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Research article

Benefit of cardiac rehabilitation in acute heart failure patients with cognitive impairment

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ABSTRACT

Aims: This study aimed to evaluate the prevalence of cognitive impairment among patients with acute heart failure (AHF), its prognosis, and the effects of cardiac rehabilitation (CR) on these patients' outcomes.

Methods: Overall, 247 consecutive AHF patients (median age, 60 years; males, 78.5 %) were evaluated from March 2015 to May 2021. Patients received an AHF disease management program coordinated by an HF specialist nurse and underwent a Luria-Nebraska Neuropsychological battery-screening test (LNNB-S) assessment during admission. Cognitive impairment was defined as an LNNB-S score $\geq$10. Patients who underwent at least one session of phase II CR and continued with the home-based exercise program were considered to have received CR. The primary endpoint was composite all-cause mortality or readmission after a 3.30-year follow-up (interquartile range, 1.69–5.09 years).

Results: Cognitive impairment occurred in 53.0 % and was associated with significantly higher composite endpoint, all-cause mortality, and readmission rates (p=<0.001, 0.001, and 0.015, respectively). In the total cohort, 40.9 % of patients experienced the composite endpoint. Multivariate analysis showed that the peak VO_2 was a significant predictor of the composite endpoint. After adjustment, CR significantly decreased the event rate of the composite endpoint and the all-cause mortality in patients with cognitive impairment (log-rank p = 0.024 and 0.009, respectively). However, CR did not have a significant benefit on the composite endpoint and the all-cause mortality in patients without cognitive impairment (log-rank p = 0.682 and 0.701, respectively).

Conclusion: Cognitive impairment is common in AHF patients and can lead to poor outcomes. CR is a standard treatment to improve prognosis.

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1. Introduction

Cognitive dysfunction is a frequent comorbidity in acute heart failure (AHF) patients and is prospectively linked to frequent hospitalisation, recurrent cardiac events, and mortality [1,2]. Cognitive dysfunction may be particularly pathogenic and thus require treatment, but the identification and treatment of cognitive impairment following AHF remain underappreciated. The complex bidirectional interaction between cognitive impairment and HF results from several common pathophysiological pathways, including neurohormonal activation, increased inflammation, and reduced cerebral perfusion [3]. However, little is known about the optimisation of promising treatment targets for this comorbidity.

Multidisciplinary cardiac rehabilitation (CR) can improve the mid-to long-term survival rates of patients with heart failure [4]. Lifestyle modifications and exercise can also improve cognitive function in patients with HF(5). Meanwhile, medical therapies (e.g., acetylcholinesterase inhibitors and memantine) for cognitive impairment may increase side effects when co-administered with cardiovascular drugs [5]. Current guidelines do not provide evidence-based recommendations for HF patients with cognitive impairment. CR may have greater clinical benefits in HF patients with cognitive impairment than in those without cognitive impairment.

The hypothesis of this study is that cognitive impairment is highly prevalent among Asian patients with acute heart failure and

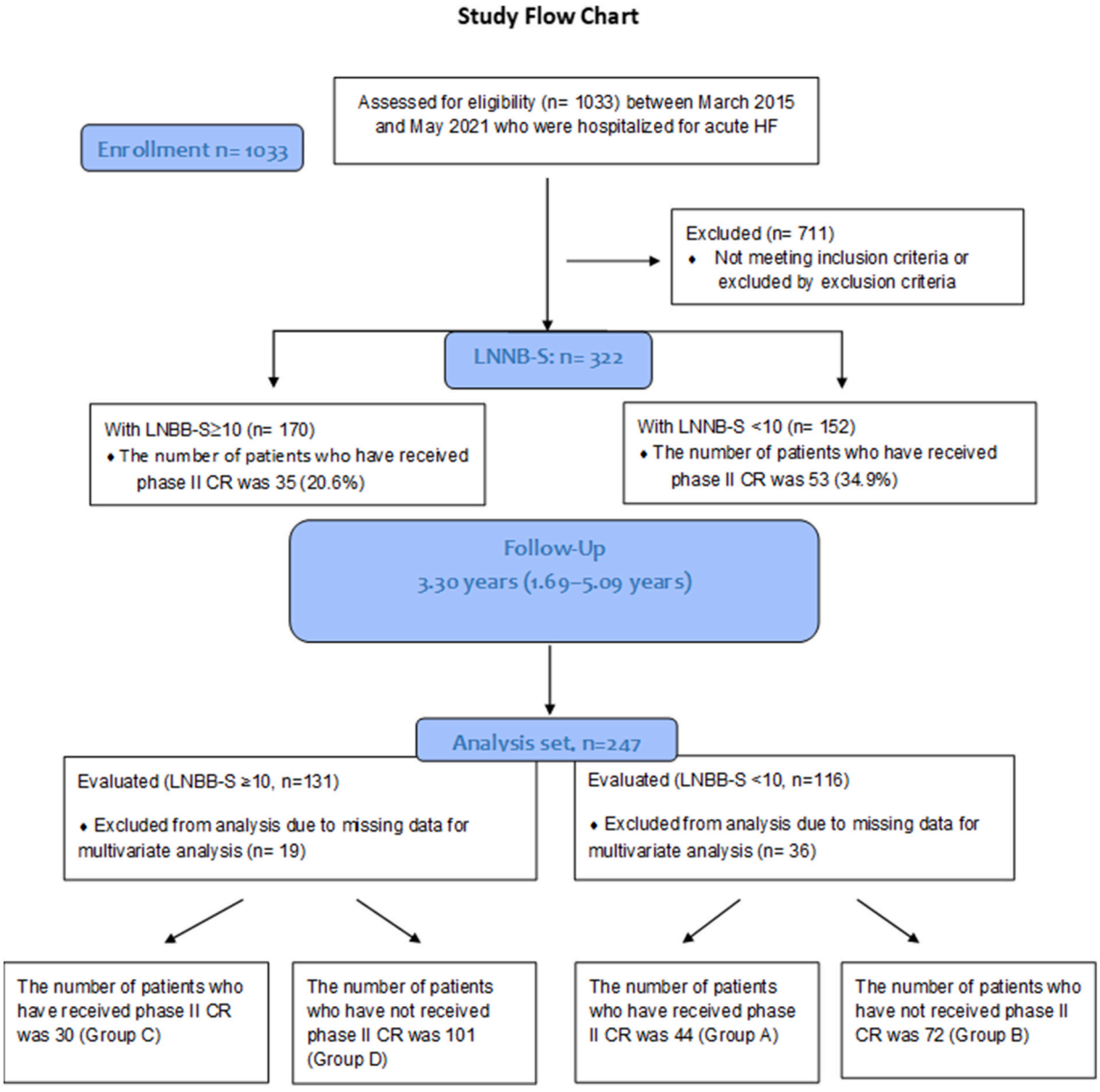

Fig. 1. Patient selection flow chart.

holds significant clinical importance. Early detection and treatment can potentially improve patient prognosis. Multidisciplinary cardiac rehabilitation may assist these patients and reduce the overall mortality rate. Therefore, we conducted this retrospective study to investigate the prevalence of cognitive impairment in patients with acute heart failure, its prognosis, and to explore the effects of multidisciplinary cardiac rehabilitation on the treatment of these patients, with the aim of improving their management.

2. Methods

2.1. Study design and patients

This retrospective study evaluated patients hospitalized for AHF between March 2015 and May 2021 at the Heart Failure Center of Kaohsiung Chang Gung Memorial Hospital. Patients who fulfilled the following inclusion criteria were enrolled in this study [1]: survived at discharge [2], underwent cognitive and psychological functional assessments [3], aged ≥20 years [4], left ventricular ejection fraction (LVEF) ≤40 % on echocardiography or other methods, and [6] heart failure disease management coordinated by an HF specialist nurse as described previously [7]. The exclusion criteria were as follows [1]: an estimated survival time of <6 months [2], long-term bedridden (>3 months) [3], terminal heart status, and [4] cannot cooperate with all functional studies. Among the 322 patients initially screened, 75 patients with missing data were excluded. Finally, 247 patients were included in the analysis (Fig. 1).

This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation Institutional Review Board (IRB, 202200636B0) and complied with the Declaration of Helsinki. The requirement for informed consent was waived by the IRB owing to the retrospective nature of this study. This study was registered at ClinicalTrials.gov (identifier: NCT05726565).

2.2. Clinical variables

Baseline demographic variables, including age, sex, LVEF (as determined by echocardiography or other methods), medical history (hypertension, diabetes mellitus, hyperlipidaemia, old stroke, atrial fibrillation, and coronary artery disease), and medications at discharge, were collected from the medical records in the Hospital Information System (HIS). Standard laboratory data were collected on admission.

2.3. Multidisciplinary cardiac rehabilitation

The heart failure disease management program, performed according to clinical guidelines [8], is a standard of care for patients with acute heart failure at the Heart Failure Center. Eligible patients were advised to undergo a cardiopulmonary exercise test (CPET) within 1 month of discharge. The CPET was conducted using an upright graded-cycle ergometer or motorised treadmill with a modified Bruce or Cornell protocol [9]. CPET variables such as oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation were continuously recorded using a respiratory mass spectrometer (Vmax Encore, VIASYS, Yorba Linda, CA, USA). Peak VO_2 was defined as the highest 15-s average value within the last 90 s of exercise with a respiratory exchange ratio of at least 1.05. The peak VO_2 measured by cycle ergometer was increased by 10 % to allow comparison with treadmill protocol. Patients who did not undergo CPET were considered to have peak VO_2 not assessed.

A heart failure disease management program that included an HF specialist nurse education program, dietitian consultation, physiatrist consultation, and psychological consultation and assessment was delivered to all patients before discharge. Patients were advised to undergo phase II CR within 1 month from discharge. Moderate continuous aerobic exercise training was prescribed individually according to the CPET result [4]. The training intensity was within 10 beats of the anaerobic threshold or 40–60 % of peak VO_2. The training intensity was gradually increased fortnightly as tolerated (Borg's scale of 12–14). Phase II CR consisted of 12 weeks of 36 sessions or more in the entire course. Only the patients who underwent at least one exercise session of phase II CR and continued with the home-based exercise program were considered to have recieved CR. Home-based exercise program was designed to be a continuation of the principles patients learn during Phase II CR. It included a mix of aerobic exercises, strength training, and flexibility exercises tailored to each patient's specific health status and abilities. We provided them with written and visual materials to guide their routines at home.

2.4. Assessment of cognitive impairment

As one of the core components of multidisciplinary CR, psychiatrist and psychologist consultations were delivered to all patients [10]. Cognitive function was assessed by an experienced psychologist using the Luria-Nebraska Neuropsychological Battery-Screening Test (LNNB-S) [11]. The initial LNNB was condensed into 15 items for the screening test by Golden [12]. The LNNB-S was measured at the point of stabilization following initial management of HF, prior to discharge. The median duration of hospitalisation for our patients was 8 days with an interquartile range of 8 days. The LNNB-S focuses on three domains: number calculation, cognitive function, and rhythm control. In this study, the LNNB-S cut-off point for cognitive impairment was set to ≥10, that is, patients with LNNB-S ≥10 may have cognitive impairment.

2.5. Follow-up

An HF specialist nurse contacted the patients by phone within 1 week of discharge and regularly every 6 months until July 30,

2022. The health status of the patients was recorded using the Hospital Information System (HIS) of the HF centre. De-identified retrospective data were extracted from the HIS by removing identifying information and replacing it with identification numbers. The patients were followed up for a mean of 3.30 years (interquartile range 1.69–5.09 years). To ensure that the home exercise program was implemented in the CR group, we conducted telephonic follow-up interviews with an HF specialist nurse.

2.6. Endpoints

The primary endpoint was a composite of all-cause mortality or readmission for HF.

The secondary endpoints were all-cause mortality, recurrent hospitalisation for HF, and changes in the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) score from baseline to 6 months and 1 year. KCCQ12 is a 12-item instrument that quantifies physical function, symptoms, social function, self-efficacy, knowledge, and quality of life. The KCCQ12 clinical summary score is a composite assessment of physical limitations and total symptom scores. Scores are calculated in the range of 0–100, with higher scores reflecting better health status.

2.7. Statistical analysis

Continuous variables showing non-normal distribution according to the Kolmogorov-Smirnov test ($p < 0.05$) were presented as the median and interquartile ranges (IQR). Meanwhile, categorical variables were presented as numbers and percentages. The Mann-Whitney *U* test was used to compare continuous variables. The chi-squared test or Fisher's exact test was used to compare categorical variables. The correlations between pairwise continuous variables were tested using Spearman's correlation coefficients. Univariate Cox proportional hazard regression was performed to identify predictors of the composite endpoint and all-cause mortality.

Table 1A
Baseline clinicodemographic characteristics in the total cohort and in the patients with (LNNB-S ≥10) and without cognitive impairment (LNNB-S <10).

Characteristic	Total (n = 247)	LNNB-S ≥10 (n = 131)	LNNB-S <10 (n = 116)	p
Age, years	60.0 (51.0–67.0)	65.0 (56.0–72.0)	54.0 (45.0–61.0)	<0.001
Male, %	194 (78.5 %)	105 (80.2 %)	89 (76.7 %)	0.512
BMI	25.8 (23.0–29.2)	25.4 (23.0–28.6)	26.1 (22.9–29.5)	0.532
Ischemic CM, %	180 (72.9 %)	94 (71.8 %)	86 (74.1 %)	0.674
Hypertension, %	167 (67.6 %)	94 (71.8 %)	73 (62.9 %)	0.139
DM, %	109 (44.1 %)	64 (48.9 %)	45 (38.8 %)	0.112
Hyperlipidaemia, %	105 (42.5 %)	62 (47.3 %)	43 (37.1 %)	0.104
AF, %	74 (30.0 %)	45 (34.4 %)	29 (25.0 %)	0.109
Old stroke, %	18 (7.3 %)	14 (10.7 %)	4 (3.4 %)	0.029
Mean BP, mmHg	92.0 (80.0–104.0)	91.0 (79.0–107.0)	92.0 (82.3–102.0)	0.677
Heart rate, beats/min	81.0 (70.0–95.0)	77.0 (64.0–94.0)	86.5 (72.0–97.0)	0.010
LVEF, %	30.0 (24.0–34.0)	31.0 (25.0–34.0)	29.6 (22.3–34.0)	0.413
NT-proBNP, pg/mL	2694.5 (977.8–7917.0)	3578.0 (1144.3–10971.3)	2270.0 (761.5–5647.5)	0.064
Serum sodium, mEq/L	138.0 (135.0–140.0)	138.0 (135.0–140.0)	138.0 (135.0–140.0)	0.996
Serum urea nitrogen, mg/dL	23.0 (16.0–35.0)	26.0 (18.0–44.0)	20.0 (14.0–27.0)	<0.001
Serum creatinine, mg/dL	1.27 (0.95–1.89)	1.40 (1.04–2.57)	1.10 (0.89–1.47)	<0.001
Haemoglobin, g/dL	13.3 (11.6–14.8)	12.8 (11.1–14.7)	13.7 (12.2–15.0)	0.108
Haematocrit, %	40.5 (35.9–44.4)	39.7 (34.2–43.9)	41.3 (37.1–44.9)	0.050
Platelet, (x1000)	201.0 (160.0–257.0)	193.0 (148.0–245.0)	217.0 (167.0–280.3)	0.022
Albumin, g/dL	3.62 (3.30–4.01)	3.50 (3.10–3.94)	3.74 (3.44–4.10)	0.002
eGFR	59.6 (35.3–83.9)	48.6 (24.3–68.9)	71.2 (52.4–92.4)	<0.001
Peak VO_2, ml/kg/mins	16.3 (13.0–18.5)[a]	13.8 (12.4–17.4)[b]	17.2 (13.7–19.4)[c]	0.001
LNNB-S	10.0 (5.0–16.0)	16.0 (12.0–20.0)	5.0 (3.0–7.0)	<0.001
BDI-II	5.0 (2.0–9.0)	5.0 (2.0–10.0)	5.0 (2.0–8.0)	0.359
BAI	5.0 (3.0–9.0)	5.0 (3.0–9.0)	5.0 (2.0–8.0)	0.993
ACEI, n (%)	46 (18.6 %)	26 (19.8 %)	20 (17.2 %)	0.600
ARB, n (%)	124 (50.2 %)	56 (42.7 %)	68 (58.6 %)	0.013
ARNI, n (%)	43 (17.4 %)	25 (19.1 %)	18 (15.5 %)	0.461
Beta-blockers, n (%)	203 (82.2 %)	105 (80.2 %)	98 (84.5 %)	0.375
MRA, n (%)	148 (59.9 %)	70 (53.4 %)	78 (67.2 %)	0.027
Anti-depressant/anti-psychotics, n (%)	16 (6.5 %)	11 (8.4 %)	5 (4.3 %)	0.193
Cardiac Rehabilitation, n (%)	74 (30.0 %)	30 (22.9 %)	44 (37.9 %)	0.010
Education (years)	12.0 (7.0–12.0)	9.0 (6.0–12.0)	12.0 (12.0–14.8)	<0.001

BMI, body mass index; CM, cardiomyopathy; DM, diabetes mellitus; AF, atrial fibrillation; BP, blood pressure; LVEF, left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; Peak VO2, peak oxygen uptake; LNNB-S, Luria-Nebraska Neuropsychological Battery-Screening test; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; ACEI, angiotensin-converting enzyme.

[a] Analysis from 158 patients (64.0 %) with CPET assessment.

[b] Analysis from 72 patients (55.0 %) with CPET assessment.

[c] Analysis from 86 patients (74.1 %) with CPET assessment.

Multivariate Cox regression by Enter method was performed to identify the predictors of the composite endpoint and all-cause mortality. Variables considered in each model were those related to HF clinical outcomes.

Kaplan–Meier curves and log-rank tests were constructed to compare the composite endpoint and all-cause mortality in the following four groups: Group A, patients without cognitive impairment and have received CR; Group B, patients without cognitive impairment and have not received CR; Group C, patients with cognitive impairment and have received CR; and Group D, patients with cognitive impairment and have not received CR. The Kruskal–Wallis test was used to evaluate differences among the groups. Multiple pairwise comparisons with Bonferroni correction were used to detect variables with significant differences among groups. Cox regression analysis was performed to assess the association between CR and patient outcomes, with the association expressed as the hazard ratio (HR) and confidence interval (CI). All statistical analyses were performed using IBM SPSS for (Version 25.0. Armonk, NY: IBM Corp.). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Our study included 1033 patients who were hospitalized for acute heart failure between March 2015 and May 2021. However, 711 patients were excluded as they did not undergo cognitive and psychological functional assessment which did not meet our inclusion criteria. Out of the 322 patients initially screened, 75 patients with one or two missing data were also excluded. Finally, we have analyzed a total of 247 patients.

The mean age of the 247 patients was 60.0 years (IQR: 51.0–67.0 years), and 78.5 % of the total cohort was male. Overall, 72.9 %, 67.6 %, 30.0 %, and 7.3 % of the patients had ischemic cardiomyopathy, hypertension, atrial fibrillation, and previous stroke, respectively (Table 1). The median LVEF was 30.0 % (IQR: 24.0–34.0 %), and the median of peak VO_2 was 16.3 ml/kg/mins (IQR: 13.0–18.5 ml/kg/mins). Most patients received renin-angiotensin-aldosterone system inhibitors (86.2 %) or beta-blockers (82.2 %).

Table 1B
Baseline clinicodemographic characteristics of the total cohort and patients who did and did not receive cardiac rehabilitation.

Characteristic	Total (n = 247)	CR (n = 74)	Non-CR (n = 173)	p
Age, years	60.0 (51.0–67.0)	57.5 (46.8–65.3)	60.0 (52.0–68.5)	0.042
Male, %	194 (78.55 %)	59 (79.7 %)	135 (78.0 %)	0.766
BMI	25.8 (23.0–29.2)	26.4 (24.0–29.8)	25.4 (22.7–28.6)	0.169
Ischemic CM, %	180 (72.9 %)	58 (78.4 %)	122 (70.5 %)	0.203
Hypertension, %	167 (67.6 %)	48 (64.9 %)	119 (68.8 %)	0.546
DM, %	109 (44.1 %)	28 (37.8 %)	81 (46.8 %)	0.193
Hyperlipidaemia, %	105 (42.5 %)	33 (44.6 %)	72 (41.6 %)	0.665
AF, %	74 (30.0 %)	22 (29.7 %)	52 (30.1 %)	0.959
Old stroke, %	18 (7.3 %)	9 (12.2 %)	9 (5.2 %)	0.054
Mean BP, mmHg	92.0 (80.0–104.0)	88.5 (78.0–99.3)	93.0 (81.0–107.0)	0.081
Heart rate, beats/min	81.0 (70.0–95.0)	83.0 (72.0–94.3 %)	80 (69.0–95.0)	0.562
LVEF, %	30.0 (24.0–34.0)	28.0 (23.8–34.8)	30.0 (23.7–34.0)	0.846
NT-proBNP, pg/mL	2694.5 (977.8–7917.0)	1472.0 (704.3–4346.3)	3710.0 (1100.8–9670.0)	0.020
Serum sodium, mEq/L	138.0 (135.0–140.0)	138.0 (135.0–139.0)	138.0 (135.0–140.0)	0.290
Serum urea nitrogen, mg/dL	23.0 (16.0–35.0)	21.0 (15.0–27.3)	24.0 (16.0–37.5)	0.032
Serum creatinine, mg/dL	1.27 (0.95–1.89)	1.21 (0.96–1.67)	1.31 (0.94–2.04)	0.296
Haemoglobin, g/dL	13.3 (11.6–14.8)	13.6 (11.7–15.1)	13.3 (11.5–14.6)	0.332
Haematocrit, %	40.5 (35.9–44.4)	41.3 (36.5–44.9)	40.3 (35.3–43.7)	0.272
Platelet, (x1000)	201.0 (160.0–257.0)	204.5 (152.5–264.5)	198.0 (163.0–256.0)	0.779
Albumin, g/dL	3.62 (3.30–4.01)	3.74 (3.30–4.30)	3.62 (3.26–3.94)	0.109
eGFR	59.6 (35.3–83.9)	64.5 (43.1–88.2)	56.7 (32.6–80.9)	0.130
Peak VO_2, ml/kg/mins	16.3 (13.0–18.5)[a]	16.5 (12.9–19.4)[b]	16.2 (13.2–18.3)[c]	0.834
LNNB-S <10	116 (47.0 %)	44 (59.5 %)	72 (41.6 %)	0.010
BDI-II	5.0 (2.0–9.0)	4.0 (2.0–8.0)	5.0 (2.0–10.0)	0.173
BAI	5.0 (3.0–9.0)	5.0 (3.0–9.0)	6.0 (2.0–9.0)	0.751
ACEI, n (%)	46 (18.6 %)	16 (21.6 %)	30 (17.3 %)	0.429
ARB, n (%)	124 (50.2 %)	39 (52.7 %)	85 (49.1 %)	0.607
ARNI, n (%)	43 (17.4 %)	11 (14.9 %)	32 (18.5 %)	0.490
Beta-blockers, n (%)	203 (82.2 %)	60 (81.1 %)	143 (82.7 %)	0.767
MRA, n (%)	148 (59.9 %)	47 (63.5 %)	101 (58.4 %)	0.451
Anti-depressant/anti-psychotics, n (%)	16 (6.5 %)	6 (8.1 %)	10 (5.8 %)	0.496
Education (years)	12.0 (7.0–12.0)	12.0 (9.0–14.0)	10.0 (6.0–12.0)	<0.001

BMI, body mass index; CM, cardiomyopathy; DM, diabetes mellitus; AF, atrial fibrillation; BP, blood pressure; LVEF, left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; Peak VO2, peak oxygen uptake; LNNB-S, Luria-Nebraska Neuropsychological Battery-Screening test; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; ACEI, angiotensin-converting enzyme.

[a] Analysis from 158 patients (64.0 %) with CPET assessment.

[b] Analysis from 73 patients (98.6 %) with CPET assessment.

[c] Analysis from 85 patients (49.1 %) with CPET assessment.

Overall, 30.0 % of the patients had received at least one session of phase II CR and continued home-based CR. On average, patients completed 28 sections, with a standard deviation of 80.7.

The median LNNB-S score was 10.0 (IQR: 5.0–16.0). There were 53.0 % (131/247) of the patients who had cognitive impairment (LNNB-S ≥10). As shown in Table 1A, the patients with cognitive impairment were significantly older (65.0 years vs. 54.0 years, $p < 0.001$) and had higher rates of old stroke (10.7 % vs. 3.4 %, $p = 0.029$). Patients with cognitive impairment had lower heart rates (77.0 vs. 86.5, $p = 0.010$), higher serum urea nitrogen (BUN) levels (26.0 vs. 20.0, $p < 0.001$), higher serum creatinine levels (1.42 vs. 1.10, $p < 0.001$), lower platelet counts (× 1000; 193.0 vs. 217.0, $p = 0.022$), lower albumin levels (3.5 vs. 3.74, $p = 0.002$), lower estimated glomerular filtration rate (eGFR) (48.6 vs. 71.2, $p < 0.001$), lower peak VO_2 (13.8 vs 17.2, $p = 0.001$), and received fewer years of education (9.0 vs. 12.0, $p < 0.001$). Patients with cognitive impairment were also less able to receive phase II CR (22.9 % vs. 37.9 %, $p = 0.010$), angiotensin receptor blockers (42.7 % vs. 58.6 %, $p = 0.013$), or mineralocorticoid receptor antagonists (53.4 % vs. 67.2 %, $p = 0.027$). As per our dataset, no patient was diagnosed with dementia during the study period. According to the data shown in Table 1B, the group of patients who received CR (74, 30 %) were found to be significantly younger (57.5 years vs. 60.0 years, $p = 0.042$), had lower NT-proBNP levels (1472.0 pg/mL vs. 3710.0 pg/mL, $p = 0.020$), lower serum urea nitrogen levels (21.0 mg/dL vs. 24.0 mg/dL, $p = 0.032$), were less likely to have cognitive impairment (59.5 % vs. 41.6 %, $p = 0.010$), and received more years of education (12.0 vs. 10.0, $p < 0.001$)

3.2. All-cause mortality and HF hospitalisation

In the total cohort, 40.9 % of patients experienced the composite end point of all-cause mortality or recurrent HF hospitalisation during the follow-up period. Compared with patients with no impairment, patients with cognitive impairment were significantly more likely to experience a composite endpoint (p=<0.001), all-cause mortality ($p = 0.001$), or readmission ($p = 0.015$). In addition, the patients with cognitive impairment patients had a more than three times higher rate of all-cause mortality than those with no cognitive impairment (23.7 % vs. 7.8 %, Table 2A). The improvements in the 6-month KCCQ12 scores showed no significant differences between the two groups (21.4 vs 24.0, $p = 0.304$). However, the improvements in the 12-month KCCQ12 scores showed greater progress in patients without cognitive impairment (20.8 vs 30.5, $p = 0.043$). Patients who did not receive cardiac rehabilitation (CR) were found to be at a significantly higher risk of experiencing a composite endpoint (45.1 % versus 31.1 %, $p = 0.040$) and all-cause mortality (20.2 % versus 6.8 %, $p = 0.008$) compared to those who received CR, as shown in Table 2B. However, there were no significant differences between the two groups in terms of recurrent hospitalisation and improvements in the 6-month and 12-month KCCQ12 scores (Table 2B).

The results of the univariate analyses are shown in Table 3A. Age, hyperlipidaemia, HR, BUN, eGFR, peak VO_2, LNNB-S, LNNB-S ≥10, prescription of beta-blockers, not receiving phase II CR, and fewer years of education were significant predictors of the composite endpoint. Meanwhile, age, diabetes mellitus (DM), BUN, creatinine, haemoglobin, haematocrit, albumin, eGFR, peak VO_2, LNNB-S, LNNB-S ≥10, and not receiving phase II CR were significant predictors of all-cause mortality. Age was positively correlated with the LNNB-S score (Spearman correlation coefficient = 0.547, $p < 0.001$), and BUN and creatinine levels were negatively correlated with eGFR (Spearman correlation coefficient = −0.803 and −0.955, both $p < 0.001$). All variables related to the outcome, except the significantly correlated ones, were selected for multivariate Cox regression analysis.

The results of multivariate analyses showed that only peak VO_2 (ml/kg/mins) < 14 vs peak $VO_2 \geq 14$ (HR: 3.483, 95 % CI: 1.830–6.630), and peak VO_2 not assessed vs peak $VO_2 \geq 14$ (HR: 4.121, 95 % CI: 2.222–7.463) were significant predictors for the composite endpoint (Table 3B). Meanwhile, peak $VO_2 < 14$ vs peak VO2 ≥14 (HR: 3.630, 95 % CI: 1.054–12.500), and peak VO_2 not assessed vs peak $VO_2 \geq 14$ (HR: 4.056, 95 % CI: 1.296–12.693) were significant predictors of all-cause mortality (Table 3B).

3.3. Impact of cardiac rehabilitation and exercise training on patient outcomes

Kaplan–Meier curves for the composite endpoint and all-cause mortality according to cognitive impairment and CR are shown in Fig. 2A and B, respectively. Patients in Group D had significantly higher event rates than those in the other three groups. After adjustment, CR was associated with a lower composite endpoint and all-cause mortality (log-rank $p = 0.024$ and 0.009, respectively) in AHF patients with cognitive impairment. Patients with cognitive impairment who received CR (Group C) had significantly lower event rates of the composite endpoint (36.7 %) than those who did not receive CR (Group D, 55.4 %) (HR: 0.492; 95 % CI: 0.257–0.940) (Table 4). Patients in Group C also had lower all-cause mortality than those in Group D (6.7 % vs 28.7 %, HR: 0.185; 95 % CI: 0.044–0.775) (Table 4). Patients in Group C were comparable to those in Group B with respect to age, sex, HF aetiology, HR, and LVEF

Table 2A
Primary and secondary outcomes in patients with cognitive impairment and those without.

	Total cohort (n = 247)	LNNB-S ≥10 (n = 131)	LNNB-S <10 (n = 116)	p
Composite end point	101 (40.9 %)	67 (51.1 %)	34 (29.3 %)	<0.001
All-cause mortality	40 (16.2 %)	31 (23.7 %)	9 (7.8 %)	0.001
Recurrent hospitalisations	83 (33.6 %)	53 (40.5 %)	30 (25.9 %)	0.015
KCCQ12 improvement in 6 months	23.1 (5.2–43.6)	21.4 (3.1–39.6)	24.0 (6.2–46.9)	0.304
KCCQ12 improvement in 12 months	26.8 (8.3–44.3)	20.8 (6.5–40.6)	30.5 (11.1–53.3)	0.043

Abbreviations: LNNB-S, Luria–Nebraska Neuropsychological Battery-Screening Test; KCCQ12, 12-item Kansas City Cardiomyopathy Questionnaire.

Table 2B
Primary and secondary outcomes in patients who did and did not receive cardiac rehabilitation.

	Total cohort (n = 247)	CR (n = 74)	Non-CR (n = 173)	p
Composite end point	101 (40.9 %)	23 (31.1 %)	78 (45.1 %)	0.040
All-cause mortality	40 (16.2 %)	5 (6.8 %)	35 (20.2 %)	0.008
Recurrent hospitalisations	83 (33.6 %)	22 (29.7 %)	61 (35.3 %)	0.399
KCCQ12 improvement in 6 months	23.1 (5.2–43.6)	25.5 (4.1–46.4)	21.4 (6.2–41.7)	0.723
KCCQ12 improvement in 12 months	26.8 (8.3–44.3)	26.6 (5.5–42.4)	27.1 (11.5–44.4)	0.597

Abbreviations: LNNB-S, Luria–Nebraska Neuropsychological Battery-Screening Test; KCCQ12, 12-item Kansas City Cardiomyopathy Questionnaire.

Table 3
Cox proportional hazards regression analysis for composite endpoint and all-cause mortality 3A: Univariate Cox regression analyses.

Variable	Composite endpoint		All-cause mortality	
	HR (95 % CI)	p	HR (95 % CI)	p
Age (per 1-year increase)	1.040 (1.023–1.057)	<0.001	1.059 (1.031–1.088)	<0.001
Sex (female vs male)	1.337 (0.803–2.227)	0.265	1.350 (0.597–3.054)	0.471
BMI	0.967 (0.925–1.011)	0.137	0.950 (0.884–1.022)	0.169
Ischemic CM	1.357 (0.846–2.177)	0.205	1.451 (0.668–3.148)	0.347
Hypertension	1.458 (0.937–2.268)	0.095	2.079 (0.958–4.514)	0.064
DM	1.294 (0.875–1.912)	0.197	2.673 (1.394–5.123)	0.003
Hyperlipidaemia	1.538 (1.040–2.274)	0.031	1.387 (0.746–2.579)	0.301
AF	1.274 (0.843–1.925)	0.251	0.937 (0.476–1.844)	0.850
Old stroke	1.684 (0.900–3.151)	0.103	1.318 (0.469–3.708)	0.601
Mean BP (mmHg)	0.996 (0.984–1.008)	0.481	0.997 (0.978–1.016)	0.750
Heart rate (beats/min)	0.988 (0.977–1.000)	0.041	0.998 (0.980–1.016)	0.809
LVEF	1.029 (0.997–1.061)	0.074	1.006 (0.960–1.055)	0.794
Serum sodium (mEq/L)	1.002 (0.949–1.059)	0.937	0.971 (0.891–1.057)	0.493
Serum urea nitrogen (mg/dL)	1.016 (1.007–1.025)	0.001	1.026 (1.013–1.039)	<0.001
Serum creatinine (mg/dL)	1.063 (0.982–1.152)	0.133	1.133 (1.021–1.257)	0.018
Haemoglobin (g/dL)	0.937 (0.863–1.018)	0.126	0.796 (0.698–0.908)	0.001
Haematocrit (%)	0.972 (0.944–1.001)	0.059	0.918 (0.877–0.961)	<0.001
Albumin (g/dL)	0.909 (0.663–1.248)	0.556	0.516 (0.316–0.843)	0.008
eGFR	0.987 (0.980–0.993)	<0.001	0.980 (0.969–0.991)	<0.001
Peak VO_2 (ml/kg/mins) <14 vs ≥ 14	3.533 (1.975–6.322)	<0.001	4.543 (1.443–14.240)	0.010
Not assessed vs ≥ 14	4.807 (2.807–2.231)	<0.001	8.023 (2.792–23.057)	<0.001
LNNB-S	1.056 (1.031–1.082)	<0.001	1.081 (1.042–1.123)	<0.001
LNNB-S (≥10 vs < 10)	1.952 (1.292–2.950)	0.001	3.203 (1.525–6.728)	0.002
BDI-II (≥16 vs < 16)	1.540 (0.822–2.885)	0.177	2.127 (0.893–5.070)	0.088
BAI	1.005 (0.974–1.038)	0.739	0.998 (0.947–1.052)	0.933
ACEI/ARB (Y vs N)	1.018 (0.618–1.678)	0.943	0.578 (0.226–1.479)	0.253
ARB (Y vs N)	0.816 (0.552–1.207)	0.310	0.729 (0.389–1.364)	0.322
ARNI (Y vs N)	0.697 (0.398–1.248)	0.224	1.113 (0.492–2.521)	0.797
Beta-blockers (Y vs N)	0.510 (0.326–0.793)	0.003	0.523 (0.261–1.048)	0.068
MRA (Y vs N)	0.710 (0.481–1.050)	0.086	0.542 (0.291–1.011)	0.054
Anti-psychotics (Y vs N)	1.701 (0.885–3.269)	0.111	0.674 (0.163–2.798)	0.587
Cardiac rehabilitation (N vs Y)	1.728 (1.084–2.753)	0.021	3.502 (1.371–8.944)	0.009
Sections of CR	0.996 (0.990–1.003)	0.256	0.958 (0.907–1.012)	0.127
Education (years)	0.939 (0.900–0.980)	0.004	0.941 (0.879–1.007)	0.077

Peak VO2 (ml/kg/mins), Not assessed vs < 14, HR: 1.360 (0.871–2.124) for composite endpoint; HR: 1.770 (0.871–3.598) for all-cause mortality.

(p = NS for all). Although patients in Group C had a significantly lower eGFR than those in Group B (p = 0.017), there was no significant between-group difference in survival rates in the composite endpoint and all-cause mortality (p = 0.935 and 0.613, respectively; Fig. 2).

In patients without cognitive impairment (Groups A and B), CR provided a clinical benefit in the composite endpoint and all-cause mortality, although this was not significant. The composite endpoint occurred in 27.3 % and 30.6 % of the patients Groups A and B (patients without cognitive impairment), respectively. These rates were significantly lower than in Group D (HR: 0.395; 95 % CI: 0.212–0.738 and HR: 0.465; 95 % CI: 0.284–0.761, respectively; Table 4, Fig. 2A). The all-cause mortality rates were 6.8 % in Group A and 8.3 % in Group B. These were also significantly lower than those in group D (HR: 0.203; 95 % CI: 0.062–0.665 and HR: 0.270; 95 % CI: 0.112–0.650, respectively) (Table 4, Fig. 2B).

4. Discussion

According to the study, CR significantly enhances the survival rate and reduces the chances of readmission in AHF patients who suffer from cognitive impairment. Cognitive impairment is prevalent among these patients and is linked to poor clinical outcomes, such

Table 3B
Multivariate Cox regression analyses*.

variable	Composite endpoint		All-cause mortality	
	HR (95 % CI)	p	HR (95 % CI)	p
Peak VO_2 (ml/kg/mins), <14 vs ≥ 14	3.483 (1.830–6.630)	<0.001	3.630 (1.054–12.500)	0.041
Not assessed vs ≥ 14	4.121 (2.222–7.643)	<0.001	4.056 (1.296–12.693)	0.016
Cardiac rehabilitation (N vs Y)	0.696 (0.379–1.279)	0.243	0.406 (0.130–1.271)	0.122
LNNB-S (≥10 vs < 10)	0.967 (0.598–1.565)	0.892	1.575 (0.659–3.762)	0.307
Sex (female vs male)	1.759 (0.979–3.163)	0.059	2.425 (0.918–6.404)	0.074
BMI	0.968 (0.920–1.018)	0.206	0.962 (0.881–1.050)	0.384
Ischemic CM	1.573 (0.963–2.568)	0.070	1.420 (0.626–3.223)	0.401
Hypertension	1.380 (0.843–2.258)	0.200	1.750 (0.747–4.102)	0.198
DM	1.076 (0.696–1.663)	0.742	1.907 (0.890–4.084)	0.097
AF	1.050 (0.663–1.661)	0.836	0.883 (0.406–1.918)	0.753
Mean BP (mmHg)	0.992 (0.979–1.004)	0.202	0.994 (0.974–1.015)	0.601
Heart rate (beats/min)	0.991 (0.979–1.003)	0.128	0.998 (0.978–1.018)	0.834
LVEF	1.036 (0.999–1.073)	0.054	0.980 (0.928–1.035)	0.471
Serum sodium (mEq/L)	0.999 (0.943–1.058)	0.978	0.930 (0.846–1.022)	0.131
Haemoglobin (g/dL)	1.029 (0.922–1.147)	0.611	0.869 (0.722–1.046)	0.137
Beta-blockers (Y vs N)	0.725 (0.444–1.184)	0.199	0.563 (0.247–1.280)	0.170
ACEI/ARB/ARNI (Y vs N)	0.779 (0.453–1.339)	0.366	0.753 (0.334–1.698)	0.495
BAI	1.024 (0.984–1.067)	0.240	1.001 (0.936–1.070)	0.977
BDI-II (≥16 vs < 16)	0.807 (0.395–1.649)	0.557	0.976 (0.359–2.657)	0.962
Old stroke	1.379 (0.662–2.872)	0.390	0.995 (0.286–3.467)	0.994
eGFR	0.992 (0.984–1.000)	0.050	0.994 (0.981–1.008	0.406
Albumin	1.105 (0.780–1.564)	0.574	0.747 (0.429–1.302)	0.304

Peak VO2 (ml/kg/mins), Not assessed vs < 14, HR: 1.183 (0.658–2.127) for composite endpoint; HR: 1.118 (0.460–2.716) for all-cause mortality.
Abbreviation: HR, hazard ratio; BMI, body mass index; CM, cardiomyopathy; DM, diabetes mellitus; AF, atrial fibrillation; BP, blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; peak VO_2, peak oxygen uptake; LNNB-S, Luria-Nebraska Neuropsychological Battery-Screening test; BDI-II, Beck Depression Inventory–II; BAI, Beck Anxiety Inventory; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist.
* Multivariate Cox Regression analysis using the Enter method.

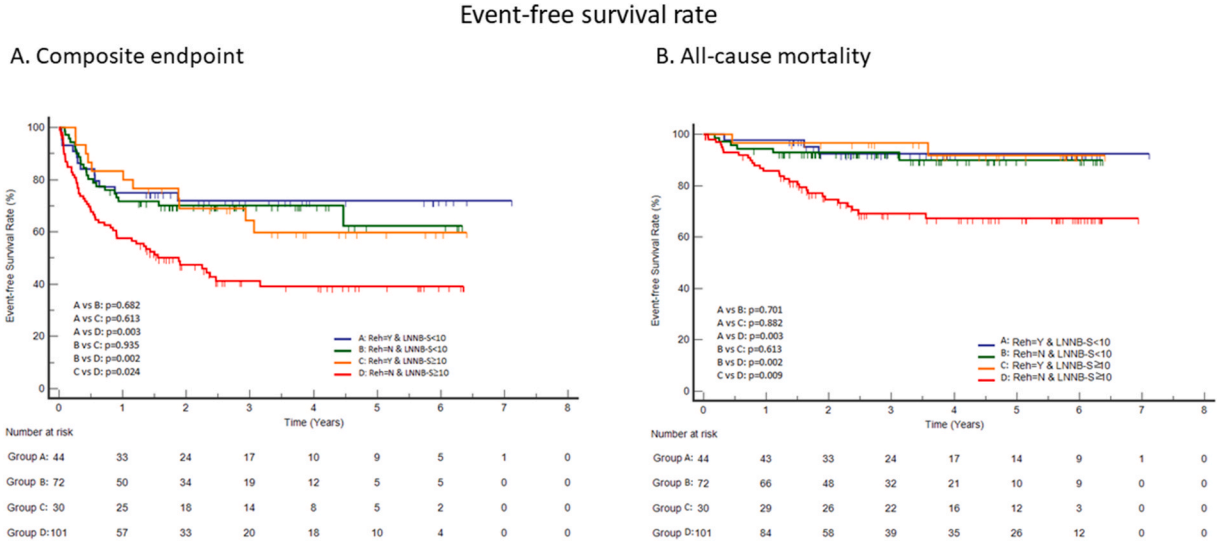

Fig. 2. Kaplan–Meier curves according to cognitive impairment and receiving cardiac rehabilitation. (A) Composite endpoint. (B) All-cause mortality.

as higher rates of all-cause mortality or readmission. Moreover, patients with cognitive impairment who suffer from AHF show lower improvement in their quality of life within one year of discharge. Additionally, this study has shown that peak VO2 levels below 14 ml/kg/min and peak VO2 levels that were not assessed are both significant predictors of mid-to long-term cardiovascular outcomes in patients with AHF (LVEF ≤40).

The high prevalence of cognitive impairment and its association with poor outcomes is consistent with previous findings [13]. Cognitive impairment is one of the most common comorbidities in discharged patients with HF, with the prevalence ranging from 25 %

Table 4
Outcomes and baseline variables in the four groups according to cognitive impairment and receiving cardiac rehabilitation.

	Group A (n = 44)	Group B (n = 72)	Group C (n = 30)	Group D (n = 101)	p
Age	56.0 (39.3–62.8)	53.5 (46.0–60.0)	59.5 (52.8–67.0)[a]	65.0 (57.0–73.0)	<0.001
Male (%)	32 (72.7 %)	57 (79.2 %)	27 (90.0 %)	78 (77.2 %)	0.342
Ischemic CM	36 (81.8 %)	50 (69.4 %)	22 (73.3 %)	72 (71.3 %)	0.505
LVEF	28.5 (22.3–35.0)	30.0 (22.3–34.0)	27.5 (25.8–33.3)	31.0 (24.0–34.0)	0.879
Heart rate	86.5 (75.5–97.0)	86.5 (70.0–97.0)	77.5 (60.8–90.5)	77.0 (66.0–94.0)	0.069
eGFR	72.3 (53.8–96.0)	70.4 (51.7–89.8)	54.4 (31.0–65.9)[b]	47.5 (22.5–71.6)	<0.001
Composite endpoint	12 (27.3 %)	22 (30.6 %)	11 (36.7 %)	56 (55.4 %)	<0.001
All-cause mortality	3 (6.8 %)	6 (8.3 %)	2 (6.7 %)	29 (28.7 %)	0.001

Group A: Patients without cognitive impairment and receiving CR.
Group B: Patients without cognitive impairment and not-receiving CR.
Group C: Patients with cognitive impairment and receiving CR.
Group D: Patients with cognitive impairment and not receiving CRStructured.
Abbreviations: CM, cardiomyopathy; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rateStructured
[a] Pairwise comparisons between Group b and Group c show no significant differences ($p = 0.069$).
[b] Pairwise comparisons between Group b and Group c show significant differences ($p = 0.017$).

to 80 % [14,15]. There are several reasons for the high prevalence of cognitive impairment in heart failure patients, including the sensitivity of our screening tool, common pathophysiological pathways between HF and cognitive impairment, and societal factors that may impact cognitive health. The high prevalence underscores the potential need for refined diagnostic criteria or additional nuanced assessment tools to differentiate levels of cognitive impairment. Despite this high prevalence, cognitive impairment is rarely documented by physicians or cardiologists. Undocumented cognitive impairments are significantly associated with 6-month mortality or readmission rates in AHF patients [16]. In a national longitudinal study of 565 HF patients in Australia, cognitive impairment, defined as a Montreal Cognitive Assessment (MoCA) score of ≤22, was found in 255 patients (45 %). The addition of cognitive function testing before discharge significantly increased the discrimination of the prediction model for 30-day readmission or death in the AHF patients [13]. The current study further demonstrated that cognitive impairment was associated with mid-to long-term CV outcomes. Thus, AHF patients should be screened using neuropsychological tests to improve their outcomes.

Cognitive impairment affects the ability of HF patients to manage their disease [17]. Treatment of HF is complex and may involve coronary interventionists, electrophysiologists, and cardiovascular surgeons. Treatment decision making in HF management requires a comprehensive understanding and interpretation of symptoms. HF patients with cognitive impairment have poor cognitive skills, including memory, attention, problem solving, and psychomotor speed [18]. Self-care maintenance is also important in HF as it involves adherence to complicated medications, dietary sodium restriction, and participation in regular exercise [19]. Patients with cognitive impairment have limited self-care abilities, leading to increased all-cause mortality, readmission, and poor quality of life.

To our best knowledge, this is the first study to demonstrate that multidisciplinary CR can improve clinical outcomes in AHF patients with cognitive impairment. In a longitudinal study of 65 patients with HF, physical inactivity predicted cognitive dysfunction at the 12-month follow-up [20]. In another study, 20 systolic HF patients (LVEF ≤35 %; functional class III) who underwent an exercise training program had significantly better cognitive measures than did controls [21]. Recent evidence has shown that exercise-based CR has a favourable effect on psycho-neurological function, thus reducing all-cause mortality [6,22]. Our results showed that the exercise training program provided a greater reduction in the CV composite endpoint in patients with cognitive impairment than in those without cognitive impairment. The multidisciplinary strategy involves an HF specialist nurse and several interventions, including education and telephone follow-up, which may also be important by increasing understanding of the underlying disease process, therefore “empowering” patients to modify their HF recovery [4].

Several neuropsychological tests for evaluating cognitive function are available, but none of these have been particularly developed for AHF patients [23]. A recent systematic review found that several brief cognitive tests, such as the Montreal Cognitive Assessment (MoCA), Mini-Mental Statement Examination (MMSE), and Mini-Cog, were used to screen the Asian HF population [24]. The LNNB-S is a neuropsychological assessment battery designed to screen for cognitive impairment in various diseases [11,25].

The LNNB was developed based on Luria’s Approach to Neuropsychological Assessment and Rehabilitation [26]. Although it has been met with some criticism [27], extensive empirical literature has proven the clinical utility of LNNB [28]. LNNB-S fundamentally constitutes a neuropsychological assessment, initially prevalent in the diagnosis of localized brain injuries, and was misconceived as being solely applicable for evaluating brain injuries. However, a decline in cognitive function signifies a deterioration in cerebral-mental capabilities; conversely, cognitive decline due to widespread brain injuries is a commonly observed phenomenon. Neuropsychological test performance is influenced by culture, values, customs, and experiences across different countries or populations [29]. Guo et al. evaluated the reliability and validity of the LNNB-S in Taiwan [30] and found that it has good psychometric properties that can be used in hospitals or rehabilitation settings. A study involving 158 stroke patients compared the sensitivity and specificity of the MMSE with that of the LNNB-S—the MMSE detected 44.9 % of the patients with cognitive impairment, while the LNNB-S detected 77.9 % of these patients—and suggested the use of the LNNB-S instead of the MMSE to enhance diagnostic accuracy [31]. A recent study that compared the application of the Community Mental Status Examination (CMSE), MMSE, and LNNB-S in 80 traumatic brain injury patients showed that the CMSE received the highest clinical priority in detecting cognitive impairment [32]. A prospective study is warranted to confirm that the CMSE is a reliable and quick tool for evaluating and managing HF-related cognitive

impairment.

In the current study, low peak VO_2 (<14 ml/kg/min) and not being assessed for peak VO_2 were found to be significant predictors for composite cardiovascular endpoint as well as all-cause mortality. Peak VO_2 assessment using the CPET is an important strategy for the prediction and management of advanced HF[33]. The current study demonstrated that patients who did not have peak VO_2 assessment (n = 89, 36 %) had poorer clinical outcomes than those with peak VO2 ≥14. Further, the non-assessed group had a higher composite endpoint HR than the peak VO_2 < 14 group (4.121 vs. 3.483, Table 3B). The CPET provides information regarding the physiology and mechanisms underlying exercise intolerance in HF and is thus helpful for evaluating functional status, developing activity recommendations, and quantifying the response to exercise training [34]. CPET also provides information on an integrated organ system response involving the pulmonary, cardiovascular, and skeletal muscle systems, which helps to identify comorbid diseases. Clinical application of the CPET is in progress. The application of CPET should be encouraged as part of comprehensive clinical and exercise test evaluations.

Previous studies have found that education was associated with better performance on neuropsychological tests [35,36]. In our study, we also discovered that educational history had a moderate correlation with the LNNB-S (Pearson Correlation: 0.503, $p < 0.001$). In patients with AHF and cognitive impairment, educational history also had a protective effect. Those with a longer educational history were less likely to have cognitive impairment (9.0 years vs. 12.0 years, $p < 0.001$), a finding similar to changes in cognitive function following acute stroke [37]. Additionally, we found that after AHF, a longer educational history also influenced the patient's willingness to participate in CR (12.0 years vs. 10.0 years, $p < 0.001$).

Although cardiac rehabilitation offers significant benefits, global referral to and utilization of cardiac rehabilitation remains limited and highly variable [38]. Furthermore, the impact of the COVID-19 pandemic has increased the importance of home-based CR and hybrid, technology-based CR programs [39]. The establishment of organizations such as the International Council of Cardiovascular Prevention and Rehabilitation (ICCPR) and the Taiwan Academy of Cardiovascular and Pulmonary Rehabilitation (TACVPR) is aimed at promoting cardiac rehabilitation to benefit patients. This study also highlights the significance of cardiac rehabilitation in the field of neuropsychology, noting that cognitive impairment in acute heart failure underscores the need for more focus on psychosocial screening and treatment within CR programs.

This study has several important implications. Cognitive impairment was prevalent in more than 50 % of the AHF patients (53 % in our study) and was associated with high mortality rates (23.7 %). Thus, neuropsychological screening should be performed before discharge. However, further prospective trials are needed to establish the optimal neuropsychological test. Exercise rehabilitation is a class IA indication in patients with stable HF according to clinical guidelines [8]. However, the referral rate (64 %) and participation rates (30 %) were very low in our study. Considering the potential benefit of CR in HF patients with cognitive impairment, more effort should be devoted to the rehabilitation of these patients. In this study, we also discovered the significance of CPET in the treatment of heart failure. While CPET is a costly test, it is valuable and worth promoting for heart failure patients due to its ability to improve patient prognosis and facilitate further cardiac rehabilitation.

This study has several limitations. First, this was a retrospective study that enrolled patients from a single medical centre. We focused on patients with AHF and reduced LVEF; therefore, our findings may not be applicable to other HF populations. Second, neuropsychological screening was performed using the LNNB-S tool, and cognitive impairment was defined according to the LNNB-S score. Other studies used a different screening tool. However, our psychologist was familiar with this tool, and its effectiveness had been validated previously [11,30,31]. Third, cognitive function after cardiac rehabilitation exercise was not evaluated, and thus, we were unable to determine whether any change in cognitive function due to exercise training contributed to clinical outcomes in HF. An interventional study is required to address this question. Indeed, while only 64 % of our HF patients have data from CPET, this also represents a limitation of the study. However, it reflects the reality of clinical practice and further demonstrates that CPET is not given due importance in the assessment of HF patients. Nevertheless, in patients who have undergone cardiac rehabilitation, the rate of CPET implementation is over ninety percent (73/74, 98.6 %). Finally, there was no blood data available in the dataset at the time of discharge for our study. Blood data obtained at the time of discharge may be a more accurate predictor of post-discharge prognosis. However, it is important to note that most patients with abnormal blood data have been treated and improved by the time of discharge. Therefore, we believe that the admission data still provides valuable insights into the patient's initial condition and can serve as a significant predictor for their prognosis.

In conclusion, cognitive impairment is highly prevalent in patients with AHF and is associated with high rates of composite CV event in the mid-to long-term follow-up. Importantly, multidisciplinary CR can be beneficial in AHF patients with cognitive impairment, decreasing composite endpoints and all-cause mortality. AHF patients should be screeded using neuropsychological tests and encouraged to participate in CR programs.

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Data availability

The data underlying this article can be shared on reasonable request to the corresponding author.

CRediT authorship contribution statement

Shyh-Ming Chen: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Ming-Kung Wu:** Investigation, Data curation, Conceptualization. **Ching Chen:** Methodology, Investigation, Data curation. **Lin-Yi Wang:** Methodology, Investigation. **Nai-Wen Guo:** Validation, Supervision, Investigation. **Chin-Ling Wei:** Methodology, Data curation. **You-Cheng Zheng:** Investigation, Data curation. **Hao-Yi Hsiao:** Investigation, Data curation. **Po-Jui Wu:** Investigation, Data curation. **Yung-Lung Chen:** Visualization, Validation. **Chien-Jen Chen:** Validation, Investigation. **Chi-Ling Hang:** Visualization, 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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