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Effect of prehabilitation-related **DIET**ary protein intake on **Q**uality **o**f **R**ecovery after elective cardiac surgery (DIETQoR) study: protocol of a randomised controlled trial

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Abstract

Introduction: Protein malnutrition is associated with higher risks of postoperative complications, mortality, prolonged postoperative stays in hospital, slower physical and mental recovery after surgery, and lower subsequent health-related quality of life. To reduce the risk of postoperative morbidity and mortality, nutritional prehabilitation programs have been developed recently to build up patient's nutritional reserve to withstand the stress of surgery. The intervention involves nutritional screening and counselling, and increasing dietary protein intake in protein-malnourished patients in the several weeks before surgery. However, there are few well-conducted preoperative studies to examine the effect of increasing dietary protein intake on the quality of recovery of malnourished patients after elective cardiac surgery.

Aim and objective: To compare the quality of postoperative recovery in patients with or without nutritional prehabilitation that includes supplementary dietary protein.

Method and analysis: In this randomised controlled trial of malnourished patients undergoing major elective cardiac surgery, 132 patients will be randomised to receive nutritional prehabilitation (target-adjusted whey protein powder supplementation and an individualized 1-hour session/week counselling by a dietician one month before operation date) or standard care (no nutritional prehabilitation). Primary outcomes will be the quality of recovery after surgery (15-item Quality of Recovery on the third postoperative day and Days (alive and) at home within 30 days). Secondary outcomes will include changes in the World Health Organization Disability Assessment Schedule 2.0, health-related quality of life (EQ-5D), and Cardiac Postoperative Morbidity Survey. An outcomes assessor will be blinded to the treatment allocation. Appropriate univariate analyses, generalized estimating equations and multiple regressions will be performed for intention-to-treat and per-protocol analyses.

Ethics and dissemination: The Joint CUHK-NTEC Clinical Research Ethics Committee approved the study protocol (CREC Ref. No.: 2021.703). The findings will be presented at scientific meetings, peer-reviewed journals and to study participants.

Trial registration number: Chinese Clinical Trial Registry (ChiCTR2200057463); Pre-results

Strength and limitations of this study

- This is the first single-centre, pragmatic, two-armed, parallel, superiority, blinded randomised controlled trial of the effect of preoperative nutritional counselling and dietary protein supplementation (nutritional prehabilitation) on the quality of recovery after surgery
- Due to the nature of the nutritional prehabilitation intervention, patients will not be blinded to the treatment allocation (nutritional prehabilitation versus no prehabilitation)
- To reduce measurement bias, blinded outcome assessors will collect post-intervention outcomes from the time of surgical admission until 30 days after surgery
- Generalisability to other settings with structurally different multimodal prehabilitation programs for cardiac surgery may be limited.

INTRODUCTION

Protein is an essential nutrient for good health and accounts for all building blocks in the body.[1] Elderly patients often have inadequate daily dietary protein intake, putting them at moderate to high risk of malnutrition.[2] Protein malnutrition is a state of deficiency or excess protein intake, imbalance of essential components, or impaired protein utilization that produces a measurable change in the body composition and function.[3]

In cardiac surgical patients, the prevalence of preoperative malnutrition varies widely from 17%[4] to 46%[5] depending on the screening methods used. The causes and mechanisms of preoperative malnutrition are complex in cardiac surgical patients. Key factors that may influence the prehospital nutritional state include: chronic starvation, comorbid inflammatory illnesses, age, weight loss over the preceding six months, low body mass index (BMI), functional status, frailty and medications.[6] A lower BMI, New York Heart Association IV class heart insufficiency, mitral valve insufficiency and renal failure were factors associated with a two to four fold higher risk of preoperative malnutrition.[7]

Protein requirements are elevated in response to surgery as protein synthesis is required for immune function and wound healing.[8] However, there is no consensus amongst professional nutritional societies on the exact target for protein intake for surgical patients.[9] Current consensus guidelines[10,11] focus on total quantity of protein intake but it is unclear if quality of protein intake affects patient outcomes. Goldfarb and colleagues found that the mean (SD) protein intake was 1.3 (0.5) g/kg/day, 0.7 (0.3) g/kg/day and 1.3 (0.6) g/kg/day in the preoperative, early postoperative, and post-discharge periods respectively but its effect on postoperative outcomes were unclear.[12] In another study of 100 well-nourished patients scheduled for cardiac surgery, there was no association between low preoperative protein intake (<0.98g/kg/day) and increased risk of postoperative outcomes (organ failure, bleeding, infection, prolonged length of stay, mortality).[13]

Significance of the present study

Protein malnutrition is associated with a higher risk of postoperative complications and mortality, prolonged postoperative stays in hospital, slower physical and mental recovery after surgery, and lower subsequent health-related quality of life; all factors associated with substantially higher healthcare costs [4,5,14-17] Poor preoperative nutritional status was associated with lower physical function levels (handgrip strength, 6-minute walk test (6MWT), days to independent walking after surgery) and prolonged intensive care unit (ICU) and hospital stays.[17] However, many healthcare professionals do not recognize protein malnutrition, may under-report malnutrition, or poorly document patient's body mass index and food intake during the patient's hospital stay.[18] This severely limits the time available before surgery for any nutritional intervention to take effect that could reduce the risk of postoperative morbidity and mortality.

In many centres, multimodal prehabilitation provides a unique opportunity to optimise the patient's physiological reserve in the 4 to 8 weeks before surgery to withstand the surgical stress response.[19] Multimodal prehabilitation includes individualised structured exercises (aerobic and resistance training), nutrition counselling and supplementation, and psychological support (eg. standardised multi-media patient education). This study protocol focuses on nutritional prehabilitation for malnourished patients to increase their dietary protein intake for building up their nutritional reserve to withstand the stress of surgery. Whether such preoperative nutritional intervention in malnourished patients several weeks before hospital admission improves their quality of recovery (QoR) after cardiac surgery is currently unknown.

Study Objectives and hypotheses

The primary objective of this randomised controlled trial (RCT) is to evaluate the effect of nutritional prehabilitation with high-quality dietary protein intake on the QoR after elective cardiac surgery in malnourished patients. There are several secondary objectives:

a. To determine whether dietitian guided counselling increases preoperative dietary protein intake in malnourished patients scheduled for elective cardiac surgery undergoing nutritional prehabilitation.
b. To evaluate the effect of nutritional prehabilitation on the length of postoperative stay in malnourished patients undergoing elective cardiac surgery.
c. To describe the interaction between preoperative dietary protein intake and physical activity on quality of recovery after elective cardiac surgery in malnourished patients undergoing nutritional prehabilitation.

The primary hypothesis is that high-quality dietary protein intake will improve the quality of QoR after cardiac surgery in malnourished patients undergoing nutritional prehabilitation.

The secondary hypotheses are the following:

a. Compared to usual care, dietician guided counselling will increase preoperative dietary protein intake in malnourished patients scheduled for elective cardiac surgery undergoing nutritional prehabilitation.
b. Nutritional prehabilitation will shorten the length of postoperative stay in malnourished patients undergoing elective cardiac surgery.
c. The combination of increased preoperative dietary protein intake and physical activity are associated with higher QoR scores after cardiac surgery in malnourished patients than either alone.

METHOD AND ANALYSIS

Study design

This single-centre, pragmatic, two-armed, parallel, superiority, blinded randomised controlled trial will be conducted at the Prince of Wales Hospital in Hong Kong, a university teaching hospital. Participants will be randomly allocated to either nutritional prehabilitation or usual care (no nutritional prehabilitation) with 1:1 allocation. Block randomisation with randomly selected block sizes will be performed according to a computer-generated sequence by one

of the research staff not involved in the screening, recruitment, or data collection. The treatment allocation will be concealed in consecutively numbered sealed opaque envelopes, to be opened by the dietician after written informed consent for the study has been obtained and after baseline Food Frequency Questionnaire (FFQ),[20] Clinical Frailty Scale (CFS)[21] and exercise capacity measurements have been conducted. The study has been designed with reference to the CONsolidated Standards Of Reporting Trials (CONSORT) statement,[22] and reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[23] The trial has been registered on the Chinese Clinical Trials Registry (ChiCTR2200057463). An overview of the study design is provided in Figure 1.

INSERT FIGURE 1 HERE

Study setting and population

This study will be conducted at the Prince of Wales Hospital in Hong Kong, a 1807-bed tertiary hospital with a dedicated Pre-Operative Assessment Clinic (POAC) and prehabilitation facilities. All elective cardiac surgical patients will be routinely admitted to a 23-bed ICU for early postoperative care and monitoring with 1:1 nursing at all times, with an expectation of discharge from ICU to a high-dependency cardiac ward within 24 hours after surgery.[24] Adults patients undergoing major to ultra-major elective cardiac surgery (coronary artery bypass graft, with or without valvular repair/replacement) will be recruited. Patients will only be recruited once; only the first attempt and assessment results will be recorded for patients who require follow-up or repeated surgery. The inclusion and exclusion criteria are shown in Table 1. We will record the reasons for exclusion.

Table 1. Eligibility criteria for the randomized controlled trial

Inclusion criteria	Exclusion criteria
1. Adults (no age restriction) undergoing elective or non-emergent major to ultra-major cardiac surgery (CABG, valve surgery or combined) 2. MUST>0 or FFMI<17 for men or FFMI<15 for women or SMI<7 for men or SMI<5.7 for women 3. Patients with estimated ≥4 weeks of surgical waiting list time	1. Redo or emergency cardiac surgery 2. Major comorbidities precluding surgery, are mentally incompetent, any current disorder impairing accurate and objective completion of the malnutrition assessment and nutritional screening questionnaires, or are unable to understand Chinese or English. 3. CKD not on dialysis requiring low protein diet, advanced stage CKD or end-stage renal disease on dialysis with protein requirements of 1.0 to 1.2 g/kg body weight/day will be excluded[25] 4. Patients with liver diseases and at risk for hepatic encephalopathy 5. Physical limitations that would preclude regular attendance to outpatient nutritional prehabilitation sessions 6. Seen by a dietician in the last 6 months 7. Patients with whey protein allergy

CABG=coronary artery bypass graft; CKD=chronic kidney disease; FFMI=fat free mass index; MUST=Malnutrition Universal Screening Test; SMI=skeletal mass index

Screening

Patients on the elective cardiac surgery waiting list are routinely assessed at the POAC clinic several weeks before the scheduled operation date. After written informed consent, patients will complete the Malnutrition Universal Screening Test (MUST) questionnaire[26] and undertake a body composition test using a bioelectrical impedance analysis device (InBody 270, InBodyUSA, Cerritos, CA) to measure fat free mass index (FFMI) and skeletal mass index (SMI) for study eligibility determination. For the purpose of this study, preoperative malnutrition will be defined as a MUST > 0 or FFMI < 17 for men or FFMI < 15 for women or SMI < 7 for men or SMI < 5.7 for women.[27]

If the inclusion criteria are met, all participants will be interviewed by a dietician to assess their usual dietary intake (frequency and usual quantity) over the past 6 months using the

locally validated semi-quantitative Food Frequency Questionnaire (FFQ)[20] at baseline. For the purpose of this study, only broad food categories with food containing protein from the 288 local food items FFQ will be used (i.e. vegetables and beans, fruits, meats, fish and seafood, eggs, dairy products and beverages.).[20] Mean daily protein intake from food items consumed will be estimated using the nutrition analysis software Food Processor Nutrition Analysis and Fitness software cloud service version 11.1 (ESHA Research, Salem, USA) including local foods selected from food composition tables from China and Hong Kong. Another research staff member, blinded to treatment allocation, will use the same modified FFQ at hospital admission before surgery in all patients to compare changes in protein intake between treatment groups.

The exercise capacity and physical activity level will also be collected at baseline and immediately before surgery in all study participants (Table 2). Although cardiopulmonary exercise testing (CPET) is the gold standard for measuring exercise capacity objectively, access to CPET is very limited in the prehabilitation period. Therefore, we will use the 6-minute walk test (6MWT) to measure the exercise capacity. The minimal clinically important difference for 6MWT is 14.0 to 30.5 metres in population with cardiac and pulmonary diseases.[28] The Chinese version of Veterans Specific Activity Questionnaire (C-VSAQ)[29] describes the different intensities of daily activities with corresponding metabolic equivalents (METs) on a scale ranging from 1 MET to 13 METs. Participants will be asked to indicate the highest MET that they are able to achieve routinely. The individual's exercise capacity will then be age-adjusted.[29]

Table 2. Assessment overview

Assessment	Baseline	Prehospital period	Admission	POD3	POM1
Enrolment					
Eligibility screen	X				
Informed consent	X				
Malnutrition screening (MUST, FFMI, SMI)	X		X		
Demographic and comorbidity data	X				
Food Frequency Questionnaire	X		X		
Clinical Frailty Scale, 6MWT, C-VSAQ	X		X		
Randomization	X				
Nutritional Intervention					
Subjective Global Assessment, 24-h food recall		X			
Protein supplement compliance/adverse effect		X			
Outcomes					
Primary					
15-item Quality of recovery				X	
DAH30					X
Secondary					
WHODAS	X				X
EuroQol EQ-5D questionnaire	X				X
Cardiac Postoperative Morbidity Survey				X	

DAH30=Days at home within 30 days of surgery; FFMI=fat free mass index; MUST=Malnutrition Universal Screening Test; POD3=postoperative Day 3; POM1=postoperative 1 month; SMI=skeletal mass index; WHODAS=World Health Organization Disability Assessment Schedule 2.0 questionnaire

Blinding

Due to the nature of the intervention and requirements of informed consent, trial participants will not be blinded to the treatment allocation. Study research personnel collecting the follow-up nutritional status and food frequency intake at hospital admission will be blinded to the treatment allocation. Outcome assessors will be blinded to the participant's group allocation.

Interventions

Control (standard care) arm

Patients in the control group will receive standard care with standardised surgical processes and perioperative care under existing protocols for preoperative patient education, standardised anaesthesia,[30] postoperative ICU sedation, analgesia and weaning from mechanical ventilation, perioperative physiotherapy, and early mobilisation.[24] In brief, the control group will receive unstructured preoperative health promotion/patient education, plus physical prehabilitation provided at the treating physician's discretion. Unstructured and general health education includes information on exercise and a healthy diet without a tailored nutritional plan and no focus on protein education. Both groups will have bioelectrical impedance analysis (FFMI and SMI) measured at baseline and immediately before surgery to determine any changes in body composition (Table 2).

Intervention (nutritional prehabilitation + standard care) arm

In addition to standard care, the nutritional prehabilitation group will receive individual 1-hour session/week counselling by a dietician, one month before scheduled operation date. The intervention involves a tailored approach to meet the nutritional needs of individual participants. This includes the following:

- Reviewing the patient's completed FFQ[20] to report on the amount of dietary protein intake consumed and net deficit daily protein intake
- Assessing the overall nutritional status using the Subjective Global Assessment[31] and a 24-hour diet recall at the initial visit
- Discussing why increasing dietary protein intake before surgery is important
- Educating patient about which foods contain high quality protein to eat (eg. chicken, fish, soy, lentils, nuts, brown rice[32]), and

- Prescribing the optimal amount of whey protein powder supplement (Beneprotein® sachets) to meet the target protein intake of 1.5 g/kg/day based on actual body weight or adjusted body weight for obese patients.
- Patients will be reminded via phone call one day before their nutritional counselling session

A Registered Dietitian (RD) will be responsible for safekeeping and dispensing of the whey protein powder supplement (Beneprotein®). Participants will be given enough sachets for one week to consume and some backup sachets. Each sachet provides 6g of protein (1 egg equivalent). They will also be given a ticked calender and asked to bring all the used sachets, unused sachets back each week to estimate the compliance rate.

Outcome measures

Primary outcome

1. Quality of Recovery (QoR)

The Chinese version of the 15-item Quality of Recovery (QoR-15)[33] will be used on postoperative Day 3. The QoR-15 includes the items measuring pain, physical comfort, physical independence, psychological support and emotional state.[33] The QoR-15 score ranges from 0 to 150, takes about 3 minutes to complete and has well established psychometric properties.[33] A poor symptom state (recovery) after surgery has been defined at a cut-off of <118.[33] Depending on patient's postoperative status, QoR-15 assessment may be deferred if the patient is unwell or unavailable. The QoR-15 assessment will be conducted at a later date after obtaining patient's agreement. The blinded outcome assessor will record the exact date of actual QoR-15 assessment.

2. Days (alive and) at home within 30 (DAH_{30}) days after cardiac surgery

The DAH is a patient-centred, generic outcome measure that will be used to measure the patient's overall recovery profile.[34] DAH is a composite measure that incorporates the details

on postoperative hospital length of stay, discharge to rehabilitation centre or nursing home, hospital readmissions, and postoperative deaths.[34] Three days difference is considered clinically meaningful.[35] The blinded outcome assessor will extract data from the electronic patient medical record to estimate the DAH_{30}.

Secondary outcomes

1. Disability-free survival at 30 days after surgery

New or residual disability after surgery is of particular concern to patients and healthcare professionals.[36] In this study, the changes in disability-free survival (baseline to postoperative 1 month, Table 2) will be measured using the Chinese (Hong Kong) version of the 12- item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 score that has been validated in surgical patients.[36] It will take five minutes to complete.[36] Patients will be asked to rate the difficulty in carrying out 12 specified activities on a 5-point Likert scale (0 = none to 4 = extreme) in the past 30 days. The total score will be converted to a scale from 0 (no disability) to 100 (maximum disability) by a blinded outcome assessor, with the following subcategories: none (0% to 4%), mild (5% to 24%), moderate (25% to 49%), severe (50% to 95%) and complete (96% to 100%) disability.[36] The 25% threshold will be used to define disability; an increase in the WHODAS score ≥ 8% from their baseline assessment will define new disability.[36]

2. Health-related quality of life

The changes (baseline to postoperative 1-month, Table 2) in health-related quality of life will be measured using the Chinese (Hong Kong) version of the EuroQoL EQ-5D.[37] Patients will be asked to rate their mobility, self-care, usual activities, pain/discomfort and anxiety/depression on five levels (no problems, slight problems, moderate problems, severe problems, extreme problems) and to rate their health state from 0 (worst imaginable) to 100 (best imaginable). The blinded outcome assessor will use the descriptive responses to estimate the EQ-5D utilities by applying a set of Hong Kong reference weights.[37]

3. Cardiac Postoperative Morbidity Survey (C-POM)[38]

The C-POM score quantifies the total morbidity burden and is currently the only validated measure of postoperative morbidity after cardiac surgery. It is a composite outcome that included the following 13 morbidity types: pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound, pain, endocrine, electrolyte, review and assisted ambulation. The blinded outcome assessor will collect the C-POM survey on the third postoperative day using information from the patient's medical records.

Other variables in data collection

Using a standardised data collection form, a research assistant will collect demographic (age, gender, BMI, education level, home living support, frailty level using CFS, comorbidities), adverse protein supplement effect as measured by elevated blood urea nitrogen (BUN) concentration BUN > 24 mg/dL (8.5 mmol/L),[39] American Society of Anesthesiologist's Physical Status, physical prehabilitation attendance, intravenous iron therapy during prehabilitation period, operation date, type of cardiac surgical procedure, duration of surgery, duration of anaesthesia, length of ICU and hospital stays. Possible contamination of control arm (ie. self-initiated changes in diet with protein supplement after providing study details) will be assessed by asking patients if they have made changes to eating habit or taken protein supplements immediately before surgery. An overview of the data collection process is shown in Table 2.

Sample size

A sample size of 60 in each group will have 90% power to detect a moderate to large quality of recovery effect (0.60) using a two group t-test with a 0.05 two-sided significance level (nQuery Advisor®, version 7.0). Allowing 10% loss to follow-up, a total of 132 patients will be required. No interim analysis has been planned.

Statistical methods

The data derived from the patient's FFQ at follow-up will be used to estimate each participant's mean protein quality score using the framework methodology outlined by Katz and colleagues.[32] Intention to treat and per-protocol analyses will be performed. We will consider satisfactory compliance with whey protein powder supplementation if the patient's intake is above 75% for the per-protocol analysis. Missing data will be checked and imputation of the missing data will be used to preserve power. Continuous variables will be reported as mean (SD) and median (IQR) as appropriate.

After checking for normality using the Shapiro-Wilk's test, we will perform independent Student's t-test or Mann-Whitney U test as appropriately to compare group differences for the magnitude of protein intake and quality, QoR-15, postoperative length of stay and DAH_{30}. We will use a generalised estimating equation with a Gaussian distribution, identity-link, exchangeable correlation with robust standard errors to estimate the mean difference in preoperative dietary protein intake and quality between treatment groups over time. Multiple regression will be used to examine the association between dietary protein intake and physical activity with 15-item QoR; an interaction effect of dietary protein intake change and physical activity change will be included in the model, after adjusting for other potential confounders (prehabilitation exposure, change in physical activity, frailty) using a directed acyclic graph approach in Figure 2. Statistical analyses will be performed using Stata version 17 (StataCorp, College Station, TX). The two-sided level of significance will be set at $P<0.05$.

INSERT FIGURE 2 HERE

Monitoring and data management

We will collect and manage the study data using REDCap electronic data capture tools[40] hosted at The Chinese University of Hong Kong. No interim analysis has been planned. No

formal data monitoring committee has been set up. There will be no formal data monitoring committee. However, the study progress and any unanticipated serious adverse events will be reported as part of an annual renewal application for local research ethics committee approval. An anonymised data set will be available after the publication of the completed study, following the deposition of the dataset into The Chinese University Research Data Repository (https://researchdata.cuhk.edu.hk/).

Patient and public involvement

Patients and the public were not involved in the development of the research question, the design of the study nor did they contribute to the editing of this document for readability or accuracy.

Ethics and dissemination

Before obtaining written informed consent (online supplemental material), the purpose of the study, procedures, risks and benefits of participation, and the time commitment involved will be explained to eligible patients by the study dietician. There will be no extra costs for patients who are allocated to the intervention group since the expenditure for every dietician consultation session will be reimbursed. We plan to disseminate the results to study participants by giving them a one-page plain language summary.

Patients may withdraw from the study without prejudice at any time during the study. Data will be kept confidential in secure offices of the Department of Anaesthesia and Intensive Care for seven years. Approval for the project (protocol version 1.1, 24/01/2022) was obtained from The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2021.703). We will notify the local research ethics committee and clinical trials registry about any protocol modifications in a timely manner. The study will adhere to local laws, Declaration of Helsinki and institutional policies.

DISCUSSION

The American Society for Enhanced Recovery and Perioperative Quality Initiative recommends that patients at risk of malnutrition be given preoperative oral nutritional supplements (immune-nutrition containing arginine/fish oil or high protein [minimum 18g protein/dose, 2 to 3 times/day) for a period of at least 7 to 14 days before surgery.[14] Of the 191 elective cardiac surgical patients in our recent unpublished audit, 51 (27%) had preoperative protein-malnutrition as determined by a dietician. Among these 51 patients, 38 (75%) were moderately malnourished while the rest were severely malnourished. These findings suggest that a substantial proportion of elective cardiac surgical patients are at risk of adverse malnutrition-related postoperative events.

Few well-conducted studies in North America or Western Europe provide a sound evidence-based approach to determining the potential or actual benefits of increasing dietary protein intake in malnourished patients before any elective surgery, and especially in cardiac surgical patients. A systematic review of 15 randomised controlled trials in 3831 mixed medical and surgical patients with malnutrition showed that nutritional support (parenteral nutrition, enteral nutrition, immunonutrition) was associated with a reduction in the risk of infection (relative risk [RR] 0.58, 95% CI: 0.50 to 0.68), non-infectious complications (RR 0.74, 95% CI: 0.63 to 0.88), a shorter length of hospital stay (mean difference [MD] -2.6, 95% CI: -5.1 to -0.2 days).[41]

Our intervention, an individualized tailored approach by a dietician, will establish an accurate estimate of the local prevalence of low dietary protein intake (<1.5 g/kg/day) presenting for major elective cardiac surgery. The trial will facilitate the feasibility and design of future studies of nutritional prehabilitation in all surgical patients after establishing the level of patient compliance to whey protein supplementation. The results of this RCT will enable us to establish magnitude of prehabilitation effect of increasing dietary protein intake on post-

operative length of hospital stay, and improving patient-centred outcomes within 30 days after cardiac surgery, using validated and reliable tools. The trial will also generate a clearer understanding of the possible additive or synergistic effects of improved dietary protein intake with physical prehabilitation on quality of recovery after surgery, especially in prefrail to frail patients. This should further clarify prehabilitation's effectiveness based on nutritional optimisation alone.

Trial status

The patient recruitment started on September 1 2022. We expect patient recruitment and one month of follow-up to be completed by August 30 2025.

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Author contributors

The protocol was jointly written by HHTC and AL and was critically reviewed DKWY, LCSC, MKHW, SSYY, MJU, RHW, GMJ. All authors except RHW, LCSC and SSYY were involved in the study concept. All authors were involved in the design of the study and approved the final version of the manuscript.

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Competing Interests

None declared.

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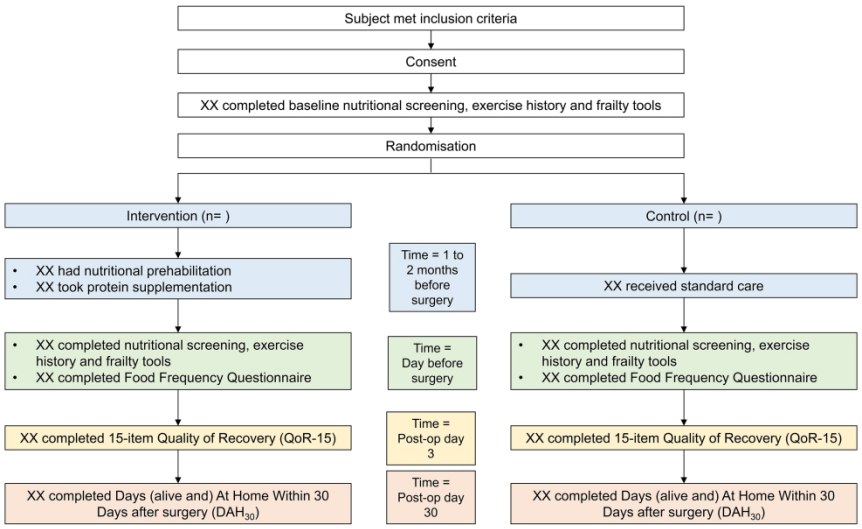
Figure Legends

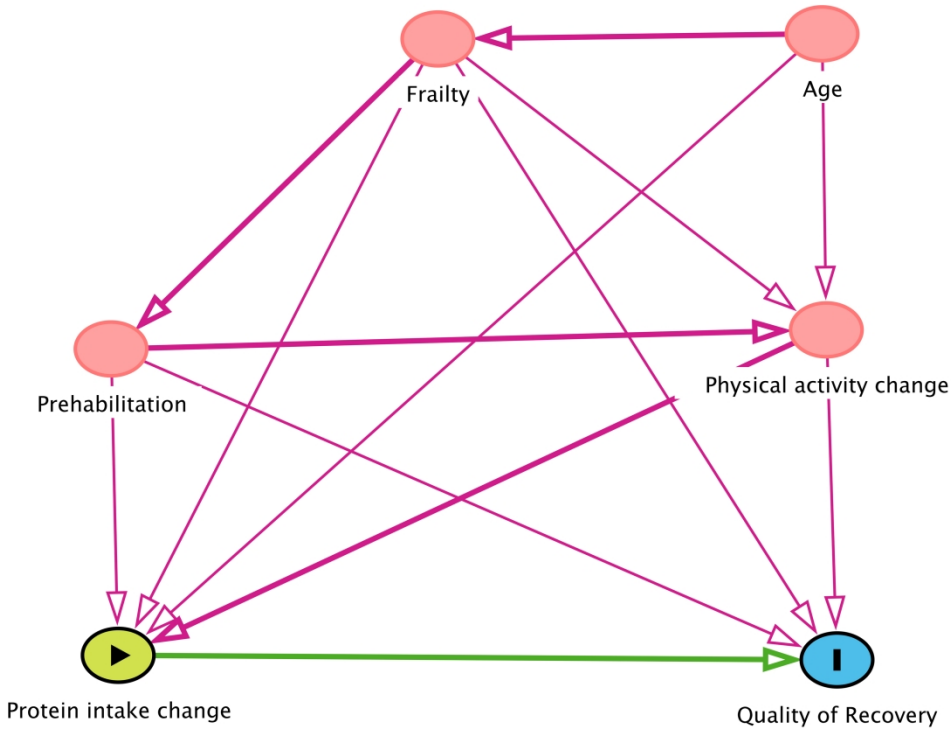
Figure 1. Patient flow diagram

Figure 2. Directed acyclic graph using DAGitty software version 3.0. Assumptions made in the nutritional prehabilitation (exposure) and quality of recovery (outcome) relationship to identify the set of variables needed for confounding adjustment. Green circle represents ancestor of exposure. Red circle represents ancestor of exposure and outcome. All red arrows lie on open biasing paths. Green arrow lies on open causal path. The bold arrows indicate no corresponding indirect paths (no causal effect between variables exists if arrow is removed). Thin arrows indicate that there are indirect pathways between variables.



Patient flow diagram

279x157mm (300 x 300 DPI)



Directed acyclic graph using DAGitty software version 3.0. Assumptions made in the nutritional prehabilitation (exposure) and quality of recovery (outcome) relationship to identify the set of variables needed for confounding adjustment. Green circle represents ancestor of exposure. Red circle represents ancestor of exposure and outcome. All red arrows lie on open biasing paths. Green arrow lies on open causal path. The bold arrows indicate no corresponding indirect paths (no causal effect between variables exists if arrow is removed). Thin arrows indicate that there are indirect pathways between variables.

147x107mm (600 x 600 DPI)

Version 1.1 (25.1.2022) Patient No:

香港中文大學
麻醉及深切治療學系

病人參與研究同意書

研究主題

一項隨機對照測試擇期心臟手術前服食相關膳食蛋白質對手術後身體康復質素的影響

研究背景

年長病人的膳食蛋白質攝入量通常不足，增加患上蛋白質營養不良的風險。 蛋白質營養不良是指蛋白質攝入量不足、過多、重要成分失衡或效用受損，以致身體功能和結構發生顯著變化。 手術後出現嚴重的後果包括有較高的併發症、住院時間較長、身心恢復較慢、後期與健康相關的生活質素降低以及死亡。

營養康復計劃包括在手術前給患上蛋白質營養不良的病人增加膳食蛋白質攝入量。 手術病人需要更高的蛋白質，以增強免疫功能和傷口癒合。 然而，只有少數優質的研究提供有關增加膳食蛋白質攝入量的方法。 因此，我們邀請您參與本研究。

研究目標

1. 確定患上營養不良的病人參與營養康復治療在營養師指導下於擇期心臟手術前改變膳食蛋白質攝入水平的可能性。
2. 評估患上營養不良的病人參與營養康復治療接受高質素膳食蛋白質攝入對擇期心臟手術後身體康復質量的影響。
3. 評估患上營養不良的病人參與營養康復治療對住院時間的影響。
4. 確定患上營養不良的病人參與營養康復治療於擇期心臟手術前進食膳食蛋白質和身體活動這二個項目協同效應下對手術後身體康復的影響。

程序

研究助理/研究調查員/護士將在手術前向您解釋研究的風險和益處。我們需要獲得您的書面知情同意書。

如果您同意參加，我們需要您完成以下項目：

- 營養不良通用篩查工具問卷(MUST)
- 為確保研究參與者資格，我們會使用生物電阻抗分析設備（InBody 270，InBodyUSA，Cerritos，CA）進行身體成分測試，以測量無脂肪質量指數 (FFMI) 和骨骼肌質量指數 (SMI)。您需要站在特殊的稱重設備上進行測量，大約需要 5 分鐘。
- 世界衛生組織 12 項殘疾評定方案 2.0 英語/中文版(香港) (WHODAS)
- 歐洲五維健康量表 英語/中文版(香港) (EuroQoL EQ-5D)

如果您符合入選標準，我們需要您完成以下項目：

- 由註冊營養師使用食物頻率問卷評估您過去 6 個月的慣常飲食攝入量。大約需要 30 分鐘。
- 6 分鐘步行測試 (6MWT) 和退伍軍人特定活動問卷 英語/中文版(C-VSAQ) 以評估您的運動能力和身體活動。大約需要 1 分鐘。

在上述評估之後，您將被隨機分配（這意味著您將有同等的機會進入兩組中的其中一組）：

- 第 1 組（營養康復計劃和蛋白質補充）或
- 第 2 組（目前的標準護理）。

如果您被隨機分配到營養康復計劃組，您將在預約手術前一個月在門診接受註冊營養師提供每週一小時的單獨諮詢療程。註冊營養師將

o 與您一起查看您的飲食攝入記錄
o 在初次就診時使用主觀總體評估 (SGA) 和 24 小時飲食回顧進行詳細的營養評估
o 與您討論為什麼在手術前增加膳食蛋白質攝入量的重要
o 向您介紹含有優質蛋白質的食物（例如雞肉、魚、大豆、扁豆、堅果、糙米），以及
o 開出最優質的乳清蛋白粉補充劑（Beneprotein® 小袋），以符合您每天 1.5 克/公斤的目標蛋白質攝入量。註冊營養師會負責乳清蛋白粉補充劑的保管和分配。 乳清蛋白粉未經素食認證； 如果你是素食主義者，你可以選擇拒絕這個提議。您將獲得足夠 1 週使用的補充劑小袋和一些備用補充劑小袋。我們會給您一個打勾的日曆，並要求您每週帶回所有使用過和未使用的小袋，以估計攝入量的規定率。

營養輔導課程的門診及跟進課程在日間手術中心進行，為期大約 4 週每週一次。首次及隨後的就診費將由醫院管理局收取，診費分別為港幣 135 元及港幣 80 元（醫管局收費率）。 您簽署付款收據後我們將退還診費。 因此，參與本研究無需額外費用。

如果您被隨機分配到對照組，您將接受常規的護理但沒有營養康復治療。

<u>在手術前一天，您將需要再次完成五個項目，大約需要 30 分鐘：</u>

1 營養不良通用篩查工具問卷(MUST)和食物頻率問卷
2. 使用生物電阻抗分析設備 (InBody 270, InBodyUSA, Cerritos, CA) 進行身體成分測試，以測量無脂肪質量指數 (FFMI) 和骨骼肌質量指數 (SMI)
3. 6 分鐘步行測試 (6MWT) 和英語/中文版退伍軍人特定活動問卷 (C-VSAQ) 以評估您的運動能力和身體活動
4. 世界衛生組織 12 項殘疾評定方案 2.0 英語/中文版(香港) (WHODAS)
5. 歐洲五維健康量表 英語/中文版(香港) (EuroQoL EQ-5D)

手術後，我們的研究團隊將在您住院期間跟進：

1. 手術後第 3 天
   - 15 項關於康復質素的問卷 英語/中文版(QoR-15)
   - 需時 3 分鐘
   - 如果您在手術後第 3 日仍感到不適，我們會徵得您的同意後，推遲進行評估

您出院後，我們的研究團隊會通過電話作進一步跟進，我們需要您完成：

2. 手術後第 30 天（1 個月）
   - 12 項世界衛生組織殘疾評估表 英語/中文版（香港）(WHODAS）
   - 歐洲五維健康量表 英語/中文版（香港）(EQ-5D)
   - 需時約 10 分鐘

研究護士/調查員會從您的病歷紀錄中收集相關資料。

利益

如果您參加此項研究，我們會在手術前評估您的營養狀況。 註冊營養師會提供營養建議和改善營養狀況的提示。 您可能會免費獲得蛋白質補充劑以提升蛋白質儲存量和增加肌肉量的可能性。 參加這項研究不需要額外的費用。 如果您屬於營養康復計劃組，每次培訓課程的費用可以報銷，因此參加本研究不需要額外費用。

風險

上述的營養評估和問卷調查都不會有額外風險。

倫理審核

此項研究已獲得香港中文大學-新界東醫院聯網臨床研究倫理聯席委員會批准(電話：3505-3935)。

保密

由此項研究獲取的所有資料將被視為機密，只作研究用途。我們會依據法律保障保密處理您的個人資料。 香港中文大學 – 新界東醫院聯網臨床倫理聯席委員會是其中一個部門有權以倫理審查為用途而接觸您有關這項研究的紀錄。 發表研究論文後，您的電子版研究數據將被存儲 7 年。

問題

研究員已和您討論並回答您的問題。若有其它疑問，您可致電 3505-2087 聯絡研究負責人張小姐，或 3505-2735 聯絡李煥坤教授。您亦可以選擇致電 3505-3935 聯絡香港中文大學 – 新界東醫院聯網臨床研究倫理聯席委員會查詢您在這項研究的權利。

拒絕參加及退出的權利

參加與否純屬自願，任何決定也不會影響您將獲得的醫療服務。您有權隨時退出此研究。

Version 1.1 (25.1.2022) Patient No:

CONSENT TO PARTICIPATE IN A RESEARCH STUDY
Department of Anaesthesia and Intensive Care
The Chinese University of Hong Kong

Title of Study

Effect of prehabilitation-related dietary protein intake on quality of recovery after elective cardiac surgery: a randomized controlled trial

Background

Elderly patients often have inadequate dietary protein intake, putting them at higher risk of protein malnutrition. Protein malnutrition is deficiency or excess of protein intake, imbalance of essential components, or impaired utilization that leads to a notable change in body function and composition. Major negative outcomes may include a higher risk of complications after surgery, longer stays in hospital, slower physical and mental recovery, lower later-on health-related quality of life, and death.

Nutritional prehabilitation involves increasing dietary protein intake in protein-malnourished patients before surgery. Protein requirements are higher in surgical patients to boost immune function and wound healing. However, there are few well-conducted studies to guide an appropriate approach to increase dietary protein intake. Therefore, you are invited to participate in this study.

The objectives of this study

1. To determine the potential for dietitian-guided change in preoperative dietary protein intake levels in malnourished patients scheduled for elective cardiac surgery undergoing nutritional prehabilitation.
2. To evaluate the effect of high-quality dietary protein intake on the quality of recovery after elective cardiac surgery in malnourished patients undergoing nutritional prehabilitation.
3. To evaluate the effect of nutritional prehabilitation on the length of postoperative stay in malnourished patients undergoing elective cardiac surgery.
4. To determine the synergistic effect of preoperative dietary protein intake and physical activity on quality of recovery after elective cardiac surgery in malnourished patients undergoing nutritional prehabilitation.

Procedures

The research assistant/research investigators/nurse will explain the risks and benefits of the study to you before surgery. Written informed consent will be obtained from you.

If you agree to participate, you will be asked to:

- Complete the Malnutrition Universal Screening Tool (MUST) questionnaire
- Undertake a body composition test using a bioelectrical impedance analysis device (InBody 270, InBodyUSA, Cerritos, CA) to measure Fat-Free Mass Index (FFMI) and Skeletal Muscle Mass Index (SMI) for study eligibility determination. This involves standing on a special weighing device for measurements, and takes about 5 minutes to do.
- Complete the English/Chinese (Hong Kong) version of the 12- item World Health Organization Disability Assessment Schedule (WHODAS) 2.0
- Complete the English/Chinese (Hong Kong) version of the EuroQoL EQ-5D

If the inclusion criteria are met, you will be:

- Seen by a Registered Dietitian to assess your usual dietary intake using a food frequency questionnaire over the past 6 months. This takes about 30 minutes.

- Assessed on your exercise capacity and physical activity using the 6-minute walk test (6MWT) and the English/Chinese version of Veterans Specific Activity Questionnaire (C-VSAQ). This takes about 1 minute to answer.

After the above-mentioned assessments, you will be randomized (this means you will have an equal chance of being in one or other of the groups) to either:

- Group 1 (nutritional prehabilitation and protein supplementation) or
- Group 2 (the current standard of care).

If you are randomized to the nutritional prehabilitation group, you will receive individual 1-hour session/week counseling by a Registered Dietitian, one month before your scheduled surgery at an outpatient clinic. The Registered Dietitian will:

- Review your dietary intake record with you
- Perform a detailed nutritional assessment using the Subjective Global Assessment (SGA) and a 24-hour diet recall at the initial visit
- Discuss with you why increasing dietary protein intake before surgery is important
- Introduce to you foods that contain high-quality protein (eg. chicken, fish, soy, lentils, nuts, brown rice), and
- A Registered Dietitian will prescribe the optimal amount of whey protein powder supplement to meet your target protein intake of 1.5 g/kg/day. The Registered Dietitian (RD) will be responsible for safekeeping and dispensing of the whey protein powder supplement. Whey protein powder is not vegetarian certified; you may choose to decline the offer if you are on a vegetarian diet. You will be given enough sachets for 1 week to consume and some backup sachets. You will also be given a ticked calendar and asked to bring all the used sachets, unused sachets back each week to estimate the compliance rate.
- The outpatient clinic and follow-up sessions (once/week, ~4 weeks) for the nutrition counselling session will be charged by the Hospital Authority (HA). The initial and subsequent outpatient consultations/visits fees at Day of Surgery will be HK$135 and HK$80 (HA rates) respectively. And you will be reimbursed in cash after signing the receipt of payment. Thus, there is no extra cost for participating in this study.

If you are randomized to the control group, you will receive our usual routine care of no nutritional prehabilitation.

On the day before your surgery, you will be asked again to:

1. Complete the MUST questionnaire and food frequency questionnaire
2. Undertake a body composition test using a bioelectrical impedance analysis device (InBody 270, InBodyUSA, Cerritos, CA) to measure Fat-Free Mass Index (FFMI) and Skeletal Muscle Mass Index (SMI)
3. Assess your exercise capacity and physical activity using the 6-minute walk test (6MWT) and the English/Chinese version of Veterans Specific Activity Questionnaire (C-VSAQ)
4. Complete the English/Chinese (Hong Kong) version of the 12- item World Health Organization Disability Assessment Schedule (WHODAS) 2.0
5. Complete the English/Chinese (Hong Kong) version of the EuroQoL EQ-5D

This will take about 30 minutes to complete all 5 steps.

After your surgery, our research team will follow up with you while in the hospital:

1. On postoperative Day 3

- You will be asked to complete the English/Chinese version of the 15-item Quality of Recovery (QoR-15)
- This will take 3 minutes to complete

If you are feeling unwell on postoperative day 3, we will obtain your agreement and conduct the assessment at a later date

After you are discharged from the hospital, our research team will call you over the phone to further follow up, and you will be asked to complete:

2. On postoperative Day 30 (1 month)
   - English/Chinese (Hong Kong) version of the 12-item World Health Organization Disability Assessment Schedule (WHODAS)
   - English/Chinese (Hong Kong) version of the EuroQoL EQ-5D
   - This will take about 10 minutes to complete

The research nurse/investigators will collect data from your medical record.

Benefits

Your nutritional status will be evaluated before surgery when participating in this study. You will later be advised by a registered dietitian on nutrition and tips to improve your nutritional status. You may receive protein supplementation for free to improve your protein storage and potentially boost your muscle mass. There will be no extra costs required for participating in this study. If you are in the nutritional prehabilitation group, there will be no extra costs required for participating since the outpatient Perioperative Medicine Clinic cost will be reimbursed.

Risks

There is no additional risk for any of the above-mentioned nutritional assessments and questionnaires.

Ethical Approval

This study is approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (NTEC-CUHK Cluster REC/IRB) (Phone: 3505-3935).

Confidentiality

All information obtained in this study will be considered confidential and used only for research purposes. Your identity will be kept confidential in so far as the law allows. NTEC-CUHK Cluster REC/IRB is one of the authorized parties to access your records related to the study for ethics review purposes. Your electronic study data will be stored for 7 years after the publication of research papers.

Questions

The researcher has discussed this with you and offered to answer your questions. If you have further questions, you can contact Ms. Helen CHEUNG (project coordinator) on 8481-4971 or Professor Anna LEE (principal investigator) on 3505-2735. You may also choose to contact the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (phone: 3505-3935) for inquiries with regards to your rights in the study.

Rights to refuse or withdraw

You understand that to participate or not in the study is voluntary, and will not affect the medical management you will receive. You also understand you have the right to withdraw from the study anytime if you wish to do so.

Version 1.0 (8.11.2021)

Patient No: _____

Department of Anaesthesia and Intensive Care
The Chinese University of Hong Kong
香港中文大學
麻醉及深切治療學系

Title of Study

Preoperative malnutrition in patients undergoing major elective surgery: prevalence, determinants and associated quality of recovery outcomes

研究主題

一項隨機對照測試擇期心臟手術前服食相關膳食蛋白質對手術後身體康復質素的影響

Consent

I agree to participate in this study. I have read the information provided and understand the explanation that has been given to me.

同意書

我已閱讀所提供資料，並瞭解一切向我所說明的解釋，我同意參加這項研究。

……	……
Name of participant 參加者姓名	Name of research assistant/investigator/nurse 研究助理/研究員/護士 姓名
……	……
參加者簽署 Signature of participant	研究助理/研究員/護士 簽署 Signature of research assistant/investigator/nurse
……	……..
Date 日期	Date 日期

Patient Details (Gum Label)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,8
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16-17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	9,12
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13,17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1, Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11,15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 13-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl. material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of prehabilitation-related DIETary protein intake on Quality of Recovery after elective cardiac surgery (DIETQoR) study: protocol of a randomised controlled trial

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Effect of prehabilitation-related **DIET**ary protein intake on **Q**uality **o**f **R**ecovery after elective cardiac surgery (DIETQoR) study: protocol of a randomised controlled trial

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Category: Study Protocol

MESH terms: coronary artery disease/rehabilitation and surgery, malnutrition, Heart valve diseases/rehabilitation and surgery, Preoperative care, dietary protein, quality of recovery

Word count: 296 (abstract), 4129 (text), 2 tables, 2 figures, 44 references

Abstract

Introduction: Protein malnutrition is associated with higher risks of postoperative complications, mortality, prolonged postoperative stays in hospital, slower physical and mental recovery after surgery, and lower subsequent health-related quality of life. To reduce the risk of postoperative morbidity and mortality, nutritional prehabilitation programs have been developed recently to build up patient's nutritional reserve to withstand the stress of surgery. The intervention involves nutritional screening and counselling, and increasing dietary protein intake in protein-malnourished patients in the several weeks before surgery. However, there are few well-conducted preoperative studies to examine the effect of increasing dietary protein intake on the quality of recovery of malnourished patients after elective cardiac surgery.

Method and analysis: This randomised controlled trial of malnourished patients undergoing major elective cardiac surgery will compare the quality of postoperative recovery in patients with or without nutritional prehabilitation, One hundred and thirty two patients will be randomised to receive nutritional prehabilitation (target-adjusted whey protein powder supplementation and an individualized 1-hour session/week counselling by a dietician one month before operation date) or standard care (no nutritional prehabilitation). Primary outcomes will be the quality of recovery after surgery (15-item Quality of Recovery on the third postoperative day. Secondary outcomes will include days (alive and) at home within 30 days), changes in the World Health Organization Disability Assessment Schedule 2.0, changes in health-related quality of life (EQ-5D), and Cardiac Postoperative Morbidity Survey. An outcomes assessor will be blinded to the treatment allocation. Appropriate univariate analyses, generalized estimating equations and multiple regressions will be performed for intention-to-treat and per-protocol analyses.

Ethics and dissemination: The Joint CUHK-NTEC Clinical Research Ethics Committee approved the study protocol (CREC Ref. No.: 2021.703-T). The findings will be presented at scientific meetings, peer-reviewed journals and to study participants.

Trial registration number: Chinese Clinical Trial Registry (ChiCTR2200057463); Pre-results

Strength and limitations of this study

- This is the first single-centre, pragmatic, two-armed, parallel, superiority, blinded randomised controlled trial of the effect of preoperative nutritional counselling and dietary protein supplementation (nutritional prehabilitation) on the quality of recovery after surgery
- Due to the nature of the nutritional prehabilitation intervention, patients will not be blinded to the treatment allocation (nutritional prehabilitation versus no prehabilitation)
- To reduce measurement bias, blinded outcome assessors will collect post-intervention outcomes from the time of surgical admission until 30 days after surgery
- As study participants may change their dietary behaviour to consume adequate protein needs before surgery, a Hawthorne effect (performance bias) cannot be fully eliminated

INTRODUCTION

Protein is an essential nutrient for good health and accounts for all building blocks in the body.[1] Elderly patients often have inadequate daily dietary protein intake, putting them at moderate to high risk of malnutrition.[2] Protein malnutrition is a state of deficiency or excess protein intake, imbalance of essential components, or impaired protein utilization that produces a measurable change in the body composition and function.[3]

In cardiac surgical patients, the prevalence of preoperative malnutrition varies widely from 17%[4] to 46%[5] depending on the screening methods used. The causes and mechanisms of preoperative malnutrition are complex in cardiac surgical patients. Key factors that may influence the prehospital nutritional state include: chronic starvation, comorbid inflammatory illnesses, age, weight loss over the preceding six months, low body mass index (BMI), functional status, frailty and medications.[6] A lower BMI, New York Heart Association IV class heart insufficiency, mitral valve insufficiency and renal failure are factors associated with a two to four fold higher risk of preoperative malnutrition.[7]

Protein requirements are elevated in response to surgery as protein synthesis is required for immune function and wound healing.[8] However, there is no consensus amongst professional nutritional societies on the exact target for protein intake for surgical patients.[9] Current consensus guidelines[10,11] focus on total quantity of protein intake but it is unclear if quality of protein intake affects patient outcomes. Goldfarb and colleagues found that the mean (SD) protein intake was 1.3 (0.5) g/kg/day, 0.7 (0.3) g/kg/day and 1.3 (0.6) g/kg/day in the preoperative, early postoperative, and post-discharge periods respectively but its effect on postoperative outcomes were unclear.[12] In another study of 100 well-nourished patients scheduled for cardiac surgery, there was no association between low preoperative protein intake (<0.98g/kg/day) and increased risk of postoperative outcomes (organ failure, bleeding, infection, prolonged length of stay, mortality).[13]

Significance of the present study

Protein malnutrition is associated with a higher risk of postoperative complications and mortality, prolonged postoperative stays in hospital, slower physical and mental recovery after surgery, and lower subsequent health-related quality of life; all factors associated with substantially higher healthcare costs [4,5,14-17] Poor preoperative nutritional status was associated with lower physical function levels (handgrip strength, 6-minute walk test (6MWT), days to independent walking after surgery) and prolonged intensive care unit (ICU) and hospital stays.[17] However, many healthcare professionals do not recognize protein malnutrition, may under-report malnutrition, or poorly document patient's body mass index and food intake during the patient's hospital stay.[18] This severely limits the time available before surgery for any nutritional intervention to take effect that could reduce the risk of postoperative morbidity and mortality.

In many centres, multimodal prehabilitation provides a unique opportunity to optimise the patient's physiological reserve in the 4 to 8 weeks before surgery to withstand the surgical stress response.[19] Multimodal prehabilitation includes individualised structured exercises (aerobic and resistance training), nutrition counselling and supplementation, and psychological support (eg. standardised multi-media patient education). This study protocol focuses on nutritional prehabilitation for malnourished patients to increase their dietary protein intake for building up their nutritional reserve to withstand the stress of surgery. Whether such preoperative nutritional intervention in malnourished patients several weeks before hospital admission improves their quality of recovery (QoR) after cardiac surgery is currently unknown.

Study Objectives

The primary objective of this randomised controlled trial (RCT) is to evaluate the effect of nutritional prehabilitation with high-quality dietary protein intake on the QoR after elective cardiac surgery in malnourished patients. There are several secondary objectives:

a. To determine whether dietitian guided counselling increases preoperative dietary protein intake in malnourished patients scheduled for elective cardiac surgery undergoing nutritional prehabilitation.
b. To evaluate the effect of nutritional prehabilitation on the length of postoperative stay in malnourished patients undergoing elective cardiac surgery.
c. To describe the interaction between preoperative dietary protein intake and physical activity on quality of recovery after elective cardiac surgery in malnourished patients undergoing nutritional prehabilitation.

METHOD AND ANALYSIS

Study design

This single-centre, pragmatic, two-armed, parallel, superiority, blinded randomised controlled trial will be conducted at the Prince of Wales Hospital in Hong Kong, a university teaching hospital. Participants will be randomly allocated to either nutritional prehabilitation or usual care (no nutritional prehabilitation) with 1:1 allocation. Block randomisation with randomly selected block sizes will be performed according to a computer-generated sequence by one of the research staff not involved in the screening, recruitment, or data collection. The treatment allocation will be concealed in consecutively numbered sealed opaque envelopes, to be opened by the dietician after written informed consent for the study has been obtained and after baseline Food Frequency Questionnaire (FFQ),[20] Clinical Frailty Scale (CFS) [21] and exercise capacity measurements have been conducted. The completed study will be reported with reference to the CONsolidated Standards Of Reporting Trials (CONSORT) statement,[22] and the protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[23] The trial has been registered on the Chinese Clinical Trials Registry (ChiCTR2200057463). An overview of the study design is provided in Figure 1.

INSERT FIGURE 1 HERE

Study setting and population

This study will be conducted at the Prince of Wales Hospital in Hong Kong, a 1807-bed tertiary hospital with a dedicated Pre-Operative Assessment Clinic (POAC) and prehabilitation facilities. All elective cardiac surgical patients will be routinely admitted to a 23-bed ICU for early postoperative care and monitoring with 1:1 nursing at all times, with an expectation of discharge from ICU to a high-dependency cardiac ward within 24 hours after surgery.[24] Adults patients undergoing major elective cardiac surgery (coronary artery bypass graft, with or without valvular repair/replacement) will be recruited. Patients will only be recruited once; only the first attempt and assessment results will be recorded for patients who require follow-up or repeated surgery. The inclusion and exclusion criteria are shown in Table 1. We will record the reasons for exclusion.

Table 1. Eligibility criteria for the randomized controlled trial

Inclusion criteria	Exclusion criteria
1. Adults (no age restriction) undergoing elective or non-emergent major cardiac surgery (CABG, valve surgery or combined)	1. Redo or emergency cardiac surgery 2. Major comorbidities precluding surgery, are mentally incompetent, any current disorder impairing accurate and objective completion of the malnutrition assessment and nutritional screening questionnaires, or are unable to understand Chinese or English.
2. MUST>0 or FFMI<17 for men or FFMI<15 for women or SMI<7 for men or SMI<5.7 for women	3. CKD not on dialysis requiring low protein diet, advanced stage CKD or end-stage renal disease on dialysis with protein requirements of 1.0 to 1.2 g/kg body weight/day will be excluded[25]
3. Patients with estimated ≥ 4 weeks of surgical waiting list time	4. Patients with liver diseases and at risk for hepatic encephalopathy 5. Physical limitations that would preclude regular attendance to outpatient nutritional prehabilitation sessions 6. Seen by a dietician in the last 6 months 7. Patients with whey protein allergy

CABG=coronary artery bypass graft; CKD=chronic kidney disease; FFMI=fat free mass index; MUST=Malnutrition Universal Screening Test; SMI=skeletal mass index

Screening

Patients on the elective cardiac surgery waiting list are routinely assessed at the POAC clinic several weeks before the scheduled operation date. After written informed consent, patients will complete the Malnutrition Universal Screening Test (MUST) questionnaire[26] and undertake a body composition test using a bioelectrical impedance analysis device (InBody 270, InBodyUSA, Cerritos, CA) to measure fat free mass index (FFMI) and skeletal mass index (SMI) for study eligibility determination. For the purpose of this study, preoperative malnutrition will be defined as a MUST > 0 or FFMI < 17 for men or FFMI < 15 for women or SMI < 7 for men or SMI < 5.7 for women.[27]

If the inclusion criteria are met, all participants will be interviewed by a dietician to assess their usual dietary intake (frequency and usual quantity) over the past one month using the locally validated semi-quantitative Food Frequency Questionnaire (FFQ)[20] at baseline. For the purpose of this study, only broad food categories with food containing protein from the 288 local food items FFQ will be used (i.e. vegetables and beans, fruits, meats, fish and seafood, eggs, dairy products and beverages.).[20] We will also ask patients about any other protein food items that they consume regularly but are not listed under the FFQ. Mean daily protein intake from food items consumed will be estimated using the nutrition analysis software Food Processor Nutrition Analysis and Fitness software cloud service version 11.1 (ESHA Research, Salem, USA) including local foods selected from food composition tables from China and Hong Kong. Another research staff member, blinded to treatment allocation, will use the same modified FFQ at hospital admission before surgery in all patients to compare changes in protein intake between treatment groups.

The exercise capacity and physical activity level will also be collected at baseline and immediately before surgery in all study participants (Table 2). Although cardiopulmonary exercise testing (CPET) is the gold standard for measuring exercise capacity objectively, access to CPET is very limited in the prehabilitation period. Therefore, we will use the 6-

minute walk test (6MWT) to measure the exercise capacity. The minimal clinically important difference for 6MWT is 14.0 to 30.5 metres in population with cardiac and pulmonary diseases.[28] The Chinese version of Veterans Specific Activity Questionnaire (C-VSAQ)[29] describes the different intensities of daily activities with corresponding metabolic equivalents (METs) on a scale ranging from 1 MET to 13 METs. Participants will be asked to indicate the highest MET that they are able to achieve routinely. The individual's exercise capacity will then be age-adjusted.[29]

Table 2. Assessment overview

Assessment	**Baseline**	**Prehospital period**	**Admission**	**POD3**	**POM1**
Enrolment					
Eligibility screen	X				
Informed consent	X				
Malnutrition screening (MUST, FFMI, SMI)	X		X		
Demographic and comorbidity data	X				
Food Frequency Questionnaire	X		X		
Clinical Frailty Scale, 6MWT, C-VSAQ	X		X		
Randomization	X				
Nutritional Intervention					
Subjective Global Assessment, 24-h food recall		X			
Protein supplement compliance/adverse effect		X			
Outcomes					
Primary					
15-item Quality of recovery				X	
Secondary					
DAH30					X
WHODAS	X				X
EuroQol EQ-5D questionnaire	X				X
Cardiac Postoperative Morbidity Survey				X	

DAH30=Days at home within 30 days of surgery; FFMI=fat free mass index; MUST=Malnutrition Universal Screening Test; POD3=postoperative Day 3; POM1=postoperative 1 month; SMI=skeletal mass index; WHODAS=World Health Organization Disability Assessment Schedule 2.0 questionnaire

Blinding

Due to the nature of the intervention and requirements of informed consent, trial participants will not be blinded to the treatment allocation. Study research personnel collecting the follow-up nutritional status and food frequency intake at hospital admission will be blinded to the treatment allocation. Outcome assessors will be blinded to the participant's group allocation.

Interventions

Control (standard care) arm

Patients in the control group will receive standard care with standardised surgical processes and perioperative care under existing protocols for preoperative patient education, standardised anaesthesia,[30] postoperative ICU sedation, analgesia and weaning from mechanical ventilation, perioperative physiotherapy, and early mobilisation.[24] In brief, the control group will receive unstructured preoperative health promotion/patient education, plus physical prehabilitation provided at the treating physician's discretion. Unstructured and general health education includes information on exercise and a healthy diet without a tailored nutritional plan and no focus on protein education. Both groups will have bioelectrical impedance analysis (FFMI and SMI) measured at baseline and immediately before surgery to determine any changes in body composition (Table 2).

Intervention (nutritional prehabilitation + standard care) arm

The primary aim of the intervention is to increase protein intake using dietetic counselling and to 'top up' with whey protein powder supplements to meet the target protein intake of 1.5 g/kg/day. In addition to standard care, the nutritional prehabilitation group will receive individual 1-hour session/week counselling by a dietician, one month before scheduled

operation date. The intervention involves a tailored approach to meet the nutritional needs of individual participants. This includes the following:

- Reviewing the patient's completed FFQ[20] to report on the amount of dietary protein intake consumed and net deficit daily protein intake
- Assessing the overall nutritional status using the Subjective Global Assessment[31] and a 24-hour diet recall at the initial visit
- Discussing why increasing dietary protein intake before surgery is important
- Educating patient about which foods contain high quality protein to eat (eg. chicken, fish, soy, lentils, nuts, brown rice[32]), and
- Prescribing the optimal amount of whey protein powder supplement (Beneprotein® sachets) to meet the target protein intake of 1.5 g/kg/day based on actual body weight or adjusted body weight for obese patients.
- Patients will be reminded via phone call one day before their nutritional counselling session

A Registered Dietitian (RD) will be responsible for safekeeping and dispensing of the whey protein powder supplement (Beneprotein®). Participants will be given enough sachets for one week to consume and some backup sachets. Each sachet provides 6g of protein (1 egg equivalent). The RD will recommend that participants consume each Beneprotein® sachet with 100mL of water. They will also be given a ticked calender and asked to bring all the used sachets, unused sachets back each week to estimate the compliance rate.

Outcome measures

Primary outcome

1. Quality of Recovery (QoR)

The Chinese version of the 15-item Quality of Recovery (QoR-15)[33] will be used on postoperative Day 3. The QoR-15 includes the items measuring pain, physical comfort,

physical independence, psychological support and emotional state.[33] The QoR-15 score ranges from 0 to 150, takes about 3 minutes to complete and has well established psychometric properties.[33] A poor symptom state (recovery) after surgery has been defined at a cut-off of <118.[33] Depending on patient's postoperative status, QoR-15 assessment may be deferred if the patient is unwell or unavailable. The QoR-15 assessment will be conducted at a later date after obtaining patient's agreement. The blinded outcome assessor will record the exact date of actual QoR-15 assessment.

Secondary outcomes

1. Days (alive and) at home within 30 (DAH_{30}) days after cardiac surgery

The DAH is a patient-centred, generic outcome measure that will be used to measure the patient's overall recovery profile.[34] DAH is a composite measure that incorporates the details on postoperative hospital length of stay, discharge to rehabilitation centre or nursing home, hospital readmissions, and postoperative deaths.[34] Three days difference is considered clinically meaningful.[35] The blinded outcome assessor will extract data from the electronic patient medical record to estimate the DAH_{30}.

2. Disability-free survival at 30 days after surgery

New or residual disability after surgery is of particular concern to patients and healthcare professionals.[36] In this study, the changes in disability-free survival (baseline to postoperative 1 month, Table 2) will be measured using the Chinese (Hong Kong) version of the 12- item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 score that has been validated in surgical patients.[36] It will take five minutes to complete.[36] Patients will be asked to rate the difficulty in carrying out 12 specified activities on a 5-point Likert scale (0 = none to 4 = extreme) in the past 30 days. The total score will be converted to a scale from 0 (no disability) to 100 (maximum disability) by a blinded outcome assessor, with the following subcategories: none (0% to 4%), mild (5% to 24%), moderate (25% to 49%), severe (50% to 95%) and complete (96% to 100%) disability.[36] The 25% threshold will

be used to define disability; an increase in the WHODAS score ≥ 8% from their baseline assessment will define new disability.[36]

3. Health-related quality of life

The changes (baseline to postoperative 1-month, Table 2) in health-related quality of life will be measured using the Chinese (Hong Kong) version of the EuroQoL EQ-5D.[37] Patients will be asked to rate their mobility, self-care, usual activities, pain/discomfort and anxiety/depression on five levels (no problems, slight problems, moderate problems, severe problems, extreme problems) and to rate their health state from 0 (worst imaginable) to 100 (best imaginable). The blinded outcome assessor will use the descriptive responses to estimate the EQ-5D utilities by applying a set of Hong Kong reference weights.[37]

4. Cardiac Postoperative Morbidity Survey (C-POM)[38]

The C-POM score quantifies the total morbidity burden and is currently the only validated measure of postoperative morbidity after cardiac surgery. It is a composite outcome that included the following 13 morbidity types: pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound, pain, endocrine, electrolyte, review and assisted ambulation. The blinded outcome assessor will collect the C-POM survey on the third postoperative day using information from the patient's medical records.

Other variables in data collection

Using a standardised data collection form, a research assistant will collect demographic (age, gender, BMI, education level, home living support, frailty level using CFS, comorbidities), adverse protein supplement effect as measured by elevated blood urea nitrogen (BUN) concentration BUN > 24 mg/dL (8.5 mmol/L),[39] American Society of Anesthesiologist's Physical Status, physical prehabilitation attendance, intravenous iron therapy during prehabilitation period, operation date, type of cardiac surgical procedure, duration of surgery, duration of anaesthesia, length of ICU and hospital stays. Possible

contamination of control arm (ie. self-initiated changes in diet with protein supplement after providing study details) will be assessed by asking patients if they have made changes to eating habit or taken protein supplements immediately before surgery. An overview of the data collection process is shown in Table 2.

Sample size

A sample size of 60 in each group will have 90% power to detect a moderate to large quality of recovery effect (0.60) using a two group t-test with a 0.05 two-sided significance level (nQuery Advisor®, version 7.0). Allowing 10% loss to follow-up, a total of 132 patients will be required. No interim analysis has been planned.

Statistical methods

The data derived from the patient's FFQ at follow-up will be used to estimate each participant's mean protein quality score using the framework methodology outlined by Katz and colleagues.[32] The primary analysis will be an Intention to treat analysis and the secondary analysis will be a per-protocol analysis. We will consider satisfactory compliance with whey protein powder supplementation if the patient's intake is above 75% for the per-protocol analysis. Missing data will be checked and imputation of the missing data will be used to preserve power. Continuous variables will be reported as mean (SD) and median (IQR) as appropriate.

After checking for normality using the Shapiro-Wilk's test, we will perform independent Student's t-test or Mann-Whitney U test as appropriately to compare group differences for the magnitude of protein intake and quality, QoR-15, postoperative length of stay and DAH_{30}. We will use a generalised estimating equation with a Gaussian distribution, identity-link, exchangeable correlation with robust standard errors to estimate the mean difference in preoperative dietary protein intake and quality between treatment groups over time. Multiple regression will also be used to examine the association between dietary protein intake and

physical activity with 15-item QoR; an interaction effect of dietary protein intake change and physical activity change will be included in the model, after adjusting for other potential confounders (prehabilitation exposure, change in DQI-I score, frailty) using a directed acyclic graph approach in Figure 2. Statistical analyses will be performed using Stata version 17 (StataCorp, College Station, TX). The two-sided level of significance will be set at $P<0.05$.

INSERT FIGURE 2 HERE

Monitoring and data management

We will collect and manage the study data using REDCap electronic data capture tools[40] hosted at The Chinese University of Hong Kong. No interim analysis has been planned. No formal data monitoring committee has been set up. There will be no formal data monitoring committee. However, the study progress and any unanticipated serious adverse events will be reported as part of an annual renewal application for local research ethics committee approval. An anonymised data set will be available after the publication of the completed study, following the deposition of the dataset into The Chinese University Research Data Repository (https://researchdata.cuhk.edu.hk/).

Patient and public involvement

Patients and the public were not involved in the development of the research question, the design of the study nor did they contribute to the editing of this document for readability or accuracy.

Ethics and dissemination

Before obtaining written informed consent (online supplemental material), the purpose of the study, procedures, risks and benefits of participation, and the time commitment involved will be explained to eligible patients by the study dietician. There will be no extra costs for patients who are allocated to the intervention group since the expenditure for every dietician

consultation session will be reimbursed. We plan to disseminate the results to study participants by giving them a one-page plain language summary.

Patients may withdraw from the study without prejudice at any time during the study. Data will be kept confidential in secure offices of the Department of Anaesthesia and Intensive Care for seven years. Approval for the project (protocol version 1.1, 24/01/2022) was obtained from The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2021.703-T). We will notify the local research ethics committee and clinical trials registry about any protocol modifications in a timely manner. The study will adhere to local laws, Declaration of Helsinki and institutional policies.

DISCUSSION

The American Society for Enhanced Recovery and Perioperative Quality Initiative recommends that patients at risk of malnutrition be given preoperative oral nutritional supplements (immune-nutrition containing arginine/fish oil or high protein [minimum 18g protein/dose, 2 to 3 times/day) for a period of at least 7 to 14 days before surgery.[14] Of the 191 elective cardiac surgical patients in our recent unpublished audit, 51 (27%) had preoperative protein-malnutrition as determined by a dietician. Among these 51 patients, 38 (75%) were moderately malnourished while the rest were severely malnourished. These findings suggest that a substantial proportion of elective cardiac surgical patients are at risk of adverse malnutrition-related postoperative events.

Few well-conducted studies in North America or Western Europe provide a sound evidence-based approach to determining the potential or actual benefits of increasing dietary protein intake in malnourished patients before any elective surgery, and especially in cardiac surgical patients. A systematic review of 15 randomised controlled trials in 3831 mixed medical and surgical patients with malnutrition showed that nutritional support (parenteral

nutrition, enteral nutrition, immunonutrition) was associated with a reduction in the risk of infection (relative risk [RR] 0.58, 95% CI: 0.50 to 0.68), non-infectious complications (RR 0.74, 95% CI: 0.63 to 0.88), a shorter length of hospital stay (mean difference [MD] -2.6, 95% CI: -5.1 to -0.2 days).[41]

There remain some potential study limitations. First, study participants may change their dietary behaviour to consume adequate protein needs before surgery after exposure to the information about the background and rationale of the randomised controlled trial. This Hawthorne effect, a type of performance bias, may be present after study participants become more aware of the possible role of preoperative nutrition on postoperative recovery. Nevertheless, any increased in protein intake in the standard care group will likely be captured at the time of the second FFQ analysis. Second, the dietetic counselling with education on high quality protein foods may lead to changes in overall diet quality; such changes may affect outcomes independent of protein intake. To control for the possible effect, we will adjust for the overall diet quality change using the Diet Quality Index-International scores[42] derived from the FFQ responses. Third, there are varied and multiple determinants of malnutrition that cannot be completely assessed at baseline.[43] In this RCT, we will measure education level, home living support, frailty level using CFS, comorbidities but other determinants, such as socioeconomic status, mental health and isolation environment will not be measured, however the randomisation process should ensure sufficient equipoise. Finally, as objective measures of protein assimilation, such as a positive nitrogen balance, are impractical and of limited precision, we will rely on subjective assessment (ticked calendar and used sachets) to demonstrate compliance. Each participant's BUN concentration will be measured to serve as a warning marker for possible adverse effects of the increased protein intake, and as a marker of increased protein intake, although it is acknowledged that there is only a moderate correlation (r = 0.50) between BUN concentration and protein intake in patients aged 60 years and above.[44]

Our intervention, an individualized tailored approach by a dietician, will establish an accurate estimate of the local prevalence of low dietary protein intake (<1.5 g/kg/day) presenting for major elective cardiac surgery. The trial will facilitate the feasibility and design of future studies of nutritional prehabilitation in all surgical patients after establishing the level of patient compliance to whey protein supplementation. The results of this RCT will enable us to establish magnitude of prehabilitation effect of increasing dietary protein intake on post-operative length of hospital stay, and improving patient-centred outcomes within 30 days after cardiac surgery, using validated and reliable tools. The trial will also generate a clearer understanding of the possible additive or synergistic effects of improved dietary protein intake with physical prehabilitation on quality of recovery after surgery, especially in prefrail to frail patients. This should further clarify prehabilitation's effectiveness based on nutritional optimisation alone.

Trial status

The patient recruitment started on September 1 2022. We expect patient recruitment and one month of follow-up to be completed by August 30 2025.

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Author contributors

The protocol was jointly written by HHTC and AL and was critically reviewed DKWY, LCSC, MKHW, SSYY, MJU, RHW, GMJ. All authors except RHW, LCSC and SSYY were involved in the study concept. All authors were involved in the design of the study and approved the final version of the manuscript.

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Competing Interests

None declared.

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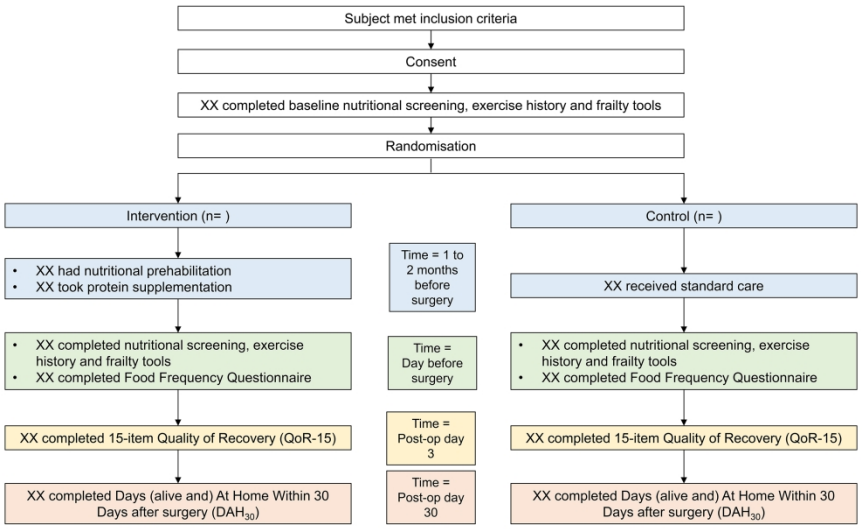
Figure Legends

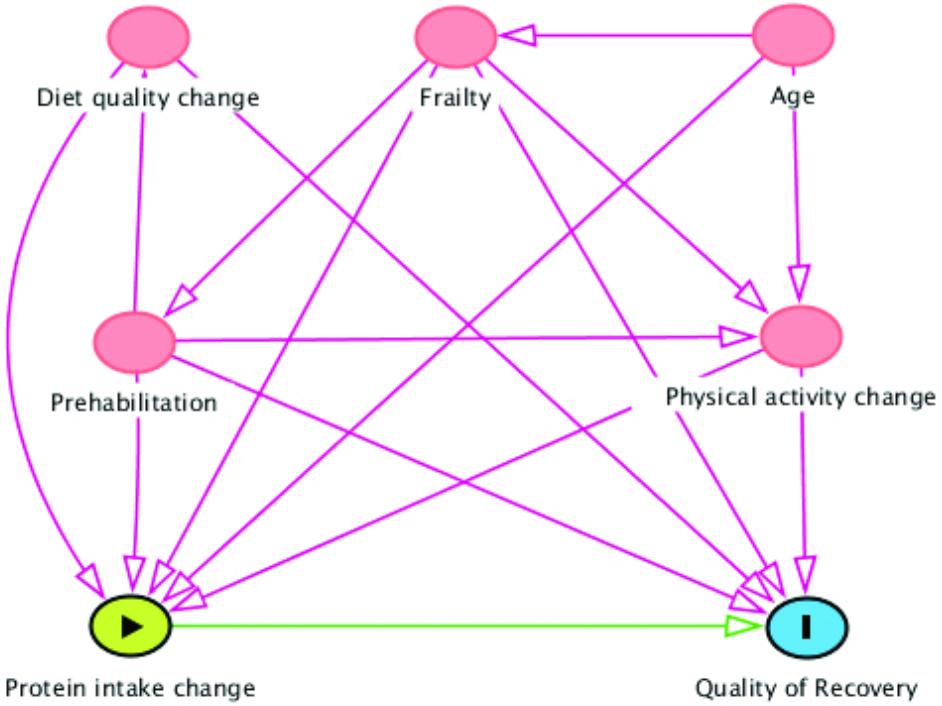
Figure 1. Patient flow diagram

Figure 2. Directed acyclic graph using DAGitty software version 3.0. Assumptions made in the nutritional prehabilitation (exposure) and quality of recovery (outcome) relationship to identify the set of variables needed for confounding adjustment. Green circle represents ancestor of exposure. Red circle represents ancestor of exposure and outcome. All red arrows lie on open biasing paths. Green arrow lies on open causal path. The bold arrows indicate no corresponding indirect paths (no causal effect between variables exists if arrow is removed). Thin arrows indicate that there are indirect pathways between variables.



Patient flow diagram

279x157mm (300 x 300 DPI)



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42x32mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,6
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1, Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8,10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 11-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl. material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.