Dose-Response Effect of Physical Prehabilitation on Major Cardiac and Cerebrovascular Events and Disability Levels After Cardiac Surgery in Frail Patients

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BACKGROUND: Prehabilitation enhances patients' resilience to surgical stress and may improve postoperative outcomes. However, the dose response of prehabilitation on outcomes remains unknown.

RESEARCH QUESTION: Does a twice-weekly supervised outpatient exercise program before elective cardiac surgery in patients with frailty have dose-response effects on 90-day postoperative major cardiac and cerebrovascular events (MACCEs) and disability levels?

STUDY DESIGN AND METHODS: This was a post hoc analysis of the PREhabilitation for improving QUality of recovery after ELective cardiac surgery (PREQUEL) trial that compared physical prehabilitation (up to 19 sessions over 10 weeks) with usual care in participants with very mild to moderate frailty. Primary outcomes included the 90-day risk of MACCEs and changes in disability levels measured by the World Health Organization Disability Assessment Schedule 2.0 score. Secondary outcomes were preoperative changes in the 6-minute walk test distance, submaximal metabolic equivalents of tasks, and frailty measures. We used a generalized estimating equation model to examine the association between the dose of prehabilitation and the risk of MACCEs. Causal inference was assessed by dose-response function models while allowing nonlinearity.

RESULTS: Of the 143 participants, 135 underwent cardiac surgery. No exercise-induced adverse events occurred in 64 participants during 551 sessions. The dose of prehabilitation was not associated with the risk of MACCEs (16 participants with 24 episodes; adjusted OR/session, 0.98; 95% CI, 0.88-1.09). However, improvements in disability levels, 6-minute walk test distance, and metabolic equivalents of tasks were directly related to the number of consecutive doses of prehabilitation before surgery. Improvements in clinical frailty after exercise training were observed in a few patients after 7 weeks of training.

INTERPRETATION: In cardiac patients with frailty, a greater number of consecutive doses of physical prehabilitation had favorable effects on improving preoperative exercise capacity and lowering disability levels at 90 days after surgery.

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KEY WORDS: cardiac surgical procedures; causality; disability; dose response; exercise therapy; frailty; postoperative complications; preoperative care

Take-Home Points

Study Question: Does a twice-weekly supervised outpatient exercise program before elective cardiac surgery in patients with frailty have dose-response effects on 90-day postoperative major cardiac and cerebrovascular events and disability levels when compared with usual care?

Results: Although no dose-response effect was apparent for a reduction in the composite outcome of major cardiac and cerebrovascular events, each additional session of exercise training improved disability levels as measured by the World Health Organization Disability Assessment Schedule 2.0 score.

Interpretation: Physical cardiac prehabilitation may have beneficial dose-response effects to enhance functional recovery in carefully selected patients with frailty.

Survival and freedom from disability are key quality recovery outcomes after surgery in the vulnerable older adult population.[1] Patients, caregivers, and health care professionals have prioritized disability-free survival, frailty, and prehabilitation as the most important research areas in cardiac surgery.[2] Older patients with frailty are particularly vulnerable and are more likely to experience an unacceptable health state 90 days after surgery compared with older patients without frailty (15.5% vs 7.9%; OR, 2.16; 95% CI, 1.31-3.57).[3]

Multimodal prehabilitation programs (individualized structured exercise training, nutrition counseling and supplementation, and psychological support) may enhance a patient's physiological and functional reserve to withstand surgical stress, resulting in improved outcomes after surgery.[4,5] Compared with usual care, even isolated exercise prehabilitation may reduce medical and surgical complications up to 30 days after surgery (OR, 0.50; 95% CI, 0.39-0.64; very low certainty of evidence).[5] Despite the many physical prehabilitation trials performed before cardiac surgery,[6,7] the dose (frequency, intensity, and duration) effect of prehabilitation on long-term functional and patient-centered outcomes has yet to be established.[8]

We hypothesized that physical prehabilitation has a dose-response effect on perioperative outcomes among patients with frailty undergoing elective cardiac surgery. In this post hoc analysis of the PREhabilitation for improving QUality of recovery after ELective cardiac surgery (PREQUEL) trial, we assessed the dose-response relationship between doses of exercise training and postoperative major cardiac and cerebrovascular events (MACCEs) and disability levels at postoperative day 90 (POD90).

Study Design and Methods

The results of the PREQUEL trial have recently been published.[9] The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved the trial (No. CREC 2017.696-T) on February 27, 2018, and the research was registered at the Chinese Clinical Trials Registry (No. ChiCTR1800016098) (https://www.chictr.org.cn/showprojEN.html?proj=27384) on May 2, 2018.[9] All participants provided written informed consent. The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Briefly, this single-center, single-blinded, parallel-arm superiority randomized controlled trial, conducted from July 2018 to March 2023, recruited patients with very

ABBREVIATIONS: 6MWT = 6-minute walk test; aOR = adjusted OR; CFS = Clinical Frailty Scale; DRF = dose response function; EFT = Essential Frailty Toolset; GST = gait speed test; IQR = interquartile range; MACCE = major cardiac and cerebrovascular event; MCID = minimal clinically important difference; METs = metabolic equivalents of tasks; POD90 = postoperative day 90; PREQUEL = PREhabilitation for improving QUality of recovery after ELective cardiac surgery; WHODAS = World Health Organization Disability Assessment Schedule

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mild to moderate frailty (using Clinical Frailty Scale [CFS] scores 4-6)[10,11] undergoing elective cardiac surgery, with last follow-up at POD90. A total of 164 patients were randomized to receive either physical prehabilitation (twice weekly) or usual care (control).[9] Participants underwent coronary artery bypass grafting, aortic valve repair or replacement, mitral valve repair or replacement, or combined coronary artery bypass grafting with valve procedures; randomization was stratified by the type of surgery.[9] Patients were excluded if they had unstable or recently unstable cardiac syndrome (New York Heart Association functional class IV, critical left main coronary disease, hospitalization for arrhythmias, congestive heart failure, or acute coronary syndrome before randomization), severe left ventricular obstructive disease (severe aortic or mitral stenosis, or dynamic left ventricular outflow obstruction), redo cardiac surgery, or any contraindications for prehabilitation (those with cognitive deficits unable to comply with study procedures, physical limitations precluding prehabilitation, or inability to regularly attend outpatient sessions).[9] The outcome assessors were blinded to the treatment allocation.

Each participant's exercise prescription was individualized and symptom-limited, following the American College of Sports Medicine guidelines.[12] The exercise training was supervised by an experienced physiotherapist, with a low instructor-to-patient ratio of between 1:1 to 1:4 (during the early phase of COVID-19 a 1:1 ratio was deliberately maintained to limit possible patient cross infection).[9] Exercise training intensity consisted of 20 to 60 minutes of aerobic exercises with sufficient training intensity to achieve between 40% and 80% of estimated oxygen uptake reserve, and resistance training of major muscle groups of upper and lower limbs, according to the participant's tolerance and performance.[9] An emergency response protocol was in place to deal with exercise-induced adverse events. Participants were also encouraged to perform home exercise (3-5 days of aerobic and 2-3 days of resistance exercise weekly).[9] For this study, the dose of prehabilitation was defined as the number of supervised consecutive exercise training sessions completed at a frequency of 2 sessions per week, and of the intensity previously defined. Compliance was calculated as the percentage of attendance at planned sessions.

Because there is currently no consensus on the best measure of frailty in perioperative patients, we measured frailty using the CFS[10,11] and the 5-m gait speed test (GST),[13] and Essential Frailty Toolset (EFT)[14] at baseline and on hospital admission.

Outcome Measures

We defined 2 primary outcomes. The first was the risk of MACCEs, a composite outcome including myocardial infarction, stroke, acute renal failure, reoperation, and death at POD90. Each component of MACCE was collected from the division of cardiothoracic surgery quality-assurance database,[9] which was identical to the data set of the Society for Cardiothoracic Surgery in Great Britain and Ireland. The second was the level of disability at POD90. We used the 12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 score to estimate participant's disability levels, converting it to a metric ranging from 0% (no disability) to 100% (maximal disability or death).[15-18] The severity of disability was classified as follows: nil ($<$ 5%), mild (5%-24%), moderate (25%-49%), severe (50%-95%), and complete ($>$ 95%).[15] The minimal clinically important difference (MCID) has been defined as a change in WHODAS scores $\geq$ 5% in surgical populations.[16]

Secondary outcomes were preoperative changes in functional exercise capacity and frailty measures from baseline (time when the patient was given a date for surgery) to surgical admission. The 6-minute walk test (6MWT) distance was used as a functional assessment in this study.[19] We chose 25 m as the MCID as per the current cardiac rehabilitation recommendations.[20] The percent predicted 6MWT achieved was calculated by comparing the distance walked with the distance predicted for a healthy Chinese population matched by age, sex, height, and BMI.[21,22] From the baseline and preoperative submaximal 6MWT distance data, the corresponding peak oxygen uptakes[19] were used to estimate the submaximal delta metabolic equivalents of tasks (METs) as a measure of exercise intensity.[23] Changes in preoperative frailty were reported as ΔCFS, ΔEFT, and Δ5-m GST.

Statistical Analysis

A complete case analysis was used. Multiple imputations were not implemented because only outcome measures, but not confounding covariates, were missing in a relatively small number of participants. Values are reported as mean ± SD, median (interquartile range [IQR]), or proportion (%). Appropriate Student *t* tests (for data considered normal by the Shapiro-Wilk test), Mann-Whitney *U* tests, or χ^2 tests were used to compare baseline characteristics between prehabilitation groups (per protocol analysis).

We estimated the common effect to characterize the adjusted association between prehabilitation dose and the risk of MACCE using generalized estimating equations.[24] The generalized estimating equation model used an exchangeable correlation structure, adjusting for the type of cardiac surgery, baseline CFS, and the waiting period (in weeks) for surgery. The common effect represents the average adjusted OR (aOR) across the myocardial infarction, stroke, acute renal failure, reoperation, and death components of MACCEs, providing a more informative result than reporting a collapsed MACCE outcome as any vs none. Thus, the dose-response effect estimate of the risk of MACCEs is expressed as the aOR per exercise training session.

The Cerulli methodology[25] was used to calculate and graph the overall average treatment effect in the dose response function (DRF) of exercise training (number of training sessions completed) on continuous outcomes (disability levels, 6MWT, METs, and frailty measures). The amount of time available for prehabilitation, irrespective of the trial arm to which participants were randomized in the PREQUEL trial,[9] was incorporated into the DRF model to account for heterogeneity in average effects.[25] The DRF model, implemented using the ctreatreg macro in Stata 18.0 (StataCorp), required a binary treatment (prehabilitation vs usual care) and a continuous treatment dose indicator (number of exercise training sessions) scaled from 0 to 100. For this study, the maximum number of sessions completed was 19, with each session equivalent to 5.26 units on the 0 to 100 dose (t) scale. This methodology uses a framework to enhance causal interpretation while accommodating a zero-treatment probability mass (ie, many participants had no prehabilitation).[25] Curvilinear dose-response relationships were confirmed through hierarchical joint tests of significance for polynomial coefficients in the DRF models, proceeding from cubic to quadratic to linear terms. To obtain the 95% CIs around the dose-response curve across the full dose range (0-100), the sample was bootstrapped 1,000 times.[25] Sensitivity analyses were performed for POD90 WHODAS scores using other frailty measures—EFT and GST.

The level of significance was set at 2-sided $P < .050$ for all analyses, and no multiple testing adjustments were made. Borderline significance was interpreted using the terminology outlined by Pocock and Ware.[26] Analyses were performed using Stata 18.0 and SPSS 29.0.2.0 (IBM Corp).

Results

In the PREQUEL trial,[9] we assessed 620 participants for eligibility, but 456 were excluded: 183 (40.1%) had a CFS score of not 4 to 6, 90 (19.7%) were unavailable for prehabilitation, 70 (15.4%) had severe left ventricular obstructive disease, 54 (11.8%) had unstable cardiac syndrome, 19 (4.2%) declined to participate, 10 (2.2%) had surgery too soon, 10 (2.2%) had other types of cardiac surgery, 7 (1.5%) had repeat cardiac surgery, and 13 (2.9%) had other reasons. Of 164 participants randomized in the PREQUEL trial,[9] 143 were included in this substudy (Fig 1). We excluded 2 participants because of interrupted sessions and 19 without both preoperative 6MWT and POD90 WHODAS data (Fig 1). The median number of days participants were followed up was 141 days (IQR, 120-214).

Seventy-nine participants (55.2%) received no exercise training before surgery, and 64 participants (44.8%) received prehabilitation (Fig 1). In patients who had undergone cardiac surgery, the range of time spent in prehabilitation was 0.5 to 20 weeks. All patients met the exercise intensity and duration criteria in all sessions. Mean compliance with attending exercise sessions ± SD was 97% ± 11%. Nine patients did not achieve 100% compliance; the median number of missed sessions was 1 session (IQR, 1-2). No exercise-induced adverse events occurred during the 551 training sessions. The baseline demographic, comorbidities, frailty levels, and physical function measures were comparable between groups (Table 1). However, more participants in the prehabilitation group received IV iron therapy while waiting for surgery than those in the usual care group (14.1% vs 3.8%, respectively; $P = .028$).

A total of 135 participants underwent cardiac surgery (94.4%) (Fig 1). The intraoperative and postoperative data were similar between groups (Table 2). Disability data were available in 134 participants (93.7%). Of the participants, 121 (84.6%) had both Δ6MWT distance and ΔWHODAS (%) data. There were 6 perioperative deaths (7.6%) in the usual care group and 1 (1.6%) in the prehabilitation group (Fig 1).

Primary Outcomes

Sixteen patients (11.9%) experienced 24 MACCE episodes (1 myocardial infarction, 3 strokes, 10 acute renal failure, 5 reoperations, and 5 deaths) at POD90. There was no association ($P = .874$) between the dose of

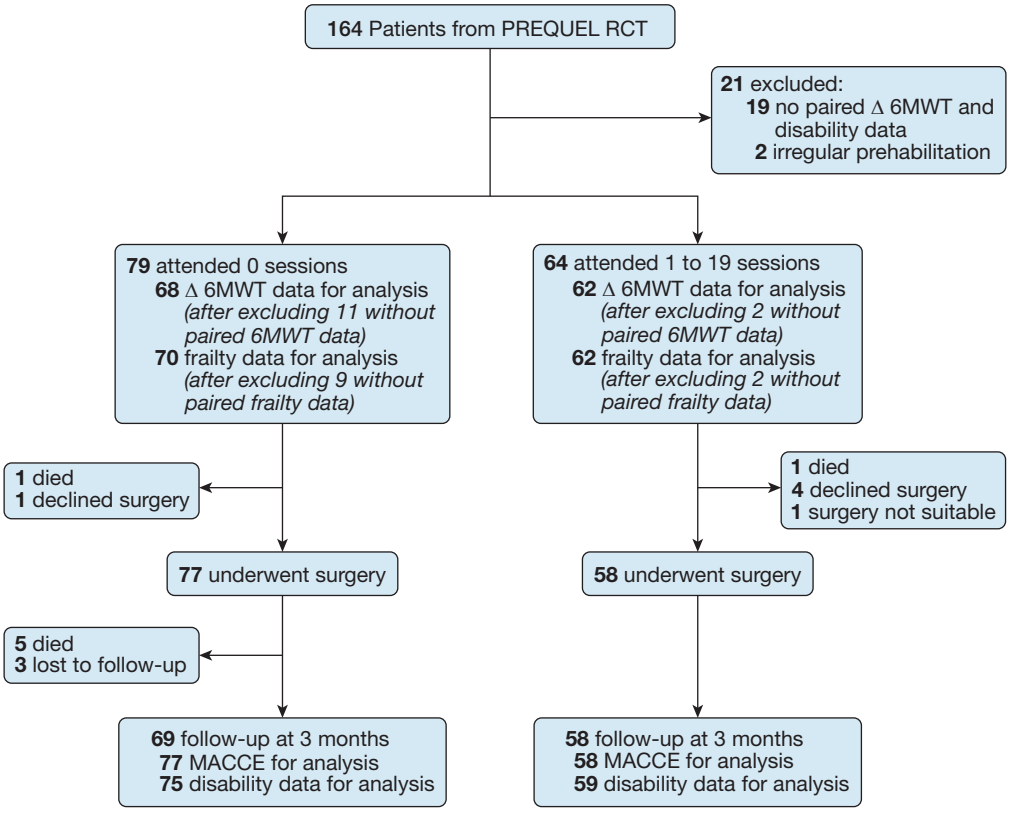

Figure 1 – *Patient flow diagram through the PREQUEL substudy of 143 participants. 6MWT = 6-min walk test; MACCE = major cardiac and cerebrovascular event; PREQUEL = PREhabilitation for improving QUality of recovery after ELective cardiac surgery; RCT = randomized controlled trial.*

prehabilitation and the risk of MACCEs (Fig 2A). The dose of prehabilitation did not appear to be associated with the composite MACCE outcome of myocardial infarction, stroke, acute renal failure, reoperation, and mortality (aOR per session, 0.98; 95% CI, 0.88-1.09) (Fig 2B). However, there was a difference in the incidence of MACCE components ($P = .037$) with acute renal failure being more common (7.4%; 95% CI, 3.0%-11.9%) than myocardial infarction (0.7%; 95% CI, 0%-2.2%), stroke (2.2%; 95% CI, 0%-4.7%), reoperation (3.7%; 95% CI, 0.6%-6.9%), and death (3.7%; 95% CI, 0.5%-6.9%).

The overall mean WHODAS scores ± SD (%) at baseline and POD90 were 14.1 ± 13.4 and 10.4 ± 24.1, respectively. A marked reduction in the prevalence of disability (WHODAS ≥ 5%) occurred from baseline (69.9%) to POD90 (27.8%), with an absolute risk reduction of 42.1% (95% CI, 30.5%-53.8%) (Fig 3A). The reductions in POD90 disability levels were significant only among those (37.1%) who received ≥ 5 consecutive exercise training sessions after adjusting for baseline WHODAS scores, baseline CFS, type of cardiac surgery, and time available for training (e-Table 1, Fig 3B). These findings persisted in 2 separate analyses: one adjusting for baseline EFT (e-Fig 1A, e-Table 2) and another for baseline 5-m GST (e-Fig 2A, e-Table 3); both analyses were consistent with the CFS analysis.

Secondary Outcomes

There was a positive curvilinear relationship between the dose of prehabilitation and 6MWT distance after adjusting for baseline 6MWT distance, CFS, and time available for training in 130 participants (90.9%) (e-Table 4, Fig 4A). Significant improvements in preoperative 6MWT distances were only observed among those (21%) who had ≥ 9 sessions of training. To achieve an MCID improvement of ≥ 25 m, participants (5%) needed ≥ 14 sessions (Fig 4A). Improvements in METs occurred from 13 sessions (0.24; 95% CI, 0.02-0.48) to 18 sessions (0.91; 95% CI, 0.05-1.78) after adjusting for baseline METs, CFS, and time available for training (e-Table 4, Fig 4B). There was a negative curvilinear relationship between the dose of prehabilitation and CFS after adjusting for baseline CFS and time available for training (e-Table 4,

TABLE 1] Baseline Characteristic of Study Participants by Exercise Training Groups

Baseline Characteristics	No Prehabilitation Training (0 Sessions) (n = 79)	Prehabilitation Training (1-19 Sessions) (n = 64)
Age, y	64 (58-69)	65 (60-71)
Female sex	27 (34.2)	15 (23.4)
BMI, kg/m^2	25.3 (23.2-28.4)	24.5 (22.5-27.3)
Cardiovascular disease risk factors	62 (78.5)	49 (76.6)
Hypertension	47 (59.5)	41 (64.1)
Obesity	4 (5.1)	3 (4.7)
Dyslipidemia	30 (38.0)	31 (48.4)
Diabetes	33 (41.8)	25 (39.1)
Cerebrovascular disease	11 (13.9)	14 (21.9)
Pulmonary	5 (6.3)	6 (9.4)
Anemia	22 (27.8)	22 (34.4)
Ejection fraction, %	58 (50-61)	60 (51-63)[a]
β-blockers	47 (59.5)	42 (65.6)
Calcium channel blockers	27 (34.2)	18 (28.1)
Angiotensin receptor blockers	19 (24.1)	21 (32.8)
Angiotensin-converting enzyme inhibitors	32 (40.5)	26 (40.6)
Vasodilating agents	34 (43.0)	36 (56.3)
Cardiac glycosides	6 (7.6)	5 (7.8)
Antiarrhythmic agents	0 (0.0)	2 (3.1)
Anticoagulants	21 (26.6)	18 (28.1)
Antiplatelets	55 (69.6)	41 (64.1)
Diuretics	29 (36.7)	21 (32.8)
Lipid-lowering agents	54 (68.4)	51 (79.7)
Clinical Frailty Scale	4 (4-4)	4 (4-4)
Essential Frailty Toolset score	1 (0-2)	1 (0-2)
5-m gait speed test, s	5.6 (4.5-6.5)	5.5 (4.4-6.4)
6MWT distance, m	336.8 [90.4]	363.1 [86.4]
Predicted 6MWT distance, m	497.7 [105.3]	498.5 [91.9]
Percent predicted 6MWT, %	69.9 [21.2]	73.7 [15.5]
Estimated peak oxygen uptake, mL/kg/min	11.0 [3.3]	11.0 [2.9]
Estimated METs	3.1 [0.9]	3.1 [0.8]
Available time for training, wk	5.6 (3.7-8.9)[a]	6.6 (4.7-10.1)
Training time, wk	NA	4.6 (2.8-6.5)
WHODAS, %	15.0 [14.3][a]	13.0 [12.3]
Nil disability (< 5%)	22 (28.2)	23 (35.9)
Mild disability (5%-25%)	42 (53.8)	30 (46.9)
Moderate disability (25%-50%)	12 (15.4)	11 (17.2)
Severe disability (50%-95%)	2 (2.6)	0 (0.0)

Data are presented as No. (%), mean [SD], or median (interquartile range). 6MWT = 6-min walk test; MET = metabolic equivalent of tasks; WHODAS = World Health Organization Disability Assessment Schedule 2.0.
[a]Missing data for 1 patient.

Fig 4C). There were subtle improvements in CFS among those (4%) who had completed ≥ 15 sessions (−0.60; 95% CI, −1.18 to −0.01) of training (Fig 4C).

The results of the DRF models for secondary outcomes, after adjusting for EFT and the 5-m GST, are outlined in e-Tables 2 and 3, respectively. We found similar

TABLE 2] Intraoperative and Postoperative Characteristics

Characteristic	No Prehabilitation Training (0 Sessions) (n = 77)	Prehabilitation Training (1-19 Sessions) (n = 58)	*P* Value
ASA Physical Status[a]			.192
II	3 (3.9)	7 (12.1)	
III	69 (90.8)	49 (84.5)	
IV	4 (5.3)	2 (3.4)	
Type of cardiac surgery			.899
CABG ± valve/other	42 (54.5)	31 (53.4)	
Valve ± other	35 (45.5)	27 (46.6)	
Logistic EuroSCORE, %	3.1 (1.5-6.9)	2.8 (1.8-4.8)	.478
Duration of surgery, min	257 (224-296)	245 (218-301)	.676
Duration of anesthesia, min	303 (269-329)	291 (255-339)	.516
Duration of cardiopulmonary bypass time, min	114 (97-144)	114 (96-135)	.502
APACHE III score[b]	51 (41-60)	49 (40-59)	.618
Duration of mechanical ventilation, min	530 (342-823)	447 (320-703)	.287
Duration of ICU stay, h	22.5 (19.8-24.1)	21.7 (19.8-23.5)	.320
ICU readmission	3 (3.9)	1 (1.7)	.634
Duration of hospital stay, d	10.0 (9.0-12.8)	11.0 (9.0-12.0)	.380
Days at home within 30 d after surgery	22.0 (13.5-23.0)	21.0 (17.8-22.0)	.628

Data are presented as No. (%), mean [SD], median (interquartile range), or as otherwise indicated. APACHE = Acute Physiology and Chronic Health Evaluation; ASA = American Society of Anesthesiologists; CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

[a]ASA Physical Status missing data for 1 patient.

positive curvilinear relationships between the dose of prehabilitation and 6MWT distance after adjusting for baseline EFT or 5-m GST (e-Figs 1B and 2B, respectively). There were corresponding dose-response effects of prehabilitation on submaximal METs, with significant effects observed when participants (6%) had completed ≥ 13 sessions (e-Figs 1C and 2C, respectively). However, no dose effects of prehabilitation on preoperative EFT (e-Fig 1D) or 5-m GST (e-Fig 2D) were observed.

Discussion

To our knowledge, our study provides the first dose-response analysis of the effects of physical prehabilitation

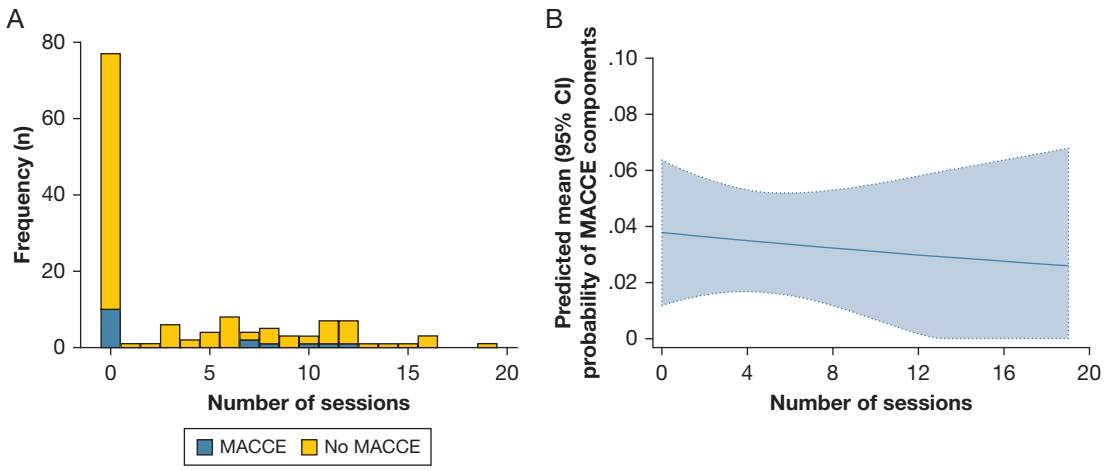

Figure 2 – *A, B, Risk of MACCE: (A) incidence of postoperative day 90 (POD90) MACCEs across range of training sessions completed, and (B) dose of prehabilitation effect on risk of POD90 MACCE components (myocardial infarction, stroke, acute renal failure, reoperation, and death). The model was adjusted for baseline Clinical Frailty Scale, time available for exercise training, and type of cardiac surgery. MACCE = major cardiac and cerebrovascular event.*

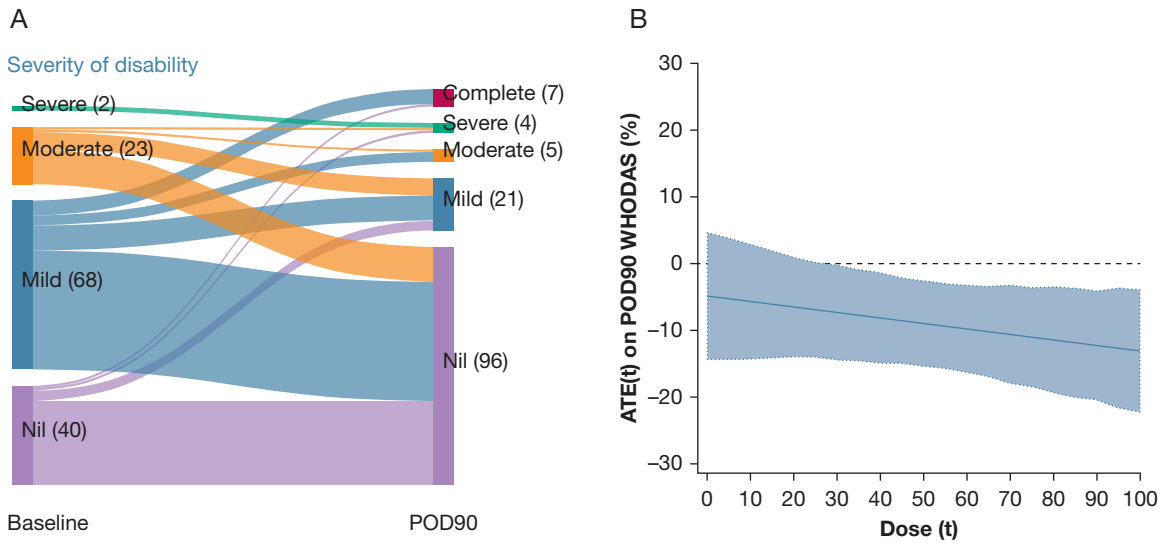

Figure 3 – *A, WHODAS score (%): Sankey diagram showing changes in severity of disability (nil: < 5%, mild: 5%-24%, moderate: 25%-49%; severe: 50%-95%; complete: > 95%) from baseline to POD90 in 133 participants (missing paired data in 1 participant). (B) Dose-response function model: ATE(t) on POD90 WHODAS (%) across range of training sessions completed. The model was adjusted for baseline WHODAS (%), baseline Clinical Frailty Scale, time available for exercise training, and type of cardiac surgery. Each training session is equivalent to 5.26 on the dose (t) 0 to 100 scale. Dose-response curves are ATE(t) and 95% CI. ATE(t) = average treatment effect given the level of treatment, with t representing the continuous treatment variable; Dose (t) = dose intensity; POD90 = postoperative day 90; WHODAS = World Health Organization Disability Assessment Schedule 2.0.*

on postoperative complications and disability levels. Using causal methodology, we identified a linear dose-effect relationship between prehabilitation and 90-day disability levels. It took approximately ≥ 3 weeks of supervised prehabilitation (twice weekly consecutive sessions) to begin observing (near clinically meaningful) disability improvements (up to 4%) after adjusting for all 3 frailty measures. When assessing physical function, 7 weeks (or more) of prehabilitation was required to achieve the MCID for the 6MWT, with gains of ≥ 25 m, alongside modest METs improvements. Of note, exercise-induced adverse effects were not observed in the patients in > 500 training sessions. Although 1 in 8 patients experienced MACCEs, with acute renal failure being the most frequent complication, the dose of prehabilitation was not associated with a reduction in MACCE risk, a finding consistent with previous systematic reviews showing no cardiac prehabilitation

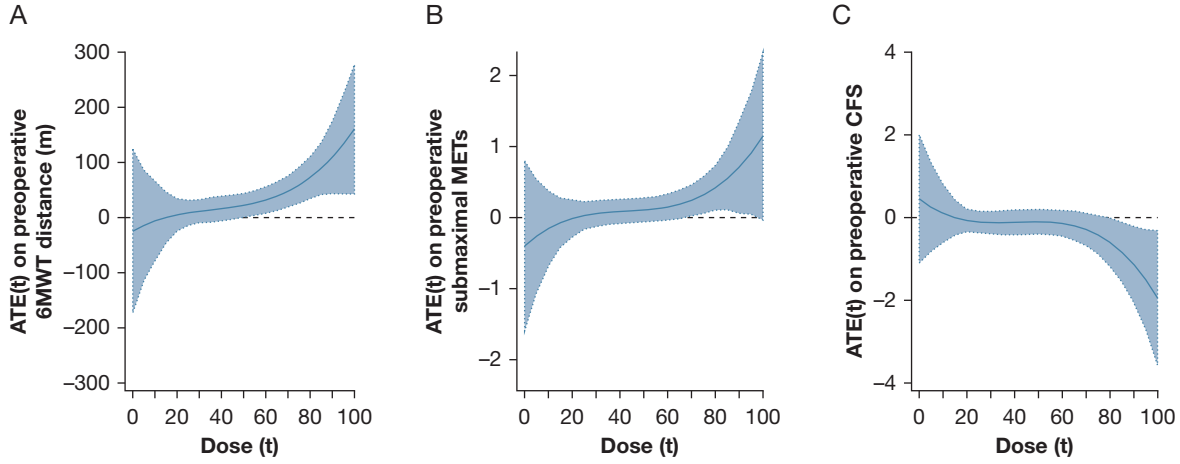

Figure 4 – *A-C, Dose-response function models: (A) ATE(t) on 6MWT distance (m) across range of training sessions completed, (B) ATE(t) on METs across range of training sessions completed, and (C) ATE(t) on CFS across range of training sessions completed. All models were adjusted for baseline outcome measures, baseline CFS, time available for exercise training, and type of cardiac surgery. Each training session is equivalent to 5.26 on the Dose (t) 0 to 100 scale. Dose-response curves are ATE (t) and 95% CI. 6MWT = 6-min walk test; ATE(t) = average treatment effect given the level of treatment, with t representing the continuous treatment variable; CFS = Clinical Frailty Scale; Dose (t) = dose intensity; MET = metabolic equivalent of tasks.*

effects on postoperative stroke, acute kidney injury, and perioperative mortality.[6,7] We also could not confirm a dose-response effect on preoperative EFT scores or 5-m GSTs. Nonetheless, subtle improvements in CFS scores were observed after 7 weeks of prehabilitation. Overall, these results suggest that in patients who can comply with prehabilitation, physical training may enhance functional recovery after surgery.

Systematic reviews of prehabilitation programs indicate that 54%[27] to 77%[28] of the included studies had a duration of at least 4 weeks before surgery to optimize patients' health status. Significant clinical and methodologic heterogeneity in the frequency, intensity, and duration of prehabilitation existed in these studies. Some authors have suggested an ideal prehabilitation duration of 6 to 8 weeks, balancing patient compliance and effectiveness in reducing the risk of postoperative complications.[29]

Patients' real adherence rates to cardiac prehabilitation programs are rarely reported.[6] This may, at least in part, explain the inconsistency in reported outcomes. Although an association between patient compliance and better clinical outcomes has not been established in prehabilitation studies, high compliance rates with enhanced recovery after surgery protocols are associated with improved outcomes.[30,31] Although compliance itself does not guarantee better outcomes, it likely contributes to them. Higher compliance rates imply exposure to greater exercise prehabilitation, but this is not necessarily true. For example, if a patient started our prehabilitation program 6 weeks before surgery and completed 6 supervised sessions (50% compliance), and another patient started 3 weeks before surgery and completed 6 supervised sessions (100% compliance), their dose of exercise prehabilitation would be equivalent, despite the wide difference in compliance. In this study, we have taken the approach of defining the combination of frequency (twice weekly), intensity (achieving between 40% and 80% oxygen uptake reserve for 20-60 minutes through aerobic exercise, and resistance training), and then quantifying the total number of sessions completed as the objective dose of exercise prehabilitation achieved.

The dose-response analysis in this study used a counterfactual design to estimate varying levels of prehabilitation exposure across participants, offering a unique and comprehensive evaluation of the dose requirement of prehabilitation on perioperative outcomes. This approach provides novel insights into the minimum prehabilitation dosage needed to accumulate and confer cumulative therapeutic benefits. Notably, we observed improvements in preoperative exercise capacity after 4 to 5 weeks of training, consistent with previous physiology literature indicating that 4 to 6 weeks of consistent strength training are needed to improve fitness levels through neural and muscular adaptations.[32] Mitigating frailty via prehabilitation within a few weeks is difficult because frailty is a chronic condition and its underlying mechanisms may involve more than a lack of exercise alone. The subtle dose-response effect on preoperative CFS we observed here is promising, similar to the result of another study on this issue.[33]

We propose a new framework that shifts the focus from being fit for surgery to a more patient-centered approach of being fit for quality of life after surgery. Although preliminary, the implications for practice and policy from our study suggest that adequate resources and funding should be provided to further explore and document the effects of hospital-based exercise prehabilitation programs, and to integrate them into existing perioperative care pathways.[34] Taken together with our data, prehabilitation of sufficient dose could provide an effective strategy to enhance both mobility and mental function perioperatively.[35]

This study had several limitations. First, home exercise compliance was not objectively documented using wearable devices,[9] introducing possible unmeasured or residual confounding. Second, the findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory. Although the causal DRF analysis technique showed positive relationships between the number of physical prehabilitation sessions at the intensity and frequency described and perioperative outcomes, it remains unclear whether delivering the same number and intensity of sessions thrice-weekly or more frequently offers equivalent benefits to twice-weekly sessions, potentially allowing for the optimal dose of prehabilitation to be provided over a shorter prehabilitation period. Third, METs values reported here were estimated because cardiopulmonary exercise testing was unavailable and likely an underestimation of those measured by cardiopulmonary exercise testing.[36] Fourth, our results may not be fully generalizable to other settings where patient race, demographics, lifestyle risk factors, frailty levels, case-mix, and health care systems may be different to our center.[37-40] Specifically, feasibility of

cardiac prehabilitation programs relies heavily on accessibility,[41] and in this regard, many patients with limited mobility and who resided far from the study center (> 20 km) were not recruited in this trial.[42] Finally, selection bias may be present in a small subgroup of patients (< 10%) who had less opportunity to engage in prehabilitation because their surgeries were scheduled earlier than planned.

Interpretation

In cardiac surgical patients with frailty, physical prehabilitation showed a favorable dose-related effect on exercise capacity before surgery, and disability scores at 90 days after surgery. Future prehabilitation studies should emphasize delivering sufficient consecutive doses of physical prehabilitation to maximize its effectiveness on clinical outcomes.

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