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Multimodal prehabilitation to improve the clinical outcomes of frail elderly patients with gastric cancer: a study protocol for a multicentre randomised controlled trial (GISSG+2201)

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ABSTRACT

Introduction Gastric cancer (GC) diagnosed in the elderly population has become a serious public health problem worldwide. Given the combined effects of frailty and the consequences of cancer treatment, older individuals with GC are more likely than young patients to suffer from postoperative complications and poor clinical outcomes. Nutrition, functional capacity and psychological state-based multimodal prehabilitation, which is dominated by Enhanced Recovery After Surgery (ERAS) pathway management, has been shown to reduce postoperative complications, promote functional recovery and decrease hospitalisation time in certain malignancies. However, no previous studies have investigated the clinical application of multimodal prehabilitation in frail older patients with GC.

Methods and analysis The study is a prospective, multicentre randomised controlled trial in which a total of 368 participants who meet the inclusion criteria will be randomised into either a prehabilitation group or an ERAS group. The prehabilitation group will receive multimodal prehabilitation combined with ERAS at least 2 weeks before the gastrectomy is performed, including physical and respiratory training, nutritional support, and therapy and psychosocial treatment. The ERAS group patients will be treated according to the ERAS pathway. All interventions will be supervised by family members. The primary outcome measures are the incidence and severity of postoperative complications. Secondary outcomes include survival, functional capacity and other short-term postoperative outcomes. Overall, the multimodal prehabilitation protocol may improve functional capacity, reduce the surgical stress response and concomitant systemic inflammation, and potentially modulate the tumour microenvironment to improve short-term and long-term clinical outcomes and patients' quality of life.

Ethics and dissemination All procedures and participating centres of this study were approved by their respective ethics committees (QYFYKYLL 916111920). The final study results will be published separately in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be the first prospective, multicentre, randomised and controlled clinical trial constructed to evaluate the impact of a perioperative multimodal prehabilitation programme on the short-term clinical outcomes and long-term prognoses of frail elderly patients who undergo radical gastric cancer (GC) surgery.
⇒ The family members will record activities in a supervision diary and receive regular guidance with a follow-up from multiple healthcare professionals (nutritionist, psychologist or specialist doctors) during the duration of the perioperative period.
⇒ Different from the traditional prehabilitation cycle, the 2-week programme involving physical and respiratory training, nutritional support and psychosocial treatment will be more comprehensive, which can effectively improve the patient's physical condition and reduce waiting time for surgery.
⇒ The preoperative intervention did not unify to an extent owing to large heterogeneity for frail elderly patients with GC.

Trial registration number NCT05352802.

INTRODUCTION

Gastric cancer (GC) is a complex gastrointestinal malignancy, which ranks fifth in incidence of any cancer type worldwide.[1 2] By 2022, GC will become the fourth leading cause of cancer-related mortality worldwide.[1 3] As the worldwide population is ageing, the incidence of GC in elderly patients (those the age of 65 years or older, as defined by the US Census Bureau[4]) is increasing.[5] According to statistics, more than 60% of individuals with GC are aged 65 years or older.[6] Elderly

patients diagnosed with GC has become a serious public health problem worldwide, which places heavy disease and economic burdens not only on patients and their families but also on society. Although radical resection remains the primary curative treatment for GC, the proportion of elderly patients undergoing surgery declines dramatically with age as a result of being unsuitable for surgery due to frailty.[7]

Frailty is a syndrome characterised by decreased physiological reserve and resistance to stressors, which leaves patients susceptible to adverse outcomes following various surgical procedures.[8 9] A number of predisposing risk factors for frailty have been identified, including older age, sarcopenia, polypharmacy and malignant diseases.[10] Elderly patients with cancer are more prone to developing clinical frailty due to lower physiological reserve and preoperative nutritional conditioning.[11] It is estimated that over half of elderly patients with GC are frail.[12 13] Fried *et al*[9] proposed five indicators of frailty: involuntary weight loss, self-reported fatigue, poor grip strength, slow walking speed and reduced physical activity. The *G8 Geriatric* Screening Tool Score is a validated, useful tool; and patients with a G8 Score ≤14 must be assessed in the hospital by a geriatric oncologist before GC treatment.[14] Meanwhile, frailty is a reversible process, and interventions targeting frailty, either by physical training or nutrition supplementation, have been proven to be effective in preventing or reducing frailty in an ageing society.[15 16] However, patients with cancer with frailty are subjected to problems including, optimal make-up of physical training programmes, the timing and approach of the nutritional intervention, and how to improve compliance.

Enhanced Recovery after Surgery (ERAS) during the perioperative period has been developed quickly in the past two decades and has achieved remarkable milestones. Moreover, the ERAS programme was feasible and effective for elderly patients with GC who were undergoing laparoscopic total gastrectomy.[17] The concept of cancer prehabilitation is a novel preoperative management strategy based on ERAS. By the evaluation of a cancer patient's functional, psychological and nutritional status, the prehabilitation protocol will make it possible to develop more effective and targeted interventions to improve the health status and functional capacity of frail patients, thus, decreasing the subsequent detrimental effects of surgery, chemotherapy and radiotherapy.[18] Recent studies have shown that prehabilitation could reduce the incidence of postoperative complications, promote functional recovery and decrease hospital length of stay by reducing changes in lymphocyte subpopulations and the immune response during major abdominal surgery.[19]

While a qualitative study suggested that prehabilitation might offer certain benefits, many unresolved problems remain, including no consensus concerning the duration of the intervention and the specific content of the multimodal prehabilitation programme.[20] Moreover, the prehabilitation protocol in this study was implemented without relevant expert consensus and guidelines. In addition, to date, no study has investigated the clinical application of multimodal prehabilitation in frail older patients with GC. Therefore, we have designed a multicentre, randomised controlled trial (RCT) protocol for frail elderly patients with surgically resectable gastric carcinoma to focus on the effects of multimodal prehabilitation compared with the traditional ERAS programme as a control on the clinical outcomes.

METHODS/DESIGN

Objective

The GISSG+2201 Study was launched by the Shandong Gastrointestinal Surgery Study Group (GISSG). The intention is to establish a multimodal prehabilitation protocol in frail elderly patients who undergo GC radical surgery, explore the feasibility and effectiveness of the measures and evaluate the effect of the programme on short-term clinical outcome, recovery index and the long-term tumour-related outcome.

Trial design

The GISSG+2201 Study is a prospective, randomised, multicentre, open-label, controlled clinical study in which patients who meet the inclusion criteria will be randomised into either an experimental group (multimodal prehabilitation combined with ERAS group) or a control group (ERAS group) in a ratio of 1:1.

Before enrolment, medical history, physical examination, and psychological and physical status will be collected in detail for evaluation and screening of frail elderly patients. All candidates meeting the study requirements will be recruited into the study cohort and managed according to a standard perioperative ERAS programme until 30 days after discharge. All clinical features and adverse events (AEs) will be recorded. Each patient will be regularly followed up after surgery for at least 3 years at an outpatient clinic until relapse or death. The study protocol follows the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials 2013 Statement.[21]

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Participant selection and data monitoring

The participants will be recruited from the 15 hospitals across mainland China listed in table 1. Methods for recruitment included referrals, word of mouth and poster advertisements. Patients who received preoperative neoadjuvant chemotherapy will also be included in this study. To help guide treatment decisions, two features of geriatric oncology medicine are being incorporated into this research: the concept of frailty and comprehensive geriatric assessment (CGA). Frailty is considered to be a geriatric syndrome of decreased

Table 1 The 15 participating centres

Number	Centre	Department	Investigator
01	The Affiliated Hospital of Qingdao University	Gastrointestinal Surgery	Yanbing Zhou
02	Shandong Provincial Hospital	Gastrointestinal Surgery	Leping Li
03	Qilu Hospital of Shandong University	Gastrointestinal Surgery	Wenbin Yu
04	Shandong University Second Hospital	Gastrointestinal Surgery	Yinlu Ding
05	Yantai Yuhuangding Hospital	Gastrointestinal Surgery	Xinxun Wang
06	Shandong Jining No.1 People's Hospital	Gastrointestinal Surgery	Ying Kong
07	The Affiliated Hospital of Weifang Medical University	Gastrointestinal Surgery	Quanhong Duan
08	Weifang People's Hospital	Oncological Surgery	Jianjun Qu
09	Dongying People's Hospital	General Surgery	Hao Wang
10	Weihai Municipal Hospital	Gastrointestinal Surgery	Huanhu Zhang
11	Weihai Central Hospital	Gastrointestinal Surgery	Xinjian Wang
12	Rizhao People's Hospital	General Surgery	Xizeng Hui
13	People's Hospital of Jimo District, Qingdao	Gastrointestinal Surgery	Hongbo Wang
14	Liaocheng People's Hospital	Gastrointestinal Surgery	Daogui Yang
15	Qingdao Municipal Hospital	Gastrointestinal Surgery	Shaofei Zhou

physiological reserve and resistance to stressors, arising from cumulative declines across multiple physiological systems.[9] The CGA is the accepted standard process for objectively appraising health status in older people with frailty.[13] The G8 Geriatric Screening Tool Score, a simple and fast screening tool for identifying CGA, will be used; patients with a G8 Score ≤14/17 are considered frail.[14] In addition, functional capacity and cardiopulmonary function will also be measured, and quality of life (QoL) and mental state (Hospital Anxiety and Depression Scale (HADS) subscales and WHO-DASII) will be evaluated by questionnaires.[22 23] Moreover, in all centres, investigators who participated in this trial will be informed of the specific purpose and content of the study, and the relevant researchers need to supervise during the intervention; blinding of participants and personnel is difficult.

The research steering group will meet at least three times: at the start, middle and completion of the study. A kick-off meeting was held on 1 August 2022. During the start-up meeting, the list of key questions was refined through further discussion. Subsequently, a modified Delphi approach was undertaken to attain consensus among an expert panel on a multimodal prehabilitation protocol. The study began recruitment in September 2022 and will be ongoing until May 2024 for a 20-month recruitment period; information on survival time and survival status will be expected before May 2027. The protocol of the current study was approved by the ethics committees of all clinical research centres, and written informed consent was obtained from the participants prior to enrolment. Figure 1 displays the CONSORT diagram, describing the flow of participants through study recruitment and data collection. Any modifications of the study protocol, which may impact the conduct of the study or participant safety, including changes in study design, inclusion and exclusion criteria, sample size and study procedures, will require a formal amendment to the protocol and must be approved by the GISSG and the local research ethics committee. In addition, an interim analysis will be conducted to comprehensively assess the efficacy and safety at the midpoint of the clinical trial. After the meeting, the principal investigator will make an important decision on whether to continue the trial, modify the protocol or terminate the trial. Study data will be monitored by the Trial Steering Committee (TSC) at times to ensure the integrity and appropriate running of the project. An independent Data and Safety Monitoring Committee was established by the TSC to assure the safety of the enrolled data.

Eligibility criteria

The inclusion criteria are as follows: (1) Aged 65–85 years; (2) Karnofsky Performance Score ≥70 or Eastern Cooperative Oncology Group Performance Status Score ≤2; (3) G8 Score ≤14; (4) Endoscopic biopsies were pathologically confirmed as gastric adenocarcinoma; (5) Patients with cT1-4aN0-3M0 by endoscopy, imaging evaluations of CT and possibility of gastric resection; laparoscopic staging was not routinely conducted during the study period; (6) Received general anaesthesia or combined spinal-epidural anaesthesia (surgery was performed by either laparotomy, laparoscopy or robotic-assisted laparoscopy); (7) Date of surgery ≥2 weeks from baseline (T0) assessment; (8) Physical conditions could meet the requirements of exercise training, and no severe concomitant disease; (9) All subjects had to be willing and able to comply with study protocol and were informed adequately that they maintained the right to drop out of the study at any time.

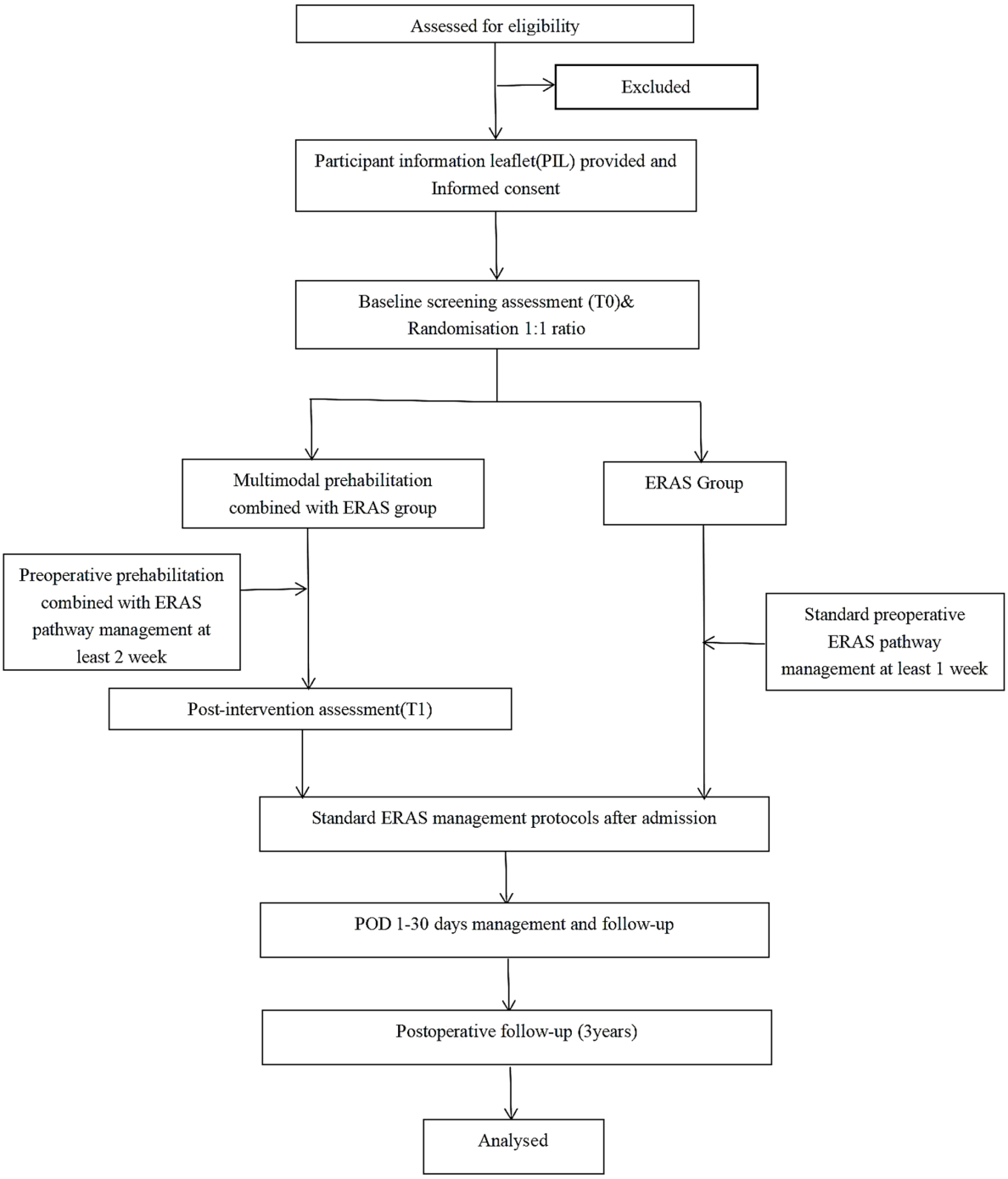

Figure 1 Recruitment and randomisation flow chart. ERAS, Enhanced Recovery After Surgery.

The exclusion criteria are as follows: (1) Patients with uncontrolled seizure disorders, central nervous system diseases and mental disorders; (2) End-stage cardiac insufficiency (left ventricular ejection fraction<30% or New York Heart Association class IV), liver cirrhosis (Child-Pugh classification C), end-stage renal failure (receives chronic dialysis), or American Society of Anaesthesiologists (ASA) grade IV; (3) Cerebral bleeding or infarction (within 6 months); (4) Patients with recurrent infectious diseases or serious concomitant disease; (5) Patients who require synchronous surgery due to other illnesses; (6) Patients who required emergency surgery within an emergency setting (obstruction, bleeding, perforation); and (7) Patients who are participating in any other clinical trials.

Randomisation and allocation

After registration and baseline assessment (T0), the eligible recruited participants will be randomly allocated, in a 1:1 ratio, to either the prehabilitation group (prehabilitation combined with ERAS group) or the ERAS group. The Pocock-Simon Minimization Method (Pocock and Simon, 1975), a dynamic and simple randomisation method, was used to randomise patients using

SAS V.9.3 (SAS Institute, Cary, North Carolina, USA) and stratify them by surgical procedure (open, laparoscopic or robotic), neoadjuvant therapy before operation, and Nutritional Risk Screening 2002 (NRS-2002) Score. In each participating centre, the above information will be presented to the data centre at the Department of Gastrointestinal Surgery, Affiliated Hospital of Qingdao University, China, where central randomisation will be performed. Subsequently, the results of the randomised assignment are sent to each centre by email.

Sample size computation

Due to the nature of the prehabilitation and ERAS programmes, the study was designed as a superiority study. According to the results of a previous study by our team and several previous retrospective studies of prehabilitaion for colorectal cancer and major abdominal surgery, preoperative nutritional supplementation and physical and respiratory training could reduce the incidence of postoperative complications by approximately 8%.[24 25] We assumed that the rate of postoperative complications would be 20% in the prehabilitation group and 28.5% in the ERAS group, with a significance level of α=2.5% (one-sided), a power of (1−β)=80% and a superiority margin of 20%.[17 26] Therefore, we calculated that 368 patients would be enrolled in this study, including 184 patients in the experimental group and 184 patients in the control group. From each clinical participating centre 25–30 eligible patients will be enrolled in the study.

Study endpoints and outcome measures

The primary outcome measures are the incidence and severity of postoperative complications within 30 days after surgery. Major postoperative complications of patients with gastrointestinal malignancy included gastrointestinal complications, surgical site complications, respiratory complications, cardiovascular complications, thromboembolic complications, urinary complications and other complications.[27] Furthermore, we need to pay more attention to complications related to surgical stress. The incidence, severity and type of complications occurring during the postoperative period will be recorded. The severity of complications will be recorded and classified according to the Clavien-Dindo Classification Score (figure 2).[28]

Secondary outcome 1

Cardiopulmonary function and physical capacity. The 6 min walk test can be used to measure exercise capacity to reflect cardiopulmonary function.[29] A difference of more than 20 m in the 6 min walk distance (6MWD) is accepted as clinically significant.[29] The respiratory function test consists of forced expiratory volume in 1 s, forced vital capacity, maximum ventilatory volume and peak expiratory flow. All measurements will be performed at baseline (T0), postintervention (T1), and post-operative day (POD) 30.

Secondary outcome 2

In this study, QoL comprises patient-reported outcomes of physical symptoms and psychosocial health status. The Quality of Life Questionnaire C30 and STO22 are sensitive tools for measuring individual performance status.[30] Furthermore, the patient's emotional state will be estimated using the WHO Disability Assessment Schedule V.2.0 Questionnaire and the HADS (validated Chinese version) at baseline (T0), postintervention (T1) and POD 30.[31 32]

Secondary outcome 3

Detection of immune and inflammatory indicators (ie, interleukin, tumour necrosis factor, C reactive protein)

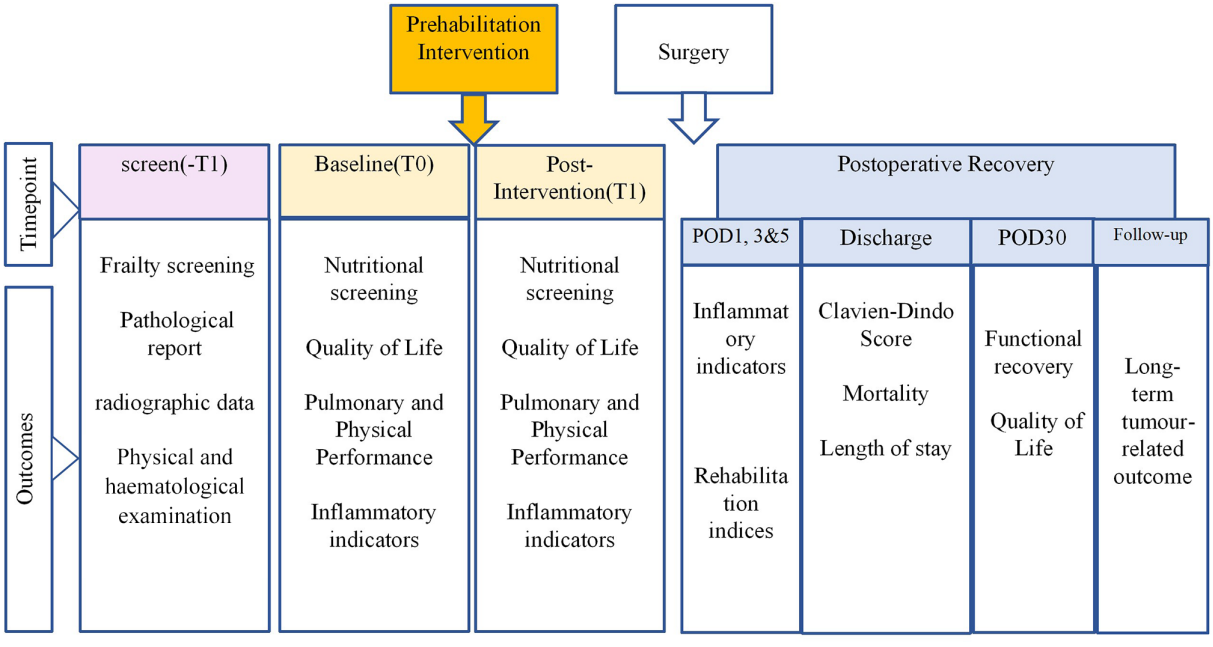

Figure 2 Key timepoints for assessing outcomes of multimodal prehabilitation intervention.

will be tested in the laboratory department of the hospital at baseline (T0), postintervention (T1) and POD 30.

Secondary outcome 4

Other postoperative observation parameters: postoperative pain severity (Visual Analogue Scale Score), postoperative delirium severity and occurrence (sum of all Confusion Assessment Method-Severity Scores), first exhaust and defecation, ureteral catheter removal, abdominal drainage tube removal, postoperative hospital stay, hospitalisation costs, 30-day all-cause mortality and 30-day hospital readmission rate.

Secondary outcome 5

Oncological outcomes: 3-year recurrence-free survival (RFS) rate and 3-year overall survival rate. RFS was defined as the time from diagnosis to recurrence or mortality.

Qualification of the investigators

Prior to study participation, the primary investigator or other investigators must follow some essential principles to guarantee the quality of the trial and the safety of patients. All group members had extensive clinical experience in elderly patients with GC. Meanwhile, each investigator had to have performed more than 100 radical gastrectomies to minimise the potential impact of the learning curve. Data quality will be monitored and regularly reviewed by the independent quality control committee consisting of the study principal investigator, local research coordinators, one ethicist and one statistician. Among them, the study principal investigator and the local study coordinator play a vital role in protecting patients. The statistician is primarily responsible for auditing data quality to reduce the risk of bias. The ethicist review whether research processes for compliance with ethical and legal requirements for human subject research.

Intervention

The prehabilitation group will receive multimodal prehabilitation combined with ERAS before gastrectomy. The ERAS group patients will be treated according to the ERAS pathway. In the study, multimodal prehabilitation included physical and respiratory training, nutritional support and therapy, and psychosocial treatment. The intervention programmes will be initiated immediately after the baseline visit (T0), which is scheduled to be a minimum of 2 weeks before the surgery. Two groups of patients will be given uniform and standardised ERAS management after admission.

Family members play an integral role in family centred prehabilitation. Family members of the participants will receive detailed training in exercising or breathing, nutrition and psychology from multiple healthcare professionals in different professional disciplines. The multimodal prehabilitation programme will be initiated under supervision of the family member and doctor after the family member has passed the training to ensure that the participants receive effective prehabilitation. At the same time, participants will be given a handbook that provides a detailed description of the interventions. All patients will be requested to fill out an activity diary daily to assess adherence for the entire duration of the study. Furthermore, participants and family members will be followed up every 2–3 days by telephone or WeChat to further address issues or doubts. Good compliance is defined as completing more than 70% of the weekly programme.

Preoperative exercise prehabilitation

Exercise training, including endurance and resistance training, was performed on alternate days.[33] All exercises will be performed under the supervision and guidance of well-trained family members and doctors. For each participant, clinical researchers will assess various comorbidities, medication status, frailty, recent diet, weight loss and fatigue in detail. Baseline exercise capacity and muscle strength will be measured using the 6MWD test and grip strength before exercise training. Patients will receive individualised exercise goals according to their exercise capacity.

Aerobic endurance exercise is the core activity of the exercise intervention programme consisting primarily of walking warm-up/jogging or stair climbing. The walking warm-up/jogging was carried out three times a week for 30 min per session.[34] Meanwhile, we encouraged the patient to walk up and down a set of five stairs (each stair 7 inchesin height) at least three times a day. Exercise intensity is monitored through the rating of perceived exertion. Moreover, moderate-to-high intensity aerobic training is recommended and defined by a modified Borg Scale of 13–16.[35] An elastic resistance band will be provided for each participant to use in the physical resistance training (one set of 12–18 repetitions, one to three sets per day) to improve overall muscle strength.

Respiratory training

(1) Patients in the prehabilitation group will undergo inspiratory threshold loading using an inspiratory threshold load trainer four or more times per day.[18] (2) Adaptive simulations of restrictive ventilatory dysfunction (increasing chest respiratory compliance and decreasing abdominal respiratory compliance) after abdominal surgery will be performed using fully elastic breathable abdominal bandages. The inspiratory/expiratory time ratio was 1:2, and each session lasted 1 hour, 3 times/day. (3) Blow balloon: patients should blow up a small balloon with strong breath and hold for over 5 s. Ten sets each time, four times a day. The purpose is to exercise the strength of all major respiratory muscle groups and increase tidal volume. (4) Expectoration training: a vibratory sputum ejection apparatus or slaps on the back with deep inspiration is used for vibration expectoration. (5) Cessation of smoking and limited alcohol consumption for at least 2 weeks.

Preoperative nutritional programme

Malnutrition and nutritional risk are prevalent in individuals with GC and obviously deteriorate after surgery, which is strongly associated with short-term and long-term outcomes in this population. Therefore, all participants needed to complete nutritional screening by the NRS-2002 and further assessment at the time of enrolment. Meanwhile, measures of total abdominal fat area, visceral fat area, and subcutaneous fat area will be obtained using the volume segmentation and thresholding tools in AW server V.2.0 software to further determine the nutritional status of patients. If the candidates suffer from malnutrition or nutritional risk, further nutritional support and therapy are needed.

The participants will be advised to change unhealthy eating habits, avoid high-energy snacks and high-fat diets, eat more vegetables and fruits, and incorporate greater intake of high-quality proteins. Based on European Society for Clinical Nutrition and Metabolism guidelines, each patient will be recommended a target energy intake of 30 kcal/kg/day and at least 2 g/kg/day of protein.[36] Specifically, participants receive different doses of iron supplementation, depending on the type and severity of anaemia. In addition, patients with malnutrition or nutritional risk diagnosed through screening are advised to supplement with appropriate oral nutrition supplements (ONS) or enteral nutrition (EN). Parenteral nutrition (PN) should be implemented to meet nutritional needs and maintain or improve nutritional status when ONS and EN are maintained for less than 3 days or half of the energy requirements cannot be met for more than 1 week.[37] Furthermore, patients with pyloric obstruction receive combined EN and PN (EN+PN or PN). Dietary counselling by registered dietitians will be provided to the patients at the nutrition outpatient clinics when necessary.

Psychosocial intervention

Cancer pain is one of the most debilitating symptoms experienced by patients with cancer, especially elderly individuals. Patients with a lack of correct cognition of the disease are prone to negative emotions. Thus, patients will be informed of all perioperative plans (including preoperative prehabilitation plans) and relevant knowledge at enrolment. Moreover, HADS is an effective and superior self-report screening tool for negative moods. The symptoms of depression and anxiety status of the study participants were determined via questionnaires.

After psychometric assessments, the patients will be taught basic mental relaxation skills, including breathing meditation (deep breathing exercises and progressive muscle relaxation with a duration of approximately 15 min each) and relaxing music (listening to the music excerpts for 30 minutes before bedtime).[38] In addition, patients with severe anxiety will be advised to consult a professional counsellor at a psychological clinic.

Standard preoperative ERAS care group

The standard ERAS care control group will not be invited to participate in prehabilitation. However, they formed an active control group, as standard preoperative ERAS protocols in gastrectomy included standard preoperative functional exercise (cessation of smoking, limited alcohol consumption and appropriate movements) and nutrition supplementation. Patients also completed the preoperative protocol as described and received preoperative psychological education. The ERAS programme was initiated by the ERAS Study group.[39] All ERAS Society guidelines are freely available at www.erassociety.org. After more than a decade of advancements, we also summarised the protocol for radical gastrectomy.[40]

Adverse events

AEs are defined as any undesirable/negative experience or outcome that did not have a causal relationship with the treatment. The prehabilitation and ERAS protocols are considered to be generally safe procedures, and we still cannot anticipate any study-related substantial AEs.[25 40] All AEs will be recorded, and appropriate management will be immediately provided. Furthermore, participants are guaranteed by state health insurance and are permitted to *withdraw from the* study *at any* stage *without any* consequences.

Postoperative management and follow-up

The patients will be regularly managed postoperatively according to a standardised ERAS protocol. Furthermore, all clinical information and postoperative symptoms will be recorded in the case report form (CRF). Patients who meet all of the following criteria will be discharged: (1) Postoperative pain is controlled with oral analgesic only. (2) No significant postoperative complications occurred, including fever, bleeding or anastomotic leakage. (3) The patient started on a semiliquid diet. (4) The walking activity can be autonomously completed. All patients will be followed up through phone interviews at least 24 hours after discharge.

Patients will be followed periodically for at least 3 years postoperatively by specially assigned personnel. To evaluate postoperative recovery, the first outpatient follow-up appointment will be scheduled at postoperative day 30. Meanwhile, postoperative adjuvant chemotherapy will be administered according to the postoperative performance status and pathological results. The patients are re-examined every 3 months within 2 years of the operation and then every 6 months for 3–5 years.[41] As shown in figure 3, the follow-up projects included physical examination, haematological examination, CT scans and gastroscopy. In addition, the follow-up information will be recorded in the CRF.

Data collection and analysis

All relevant data (including baseline characteristics, clinical manifestations, laboratory data and follow-up data) are timely, completely and correctly registered using a

	STUDY PERIOD													
	screen	Baseline	Post-intervention	Post-Operatively	Follow-up									
TIMEPOIT*	-T1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13
ENROLMENT															
Inclusion/exclusion screen	×														
Informed consent	×														
Demographic	×														
Allocation		×													
INTERVENTIONS															
multimodal prehabilitation intervention		×													
Standard ERAS intervention		×	×	×											
ASSESSMENTS:															
Physical examination	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Quality of life		×	×		×										
Function capacity		×	×		×										
Hematologic examination	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Image material	×						×		×		×		×	×	×
Gastroscopy	×								×				×		×
Pathological report	×				×										
Postoperative recovery course				×											
Adverse event			×	×											
Chemotherapy					×										
Tumor assessment				×	×	×	×	×	×	×	×	×	×	×	×
Follow-up information					×	×	×	×	×	×	×	×	×	×	×

NOTE: The symbol of × represent that the program needs to be collected. T0, a minimum of 2 weeks before the surgery. T1, 1 day before surgery. Follow-up T3~T11 refers to time points that listed in the following: T3, 1 months after surgery; T4, 3 months after surgery; T5, 6 months after surgery; T6, 9 months after surgery; T7, 12 months after surgery; T8, 15 months after surgery; T9, 18 months after surgery; T10, 21 months after surgery; T11, 24 months after surgery; T12, 30 months after surgery; T13, 36 months after surgery.

Figure 3 The items of enrolment, interventions and assessments in the flow chart. ERAS, Enhanced Recovery After Surgery.

standardised CRF by independent investigators. Moreover, all data are checked at monthly intervals. Any data errors need to be crossed out and corrected with the signature and date of the researcher to keep track of each piece of data.

Descriptive statistical analyses are applied for all the data and presented as the means and standard errors, median scores or proportions of respondents. Continuous variables are compared between two groups using independent t tests or White's non-parametrical t tests. The χ^2 test or Fisher's exact test is adopted to compare count data. For multiple-group comparisons, one-way analysis of variance or the least significance difference (LSD) test is applied. Furthermore, the Kaplan-Meier method is used for survival estimates. All statistical analyses are performed using SPSS software (V.26.0; IBM Corp, Armonk, New York, USA), and $p<0.05$ was considered to indicate a statistically significant difference.

Strengths and limitations

To date, ERAS has made remarkable progress in the perioperative management of GC. The ERAS pathway and multimodal prehabilitation protocol for frail older adults still lack high-quality evidence from evidence-based medicine. This trial will be the first prospective, multicentre, randomised, and controlled clinical trial to evaluate the impact of a perioperative multimodal prehabilitation programme on the short-term clinical outcomes and long-term prognoses of frail elderly patients who undergo radical GC surgery. Since the ERAS project started in 1997 by HK, our group has been actively pursuing the application of the ERAS protocol in radical gastrectomy and has accumulated rich experience with perioperative management to ensure the safety of patients and accelerate recovery after surgery.[25] In 2021, we published the first multicentre RCT on perioperative ERAS management for patients with GC who underwent laparoscopic surgery.[40] Furthermore, in this study, a preoperative multimodal prehabilitation programme suitable for frail elderly patients with GC was explored to demonstrate feasibility and effectiveness. This can likely enhance the functional capacities of the patients and optimise postoperative outcomes.

However, the preoperative intervention did not unify to an extent owing to large heterogeneity for frail elderly patients with GC. Patient awareness and compliance should be improved to increase the completeness of the intervention programme. Moreover, unified and standardised efficacy evaluation systems are indispensable at individual research centres.

DISCUSSION

Preoperative prehabilitation for gastrointestinal tumours aims to improve patient functional status and optimise clinical outcomes.[24 42] To maximise efficacy, the prehabilitation programme must be closely integrated with other elements of the ERAS programme from the time of diagnosis to surgery.[43] This study is intended to provide medical evidence-based support for the feasibility and effectiveness of multimodal prehabilitation programmes.

The most recent evidence suggests that exercise prehabilitation could improve fitness before surgery, but the long-term outcomes of patients and exercise modalities remain to be unidentified.[44] Skeletal muscle is a vital organ used for synthesising and storing macronutrients, while having a crucial role in maintaining homoeostasis.[45] In terms of frailty and sarcopenia, the European Working Group on Sarcopenia in Older People suggested that sarcopenia and frailty are not the same variables, but sarcopenia overlaps with the physical domain of frailty.[46] Meanwhile, they considered sarcopenia as a disease, while physical frailty was considered a broad geriatric syndrome. Sarcopenia (the loss of muscle mass, strength and function with ageing) is one of the most important physiological and pathological bases of frailty and results in physical dysfunction.[46] Hence, frail elderly individuals should adhere to aerobic and resistance exercise to effectively improve muscle mass, strength and physical function.[47] Additionally, skeletal muscle functional maintenance could not only ensure independence in daily activity but also prevent some of the metabolic disturbances.

Cancer treatments could also lead to disturbances in whole-body inflammatory and metabolic responses by the release of both proinflammatory and anti-inflammatory cytokines, such as tumor necrosis fact0r (TNF), interleukin (IL) 1, IL-6 and IL-8.[48 49] Adequate and early nutritional supplementation, combined with exercise training, may improve overall nutritional status, and promote protein synthesis to help reduce the inflammatory response before surgery. The clinical state of the patient was drastically improved to allow early rehabilitation after surgery. In the present study, inflammation and immunological indices will be detected after prehabilitation intervention and surgery are completed to then explore the changes in the body stress response. The suffering of anxiety symptoms in abdominal malignancies peaked before surgery, which was related to socioeconomic factors of the patients.[19] A previous study indicated that patients with colorectal cancer undergoing emotional management could effectively alleviate preoperative psychological disturbances and improve postoperative immune function.[50] Patients with strong emotional competencies more effectively manage the emotional impact of cancer diagnosis and surgery, reducing the level of anxiety and depressive symptoms and improving the QoL after surgery. In addition, frail patients are at high risk of perioperative psychological distress so it is suggested to provide prompt mental health interventions for these patients.

With the development of biopsychosocial medical models, clinicians and patients must be fully aware that the preoperative stage is the critical period for patients to recover after surgery. Moreover, it is also necessary to improve the multimodal prehabilitation protocol based on nutrition, functional capacity and psychological state, which are dominated by ERAS pathway management. Overall, the results of this trial may provide clinical evidence for the application of multimodal prehabilitation with frail GC in elderly patients. The multimodal prehabilitation protocol may improve functional capacity, postoperative outcomes and QoL and provide patients, healthcare professionals and policy makers with further guidance for perioperative management. Furthermore, the implementation of effective interventions may reduce the surgical stress response and concomitant inflammation and can even modulate the tumour microenvironment, offering a potential opportunity to improve patient survival.

Trial status

At the time of manuscript submission, recruitment for the GISSG^{+}2201 Trial is ongoing. The protocol version is V.1.0, 1 March 2022. The study began recruitment in September 2022 and will be ongoing until May 2024.

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