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Randomized Control Trials

Effects of preoperative beta-hydroxy-beta-methylbutyrate, arginine, and glutamine supplementation on cardiac surgery: A randomized controlled trial

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SUMMARY

Background & aims: In older patients undergoing cardiac surgery, physical function is a critical determinant of postoperative outcomes. Beta-hydroxy–beta-methylbutyrate (HMB) supplementation has been shown to promote muscle protein anabolism and inhibit catabolism, thereby preventing muscle weakness. However, its efficacy in older patients undergoing cardiac surgery remains unknown. This study aimed to examine the effects of preoperative HMB supplementation on postoperative physical function and complications in this population.

Methods: In this single-center, open-label, randomized controlled trial, patients aged ≥65 years scheduled for cardiac surgery were randomized to receive HMB supplementation or no nutritional intervention. The HMB group received HMB 1200 mg, L-glutamine 7000 mg, and L-arginine 7000 mg, once or twice daily, for at least 2 weeks before surgery. Evaluations were performed at baseline and before and after surgery. The primary outcome was the 6-min walking distance (6MWD) before and after surgery. Secondary outcomes included the incidence of complications, muscle mass and strength, physical performance, and length of hospital stay.

Results: Forty-four patients with a mean age of 72.5 years (women, 38 %) were randomized to the HMB (n = 22) or control (n = 22) group. Compared with the control group, the HMB group demonstrated a statistically significant improvement in the 6MWD both at the pre-surgery (448.0 ± 73.5 m vs. 375.5 ± 58.8 m; $P = 0.01$) and post-surgery time points (428.9 ± 76.4 m vs. 304.5 ± 52.3 m; $P = 0.001$). Muscle strength and physical performance also showed significant improvements in the HMB group. However, no significant difference in muscle mass was observed between the groups at any time point. The HMB group had a shorter hospital length of stay compared with that of the control group (16.1 ± 3.8 days vs. 20.4 ± 7.6 days, $P = 0.03$), and no adverse events were observed with the intervention.

Conclusions: Preoperative HMB supplementation in older adults undergoing cardiac surgery resulted in significant improvements in postoperative exercise capacity and physical function, along with a reduction in the length of hospital stay, without affecting muscle mass.

Abbreviations: BIA, bioelectrical impedance analysis; eGFR, estimated glomerular filtration rate; GH, growth hormone; HMB, Beta-hydroxy–beta-methylbutyrate; IGF-1, insulin-like growth factor-1; PhA, phase angle; SPPB, Short Physical Performance Battery.

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1. Introduction

Prehabilitation, a strategy aimed at enhancing patients' functional capacity prior to surgery to improve postoperative outcomes, has garnered significant attention due to the increasing age and prevalence of frailty and comorbidities among patients awaiting cardiac surgery [1]. Frailty is associated with an increased risk for major complications after cardiac surgery in older patients and is a strong predictor of postoperative morbidity and mortality [2,3]. Prehabilitation includes multiple-domain interventions, including exercise prescription, nutritional support, respiratory muscle training, lifestyle modification, and psychological support [4,5]. However, preoperative unsupervised exercise training often presents challenges, including concerns regarding the safety of such exercises, potential worsening of heart failure, and patient fear and anxiety [6].

Consequently, our emphasis shifted to nutritional support to prevent postoperative loss of muscle mass and strength. Beta-hydroxy−beta-methylbutyrate (HMB) is an active metabolite of the essential amino acid leucine [7]. Approximately 5 % of all leucine is converted into HMB, which is widely used as a nutritional supplement to maintain skeletal muscle mass. HMB exerts its effects on muscle protein metabolism through multiple mechanisms. It promotes muscle protein synthesis by increasing the activity of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis and stimulating the mammalian target of rapamycin signaling pathway [8]. Activation of the mTOR pathway plays a crucial role in muscle protein synthesis, leading to increased protein production and muscle growth. Furthermore, HMB reduces protein breakdown by modulating catabolic signaling pathways, including ubiquitin-proteasome and autophagy-lysosome systems [9]. HMB helps to preserve muscle mass and inhibits proapoptotic pathways in catabolic states that often occur after surgery [10].

In addition to the effects of HMB, other amino acids such as arginine and glutamine have also been recognized for their potential roles in promoting muscle protein synthesis and supporting recovery from surgery. Both arginine and glutamine are conditionally essential amino acids that become crucial during periods of high physiological stress, such as surgery [11]. Glutamine has been shown to improve nitrogen balance, shorten hospital stays, and reduce infection rates in surgical patients [12]. Arginine has demonstrated benefits in promoting protein anabolism and wound healing [13]. The combination of these three amino acids may offer synergistic effects in supporting muscle protein synthesis and overall recovery from surgery.

In older adults with sarcopenia, HMB supplementation significantly improved muscle strength, physical performance, and muscle quality and reduced inflammatory marker levels [14]. A prior study in the field of orthopedics reported that preoperative HMB supplementation prevented postoperative muscle weakness [15]. However, studies examining the effects of preoperative nutritional support in patients undergoing cardiac surgery are scarce [16]; specifically, evidence on the efficacy of HMB supplementation remains elusive.

Therefore, this study aimed to investigate the effects of preoperative HMB supplementation on postoperative physical function and complications in older patients undergoing cardiac surgery.

2. Material & methods

2.1. Study design

This prospective, randomized, open-label, controlled trial was conducted at a 1000-bed teaching hospital in Kobe, Japan. The study was registered at UMIN (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno = R000034773; unique identifier: UMIN000030490), and the study protocol was published [17]. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki, approved by the Kobe University Institutional Review Board (approval no. 300002) on May 24, 2018, and reported according to the CONSORT statement. All patients provided written informed consent before participating in the study.

2.2. Recruitment and eligibility

The recruitment period was from December 2018 through March 2023. At the baseline visit, demographic, socioeconomic status, and medical history data were collected, and all patients underwent physical examination and laboratory testing. Patient eligibility was assessed after the completion of all baseline measurements.

The inclusion criteria were age ≥65 years and feasibility of nutritional supplementation for at least 2 weeks before surgery. The exclusion criteria were as follows: 1) B-type natriuretic peptide level >500 pg/mL; 2) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2; 3) presence of a pacemaker or implantable cardioverter-defibrillator; 4) severe liver function impairment; 5) inability to complete the exercise test; and 6) use of protein or amino supplements on a routine basis.

2.3. Randomization and allocation concealment

Eligible patients were randomized at a 1:1 ratio to receive HMB supplementation or no nutritional intervention using a permuted block randomization scheme, stratified by age (<75 vs. ≥ 75) and sex. Due to the nature of the intervention, blinding of patients and clinicians was not feasible. However, data management and outcome assessment were performed by blinded researchers, separate from the staff who managed patients' allocation.

2.4. Interventions

The intervention group received HMB supplementation (Abound®; Abbott, State of Illinois, USA) for a minimum of 14 days before surgery. One pack of Abound® (24 g) consists of 1500 mg of HMB-Ca, 7000 mg of L-glutamine, 7000 mg of L-arginine, and 0 mg of protein, providing 79 kcal of energy. Patients without chronic kidney disease received one pack of Abound® twice per day, while

those with chronic kidney disease (eGFR <60 mL/min/1.73 m^2) received one pack of Abound® per day. Compliance with HMB supplementation was manually recorded daily on a prescribed form during the intervention period. In addition, compliance was verified via telephone by a dietitian and by checking empty packages of the nutritional supplement. Patients with a compliance rate of <50 % were considered to be dropped out. The control group did not participate in any nutritional support program and only received routine clinical care during the hospital stay.

In both groups, patients received instructions from a physical therapist regarding exercise during the waiting period before surgery. Specifically, resistance training and aerobic exercise were prescribed for each patient according to their abilities. Dietary intake was evaluated by a dietitian using the Food Frequency Questionnaire, which is a reliable method for measuring consumption of specific foods or nutrients [18].

2.5. Study outcomes

All evaluations were conducted at baseline (T1), on the day before surgery (T2), and 2 weeks after surgery (T3). HMB supplementation was taken between T1 and T2.

2.5.1. Primary outcome

The primary outcome was the 6-min walking distance (6MWD) measured on T2 and T3 by a physiotherapist blinded to the allocation.

2.5.2. Secondary outcomes

Secondary outcomes included physical function, muscle mass and strength, length of hospital stay, and incidence of complications. Physical function was assessed by grip strength, knee extensor muscle strength, Short Physical Performance Battery (SPPB) scores, and gait speed. Details of the measurement methods were published previously [17]. Muscle mass was assessed by bioelectrical impedance analysis (BIA) using the InBody S10 (Bio-Space Japan, Tokyo, Japan) device. Muscle quality was assessed based on the phase angle (PhA) determined by BIA, and as the ratio of muscle strength to muscle mass separately in the upper and lower extremities, as previously described [19–21]. The PhA is associated with key cellular properties; a higher PhA correlates with enhanced cellular function, indicating superior muscle quality [22]. The ratio of muscle strength to muscle mass is an indicator of muscle quality during exercise. Blood samples were collected after an overnight fast and were used to determine the levels of blood urea nitrogen, creatinine, cholesterol, and proteins, including albumin, transferrin, transthyretin, and retinol-binding protein.

2.6. Sample size calculation

For analysis of the primary outcome with a power of 80 %, a total of 182 patients (91 in each group) were needed to demonstrate a minimal clinically important difference of 25 m in the 6MWD. The minimal clinically important difference in the 6MWD was calculated based on prior studies, which reported a minimum difference of 30 m [23,24]. Assuming a standard deviation in the 6MWD of 100 m, according to our previous study [25], and a dropout rate of up to 10 %, a total of 200 patients were planned to be recruited.

2.7. Statistical analysis

Data analysis was performed based on the intention-to-treat method; all patients who started the allocated intervention were included in the analysis. The Shapiro–Wilk test was used to determine data normality. Continuous data were summarized as mean values with standard deviations if normally distributed or median values with interquartile ranges (25th–75th percentiles) if skewed. Categorical data were summarized as numbers with percentages.

Differences between the two groups at T2 and T3 were evaluated using the chi-square or Fisher's exact test for categorical data and Student's t-test or Mann–Whitney's U test for continuous data depending on their distribution. Although baseline randomization was ensured by the study design, we conducted additional sensitivity analyses by employing analysis of covariance adjusted for baseline values and by comparing differences from baseline using a t-test for continuous variables.

All analyses were performed using R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). For all tests, *P*-values less than 0.05 were considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

The study flow diagram is shown in Fig. 1. Of the 64 patients assessed for eligibility, 20 were excluded, and 44 were randomized to the HMB (n = 22) or control group (n = 22). After randomization, one patient in the HMB group dropped out after the T2 evaluation and was not evaluated at T3. Eventually, 44 patients were included in the intention-to-treat analysis.

Table 1 shows the patients' baseline demographic and clinical characteristics. The mean age was 72.5 years, and 36 % were women. Approximately half of the patients (45 %) had hypertension, 20 % had chronic obstructive pulmonary disease, and 16 % had chronic kidney disease. Baseline energy and protein intake were 32.7 kcal/kg/day and 1.1 g/kg/day, respectively. Based on the baseline renal function assessment, 8 (36.3 %) patients received one pack and 14 (63.7 %) patients received two packs of nutritional supplements per day. During the intervention period of 689 patient days (median, 30.5 days; range, 18–39 days per patient), the treatment adherence rate in the HMB group was 95.2 % (range, 77.3–100.0 %), and no patients dropped out of taking supplements. No serious adverse events, such as serious renal or hepatic dysfunction, were recorded in the HMB group.

Table 2 compares the intra- and postoperative characteristics between the two groups. Valve surgery was performed in 95 % of cases, with no significant differences in surgical variables, such as operative time or cardiopulmonary bypass time, between the groups.

3.2. Primary outcome

The baseline 6MWD was 405.6 ± 61.1 m. Compared with the control group, the HMB group demonstrated a statistically significant improvement in the 6MWD relative to the baseline values both at T2 (448.0 ± 73.5 m vs. 375.5 ± 58.8 m; group difference, 72.5 (30.3–114.7); $P = 0.01$) and T3 (428.9 ± 76.4 m vs. 304.5 ± 52.3 m; group difference, 124.4 (82.1–166.8); $P = 0.001$; Table 3, Fig. 2a). Statistical adjustment for baseline values did not alter the observed advantage of the HMB group. The difference from baseline in the HMB and control groups was 27.0 ± 28.9 m and −12.6 ± 15.7 m at T2, and 12.1 ± 44.9 m −83.6 ± 42.3 m at T3, respectively (Supporting Information Table S1, Fig. 2b), with the HMB group demonstrating a significantly lower postoperative decline in the 6MWD.

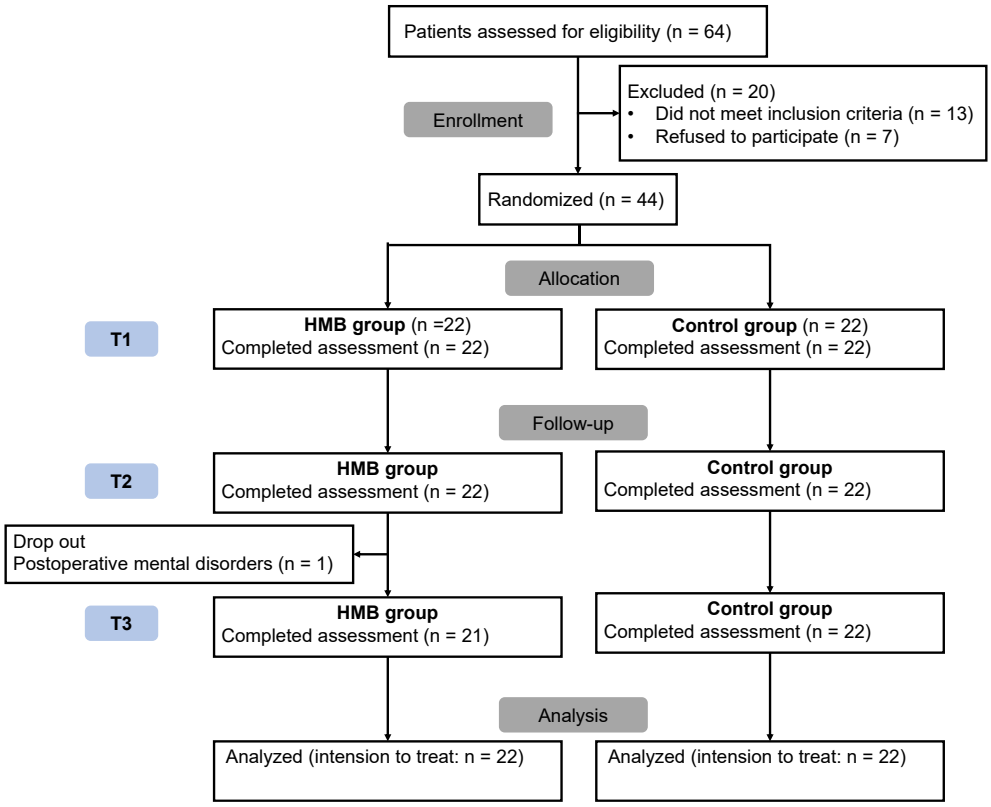

Fig. 1. Study flowchart. HMB, beta-hydroxy−beta-methylbutyrate.

3.3. Secondary outcomes

Physical function, including grip strength, knee extensor muscle strength, SPPB scores, and gait speed, showed similar trends, with significantly better values in the HMB group than in the control group at both T2 and T3 (Table 3, Fig. 3). This trend was similar after the analysis of covariance adjusted for baseline values. In contrast, muscle mass assessed by BIA did not differ between groups, both at T2 and T3 (HMB vs. control: group difference, 0.2 [−6.1 to 6.5], $P = 0.95$ at T2, and -0.1 [−6.2 to 6.0], $P = 0.98$ at T3; Table 3). Regarding muscle quality, compared with the control group, the HMB group showed significant improvement from baseline at T2, including PhA and upper and lower muscle quality; however, the results were inconsistent at T3 (Fig. 4). Upper and lower extremity MQ were significantly improved in the HMB group at T2 ($P < 0.05$ for each). Importantly, the improvement in lower extremity MQ persisted at T3 ($P = 0.0014$). The length of intensive care unit stay did not differ between the groups, whereas the length of hospital stay was significantly shorter in the HMB group than in the control group (16.1 ± 3.8 days vs. 20.4 ± 7.6 days, $P = 0.03$; Table 2). Postoperative rehabilitation progressed smoothly in the HMB group, with a significantly lower number of days to postoperative walking independence in the HMB group. In-hospital complications occurred in 3 (14 %) patients in the HMB group and 5 (23 %) patients in the control group without a significant between-group difference ($P = 0.29$). The majority of postoperative complications were infections, predominantly pneumonia and urinary tract infections.

4. Discussion

To the best of our knowledge, this is the first randomized controlled trial evaluating the effects of preoperative HMB supplementation on physical function. In this study, preoperative HMB supplementation provided a significant benefit over usual care and helped to prevent the decline of physical function in older adults who underwent cardiac surgery. Furthermore, HMB supplementation resulted in a shorter length of hospital stay compared with that in the control group. No significant difference was found in muscle mass at any time point, regardless of the intervention; however, muscle quality did improve with the HMB intervention (Fig. 5).

The discrepancy observed between the positive changes in muscle strength and exercise capacity with HMB supplementation and the lack of change in muscle mass could be explained by the multifactorial character of muscle function. Muscle strength is determined not only by muscle mass but also by neurological factors, muscle quality, and metabolic efficiency [26]. In the present study, while HMB supplementation did not alter muscle mass, it improved muscle quality before surgery. In fundamental studies involving rats, HMB supplementation increased muscle adenosine triphosphate content and enhanced branched-chain amino acid concentrations [27]. Furthermore, HMB has been shown to reduce excessive inflammation or protein degradation [28,29], which could contribute to enhanced muscle strength without a concomitant increase in muscle mass. This is supported by recent trials which indicated that HMB significantly enhances muscle quality and reduces inflammatory factors in patients with sarcopenia [14]. Similarly, in the current study, short-term HMB intake successfully improved muscle quality, resulting in enhanced muscle strength per unit area or PhA. Consequently, we concluded that muscle strength and physical performance can be preserved despite the unavoidable loss of muscle mass postoperatively. Morisawa et al. [30] demonstrated that preoperative muscle quality, as assessed by PhA, has a significant impact on postoperative activities of daily living, which is consistent with our findings. Nonetheless, further

Table 1
Patient baseline demographic and clinical characteristics.

Characteristic	Overall, N = 44[a]	HMB group, N = 22[a]	Control group, N = 22[a]
Age, years	72.5 ± 4.9	71.8 ± 4.9	73.3 ± 4.8
Sex, female	16 (36 %)	7 (32 %)	9 (41 %)
BMI, kg/m^2	21.5 ± 3.3	21.5 ± 3.2	21.5 ± 3.5
NYHA, I/II/III, n	3/23/18	2/13/7	1/10/11
Laboratory data			
BNP, pg/mL	165.2 ± 134.5	127.6 ± 109.0	199.4 ± 148.3
Hemoglobin, g/dL	13.4 ± 1.2	13.2 ± 1.3	13.5 ± 1.2
eGFR, mL/min/1.73m[b]	64.3 ± 16.2	61.6 ± 13.8	66.8 ± 18.2
BUN, mg/dL	17.3 ± 4.4	17.4 ± 4.3	17.2 ± 4.7
MNA-SF	11.5 ± 2.6	11.9 ± 1.9	11.1 ± 3.1
LVEF, %	63.1 ± 9.1	63.3 ± 10.0	63.3 ± 10.0
Comorbidities, n (%)			
Hypertension	20 (45 %)	7 (32 %)	13 (59 %)
Diabetes mellitus	10 (23 %)	4 (18 %)	6 (27 %)
Chronic kidney disease	7 (16 %)	2 (9 %)	5 (23 %)
Dyslipidemia	13 (30 %)	6 (27 %)	7 (32 %)
COPD	9 (20 %)	4 (18 %)	5 (23 %)
Physical function			
Grip strength, kg	28.4 ± 8.9	30.2 ± 8.2	26.8 ± 9.4
SPPB Score, points	11.5 ± 0.9	11.7 ± 0.7	11.4 ± 1.1
Gait speed, m/s	1.0 ± 0.1	1.1 ± 0.1	1.0 ± 0.1
Quadriceps isometric strength, N/kg	4.2 ± 1.1	4.4 ± 1.0	3.9 ± 1.1
6-min walking distance, m	405.6 ± 61.1	421.0 ± 62.3	391.6 ± 57.8
Appendicular skeletal muscle mass, kg	17.4 ± 4.9	17.5 ± 4.6	17.3 ± 5.2
Muscle quality			
Phase angle, degree	4.9 ± 0.7	5.0 ± 0.7	4.9 ± 0.7
Upper extremity MQ	13.9 ± 2.3	14.5 ± 2.5	13.2 ± 1.9
Lower extremity MQ	36.1 ± 9.3	38.4 ± 7.8	34.0 ± 10.1
Energy intake, kcal/kg	32.7 ± 8.6	34.5 ± 9.2	31.1 ± 7.8
Carbohydrates, %	52.2 ± 8.6	54.1 ± 6.2	50.5 ± 10.1
Protein, %	14.0 ± 2.3	13.8 ± 1.7	14.3 ± 2.7
Fat, %	24.0 ± 7.6	23.4 ± 8.1	24.5 ± 7.1
Protein intake, g/kg	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.4
Japan score	3.0 ± 2.5	3.3 ± 3.2	2.7 ± 1.8
Euroscore II	2.2 ± 1.1	2.3 ± 1.0	2.1 ± 1.3

BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HMB, beta-hydroxy–beta-methylbutyrate; LVEF, left ventricular ejection fraction; MNA-SF, Mini Nutritional Assessment Short Form; MQ, muscle quality; NYHA, New York Heart Association; SPPB, Short Physical Performance Battery.
[a] Mean ± standard deviation; n (%).
[b] Welch's two-sample t-test; Pearson's chi-square test; Fisher's exact test.

Table 2
Intra- and postoperative characteristics of the intervention and control groups.

Outcome	Overall, N = 44[a]	HMB group, N = 22[a]	Control group, N = 22[a]	P value
Type of surgery, n (%)				0.17
Valve	42 (95 %)	22 (100 %)	20 (90 %)	
Valve + CABG	2 (5 %)	0 (0 %)	2 (10 %)	
Duration of surgery, min	343.6 ± 65.8	339.3 ± 60.7	347.6 ± 71.4	0.69
CPB time, min	205.7 ± 52.1	210.7 ± 51.3	201.1 ± 53.6	0.57
ACC time, min	152.5 ± 48.6	161.5 ± 50.1	144.3 ± 46.9	0.27
In-hospital complications, %	8 (18 %)	3 (14 %)	5 (23 %)	0.29
POAF, %	20 (45 %)	9 (41 %)	11 (50 %)	0.75
ICU mobility scale				
Day 1	2.9 ± 1.3	3.1 ± 1.2	2.8 ± 1.3	0.40
Day 2	5.7 ± 2.6	6.4 ± 2.7	5.0 ± 2.5	0.11
Day 3	7.2 ± 2.6	8.0 ± 2.3	6.3 ± 2.7	**0.04**
Time to independent walking, day	3.8 ± 1.5	3.2 ± 1.3	4.4 ± 1.5	**0.01**
Length of ICU stay, day	2.7 ± 1.0	2.6 ± 0.9	2.9 ± 1.1	0.33
Length of hospital stay, day	18.4 ± 6.4	16.1 ± 3.8	20.4 ± 7.6	**0.03**
Dietary intake				
1–7- day energy intake, kcal/kg	14.8 ± 4.9	14.8 ± 4.2	14.9 ± 5.5	0.94
1–7- day protein intake, g/kg	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.72
8–14- day energy intake, kcal/kg	23.7 ± 6.4	24.6 ± 5.3	22.8 ± 7.3	0.40
8–14- day protein intake, g/kg	1.0 ± 0.3	1.0 ± 0.2	0.9 ± 0.3	0.36

ACC, aortic cross-clamping; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; HMB, beta-hydroxy–beta-methylbutyrate; ICU, intensive care unit; POAF, postoperative atrial fibrillation.
[2] Welch's two-sample t-test; Pearson's chi-square test; Fisher's exact test.
[a] Mean ± standard deviation; n (%).

Table 3
Exercise capacity, muscle strength, muscle mass, and physical performance in the intervention and control groups.

Outcome	Group		Effect size[b]	Group difference (95 % CI)	P value[c]	P value[d]
	HMB group[a]	Control group[a]				
6-min walking distance, m						
T2	448.0 ± 73.5	375.5 ± 58.8	1.09	72.5 (30.3–114.7)	**0.01**	**0.0001**
T3	428.9 ± 76.4	304.5 ± 52.3	1.03	124.4 (82.1–166.8)	**0.001**	**0.0001**
Grip strength, kg						
T2	31.2 ± 8.3	25.0 ± 9.64	0.70	6.3 (6.0–12.0)	**0.03**	**0.0003**
T3	28.9 ± 7.77	24.0 ± 8.04	0.62	4.9 (−0.2 to 10.0)	0.06	**0.02**
Quadriceps isometric strength, N/kg						
T2	4.7 ± 1.0	3.5 ± 1.1	1.14	1.2 (0.5–1.8)	**0.0007**	**0.0001**
T3	4.3 ± 0.9	3.1 ± 1.0	1.31	1.2 (0.6–1.8)	**0.0002**	**0.0001**
SPPB score, point						
T2	11.9 ± 0.3	11.1 ± 1.3	0.84	0.8 (0.2–1.4)	**0.01**	**0.005**
T3	11.8 ± 0.5	9.7 ± 2.2	1.31	2.1 (1.1–3.1)	**0.0002**	**0.0002**
Gait speed, m/s						
T2	1.1 ± 0.1	1.0 ± 0.1	0.71	0.1 (0.0–0.2)	**0.03**	0.06
T3	1.0 ± 0.2	0.8 ± 0.2	1.32	0.2 (0.1–0.3)	**0.0002**	**0.0002**
Appendicular skeletal muscle mass, kg						
T2	18.1 ± 4.8	20.1 ± 11.5	−0.231	−2.05 (−7.58 to 3.48)	0.50	0.97
T3	16.8 ± 4.6	17.2 ± 5.8	−0.074	−0.387 (−3.75 to 2.98)	0.82	0.82
Phase angle, degree						
T2	5.0 ± 0.6	4.7 ± 0.7	0.470	0.30 (−0.10 to 0.69)	0.14	**0.017**
T3	4.4 ± 0.7	4.2 ± 0.9	0.189	0.16 (−0.37 to 0.68)	0.56	0.85
Upper extremity MQ						
T2	15.0 ± 2.6	12.3 ± 2.2	1.13	2.70 (1.18–4.21)	**0.001**	**0.002**
T3	15.3 ± 2.9	13.2 ± 2.9	0.73	2.12 (0.24–3.99)	**0.028**	0.364
Lower extremity MQ						
T2	38.7 ± 7.0	28.3 ± 12.2	1.04	10.41 (4.16–16.66)	**0.002**	**0.017**
T3	38.2 ± 8.2	26.8 ± 8.5	1.36	11.42 (5.99–16.85)	**< 0.001**	**0.0014**

CI, confidence interval; HMB, beta-hydroxy−beta-methylbutyrate; MQ, muscle quality; SPPB, Short Physical Performance Battery.
[a] mean ± standard deviation.
[b] Cohen's d: small >0.20, medium >0.50, large >0.80.
[c] Analyzed by ANOVA.
[d] Calculated using ANCOVA using generalized estimation equation, adjusted for the effect of baseline value (T1).

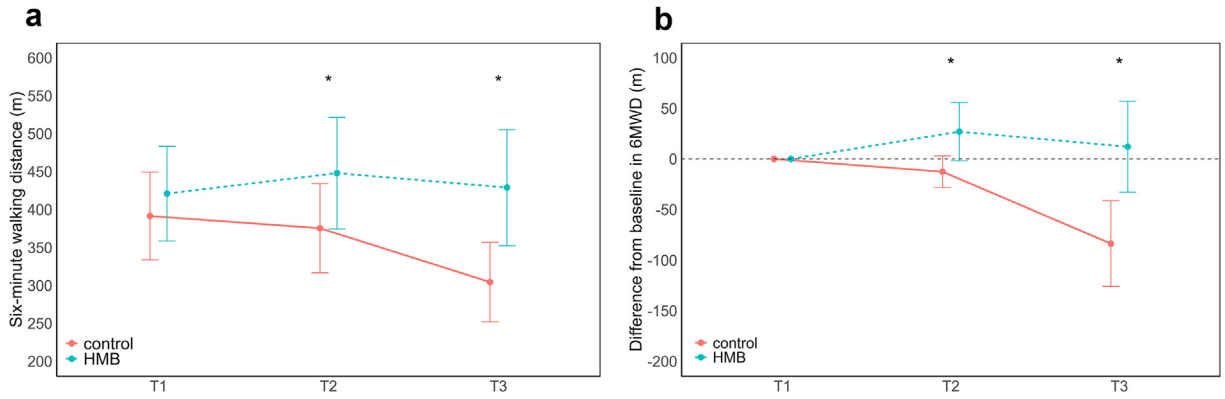

Fig. 2. Change in the 6MWD evaluated at baseline (T1), a day before surgery (T2), and 2 weeks after surgery (T3) in the two groups. (a) Absolute values recorded at each time point; (b) Changes in values from T1 to T2 and from T1 to T3. Values are presented as raw mean ± standard deviation at each time point. *$P < 0.05$. HMB, beta-hydroxy−beta-methylbutyrate; 6MWD, 6-min walking distance.

studies are warranted to determine the extent to which preoperative HMB supplementation suppresses postoperative catabolism, as the patients did not continue HMB intake post-surgery.

These beneficial effects may also be attributed to the synergistic effects of arginine and glutamine included in the supplement. Although evidence directly linking arginine and glutamine to improvements in muscle mass and strength is limited, some studies suggest potential benefits. Arginine may improve metabolic parameters such as insulin resistance [31], indirectly benefiting muscle health and function, and enhance exercise tolerance through improved vascularity [32,33]. Glutamine, crucial for maintaining gut barrier function and supporting immune cells, may contribute to overall recovery by reducing inflammation and enhancing immune responses, although glutamine alone has no effect on aerobic performance and body composition [34]. Future research is needed to further elucidate the specific roles of these amino acids and their optimal combination in perioperative nutritional support.

While studies specifically investigating the combination of HMB, arginine, and glutamine are limited, research in older adults has explored the effects of HMB combined with arginine and lysine. Baier et al. [35] demonstrated that HMB + arginine + lysine supplementation improved protein metabolism in elderly individuals. Similarly, Flakoll [36] reported that this combination led to positive

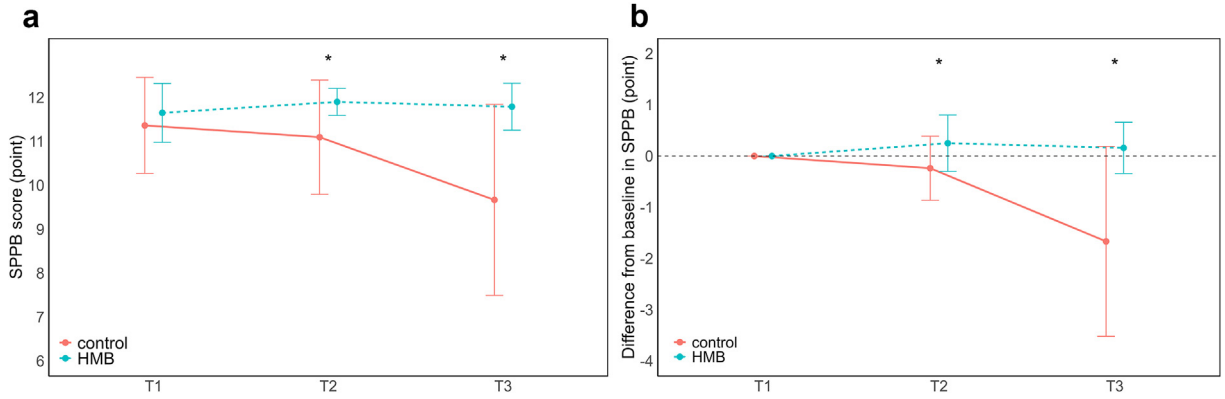

Fig. 3. Change in SPPB scores evaluated at baseline (T1), a day before surgery (T2), and 2 weeks after surgery (T3) in the two groups. (a) Absolute values recorded at each time point; (b) Changes in values from T1 to T2 and from T1 to T3. Values are presented as raw mean ± standard deviation at each time point. *$P < 0.05$. HMB, beta-hydroxy–beta-methylbutyrate; SPPB, short physical performance battery.

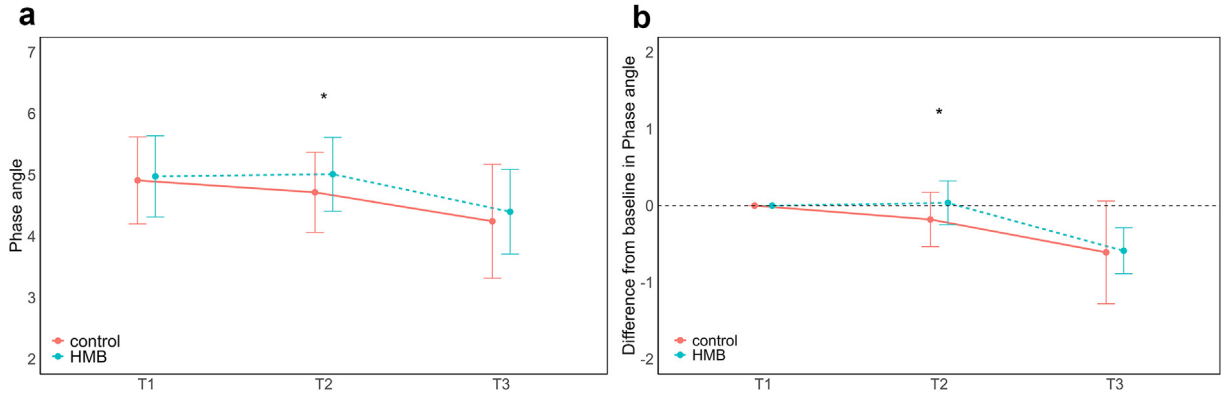

Fig. 4. Change in the phase angle at baseline (T1), a day before surgery (T2), and 2 weeks after surgery (T3) in the two groups. (a) Absolute values recorded at each time point; (b) Changes in values from T1 to T2 and from T1 to T3. Values are presented as raw mean ± standard deviation at each time point. *$P < 0.05$. HMB, beta-hydroxy–beta-methylbutyrate.

changes in measures of muscle strength, lean body mass, and protein synthesis. These findings align with our observations, suggesting that the combination of HMB and arginine, even with variations in the third amino acid component, may exert synergistic effects on muscle function and protein metabolism. This highlights the potential of amino acid-related cocktail interventions to enhance muscle health and physical performance in older adults. On the other hand, some studies have reported that HMB + arginine + glutamine is effective in wound healing and pressure ulcer management [37]. However, these studies often focused on bedridden older individuals with severely impaired nutritional status. This may explain why we did not observe a significant reduction in postoperative complications, which was one of our secondary endpoints.

While some prior studies suggest that HMB may require approximately 3 months to improve muscle mass, others have reported no significant changes in muscle mass even after 3 months of HMB supplementation; thus, the lack of observed muscle mass improvement in this study is consistent with these findings [14,38,39]. In our study, both groups were only provided exercise instructions without a supervised exercise intervention. Consequently, while additional synergistic effects might be anticipated with exercise, the findings demonstrate that HMB supplementation alone can enhance postoperative outcomes through improved muscle quality rather than increased muscle mass. There is currently no consensus regarding the optimal duration of HMB supplementation. However, clinical studies involving community-dwelling older adults have noted improvements in muscle mass and quality following 8–12 weeks of administration [36,40]. Although the optimal duration of preoperative intervention is seldom reported, there are isolated instances of enhanced postoperative outcomes following a preoperative period of 5 days in orthopedic surgery [15] and 30 days in cardiac surgery [41]. In our study, the preoperative period was approximately 1 month, which may have been sufficient to contribute to improved postoperative recovery by mitigating muscle damage associated with surgery and subsequent rehabilitation exercises. It is important to note that postoperative HMB intervention was not feasible in this instance due to concerns regarding Acute kidney injury [42]. Further research is needed to explore the potential effects of postoperative HMB administration on muscle mass and overall recovery.

In recent years, due to the increasing number of patients of older age with frailty and multiple comorbidities, prehabilitation, which emphasizes exercise prescription and nutritional support, is strongly recommended as a tool to improve postoperative outcomes [1,4,43,44]. Regarding exercise training, according to current guidelines, most exercise training methods are generally contraindicated in patients with severe valvular heart disease indicated for surgery [45], leading clinicians to advise patients not to exercise while they wait for surgery. In particular, unsupervised home-based exercise presents considerable challenges due to the absence of standardized exercise intensity and safety. In contrast, nutritional support is a more feasible intervention in the real world, encountering fewer obstacles and enjoying greater patient

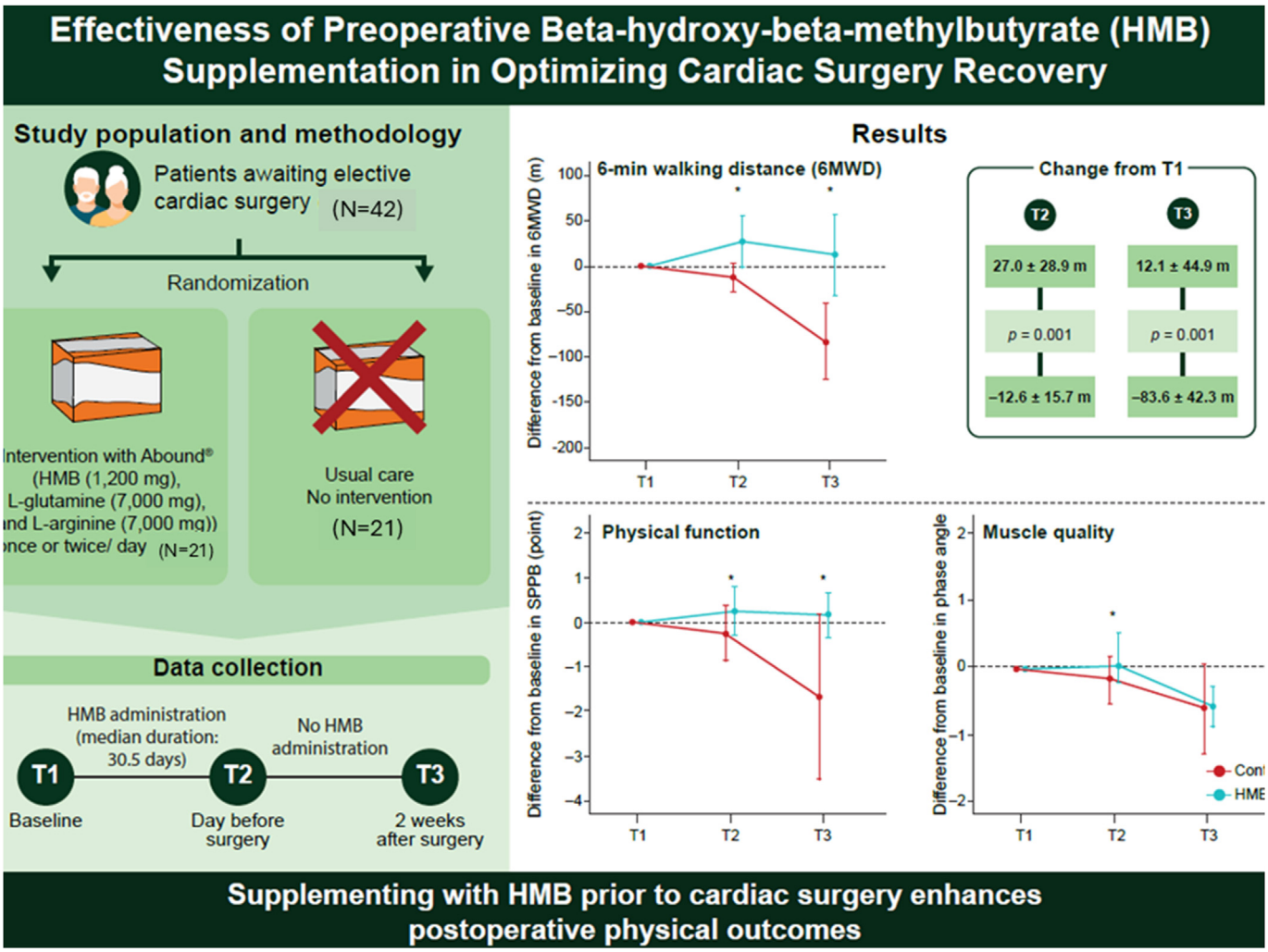

Fig. 5. Summary of the study.

acceptance [6]. In fact, adherence was extremely high in this study at 95 %, even surpassing those observed in clinical trials with community-dwelling older patients [46]. This heightened adherence may be attributed to the imminent nature of the surgery, and the ease with which family support and motivation are maintained. Furthermore, although renal failure is a common comorbidity in patients undergoing cardiac surgery, we found no increase in the incidence of adverse reactions or complications due to worsening renal function, suggesting the safety of the intervention for clinical application. Additionally, recent focus has been placed on postoperative decline in physical function, with the ability to perform activities of daily living as a prognostic factor [47,48]. In the present study, the HMB group exhibited a lower decline in the 6MWD by 95 m compared with the control group, surpassing the clinically significant threshold of 30–48 m which is commonly observed in patients with heart failure [23,24]. It is also greater than the estimated mean difference of 60.4 m in response to changes in clinical status after cardiac rehabilitation [49]. These findings propose that preoperative HMB supplementation could become standard care in the perioperative period.

This study has some limitations. First, because of the open-label design, it was more prone to detection bias and placebo effect than closed-label placebo treatments [50]. Despite the recognized advantages of a placebo-controlled design, various logistical and practical challenges precluded its implementation in this study. However, to minimize bias and maintain objectivity, outcome assessments and treatment assignments were performed by independent researchers. Moreover, established objective methods for assessing physical function were used. While these results are promising, it's important to consider the potential impact of bias and placebo effects. Additionally, although the intervention primarily focused on HMB, arginine, and glutamine, the potential influence of other components in the supplement on the observed outcomes cannot be completely ruled out. Second, the number of patients in this study was small and did not reach the calculated sample size. The trial was stopped earlier than expected due to a greater than expected difference between the HMB group and the control group in the primary outcome (6MWD). While significant improvements in 6MWD, along with consistent improvements in other measures of physical function, support the clinical validity of our findings, smaller sample sizes may have reduced the precision of subgroup analyses, making it more difficult to assess the effects of interventions in specific populations and reducing the generalizability of the results. This was due to differences in the primary outcome that were greater than expected, which is why the study ended earlier than expected. Third, this study did not include a

postoperative HMB intervention due to concerns regarding potential complications, such as acute kidney injury, and the lack of research on the safety of high-volume protein interventions in the very early postoperative period after elective surgery. Therefore, the results observed in this study, particularly those at T3, may have been different if postoperative HMB supplementation had been provided. Finally, the study was conducted in Japanese patients, with an average body mass index of 21.5, which is lower than that reported in Europe and the United States. Hence, the worldwide applicability of our findings should be considered carefully.

5. Conclusions

In this single-center randomized trial, HMB supplementation proved effective in improving postoperative muscle strength and exercise capacity in older patients undergoing cardiac surgery, although without a protective effect on muscle mass. Furthermore, HMB supplementation facilitated early postoperative discharge. Therefore, preoperative HMB supplementation could be a valuable prehabilitation strategy, particularly for patients with diminished physical function.

Author contributions

Masato Ogawa: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Writing - original draft; Writing - review & editing.

Seimi Satomi-Kobayashi: Conceptualization; Funding acquisition; Project administration; Writing - review & editing.

Naofumi Yoshida: Conceptualization; Software; Visualization; Writing - review & editing.

Kodai Komaki: Investigation; Writing - review & editing.

Takumi Hirabayashi: Investigation; Writing - review & editing.

Kumiko Wakida: Investigation; Writing - review & editing.

Saori Saitoh: Investigation; Writing - review & editing.

Takeshi Inoue: Conceptualization; Writing - review & editing.

Tomoya Yamashita: Project administration; Supervision; Writing - review & editing.

Yoshitada Sakai: Project administration; Supervision; Writing - review & editing.

Michiko Takahashi: Conceptualization; Writing - review & editing.

Kenji Okada: Supervision; Writing - review & editing.

Ken-ichi Hirata: Supervision; Writing - review & editing.

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Conflict of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.12.030.

References

[1] Engelman DT, Ben Ali W, Williams JB, Perrault LP, Reddy VS, Arora RC, et al. Guidelines for perioperative care in cardiac surgery: enhanced recovery after surgery society recommendations. JAMA Surg 2019;154:755–66.
[2] Ogawa M, Izawa KP, Satomi-Kobayashi S, Tsuboi Y, Komaki K, Gotake Y, et al. Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery. PLoS One 2017;12:e0190359.
[3] Sepehri A, Beggs T, Hassan A, Rigatto C, Shaw-Daigle C, Tangri N, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. J Thorac Cardiovasc Surg 2014;148:3110–7.
[4] McCann M, Stamp N, Ngui A, Litton E. Cardiac prehabilitation. J Cardiothorac Vasc Anesth 2019;33:2255–65.
[5] Humphrey R, Malone D. Effectiveness of preoperative physical therapy for elective cardiac surgery. Phys Ther 2015;95:160–6.
[6] Kimura C, Bidwell S, Shankar K, Shelton E, Shelton A, Kin C. Adherence to a home-based prehabilitation program for patients undergoing colorectal surgery. J Gastrointest Surg 2023;27:565–7.
[7] Van Koevering M, Nissen S. Oxidation of leucine and alpha-ketoisocaproate to beta-hydroxy-beta-methylbutyrate in vivo. Am J Physiol 1992;262:E27–31.
[8] Gerlinger-Romero F, Guimarães-Ferreira L, Giannocco G, Nunes MT. Chronic supplementation of beta-hydroxy-beta methylbutyrate (HMβ) increases the activity of the GH/IGF-I axis and induces hyperinsulinemia in rats. Growth Hormone IGF Res 2011;21:57–62.
[9] Eley HL, Russell ST, Tisdale MJ. Mechanism of attenuation of muscle protein degradation induced by tumor necrosis factor-alpha and angiotensin II by beta-hydroxy-beta-methylbutyrate. Am J Physiol Endocrinol Metab 2008;295:E1417–26.
[10] Fitschen PJ, Wilson GJ, Wilson JM, Wilund KR. Efficacy of β-hydroxy-β-methylbutyrate supplementation in elderly and clinical populations. Nutrition 2013;29:29–36.
[11] Peng X, Yan H, You Z, Wang P, Wang S. Clinical and protein metabolic efficacy of glutamine granules-supplemented enteral nutrition in severely burned patients. Burns 2005;31:342–6.
[12] Wilmore DW. The effect of glutamine supplementation in patients following elective surgery and accidental injury. J Nutr 2001;131:2543S. 9S; discussion 50S-1S.
[13] Cui XL, Iwasa M, Iwasa Y, Ohmori Y, Yamamoto A, Maeda H, et al. Effects of dietary arginine supplementation on protein turnover and tissue protein synthesis in scald-burn rats. Nutrition 1999;15:563–9.
[14] Yang C, Song Y, Li T, Chen X, Zhou J, Pan Q, et al. Effects of beta-hydroxy-beta-methylbutyrate supplementation on older adults with sarcopenia: a randomized, double-blind, placebo-controlled study. J Nutr Health Aging 2023;27:329–39.
[15] Nishizaki K, Ikegami H, Tanaka Y, Imai R, Matsumura H. Effects of supplementation with a combination of β-hydroxy-β-methyl butyrate, L-arginine, and L-glutamine on postoperative recovery of quadriceps muscle strength after total knee arthroplasty. Asia Pac J Clin Nutr 2015;24:412–20.
[16] Martínez-Ortega AJ, Piñar-Gutiérrez A, Serrano-Aguayo P, González-Navarro I, Remón-Ruíz PJ, Pereira-Cunill JL, et al. Perioperative nutritional support: a review of current literature. Nutrients 2022;14.
[17] Ogawa M, Yoshida N, Satomi-Kobayashi S, Tsuboi Y, Komaki K, Wakida K, et al. Efficacy of preoperative amino acid supplements on postoperative physical function and complications in open heart surgery patients: a study protocol for a randomized controlled trial. J Cardiol 2019;74:360–5.
[18] Date C, Yamaguchi M, Tanaka H. Development of a food frequency questionnaire in Japan. J Epidemiol 1996;6:S131–6.
[19] Di Vincenzo O, Marra M, Di Gregorio A, Pasanisi F, Scalfi L. Bioelectrical impedance analysis (BIA) -derived phase angle in sarcopenia: a systematic review. Clin Nutr 2021;40:3052–61.
[20] Hairi NN, Cumming RG, Naganathan V, Handelsman DJ, Le Couteur DG, Creasey H, et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. J Am Geriatr Soc 2010;58:2055–62.
[21] Lees MJ, Wilson OJ, Hind K, Ispoglou T. Muscle quality as a complementary prognostic tool in conjunction with sarcopenia assessment in younger and older individuals. Eur J Appl Physiol 2019;119:1171–81.
[22] Lukaski HC, Kyle UG, Kondrup J. Assessment of adult malnutrition and prognosis with bioelectrical impedance analysis: phase angle and impedance ratio. Curr Opin Clin Nutr Metab Care 2017;20:330–9.
[23] Jain SS, Cohen DJ, Zhang Z, Uriel N, Sayer G, Lindenfeld J, et al. Defining a clinically important change in 6-minute walk distance in patients with heart failure and mitral valve disease. Circ Heart Fail 2021;14:e007564.
[24] Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. Cardiopulm Phys Ther J 2013;24:21–9.

[25] Ogawa M, Satomi-Kobayashi S, Yoshida N, Tsuboi Y, Komaki K, Nanba N, et al. Relationship between oral health and physical frailty in patients with cardiovascular disease. J Cardiol 2021;77:131–8.
[26] Kuschel LB, Sonnenburg D, Engel T. Factors of muscle quality and determinants of muscle strength: a systematic literature review. Healthcare (Basel) 2022;10.
[27] Holeček M, Vodeničarovová M. Effects of beta-hydroxy-beta-methylbutyrate supplementation on skeletal muscle in healthy and cirrhotic rats. Int J Exp Pathol 2019;100:175–83.
[28] Nunes EA, Kuczera D, Brito GA, Bonatto SJ, Yamazaki RK, Tanhoffer RA, et al. Beta-hydroxy-beta-methylbutyrate supplementation reduces tumor growth and tumor cell proliferation ex vivo and prevents cachexia in Walker 256 tumor-bearing rats by modifying nuclear factor-kappaB expression. Nutr Res 2008;28:487–93.
[29] Smith HJ, Mukerji P, Tisdale MJ. Attenuation of proteasome-induced proteolysis in skeletal muscle by {beta}-hydroxy-{beta}-methylbutyrate in cancer-induced muscle loss. Cancer Res 2005;65:277–83.
[30] Morisawa T, Saitoh M, Takahashi T, Watanabe H, Mochizuki M, Kitahara E, et al. Association of phase angle with hospital-acquired functional decline in older patients undergoing cardiovascular surgery. Nutrition 2021;91–92:111402.
[31] de Luis D, Izaola O, de la Fuente B, Aller R. Effect of L-arginine supplementation on insulin resistance and adipocitokines levels in head and neck cancer non diabetic patients after surgery. Nutr Hosp 2014;30:870–5.
[32] Kiani AK, Bonetti G, Medori MC, Caruso P, Manganotti P, Fioretti F, et al. Dietary supplements for improving nitric-oxide synthesis. J Prev Med Hyg 2022;63:E239. e45.
[33] Vanhatalo A, Bailey SJ, Blackwell JR, DiMenna FJ, Pavey TG, Wilkerson DP, et al. Acute and chronic effects of dietary nitrate supplementation on blood pressure and the physiological responses to moderate-intensity and incremental exercise. Am J Physiol Regul Integr Comp Physiol 2010;299:R1121–31.
[34] Ramezani Ahmadi A, Rayyani E, Bahreini M, Mansoori A. The effect of glutamine supplementation on athletic performance, body composition, and immune function: a systematic review and a meta-analysis of clinical trials. Clin Nutr 2019;38:1076–91.
[35] Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. J Parenter Enter Nutr 2009;33:71–82.
[36] Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. Nutrition 2004;20:445–51.
[37] Kisil I, Gimelfarb Y. Long-term supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine for pressure ulcer in sedentary older adults: a retrospective matched case-control study. J Yeungnam Med Sci 2023;40:364–72.
[38] Peng LN, Cheng YC, Yu PC, Lee WJ, Lin MH, Chen LK. Oral nutritional supplement with β-hydroxy-β-methylbutyrate (HMB) improves nutrition, physical performance and ameliorates intramuscular adiposity in pre-frail older adults: a randomized controlled trial. J Nutr Health Aging 2021;25:767–73.
[39] Nasimi N, Sohrabi Z, Dabbaghmanesh MH, Eskandari MH, Bedeltavana A, Famouri M, et al. A novel fortified dairy product and sarcopenia measures in sarcopenic older adults: a double-blind randomized controlled trial. J Am Med Dir Assoc 2021;22:809–15.
[40] Berton L, Bano G, Carraro S, Veronese N, Pizzato S, Bolzetta F, et al. Effect of oral beta-hydroxy-beta-methylbutyrate (HMB) supplementation on physical performance in healthy old women over 65 Years: an open label randomized controlled trial. PLoS One 2015;10:e0141757.
[41] Norouzi M, Nadjarzadeh A, Maleki M, Khayyatzadeh SS, Hosseini S, Yaseri M, et al. Evaluation of the recovery after heart surgery following preoperative supplementation with a combination of beta-hydroxy-beta-methylbutyrate, L-arginine, and L-glutamine: a double-blind randomized placebo-controlled clinical trial. Trials 2022;23:649.
[42] Vives M, Hernandez A, Parramon F, Estanyol N, Pardina B, Muñoz A, et al. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovascular Dis 2019;12:153–66.
[43] Marmelo F, Rocha V, Moreira-Goncalves D. The impact of prehabilitation on post-surgical complications in patients undergoing non-urgent cardiovascular surgical intervention: systematic review and meta-analysis. Eur J Prev Cardiol 2018;25:404–17.
[44] Steinmetz C, Bjarnason-Wehrens B, Walther T, Schaffland TF, Walther C. Efficacy of prehabilitation before cardiac surgery: a systematic review and meta-analysis. Am J Phys Med Rehabil 2023;102:323–30.
[45] Makita S, Yasu T, Akashi YJ, Adachi H, Izawa H, Ishihara S, et al. JCS/JACR 2021 guideline on rehabilitation in patients with cardiovascular disease. Circ J 2022;87:155–235.
[46] Kim HK, Suzuki T, Saito K, Yoshida H, Kobayashi H, Kato H, et al. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. J Am Geriatr Soc 2012;60:16–23.
[47] Ogawa M, Satomi-Kobayashi S, Hamaguchi M, Komaki K, Izawa KP, Miyahara S, et al. Postoperative dysphagia as a predictor of functional decline and prognosis after undergoing cardiovascular surgery. Eur J Cardiovasc Nurs 2023;22:602–9.
[48] Morisawa T, Saitoh M, Otsuka S, Takamura G, Tahara M, Ochi Y, et al. Hospital-Acquired functional decline and clinical outcomes in older cardiac surgical patients: a multicenter prospective cohort study. J Clin Med 2022;11.
[49] Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness–a systematic review. Physiotherapy 2012;98:277–86.
[50] Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. Br Med J 2012;344:e1119.