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Impact of an enhanced recovery after surgery program integrating cardiopulmonary rehabilitation on post-operative prognosis of patients treated with CABG: protocol of the ERAS-CaRe randomized controlled trial

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Abstract

Background Coronary artery bypass grafting is associated with a high occurrence of postoperative cardiopulmonary complications. Preliminary evidence suggested that enhanced recovery after surgery can effectively reduce the occurrence of postoperative cardiopulmonary complications. However, enhanced recovery after surgery with systematic integration of cardiopulmonary rehabilitation (ERAS-CaRe) into for Coronary artery bypass grafting has not been evaluated so far. We thus design the ERAS-CaRe randomized-controlled trial to evaluate possible superiority of embedding cardiopulmonary rehabilitation in ERAS over ERAS alone as well as to investigate effects of differential timing of cardiopulmonary rehabilitation within enhanced recovery after surgery (pre-, post-, perio-operative) on post-operative cardiopulmonary complications following Coronary artery bypass grafting surgery.

Methods ERAS-CaRe is a pragmatic, randomized-controlled, parallel four-arm, clinical trial. Three hundred sixty patients scheduled for Coronary artery bypass grafting in two Chinese hospitals will be grouped randomly into (i) Standard enhanced recovery after surgery or (ii) pre-operative ERAS-CaRe or (iii) post-operative ERAS-CaRe or (iv) perio-operative ERAS-CaRe. Primary outcome is the occurrence of cardiopulmonary complications at 10 days after Coronary artery bypass grafting. Secondary outcomes include the occurrence of other individual complications

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including cardiac, pulmonary, stroke, acute kidney injury, gastrointestinal event, ICU delirium rate, reintubation rate, early drainage tube removal rate, unplanned revascularization rate, all-cause mortality, ICU readmission rate, plasma concentration of myocardial infarction-related key biomarkers etc.

Discussion The trial is designed to evaluate the hypothesis that a cardiopulmonary rehabilitation based enhanced recovery after surgery program reduces the occurrence of cardiopulmonary complications following Coronary artery bypass grafting and to determine optimal timing of cardiopulmonary rehabilitation within enhanced recovery after surgery. The project will contribute to increasing the currently limited knowledge base in the field as well as devising clinical recommendations.

Trial registration The trial was registered at the Chinese Clinical Trials Registry on 25 August 2023 (ChiCTR2300075125; date recorded: 25/8/2023, https://www.chictr.org.cn/).

Keywords Coronary artery bypass grafting, Enhanced recovery after surgery, Cardiopulmonary rehabilitation, Full disease cycle, Randomized controlled trial, Cardiopulmonary complications

Background

Coronary artery bypass graft (CABG) surgery is generally recommended with major occlusion of any of the main coronary arteries and contraindication or previous unsuccessful attempts of percutaneous coronary intervention (PCI). In particular, CABG can effectively improve survival when severe stenosis of the left main coronary artery (≥50% in diameter) occurs, and triple large coronary arteries are severely narrowed (≥70% in diameter) with or without involvement of the proximal anterior descending artery [1]. Despite progress in recent decades, CABG surgery is invasive and considered a high-risk procedure, associated with 30-day morbidity and mortality rates to 14.0% and 2.0%, respectively. Moreover, postoperative complications, including pneumonia (1-3.9%) [2], periprocedural myocardial infarction(PMI) (9.7-12.5%) [3, 4], atrial fibrillation(5-40% within 2–4 days postoperatively) [5, 6], stroke (1.6–8.4%) [7, 8], and acute kidney injury (5–42%) [9–11] affect treatment success and patients' quality of life.

Programs targeting the prevention of such complications including Enhanced recovery after cardiac surgery (ERAS-cardiac) with demonstrated effectiveness are thus of pivotal importance [12–14]. ERAS-Cardiac [15, 16] is an umbrella term for multimodal and interdisciplinary intervention programs targeting perioperative management of a patient with the aim of promoting early recovery after cardiac surgery. ERAS-Cardiac usually includes three phases [17] the pre-, peri- and post-surgery, including smoking and alcohol cessation, dietary modifications, and psychological care, among others. ERAS programs after CABG have been shown to reduce bronchopneumonia rate from 18.8 to 9.7% [18], atrial fibrillation from 39 to 26% [19], stroke from 3 to 0% [20]. Moreover, the mean length of ICU and hospital stay decreased by 1–3 days and 1–7 days, respectively [18, 21]. An additional file shows this in more detail (see Additional file 1). Although ERAS has the potential to reduce postoperative complications, postoperative bed rest and reduced activity in CABG patients can result in decline in in muscle strength and decreased cardiopulmonary endurance.

Cardiopulmonary rehabilitation (CR) [22] is a complementary multidisciplinary intervention program that targets the above problems. CR includes physical and occupational therapy with specific such as positive airway pressure treatment, respiratory muscle training and aerobic exercise. There is low to moderate quality evidence suggesting that pre- and post-operative CR in patients undergoing CABG surgery is superior to standard care as regards the reduction of post-operative complications [23–26] and readmissions(10-19.1%) [27] as well as lengths of inpatient stay (1-3days) [28, 29]. An additional file shows this in more detail (see Additional file 2).

Although ERAS-Cardiac guidelines generally emphasize the importance of rehabilitation, no specific intervention protocols are provided to date. In particular, it is unclear which particular rehabilitation interventions can be routinely embedded in ERAS-Cardiac; and how rehabilitation interventions ought to be timed, that is before (pre) or after (post) surgery or in both stages (perio).

Based on the above rationale, we design an enhanced recovery after surgery program integrating cardiopulmonary rehabilitation (ERAS-CaRe) and developed a protocol for a pragmatic, randomized controlled, four parallel arms, clinical trial to evaluate this program. The ERAS-Care trial aims to determine possible superiority of CR-embedded ERAS over ERAS alone as well as to investigate effects of differential timing of the rehabilitation component within ERAS (pre-, post-, perio-operative) on post-operative cardiopulmonary complications and other complications including post-operative cardiac complications, post-operative pulmonary complications, stroke, acute kidney injury, ICU delirium, reintubation, revascularization, all-cause mortality, medical costs, and length of stay in the context of CABG surgery.

Methods/design

Study design

This study is a pragmatic, multi-center, randomized controlled, parallel group, clinical trial. Table 1 shows the overview of the trial registration information. This trial protocol has been developed according to SPIRIT [30, 31] for pragmatic trials and non-pharmacological treatment interventions.

Trial objectives

The primary objective of the planned trial is to determine whether systematically embedding CR within ERAS is superior to ERAS without CR, in reducing the

Table 1 The WHO trial registration data set for the ERAS-Care trial

Data category	Information
Primary registry and trial identifying number	Chinese Clinical Trial Registry number: ChiCTR2300075125
Date of registration in primary registry	August 25, 2023
Secondary identifying numbers	N/A
Trial protocol version	Version 1
Source(s) of monetary or material support	N/A
Primary sponsor	N/A
Secondary sponsor	N/A
Contact for public queries	Yu Zheng, zhengyu8710@163.com
Contact for scientific queries	Yu Zheng, zhengyu8710@163.com
Public title	Impact of an enhanced recovery after surgery program integrating cardiopulmonary rehabilitation on post-operative prognosis of patients treated with CABG: rationale and design of the ERAS-CaRe randomized controlled trial
Scientific title	Impact of an enhanced recovery after surgery program integrating cardiopulmonary rehabilitation on post-operative prognosis of patients treated with CABG: rationale and design of the ERAS-CaRe randomized controlled trial
Countries of recruitment	China
Health condition(s) or problem(s) studied	Patients with coronary artery disease undergoing CABG
Intervention(s)	Standard ERAS
	Pre-operative ERAS-CaRe
	Post-operative ERAS-CaRe
	Perio-operative ERAS-CaRe
Key inclusion and exclusion criteria	Ages eligible for study: aged 18 year or older
	Sexes eligible for study: both
	Accepts health volunteers: No
	Inclusion criteria: see Table 2 Exclusion criteria: see Table 2
Study type	Type: Pragmatic, randomized controlled, parallel group, clinical trial
	Allocation: Block randomization
	Intervention model: Parallel assignment
	Masking: Assessor, physician, data analyst, and statistician blinded
	Primary purpose: Prevention and improvement
	Phase: N/A
Date of first enrollment	Not yet started
Target sample size	360
Recruitment status	Recruiting
Primary outcome(s)	Occurrence of post-operative cardiopulmonary complications within the first 10 post-operative days
Key secondary outcomes	Occurrence of PCCs; occurrence of PPCs; occurrence of stroke; occurrence of acute kidney injury; other complications include ICU delirium rate, gastrointestinal event and revascularization; reintubation rate; early drainage tube removal rate; time to remove mechanical ventilation length; total LOS; ICU readmission rate; overall readmission rate; LVEF; cTnT; hs-CRP; Self-reported METs; Inpatient all-cause mortality; ICU LOS; Total medical expenses

CABG coronary artery bypass graft, *ERAS-CaRe* enhanced recovery after surgery program integrating cardiopulmonary rehabilitation program, *hs-CRP* hypersensitive C-reactive protein, *ICU* intensive care unit, *LOS* length of stay, *LVEF* left ventricular ejection fraction, *METs* metabolic equivalents, *PPCs* post-operative pulmonary complications, *PCCs* post-operative cardiac complications, *RCTs* randomized controlled trials

occurrences of post-operative cardiopulmonary complications within 10 days following CABG. Herein, differences between pre-operative, post-operative, and full peri-operative integration of CR into ERAS will also be analyzed in order to determine an optimal protocol.

Secondary objectives are to investigate whether pre-, post-, and/or peri- ERAS-CaRe are more effective than control in improving specific subtypes of complications (including cardiac complications, pulmonary complications; stroke, acute kidney injury, gastrointestinal event, reintubation rate, early drainage tube removal rate, unplanned revascularization rate, all-cause mortality, ICU readmission rate, left ventricular ejection fraction (LVEF), serum cardiac troponin T concentration (cTnT), hypersensitive C-reactive protein (hs-CRP), self-reported metabolic equivalents (METs), ICU LOS, total LOS, ICU readmission rate, overall readmission rate, and total medical expenses.

Ethics statement

The trial has been prospectively registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn): ChiCTR2300075125. The institutional review board in the First Affiliated Hospital of Nanjing Medical University has approved the trial (protocol reference: 2023-SR-348). In accordance with the Declaration of Helsinki of 1964 as revised in 2013, the International Conference of Harmonization Guidelines for Good Clinical Practice and the requirement of the local ethics committees, written informed consent will be obtained from all enrolled participants. Any important changes regarding the study protocol in terms of eligibility criteria, interventions, outcomes or analyses will be conducted under the supervision and approval of the institutional review board.

Trial setting

The trial is implemented at First Affiliated Hospital of Nanjing Medical University (Nanjing, Eastern China), a metropolitan primary referral hospital with 3700 beds and Qingdao Hospital, University of Health and Rehabilitation Sciences (Qingdao, Northern China), a 2000-bed primary referral hospital which have implemented ERAS guidelines to all surgical units. Hospitals will be selected based on their capacity to treat the target patient population, the availability of specialized medical staff, and their experience in conducting clinical trials. First Affiliated Hospital of Nanjing Medical University will implement this program standard operation procedures (SOPs) which discussed and approved by relevant medical staff including the procedure of enrollment, randomization, rehabilitation intervention, assessment and data collection and regular visits to the participating staff. Each hospital will have a designated principal investigator responsible for overseeing the trial at their respective site.

Trial status

The trial is ongoing and is actively enrolling. The number of enrolled patients as of the submission date of the manuscript was 200.

Eligibility and withdrawal criteria

The target population for this trial encompasses those who meet the consolidated criteria below, and Table 2 is listed for ease of reading.

Eligibility criteria

The target population for this study comprises patients who meet the following inclusion criteria: (i) aged 18 years or older; (ii) diagnosed with coronary heart disease through coronary angiogram and laboratory examination based on symptoms and signs of the patient; (iii) met indications of CABG with or without valvular surgery defined as at least 2 vessel lesions or significant left major coronary arteries stenosis or SYNTAX score $\geq$ 33; (iv) with normal cognition and being able to cooperate with the CR training; (v) agreed to participate in the trial and signed the consent form [1, 22, 32].

Patients will be excluded if they meet any of the following criteria: (i) pregnant; (ii) undergoing aortic surgery or equivalent surgery within 6 months; (iii) history of cardiogenic shock or sudden cardiac arrest and severe hypertension; (iv) having complications with persistent ischemia, hemodynamic impairment, or at risk of arterial occlusion with massive myocardial infarction; (v) having complications with unstable angina, malignant arrhythmia and severe cardiac insufficiency New York Heart Association (NYHA) of IV or LVEF < 35%); (vi) having acute myocardial infarction complicated with severe mechanical complications such as ventricular aneurysm formation, mitral regurgitation caused by papillary muscle rupture, or rupture of free wall; (vii) having peripheral neuropathy, peripheral artery disease, superficial thrombophlebitis, deep vein thrombosis, and thus unable to tolerate rehabilitation training; (viii) terminal disease like cancer, malignancies, liver failure, or other severe systemic diseases; (ix) participated in other trials within 6 months; (x) Having substance abuse, depression etc. [1, 22, 33–35].

Withdrawal from the trial

In the trial, patients will be withdrawn for either of the following: (i) making such a request during the trial to withdraw the consent form and request to withdraw from the trial; (ii) developing a serious disease during the trial,

Table 2 Trial inclusive, exclusive and withdrawal criteria

Inclusion criteria
• Aged 18 years or older
• Diagnosed with coronary heart disease through coronary angiogram and laboratory examination based on symptoms and signs of the patient
• Met indications of CABG with or without valvular surgery defined as at least 2 vessel lesions or significant left major coronary arteries stenosis or SYNTAX score ≥ 33
• With normal cognition and being able to cooperate with the CR training
• Agreed to participate in the trial and signed the consent form
Exclusion criteria
A. Unable to tolerate intervention or high-risk profile:
• Pregnant
• Undergoing aortic surgery or equivalent surgery within 6 months
• History of cardiogenic shock or sudden cardiac arrest and severe hypertension
• Having complications with persistent ischemia, hemodynamic impairment, or at risk of arterial occlusion with massive myocardial infarction
• Having complications with unstable angina, malignant arrhythmia and severe cardiac insufficiency (NYHA of IV or LVEF < 35%)
• Having acute myocardial infarction complicated with severe mechanical complications such as ventricular aneurysm formation, mitral regurgitation caused by papillary muscle rupture, or rupture of free wall
• Having peripheral neuropathy, peripheral artery disease, superficial thrombophlebitis, deep vein thrombosis
B. Competing risk
• Terminal diseases like cancer, malignancies, liver failure, or other severe systemic diseases
C. Anticipated lack of collaboration with rehabilitation training or anticipated lack of compliance
• Having substance abuse, depression etc.
D. Competing intervention
• Participated in other trials within 6 months
Withdrawal criteria
• The patient makes such a request during the trial to withdraw the consent form and request to withdraw from the trial
• The patient develops a serious disease during the trial, such as malignancies or severe systemic diseases, and continuing participation becomes a risk to the patient in the opinion of the physician responsible for the treatment
• The patient develops a severe adverse reaction during the treatment

CABG Coronary artery bypass graft, *CR* cardiopulmonary rehabilitation, *LVEF* Left ventricular ejection fraction, *NYHA* New York Heart Association

such as malignancies or severe systemic diseases, and continuing participation becomes a risk to the patient in the opinion of the physician responsible for the treatment; (iii) developing a severe adverse reaction during the treatment [36].

Recruitment, randomization and allocation

Patients will be selected from candidates electively undergoing CABG surgery at the First Affiliated Hospital of Nanjing Medical University and Qingdao Hospital, University of Health and Rehabilitation Sciences. They will be assessed by a multidisciplinary team consisting of a registered nurse, anesthetist, and surgeon from the admitting surgical team 7 days prior to their operation.

For generating the allocation sequence in our study, we utilized a computerized block randomization approach. This was implemented using the R statistical software (version 4.2.0), ensuring a balanced distribution of participants across the four study groups. The randomization was structured with a predetermined block size of 8, which was chosen to maintain a consistent and equitable allocation ratio throughout the enrollment process [37].

Mechanism of implementing the allocation sequence & Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions: After generating the allocation sequence, the sequence will be securely transferred to an independent data manager who is not involved in participant recruitment or assessment. This manager will maintain the allocation concealment in sealed, opaque envelopes, each corresponding to a participant number. When a participant is enrolled and consented, a designated clinical staff member, blinded to the sequence, will open the next sequential envelope to assign the participant to their respective group. This process ensures allocation concealment and minimizes selection bias.

Figure 1 demonstrates the overview of recruitment, randomization, and allocation based on the SPIRIT principle [31].

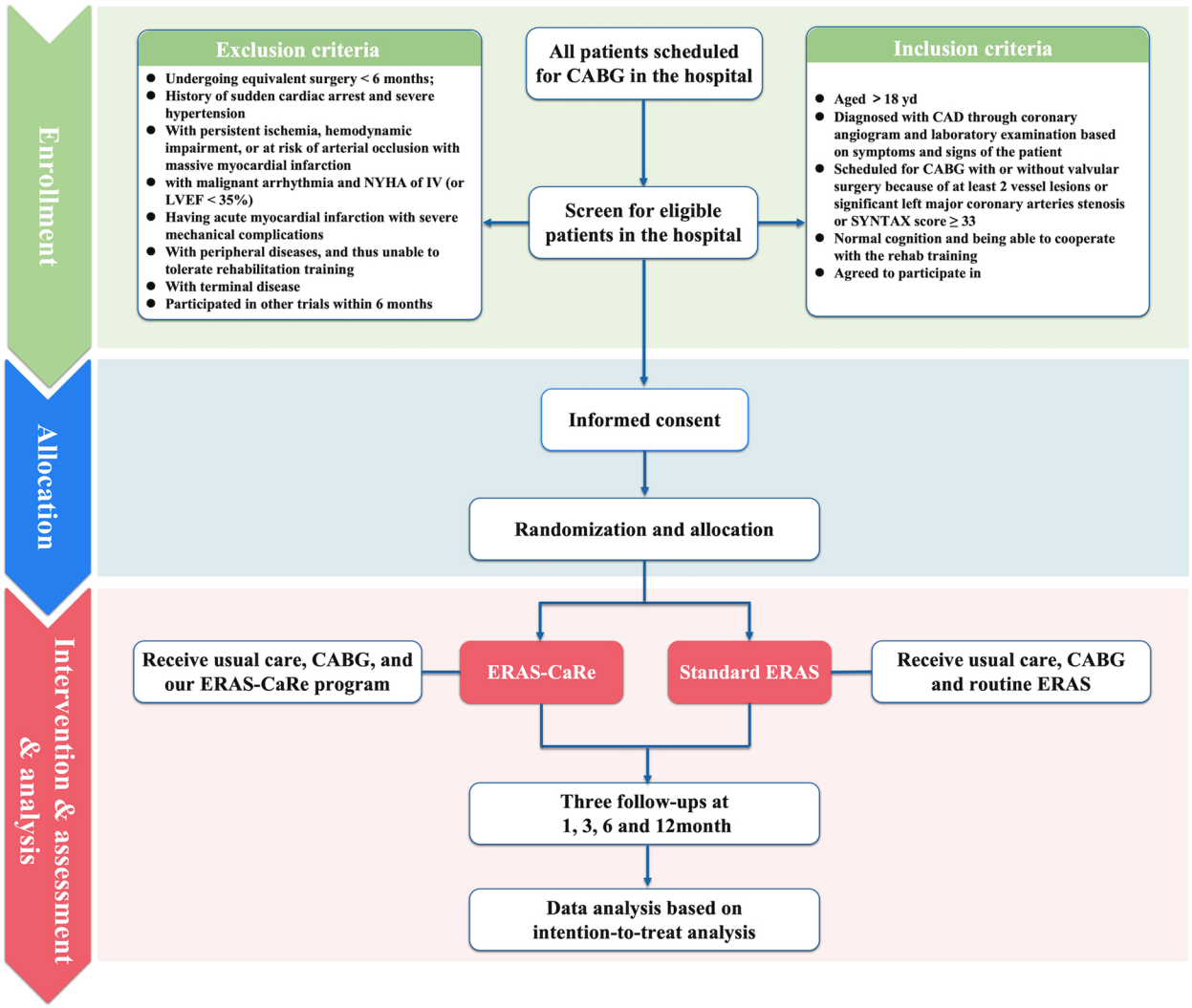

Fig. 1 Flow chart of the ERAS-CaRe trial. CABG: Coronary artery bypass graft; CAD: coronary artery disease; CR: cardiopulmonary rehabilitation; ERAS-CaRe: enhanced recovery after surgery program integrating cardiopulmonary rehabilitation program; ERAS: enhanced recovery after surgery; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association

Interventions

Interventions are described according to the TIDieR standard [38].

Brief name

ERAS-CaRe (enhanced recovery after surgery program integrating cardiopulmonary rehabilitation program) for CABG (coronary artery bypass grafting).

Why

Evidence suggests that preoperative and postoperative cardiopulmonary rehabilitation can reduce complications and rehospitalization rates after CABG surgery [39]. Integrating CR into the ERAS pathway may be superior to a standalone ERAS approach. The timing of CR within the ERAS pathway (preoperative, postoperative, perioperative) may further influence the occurrence of postoperative cardiopulmonary complications.

What (materials and procedures)

Control group: Standard ERAS

Patients included will receive usual care, CABG and routine ERAS according to ERAS-cardiac guidelines [32]. Usual care mainly comprises pharmacotherapy (like aspirin and clopidogrel) before and after CABG. The ERAS pathway follows and runs through three stages [34] as detailed in Table 3.

Table 3 ERAS-CaRe trial interventions content

Components		ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative								
• Cessation of smoking and hazardous alcohol consumption		×	×	×	×	Supervised by nurses. Smoking and alcohol cessation advised and promoted before surgery [1].	As needed.	Reduce cardiopulmonary complications.
• Medical optimization of chronic disease		×	×	×	×	Supervised by respective specialists. Medical optimization before surgery, including renal, pulmonary, and endocrine function [15].	As needed.	Reduce complications.
• Measurement of Hemoglobin A1c for glycemic control		×	×	×	×	Supervised by nurses. Optimal pre-operative glycemic control, defined by a hemoglobin A1c level of less than 6.5% [32].	As needed.	Reduce complications.
• Correction of Nutritional Deficiency		×	×	×	×	Supervised by nutritional experts. Patients screened for nutritional deficiency and oral nutritional supplementation should be given at least a week before surgery for malnourished patients [17].	As needed.	Reduce complications and enhance surgical tolerance.
• Preoperative fasting and carbohydrate treatment		×	×	×	×	Supervised by nurses. Fasting for 8 h before anesthesia except for an oral carbohydrate beverage given 2–4 h before anesthesia [32].	Immediately before surgery.	Reduce insulin resistance, improve post-operative glucose control, and enhance return of gut function.
· Pre-CR	***Education***	NA	×	NA	×	Supervised by physical therapists. Patients are introduced with definition, components and benefits of CR [22].	20 min after admission.	Improve compliance, decrease anxiety and improve health outcomes.

Table 3 (continued)

Components		ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative								
	Diaphragmatic breathing	NA	×	NA	×	Supervised by respiratory therapists in on-site sessions. In sitting or supine position with hands placed on the abdomen, patients inhale slowly and deeply through nose to maximal lung capacity, then exhale slowly with pursed lips (ratio of inhalation to exhalation is 1:3) [22].	Fifteen repetitions of each set followed by 2–3 min rest for three sets per day, every day from admission day to operation.	Improve ventilation, increase pulmonary volume, and reduce cardiopulmonary complications.
	Airway clearance techniques	NA	×	NA	×	Supervised by respiratory therapists in on-site sessions. It includes *Active Circulatory Breathing Technique (ACBT)* [40]: use of relaxed breathing control (BC) and chest exhalation technique (CET), combined with forced exhalation technique (FET) to mobilize secretions; *Effective Cough*: patients place their hands on the chest and upper abdomen, then inhale slowly and deeply to maximal inspiratory capacity followed by a forced cough with glottis opening. If coughing is difficult or painful, huffing will be taught and performed; *Autogenic Drainage (AD)*: this breathing technique uses high expiratory flow rates at varying lung volumes; Airway Oscillating Devices: includes Flutter and Acapella [41, 42].	Ten repetitions each set followed by 2–3 min rest for three sets per day, every day from admission day to operation. If patient has no sputum, it is also necessary to practice before surgery to avoid the postoperative wound pain affecting the training effects.	Enhance mucous clearance and reduce cardiopulmonary complications.

Table 3 (continued)

Components		ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative								
	Respiratory muscle training	NA	×	NA	×	Supervised by respiratory therapists in on-site sessions. ***Inspiratory muscle training*** uses incentive spirometer, patients inhale slowly through the mouthpiece until they reach the target volume. ***Expiratory muscle training*** is performed using traditional abdominal pouch or freehand diaphragm strength resistance training [22].	Ten repetitions each set followed by 2–3 min rest for three sets per day from admission day to operation [22].	Strengthen respiratory muscles and reduce cardiopulmonary complications.
	Aerobic training	NA	×	NA	×	Directly supervised by physical therapist. Indoor walking and cycling in the ward, physical therapy room, or hospital hall [43].	20 min per day, every day from admission day to operation [22].	Improve cardiopulmonary endurance, improve limb mobility and reduce complications.
Intra-operative								
• Rigid sternal fixation		×	×	×	×	Sternotomy closure with rigid plate fixation [32].	During operation.	Improve or accelerate sternal healing and reduce mediastinal wound complications.
• Blood management		×	×	×	×	Tranexamic acid or epsilon aminocaproic acid is recommended during on-pump cardiac surgical procedures [32].	During operation.	Reduce major hemorrhage or tamponade requiring reoperation.
• Control of body temperature		×	×	×	×	Avoiding hyperthermia while rewarming on cardiopulmonary bypass.	During operation.	Reduce cognitive deficits, infection, and renal dysfunction.
• Surgical site infection management		×	×	×	×	Prevention of incision infection by using a care bundle including topical intranasal therapies, depilation protocols, and appropriate timing and stewardship of peri-operative prophylactic antibiotics.	During operation.	Reduce surgical site infection and reduce complications.
• Sedation management		×	×	×	×	Use of dexmedetomidine or propofol infusion for post-operative sedation in the ICU while intubated.	Near end of surgery.	Reduce complications.

Table 3 (continued)

Components	ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative							
Post-operative							
• Multimodal opioid-sparing pain management	×	×	×	×	Supervised by cardiac surgeons and nurses. Pain assessments must be done in intubated patients to ensure the lowest effective opioid dose. Standardized analgesic regimen is consist of regular acetaminophen, tramadol, dexmedetomidine, and pregabalin (or gabapentin).	As indicated.	Reduce pain.
• Multimodal approach to control of nausea and vomiting	×	×	×	×	Supervised by cardiac surgeons and nurses. Regular postoperative ondansetron and promethazine are needed for breakthrough nausea and vomiting if patient aged > 70 y.	As indicated.	Minimize postoperative nausea, support energy and protein intake.
• Delirium management	×	×	×	×	Supervised by cardiac surgeons and nurses. Systematic delirium screening tool should be used. Nonpharmacologic strategies are the first-line component of management.	As indicated.	Improve cognitive function.
• Maintain postoperative normothermia	×	×	×	×	Supervised by nurses. Prevention of hypothermia by using forced-air warming blankets, raising ambient room temperature, and warming irrigation and intravenous fluids to avoid hypothermia in the early post-operative period.	As indicated.	Reduce complications.

Table 3 (continued)

Components		ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative								
• Early extubation		×	×	×	×	Supervised by cardiac surgeons and nurse. Patients should be extubated from ventilatory support once hemodynamic and pulmonary function is stable.	Early removal as indicated.	Reduce ventilator-associated pneumonia and significant dysphagia.
• Lines and drain management		×	×	×	×	Supervised by cardiac surgeons and nurses. Early removal of any orogastric/nasogastric tubes, central venous access, invasive hemodynamic monitoring, urinary catheter and chest tubes.	Early removal as indicated.	Support ambulation and mobilization.
• Goal-directed fluid therapy		×	×	×	×	Supervised by cardiac surgeons and nurses. Goal-directed fluid therapy uses monitoring techniques to guide clinicians in administering fluids, vasopressors, and inotropes.	As indicated.	Avoid hypotension and low cardiac output.
• Post-CR	***Positioning***	NA	NA	×	×	Supervised by physical therapists and nurses. Gradually adjust to semi-reclining position, sitting position, out of bed to chair, and standing position.	As indicated.	Improve oxygenation, ventilation/perfusion ratio, and reduce complications.
	Diaphragmatic breathing	NA	NA	×	×	Supervised by respiratory therapists in on-site sessions. In sitting or supine position with hands placed on the abdomen, patients inhale slowly and deeply through nose to maximal lung capacity, then exhale slowly with pursed lips (ratio of inhalation to exhalation is 1:3).	Fifteen repetitions each set followed by 2–3 min rest for three sets per day, every day from post-operative day 1 to discharge day with optional continuation as home exercise. For patients undergoing mechanical ventilation, adjust the parameters of ventilator appropriately during training and try to perform it in a state of autonomous breathing.	Improve ventilation, increase pulmonary volume, and reduce cardiopulmonary complications.

Table 3 (continued)

Components		ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative								
	Airway clearance techniques	NA	NA	×	×	Supervised by respiratory therapists in on-site sessions. It includes *Active Circulatory Breathing Technique (ACBT)*: use of relaxed breathing control (BC) and chest exhalation technique (CET), combined with forced exhalation technique (FET) to mobilize secretions; *Effective Cough*: patients place their hands on the chest and upper abdomen, then inhale slowly and deeply to maximal inspiratory capacity followed by a forced cough with glottis opening. If coughing is difficult or painful, huffing will be taught and performed; *Autogenic Drainage (AD)*: this breathing technique uses high expiratory flow rates at varying lung volumes; *Airway Oscillating Devices*: includes Flutter and Acapella [40, 41].	Ten repetitions each set followed by 2–3 min rest for three sets per day, every day from post-operative Day 1 to discharge day with optional continuation as home exercise.	Enhance mucous clearance and reduce cardiopulmonary complications.
	Respiratory muscle training	NA	NA	×	×	Supervised by respiratory therapists in on-site sessions. *Inspiratory muscle training* uses incentive spirometer, patients inhale slowly through the mouthpiece until they reach the target volume. *Expiratory muscle training* is performed using traditional abdominal pouch or freehand diaphragm strength resistance training.	Ten repetitions each set followed by 2–3 min rest for three sets per day from post-operative day 1 to discharge day with optional continuation as home exercise.	Strengthen respiratory muscles and reduce cardiopulmonary complications.

Table 3 (continued)

Components	ERAS	Pre-CaRe group	Post-CaRe group	Peri-CaRe group	Supervision and contents	Schedule/intensity/duration/frequency	Rationale
Pre-operative							
Aerobic training	NA	NA	×	×	Supervised by physical therapists. After the patient's circulation is stabilized, passive or active limb movements are performed on the bed, followed by a gradual transition from active limb movements on the bed to bedside activities, in-ward walking, treadmill training, upstairs and downstairs training.	Exercise equivalent was controlled at 2–4 METs and within 12–13 on Borg rating of perceived exertion scale, starting from 5–10 min and gradually increasing to 20 min per day from postoperative day 1 to discharge day with optional continuation as home exercise.	Improve cardiopulmonary endurance, improve limb mobility and reduce complications.

ACBT Active Circulatory Breathing Technique, *AD* Autogenic Drainage, *BC* breathing control, *FET* forced exhalation technique, *CABG* coronary artery bypass graft, *CR* cardiopulmonary rehabilitation, *ERAS* enhanced recovery after surgery, *ERAS-CaRe* ERAS with systematic integration of cardiopulmonary rehabilitation, *ICU* intensive care unit, *LOS* length of stay, *METs* metabolic equivalents

Experimental groups: ERAS-CaRe

Patients under ERAS-CaRe will receive usual care, CABG, and our ERAS-CaRe program. According to timing of the intervention three groups are foreseen: (i) pre-operative ERAS-CaRe, (ii) post-operative ERAS-CaRe, (ii) peri-operative ERAS-CaRe. Pre-, post-, and pre + post- CR share the same protocol, which comprises cardiopulmonary rehabilitation education, diaphragmatic breathing, airway clearance techniques, positioning, respiratory muscle exercises, and aerobic training. Specific supervision context and contents, schedule, intensity, duration, frequency, and rationale are provided in Table 3. A flowchart of the CR-ERAS program is given in Fig. 2.

Who provides

Intervention will be delivered by rehabilitation doctors, cardiologists, cardiac surgeons, anesthesiologists, physical therapists, respiratory therapists, nutritionists and nurses. All health professionals will receive one day of trial-related training provided by the principal investigators of the respective study sites before the start of the project, and weekly guidance from supervisors at each center will also be provided. All surgeons and anesthesiologists involved in the study should have at least one year of experience with CABG surgeries and will undergo standardized training for ERAS.

How

All interventions are given to patients on a one-on-one, face-to-face basis during outpatient visits or hospitalization and described in Table 3.

Where

Preoperative nutritional screening, chronic disease medical optimization, blood pressure, and HBA1c level control of the ERAS will be completed in the outpatient clinic involving nutritionists and chronic disease specialists. Intraoperative interventions will be conducted by surgeons and anesthesiologists during the surgery. The remaining ERAS interventions and all CR interventions will be completed in the ward by a team of doctors, nurses, and therapists.

When and how much

Preoperative, intraoperative, and postoperative interventions will take place at planned times. The preoperative ERAS-CaRe intervention will start after the patient is admitted and continue daily until the day of surgery. The postoperative ERAS-CaRe intervention will begin on the first day after surgery and continue until discharge. For scheduling, intensity, duration, and frequency see Table 3.

Tailoring

No personalization or adaptation is implemented in this study.

How well (planned)

Adherence to the intervention will be assessed by therapists, who will document whether the preoperative and postoperative interventions are completed in each item. Before initiating the intervention, the therapist will reiterate the components and benefits of CR. The therapist will accompany the patient throughout the intervention, aiming to enhance patient compliance.

Outcomes

Primary outcome

The primary outcome of the ERAS-CaRe trial is the occurrence of post-operative cardiopulmonary complications within the first 10 post-operative days. It involves two parts: post-operative pulmonary complications (PPCs) and post-operative cardiac complications (PCCs) [36]. Data on PPCs and PCCs will be collected prospectively according to pre-agreed definitions as follows. PPCs are defined with the Melbourne Group Scale (MGS) diagnostic scoring tool, and are liable and valid following thoracic surgery with high inter-rater reliability [40–42]. A PPC will be diagnosed when the following four or more factors are identified: (i) new abnormal breath sounds different to pre-operative; (ii) chest X-ray findings of atelectasis or consolidation; (iii) raised white cell count (WCC) ($>11\times10^9$/L); (iv) temperature > 38 °C; (v) purulent sputum differing from pre-operative status; (vi) signs of infection on sputum culture; (vii) pulse oximetry oxygen saturation < 90% without oxygen therapy; and (viii) pneumonia diagnosed based on physician's experience [42]. When a positive diagnosis of a PPC is confirmed, the patient will receive specific respiratory interventions provided by the doctors from Department of Respiration. PCCs are defined as acute myocardial infarction, ventricular tachycardia/fibrillation, primary cardiac arrest, angina, complete heart block, any cardiac-related death, or atrial arrhythmia [36].

Secondary outcomes

Secondary outcomes are listed as follows:

- The occurrence of PCCs is defined as above within the first 10 post-operative days.
- The occurrence of PPCs is defined as the same as above within the first 10 post-operative days.

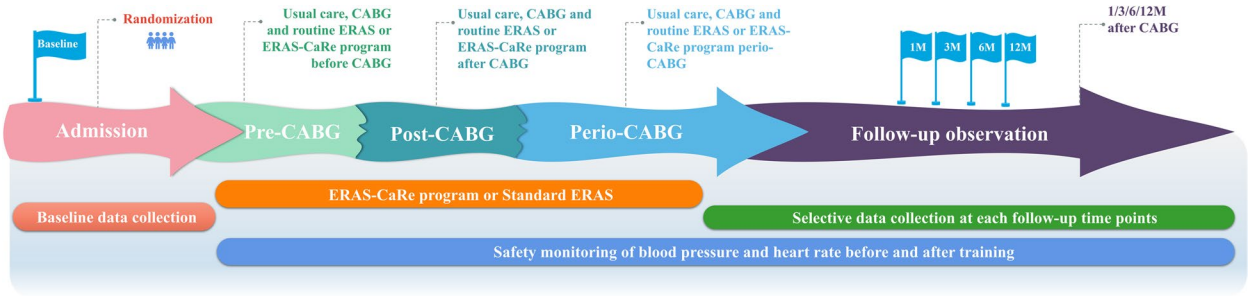

Fig. 2 Flow diagram of ERAS-CaRe program. CABG: Coronary artery bypass graft; CAD: coronary artery disease; CR: cardiopulmonary rehabilitation; ERAS-CaRe: enhanced recovery after surgery program integrating cardiopulmonary rehabilitation program; ERAS: enhanced recovery after surgery

- The occurrence of stroke is defined as the proportion of patients with new or recurrent stroke after CABG surgery within the first 10 post-operative days [43].
- The occurrence of acute kidney injury is defined as the proportion of patients with acute kidney injury after CABG surgery.
- The occurrence of gastrointestinal event is defined as the proportion of patients with any gastrointestinal event using the Society of Thoracic Surgeons Adult Cardiac Surgery Database definition within the first 10 post-operative days [44].
- Reintubation rate is defined as the percentage of reintubation in extubation after tracheotomy calculated within 10 days after CABG [45].
- ICU delirium rate is defined as the percentage of delirium within 10 days after CABG. ICU delirium is clinically diagnosed using screening tools such as the Confusion Assessment Method for the ICU [46].
- Early drainage tube removal rate is defined as the proportion of the number of people with drainage tubes removed within 10 day [47].
- Unplanned revascularization rate refers to the rate of repeated episodes of coronary revascularization with CABG across index hospitalization and follow-up period.
- All-cause mortality is defined as mortality from any cause after registration. The causes of death were classified as cardiovascular (e.g., malignant arrhythmia, myocardial infarction, or stroke) and non-cardiovascular (e.g., new cancer or severe systemic disease). The number of deaths due to any cause was calculated as a percentage of the total number of patients included [16].
- ICU readmission rate is defined as any overnight stay past midnight in a hospital ICU center (including the emergency department) within 10 days of discharge from the initial procedure. The ICU readmission rate is the proportion of readmissions (due to cardiovascular and cerebrovascular diseases, re-operations, post-operative infections, etc.) to the total population.
- The readmission rate is the proportion of readmissions (due to cardiovascular and cerebrovascular diseases, re-operations, post-operative infections, etc.) to the total population. Readmission was defined as any overnight stay past midnight in a hospital within a follow-up 12 months of discharge from the initial procedure. Because adjudication of observation status or readmission is not readily apparent in the electronic health record, patients were considered to be readmitted if they were in a hospital (including the emergency department) past midnight [48].
- Plasma concentration of myocardial infarction-related key biomarkers (PCMIKB) will be reflected with the concentration of cardiac troponin T (cTnT), cardiac troponin I (cTnI), creatine kinase (CK) creatine kinase myocardial band (CK-MB), lactic dehydrogenase (LDH), alpha-hydroxybutyric dehydrogenase (HBDH), and aspartic transaminase (AST).
- Cardiac function will be measured with two-dimensional echocardiography and reflected in left ventricular ejection fraction (LVEF).
- Pulmonary function will be reflected in the time to remove the mechanical ventilation length and the mechanical ventilation length evaluated by the hour [49].
- Exercise endurance will be measured with Metabolic equivalents (METs) [50]. METs refer to the average oxygen consumption of 3.5 ml/kg per minute, or 1METs, usually in a quiet state.
- ICU LOS is the addition of the acute period after CABG and total LOS during ICU and ICU readmission.
- Total LOS is the addition of the acute period after CABG, total LOS during the recovery and readmission.

- Total medical expenses will be calculated by the addition of the cost of each admission over the course of the trial.

Data collection

A blinded assessor will evaluate patients for PPCs and PCCs on each expected day, including post-operative day 1, day 7 and the discharge day. As references, medical records like radiologist reports and laboratory sheets will be examined. On the discharge day, patients will get a log sheet where they can record any self-identified respiratory symptoms that they may experience throughout the next one-month, three-month, six-month and twelve-month periods. All noted data may be used as a reference for diagnosing PPCs and PCCs while they are staying at home. On their follow-up days, patients will be asked to provide the assessor with their log sheets for recording. If any serious symptoms appear, it will be advised that patients should be readmitted to the hospital.

Data in terms of the occurrence of PCCs and the occurrence of PPCs will be collected within the first 10 post-operative days. The occurrence of gastrointestinal event, the occurrence of stroke, the occurrence of acute kidney injury, delirium rate, reintubation rate, early drainage tube removal rate, unplanned revascularization rate, inpatient all-cause mortality, ICU readmission rate and the readmission rate will be collected throughout the index hospitalization and follow-up period. All time-to-event outcomes, including date and type of events, will be recorded by the research assistants according to death certificate (for mortality outcomes) or through medical records (for non-fatal outcomes). Exercise endurance (METs) will be reviewed and confirmed by the treating physician. PCMIKB, cardiac function, and pulmonary function will be measured across all follow-up time points as well as on the admission day. Total hospital LOS and total medical costs will be reported at the close-out. Scheduled data collection at each time point is presented in Table 4 for details.

Blinding

In our clinical trial, due to the nature of the intervention, complete blinding is not feasible for patients and physiotherapists. However, we have implemented measures to blind other key parties. Medical staff and surgeons, though providing co-interventions, are excluded from specific clinical rehabilitation sessions linked to the trial interventions, thereby maintaining their blinding. Assessors, crucial to unbiased data collection, are kept blind by being entirely uninvolved in any trial procedures or interventions. For data analysts and statisticians, we ensure blinding through the use of anonymized data sets, where group labels are not disclosed. This approach is underpinned by regular training to reinforce the importance of blinding and audits to assess its effectiveness. A contingency plan is in place for inadvertent unblinding, involving immediate reporting and measures to minimize the impact on the trial's integrity.

Data management

Standardized case report forms (CRF) have been developed specifically for the trial. All data will be entered into electronic standardized case report forms (eCRF) and stored in a bespoke trial cloud database upon its collection. Data entry will be independently performed, dated, and signed by two trial assistants. Typos and missing data will be detected by specifically designed computer programs. When discrepancies occur, consensus will be achieved by checking raw-data, repeated patient interviews or discussion. Confidentiality of data is assured by restricted access to the cloud database granted to authorized investigators only, for example, members of the data safety monitoring board (DSMB). The primary investigator, coordinators, DSMB members, data analysts, statisticians, and trial assistants will meet periodically to (1) monitor and review patient safety in the trial; (2) request and perform interim data analyses; (3) review patient recruitment, accrual and withdrawal;(4) discuss continuing or modifying the trial; and (5) stop the trial upon any severe adverse events (e.g., any events result in death or persistent disability, or require inpatient hospitalization or prolonged hospitalization) considered to have been caused by the CR-ERAS program.

Sample size calculation

Previous studies have reported that the occurrence of post-operative complications with undergoing CABG was around 40% [27, 33]. An absolute risk reduction of 15% was regarded as a clinically meaningful effect for the occurrence of post-operative cardiopulmonary complications at any point in time over the 12 months observation period. Sample size calculation was performed for a Cox proportional hazard model with a two-sided false discovery rate of 0.01 and a power of 80%. The minimum sample size was estimated as $n=320$, i.e., 80 per group. Taking dropouts, non-compliance, and uncertainty of baseline risk into account, 10% attrition was considered realistic, and the target sample size was determined as 360 (90 per group).

Strategies for achieving adequate participant enrollment to reach target sample size

Our recruitment strategy is designed to ensure adequate enrollment to reach our target sample size of 360 participants. We will employ multiple methods, including

Table 4 Scheduled events and timeline of ERAS-CaRe trial

		STUDY PERIOD								
		Eligibility	Allocation	Post-allocation						Close-out
	TIMEPOINT	0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_x
		Listed for CABG surgery	Admission day	Post-operative day 1	Post-operative day 7	Discharge day	Follow-up 1 month	Follow-up 3 month	Follow-up 6 month	Follow-up 12 month
ENROLLMENT	Eligibility screen	×								
	Informed consent	×								
	Randomization		×							
ASSIGNMENT	Standard ERAS		×							
	Pre- ERAS-CaRe		×							
	Post- ERAS-CaRe		×							
	Perio- ERAS-CaRe		×							
VARIABLES	Demographics		×							
	Clinical characteristics		×							
	Occurrence of post-operative cardiopulmonary complications			×	×	×				
	Occurrence of PPCs			×	×	×				
	Occurrence of PCCs			×	×	×				
	Occurrence of stroke			×	×	×	×	×	×	×
	Occurrence of acute kidney injury			×	×	×	×	×	×	×
	Occurrence of gastrointestinal event			×	×	×	×	×	×	×
	Reintubation rate			×	×	×	×	×	×	×
	ICU delirium rate			×	×	×	×	×	×	×
	Early drainage tube removal rate			×	×	×	×	×	×	×
	Unplanned revascularization rate			×	×	×	×	×	×	×
	All-cause mortality			×	×	×	×	×	×	×
	ICU readmission rate			×	×	×	×	×	×	×
	Readmission rate			×	×	×	×	×	×	×

Table 4 (continued)

	STUDY PERIOD								
	Eligibility	**Allocation**	**Post-allocation**						**Close-out**
TIMEPOINT	**0**	**t_0**	**t_1**	**t_2**	**t_3**	**t_4**	**t_5**	**t_6**	**t_x**
	Listed for CABG surgery	**Admission day**	**Post-operative day 1**	**Post-operative day 7**	**Discharge day**	**Follow-up 1 month**	**Follow-up 3 month**	**Follow-up 6 month**	**Follow-up 12 month**
PCMIKB		×	×	×	×	×	×	×	×
LVEF		×	×	×	×				
Pulmonary function		×	×	×	×				
Exercise endurance		×	×	×	×	×	×	×	×
ICU LOS					×				×
Total LOS									×
Total medical expenses									×

ERAS enhanced recovery after surgery, *ERAS-CaRe* ERAS with systematic integration of cardiopulmonary rehabilitation, *PCCs* post-operative cardiac complications, *PPCs* post-operative pulmonary complications, *LOS* length of stay

engaging referring physicians at our two primary hospitals to identify eligible patients and conducting information sessions for patients scheduled for CABG surgery. To maintain interest and minimize dropouts, we will provide comprehensive information about the trial's benefits, maintain regular communication with participants, and offer flexible scheduling for assessments and interventions. Our multidisciplinary team will closely monitor the recruitment process, making adjustments as necessary to achieve our enrollment goals.

Statistical analysis

Outcome analysis will be performed on an intention-to-treat (ITT) basis and presented with Kaplan-Meier curves [51]. Per-protocol analysis of all primary and secondary outcomes will also be performed in patients who adhere to the cardiopulmonary rehabilitation regimens as specified in the section on interventions.

The primary and secondary time-to-event outcomes, including the occurrence of post-operative cardiovascular complications, the occurrence of PCCs, the occurrence of PPCs, the occurrence of stroke, the occurrence of acute kidney injury, delirium rate, reintubation rate, early drainage tube removal rate, unplanned revascularization rate, inpatient all-cause mortality, ICU readmission rate, and the readmission rate. Total medical expenses will be analyzed with generalized linear models for gamma-distributed outcome (dependent on the validity of the distributional assumption). For secondary outcomes with normal and non-normal distributions, including PCMIKB, cardiac function, pulmonary function, exercise endurance, ICU LOS, and total LOS, group differences will be estimated with mixed effects linear regression.

Data is assumed to be missing at random (MAR). The validity of assumptions about missing data and possible effects of missing values on results will be evaluated as delineated in the sensitivity analysis [52]. To examine the effects of unit-missing values, that is, dropout from the study, all analyses will be repeated with inverse probability weights derived from propensity scores for dropout estimated from baseline variables and outcomes at previous time points. Several scenarios using counterfactual violating the MAR assumption will also be calculated to estimate possible effects of such violation on the results [53]. To examine the effects of item-missing values, multiple imputation using chained-equations will be performed. All main analyses will be performed without adjustments [54]. To analyze potential effects of confounders, all analyses will be repeated with adjustments for patient characteristics at baseline that may have an impact on the outcomes among groups, including age, gender, weight, height, BMI, comorbidities, smoking status, smoking index, physical status.

The null hypothesis is that systematically embedding CR within ERAS plays no role, that is, groups do not differ with regard to analyzed outcomes. In general, 4-group trials are compatible with 6 different types of analysis for the comparison of groups, and all 6 pairwise comparisons between groups will be performed. 2-tailed tests will be Bonferroni adjusted for multiplicity of testing, which yields an acceptable alpha error of 0.008. All test statistics will be reported with 99.2% CIs. All analyses will be performed using Stata version 16 or later (StataCorp, College Station, TX, USA).

Discussion

Patients undergoing CABG surgery continue to experience cardiopulmonary complications including myocardial infarction and pneumonia [1]. While ERAS-Cardiac can contribute to reduce postoperative complications, length of hospital stay (LOS), and associated medical expenses [13, 32, 35, 44], it lacks specialized strategies and points of entry for rehabilitation interventions which might further contribute to improved outcomes. Post-CABG CR [1, 22], is a Class 1 A recommendation of the American Heart Association/American College of Cardiology and the European Society of Cardiology. Yet, there is a noticeable absence of a standardized intervention timelines and content. For this reason, we developed a CR framework that can be embedded in ERAS programs tailored to CABG patients. Moving beyond the limited focus of earlier research, our study integrates a full spectrum of perioperative CR-ERAS interventions and further aims to determine optimal timing of rehabilitation interventions within ERAS. The embedded rehabilitation program suggested here moves beyond early mobilization and incorporates position management, respiratory muscle training, airway clearance, and aerobic exercises [24, 25, 55].

Our study navigates through challenges such as ensuring adherence to the ERAS-CaRe plan and maintaining uniformity across interventions. We tackle these through meticulous planning and stringent adherence protocols. Therapists are integral to this process, ensuring compliance by accompanying patients throughout the intervention and highlighting the benefits of CR. This proactive approach is tailored to boost patient engagement and program fidelity.

Nonetheless, we also found some limitations during the process, and made some attempts to solve them. First, the short hospital stays typical for CABG patients limit the window for rehabilitation interventions, this particularly applies to the pre-surgery phase. For this reason, we foresee outpatient visits and remote consulting

sessions instructing patients on home-exercise and other measures. Second, although we have established standardized procedures, the details of treatment may vary from center to center and from therapist to therapist. To address this issue, we provided standardized training to each therapist at the beginning of the project. At the same time, the head of the sub-center will evaluate the therapists' operation in the hospital every 6 months. Third, some of the outcomes require long-term follow-up and there is patient shedding. We have a dedicated staff for postoperative follow-up, and we review the patient's condition through telephone contact and free clinics. Fourth, cardiopulmonary rehabilitation interventions cannot be double-blind, and patients may be conflicted because of inconsistencies in the rehabilitation intervention programs between the four groups. Fifth, there are no guidelines summarizing standardized processes for CR programs and interventions, and our intervention frequency and content were designed based on the literature and recommendations from those with clinical experience. We combined ERAS and CR interventions, but lacked a gradient progression training approach for CABG patients of different ages. To address this, we will monitor the patients' blood pressure and heart rate during the intervention to ensure the safety of their training. Meanwhile, in the aerobic exercise component, we will personalize the exercise for patients who cannot perform the intended intervention.

By seamlessly integrating CR into the ERAS pathway, our trial strives to enhance patient outcomes, aiming to reduce complications and foster overall recovery. This novel approach promises to establish a new benchmark in post-CABG care, championing a more holistic and patient-centric recovery model. We anticipate that the developed ERAS-CaRe results in a significant reduction in postoperative cardiopulmonary and other complications, shorter hospital stay, decreased medical expenses, and enhanced quality of life post-surgery.

Abbreviations

ACBT	Active Circulatory Breathing Technique
AD	Autogenic Drainage
BC	breathing control
FET	forced exhalation technique
CABG	coronary artery bypass graft
CAD	coronary artery disease
CR	cardiopulmonary rehabilitation
CR-ERAS	cardiopulmonary rehabilitation based on ERAS Programs
cTnT	serum cardiac troponin T concentration
CRF	case report forms
DSMC	data safety monitoring committee
ERAS	enhanced recovery after surgery
ERAS-Cardiac	ERAS program for cardiac surgery
ERAS-CaRe	ERAS with systematic integration of cardiopulmonary rehabilitation
hs-CRP	hypersensitive C-reactive protein
ICU	intensive care unit
LOS	length of stay
LVEF	left ventricular ejection fraction
METs	metabolic equivalents
MGS	Melbourne group scale
PCI	percutaneous coronary intervention
PCCs	post-operative cardiac complications
PMI	periprocedural myocardial infarction
PPCs	post-operative pulmonary complications
RCTs	randomized controlled trials
SOP	standard operation procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03286-1.

Additional file 1. Studies for ERAS in cardiac surgery focusing on complications (XLS 17 kb).

Additional file 2. Studies for cardiopulmonary rehabilitation in cardiac surgery focusing on outcomes (XLS 18 kb).

Additional file 3. Ethics English (PDF 506 kb).

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Authors' contributions
All authors contributed to the study conception and design. YZ, XWW, Jan and YQY conceived and designed the study. YQY and LW drafted and revised the protocol. XTZ DJP PL and XHZ is coordinating the trial and revised the study design and protocol. YWL planned the statistical analysis. YQY, XTZ, DJP, SRL and XHZ is responsible for data management. YQY, XTZ, DJP, YZ, SRL, YC, LFX, CYL and WJJ are responsible for data acquisition, protocol adherence, and trial co-ordination. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requests.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University (Reference No. 2023-SR-348). Modifications to the study protocol in this trial, including eligibility criteria, intervention, outcome measures, or analytical methods, will be performed under the vigilant supervision and endorsement of the respective review committees. Informed consent was obtained from all individual participants included in the study.

Consent for publication
The authors affirm that human research participants provided informed consent for publication of the images.

Competing interests
The authors declare no competing interests.

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