonarow GC, Goldberg LR, *et al*. Cardiac rehabilitation for patients with heart failure: JACC expert panel. J Am Coll Cardiol 2021;77:1454-1469.
3. Marengoni A, Zucchelli A, Vetrano DL, *et al*. Heart failure, frailty, and pre-frailty: A systematic review and meta-analysis of observational studies. Int J Cardiol 2020;316:161-171.
4. Afilalo J. Evaluating and treating frailty in cardiac rehabilitation. Clin Geriatr Med 2019;35(4):445-457.
5. Kitai T, Shimogai T, Tang WHW, *et al*. Short physical performance battery vs. 6-minute walking test in hospitalized elderly patients with heart failure. Eur Heart J Open 2021;1(1):oeab006.
6. Matsue Y, Kamiya K, Saito H, *et al*. Prevalence and prognostic impact of the coexistence of multiple frailty domains in elderly patients with heart failure: The FRAGILE-HF cohort study. Eur J Heart Fail 2020;22(11):2112-2119.
7. Taylor RS, Dalal HM, Zwisler AD. Cardiac rehabilitation for heart failure: 'Cinderella' or evidence-based pillar of care?. Eur Heart J 2023;44(17):1511-1518.
8. Heidenreich PA, Bozkurt B, Aguilar D, *et al*. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. J Card Fail 2022;02:010.
9. Santoso A, Maulana R, Alzahra F, *et al*. The effects of aerobic exercise on N-terminal pro-B-type natriuretic peptide and cardiopulmonary function in patients with heart failure: A meta-analysis of randomised clinical trials. Heart Lung Circ 2020;29(12):1790-1798.
10. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. Front Cardiovasc Med 2019;6:69.
11. Laoutaris ID, Piotrowicz E, Kallistratos MS, *et al*. Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial. Eur J Prev Cardiol 2021;28(15):1626-1635.
12. Hansen D, Abreu A, Ambrosetti M, *et al*. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: Why and how: A position statement from the secondary prevention and rehabilitation section of the European Association of Preventive Cardiology. Eur J Prev Cardiol 2024;31(13):e102.
13. Pandey A, Keshvani N, Zhong L, *et al*. Temporal trends and factors associated with cardiac rehabilitation participation among medicare beneficiaries with heart failure. JACC Heart Fail 2021;9(7):471-481.
14. Dai KZ, Laber EB, Chen H, *et al*. Hand grip strength predicts mortality and quality of life in heart failure: Insights from the Singapore cohort of patients with advanced heart failure. J Card Fail 2023;29(6):911-918.
15. Burke MA. Quantifying the eyeball test: Grip strength at the nexus of frailty, cachexia and sarcopenia in heart failure. J Card Fail 2023;29(6):919-921.
16. Parra MT, Sada I, Gold R, *et al*. Associations between muscle quality and N-terminal pro-B-type natriuretic peptide (NT-proBNP): The multi-ethnic study of atherosclerosis. Am J Med Sci 2024;367(3):160-170.
17. Oreopoulos A, Ezekowitz JA, McAlister FA, *et al*. Association between direct measures of body composition and prognostic factors in chronic heart failure. Mayo Clin Proc 2010;85(7):609-617.
18. Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
19. Aida K, Kamiya K, Hamazaki N, *et al*. Optimal cutoff values for physical function tests in elderly patients with heart failure. Sci Rep 2022;12(1):6920.
20. Roberts HC, Denison HJ, Martin HJ, *et al*. A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach. Age Ageing 2011;40(4):423-429.
21. Umehara T, Kaneguchi A, Kawakami W, *et al*. Association of muscle mass and quality with hand grip strength in elderly patients with heart failure. Heart Vessels 2022;37(8):1380-1386.
22. Abe T, Loenneke JP. Handgrip strength dominance is associated with difference in forearm muscle size. J Phys Ther Sci 2015;27(7):2147-2149.
23. Abe T, Counts BR, Barnett BE, *et al*. Associations between handgrip strength and ultrasound-measured muscle thickness of the hand and forearm in young men and women. Ultrasound Med Biol 2015;41(8):2125-2130.
24. Nakade T, Maeda D, Matsue Y, *et al*. Prognostic impact of sarcopenia assessed using modified asian working group for sarcopenia 2019 criteria in heart failure. Can J Cardiol 2024;S0828-282X(24)00924-3.
25. Blanquet M, Massoulié G, Boirie Y, *et al*. Handgrip strength to screen early-onset sarcopenia in heart failure. Clin Nutr ESPEN 2022;50:183-190.
26. Radi B, Santoso A, Siswanto BB, Kusmana D. GW27-e0560 six-minute walking distance, but not systolic function, was predictor of adverse cardiac events in heart failure patients who underwent early exercise program. J Am Coll Cardiol 2016;68(16) Suppl:C166.

27. Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(1):1-39.e14.
28. McDonagh TA, Metra M, Adamo M, *et al.* 2023 focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2024;45(1):53.
29. Kara M, Kaymak B, Ata AM, *et al.* STAR-sonographic thigh adjustment ratio: A golden formula for the diagnosis of sarcopenia. Am J Phys Med Rehabil 2020;99(10):902-908.
30. Yamamoto S, Yamasaki S, Higuchi S, *et al.* Prevalence and prognostic impact of cognitive frailty in elderly patients with heart failure: Sub-analysis of FRAGILE-HF. ESC Heart Fail 2022;9(3):1574-1583.
31. Díaz Muñoz GA, Calvera Millán SJ. Comparing the Camry dynamometer to the Jamar dynamometer for use in healthy Colombian adults. Rev Salud Bosque 2019;9(2):18-26.
32. Konishi M, Kagiyama N, Kamiya K, *et al.* Impact of sarcopenia on prognosis in patients with heart failure with reduced and preserved ejection fraction. Eur J Prev Cardiol 2021;28(29):1022-1029.
33. Yamada S, Adachi T, Izawa H, *et al.* Prognostic score based on physical frailty in patients with heart failure: A multicenter prospective cohort study (FLAGSHIP). J Cachexia Sarcopenia Muscle 2021;12(6):1995-2006.
34. Chung CJ, Wu C, Jones M, *et al.* Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail 2014;20(5):310-315.
35. Deka P, Pozehl BJ, Pathak D, *et al.* Predicting maximal oxygen uptake from the 6 min walk test in patients with heart failure. ESC Heart Fail 2021;8(1):47-54.
36. Lam NW, Goh HT, Kamaruzzaman SB, *et al.* Normative data for hand grip strength and key pinch strength,stratified by age and gender for a multiethnic Asian population. Singapore Med J 2016;57(10):578-584.
37. Bakker EA, Snoek JA, Meindersma EP, *et al.* Absence of fitness improvement is associated with outcomes in heart failure patients. Med Sci Sports Exerc 2018;50(2):196-203.
38. Siswanto BB, Radi B, Radi B, *et al.* Heart failure in NCVC Jakarta and 5 hospitals in Indonesia. Global Heart 2010;5(1):35-38.
39. Ishiyama D, Yamada M, Makino A, *et al.* The cut-off point of short physical performance battery score for sarcopenia in older cardiac inpatients. Eur Geriatr Med 2017;8(4):299-303.
40. Richter D, Guasti L, Walker D, *et al.* Frailty in cardiology: Definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, EPCCS. Eur J Prev Cardiol 2022;29(1):216-227.
41. Guralnik JM, Ferrucci L, Pieper CF, *et al.* Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55(4):M221-M231.
42. Swiecicka A, Piasecki M, Stashuk DW, *et al.* Frailty phenotype and frailty index are associated with distinct neuromuscular electrophysiological characteristics in men. Exp Physiol 2019;104(8):1154-1161.
43. Reid KF, Pasha E, Doros G, *et al.* Longitudinal decline of lower extremity muscle power in healthy and mobility-limited older adults: Influence of muscle mass, strength, composition, neuromuscular activation and single fiber contractile properties. Eur J Appl Physiol 2014;114(1):29-39.
44. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure. JACC Heart Fail 2019;7(12):1001-1011.
45. Areas GPT, Mazzuco A, Caruso FR, *et al.* Flow-mediated dilation and heart failure: A review with implications to physical rehabilitation. Heart Fail Rev 2019;24(1):69-80.
46. Meyer B, Mörtl D, Strecker K, *et al.* Flow-mediated vasodilation predicts outcome in patients with chronic heart failure: comparison with B-type natriuretic peptide. J Am Coll Cardiol 2005;46(1):1011-1018.