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Pre-Operative Resistance Training and Amino Acid Supplementation in Frail Patients With Gastrointestinal Cancer: A Randomized Clinical Trial

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Keywords: amino acids | gastrointestinal cancer | preoperative exercise | preoperative frailty

ABSTRACT

Aim: To investigate the impact of preoperative exercise and nutritional interventions on postoperative complications, physical function, and activities of daily living (ADL) 1 year postoperatively in frail older patients with gastrointestinal cancer.

Methods: This single-center, randomized controlled trial enrolled 62 patients aged ≥ 70 years scheduled to undergo elective surgery for gastrointestinal cancer with decreased grip strength or walking speed between October 2017 and December 2022. Participants were randomly assigned to control ($n = 33$) and intervention ($n = 29$) groups; the latter performed resistance exercises and consumed amino acid-containing jelly daily at home for 14 days. All participants were followed-up for 1 year.

Results: After exclusion, 27 and 18 patients were enrolled in the control and intervention groups, respectively. The average age was 80.4 years, and 37.8% were male. Postoperative complications were observed in 51.9% and 44.4% of the control and intervention groups, respectively (95% confidence interval [CI] 0.62–2.19), with postoperative delirium observed in 25.9% and 33.3%, respectively (95% CI 0.31–1.94). There were no significant inter-group differences in grip strength, walking speed, or skeletal muscle index. However, the intervention group showed superior knee extension strength maintenance (preoperatively: 100.2% ± 18.3% vs. 119.1% ± 68.8%, $p = 0.19$; discharge: 86.7% ± 22.0% vs. 119.3% ± 72.0%, $p = 0.044$), and lower rates of decreased ADLs or death 1 year postoperatively (42.3% vs. 23.5%; RR 0.56, 95% CI 0.08–1.92).

Conclusions: This 14-day preoperative exercise and nutritional intervention program did not significantly reduce postoperative complications in frail older patients with gastrointestinal cancer; however, it aided in maintaining knee extension strength at discharge.

1 | Introduction

The number of older patients with gastrointestinal cancer is rising with the increasing proportion of aging individuals within the general population [1]. Frailty is a multifaceted syndrome characterized by decreased physical function, malnutrition, cognitive impairment, psychological health deterioration, and social instability, increasing the risk of mortality, hospitalization, and falls under stress [2–4]. The prevalence of frailty in patients with cancer is higher than in the general population [5]. The decline in the quality of life (QOL) in patients with cancer is influenced by the disease stage, treatment, weight loss, and loss of appetite [6, 7]. In particular, patients with gastrointestinal cancer commonly suffer from malnutrition at diagnosis due to obstruction or absorption disorders [8]. The incidence of postoperative complications is higher in patients with frailty, negatively affecting survival [9–11]. Assessing frailty before surgery is imperative for predicting postoperative complications. Our research group previously reported that overall health status assessed using comprehensive geriatric assessment (CGA) was associated with postoperative delirium, independent of the progression of gastrointestinal cancer [12], while decreased physical function was related to postoperative mortality in gastrointestinal cancer surgery [13]. Combining CGA with cancer assessments can clarify the risk of postoperative mortality [14].

Frailty is a complex condition observed in older adults, characterized by the interaction and progression of multiple factors including decreased physical function, malnutrition, and social isolation [15]. This so-called "frailty cycle" significantly affects the health and QOL of older adults [16]. Interventions for frailty should combine multiple approaches such as physical rehabilitation, social support, nutritional therapy, and cognitive training for the greatest effectiveness [17, 18]. Therefore, the present study examined the effects of combined exercise and nutritional interventions in patients with decreased physical function.

Decreased physical function leads to reduced activity and dietary intake, whereas malnutrition reduces skeletal muscle mass and physical function. In contrast, low skeletal muscle mass is associated with insulin resistance, inflammation, and adverse drug events [19, 20], which increases the frequency of postoperative complications [21, 22]. Maintaining skeletal muscle function and improving nutritional status can reduce surgical-stress induced frailty progression, thereby reducing postoperative complications and the risk of mortality while preventing a decline in activities of daily living (ADL). Exercise therapy can increase muscle strength and mass [23, 24], and improve insulin resistance [25] in older adults, which aids in reducing postoperative complications and improves prognosis. Amino acids, particularly leucine, activate the mammalian target of rapamycin signaling pathway [26, 27] and promote the synthesis of muscle protein, thereby contributing to the maintenance and increase in muscle mass and strength, as well as improving insulin resistance [28, 29]. Therefore, supplementation with amino acids such as leucine may play an important role in maintaining or improving skeletal muscle function in older patients during the perioperative period.

This study investigated the impact of combined resistance exercise and supplementing amino acids on perioperative physical function, the frequency of postoperative complications, and 1-year prognosis in older patients with gastrointestinal cancer with decreased physical function.

2 | Methods

2.1 | Ethics

This study was approved by the Clinical Research Committee (Ethics Review Number 16124-4) and was registered with the University Hospital Medical Information Network (UMIN), Japan (UMIN000024526) and retrospectively registered with Japan Registry of Clinical Trials (jRCT), Japan (jRCT1053240193). This study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants, and all participants were assured of their right to withdraw consent.

2.2 | Design

This was a single-center, open-label, prospective, randomized controlled trial, following the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines [30].

2.3 | Participants

Patients aged ≥70 years scheduled for elective gastrointestinal cancer surgery at the University Hospital were recruited between October 2017 and December 2022. The inclusion criteria were: patients who showed decreased grip strength or walking speed in the preoperative evaluations and agreed to participate in the study. Decreased grip strength was defined as grip strength <26 kg in men and <18 kg in women, whereas decreased walking speed was defined as walking speed <1.0 m/s. The exclusion criteria were patients with exertional angina, chronic heart failure (New York Heart Association [NYHA] classification II or higher), tachyarrhythmia, chronic respiratory failure (Hugh-Jones classification II or higher), active multiple cancers, chronic renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2), severe liver dysfunction (aspartate transferase or alanine transaminase >100 IU/L), and cognitive impairment (Mini-Mental State Examination [MMSE] <20 points); undergoing preoperative chemotherapy; and unable to walk independently; as well as those participating in other clinical trials.

2.4 | Randomization

Randomization was performed using Research Electronic Data Capture (REDCap), developed by Vanderbilt University and used under a University-approved licensing agreement. Eligibility and inclusion were determined by the staff conducting the preoperative evaluation. Participants were randomly assigned to the control and intervention groups in a 1:1 ratio and stratified by age, MMSE score, and Geriatric Depression Scale-15 (GDS-15) using REDCap, which provided an independent and automated allocation concealment mechanism. The allocation sequence was concealed until the participants were assigned to their respective groups. The participants were not blinded.

2.5 | Interventions

The participants in the intervention group performed resistance exercises and consumed amino acid-containing jelly daily at home for 14 days. The duration of the intervention was set with reference to an estimated preoperative waiting period. The resistance exercise program was directly adopted from our hospital's fall prevention class, which is routinely offered to older adults with a history of falls or lower limb muscle weakness. As no serious adverse events have been reported in this program to date, it is considered a safe and feasible intervention in our clinical setting. Specifically, the resistance exercises constituted four types of bodyweight training (20 seated knee extensions, 20 standing thigh lifts, 10 standing calf raises, and 5–10 squats), performed twice daily. Compliance was confirmed by self-recording in a training log. The amino acid-containing jelly (Amino L40) included 40% leucine and was consumed once daily. The dosage was based on the product instructions, considering feasibility in clinical practice. Both groups wore an activity tracker for 2 weeks.

2.6 | Assessments

Assessments were conducted 2 weeks preoperatively, immediately preoperatively, at discharge, and 1 year postoperatively. The primary endpoint was postoperative complication occurrence, including delirium. Secondary endpoints included changes in physical function over time and death or a decline in ADL 1 year postoperatively. The presence of postoperative complications was determined by reviewing medical records postoperatively by independent physicians blinded to the group assignments. The CGA and physical function evaluations were conducted as described previously [13]. The CGA includes the Barthel Index (ADL), Lawton's Instrumental Activities of Daily Living (IADL), MMSE [31], Vitality Index, GDS-15, and Apathy Scale [32]. Physical function evaluations included isometric knee extension strength, grip strength, walking speed, and skeletal muscle mass index (SMI). Knee extension strength was measured five times on each side using a handheld dynamometer (μ-tas F-1, Anima Co. Ltd.), and the average value was recorded. Grip strength was measured thrice per side, and the average was recorded (Toei Light Co. Ltd.). Walking speed and SMI (measured using an MC-190; Tanita Corporation) were also recorded. Changes in grip strength, knee extension strength, walking speed, and SMI over time were calculated as percentages of the baseline values at 2 weeks preoperatively. Cancer-related information, including disease name, stage, surgical procedure, and performance status (PS), was obtained as described previously [14], while blood test results were obtained from electronic medical records. Frailty was assessed using the Japanese version of the Cardiovascular Health Study (J-CHS) criteria [33]. Daily steps and energy expenditure were recorded using a three-axis accelerometer (Mediwalk MT-KT02DZ, Terumo, Tokyo, Japan). The compliance rates for the activity tracker and resistance exercises were calculated based on the number of days the tracker was worn and the number of completed exercises out of the prescribed number, respectively. One-year postoperative follow-up was conducted using electronic medical records. Information on postoperative complications, mortality, and cancer-related data of the participants has also been independently registered in the Osaka Cancer Registry, which operates separately from this study.

2.7 | Statistical Analysis

All statistical analyses were performed using EZR [34] version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria), a modified version of the R commander designed to add statistical functions and is frequently used in biostatistics.

The required sample size was calculated as 92, assuming a postoperative complication rate of 50% in frail patients and expecting a reduction to 20% with the interventions, with an α error of 0.05, a β error of 0.20, and a power of 0.80. We planned to enroll 100 participants to account for dropouts. However, conducting the interventions within the scheduled period before surgery proved difficult, and the recruitment process was further affected by the COVID-19 pandemic, causing challenges in recruiting participants. Consequently, we decided to stop recruitment after 53 months, without achieving the initially planned number of participants.

Continuous and categorical variables were compared using the two-sided Student's t-test and the two-sided Fisher's exact test, respectively. Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Participants

Figure 1 presents a patient flowchart. Consent was obtained from 62 individuals, of whom 17 were excluded for the following reasons: three withdrew consent, three had changes in treatment plans, five had changes in surgical schedules, two were unable to follow the protocol, and one was found to have multiple cancers. In total, 45 patients were enrolled, with 27 and 18 in the control and intervention groups, respectively. The average age was 80.4 years, and 37.8% were male. Survival data were available for all participants at the 1-year follow-up; however, one participant from each group could not be evaluated by the assessors. The postoperative diagnoses included esophageal, gastric, gastrointestinal stromal, duodenal, liver, metastatic liver, bile duct, pancreatic, colon, and cecal cancers. No adverse or side effects related to the intervention were reported.

3.2 | Baseline Characteristics

The baseline characteristics are shown in Table 1. No significant differences were observed in age, sex, or body mass index (BMI) between the control and intervention groups. The types of cancer, clinical stages of cancer, surgical methods, and performance

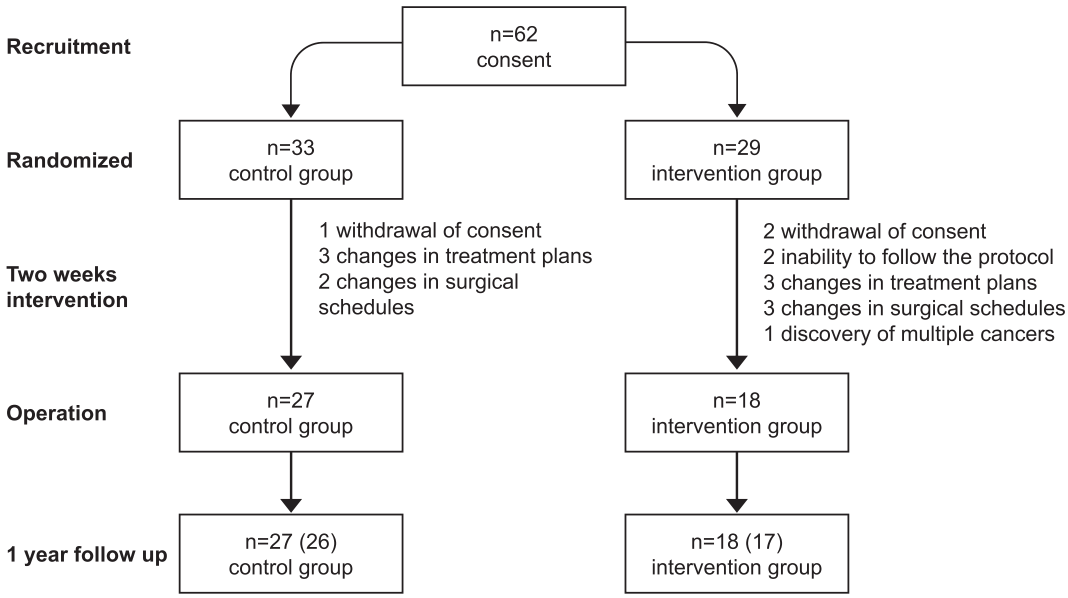

FIGURE 1 | Flowchart of the study and participants. The flowchart shows recruitment, randomization, and analysis of study participants. Of the 62 patients who provided consent, 17 were excluded. The final analysis included 45 patients, with 27 and 18 in the control and intervention groups, respectively. All participants were followed up for 1 year for survival; however, the evaluation data were missing for one participant in each group.

statuses were also similar between the two groups. While not statistically significant, laparoscopic surgery was more frequently performed in the control group than in the intervention group. There were no significant differences in components of the CGA, including the Barthel Index, Lawton's IADL, MMSE, Vitality Index, GDS-15, and Apathy Scale. The results of physical function evaluations, including grip strength, isometric knee extension strength, walking speed, and SMI, also showed no significant differences. The serological evaluation revealed no significant differences in hemoglobin, serum albumin, serum creatinine, and serum C-reactive protein values between the two groups.

3.3 | Adherence to Exercise

The rates of exercise adherence are shown in Table 2. The compliance rate for wearing the activity tracker was 98.0% and 96.4% in the control and intervention groups, respectively, with participants wearing the activity tracker for nearly the entire 2-week pre-surgery period ($p = 0.45$). Only participants in the intervention group performed resistance training, with an average rate of adherence to exercise of 85.2%.

3.4 | Postoperative Complications

The incidence of postoperative complications is shown in Table 3. Overall postoperative complications, the primary endpoint, were observed in 51.9% and 44.4% of the control and intervention groups, respectively (relative risk [RR] 0.86, 95% confidence interval [CI] 0.62–2.19). Postoperative delirium occurred in 25.9% and 33.3% of the control and intervention groups, respectively (RR 1.29, 95% CI 0.31–1.94). Other complications included infections, anastomotic leakage, and various less frequent events grouped under others. No significant differences were observed between the groups in any complications. The severity of complications was classified using the Clavien–Dindo system: grade I in 9 patients, grade II in 7, grade IIIa in 3, grade IVa in 1, and grade V in 2. Among the grade V cases, one patient in the intervention group died due to septic shock, and one patient in the control group died due to hemorrhagic shock.

3.5 | Changes in Physical Function

The changes in physical function over time are shown in Figure 2. Grip strength was almost identical between the two groups at all three time points, with differences of less than 1% (preoperatively: 99.5% ± 8.9% vs. 100.1% ± 19.2%, $p = 0.88$; discharge: 96.0% ± 9.0% vs. 97.5% ± 14.5%, $p = 0.70$). Knee extension strength increased to 119.1% preoperatively in the intervention group; however, no significant intergroup differences were observed. Knee extension strength decreased to 86.7% in the control group but was maintained at 119.3% in the intervention group at discharge, with a significant difference between the groups (preoperatively: 100.2% ± 18.3% vs. 119.1% ± 68.8%, $p = 0.19$; discharge: 86.7% ± 22.0% vs. 119.3% ± 72.0%, $p = 0.044$). Walking speed and SMI showed similar trends, with a decrease in the control group at discharge; however, the difference between the groups was not significant (walking speed: preoperatively: 98.1% ± 25.9% vs. 115.7% ± 60.5%, $p = 0.16$; discharge: 80.0% ± 22.4% vs. 92.5% ± 50.0%, $p = 0.29$; SMI: preoperatively: 99.8% ± 7.1% vs. 101.3% ± 5.1%, $p = 0.45$; discharge: 91.9% ± 8.8% vs. 95.1% ± 11.4%, $p = 0.34$).

3.6 | One-Year Follow-Up

The results of the 1-year follow-up survey are presented in Table 3. Overall, 14.8% of participants in the control group and 5.6% in the intervention group died during the 1-year follow-up

TABLE 1 | Baseline characteristics of participants in the control and intervention groups.

Variable	Control group (n = 27)	Intervention group (n = 18)	p
Age (years)	80.6 ± 5.4	80.0 ± 3.4	0.68
Sex (male, n %)	9 (33.3%)	8 (44.4%)	0.54
BMI (kg/m^2)	22.0 ± 3.3	21.6 ± 5.3	0.78
Cancer type (%)			0.27
Upper gastrointestinal	6 (22.2%)	3 (16.7%)	
Hepatobiliary pancreas	8 (29.6%)	10 (55.6%)	
Lower gastrointestinal	13 (48.1%)	5 (27.8%)	
Clinical stage (%)			0.47
0–1	10 (37.0%)	6 (33.3%)	
2	10 (37.0%)	7 (38.9%)	
3	4 (14.8%)	2 (11.1%)	
4	3 (11.1%)	3 (16.7%)	
Surgery method (%)			0.09
Open surgery	7 (25.9%)	9 (50.0%)	
Laparoscopic surgery	20 (74.1%)	9 (50.0%)	
Preoperative chemotherapy (yes, %)	1 (3.7%)	1 (5.6%)	1.00
Performance status (%)			1.00
0	23 (85.2%)	17 (94.4%)	
1	2 (7.4%)	1 (5.6%)	
2	1 (3.7%)	0 (0.0%)	
3	1 (3.7%)	0 (0.0%)	
Comprehensive geriatric assessment			
MMSE	26.1 ± 2.3	25.9 ± 2.1	0.82
Barthel index	96.9 ± 7.9	98.1 ± 3.5	0.55
IADL (Lawton's scale)	6.2 ± 2.2	6.7 ± 1.4	0.46
Vitality index	9.8 ± 0.7	10.0 ± 0.0	0.26
GDS-15	2.7 ± 3.0	3.2 ± 2.7	0.63
Apathy scale	10.7 ± 6.1	9.9 ± 5.6	0.66
Total number of medications	6.1 ± 2.9	4.9 ± 2.8	0.18
Grip strength (kg) men	21.9 ± 4.3	24.5 ± 5.6	0.29
Grip strength (kg) women	15.8 ± 1.9	15.5 ± 3.2	0.74
Isometric knee extension strength (kg)			
Men	21.8 ± 7.0	25.5 ± 7.3	0.30
Women	17.0 ± 4.6	14.7 ± 5.7	0.24
Walking speed (m/s)	1.1 ± 0.2	1.0 ± 0.3	0.72
SMI (kg/m^2) men	7.2 ± 1.0	6.8 ± 1.2	0.43
SMI (kg/m^2) women	6.0 ± 0.6	6.0 ± 1.0	0.96
J-CHS criteria frailty			0.76
Prefrail	14 (51.9%)	11 (61.1%)	
Frail	13 (48.1%)	7 (38.9%)	
Hemoglobin (g/dL)	11.6 ± 2.2	12.7 ± 1.9	0.11
Serum albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.4	0.57
Serum creatinine (mg/dL)	0.86 ± 0.26	0.81 ± 0.31	0.55
CRP (mg/dL)	0.84 ± 2.4	0.94 ± 1.47	0.87

Note: Continuous variables are expressed as mean ± SD and were compared using Student's *t*-test. Categorical variables are expressed as counts and percentages, and were compared using Fisher's exact test. *p*-values indicate statistical significance between groups.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; GDS-15, Geriatric Depression Scale-15; IADL, Lawton's Instrumental Activities of Daily Living; J-CHS, the Japanese version of the Cardiovascular Health Study; MMSE, Mini Mental Status examination; SMI, skeletal muscle mass index.

period (RR 0.38, 95% CI 0.01–3.92). One death in the control group was classified as Clavien–Dindo grade V and was related to postoperative bleeding, while one death in the intervention group was related to infection. In addition, three other deaths occurred in the control group within 1 year after discharge. Two of these were attributed to the progression of gastrointestinal cancer, and the cause of the remaining death was unknown. The proportion of patients with decreased ADL or death was lower in the intervention group than in the control group; however, the difference was not statistically significant (42.3% in the control group vs. 23.5% in the intervention group; RR 0.56, 95% CI 0.08–1.92).

4 | Discussion

This study investigated the effects of preoperative exercise and nutritional intervention on the frequency of postoperative complications and physical function in frail older patients following surgery for gastrointestinal cancer. While the intervention was feasible and safe, no significant differences were observed in the incidence of postoperative complications. However, the intervention group showed a trend toward better maintenance of physical function at discharge, indicating that a 2-week preoperative exercise and nutritional intervention may contribute to maintaining physical function during the perioperative period, even if it does not directly impact the incidence of postoperative complications.

Evidence supporting prehabilitation for maintaining postoperative physical function is increasing; however, no consensus exists on whether it reduces postoperative complications [35, 36].

TABLE 2 | Adherence to exercise and physical activity in the control and intervention groups.

Variable	Control group ($n = 27$)	Intervention group ($n = 18$)	p
Activity tracker compliance (%)	98.0 ± 6.1	96.4 ± 7.9	0.45
Exercise adherence rate (%)	N/A	85.2 ± 20.0	N/A
Daily steps (steps/day)	4045.9 ± 2161.6	3816.9 ± 2142.2	0.73
Total daily energy expenditure (kcal/day)	1511.7 ± 250.0	1491.7 ± 226.0	0.79

Note: Continuous variables are presented as mean ± SD and were compared using Student's *t*-test. *p*-values indicate statistical significance between groups. Data are not available for the control group as the exercise was not performed by this group.
Abbreviation: N/A, not applicable.

TABLE 3 | Incidence of postoperative complications and 1-year follow-up results in frail cancer patients.

Variable	Control group ($n = 27$)	Intervention group ($n = 18$)	95% CI
Postoperative complications (%)	14 (51.9%)	8 (44.4%)	0.62–2.19
Delirium (%)	7 (25.9%)	6 (33.3%)	0.31–1.94
Infection	2 (7.4%)	3 (16.7%)	0.08–2.40
Anastomotic leakage	3 (11.1%)	2 (11.1%)	0.18–5.40
Others	5 (18.5%)	3 (16.7%)	0.30–4.08
One-year follow-up results			
Death	4 (14.8%)	1 (5.6%)	0.01–3.92
Decreased ADL or death	11 (42.3%)	4 (23.5%)	0.08–1.92

Note: Postoperative complications are presented as counts and percentages, including delirium, infections, anastomotic leakage, and other events. Others included, in one case each, pleural effusion, abdominal wall hernia, paralytic ileus, abdominal distension, common peroneal nerve palsy, and atrial fibrillation, as well as deaths due to septic shock in the intervention group and hemorrhagic shock in the control group. Some patients experienced more than one complication; therefore, the sum of individual categories does not match the total number of patients with postoperative complications. One-year follow-up results, including death and decreased activities of daily living (ADL), are also shown. In the intervention group, the evaluation of ADL was unavailable in one participant. The 95% confidence interval (95% CI) was provided for comparison between the groups.

Some studies have shown that respiratory prehabilitation improves postoperative respiratory function [35, 37] and reduces the frequency of aspiration pneumonia [38]. A 4-week prehabilitation for colorectal cancer contributes to maintaining postoperative physical function compared to postoperative rehabilitation, without a significant difference in postoperative complications [39]. A randomized controlled trial of frail older patients with colorectal cancer showed that a CGA-based intervention did not improve complications or 30-day postoperative outcomes [40]. However, our study differs from previous studies in that we targeted older patients with decreased physical function, a component of frailty, including high-risk patients with gastrointestinal cancer, and the prescription of combined resistance exercise with amino acid supplementation to counteract the decline in physical function and malnutrition. The frequency of postoperative complications was lower in the intervention group; however, the difference was not statistically significant. In this study, the exercise intervention targeted the gluteal and lower limb muscles, which may not contribute to improving respiratory function, and could potentially explain the lack of a significant reduction in complications. Falls were not examined in this study, which could be a potential area for future research considering the direct relationship between the function of the lower limb muscles and fall prevention. Additionally, the interpretation of the trend toward increased postoperative delirium in the intervention group should be approached with caution. Exercise-induced fatigue and metabolic changes due to amino acid intake may contribute to delirium. Previous studies have reported a link between serum amino acid levels and the risk of delirium [41].

Perioperative skeletal muscle function was better maintained in the intervention than the control group. Muscle strength and mass may increase after 8–12 weeks of exercise, even in older adults [23, 24]. Maintaining physical function is crucial in older adults as it affects levels of social activity and QOL, resulting in a decline in physical function observed after short-term intervention in this study.

Although fewer deaths were observed during the 1-year follow-up in the intervention group, this difference is unlikely to reflect an effect of the intervention, given the short duration of the intervention, the limited number of events, and the absence of statistical significance. We were also interested in long-term functional outcomes, particularly the maintenance of ADL at 1 year after surgery, which is more likely to be influenced by the preoperative intervention than overall survival. Because all patients who died had already experienced a decline in ADL prior to death, we used a composite outcome of death or ADL decline to better capture clinically meaningful functional deterioration. Although this outcome was less frequent in the intervention group, the difference was not statistically significant.

Several considerations for improving the intervention methods exist. The selection criteria for the participants, as well as the duration and type of intervention, may have influenced the results of this study. Additionally, we targeted patients with decreased grip strength or walking speed. Our previous study showed knee extension strength had a stronger correlation with survival prognosis than grip strength [13]. The present study showed minimal changes in grip strength during the perioperative period. Grip strength may not be the best indicator of the effectiveness of training [42], which is supported by this study. Therefore, selecting patients based on knee extension strength may identify those

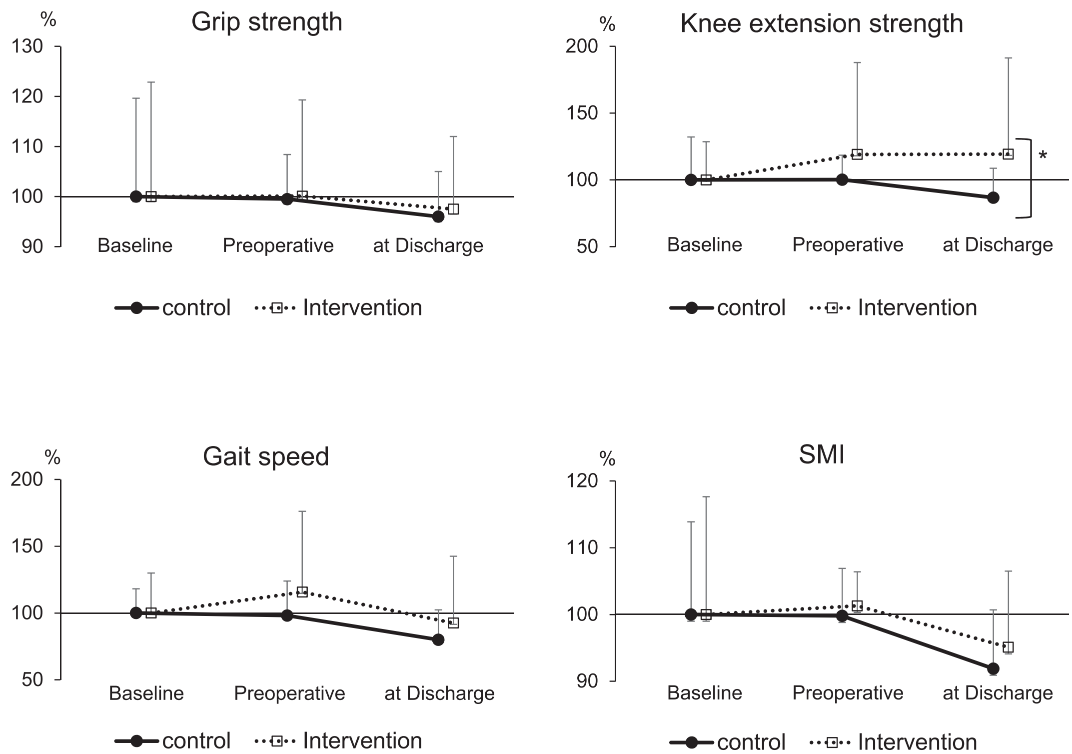

FIGURE 2 | Changes in physical function over time. The graphs show the percentage changes from baseline in grip strength, knee extension strength, walking speed, and skeletal muscle index (SMI) at three time points: Two weeks preoperatively, immediately preoperatively, and at discharge. Values are presented as mean ± SD. Statistical significance between groups was assessed using the Student's *t*-test. *$p < 0.05$, indicates a significant difference in knee extension strength between the groups at discharge.

requiring intervention more accurately. Additionally, the intervention period is limited by the scheduled surgery, with most preoperative interventions lasting 2–4 weeks in systematic reviews [36, 43, 44]. Several types of interventions, including aerobic, resistance, and balance exercises, and stretching, are considered effective for improving frailty [45, 46]. Vitamin D deficiency is associated with low muscle power and mass [47], and supplementation has potential benefits in improving skeletal muscle function. Combining psychological and social support may further enhance the effectiveness of the intervention [17, 18].

In this study, preoperative exercise and nutritional interventions in frail older patients undergoing surgery for gastrointestinal cancer did not significantly reduce postoperative complications. However, it aided in maintaining physical function at discharge. The results suggest that preoperative interventions targeting physical function, a component of frailty, can help maintain QOL post-discharge. Future research should focus on optimizing perioperative interventions to ensure the safety and maintenance of ADL in older adults.

4.1 | Limitations

We did not conduct intent-to-treat, survival, or multivariate analyses owing to the limited number of outcome events. The cut-off value of grip strength for males was set at < 26 kg according to the J-CHS criteria [48] at the time of study initiation, despite the 2019 Asian Working Group for Sarcopenia (AWGS) [49] and revised J-CHS criteria [33] suggesting < 28 kg. There is no established standardized protocol for amino acid supplementation in older surgical patients. In this study, we used a commercially available product and followed the manufacturer's recommended dosage and frequency. While this enhances feasibility, the optimal regimen in terms of amount and duration remains unclear, and the 2-week intervention may have been insufficient. Although there were no statistically significant differences in baseline characteristics, laparoscopic surgery was more common in the control group. Since laparoscopic procedures are typically associated with fewer complications and faster recovery, this imbalance could have favored the control group. Nevertheless, the intervention group showed better outcomes in terms of postoperative complications and maintenance of knee extension strength, suggesting that the intervention itself may have contributed to these effects. The lack of difference in the average steps and total energy expenditure between the two groups during the 2-week preoperative period may have been influenced by the Hawthorne effect [50] in the control group, and the inability to detect resistance exercises using activity trackers. However, the independent contributions of exercise and nutritional therapy could not be assessed. Furthermore, since this was a single-center study conducted at a university hospital and targeted older patients with decreased physical function, selection bias may have existed. Therefore, the findings may not be generalizable to cancer care in general community hospitals. Additional research is required to determine the validity of similar interventions in older patients without frailty.

5 | Conclusions

This study investigated the effects of preoperative exercise and nutritional interventions in frail older patients undergoing gastrointestinal cancer surgery. The 14-day resistance exercise and amino acid supplementation did not significantly reduce the incidence of postoperative complications. Nevertheless, this intervention contributed to the maintenance of physical function at discharge. Overall, these findings highlight the potential benefits of preoperative interventions in maintaining physical function and QOL in older adults undergoing surgery. In particular, knee extension strength was significantly maintained in the intervention group at discharge, indicating that such interventions could improve post-discharge QOL. Furthermore, the proportion of patients with decreased ADL or death was lower in the intervention group at 1-year follow-up, suggesting positive long-term effects of the intervention. Further research is required to determine the optimal preoperative intervention methods. Nevertheless, the results of this study suggest that comprehensive measures for frailty, including exercise and nutrition, are effective even in the context of preoperative care for gastrointestinal cancer surgery. Therefore, future studies should aim to optimize perioperative interventions to ensure safety and maintain ADL to improve long-term outcomes in older patients.

Author Contributions

Concept and design: H.A., Y.Y., K.S., H.R., and K.Y. Acquisition, analysis, or interpretation of data: Y.Y., M.S., M.T., M.I., and T.F. Drafting of the manuscript: T.F., H.A., K.S., and K.Y. Critical review of the manuscript for important intellectual content: all authors. Statistical analysis: T.F., H.A., and Y.Y. Obtained funding: H.R. Administrative, technical, or material support: M.S. and Y.Y. Supervision: K.S., H.R., and K.Y. Provision of therapy intervention for all patients and the educational program: M.S., M.T., M.I., and Y.Y.

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Ethics Statement

This study was approved by the Clinical Research Committee (Ethics Review Number 16124-4) and was registered with the University Hospital Medical Information Network (UMIN), Japan (UMIN000024526). This study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards.

Consent

Written informed consent was obtained from all participants, and all participants were assured of their right to withdraw consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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