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Impact of resistance exercise rehabilitation and whey protein supplementation in elderly patients with heart failure with preserved ejection fraction with sarcopenia: a study protocol for a randomised controlled trial

Mo Zhou ,[1] Rui Li,[1] Yi Chen,[1] Yan Gao,[1] Yuhao Wei,[2,3] Meishan Lu,[3,4] Jieren Xi,[3,4] Zhizhou Lin,[3,4] Xiaoyun Zheng,[1] Hong Jiang[3]

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For numbered affiliations see end of article.

Correspondence to
Xiaoyun Zheng; atfcn@126.com and Hong Jiang; drjh@163.com

ABSTRACT

Introduction Heart failure with preserved ejection fraction (HFpEF) affects more than half of the patients with heart failure. HFpEF and sarcopenia can interact with each other and contribute to reduced physiological function and increased mortality in elderly patients. Resistance training (RT) or resistance exercise rehabilitation (RER) may have benefits for elderly HFpEF patients with sarcopenia. Whey protein supplementation (WPS) may increase the effects of exercise on strength and muscle mass, in addition to promoting heart function and quality of life (QoL). However, studies are needed to evaluate effects of RER and WPS in patients with HFpEF with sarcopenia.

Methods and analysis This is a prospective, randomised, controlled clinical trial in which patients with HFpEF with sarcopenia will be randomly allocated to three groups, control, RT and RT+WP. Participants in all groups will receive basic intervention including standard medicine treatment, home-based aerobic exercise and basic nutritional intervention. The RT group will undergo resistance exercise programmes, and the RT+WP group will receive daily WPS apart from resistance exercise. The study variables will be evaluated at baseline and 12 weeks. Primary outcome measure is the change of 6 min walking distance. Secondary outcomes include parameters of muscle status, cardiac function, nutritional status, QoL and major adverse cardiovascular events. The primary efficacy analysis will follow the intention-to-treat principle.

Ethics and dissemination This study was approved by Ethics Committee of China-Japan Friendship Hospital for Clinical Research (No. 2022-KY-003). The results of this study will be disseminated via peer-reviewed publications and presentations at conferences.

Trial registration number ChiCTR2200061069.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Integrated management of standard medicine treatment, aerobic exercise, basic nutritional intervention, resistance exercise and whey protein supplementation may further improve the symptoms of heart failure patients with poor muscle status.
⇒ The Cardiac Rehab Exercise Management System used here can detect arrhythmia and provide an early warning to both the exercising patients and their doctors to further reduce risks.
⇒ The wearable system will monitor the whole training process in real time to ensure the specified intensity and duration for patients.
⇒ The main limitation of this single-centre study is the small sample size.
⇒ A long-term follow-up may also be needed, and extending the exercise for 6 months may give us better data on adherence.

INTRODUCTION

Heart failure (HF) is an end-stage manifestation of other forms of heart disease, such as ischaemic heart disease, hypertensive heart disease, valvular heart disease and so on, associated with poor quality of life (QoL), high readmission rate and mortality. The prevalence of HF in developed countries is 1.5%–2.0%, and ≥10% in individuals aged ≥70 years.[1] An epidemiological survey[2] in 2003 shows that the prevalence of HF is 0.9% among adults aged 35–74 in China, and the prevalence increases significantly with age. The China-HF study[3] shows that the mortality of hospitalised patients with HF is 4.1%. Approximately 50% of patients with HF have preserved ejection fraction. In the general population aged ≥60 years, 4.9% were identified to have heart failure with preserved ejection fraction (HFpEF).[4] An important opportunity remains for identifying evidence-based therapies in patients with HFpEF.

Sarcopenia has been found to be an important comorbidity of HF.[5] It shares several

pathogenetic pathways with HF, including malnutrition, systemic inflammation, endocrine imbalances and oxidative stress.[6] Zhang *et al*.'s study[7] shows that prevalence estimates of sarcopenia in patients with HF range from 10% to 69%, and the overall prevalence is 34%. Recently, accumulating studies have suggested that HF and sarcopenia can interact with each other and contribute to reduced physiological function and increased mortality in elderly patients.[8] A multicentre study[9] shows that sarcopenia is strongly linked to reduced muscle strength, exercise capacity and QoL in HF patients. Thus, developing new treatment strategies for sarcopenia in elderly patients with HF will be helped.

Resistance training (RT) or resistance exercise rehabilitation (RER) has been used to treat muscle dysfunction related to HF. A meta-analysis shows that RER can enhance muscle strength, aerobic capacity (6 min walk distance) in patients with chronic HF and the training duration ranges from 8 to 24 weeks.[10] Being complementary to aerobic exercise rehabilitation, RER is shown to be an effective and relative safe way to increase muscle mass, enhance cardiac diastolic function and improve exercise capacity and QoL in elderly HFpEF patients with sarcopenia.[11–14] In addition, the completion and compliance of cardiac rehabilitation in elderly patients with HF are poor, which is an unsolved problem. Our previous research[15] shows that, compared with traditional outpatient rehabilitation, the realisation of H2H (Hospital-to-Home) mode through the 'Internet+Telemedicine+Wearable Device' using remote ECG monitoring system (REMS) can effectively and safely guide the home-based cardiac rehabilitation and increase the compliance of patients with HF with reduced ejection fraction.

Whey protein is rich in branched-chain amino acids, which play an important role in forming skeletal muscles because they account for approximately 35% of the essential amino acids that form skeletal muscles,[16] and enhancing protein synthesis and inhibiting proteolysis.[17] Excess protein intake can enhance both muscle mass and also muscle function.[18 19] Therefore, incorporation of whey protein supplementation (WPS) in cardiac rehabilitation is expected to have an additional effect on the improvement of skeletal muscle functions, which may further improve the symptoms of HF patients with poor muscle status.

Thus, our main objective is to evaluate the impact of RER and WPS in elderly patients with HFpEF and sarcopenia. As a secondary objective, the safety and effectiveness of the REMS for our target patients to do home-based resistance exercise will be evaluated.

METHODS

Study design

This study is a prospective, randomised, controlled clinical trial which will occur at the China-Japan Friendship Hospital in Beijing, China, a general tertiary-level hospital directly under the National Health Commission. This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidance for protocols of clinical trials.[20] A flow chart of the study design is shown in figure 1

Eligibility criteria

All those elderly patients with a clinical diagnosis of HFpEF (NYHA functional class I or II) complicated with sarcopenia will be screened. The complete list of patient inclusion and exclusion criteria is provided in box 1.

Sample size

There will be three study groups including (1) the control group, (2) the resistance training group (RT group) and (3) the resistance training+whey protein group (RT+WP group) in our study. With reference to previous studies,[21–23] we assume that the 6 min walking distance (6MWD) in the three groups are 300, 350 and 400 m separately, with a SD of 50 m in each group. Thus, a minimum sample size of 8 per group would be needed to guarantee 95% confidence and 90% power to the study. Considering an estimated follow-up loss of 20%, 30 subjects are required in total.

Randomisation and blinding

The clinical research data management platform of China-Japan Friendship Hospital was commissioned to generate a random sequence of 30 numbers using SAS V.9.4 software. The random sequence is placed into a sealed envelope by a staff member who is not involved in the study to avoid selection bias. Patients are randomly assigned to three groups in a 1:1:1 ratio based on the patient's admission time. Allocation concealment is ensured and the randomisation code will not be released until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. Researchers involved in patients' assessments, data management and analysis are blinded to treatment allocation. The therapist and patients cannot be blinded due to the intervention of nutrition and rehabilitation.

Trial interventions

Participants in the three groups will all receive basic intervention including standard medicine treatment, home-based aerobic exercise and basic nutritional intervention. The RT group will undergo resistance exercise programmes, and the RT+WP group will receive daily WPS apart from resistance exercise.

Basic intervention

Medicine

It is essential for HF patients to be prescribed guideline-directed medical therapy (GDMT) to release symptoms and improve outcomes. During the course of the study, participants in all the three groups will receive GDMT, determined by cardiologists in each visit (0, 4, 8 and 12 weeks). If participants have any concomitant diseases, medications or therapies determined by specialists in corresponding fields should continue to be used.

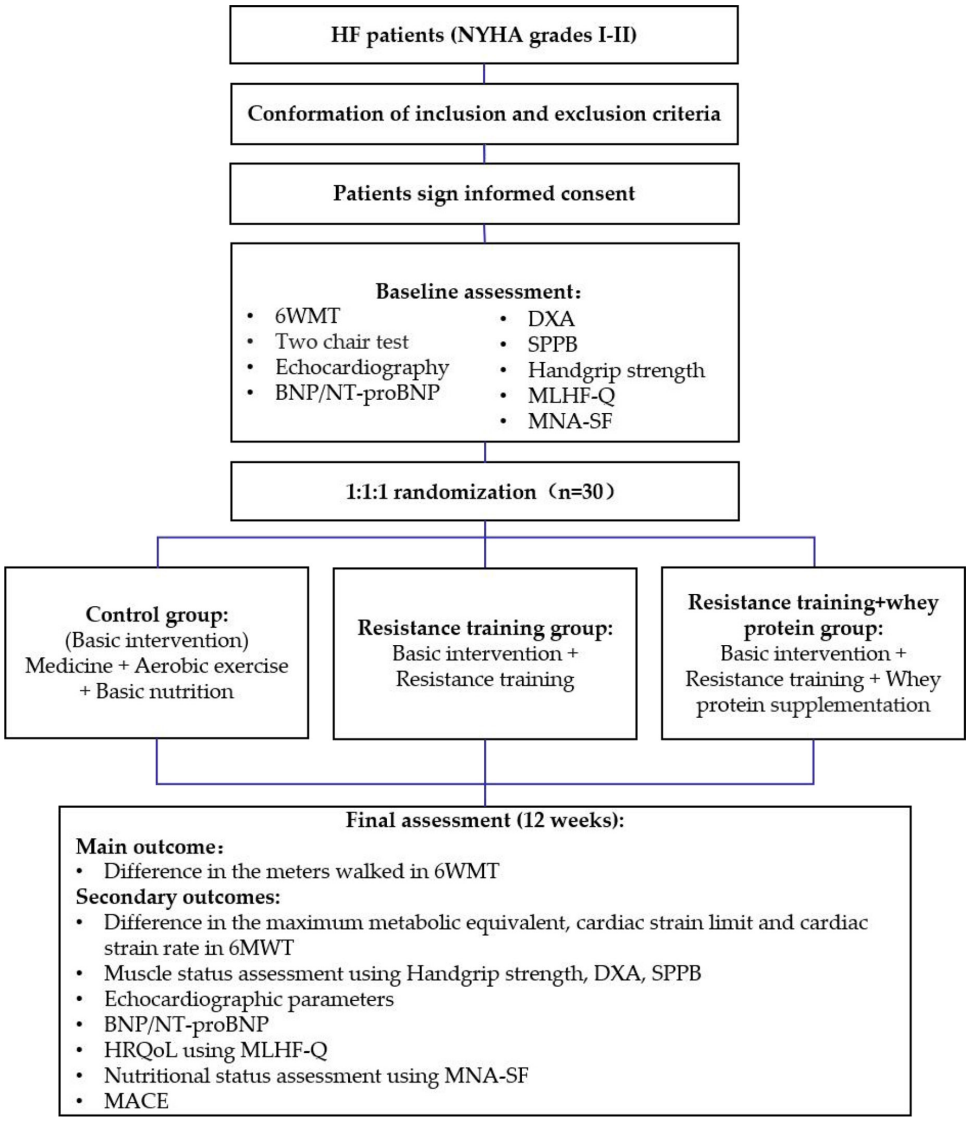

Figure 1 Study flow chart. 6MWT, 6 Min Walk Test; BNP, B-type natriuretic peptide; DXA, dual-energy X-ray absorptiometry; HRQoL, health-related quality of life; MACE, major adverse cardiovascular events; MLHF-Q, Minnesota Living with Heart Failure Questionnaire; MNA-SF, Mini Nutritional Assessment-Short Form; NT-proBNP,N-terminal pro-B-type natriuretic peptide; SPPB, short physical performance battery.

Prescription will be provided to each patient individually in face-to-face visit in outpatient or inpatient department. In case of drug-related adverse events or disease remission/progress, specialists should adjust the relevant drugs individually according to the patient's condition. Medication information will be recorded in the case report form (CRF) at each follow-up.

Aerobic exercise

Aerobic or endurance exercise (ie, walking, jogging and cycling), as a baseline activity, is the most adopted modality in HF patients.[24] Physical therapists will give each participant in all the three groups an individualised aerobic exercise prescription based primarily on the result of 6 Min Walk Test (6MWT) and the Borg Scale of perceived effort. Each group will undergo a moderate-intensity continuous aerobic exercise session performed twice per week for 12 weeks. Each session will be last for 40–50 min, including a 5–10 min warm up, 30 min of moderate aerobic exercise and 5–10 min cool down. Each session should be separated by at least 48 hours of rest. Participants should take notes on each session of aerobic exercise in a designed card, which will be collected by researchers at each visit.

Basic nutrition

All patients require basic nutritional intervention. A professional dietitian will use the 24-hour diet recall method to obtain detailed information about all foods and beverages from each patient in basal and final assessments. Individualised nutritional prescriptions will be given according to Academy of Nutrition and Dietetics Evidence-Based Practice Guideline for the Management of Heart Failure in Adults published by the American Academy of Nutrition and Dietetics in 2018,[25] ensuring that the composition ratio of high-quality protein is about

Box 1 Trial inclusion and exclusion criteria

Inclusion criteria

1. Aged ≥65 years old.
2. Meet the diagnostic criteria of sarcopenia (2019 AWGS2 standard,[27] can be diagnosed once meeting (1)+(2) or (1)+(3) or (1)+(2)+(3)).
   - Appendicular skeletal muscle mass: dual-energy X-ray absorptiometry (male<7.0 kg/m^2, female<5.4 kg/m^2).
   - Muscle strength: handgrip strength (male<28.0 kg, female<18.0 kg).
   - Physical performance (meet at least one of the following three items):
     - 6 m walking speed<1.0 m/s.
     - Short Physical Performance Battery<9.
     - 5-time chair stand test ≥12s.
3. Meet the diagnostic criteria of HFpEF (2018 Chinese guidelines for the diagnosis and treatment of HF[28]).
   - Typical symptoms and/or signs.
   - Left ventricular ejection fraction≥50%.
   - Elevated natriuretic peptide levels (BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL), and meet at least one of the following:
     - left ventricular hypertrophy and/or left atrial enlargement.
     - diastolic function abnormality.
       - exclude non-cardiac diseases that cause similar symptoms.
       - NYHA functional class I and II.
4. Clearly understand the content and purpose of the study and sign the informed consent form (online supplemental file 1).

Exclusion criteria

⇒ Aerobic exercise and resistance exercise cannot be carried out due to physical disability.
⇒ Daily activities cannot be carried out due to cardiopulmonary diseases.
⇒ Other clinical trial drugs were taken or in other medical device trial within 30 days before admission.
⇒ II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for HF.
⇒ Uncontrolled hypertension or postural hypotension.
⇒ ACS was happened in 3 months before admission; coronary revascularisation is planned.
⇒ Impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2).
⇒ Impaired hepatic function (serum transaminase level twice higher than the normal reference value).
⇒ Cancer or other systemic diseases with a life expectancy of less than 12 months.
⇒ Allergies to milk proteins.
⇒ Unable to participate in this study after clinical evaluations by investigators.

ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; NT-proBNP,N-terminal pro-B-type natriuretic peptide.

50% and the protein intake is controlled at 1.2 g/(kg·d). Patients are instructed to record the dietary diary which will be collected by researchers at each visit and will receive a phone follow-up once a week.

Resistance training

Patients in the RT group and the RT+WP group will participate in RT. Patients will undergo a pretest to assess muscle strength measuring one-repetition maximum (1-RM),[26] allowing physical therapists to develop individualised RT prescriptions.

The RT programme consists of three phases of exercise training. The initial phase of exercise (phase 1) will be conducted in hospital using a group format (2–5 participants/group) twice a week for 2 weeks (from weeks 0 to 2), to prepare the participants for home-based RT (phases 2 and 3) and also to minimise injury. After then, the participants will receive an educational video by WeChat (a communication APP) for reference when conducting RT at home. The second phase (phase 2) will last from weeks 3 to 4 at home, with the same exercise level as in phase 1. During the third exercise phase (phase 3), last from weeks 5 to 12, progressive home-based RT will be added. Participants should take notes on each session of resistance exercise in a designed card, which will be collected by researchers at each visit.

During phases 1 and 2, the patients will train twice a week for 1 sets of 10 repetitions to muscle fatigue with 1 min of rest between sets for each exercise at an intensity corresponding to approximately 40%–50% 1-RM for the upper extremity and 50%–60% 1-RM for the lower extremity and Rating of Perceived Exertion (RPE)<15. During phase 3, they will train twice a week for 2 sets of 10 repetitions to muscle fatigue with 1 min of rest between sets for each exercise at an intensity corresponding to approximately 50%–60% 1-RM for

Table 1 Trial outcome measures and assessment tools

Primary outcome	
6 min walk distance	6MWT
Secondary outcomes	
MME, CSL, CSR	DCW device
Muscle strength	Handgrip strength by dynamograph
Muscle mass	ASM by DXA
Muscle function	SPPB
E/e′ ratio, LAVI, LVEDd, LVESV, LVEF	Echocardiography
BNP/NT-proBNP	Laboratory examination
Quality-of-life assessment	MLHF-Q
Nutritional assessment	MNA-SF
MACE	Number of events

ASM, appendicular skeletal muscle mass; BNP, B-type natriuretic peptide; CSL, cardiac strain limit; CSR, cardiac strain rate; DCW, digital cardiopulmonary walking test; DXA, dual-energy X-ray absorptiometry; LAVI, left atrial volume index; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiovascular events; MLHF-Q, Minnesota Living with Heart Failure Questionnaire; MME, maximum metabolic equivalent; MNA-SF, Mini Nutritional Assessment-Short Form; 6MWT, 6 Min Walk Test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SPPB, short physical performance battery.

Table 2 Trial structure of the study

	Screening	Enrolment	Postallocation		
		T0	T1	T2	T3
		Visit 1	Visit 2	Visit 3	Visit 4
	(−14~−1d)	Baseline	+4 weeks	+8 weeks	+12 weeks
Enrolment					
Medical history	*				
Inclusion/ exclusion criteria	*				
Consent form		*			
Comorbidity	*		*	*	*
Concomitant medication	*		*	*	*
Vital signs	*		*	*	*
Physical examination	*		*	*	*
Blood routine	*		*	*	*
Blood chemistry	*		*	*	*
Troponin T/I	*		*	*	*
ECG	*		*	*	*
Compliance			*	*	*
Interventions					
Aerobic exercise		—	—	—	—
Resistance exercise		—	—	—	—
Basic nutrition		—	—	—	—
Whey protein		—	—	—	—
Assessments					
6MWT		*			*
Handgrip strength	*	*	*	*	*
SPPB	*	*	*	*	*
DXA	*	*			*
Echocardiography	*	*	*	*	*
BNP/NT-proBNP	*	*	*	*	*
MLHF-Q		*	*	*	*
MNA-SF		*	*	*	*
MACE		—	—	—	—

The time window for each visit is ±3 days. Training to use the remote ECG monitoring APP was conducted in visit 1.
BNP, B-type natriuretic peptide; DXA, dual-energy X-ray absorptiometry; MACE, major adverse cardiovascular events; MLHF-Q, Minnesota Living with Heart Failure Questionnaire; MNA-SF, Mini Nutritional Assessment-Short Form; 6MWT, 6 Min Walk Test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SPPB, short physical performance battery.

the upper extremity and 60%–70% 1-RM for the lower extremity and RPE<15. The same as the aerobic exercise, each session should be separated by at least 48 hours of rest.

The specified movements of the RT programme are as follows: (1) seated leg flexion and extension (quadriceps exercise), (2) seated chest push (pectoralis major and front serratus exercise), (3) seated hip flexion (quadriceps, rectus abdominis and iliopsoas muscle exercise), (4) seated flying bird (obliques, deltoids and triceps exercise), (5) seated straight arm and front lift (deltoids and biceps exercise), (6) seated arm bends and raises (biceps exercise), (7) standing leg extended backward (gluteus maximus and hamstring muscle exercise) and (8) standing hip abduction (lateral femoral muscles and gluteus medius exercise).

Whey protein supplementation

For participants in the RT+WP group, they will be provided for 30 g whey protein powder (Kou Ji brand) daily for 12 weeks, which contain 27 g of whey protein and should be administered with 100–150 mL warm water. A professional dietitian will give each of them a prescription ensuring the composition ratio of high-quality protein is about 50% and the protein intake is controlled at 1.2 g/(kg-d). Patients will be advised on how to prepare the supplement and on its ingestion schedule (before breakfast and lunch or 30 min after resistance exercises in addition to the meals). Also, they will be instructed not to consume other nutritional supplements during the study. Patients are instructed to record the dietary diary which will be collected by researchers at each visit and will receive a phone follow-up once a week.

Remote ECG monitoring system

In the RT group and the RT+WP group, patients will use Cardiac Rehab Exercise Management System (CREMS) while exercising in hospital or at home. They will be instructed how to monitor their own exercise training at the beginning of the trial. CREMS is a new generation of cardiovascular rehabilitation training system produced by CAS Institute of Healthcare Technologies (Nanjing, China). It can provide cardiac rehabilitation suggestions and automatically generate personalised exercise prescription. As a remote ECG monitoring system, the CREMS will monitor the whole training process in real time, to ensure the specified intensity and duration according to the exercise prescription and provide a training report at the end of the monitoring. During exercise, if an abnormal ECG such as arrhythmia occurs, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise and upload real-time data. In addition, when patients have chest discomfort, palpitation and dizziness, they can mark the data through One-Tap Marking button. These data will be uploaded to the data centre, and a specialist will check and analyse the report and will give a corresponding diagnosis and management in time.

Adherence

During the 12 weeks, participants are required to exercise strictly following the prescription and use the designed cards to record each process of ER and WPS. Researchers will make telephone reminders every week and then give face-to-face reminders on each visit to emphasise the importance of adherence. Compliance of exercise rehabilitation and protein supplementation is expressed in rate.

Outcome assessments

The primary outcome is an improvement in the metres walked in 6MWT. The secondary outcomes are as follows: (1) difference in the maximum metabolic equivalent, cardiac strain limit and cardiac strain rate in the 6MWT; (2) improvement in muscle strength, muscle mass and muscle function; (3) difference in echocardiographic parameters, including E/e′ ratio, left atrial volume index, left ventricle end-diastolic diameter, left ventricle end-systolic volume and LVEF (left ventricular ejection Fraction in echocardiography; (4) difference in biomarkers, including BNP/NT-proBNP; (5) changes in health-related QoL evaluated by Minnesota Living with Heart Failure Questionnaire (MLHF-Q); (6) changes in nutritional status assessment by Mini Nutrition Assessment-Short Form (MNA-SF) and (7) major adverse cardiovascular events including worsening HF event, HF hospitalisation, myocardial infarction, stroke, revascularisation and cardiovascular mortality. Researchers involved in participants' assessments will be blinded to treatment allocation. The outcome measures and assessment tools are summarised in table 1.

Participant discharge

(1) Patients may withdraw the informed consent at their own or their legal representatives' request at any time. (2) Researchers may withdraw a patient halfway from the trail if serious adverse events occur. (3) The compliance of maintaining RER and WPS is below 80%.

Trial structure

The trial structure of the study is described in table 2.

Data collection and management

All patients' data are recorded by trained clinical researchers using a standardised CRF. Participants' names and addresses will be collected for the purpose of managing participant interviews. Investigators will ensure that the participants' anonymity is maintained on all other documents. Raw data should be recorded in a timely and accurate manner. Copies of laboratory reports should also be kept. All CRFs are stored in locked file cabinets in areas with limited access. Data administrators from Cardiac Technology in Beijing, China are responsible for the data entry and management. The database was built using PHP language under Linux system. Two data managers independently perform dual input and proofreading to ensure data accuracy. The clinical research data management platform of China-Japan Friendship Hospital is responsible for data monitoring, which is independent of the study organisers. All individuals involved in data management and analysis are blinded to treatment allocation. Principal investigators have direct access to data sets. Any information that identifies any participant will be concealed in data dispersed to project team members.

Statistical analysis

Calculations will be performed using the SAS V.9.4 software. All statistical tests will be two-tailed and a value of $p<0.05$ will be considered statistically significant in all analyses. Analysis of outcomes will be conducted based on the intention-to-treat principle.

Quantitative data will be presented as mean±SD (normally distributed) or median and IQR (not normally

distributed) . Qualitative data will be described as absolute number and relative number (%). Analysis of variance for repeated-measures will apply to compare the differences among three groups. Ordinal data will be compared by Wilcoxon rank sum test.

ETHICS AND DISSEMINATION

The study protocol (V1.0, 20211210) and informed consent documents (V1.0, 20211210) have been reviewed and approved by the Ethics Committee of China-Japan Friendship Hospital for Clinical Research. Written informed consent will be obtained from all participants prior to study enrolment. If there is any change to the protocol, approval must be sought again from the Ethics Committee and participants will be required to provide renewed informed consent. The study has been registered on the website of Chinese Clinical Trial Registry (ChiCTR2200061069, registered on 15 June 2022), and the trial will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Findings will be published in peer-reviewed journals. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Patient and public involvement statement

During the stage of study design, several target patients and their relatives were invited to participate in surveys and discussions, which allowed investigators to know their demand and desire. We also selected several patients to use the CREMS in advance, which helped us to identify problems in application. In addition, we invited medical specialists including rehabilitation therapists, dietitians and statistical analysts to discuss the study design. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians and patients who wish to be notified.

Author affiliations
[1]Department of Health Care, China-Japan Friendship Hospital, Beijing, Beijing, China
[2]China-Japan Friendship School of Clinical Medicine, Peking University, Beijing, Beijing, China
[3]Department of Integrative Cardiology, China-Japan Friendship Hospital, Beijing, Beijing, China
[4]Beijing University of Chinese Medicine, Beijing, Beijing, China

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Contributors XZ, HJ, MZ and RL conceived the original concept of the study. MZ registered the trial and wrote the draft of the protocol manuscript. YC, YG, YW, ML, JX and ZL contributed to the design of the study. All authors have read and agreed to the published version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no data sets generated and/or analysed for this study.

ORCID iD
Mo Zhou http://orcid.org/0000-0001-6280-5232

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