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Prognostic impact of a 3-week multimodal prehabilitation program on frail elderly patients undergoing elective gastric cancer surgery: a randomized trial

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Abstract

Background Research indicates that prehabilitation is effective in optimizing physical status before surgery, although this method may be considered "aggressive" for frail elderly patients. This study aimed to evaluate whether multimodal prehabilitation decreases postoperative complications and improves functional recovery in frail elderly patients undergoing gastric cancer surgery, in comparison to usual clinical care.

Methods This study was a single-center, single-blind, randomized controlled trial. Patients over 65 years old with a Fried Frailty Index of 2 or higher, scheduled for gastric cancer surgery, were considered for inclusion. Eligible participants were randomized in a 1:1 ratio to either the intervention or control group. The intervention group underwent a 3-week multimodal prehabilitation program prior to surgery, in addition to perioperative care guided by ERAS protocols. The control group received only the latter. The primary outcome was the comprehensive complications index (CCI) measured at 30 days after surgery. Secondary outcomes included 30-day overall complications, functional walking capacity as assessed by 6-minute walking distance (6MWD) at 4 weeks postoperatively, and 3-month postoperative quality of life. This study was registered at ClinicalTrials.gov (No. NCT06510088).

Results Among the 112 eligible patients, the median age was 74 years, with 58 (52.7%) being female. No between-group difference was found in the primary outcome measure, 30-day CCI. The Median (Q1-Q3) CCI for the intervention and control groups was 0 (0-12.2) and 0 (0-22.6) ($P=0.082$), while the mean (SD) CCI was 6.1 (15.8) and 9.8 (12.7), respectively ($P=0.291$). Notably, the incidence of severe complications (CCI > 20) was significantly lower in the intervention group compared to the control group (11.1% vs. 25.9%, $P=0.046$), particularly in terms of medical complications (12.3% vs. 29.3%, $P=0.025$). Preoperatively, 27 patients (47.4%) in the intervention group exhibited an increase in the 6MWD of at least 20 m, compared to 16 patients (27.6%) in the control group ($P=0.028$). At 4 weeks postoperatively, more patients in the intervention group returned to their baseline 6MWD levels (63.2% vs. 43.1%, $P=0.031$). Secondary parameters of functional capacity in the postoperative period generally favored the multimodal prehabilitation approach.

Conclusions In frail elderly patients undergoing elective gastric cancer surgery, a prehabilitation program did not affect the 30-day postoperative complication rate or CCI but reduced severe complications and improved perioperative functional capacity.

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Keywords Elderly, Frail, Gastric cancer, Multimodal prehabilitation

Introduction

Gastric cancer remains a significant health concern globally, especially among elderly individuals, where it poses a considerable burden due to its aggressive nature and limited therapeutic options [1]. Population aging, a result of demographic transition, presents a critical societal challenge [2, 3]. According to a 2022 report by the World Health Organization (WHO), the median age at gastric cancer diagnosis is 69 years [4], with patients over 75 years facing heightened risks of morbidity and mortality [2, 5]. Although surgical resection remains the primary treatment for gastric cancer, the proportion of elderly patients undergoing surgery declines with age due to preoperative frailty [6, 7]. Frailty, marked by age-related declines in energy, muscle strength, weight, and activity levels, is common among elderly gastric cancer patients and correlates with poorer surgical outcomes, including higher morbidity and mortality [7]. Therefore, interventions aimed at enhancing the functional status and resilience of frail elderly patients undergoing surgery for gastric cancer are critically important.

Numerous studies have demonstrated that prehabilitation can diminish complications, hospital readmissions, length of hospital stay (LOS), and care dependence by enhancing functional reserve. However, these studies did not differentiate between age groups and frailty status, making it difficult to interpret the relationship between the outcomes and advanced age or frailty. It is hypothesized that patients at higher risk for postoperative complications, such as frail elderly individuals, are more likely to benefit from prehabilitation. Nonetheless, conclusive evidence on multimodal rehabilitation specifically designed for this vulnerable population remains insufficient.

Prehabilitation seeks to optimize patients' preoperative risk factors during the waiting period before surgery [8]. This preoperative phase is a critical time to modify health behaviors to reduce the stress of surgery and enhance the recovery process. Multimodal prehabilitation encompasses various interventions, including physical exercise, nutritional optimization, and psychological support, aiming to bolster physiological reserve in anticipation of the expected adverse effects of surgery and to support the postoperative recovery of functional capacity, particularly in patients with lower preoperative fitness levels [9–12]. Several studies have demonstrated that prehabilitation can diminish complications, hospital readmissions, LOS, and care dependence by enhancing functional reserve [9, 13]. However, in the course of their research, the age group and frailty status of the patients were not differentiated and the relationship between the results and advanced age/frailty cannot be well interpreted. It is hypothesized that patients at higher risk for postoperative complications, such as frail elderly individuals, are more likely to benefit from prehabilitation. Nonetheless, definitive evidence on multimodal prehabilitation specifically tailored to this vulnerable population is lacking.

Therefore, we implemented a randomized clinical trial to provide evidence regarding the potential advantages of multimodal prehabilitation on the outcomes of frail elderly patients undergoing elective gastric cancer surgery.

Materials and methods

Trial Design and Study participants

This prospective, single-blind, randomized controlled trial received approval from the Ethics Committee and Institutional Review Board of Taizhou Hospital of Zhejiang Province (ethical approval no. K20240528). Written informed consent was obtained from all participants involved in the study. The reporting of this trial adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Supplementary material, *CONSORT* checklist, http://www.consort-statement.org/) and was conducted in accordance with the ethical principles outlined in the Helsinki Declaration of 1975. This study was registered at ClinicalTrials.gov (No. NCT06510088). Patients over the age of 65 with a Fried Frailty Index score of 2 or higher [14], who were scheduled for surgical resection of gastric adenocarcinoma, and whose life expectancy was estimated by the surgeon to be greater than six months, were considered for inclusion in this study. Patients were excluded from the study if they: (1) were scheduled for neoadjuvant therapy; (2) had metastatic cancer; (3) were unable to swallow or participate in exercise and fitness assessments due to pre-existing conditions (e.g., orthopedic, neuromuscular, or cardiorespiratory diseases). In addition, patients who were lost to follow-up were also excluded. Enrollment began on March 1, 2019, was paused due to the COVID-19 pandemic from February 2020 through December 2020, and ultimately ended on December 31, 2023. The CONSORT diagram for this study is depicted in Fig. 1.

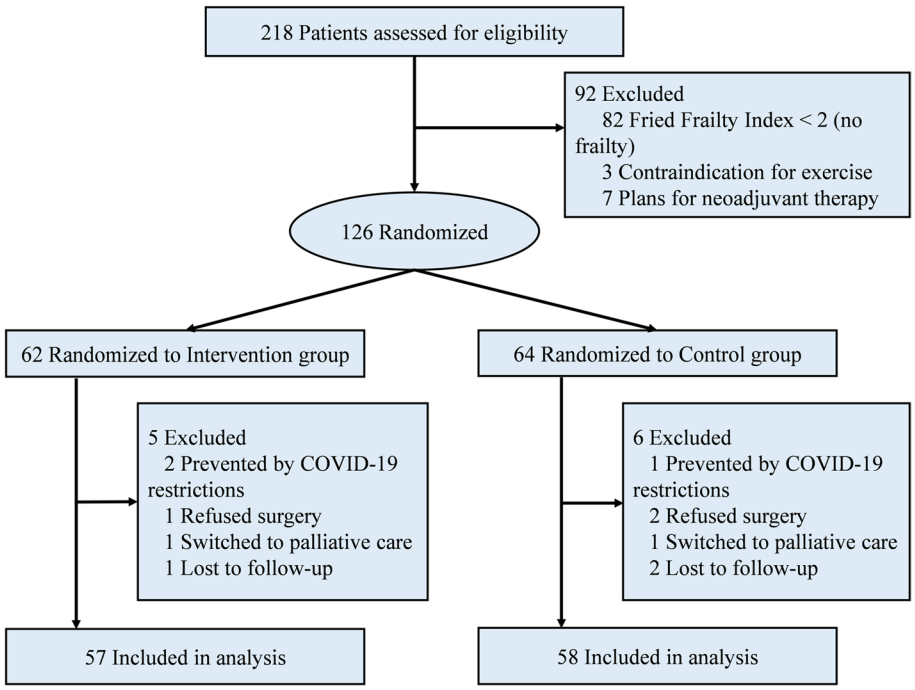

Fig. 1 Aerobic and resistance exercise guidance of the Intervention group and the Borg scale score. HR, heart rate

Study procedures

Eligible patients were randomly assigned in a 1:1 ratio to receive either multimodal prehabilitation (intervention group) or usual clinical care (control group). Randomization was accomplished using computer-generated random numbers organized into 12 blocks of 10. An independent researcher (Mengya Zhou) placed the allocations in sealed, opaque envelopes that were consecutively numbered. The allocation remained concealed until the completion of the baseline assessment, at which point the envelopes were opened in numerical order. Outcome assessors, surgeons, and anesthesiologists were blinded to the group assignments. Due to the nature of the intervention, blinding patients or intervention staff was not feasible. Assessments were conducted at three time points: before the commencement of prehabilitation (baseline assessment), a few days before surgery (preoperative assessment), and four weeks post-surgery (4-week assessment). Perioperative management adhered to the principles of the Enhanced Recovery After Surgery (ERAS) program.

Multimodal Prehabilitation

Participants in the intervention group engaged in a 3-week, individualized, supervised multimodal prehabilitation program. This program included four components: aerobic and resistance exercises, respiratory training, nutritional counseling with whey protein supplementation, and psychological adjustment. Smoking cessation interventions were also included if necessary. The intervention was based on a combination of home and hospital settings. A multidisciplinary team comprising surgeons, anesthesiologists, kinesiologists, dietitians, physiotherapists, and nurses with psychology training will propose an individualized treatment strategy to the patient. The prehabilitation program commenced immediately following the baseline visit, which was scheduled approximately four weeks prior to the planned operation.

Aerobic and resistance exercises

Aerobic and resistance exercises represent the core activities of multimodal prehabilitation program. During these sessions, patients performed 30 min of moderate aerobic exercise and 25 min of resistance exercises using an elastic band. A 30-minute home-based exercise of aerobic endurance exercise (jogging, walking, cycling, at discretion) was required for at least 3 days per week. Aerobic exercise intensity was gauged using two primary metrics: target heart rate (HR) and perceived rate of exertion (Borg Scale) [15]. The program aimed to achieve a moderate-to-high training intensity, corresponding to a Borg Scale score of 13 to 16, and to maintain the target heart rate (HR), calculated using the formula: (220 - age - resting HR) × 70% + resting HR. Furthermore, patients were supervised and guided by a trained physiotherapist

on a one-on-one basis during the entire resistance exercise phase at the hospital rehabilitation unit. Resistance exercises focusing on the major muscle groups, including the upper and lower extremities, chest, and core muscles, were conducted 2–3 times per week. Each exercise was repeated 8–12 times in 3 sets. A designated physiotherapist supervised the resistance exercises and offered corrective guidance. Training intensity was continuously monitored and fine-tuned based on Borg scale assessments. A detailed description of the aerobic and resistance exercises is shown in Fig. 2.

Respiratory training

Respiratory training was conducted using a TRI-BALL® respiratory trainer. Easy to handle and train with small size and light design. The initial session of respiratory training was conducted under the demonstration and guidance of a clinical physician. Subsequent sessions were performed by the patients at home, who also kept a daily log of their activities. Patients were instructed to engage in respiratory training at least three times daily, with each session lasting 10 min. TRI-BALL® encourages the patient to achieve a maximum prolonged inhalation, named SMI technique (Sustained Maximal Inspiration). SMI is a deep, slow breathing exercise repeated several times a day that strengthens the respiratory muscles, causing the intercostal muscles and diaphragm to contract, thereby expanding the chest cavity. This process increases lung capacity, enhances lung expansion, and improves coughing ability, helping to prevent mucus accumulation and aiding in the recovery of lung function after surgery.

Nutrition intervention

A registered dietitian assessed the nutritional status of all participants. Nutritional status was evaluated using the Nutritional Risk Screening 2002 (NRS2002) scale, which is both valid and reliable for identifying nutritional risk in elderly hospitalized patients. NRS 2002 score of ≥ 3 indicated nutritional risk. At baseline, participants completed a 3-day total food recall questionnaire to evaluate their daily caloric and protein intake. The dietary goal for participants is to achieve a daily caloric intake that supports a balanced diet, emphasizing a reduction in calories from fats and sugars while ensuring adequate intake of essential nutrients. Specifically, in accordance with the recommended daily intake of fruits and vegetables outlined in the Chinese Dietary Guidelines, participants are instructed to consume at least 300–500 g of vegetables and 200–350 g of fruit per day. Additionally, target protein intake was 1.5 g/kg/d [16]. If the patient did not meet the protein requirement by diet al.one, they were provided with whey protein supplementation (Details are provided in Supplementary Material 1). Thirteen participants required daily whey protein supplementation to meet the recommended protein intake. These participants were instructed to consume the supplement within one hour after exercise to optimize muscle protein synthesis [17, 18].

The research team instructed patients and their families to use the FatSecret APP or the website https://www.

	Aerobic exercise	Resistance exercise	Borg scale score	
Forms	Aerobic exercise at the patient's discretion in these forms: ✓ brisk walking ✓ Jogging ✓ bicycling ✓ water exercise ✓ seated stepping or recumbent bicycling may be more tolerable forms of exercise for older patients with arthritis or balance disorders.	Resistance exercises involving major muscle groups (upper and lower extremities, chest, and core muscles) in five forms: ✓ Standing shoulder press ✓ Bench press ✓ Sit-ups ✓ Squats ✓ Stair climbers	6	Zero exertion
			7	Very easy
			8	Minimal recognition of effort
			9	Very light (comfortable walking pace)
			10	Can just start to hear your breathing
Frequency	3 times/week or more	2-3 times/week	11	Conversation is easy, you feel you could run for a while at this pace
	Most popular one-week program: Aerobic → Resistance → Rest → Aerobic → Resistance → Aerobic → Rest		12	Light exertion
Duration & Repetition times	➢ 1 set each time, 30min per set	➢ 3 sets, 2 minutes apart ➢ Repeat 8-12 repetitions of each muscle group in each set, with 1min intervals between each program ➢ Next exercise at least one day apart	13	Somewhat hard
			14	You can hear your breathing but you are not struggling
Intensity	Measure resting heart rate (HR) and calculate target HR: ➢ Target HR = (220 - age - resting HR) * 70% + resting HR ➢ Reach target heart rate within 5 minutes of starting exercise ➢ Adjust intensity and pace of exercise based on target HR and Borg Scale score (maintaining target HR and Borg scale score at 13-16. If target HR and Borg Scale score are inconsistent, then target HR will take precedence)	Maximum strength assessment by a physical therapist after the baseline visit ➢ Repeat each set 8 to 12 times, starting at 30% to 40% of maximum strength on the 1st repetition and gradually increasing to 70% to 80% (maintaining Borg scale score at 13-16), resting 1 to 3 minutes between sets	15	Hard. You can talk but not in full sentences.
			16	Hard work
			17	Very hard. Starting to get uncomfortable and tired
			18	You can no longer talk because your breathing is heavy
			19	Very, very hard. Your body is screaming at you to stop
			20	Max exertion

Fig. 2 CONSORT Flow Diagram

fatsecret.cn/ for daily calorie tracking (Details are provided in Supplementary Material 1). This approach aimed to enhance patients' self-management skills, enabling them to make appropriate dietary adjustments based on their individual needs.

Psychological intervention

Anxiety-coping interventions included relaxation techniques and deep breathing exercises, administered in a one-to-one format by a nurse trained in psychological care. Participants identified as being at greater risk for psychological distress were referred to a medical psychologist for further treatment. Additionally, the intervention encompassed counseling on smoking and alcohol cessation.

Control conditions - usual clinical care

Perioperative care of the control group was based on standardized ERAS recommendations that have been widely implemented to minimize heterogeneity in perioperative care. Typically, participants did not receive any preoperative interventions related to exercise, nutrition, or mental health.

Outcomes

The primary outcome was 30-day postoperative complications determined using the Comprehensive Complication Index (CCI). The CCI, a validated index for assessing morbidity and mortality, aggregates all complications using the Clavien-Dindo classification system, resulting in a score from 0 (no complications) to 100 (death) [19]. The CCI was calculated using the online CCI calculator available at http://www.assessurgery.com. A CCI score more than 20 was considered to define severe complications significantly impacting surgical outcomes based on prior research involving a similar surgical cohort [9]. Secondary outcomes included postoperative 6-minute walking distance (6MWD), other postoperative endpoints (such as transfusion requirements, recovery of gastrointestinal function, LOS, hospital readmission), 3-month postoperative quality of life (QoR-9 scale), physical activity [Short Form (36) health survey (SF-36)] [20], and psychological status (Hospital Anxiety and Depression scale) [21]. Functional capacity was assessed using the 6-MWD, a reliable measure of exercise tolerance in patients undergoing colorectal surgery [22], with changes of at least 20 m deemed clinically significant [23].

Additionally, in our original trial registration (No. NCT06510088), both postoperative complications and functional capacity were listed as co-primary outcomes. However, during the analysis, we recognized that postoperative complications should be the primary focus because of their critical impact on patient recovery. Therefore, we have made a post-hoc decision to designate postoperative complications as the sole primary outcome. We explicitly clarify this change to ensure transparency regarding the deviation from the original registration and to align our analysis with clinical priorities.

Sample size and statistical analysis

An intention-to-treat population analysis was conducted. The calculation for the sample size was derived from the mean (standard deviation, SD) CCI (10.5 [14]) observed in our population, with a 30% reduction in the CCI deemed clinically significant. By employing an α of 0.05, a power of 0.90 (2-sided test), and accounting for an anticipated dropout rate (e.g., surgeries not performed) of 10%, the target was set to enroll 120 participants (60 per group).

Statistical analyses were performed using the SPSS (version 26.0) and R software (version 4.2.3). Continuous variables are depicted as the mean (SD) or median [first quartile (Q1) - third quartile (Q3)] and were compared using either independent sample t-tests or Mann-Whitney U tests. Qualitative variables were expressed as percentages and compared across groups utilizing either Pearson's chi-square test or Fisher's exact test. To identify independent predictors of postoperative complications, a multivariate logistic regression analysis was conducted. Statistical significance was established at $P<0.05$.

Results

Patient characteristics

From March 1, 2019, to December 31, 2023, a total of 218 potential patients were screened for eligibility. Of these, 92 patients were excluded for various reasons: 82 did not meet the frailty criteria, 3 had contraindications for exercise, and 7 were scheduled for neoadjuvant treatment. Consequently, 126 frail patients were randomized into the intervention group ($n=62$) or the control group ($n=64$). After randomization, an additional 11 patients were excluded due to surgery refusal, COVID-19 restrictions, transition to palliative care, or loss to follow-up. Thus, the final analysis included 115 patients, with 57 in the intervention group and 58 in the control group.

The baseline physical conditions and surgical characteristics were similar between the intervention and control groups, with no statistically significant differences observed (Table 1). Both groups exhibited a high prevalence of minimally invasive surgery, at 87.7% in the intervention group and 82.8% in the control group. Adverse events were reported by 7 of the 123 participants, primarily consisting of lightheadedness or nausea attributed to the exercise intervention ($n=4$) or protein supplements ($n=3$). Notably, no serious adverse events related to the program were recorded.

Table 1 Baseline and Surgical characteristics in the intervention vs. control groups

Variables	Intervention Group ($n=57$)	Control Group ($n=58$)
Age, Median (Q1-Q3), y	73 [70.5, 77]	74 [68, 78]
Sex		
Female	24 (42.1)	30 (51.7)
Male	33 (57.9)	28 (48.3)
Body mass index, Median (Q1-Q3), kg/m^2 [a]	25.1 [23.0, 27.2]	25.5 [23.7, 27.8]
Education level above high school	40 (70.2)	35 (60.3)
Smoking status		
None	15 (26.3)	12 (20.7)
Former	30 (52.6)	30 (51.7)
Current	12 (21.1)	16 (27.6)
Alcohol use (current), No. (%), d	9 (15.8)	6 (10.3)
ASA physical status classification, No. (%)		
II	37 (64.9)	33 (56.9)
III	20 (35.1)	25 (43.1)
Fried Frailty Index, No. (%) [b]		
2	23 (40.4)	24 (41.4)
3	27 (47.4)	26 (44.8)
4	6 (10.5)	8 (13.8)
5	1 (1.8)	0 (0)
Comorbidities, No. (%)		
Hypertension	29 (50.9)	33 (56.9)
Diabetes	18 (31.6)	21 (36.2)
Cardiovascular diseases	16 (28.1)	19 (32.8)
Dyslipidemia	25 (43.9)	26 (44.8)
Asthma	2 (3.5)	1 (1.7)
Chronic obstructive pulmonary disease	6 (10.5)	3 (5.2)
Obstructive sleep apnea	5 (8.8)	5 (8.6)
Others	11 (19.3)	15 (25.8)
Charlson comorbidity index, Median (Q1-Q3) [c]	3 (2–5)	3 (3–5)
Nutritional status—NRS2002, No. (%)		
< 3	18 (31.6)	23 (39.7)
≥ 3	39 (68.4)	35 (60.3)
Metabolic status		
Hemoglobin level, Median (Q1-Q3), g/L	127.9 [118.5, 139]	124.8 [119.4, 137.7]
C-reactive protein level, Median (Q1-Q3), mg/L	5.4 [2.1, 12.8]	4.5 [1.3, 10.7]
Albumin level, Mean (SD), g/L	42.1 (3.35)	41.6 (4.8)
Pathological TNM stage		
I	7 (12.3)	11 (19.0)
II	27 (47.4)	28 (48.3)
III	23 (40.4)	19 (32.8)
Aerobic capacity		
Baseline 6MWD, Mean (SD), m	332.8 [309, 376.4]	328 [300.5, 369]
EORTC QLQ-C30-global health, Median (Q1-Q3)	66 [66, 83]	66 [50, 83]
Surgical data		
Duration of surgery, Mean (SD), min	156.2 (11.7)	151.8 (12.1)
Estimated blood loss, Median (Q1-Q3), mL	80 [50, 100]	100 [50, 100]
Intraoperative transfusion	0 (0)	1 (1.7)

Table 1 (continued)

Variables	Intervention Group ($n=57$)	Control Group ($n=58$)
Surgical approach, No. (%)		
Open	7 (12.3)	10 (17.2)
Minimally invasive	50 (87.7)	48 (82.8)

Abbreviation: *6-MWD* 6-minute walking distance, *ASA* American Society of Anesthesiologists, *EORTC QLQ-C30* European Organsation for Research and Treatment Of Cancer, Quality Of Life Of Cancer Patients Module, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation, *TNM* tumor, node, metastasis

[a] Calculated as weight in kilograms divided by square of height in meters

[b] Higher scores indicate greater frailty

[c] Scores range from 0 to 24, with higher scores indicating greater comorbidities

In addition, the following data summarizes adherence to each component of the intervention: 85% of participants completed three sessions of moderate-intensity aerobic exercise each week. Additionally, 83% of participants performed at least two resistance training sessions per week, with 68% achieving three sessions. Adherence to respiratory training was 92%. Moreover, all participants consistently followed the recommended daily intake of whey protein.

Primary outcomes

Complications

A detailed description of postoperative complications is presented in Table 3. No between-group difference was found in the primary outcome measure, 30-day CCI. The Median (Q1-Q3) CCI for the intervention and control groups was 0 (0-12.2) and 0 (0-22.6) ($P=0.082$), while the mean (SD) CCI was 6.1 (15.8) and 9.8 (12.7), respectively ($P=0.291$). Notably, the incidence of severe complications (CCI > 20) was notably lower in the intervention group compared to the control group (11.1% vs. 25.9%, $P=0.046$). We also did not identify between-group differences in 30-day overall complications (25.9% vs. 39.7%, $P=0.123$) and surgical complications (14.0% vs. 17.2%, $P=0.636$). Additionally, patients in the intervention group experienced fewer medical complications (12.3% vs. 29.3%, $P=0.025$), particularly those related to cardiovascular or respiratory issues. In addition, multivariable logistic regression analyses revealed that a Charlson Comorbidity Index score < 3 (odds ratio, OR [95% confidence interval, CI] 2.017 [1.241–3.816]; $P=0.027$) and multimodal prehabilitation (OR [95% CI] 1.971 [1.232–3.195], $P=0.039$) were found to be independent protective factors for 30-day overall complications, whereas Fried Frailty Index and surgical approach, were not (Table 2).

Secondary outcomes

Functional walking capacity

Post-intervention changes in the 6MWD for both groups are presented in Table 4. During the preoperative period, the median 6MWD increased by 40.5 m in the intervention group compared to an increase of only 9 m in the control group ($P=0.047$). In the intervention group, 27 out of 57 patients (47.4%) experienced a preoperative increase in 6MWD of 20 m or more from baseline, considered the minimal important difference, while this improvement was seen in only 16 out of 58 patients (27.6%) in the control group ($P=0.028$). At 4 weeks post-surgery, 34 patients (63.2%) in the intervention group had either recovered to or exceeded their baseline 6MWD, whereas only 25 patients (43.1%) in the control group achieved this level of improvement or maintenance in their walking capacity ($P=0.031$).

Surgical outcomes

The surgical outcome data are summarized in Table 3. There were no significant differences in the LOS, with a Median (*Q1-Q3*) of 8 [6–10] days in the intervention group and 8 [7–11] days in the control group ($P=0.493$). Hospital readmission rates within 30 days were 5.3% in the intervention group and 5.2% in the control group ($P=0.983$). Admissions to the intensive care unit (ICU) were 12.3% for the intervention group and 13.8% for the control group ($P=0.810$), with ICU stays lasting a Median (*Q1-Q3*) of 2 [1–3] days versus 2 [1–4] days ($P=0.224$). One participant in the intervention group died within 30 days post-surgery due to anastomotic leakage. No statistically significant differences were observed between the two groups in terms of the Median (*Q1-Q3*) time to first aerofluxus (3 [3, 4] vs. 3 [3, 4] days, $P=0.361$), first defecation (5 [5, 6] vs. 6 [5, 6] days, $P=0.169$), first liquid diet (3 [3, 4] vs. 4 [3, 4] days, $P=0.129$), or first half-liquid diet (8 [7, 8] vs. 8 [7-8.5] days, $P=0.176$).

Functional outcomes

Table 5 presents the predetermined secondary functional outcomes over time. There were no significant differences in various pulmonary function indices between the control and intervention groups, nor were there notable differences between pre- and post-intervention conditions within each group. Similarly, QoR-9 scores did not

Table 2 Postoperative outcomes in the intervention vs. control groups

Variables	Intervention Group ($n=57$)	Control Group ($n=58$)	*P* value
Comprehensive Complication Index			
Mean (SD)	6.1 (15.8)	9.8 (12.7)	0.291
Median (Q1-Q3)	0 (0-12.2)	0 (0-22.6)	0.082
Comprehensive Complication Index > 20, No. (%)	6 (10.5)	15 (25.9)	0.033
Delayed gastric emptying	1 (1.8)	1 (1.7)	0.990
Anastomotic leakage	1 (1.8)	1 (1.7)	0.990
Intra-abdominal abscess	1 (1.8)	2 (3.4)	0.569
Bleeding	1 (1.8)	1 (1.7)	0.990
Ileus	0 (0)	2 (3.4)	0.157
Pulmonary complications	1 (1.8)	5 (8.6)	0.098
Cardiovascular complications	1 (1.8)	2 (3.4)	0.569
Neurological complications	0 (0)	1 (1.7)	0.319
Overall complications, No. (%)	14 (24.6)	23 (39.7)	0.083
Number of patients with medical complication, No. (%) [a]	7 (12.3)	17 (29.3)	0.025
Cardiovascular	2 (3.5)	4 (6.9)	0.414
Neurological	2 (3.5)	1 (1.7)	0.548
Pulmonary	4 (7.0)	9 (15.5)	0.257
Urological	2 (3.5)	3 (5.2)	0.662
Thromboembolic	0 (0)	1 (1.7)	0.319
Others	1 (1.8)	4 (6.9)	0.176
Number of patients with surgical complication, No. (%) [a]	8 (14.0)	10 (17.2)	0.636
Delayed gastric emptying	2 (3.5)	3 (5.2)	0.662
Anastomotic leakage	1 (1.8)	1 (1.7)	0.990
Intra-abdominal abscess	2 (3.5)	2 (3.4)	0.986
Bleeding	1 (1.8)	1 (1.7)	0.990
Ileus	0 (0)	2 (3.4)	0.157
Cholecystitis	1 (1.8)	0 (0)	0.311
Abdominal wound complication	1 (1.8)	2 (3.4)	0.569
Number of patients with both medical and surgical complication, No. (%)	4 (7.0)	7 (12.1)	0.357
Time to first, Median (Q1-Q3), d [c]			
Aerofluxus	3 [3, 4]	3 [3, 4]	0.361
Defecation	5 [5, 6]	6 [5, 6]	0.169
Liquid diet	3 [3, 4]	4 [3, 4]	0.129
Half-liquid diet	7 [6, 8]	8 [7, 8]	0.176
In-hospital mortality	1 (1.8)	0 (0)	0.311
Length of postoperative hospital stay, Median (Q1-Q3), d	8 [6, 10]	8 [7, 11]	0.493
ICU admission	7 (12.3)	8 (13.8)	0.810
ICU days of stay	2 [1, 3]	2 [1, 4]	0.224
Hospital readmission < 30 days, No. (%)	3 (5.3)	3 (5.2)	0.983

Abbreviation: *ICU* Intensive Care Unit, *Q1* first quartile, *Q3* third quartile

[a] More than one complication may be present in a patient

[b] Delirium, collapse, decubitus

[c] Data on relevant variables were missing for very few participants, and all missing values were filled in with the corresponding median values in each group

differ significantly between the intervention and control groups. No significant between-group differences were observed for physical activity (SF-36 scale) or for psychological status (HADS Anxiety and Depression score).

Discussion

In this randomized clinical trial, multimodal prehabilitation did not appear to reduce the overall 30-day complication rate in frail elderly patients undergoing elective gastric cancer surgery in the context of the ERAS, with

Table 3 Impact of the intervention on aerobic capacity

6-MWD	Intervention Group ($n=57$)	Control Group ($n=58$)	*P* value
Preoperative, Median (Q1-Q3), m	374 [320.5, 417]	337 [296, 378]	0.044*
Difference from baseline ≥ 20 m, No. (%) [a]	27 (47.4)	16 (27.6)	0.028*
Postoperative (4 weeks), Median (Q1-Q3), m	348.5 [311, 405]	327 [295, 362]	0.274
Recovered at 4 weeks postoperatively, No. (%) [b]	34 (63.2)	25 (43.1)	0.031*

Abbreviation: *6-MWD* 6-minute walking distance, *Q1* first quartile, *Q3* third quartile

[a] Improvement of 6MWD of 20 m or more compared with baseline

[b] Recovered to 6MWD within 20 m of the baseline value or above

no between-group difference in the primary outcome measure, 30-day CCI. However, in further subgroup analyses, multimodal prehabilitation significantly reduced the incidence of severe complications (CCI > 20) and medical complications. Furthermore, multimodal prehabilitation could improve the perioperative functional walking capacity, indicating better functional recovery after prehabilitation. No between-group differences were observed regarding disability, psychological status, and mortality, except for LOS. Additionally, the multivariable logistic regression analysis indicated that multimodal prehabilitation functioned as an independent protective factor against complications.

Preoperative prehabilitation seeks to improve patients' preoperative functionality and physiological reserves, thereby reducing surgical stress and facilitating postoperative recovery [13, 24]. Compared with previously published preoperative prehabilitation protocols for thoracic and colorectal surgery [9, 25], we have made some improvements to the intervention measures to facilitate clinical implementation and dissemination. Firstly, the duration of the multimodal prehabilitation program we proposed is only 2 weeks, aiming to maximize patient compliance, which is also one of the innovations. Previous studies mostly recommended intervention programs lasting 4 weeks or more [8, 14], but considering that most patients wish to undergo surgery as soon as possible, such a long duration may lead to lower acceptability and compliance. In this study, only a very small number of participants were excluded due to low compliance. Secondly, patients were allowed to select their preferred mode of aerobic exercise rather than adhering to a fixed regimen as seen in most studies. Provided the exercise recommendations' frequency, duration, and intensity requirements are met, patients could make slight adjustments to their training plans. Thirdly, recognizing the challenges in implementing and disseminating a supervised hospital-based exercise program, we developed a straightforward home-based regimen, incorporating simple images, completion diaries, and regular visits to promote adherence.

Elderly patients have an increased risk of surgical complications because of malnutrition, underlying diseases, and decreased physical performance [26]. Preoperative frailty has been shown to be associated with an increased risk of postoperative complications and increased LOS after abdominal surgery [27]. However, evidence regarding the effect of multimodal prehabilitation before abdominal surgery in frail patients is limited. Previous studies supported the validity of the CCI as a measure of postoperative morbidity and suggested that, compared with traditional morbidity measures (e.g., overall rate of complications, rate of severe complications), it provides a more comprehensive and sensitive endpoint for surgical research [28, 29]. In this study, the percentage of patients who experienced severe complications decreased by nearly 50% following the multimodal prehabilitation program. Other studies have also reported a reduction in medical complications, which is consistent with the hypothesis that rehabilitation specifically targeting cardiorespiratory health and metabolic balance [12]. The precise underlying mechanisms, however, remain unclear. Additionally, Chia et al. [30] conducted an observational study comparing prehabilitation to standard clinical care, showing a reduction in LOS from 11 to 8 days among frail patients undergoing colorectal surgery. Conversely, our study did not find significant differences in LOS between the groups. Notably, the median LOS in our study was considerably shorter than that observed by Chia et al. [30], potentially due to differences in the care context, such as the implementation of ERAS. In the past decades, the implementation of ERAS has significantly improved the prognosis of surgical patients. However, ERAS interventions are limited, and multimodal prehabilitation serves as a direct complement to this program.

Enhanced cardiorespiratory fitness prior to surgery is believed to augment physiological reserve and increase the patient's ability to tolerate surgical stress [31]. Aerobic exercise can improve cardiopulmonary function and reduce the incidence of cardiovascular complications. Respiratory training effectively decreases the risk of postoperative pulmonary complications by enhancing lung

Table 4 Impact of the intervention on lung function, quality of life, physical activity, and Psychological Status

Variables	Intervention Group ($n=57$)	Control Group ($n=58$)	*P* value
Pulmonary function test			
FEV1 (L), Mean (SD)			
Baseline	2.41 (0.62)	2.38 (0.55)	0.870
Before surgery	2.59 (0.51)	2.42 (0.53)	0.748
4 weeks after surgery	2.04 (0.58)	1.89 (0.50)	0.776
FVC (L), Mean (SD)			
Baseline	3.20 (0.75)	3.02 (0.69)	0.853
Before surgery	3.38 (0.77)	2.99 (0.62)	0.532
4 weeks after surgery	2.74 (0.66)	2.38 (0.68)	0.561
FEV1 / FVC (%), Mean (SD)			
Baseline	76.1 (11.5)	80.2 (7.8)	0.607
Before surgery	74.0 (14.5)	79.6 (8.2)	0.583
4 weeks after surgery	75.7 (10.1)	79.9 (8.7)	0.650
PEF (L/min), Mean (SD)			
Baseline	316.4 (112.3)	335.1 (106.9)	0.812
Before surgery	376.8 (89.2)	368.3 (110.1)	0.902
4 weeks after surgery	289.5 (81.9)	259.5 (86.0)	0.688
Quality of Life			
QoR-9, Median (Q1-Q3) [a]			
1 week after surgery	14 [12–15]	13 [12–15]	0.796
2 weeks after surgery	16 [15–17]	15.5 [14–17]	0.647
4 weeks after surgery	17 [17–18]	17 [16–18]	0.562
Physical Activity			
Total Physical SF-36 subscale, Mean (SD) [b]			
Baseline	49.5 (19.3)	51.8 (17.5)	0.836
Before surgery	56.7 (18.6)	58.6 (19.5)	0.921
4 weeks after surgery	49.3 (20.2)	51.2 (14.6)	0.648
Total Mental SF-36 subscale, Mean (SD) [b]			
Baseline	53.7 (22.4)	58.5 (20.4)	0.901
Before surgery	59.3 (20.6)	66.2 (19.6)	0.933
4 weeks after surgery	54.1 (21.9)	62.5 (15.4)	0.647
Psychological Status			
HADS Anxiety score, Median (Q1-Q3) [c]			
Baseline	5 [3, 8]	5 [2, 7]	0.769
Before surgery	4 [2, 6]	4 [2, 6.5]	0.835
4 weeks after surgery	3 [2, 5]	3.5 [2, 5]	0.851
HADS Depression score, Median (Q1-Q3) [c]			
Baseline	4 [2, 5]	3 [2, 5]	0.811
Before surgery	2 [0, 4]	3 [0, 6]	0.627
4 weeks after surgery	2 [1, 3]	2 [1, 3]	0.714

Abbreviations: *6MWD* 6-minute walk distance, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *HADS* Hospital Anxiety and Depression Scale, *PEF* peak expiratory flow, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

[a] Scores range from 0 to 18, with higher values indicating better recovery

[b] Scores range from 0 to 100, with higher values indicating better health

[c] Scores range from 0 to 21, with higher values indicating worse health

capacity and airway patency. A comprehensive prehabilitation program improves the overall health status of patients, thereby reducing both the incidence and severity of postoperative complication. These mechanisms collectively facilitate postoperative recovery and enhance patients' quality of life, further underscoring the significance of prehabilitation programs in postoperative recovery. In terms of aerobic training modalities utilized in prehabilitation programs, the literature describes endurance exercise training, resistance training, inspiratory muscle training, or a combination of these methods. However, there is a scarcity of studies examining the impact of improved aerobic capacity on postoperative adverse events [32]. While lung function tests suggested a potential benefit of these interventions, no significant differences were observed in major lung function indicators. This finding can largely be attributed to the fact that baseline pulmonary function was predominantly within normal ranges. Additionally, the incidence of pulmonary complications was notably higher in the control group compared to the intervention group. Nevertheless, the stability of the results of the lung function indexes is still questionable due to the limited sample size, necessitating further investigation.

There is no universally accepted measure of perioperative functional capacity. We selected this measure as it effectively mirrors daily activities, involves a wide range of bodily systems engaged in exercise, and is both well-tolerated and easy to administer. The 6MWD has previously been shown to predict postoperative complications and cancer survival in patients undergoing pulmonary surgery [33]. Previously, 6MWD has also been shown to predict postoperative complications and cancer survival in a pulmonary surgery population [12]. Our findings showed improved functional recovery both pre- and postoperatively compared to baseline levels. Specifically, the intervention group exhibited a preoperative mean 6MWD surpassing baseline levels, whereas the control group's performance did not improve significantly. Following multimodal rehabilitation, a greater number of participants experienced a minimum 20-meter enhancement in the postoperative 6MWD than their baseline levels. At the 4-week postoperative assessment, the 6-minute walk distance (6MWD) showed a significant difference between the two groups, favoring prehabilitation. Overall, prehabilitation leads to a faster return to baseline functional levels, and in some cases, even surpassing the initial values—a trend not observed in the control group.

It is worth noting that multimodal prehabilitation had no detectable impact on quality of life and psychological status. On the one hand, it could be argued that the short duration of the program and the lack of more comprehensive psychological interventions may explain the lack

Table 5 Univariable and Multivariable Logistic Regression Analysis of Postoperative complications

Variable	Univariable Logistic Analysis			Multivariable Logistic Analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, y						
< 75	1	Reference	-	-	-	-
≥ 75	1.652	0.604–4.562	0.329	-	-	-
Sex						
Male	1	Reference	-	-	-	-
Female	0.723	0.216–2.117	0.598	-	-	-
Preoperative BMI	0.806	0.547–1.311	0.369	-	-	-
ASA physical status classification						
II	1	Reference	-	-	-	-
III	0.875	0.407–2.083	0.766	-	-	-
IV	1.072	0.374–3.158	0.910	-	-	-
Fried Frailty Index						
2	1	Reference	-	-	-	-
3	1.465	0.545–3.831	0.446	-	-	-
4	1.725	0.722–4.156	0.219	-	-	-
5	1.594	0.333–2.942	0.611	-	-	-
Charlson comorbidity index						
< 3	1	Reference	-	-	-	-
≥ 3	2.351	1.380–4.022	0.002	2.017	1.241–3.816	0.027
Smoking status						
None	1	Reference	-	-	-	-
Current	1.079	0.371–2.425	0.872	-	-	-
Alcohol use						
None	1	Reference	-	-	-	-
Current	1.158	0.564–2.397	0.708	-	-	-
Metabolic status						
Preoperative C-reactive protein level	0.939	0.804–1.131	0.476	-	-	-
Preoperative albumin level	0.815	0.573–1.169	0.244	-	-	-
Preoperative hemoglobin level	0.901	0.636–1.318	0.281	-	-	-
Pathological TNM stage [a]						
I	1	Reference	-	-	-	-
II	1.532	0.862–2.747	0.155	-	-	-
III	1.056	0.531–2.104	0.921	-	-	-
Aerobic capacity						
Baseline 6MWD ≥ 400 m	1	Reference	-	-	-	-
Baseline 6MWD < 400 m	1.498	0.526–2.208	0.262	-	-	-
Multimodal prehabilitation						
Yes	1	Reference	-	-	-	-
No	2.009	1.061–3.512	0.008	1.971	1.232–3.195	0.039
Estimated blood loss	0.425	0.151–1.239	0.121	-	-	-
Duration of surgery	0.820	0.459–1.261	0.593	-	-	-
Intraoperative transfusion	1.026	0.702–1.479	0.918			
Surgical approach						
Minimally invasive	1	Reference	-			
Open	0.815	0.483–1.625	0.581			-
Intraoperative transfusion	1.018	0.714–1.463	0.922			

Abbreviations: *6-MWD* 6-minute walking distance, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *CI* confidence interval, *OR* odds ratio, *TNM* tumor, node, metastasis

of effect on both quality of life and psychological status. On the other hand, most patients experienced good perioperative recovery without signs of anxiety or depression, hence short-term assessments of health-related quality of life and psychological well-being did not show significant improvements.

It is noteworthy that multimodal prehabilitation did not demonstrate a discernible impact on quality of life and psychological status. One possible explanation is the short duration of the program and the absence of more comprehensive psychological interventions, which may account for the lack of effect on both quality of life and psychological status. Conversely, the majority of patients experienced satisfactory perioperative recovery without exhibiting signs of anxiety or depression. Consequently, short-term assessments of health-related quality of life and psychological well-being did not reveal significant improvements.

The findings of this randomized trial should be interpreted with certain limitations in mind. First, due to the nature of the intervention, neither participants nor intervention staff were blinded, thereby introducing a potential risk of performance bias. It is important to note, however, that outcome assessors were blinded to group assignments. Second, the small sample size may have increased the likelihood of false-positive and false-negative results. Third, the majority of our sample consisted of cases undergoing minimally invasive surgery, which may limit the generalizability of our findings to settings with a higher prevalence of open surgery. Additionally, this trial was conducted at a center with well-established ERAS protocols; therefore, our results are applicable only to similar care contexts.

Conclusions

In frail elderly patients undergoing elective gastric cancer surgery in the context of ERAS, a prehabilitation program involving exercise, nutritional, and psychological interventions did not appear to affect 30-day postoperative complications rate and 30-day CCIs. It did, however, reduce the incidence of severe and medical complications while improving perioperative functional capacity.

Abbreviations

CCI	Comprehensive Complication Index
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
ERAS	Enhanced Recovery After Surgery
HR	Heart rate
LOS	Length of hospital stay
ICU	Intensive care unit
IQR	Interquartile range
OR	Odds ratio
WHO	World Health Organization
6MWD	6-minute walking distance
SF-36	Short Form (36) health survey
SD	Standard deviation

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

Jianhui Chen: Conceptualization, Data curation, Formal analysis, Writing – original draft. Chen Hong: Conceptualization, Data curation. Rui Chen: Conceptualization, Writing – review & editing. Mengya Zhou: Conceptualization, Randomization. Senbin Lin: Conceptualization, Supervision, Writing – review and editing.

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Data availability

The data used in this paper will be provided by the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University. Informed consent was obtained from each participant before enrollment in the study.

Consent for publication

This is not applicable for this study.

Competing interests

The authors declare no competing interests.

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