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Early intravenous branched-chain amino acid-enriched nutrition supplementation in older patients undergoing gastric surgery: a randomized clinical trial

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Abstract

Background The initiation time and formula for supplemental parenteral nutrition after surgery require optimization, especially in older patients undergoing major gastrointestinal surgery. This study aimed to assess the effect of early supplementation with a branched-chain amino acid (BCAA)-enriched formula (BAF) on short-term postoperative outcomes in older patients undergoing gastric surgery.

Methods This single-center, prospective, double-blinded, randomized clinical trial was conducted from March 10, 2020, to September 15, 2022. Patients aged 65–80 years with gastric cancer scheduled for curative resection were assessed for eligibility and randomly allocated to a high-proportion BCAA (HBCAA) (early supplementation with the BAF) or control (routine nutrition) group. The primary outcome was the standardized length of hospital stay (LOS).

Results A total of 150 patients were randomized. Thirteen patients were excluded due to the resection of other organs, presence of metastasis, or withdrawal of consent. Finally, we included 70 and 67 patients in the HBCAA and control groups, respectively (mean age: 70.5 ± 4.2 years; 96 men [70.1%]). The standardized LOS was significantly shorter in the treatment group than in the control group (median [interquartile range]: 8.0 [7.8, 8.0] vs. 8.5 [8.0, 9.0] days; mean difference, 0.38; 95% confidence interval [CI], 0.02–0.74 days; $P < .001$). Patients in the HBCAA group showed better gastrointestinal function with faster defecation (4.0 [3.6, 5.0] vs. 5.0 [4.0, 5.5] days; mean difference, 0.6 days; 95% CI, 0.26–0.94 days; $P < .001$) and semi-liquid diet initiation (8.0 [7.5, 8.0] vs. 8.0 [8.0, 8.8] days; mean difference, 0.36 days; 95% CI, 0.03–0.7 days; $P < .001$) and had lesser weight loss at postoperative day 5 than those in the control group did (3.5 [2.7, 6.5] vs. 4.9 [3.3, 7.6]%; mean difference, 1.23%; 95% CI, 0.27–2.19%; $P = .011$).

Conclusions In this randomized clinical trial, compared with routine nutrition, early supplementation with a BAF was associated with a shorter standardized LOS in older patients undergoing gastric surgery, suggesting that it may be a favorable strategy for patients with a poor tolerance to external nutrition who are undergoing major surgery.

Trial registration ClinicalTrials.gov; Identifier: ChiCTR2000029635.

Keywords Branched-chain amino acids, Early supplementation, Gastric surgery, Older patients, Parenteral nutrition, Malnutrition

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Background

Gastric cancer (GC) is the second most frequently diagnosed cancer in China. Its absolute incidence and associated mortality rates increase with aging [1, 2]. Gastrectomy remains the most effective treatment for GC, making its management crucial, particularly in older patients.

Age-related changes challenge perioperative outcomes, with nutritional status being key to recovery [3]. Malnutrition incidence rates in patients with GC range from 65 to 85% [4, 5], and it is an independent risk factor for postoperative complications and an increased length of hospital stay (LOS) [1, 2]. Proper nutritional care is essential for better surgical outcomes and quality of life in older adults. Several studies have reported that enhanced recovery after surgery (ERAS) protocols and nutritional support improve short-term clinical outcomes in patients undergoing gastrectomy [6, 7]. The European Society for Parenteral and Enteral Nutrition guidelines recommend early enteral nutrition (EN) for patients after surgery [2, 8]. However, older patients with GC may experience delayed EN due to cancer-induced cachexia, age-related weakness [4], the extent of the gastrectomy (invariably with lymphadenectomy), and surgical stress-related hypercatabolism [9, 10]. Therefore, timely supplemental parenteral nutrition (PN) is crucial for bridging the gap caused by this delay. However, no PN formula has been designed specifically for the perioperative period. Given the distinct perioperative metabolism of fat mobilization and skeletal muscle protein decomposition in response to stress [4, 9, 11] and the different roles of various amino acids [12–16], we developed a branched-chain amino acid (BCAA)-enriched formula (BAF), based on our previous study [17], to replace commonly used formulations (i.e., 18AA, 18AA-I, and 18AA-II) [18].

We hypothesize that early supplementation with a BCAA-enriched formula will significantly improve short-term postoperative outcomes, including reduced length of hospital stay and improved gastrointestinal function, in older patients undergoing gastric surgery. This randomized clinical trial aimed to assess the effects of early supplementation with a BAF on short-term postoperative outcomes in older patients undergoing gastric surgery. Furthermore, we investigated how BAF supplementation affects clinical outcomes, including postoperative catabolism and anabolism, intestinal barrier function, and immune function.

Methods

Trial design

From March 10, 2020, to September 15, 2022, we conducted a single-center, prospective, double-blind, randomized control trial at Zhongshan Hospital, Fudan University, China. The trial protocol and statistical analysis plan are available online (Additional File 1). Ethical approval (B2019-279) was obtained from the Ethics Committee of Zhongshan Hospital. Written informed consent was obtained from all the participants. The trial was registered at ClinicalTrials.gov (ChiCTR2000029635) and followed the Consolidated Standards of Reporting Trials guidelines. Trial oversight was monitored by the Shenkang Development Center, which was independent of the investigators.

Trial participants

Patients aged 65–80 years with GC, a body mass index of 18.5 to 28.0 kg/m^2, and an American Society of Anesthesiologists physical status class I–II who were scheduled for curative resection were eligible for the trial. Patients were excluded if they had received preoperative chemoradiotherapy; had metabolic disease (i.e., diabetes or thyroid disease), previous major gastrointestinal or other major surgeries, combined metastatic cancer, or cachexia (weight loss > 20% in the last month or an albumin level < 30 g/L) affecting recovery; or had undergone surgical procedure and experienced pathological diagnosis changes. The detailed exclusion criteria are described in the trial protocol.

Randomization and blinding

Eligible patients were randomly assigned using computer-generated random numbers (SPSS 22.0; IBM SPSS Inc., Armonk, NY, USA). An independent researcher concealed the allocations in consecutively numbered, sealed, opaque envelopes until informed consent was obtained. The physician in the pharmacy unit at the intravenous drug allocation center prepared the PN infusions and subsequently delivered them in unified PN bags of uniform volume and labeling to the unknown investigators. No visual or physical differences were detectable that could reveal the treatment allocation. Only the pharmacist was aware of the group allocation and acted as the unblinded investigator. The anesthesiologist, surgeon, patients, trained follow-up investigators, and data collectors were blinded to the treatment allocation. The statistician was independent and blinded to the interventions.

Anesthesia and perioperative care

This trial was based on ERAS protocols (Additional Table 1 in Additional File 2) which were implemented by a multidisciplinary team.

An epidural catheter was inserted between thoracic vertebral levels T8 and T11 before the induction of general anesthesia. Following successful internal jugular vein and radial artery catheter access, general anesthesia was induced with sufentanil 0.2 μg/kg, plasma

target-controlled infusion (TCI) of propofol 3 μg/mL, plasma TCI of remifentanil 3 ng/mL, and rocuronium 0.6 mg/kg, and maintained by combined intravenous–inhalation anesthesia. Epidural blockade was established with 0.375% ropivacaine 6–10 mL and maintained with 0.375% ropivacaine at 3–5 mL/h during surgery.

Using standard intraoperative monitoring, the mean arterial pressure and heart rate were controlled within ± 20% of baseline values, and end-tidal CO_2 was maintained at 30–40 mmHg. Balanced acetated Ringer's solution was administered at 5–7 mL/kg/h. Colloids were initiated in patients with significant blood loss but without renal impairment. A warm air heater was used to maintain perioperative normothermia.

Postoperative pain management was achieved by patient-controlled epidural analgesia, including 0.12% ropivacaine and 0.4 μg/mL sufentanil, targeting a resting pain score of < 4 (score = 0 [no pain], score = 10 [worst pain imaginable]). Postoperative care followed the local clinical practice.

Intervention procedures

The formulated solutions have already been marketed, and we formulated the intervention solution according to the drug instructions. The pharmacy at the intravenous drug allocation center prepared the PN solutions according to standard operating procedures.

The BAF formulation consisted of the following components: 780 mL BCAA solution (3AA), which included 3.38 g L-isoleucine, 4.12 g L-leucine, and 3.15 g L-valine per 250 mL, with the national medicine permission number (NMPN) H19993799; 100 mL arginine hydrochloride solution (5 g per 20 mL), with NMPN H31021692; 120 mL alanyl-glutamine solution (10 g per 50 mL), with NMPN H20053877; and 2 mL vitamin B6 solution (0.1 g per 2 mL), with NMPN H41021737.

The solutions were subsequently administered via a central venous catheter. Intraoperatively, patients in the high-proportion BCAA (HBCAA) and control groups received 500 mL BAF and 500 mL Ringer's solution, respectively, within 2 h after induction. Postoperatively, patients in the HBCAA group were administered 1000 mL BAF and 100 mL dextrose (50%), whereas the control group patients were administered 1000 mL dextrose (5%) and 100 mL sodium chloride (0.9%). Therefore, the dose and intervention volume of dextrose were the same across the two groups. From postoperative day (POD) 1, patients received 1100 mL of the intervention solutions at a rate of 200 mL/h, which was reduced to 550 mL during fluid diet initiation until semi-liquid intake or hospital discharge (Additional Figure 1 in Additional File 2). Additional nutrients, including potassium chloride injection and compounded vitamin injection, were supplemented by assessing each patient's fluid status, electrolyte levels, and nutritional needs. Based on these assessments, the attending physician adjusted it to ensure that both groups received the recommended PN.

Outcomes and measures

The primary outcome was the standardized LOS, defined as the time from surgery to discharge, based on the following criteria: stable vital signs, good wound healing without infection or considerable pain, free ambulation, sufficient oral intake of a semi-liquid diet, and no requirement for intravenous therapy.

The secondary outcomes were indicators closely related to primary outcomes, clinically significant to reflect short-term postoperative prognosis, be measurable and have easily accessible data, including the time to first flatus and defecation (postoperative gastrointestinal function recovery time), time to liquid and semi-liquid diet initiation, postoperative ambulation, weight loss (from baseline to POD 5), frequency and intensity of postoperative nausea and vomiting (PONV), time to gastrointestinal tube and urinary catheter removal, major postoperative complications (anastomotic leak, arrhythmia, congestive heart failure, respiratory failure, pneumonia, wound infection, bleeding, renal failure, intestinal obstruction, and deep vein thrombosis), hospitalization cost, readmission, and mortality rate within 28 days postoperatively.

The levels of the following indicators were measured preoperatively and on POD 1, 3, and 5 (at 6:00 am): albumin, prealbumin, blood glucose, free fatty acids (FFAs), CD4 + /CD8 + ratio, interleukin (IL)-6, D-lactate, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, serum creatinine, urinary 3-methylhistidine (3-MH), and urinary creatinine. The ratio of urinary 3-MH to creatinine was used as a nutritional indicator of protein metabolism. Blood D-lactate, urinary 3-MH, and urinary creatinine levels were analyzed using a D-lactate colorimetric assay kit (MAK058; Sigma-Aldrich Co. LLC, St. Louis, MO, USA), a urinary 3-MH ELISA kit (abx257295; Abbexa LTD, CB4 0GJ, UK), and a urinary creatinine colorimetric assay kit (500701; Cayman Chemical, Ann Arbor, MI, USA), respectively. The remaining indicators were measured at the laboratory at the study site.

Follow-up personnel assessed the clinical indicators related to the patient's outcomes twice daily (8:00 am and 4:00 pm). After discharge, complications and readmission status were monitored via a follow-up phone call 28 days post-surgery.

Adverse events

Unexpected experiences observed in patients during the trial, whether or not considered related to the solutions, were reported as adverse events. Events and rescue interventions were recorded and reported according to the adverse event procedures. Serious adverse events were reported individually to the sponsor, the Ethics Committee, and the health administrative department within 24 h.

Statistical analysis

Previous studies revealed that the overall standardized LOS after surgery for gastrointestinal tumors was 7.7 days, with a standard deviation of approximately 1.7 days. Moreover, the between-group difference was clinically valuable if it reached 1 day. Hence, we used a targeted standardized LOS decrease of 1 day, a two-tailed type I error rate of 5%, and a statistical power of 80% to obtain a sample size of 65 patients in each group. The sample size was increased to 150 to accommodate participant withdrawal and loss to follow-up.

The full analysis set adhered to the intention-to-treat principle. Variables were reported as number (percentage), mean (standard deviation), or median (interquartile range). The normality of continuous data was assessed using the Shapiro–Wilk test. Between-group comparisons were performed using the chi-square or Fisher exact test and the Mann–Whitney U test for categorical and continuous variables, respectively. Time-based measurements within each group were compared using a repeated-measures analysis of variance.

For each hypothesis, a two-tailed $P<0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (version 27.0). The sample size was estimated using the Power Analysis and Sample Size Statistical Software (Version 11, Kaysville, UT, USA).

Results

Patients

We screened 792 patients, of whom 150 consenting patients were randomized into two groups (Fig. 1). Thirteen patients were excluded owing to the resection of other organs, presence of metastasis, and withdrawal of consent; therefore, 137 patients (median [interquartile range] age, 70.0 [67.0, 73.0] years; 96 [70.1%] men and 41 [29.9%] women) were included in the final study (70 and 67 patients in the HBCAA and control groups, respectively) (Table 1).

All the respondents were of Chinese ethnicity. Most participants had no complications (116 participants [84.7%]). Forty-two (30.7%), 42 (30.7%), and 53 (38.7%) participants had Stage I, Stage II, and Stage III disease, respectively. There were no significant differences in the demographic or clinical characteristics at baseline between participants who completed the study and those who were unavailable for follow-up (Additional Table 2 in Additional File 2). The overall adherence rate of the intervention group was 91.3%. Most participants in the HBCAA (70 participants [93.3%])

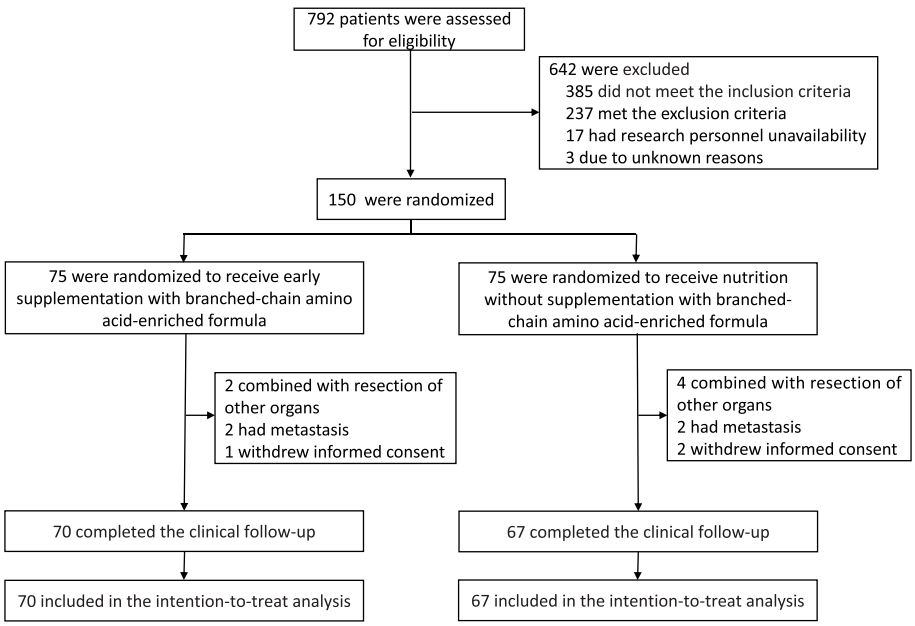

Fig. 1 CONSORT flow diagram

Table 1 Baseline demographic and clinical characteristics

Characteristic	Total Missing data, No. (%)	Participants ($N=137$)	
		HBCAA group ($N=70$)	Control group ($N=67$)
Sex, n (%)			
Male	0	46 (65.7%)	50 (74.6%)
Female		24 (34.3%)	17 (25.4%)
Age, y	0	70.3 (3.9)	70.6 (4.5)
Height, cm	0	166 (8.7)	165 (6.8)
Weight, kg	0	62.7 (10.3)	63.2 (10.2)
BMI, kg/m^2	0	22.6 (2.9)	23.2 (2.7)
NRS-2002 score, n%			
2	0	11 (15.7%)	15 (22.4%)
3	0	24 (34.3%)	27 (40.3%)
4	0	21 (30%)	12 (17.9%)
≥ 5	0	14 (20%)	13 (19.4%)
TNM stage, n%	0		
I	0	18 (25.7%)	24 (35.8%)
II		21 (30.0%)	21 (31.3%)
III		31 (44.3%)	22 (32.8%)
Surgery, n (%)			
Total gastrectomy	0	38 (54.3%)	35 (52.2%)
Proximal gastrectomy		4 (5.7%)	3 (4.5%)
Distal gastrectomy		28 (40.0%)	29 (43.3%)
Baseline values at randomization			
Glucose, mmol/L	4 (2.9)	5.64 (1.14)	5.30 (0.971)
Total bilirubin, μmol/L	0	11.5 (5.51)	11.0 (4.88)
Albumin, g/L	0	41.5 (3.72)	41.4 (3.48)
FFA, mmol/L	0	0.734 (0.311)	0.715 (0.358)
ALT, U/L	0	16.0 (8.84)	16.9 (14.8)
AST, U/L	0	48.5 (35.4)	43.6 (18.9)
BUN, mmol/L	0	5.96 (1.53)	5.67 (1.19)
Serum creatinine, mol/L	0	80.5 (15.9)	82.4 (15.8)
CD4 + /CD8 + ratio	20 (14.6)	2.04 (1.08)	1.91 (1.01)
IL-6, pg/mL	0	3.81 (2.87)	3.90 (3.22)

Data are presented as mean (SD) unless otherwise indicated

Abbreviations: *HBCAA* High-proportion branched-chain amino acids, *BMI* Body mass index (weight in kilograms divided by height in meters squared), *NRS-2002* Nutritional Risk Screening 2002, *FFA* Free fatty acid, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *BUN* Blood urea nitrogen, *IL-6* Interleukin 6, *SD* standard deviation

and control groups (67 participants [89.3%]) attended at least 80% of all sessions.

Primary outcome

The standardized LOS was significantly shorter in the HBCAA group than in the control group (8.0 [7.8, 8.0] vs. 8.5 [8.0, 9.0] days; mean difference, 0.38 days; 95% confidence interval [CI], 0.02–0.74 days; $P<0.001$) (Fig. 2A).

Secondary outcomes

No significant differences were observed in the surgical procedure or intraoperative parameters (Additional Table 3 in Additional File 2).

Among the postoperative indicators, the times to defecation (4.0 [3.6, 5.0] vs. 5.0 [4.0, 5.5] days; mean difference, 0.6 days; 95% CI, 0.26–0.94 days; $P<0.001$, Fig. 2B) and semi-liquid diet initiation (8.0 [7.5, 8.0] vs. 8.0 [8.0, 8.8] days; mean difference, 0.36 days; 95% CI, 0.03–0.7 day; $P<0.001$, Fig. 2C) were significantly shorter in the HBCAA group than in the control group. The HBCAA group had lesser weight loss than the control group did (3.5 [2.7, 6.5] vs. 4.9 [3.3, 7.6]%; mean difference, 1.23%; 95% CI, 0.27–2.19%; $P=0.013$, Fig. 2D).

The postoperative times to first flatus, liquid diet initiation, and gastrointestinal and ureteral tube removal showed no significant between-group differences. PONV

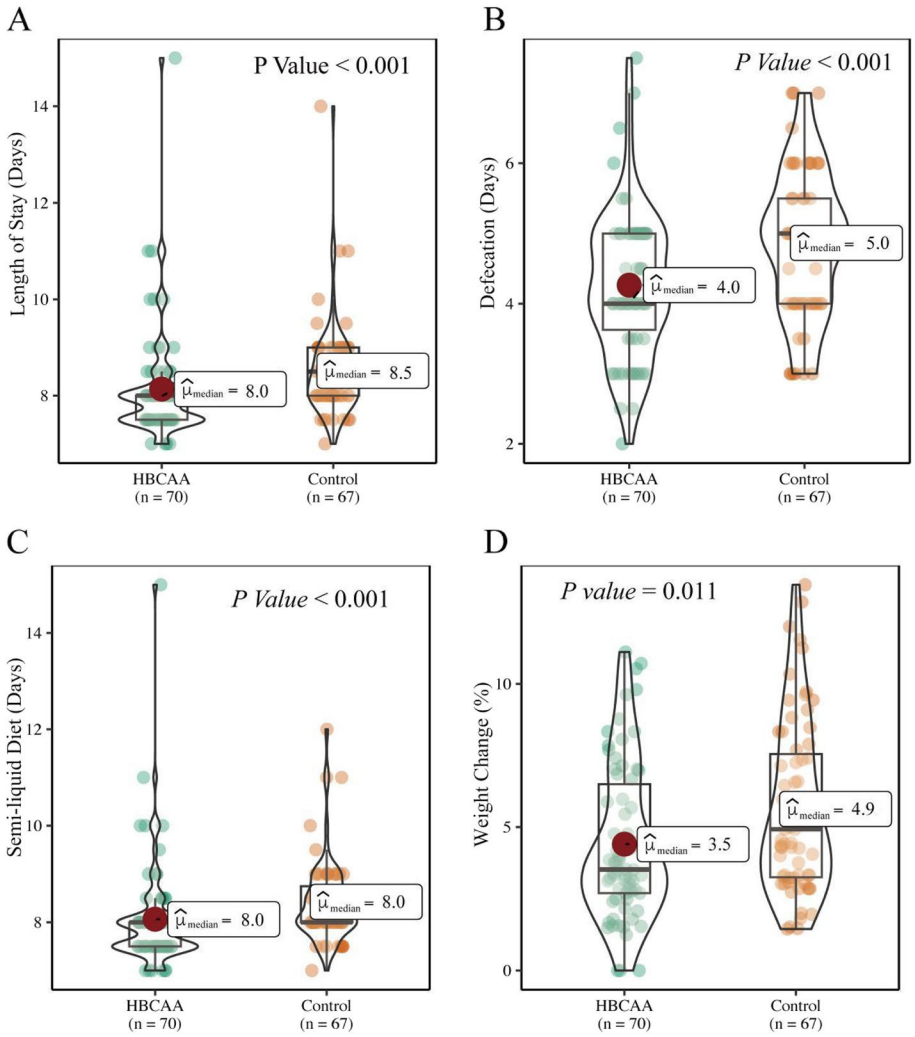

Fig. 2 Primary and secondary outcomes

occurred in 1 (1.4%) patient in the HBCAA group and 2 (3.0%) in the control group (risk difference, 1.56%; 95% CI, -3.38–6.49%; $P=0.969$). There was no significant intergroup difference in the major postoperative complication rates (HBCAA group, 15 [21.4%]; control group 10 [14.9%]; risk difference, -6.5%; 95% CI, -19.36–6.35%; $P=0.445$). Readmission within 28 days was reported for 1 (1.4%) patient in the HBCAA group and 3 (4.5%) in the control group, with no significant between-group difference (risk difference, 3.05%; 95% CI, -2.63–8.73%; $P=0.581$). No deaths occurred in either of the groups (Table 2).

Table 3 shows the comparison of the differences in various postoperative parameters based on the POD between the HBCAA and control groups, assessed using generalized linear models. All participants exhibited normal baseline D-lactate levels. The HBCAA group showed a significant reduction in D-lactate levels compared with the control group. The reduction was evident on POD 3, reaching statistical significance on POD 5. Unlike the control group, the HBCAA group demonstrated a significant reduction in FFA levels from POD 1, which persisted for the entire duration of the trial. However, no significant between-group differences were observed in the 3-MH/creatinine, albumin, prealbumin, or fasting blood glucose levels. The CD4 + /CD8 + ratio significantly increased in the HBCAA group compared with that in the control group on PODs 3 and 5, although the difference was not significant. IL-6 levels increased immediately on POD 1, but there was no significant difference between the groups. Blood urea nitrogen levels significantly increased in the HBCAA group from POD 1 until the end of the follow-up period. No significant differences were observed in serum creatinine levels or hepatic function indicators.

Table 2 Primary and secondary outcome parameters

Outcomes	HBCAA group ($n=70$)	Control group ($n=67$)	Mean/risk difference (95% CI)	*P*
Primary outcome				
Standard LOS, d	8 (7.5, 8)	8.5 (8, 9)	0.38 (0.02 to 0.74)	< .001
Secondary outcomes				
Postop. First flatus, d	3 (2.5, 3.5)	3 (3, 4)	0.15 (-0.12 to 0.42)	.179
Postop. First defecation, d	4 (3.6, 5)	5 (4, 5.5)	0.60 (0.26 to 0.94)	< .001
PONV, n (%)	1 (1.43)	2 (2.99)	1.56 (-3.38 to 6.49)	.969
Postop. Liquid diet, d	5 (5, 6)	5 (5, 6)	-0.05 (-0.40 to 0.29)	.834
Postop. Semi-liquid diet, d	8 (7.5, 8)	8 (8, 8.75)	0.36 (0.03 to 0.70)	< .001
Gastrointestinal tube removal, d	2 (1, 3)	2 (1, 4)	0.28 (-0.18 to 0.74)	.251
Ureter tube removal, d	4 (4, 4)	4 (4, 4)	0.159 (-0.10 to 0.42)	.437
Postop. Ambulation, d	2 (2, 2)	2 (2, 2.75)	0.08 (-0.11 to 0.27)	.633
Weight loss, %	3.5 (2.7, 6.5)	4.9 (3.3, 7.6)	1.23 (0.27 to 2.19)	.011
Major complications, n (%)	15 (21.43)	10 (14.93)	-6.5 (-19.36 to 6.35)	.445
Hospitalization costs, mean (SD), ¥	58,733.6 (9517.7)	57,475.3 (8274.4)	2942.41 (-2570.12 to 7095.87)	.253
28-day mortality, n (%)	NA	NA		
28-day readmission, n (%)	1 (1.43)	3 (4.48)	3.05 (-2.63 to 8.73)	.581

Data are presented as median (IQR) unless otherwise indicated, with the *P*-value representing the significance level for differences between the HBCAA and control group (Student's t-test, the Mann–Whitney U test, Pearson's χ^2 test, or Fisher's exact test)

Abbreviations: *HBCAA* High-proportion branched-chain amino acids, *CI* Confidence interval, *LOS* Length of hospital stay, *Postop* Postoperative, *PONV* Postoperative nausea and vomiting, *SD* Standard deviation, *IQR* Interquartile range

No adverse events occurred during the course of the clinical trial.

Discussion

To our knowledge, this is the first clinical trial to demonstrate the short-term clinical benefits of early BAF supplementation with PN in older patients who underwent gastric surgery. The standardized LOS was shorter in the HBCAA group than in the control group. Patients in the HBCAA group showed decreased D-lactate levels and a shorter time to defecation than patients in the control group did, indicating earlier gastrointestinal function recovery. Furthermore, the FFA levels improved from POD 1, and weight loss was lesser in the HBCAA group than in the control group, suggesting some improvement in nutritional status [19]. Therefore, early BAF supplementation improved post-gastrectomy clinical outcomes in older patients with poor EN tolerance, suggesting that early BAF supplementation may enhance post-abdominal surgery recovery in patients at nutritional risk.

Patients with malnutrition are predisposed to morbidity and mortality [20], and severe malnutrition is common in patients with gastrointestinal cancer [21]. The global aging population has led to a growing demand for surgical interventions, yet the physiological changes associated with aging—especially in nutritional status—play a critical role in determining older adults' resilience to surgical stress and postoperative recovery [22]. Current literature underscores the importance of immunonutrition in improving wound healing and reducing hospital stays [3, 23]. Therefore, indicating an urgent need to optimize perioperative nutritional interventions to improve their clinical outcomes. However, although the ERAS protocol is well developed, the perigastrectomy nutrition guidelines remain limited, particularly in older patients. A recent study indicated that post-gastrectomy nutritional support varies among different institutions, with a high prevalence of postoperative nutritional deficits in Asians [24]. Although early EN is strongly recommended [25], its use after gastrectomy is frequently debated as most patients may develop ileus for several days. Moreover, gastrointestinal tolerance limits the dose administered and absorption rates. These conditions frequently reduce EN efficacy [26]. Total PN is an effective EN alternative and is not associated with the risk of increased infectious complications in the short term [27, 28]. Evidence suggests that early supplemental PN is preferable for reducing the incidence of nosocomial infections after major abdominal surgery [29]. Therefore, we used early supplemental PN to bridge the nutritional gap resulting from the absence of EN and oral nutrition.

Owing to pre-existing nutritional risks and difficulties in obtaining adequate nutrition, older patients rapidly develop a negative energy balance after gastric surgery [30]. Moreover, a recent retrospective cohort study indicated that lower amino acid doses in PN are associated with a longer hospital LOS and higher total medical

Table 3 Between-group comparison of laboratory parameters

	Group	Baseline	POD 1	POD 3	POD 5
D-lactate, mg/L	HBCAA (*N* = 70)	23.5 (7.22)	31.5 (9.73)	28.4 (8.85)	23.2 (8.10)
	Control (*N* = 67)	24.6 (8.01)	32.2 (9.76)	30.8 (7.49)	28.1 (8.44)
	H	0.857	0.122	2.423	10.168
	P value	.355	.727	.12	< .001***
Wald X^2 Group = 5.172; Wald X^2 Time = 101.258; Wald X^2 Interaction = 7.445					
P (Group) = .023; P (Time) < .001***; *P* (Interaction) = .059					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
FFA, mmol/L	HBCAA (*N* = 70)	0.734 (0.311)	0.551 (0.190)	0.573 (0.164)	0.630 (0.216)
	Control (*N* = 67)	0.715 (0.358)	0.624 (0.136)	0.681 (0.218)	0.834 (0.240)
	H	0.316	9.143	8.679	24.509
	P value	.574	.002**	.003**	< .001***
Wald X^2 Group = 17.446; Wald X^2 Time = 64.865; Wald X^2 Interaction = 13.163					
P (Group) < .001***; *P* (Time) < .001***; *P* (Interaction) = .004**					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
3-MH/Cr	HBCAA (*N* = 70)	1.94 (0.989)	3.12 (3.42)	3.35 (2.27)	2.89 (2.29)
	Control (*N* = 67)	1.84 (0.961)	2.97 (2.28)	3.10 (2.37)	2.93 (2.68)
	H	0.197	0.687	1.367	0.414
	P value	.657	.407	.242	.52
Wald X^2 Group = 0.159; Wald X^2 Time = 70.816; Wald X^2 Interaction = 0.475					
P (Group) = .690; *P* (Time) < .001***; *P* (Interaction) = .924					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
CD4 + /CD8 + ratio	HBCAA (*N* = 70)	2.04 (1.08)	1.75 (1.11)	2.05 (1.03)	2.33 (1.21)
	Control (*N* = 67)	1.91 (1.01)	1.76 (1.01)	2.00 (1.23)	1.96 (1.07)
	H	0.298	0.016	1.134	4.27
	P value	.585	.901	.287	.039*
Wald X^2 Group = 0.617; Wald X^2 Time = 79.150; Wald X^2 Interaction = 23.278					
P (Group) = .432; *P* (Time) < .001***; *P* (Interaction) < .001***					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
IL-6, pg/mL	HBCAA (*N* = 70)	3.81 (2.87)	49.1 (38.8)	23.6 (25.4)	11.1 (9.14)
	Control (*N* = 67)	3.90 (3.22)	44.6 (33.8)	21.5 (23.1)	11.2 (9.31)
	H	0.088	0.356	0.652	0.093
	P value	.767	.551	.419	.76
Wald X^2 Group = 0.461; Wald X^2 Time = 269.569; Wald X^2 Interaction = 0.821					
P (Group) = .497; *P* (Time) < .001***; *P* (Interaction) = .845					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
BUN, mmol/L	HBCAA (*N* = 70)	5.96 (1.53)	7.03 (1.83)	8.64 (2.65)	8.76 (2.97)
	Control (*N* = 67)	5.67 (1.19)	5.56 (1.61)	4.79 (1.84)	4.86 (1.81)
	H	1.279	21.459	62.214	59.76
	P value	.258	< .001***	< .001***	< .001***
Wald X^2 Group = 82.194; Wald X^2 Time = 31.113; Wald X^2 Interaction = 106.269					
P (Group) < .001***; *P* (Time) < .001***; *P* (Interaction) < .001***					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
Serum creatinine, mol/L	HBCAA (*N* = 70)	80.5 (15.9)	87.6 (19.4)	75.3 (17.1)	69.6 (15.9)
	Control (*N* = 67)	82.4 (15.8)	89.8 (25.9)	78.3 (18.7)	74.7 (15.1)
	H	0.297	0.026	0.261	2.286
	P value	.586	.872	.61	.131
Wald X^2 Group = 1.218; Wald X^2 Time = 213.171; Wald X^2 Interaction = 4.13					
P (Group) = .27; *P* (Time) < .001***; *P* (Interaction) = .248					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**

Table 3 (continued)

Total bilirubin, μmol/L	HBCAA (*N* = 70)	11.5 (5.51)	15.4 (7.92)	13.4 (6.32)	11.7 (6.98)
	Control (*N* = 67)	11.0 (4.88)	15.4 (5.70)	14.2 (6.11)	13.5 (6.57)
	H	0.007	1.702	1.082	6.9
	P value	.933	.192	.298	.009***
Wald X^2 Group = 0.35; Wald X^2 Time = 78.836; Wald X^2 Interaction = 6.199					
P (Group) = .554; *P* (Time) < .001; *P* (Interaction) = .102					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
ALT, U/L	HBCAA (*N* = 70)	16.0 (8.84)	41.5 (34.5)	27.3 (21.1)	22.2 (12.1)
	Control (*N* = 67)	16.9 (14.8)	37.8 (20.6)	27.3 (19.5)	19.8 (8.14)
	H	0.111	0.02	0.002	0.211
	P value	.74	.887	.962	.646
Wald X^2 Group = 0.07; Wald X^2 Time = 116.257; Wald X^2 Interaction = 1.816					
P (Group) = .791; *P* (Time) < .001***; *P* (Interaction) = .612					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
AST, U/L	HBCAA (*N* = 70)	19.1 (5.92)	48.5 (35.4)	28.9 (16.0)	22.1 (12.8)
	Control (*N* = 67)	20.6 (9.04)	43.6 (18.9)	28.7 (15.5)	22.9 (11.0)
	H	0.574	0.008	0.035	4.44
	P value	.449	.928	.851	.035*
Wald X^2 Group = 0.003; Wald X^2 Time = 132.713; Wald X^2 Interaction = 3.251					
P (Group) = .955; *P* (Time) < .001***; *P* (Interaction) = .355					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
Albumin, g/L	HBCAA (*N* = 70)	41.5 (3.72)	35.7 (4.78)	34.8 (2.93)	36.7 (3.72)
	Control (*N* = 67)	41.4 (3.48)	36.3 (3.00)	35.8 (3.11)	37.8 (3.21)
	H	0.073	2.808	4.549	4.21
	P value	.787	.094	.033*	.04*
Wald X^2 Group = 3.063; Wald X^2 Time = 356.974; Wald X^2 Interaction = 2.282					
P (Group) = .08; *P* (Time) < .001; *P* (Interaction) = .516					
	Group	**Baseline**	**POD 1**	**POD 3**	**POD 5**
Glucose, mmol/L	HBCAA (*N* = 70)	5.64 (1.14)	5.97 (1.14)	5.32 (0.914)	5.66 (0.727)
	Control (*N* = 67)	5.30 (0.971)	6.03 (1.59)	5.17 (1.08)	5.42 (0.786)
	H	6.683	0.086	1.729	5.724
	P value	.01	.77	.189	.017*
Wald X^2 Group = 1.521; Wald X^2 Time = 57.466; Wald X^2 Interaction = 2.901					
P (Group) = .217; *P* (Time) < .001***; *P* (Interaction) = .407					

Data are presented as mean (SD), and comparisons between time-based measurements within each group were performed using generalized estimating equation modelling

Abbreviations: *POD* Postoperative day, *HBCAA* High-proportion branched-chain amino acids, *FFA* Free fatty acid, *3-MH/Cr* Urinary 3-methylhistidine/creatinine, *IL-6* Interleukin 6, *BUN* Blood urea nitrogen, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *SD* Standard deviation

* *P* < .05; ** *P* < .01; *** *P* < .001

costs [31]. Therefore, patients in the intervention group received 82.2 g/day of amino acid supplementation, meeting the amino acid requirement of 0.8–1.5 g/kg/day in the early postoperative period, as recommended by the American Society for Parenteral and Enteral Nutrition. Furthermore, our BAF was specified for the perioperative period to modulate perioperative metabolism and systemic inflammatory responses while supporting the required protein synthesis [32]. Compared with conventionally used PN formulas, it provided higher proportions of BCAAs and immune-boosting nutrients [33], such as arginine and glutamine, the use of which has been reported to result in immune system improvement [13, 34–36]. The reduced weight loss and FFA levels over the trial's duration suggested that our intervention ameliorated the perioperative metabolism and reduced fat mobilization. The CD4 + /CD8 + ratio is a sensitive index that reflects cellular immune function; a higher CD4 + /CD8 + ratio indicates greater cellular immune function [37, 38]. Although no significant differences were

observed in the CD4+/CD8+cell counts between the groups, this does not imply that the BAF supplementation had no effect on immunity. Another study on early postoperative enteral immunonutrition found fewer infections and lower anastomotic leak rates, along with a greater reduction in CD4+T-cell counts [23]. This effect was likely due to the specific components of the immunodiet and its focus on enteral rather than parenteral nutrition. Older patients undergoing major abdominal tumor surgery experience immune depression. A lower CD4+/CD8+ratio is associated with lower thymic output in older people [39]. Moreover, immune function is associated with multiple factors, including altered immune capabilities, in patients with tumors at different TNM stages [40]. Therefore, the recovery of cellular immune function may require a longer follow-up period. Further studies are needed to explore different nutritional strategies and optimize perioperative care for older patients, particularly regarding their effects on cellular immune function. IL-6 levels increased immediately on POD 1, to about 10 times the preoperative level, and gradually decreased on POD 3 and POD 5, corroborating that IL-6 is an acute-phase response mediator [41].

Abe et al., Narendra et al., and Tian et al. have reported that the average LOS after gastrectomy, median LOS after gastrointestinal surgery, and LOS in the ERAS group after laparoscopic distal gastrectomy were 10 days [42], 8.0 (4.5–11.5) days [43], and 7.27 ± 1.83 days [44], respectively. The different discharge criteria, among other reasons, may account for the differences in the aforementioned findings. In our trial, we used standardized LOS and defined discharge criteria to obtain more reliable outcomes—the standard LOS in our trial was 8.0 (7.5–8.5) days. Moreover, implementing the ERAS protocol standardized the procedure and improved the overall clinical outcomes [45, 46]. The mean difference of 0.38 days is important for increasing patient satisfaction, improving quality of life, reducing medical burden, and enhancing healthcare resource utilization.

During gastrectomy, surgery- and anesthesia-related intestinal barrier injuries may predispose patients to surgical infections and negative clinical outcomes [47, 48]. Therefore, preservation of the postoperative intestinal barrier is pivotal for improving clinical outcomes. Multiple studies have reported the beneficial effects of glutamine and arginine on gut barrier function in critically ill patients with experimentally induced intestinal inflammation [49–53]. However, to our knowledge, this is the first clinical trial to evaluate the effects of early glutamine and arginine supplementation on the gut barrier function of older patients with GC. In the HBCAA group, we observed relatively low levels of D-lactate, a surrogate intestinal barrier function marker [54], corroborating the findings of previous studies. Furthermore, patients in the HBCAA group demonstrated earlier defecation, indicating earlier gastrointestinal function recovery than that in patients in the control group [55]. Therefore, BAF supplementation may enhance postoperative bowel movement recovery through intestinal barrier protection in older patients undergoing gastric surgery.

Strengths and limitations

The strength of this study lies in the use of a novel perioperative parenteral nutrition formula within the ERAS framework. We conducted a comprehensive assessment of short-term postoperative outcomes, validating the formula's effectiveness. Our findings suggest that supplementation with this formula may be a favorable recovery strategy for older patients with poor tolerance for enteral nutrition after major surgery. Additionally, by detecting related laboratory markers, we not only provide evidence to support clinical observations but also establish a foundation for further investigation into the underlying mechanisms. However, there were also some limitations. First, it was a small single-center study with participants exclusively from one ethnic group, which could limit the generalizability of the findings. To confirm these results, a multicenter study that includes diverse ethnic groups is required. Second, although nitrogen requirements should be calculated based on the ideal or adjusted body weight, we did not calculate the energy target using indirect calorimetry. However, individualized nutrition is often unnecessary for patients without serious comorbidities. Third, we investigated the short-term clinical outcomes. Future studies should implement a longer follow-up period to evaluate the effects of BAF supplementation on overall survival and tumor recurrence.

Conclusions

Early BAF supplementation was associated with a shorter standardized LOS in older patients who underwent gastrectomy for GC. Our results indicate that supplementation with this formula may be a favorable recovery strategy for older patients with compromised tolerance for external nutrition following major surgery.

Abbreviations

3-MH	3-Methylhistidine
BAF	Branched-chain amino acid-enriched formula
BCAA	Branched-chain amino acid
CI	Confidence interval
EN	Enteral nutrition
ERAS	Enhance recovery after surgery
FFA	Free fatty acid
GC	Gastric cancer
HBCAA	High-proportion branched-chain amino acid
IL	Interleukin
LOS	Length of hospital stay
NMPN	National medicine permission number
POD	Postoperative day

PN	Parenteral nutrition
PONV	Postoperative nausea and vomiting
TCI	Target-controlled infusion

Supplementary Information

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Additional file 1. Trial protocol.

Additional file 2: Additional Table 1. Perioperative Enhanced Recovery after Surgery (ERAS) Measures. Additional Table 2. Demographic and Clinical Characteristics. Additional Table 3. Surgical Procedure and Intraoperative Parameters. Additional Figure 1. Intervention Protocol.

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Authors' contributions
Yimei Ma: Writing - Original Draft. Xining Zhao: Writing - Original Draft. Yan Pan: Investigation. Yuying Yang: Formal Analysis. Ying Wang: Investigation. Shengjin Ge: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding Acquisition.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval (B2019-279) was obtained from the Ethics Committee of Zhongshan Hospital. Written informed consent was obtained from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Martínez-Escribano C, Arteaga Moreno F, Pérez-López M, Cunha-Pérez C, Belenguer-Varea Á, Cuesta Peredo D, et al. Malnutrition and increased risk of adverse outcomes in elderly patients undergoing elective colorectal cancer surgery: a case-control study nested in a cohort. Nutrients. 2022;14:207.
2. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN practical guideline: clinical nutrition in surgery. Clin Nutr. 2021;40:4745–61.
3. Boccardi V, Marano L. Improving geriatric outcomes through nutritional and immunonutritional strategies: focus on surgical setting by a comprehensive evidence review. Ageing Res Rev. 2024;96:102272.
4. Carli F, Gillis C. Surgical patients and the risk of malnutrition: preoperative screening requires assessment and optimization [Patients chirurgicaux et risque de malnutrition: le depistage preoperatoire necessite evaluation et optimisation subsequentes]. Can J Anaesth. 2021;68:606–10.
5. Xu R, Chen XD, Ding Z. Perioperative nutrition management for gastric cancer. Nutrition. 2022;93:111492.
6. Cao S, Zheng T, Wang H, Niu Z, Chen D, Zhang J, et al. Enhanced recovery after surgery in elderly gastric cancer patients undergoing laparoscopic total gastrectomy. J Surg Res. 2021;257:579–86.
7. Franceschilli M, Siragusa L, Usai V, Dhimolea S, Pirozzi B, Sibio S, et al. Immunonutrition reduces complications rate and length of stay after laparoscopic total gastrectomy: a single unit retrospective study. Discov Oncol. 2022;13:62.
8. Pędziwiatr M, Mavrikis J, Witowski J, Adamos A, Major P, Nowakowski M, et al. Current status of enhanced recovery after surgery (ERAS) protocol in gastrointestinal surgery. Med Oncol. 2018;35:95.
9. Chabot K, Gillis C, Carli F. Prehabilitation: metabolic considerations. Curr Opin Clin Nutr Metab Care. 2020;23:271–6.
10. Sloun BV, Goossens GH, Erdos B, Lenz M, van Riel N, Arts CW. The impact of amino acids on postprandial glucose and insulin kinetics in humans: a quantitative overview. Nutrients. 2020;12:3211.
11. Gillis C, Wischmeyer PE. Pre-operative nutrition and the elective surgical patient: why, how and what? Anaesthesia. 2019;74:27–35.
12. Wu JM, Ho TW, Lai IR, Chen CN, Lin MT. Parenteral glutamine supplementation improves serum albumin values in surgical cancer patients. Clin Nutr. 2021;40:645–50.
13. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. 2018;10:1564.
14. Bonvini A, Coqueiro AY, Tirapegui J, Calder PC, Rogero MM. Immunomodulatory role of branched-chain amino acids. Nutr Rev. 2018;76:840–56.
15. Cogo E, Elsayed M, Liang V, Cooley K, Guerin C, Psihogios A, et al. Are supplemental branched-chain amino acids beneficial during the oncological peri-operative period: a systematic review and meta-analysis. Integr Cancer Ther. 2021;20:1534735421997551.
16. Luiking YC, Poeze M, Deutz NE. A randomized-controlled trial of arginine infusion in severe sepsis on microcirculation and metabolism. Clin Nutr. 2020;39:1764–73.
17. Wang Y, Zhao X, Ma Y, Yang Y, Ge S. The effects of vitamin B6 on the nutritional support of BCAAs-enriched amino acids formula in rats with partial gastrectomy. Clin Nutr. 2023;42:954–61.
18. Shi Y, Song H, Liu J, Lin J, Fang L. Comprehensive evaluation of clinical application of balanced compound amino acid injection. Front Nutr. 2022;9:880256.
19. Cahill GF Jr. Fuel metabolism in starvation. Annu Rev Nutr. 2006;26:1–22.
20. Sánchez-Torralvo FJ, González-Poveda I, García-Olivares M, Porras N, Gonzalo-Marín M, Tapia MJ, et al. Poor physical performance is associated with postoperative complications and mortality in preoperative patients with colorectal cancer. Nutrients. 2022;14:1484.
21. GlobalSurg Collaborative and NIHR Global Health Unit on Global Surgery. Impact of malnutrition on early outcomes after cancer surgery: an international, multicentre, prospective cohort study. Lancet Glob Health. 2023;11:e341-9.
22. McIsaac DI, MacDonald DB, Aucoin SD. Frailty for perioperative clinicians: a narrative review. Anesth Analg. 2020;130:1450–60.
23. Marano L, Porfidia R, Pezzella M, Grassia M, Petrillo M, Esposito G, Braccio B, Gallo P, Boccardi V, Cosenza A, et al. Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. Ann Surg Oncol. 2013;20:3912–8.
24. Seo JM, Joshi R, Chaudhary A, Hsu HS, Trung LV, Inciong JF, et al. A multinational observational study of clinical nutrition practice in patients undergoing major gastrointestinal surgery: the nutrition insights day. Clin Nutr ESPEN. 2021;41:254–60.
25. Fujitani K, Tsujinaka T, Fujita J, Miyashiro I, Imamura H, Kimura Y, et al. Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer. Br J Surg. 2012;99:621–9.

26. Oshima T, Pichard C. Parenteral nutrition: never say never. Crit Care. 2015;19:S5.
27. MacFie J. Enteral versus parenteral nutrition: the significance of bacterial translocation and gut-barrier function. Nutrition. 2000;16:606–11.
28. Jeejeebhoy KN. Total parenteral nutrition: potion or poison? Am J Clin Nutr. 2001;74:160–3.
29. Gao X, Liu Y, Zhang L, Zhou D, Tian F, Gao T, et al. Effect of early vs late supplemental parenteral nutrition in patients undergoing abdominal surgery: a randomized clinical trial. JAMA Surg. 2022;157:384–93.
30. Wade CE, Kozar RA, Dyer CB, Bulger EM, Mourtzakis M, Heyland DK. Evaluation of nutrition deficits in adult and elderly trauma patients. JPEN J Parenter Enteral Nutr. 2015;39:449–55.
31. Takagi K, Murotani K, Kamoshita S, Kuroda A. Dose-dependent effects of amino acids on clinical outcomes in adult medical inpatients receiving only parenteral nutrition: a retrospective cohort study using a Japanese medical claims database. Nutrients. 2022;14:3541.
32. Adiamah A, Skořepa P, Weimann A, Lobo D. The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer: a systematic review and meta-analysis. Ann Surg. 2019;270:247–56.
33. Wijnands KA, Castermans TM, Hommen MP, Meesters DM, Poeze M. Arginine and citrulline and the immune response in sepsis. Nutrients. 2015;7:1426–63.
34. Popovic PJ, Zeh HJ 3rd, Ochoa JB. Arginine and immunity. J Nutr. 2007;137:1681S-S1686.
35. Song GM, Tian X, Liang H, Yi LJ, Zhou JG, Zeng Z, et al. Role of enteral immunonutrition in patients undergoing surgery for gastric cancer: a systematic review and meta-analysis of randomized controlled trials. Med (Baltim). 2015;94:e1311.
36. Li XK, Cong ZZ, Wu WJ, Xu Y, Zhou H, Wang GM, et al. Enteral immunonutrition versus enteral nutrition for patients undergoing esophagectomy: a randomized controlled trial. Ann Palliat Med. 2021;10:1351–61.
37. Salih MM, Almehmadi M, Shafie A, Alsharif A, Alsiwiehri N, El-Askary A, et al. Evaluation of CD4+:CD8+ ratio in patients with cervical cancer and the levels of inflammatory markers. In Vivo. 2022;36:2414–21.
38. Wik JA, Skålhegg BS. T cell metabolism in infection. Front Immunol. 2022;13:840610.
39. Garrido-Rodríguez V, Herrero-Fernández I, Castro MJ, Castillo A, Rosado-Sánchez I, Galvá MI, et al. Immunological features beyond CD4+/CD8+ ratio values in older individuals. Aging. 2021;13:13443–59.
40. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nat Rev Cancer. 2020;20:662–80.
41. Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. Clin Sci (Lond). 1990;79:161–5.
42. Abe N, Kakamu T, Kumagai T, Hidaka T, Masuishi Y, Endo S, et al. Polypharmacy at admission prolongs length of hospitalization in gastrointestinal surgery patients. Geriatr Gerontol Int. 2020;20:1085–90.
43. Narendra K, Kiss N, Margerison C, Johnston B, Chapman B. Impact of nutritional status/risk and post-operative nutritional management on clinical outcomes in patients undergoing gastrointestinal surgery: a prospective observational study. J Hum Nutr Diet. 2020;33:587–97.
44. Tian Y, Cao S, Liu X, Li L, He Q, Jiang L, et al. Randomized controlled trial comparing the short-term outcomes of enhanced recovery after surgery and conventional care in laparoscopic distal gastrectomy (GISSG1901). Ann Surg. 2022;275:e15-21.
45. Xiao SM, Ma HL, Xu R, Yang C, Ding Z. Enhanced recovery after surgery protocol for elderly gastric cancer patients: a prospective study for safety and efficacy. Asian J Surg. 2022;45:2168–71.
46. Tian Y, Li Q, Pan Y. Prospective study of the effect of ERAS on postoperative recovery and complications in patients with gastric cancer. Cancer Biol Med. 2021;19:1274–81.
47. Tan S, Zhou F, Zhang Z, Wang J, Xu J, Zhuang Q, et al. Beta-1 blocker reduces inflammation and preserves intestinal barrier function after open abdominal surgery. Surgery. 2021;169:885–93.
48. Liu L, Shang L, Jin D, Wu X, Long B. General anesthesia bullies the gut: a toxic relationship with dysbiosis and cognitive dysfunction. Psychopharmacology. 2022;239:709–28.
49. Tremel H, Kienle B, Weilemann LS, Stehle P, Fürst P. Glutamine dipeptide-supplemented parenteral nutrition maintains intestinal function in the critically ill. Gastroenterology. 1994;107:1595–601.
50. Viana ML, Santos RG, Generoso SV, Arantes RM, Correia MI, Cardoso VN. Pretreatment with arginine preserves intestinal barrier integrity and reduces bacterial translocation in mice. Nutrition. 2010;26:218–23.
51. Beutheu S, Ghouzali I, Galas L, Déchelotte P, Coëffier M. Glutamine and arginine improve permeability and tight junction protein expression in methotrexate-treated Caco-2 cells. Clin Nutr. 2013;32:863–9.
52. Costa KA, Soares AD, Wanner SP, dos Santos RD, Fernandes SO, dos Santos MF, et al. L-arginine supplementation prevents increases in intestinal permeability and bacterial translocation in male Swiss mice subjected to physical exercise under environmental heat stress. J Nutr. 2014;144:218–23.
53. Achamrah N, Déchelotte P, Coëffier M. Glutamine and the regulation of intestinal permeability: from bench to bedside. Curr Opin Clin Nutr Metab Care. 2017;20:86–91.
54. Kong C, Li SM, Yang H, Xiao WD, Cen YY, Wu Y, et al. Screening and combining serum biomarkers to improve their diagnostic performance in the detection of intestinal barrier dysfunction in patients after major abdominal surgery. Ann Transl Med. 2019;7:388.
55. Dudi-Venkata NN, Seow W, Kroon HM, Bedrikovetski S, Moore JW, Thomas ML, et al. Safety and efficacy of laxatives after major abdominal surgery: systematic review and meta-analysis. BJS Open. 2020;4:577–86.

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