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The effect of supplementary parenteral nutrition with different energy intakes on clinical outcomes of patients after gastric cancer surgery

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Abstract

Background To investigate the effect of postoperative supplementary parenteral nutrition (SPN) containing varying energy intake levels during the early postoperative period on the clinical outcomes of patients diagnosed with gastric cancer.

Methods Data from 237 patients, who were diagnosed with gastric cancer between January 2016 and June 2022, were retrospectively analyzed. Patients were divided into 2 groups based on mean daily SPN energy intake: low (L-SPN; < 20 kcal/kg/day); and high (H-SPN; ≥ 20 kcal/kg/day). Data regarding gender, age, body mass index, preoperative Nutrition Risk Screening 2002 (NRS 2002) score, American Society of Anesthesiologists Physical Status classification system, age-adjusted Charlson Comorbidity Index, diabetes, hypertension, chronic lung disease, and the Tumor-Node-Metastasis (TNM [Eighth edition]) classification were collected for propensity score matching (PSM). Postoperative indicators were monitored. A power analysis was performed during the design phase of this study to ensure that statistical power exceeded 80% to reliably detect differences between the 2 groups.

Results After PSM, data from 128 patients were analyzed (H-SPN, $n=64$; L-SPN, $n=64$). The H-SPN group experienced shorter postoperative hospital stay (8.11 ± 6.00 days vs. 10.38 ± 7.73 days; $P=0.045$) and a lower number of infectious complications (36 [56.3%] vs. 60 [93.8%]; $P<0.001$), particularly pulmonary infections, compared with the L-SPN group. Additionally, no increase in hospitalization costs or non-infectious complications occurred in the H-SPN group. Subgroup analysis revealed that H-SPN significantly reduced the incidence of infectious complications among

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those < 65 years of age (hazard ratio [HR] [95% confidence interval (CI) 0.240 0.069–0.829]; *P* = 0.024), NRS 2002 score ≥ 3 (HR 0.417 [95% CI 0.156–0.823]; *P* = 0.028), age-adjusted Charlson Complexity Index < 2 (HR 0.106 [95% CI 0.013–0.835]; *P* = 0.033), and TNM stage III (HR 0.504 [95% CI 0.224–0.921]; *P* = 0.046).

Conclusions H-SPN effectively reduced postoperative infectious complications and the length of hospital stay, suggesting that early postoperative H-SPN may be an advantageous nutritional support strategy for patients diagnosed with gastric cancer.

Keywords Nutritional therapy, Gastric cancer, Energy intake, Postoperative, Retrospective analysis

Introduction

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer-related mortality worldwide [1]. Early gastric cancer often presents with no obvious symptoms; however, advanced gastric cancer can cause indigestion, weight loss, and abdominal pain, ultimately resulting in a malnutrition rate of 41.6–86.1%, which is the highest among all tumor types [2]. Although radical resection is the primary treatment for patients with locally advanced gastric cancer, it can increase energy consumption and protein breakdown, further exacerbating malnutrition, increasing the risk for postoperative complications, prolonging hospital stay, and elevating mortality rates [3, 4]. Therefore, an appropriate postoperative nutritional support strategy is crucial to facilitate wound healing and reduce postoperative infectious complications in patients diagnosed with gastric cancer.

Although guidelines from the European Society for Parenteral and Enteral Nutrition and the Enhanced Recovery After Surgery Society recommend that enteral nutrition (EN) be initiated as soon as possible postoperatively if the gastrointestinal tract functions normally [4, 5], EN or oral nutritional supplements (ONS) alone are often insufficient to meet the energy and protein demands of patients in the early postoperative period [6]. Compared with EN, parenteral nutrition (PN) enables more precise control over the proportions of various nutrients, thereby ensuring that prescribed energy requirements are fulfilled. Supplementary PN (SPN) is a mixed nutritional support treatment strategy in which partial energy and protein requirements are supplemented by PN when EN is insufficient [6]. In addition, findings from smaller studies suggest that peripheral PN is a feasible approach for providing nutritional support to selected patients during the perioperative period [7, 8]. A recent randomized controlled trial demonstrated that, in patients undergoing major abdominal surgery, early initiation of SPN (beginning on postoperative day [POD] 3) can reduce hospital-related infectious complications compared with later initiation (beginning on POD 8), particularly in patients with high nutritional risk and poor tolerance to EN after major abdominal surgery [9].

However, there is a lack of relevant research investigating the quantitative aspects of energy intake in postoperative SPN among patients diagnosed with gastric cancer. The target energy requirements for patients with gastric cancer during the perioperative period is generally recommended to be 25–30 kcal/kg/day. Zaloga [10] reported that, due to stressful conditions, the nutritional needs of postoperative or critically ill patients may be lower than expected, known as "permissive underfeeding". Compared with low-calorie PN, high-calorie PN has been found to be associated with a greater metabolic burden, more postoperative complications, longer hospital stay, and greater hospitalization costs [11, 12]. Recent studies have focused on whether 70% [13, 14] or 80% [15] of the estimated energy demand is sufficient to explore correlations with clinical outcomes. Gao et al. [13] found that patients who reached 70% energy in the early stage experienced better clinical outcomes and fewer nosocomial infections. Lee et al. [14] reported that patients with severe disease, who reached 70% caloric intake, spent less time on a ventilator. Nurkkala et al. [15] found that patients who did not reach 80% of energy goals were undernourished and experienced postoperative intestinal obstruction and anorexia. However, these studies did not report specific energy intake values. Therefore, further exploration is needed to determine whether supplementing PN with a specific amount of energy intake at an early stage can maximize patient benefits.

Based on the above findings, we performed a retrospective review of data housed in a prospectively collected database to investigate the impact of SPN with varying energy intake on clinical outcomes in the early postoperative period (POD 3–7) among patients with gastric cancer, aiming to identify the appropriate amount of energy intake. We anticipate that our findings will provide a reference for nutritional therapy in patients with gastric cancer during the postoperative period, thereby providing an objective basis for designing appropriate nutritional treatment strategies.

Methods

Study design and population

The present investigation was a retrospective review of prospectively collected data. Data from 237 patients

diagnosed with gastric cancer, who underwent gastrectomy at a single center between January 2016 and June 2022, were extracted from a prospective electronic database. All surgeries were performed by the same team of experienced surgeons who selected the digestive tract reconstruction technique. All patients were managed using the same enhanced recovery after surgery (i.e., "ERAS") protocol established at our institution in 2015. Details of this protocol have been described in our previous study [16]. This study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (No. MTCA, ECFAH of FMU [2015] 084−2). Informed written consent was obtained from all participants.

The inclusion criteria were as follows: preoperative pathological diagnosis of gastric cancer and underwent gastric resection surgery; SPN initiated at PODs 3–7; and able to tolerate EN or ONS after surgery. The exclusion criteria were as follows: presence of other cancers; gastric stump cancer, neuroendocrine tumor, gastric stromal tumor, or gastric lymphoma; preoperative perforation or pyloric obstruction; non-radical resection; and incomplete clinical data.

Postoperative nutritional support

A trained clinician developed the postoperative nutritional support strategies, including SPN, EN, and ONS. SPN was infused through central venous catheters or peripheral puncture central venous catheters that were retained preoperatively, whereas EN was infused through a feeding jejunostomy tube that was retained intraoperatively. The infusion of SPN and EN, or the intake of ONS, was recorded in the nursing record, and energy intake was calculated based on this. SPN was started on POD 3. Based on the mean daily energy intake of SPN from POD 3 to POD 7, patients with a mean intake≥20 kcal/kg/day were allocated to the H-SPN group, while those with an intake<20 kcal/kg/day were allocated to the L-SPN group. Starting from POD 1, a meal replacement beverage (Ensure, Abbott Laboratories B.V., Zwolle, The Netherlands) was used for EN or ONS, providing an average daily energy intake of 10 kcal/kg/day.

Data collection

Clinicopathological data, including gender, age, body mass index (BMI), preoperative Nutrition Risk Screening (NRS) 2002 score [17]; American Society of Anesthesiologists (ASA) physical status classification system, age-adjusted Charlson Complexity Index (aCCI) [18], diabetes [19], hypertension [20], chronic lung disease [21], and Tumor-Node-Metastasis (TNM) classification (Eighth edition) [3], were collected for propensity score matching (PSM). Intraoperative indicators, including laparoscopic surgery, surgical procedure, and operative duration, were also collected. Nutritional indicators, including serum albumin (ALB) and hemoglobin (HB) levels on POD 7, were the first observation indicators. Short-term prognostic indicators included infectious complications [22], noninfectious complications [22], total hospital stay, postoperative hospital stay, and hospital expenses, and also served as the secondary observation indicators. Finally, inflammatory indicators, including white blood cell (WBC) count, neutrophil percentage (NE%), and serum C-reactive protein (CRP) level on POD 7, comprised the third observation indicators. Additionally, postoperative liver function indicators, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, were measured.

Statistical analysis

A previous meta-analysis reported an infection rate of 10–30% among patients who underwent abdominal surgery [23]. In this study, an infection rate of 30% was assumed for patients in the L-SPN group and 10% for those in the H-SPN group, with $\alpha=0.05$ and $\beta=0.2$, ultimately requiring at least 59 participants in each group. Continuous variables are expressed as mean±standard deviation, while categorical variables are expressed as frequency (%). Univariate analysis was performed using the Student's *t*-test for normally distributed continuous variables, the Wilcoxon–Mann–Whitney U test for non-normally distributed continuous variables, and the chi-squared or Fisher's exact test for categorical variables. PSM was used to eliminate confounding biases from the observational cohort. Post-hoc analysis of postoperative complications was performed in the following subgroups: gender (male vs. female); age (≥65 vs. < 65 years); BMI (<18.5 kg/m^{2}vs. 18.5–24.9 kg/m^{2}vs. ≥ 25 kg/m^2); NRS 2002 score (<3, ≥ 3); aCCI score (<2, ≥ 2); and TNM classification (<III vs. III). A Cox proportional hazards regression model was used to estimate hazard ratio (HR) and corresponding 95% confidence interval (CI). Survival rates were estimated using Kaplan–Meier curves. All statistical tests were two-sided, and differences with $P<0.05$ were considered to be significant. Analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Study population and baseline characteristics

During the study period, 320 patients underwent gastrectomy at the authors' institution, of whom data for 237 were included and 83 excluded (Fig. 1). The reasons for exclusion were as follows: other cancers ($n=5$); gastric stump cancer, neuroendocrine tumor, gastric stromal tumor, or gastric lymphoma ($n=7$); preoperative perforation or pyloric obstruction ($n=14$); nonradical resection ($n=44$); and incomplete clinical data ($n=13$).

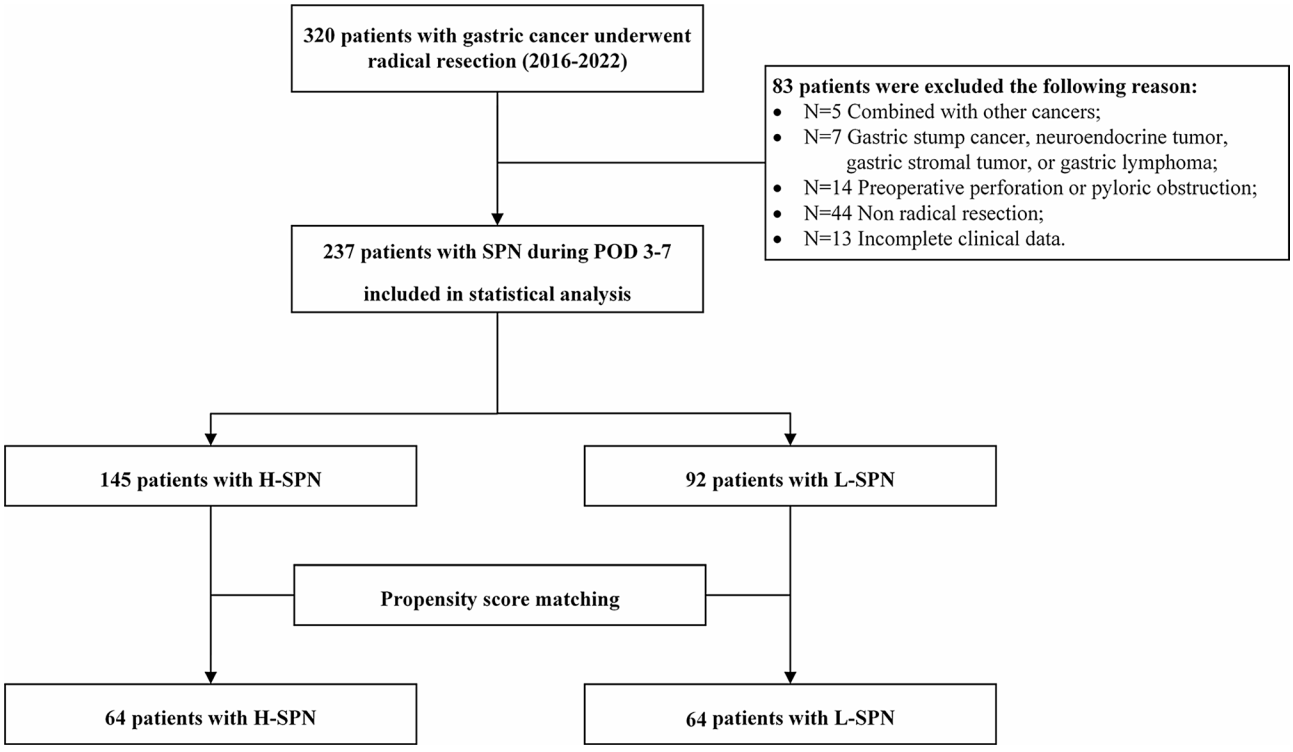

Fig. 1 The flow diagram of patients enrolled in this study

Clinical and demographic characteristics of the patients were summarized in Table 1. Before PSM, compared with patients who received L-SPN, those who received H-SPN had a higher proportion of females (18.5% vs. 31.7%; $P=0.034$) and a lower BMI (24.31±2.91 kg/m^{2}vs. 21.26±2.49 kg/m^2; $P=0.008$). After PSM, paired cohorts for H-SPN and L-SPN were derived (64 patients each). These cohorts were well-matched for sex, age, BMI, NRS 2002 score, ASA grade, aCCI score, diabetes, hypertension, chronic lung disease, and TNM stage, and were all comparable (all $P>0.05$).

Nutritional therapy

Between POD 3 and 7, patients in the H-SPN group received more total energy (1609±275 vs. 1137±255 kcal/day; $P<0.001$) and mean energy (27.28±8.46 vs. 19.94±6.92 kcal/day; $P<0.001$) than those in the L-SPN group. During the same period, total protein (58.81±7.23 vs. 41.30±7.14 g/day; $P<0.001$) and mean protein (1.00±6.83 vs. 0.72±4.68 g/day; $P<0.001$) intake were also higher in the H-SPN group than in the L-SPN group (Tables 2**and** Fig. 2).

Intra- and postoperative indicators

As shown in Table 2, intraoperative indicators, including laparoscopic surgery, operative procedure, and operative duration, were not significantly different between the 2 groups (all $P>0.05$). Compared with patients with H-SPN, those with L-SPN experienced longer postoperative hospital stay (8.11±6.00 days vs. 10.38±7.73 days; $P=0.045$). Although nutritional indicators, including ALB and HB, inflammatory indicators, including WBC, NE%, and CRP, and total hospitalization costs were not significantly different between the 2 groups (all $P>0.05$). These indicators exhibited a decreasing trend in the H-SPN group. In addition, postoperative ALT and AST levels in the 2 groups were not significantly increased and exhibited no significant differences ($P>0.05$).

The median follow-up was 51.0 months (range, 3.5–86.5 months) for patients with H-SPN and 48.0 months (range, 2.0–80.5 months) for those with L-SPN. As shown in Fig. 3, there was no significant difference in survival rates between the 2 groups ($P>0.05$).

Postoperative complications

In terms of complications, there was a statistically significant difference between the 2 groups in the incidence of infectious complications (H-SPN, 14 [21.9%] vs. L-SPN, 25 [39.1%]; $P=0.035$), especially pulmonary infections (H-SPN, 1 [1.56%] vs. L-SPN, 9 [13.8%]; $P=0.008$). The study achieved a statistical power of 98% with a sample size of 64 in each group, indicating a high probability of detecting differences in infectious complications between the groups. Because some patients experienced>1 postoperative events, the total number of events were also counted, which was greater than that of patients

Table 1 Patient clinical and demographic characteristics, by SPN group (before and after PSM, $n=237$)

Variables	Before PSM			After PSM		
	H-SPN ($n=145$)	L-SPN ($n=92$)	*P* value	H-SPN ($n=64$)	L-SPN ($n=64$)	*P* value
Gender (%)			0.034			0.112
Male	99 (68.3%)	75 (81.5%)		48 (75.0%)	56 (87.5%)	
Female	46 (31.7%)	17 (18.5%)		16 (25.0%)	8 (12.5%)	
Mean age (years)	60.48 ± 10.58	61.49 ± 9.57	0.463	61.30 ± 9.84	62.03 ± 9.42	0.667
BMI (kg/m^2)	21.26 ± 2.49	24.31 ± 2.91	0.008	23.35 ± 2.27	23.04 ± 2.15	0.426
NRS 2002 score			0.894			0.475
< 3	78 (53.8%)	51 (55.4%)		39 (60.9%)	34 (53.1%)	
≥ 3	67 (46.2%)	41 (44.6%)		25 (39.1%)	30 (46.9%)	
ASA grade (%)			1.000			1.000
< 3	131 (90.3%)	83 (90.2%)		60 (93.8%)	60 (93.8%)	
≥ 3	14 (9.7%)	9 (9.8%)		4 (6.2%)	4 (6.2%)	
aCCI grade (%)			0.213			1.000
< 2	56 (38.6%)	28 (30.4%)		20 (31.2%)	21 (32.8%)	
≥ 2	89 (61.4%)	64 (69.6%)		44 (68.8%)	43 (67.2%)	
Diabetes			0.082			1.000
Yes	15 (10.3%)	17 (18.5%)		11 (17.2%)	10 (15.6%)	
No	130 (89.7%)	75 (81.5%)		53 (82.8%)	54 (84.4%)	
Hypertension			0.590			1.000
Yes	22 (15.2%)	17 (18.5%)		10 (15.6%)	9 (14.1%)	
No	123 (84.8%)	75 (81.5%)		54 (84.4%)	55 (85.9%)	
Chronic lung disease			1.000			0.656
Yes	32 (22.1%)	20 (21.7%)		11 (17.2%)	14 (21.9%)	
No	113 (77.9%)	72 (78.3%)		53 (82.8%)	50 (78.1%)	
TNM stage, n (%)			0.271			0.855
< III	50 (34.5%)	39 (42.4%)		25 (39.1%)	23 (35.9%)	
III	95 (65.5%)	53 (57.6%)		39 (60.9%)	41 (64.1%)	

ASA, American Society of Anesthesiologists; aCCI, age adjusted Charlson Complexity Index; BMI, body mass index; H-SPN, high calorie SPN; L-SPN, low calorie SPN; NRS, nutrition risk screening; PSM, propensity score matching; SPN, supplementary parenteral nutrition; TNM, Tumor-Node-Metastasis

who experienced complications (Table 3). There were 36 (56.3%) complications in the H-SPN group and 60 (93.8%) in the L-SPN group, and the difference was statistically significant ($P<0.001$). Not surprisingly, there was no difference in noninfectious complications between the 2 groups (H-SPN, $n=14$ [21.9%] vs. L-SPN, $n=21$ [32.8%]; $P=0.234$). Compared with patients in the H-SPN group, those in the L-SPN group experienced more infectious complications (22 [34.4%] vs. 39 [60.9%]; $P=0.004$). Among 7 infectious complications, pulmonary infection was the only complication that was statistically different between the 2 groups (H-SPN, 1 [1.56%] vs. L-SPN, 12 [18.75%]; $P=0.002$), although abdominal infection exhibited borderline significance (H-SPN, 4 [6.25%] vs. L-SPN, 12 [18.75%]; $P=0.059$).

The actual number of patients who experienced infectious complications were recorded and analyzed, with results presented in Fig. 4. In the post hoc subgroup analysis of infectious complications, no interactions were identified (all $P>0.05$). Nevertheless, compared with H-SPN, L-SPN was associated with an increased risk for infectious complications, which were observed in those < 65 years of age (HR 0.240 [95% CI 0.069–0.829]; $P=0.024$), NRS 2002 score ≥ 3 (HR 0.417 [95% CI 0.156–0.823]; $P=0.028$), aCCI score < 2 (HR 0.106 [95% CI 0.013–0.835], $P=0.033$), and TNM stage III (HR 0.504 [95% CI 0.224–0.921]; $P=0.046$).

Discussion

To the best of our knowledge, this was the first study to quantitatively evaluate the effect of varying SPN energy levels among patients in the early postoperative stage after diagnosis of gastric cancer on postoperative complications, nutritional and inflammatory indicators, hospital stay, and hospitalization costs. Without increasing the cost of hospitalization, administration of H-SPN in the early postoperative stage significantly reduced the incidence of infectious complications and shortened the length of hospital stay. Moreover, subgroup analysis revealed that for patients < 65 years of age, with a preoperative NRS 2002 score ≥ 3, aCCI score < 2, and TNM stage III, H-SPN yielded a greater advantage in reducing the incidence of infectious complications. Results of this study provide a theoretical basis for the administration of early postoperative SPN in clinical practice, thus

Table 2 Intraoperative and postoperative indicators after PSM by SPN group

Variables	H-SPN ($n=64$)	L-SPN ($n=64$)	*P* value
Operative duration (min)	188.59 ± 50.24	186.11 ± 43.31	0.932
Laparoscopic surgery			0.656
Yes	53 (82.8%)	50 (78.1%)	
No	11 (17.2%)	14 (21.9%)	
Jejunostomy			0.352
Yes	19 (29.7%)	25 (39.1%)	
No	45 (70.3%)	39 (60.9%)	
Operative procedure			0.722
Subtotal gastrectomy	37 (57.8%)	34 (53.1%)	
Total gastrectomy	27 (42.2%)	30 (46.9%)	
Total energy during POD3-7 (kcal/d)	1609 ± 275	1137 ± 255	< 0.001
Mean energy during POD3-7 (kcal/d)	27.28 ± 8.46	19.94 ± 6.92	< 0.001
Total protein during POD3-7 (g/d)	58.81 ± 7.23	41.30 ± 7.14	< 0.001
Mean protein during POD3-7 (g/d)	1.00 ± 6.83	0.72 ± 4.68	< 0.001
Nutritional indicators at POD 7			
Albumin (g/L)	34.44 ± 3.33	34.56 ± 3.12	0.786
Hemoglobin (g/L)	112.70 ± 17.72	114.58 ± 18.45	0.175
Inflammatory indicators at POD 7			
White blood cells (10^9/L)	8.45 ± 3.07	8.80 ± 3.11	0.147
Neutrophil percentage (%)	73.55 ± 8.65	73.82 ± 9.42	0.905
C-reactive protein (g/L)	78.59 ± 40.97	79.48 ± 38.72	0.444
ALT at POD7 (U/L)	33.60 ± 32.14	30.52 ± 20.82	0.571
AST at POD7 (U/L)	26.49 ± 16.94	23.85 ± 10.72	0.423
Postoperative hospital stay (days)	8.11 ± 6.00	10.38 ± 7.73	0.045
Total hospitalization costs (¥)	81056.17 ± 25054.92	82323.26 ± 24011.97	0.374
Drug costs (¥)	20628.37 ± 10819.67	20477.64 ± 12327.1	0.329

SPN, supplementary parenteral nutrition; H-SPN, high calorie SPN; L-SPN, low calorie SPN; POD, postoperative day; ALT, alanine transaminase; AST, aspartate transaminase

providing an objective basis for informing the design of appropriate nutritional treatment strategies.

Previous studies have reported that early postoperative EN does not increase gastrointestinal complications and can significantly reduce postoperative infectious complications, mortality, and hospital stay [24, 25]. However, for various reasons, such as intestinal injury, peristalsis disorders, and intestinal wall edema, patients often develop gastrointestinal dysfunction after abdominal surgery, making it difficult to obtain sufficient nutrition solely through EN. Therefore, using SPN to compensate for the energy deficiency caused by EN support alone is a reasonable measure. Several studies have demonstrated that early postoperative EN combined with SPN can help patients undergoing abdominal surgery achieve better energy goals and improve clinical prognosis compared with those receiving EN alone [26, 27]. Casaer et al. [28] reported that using EN in combination with SPN during the first 2 days of intensive care unit hospitalization, which is the early stage after stress, can increase the incidence of infectious complications. This may be due to insulin resistance under stress and a decrease in patient ability to regulate the energy supply, coupled with large doses of glucose supplementation, leading to some degree of overnutrition. A recent randomized controlled trial reported that among patients undergoing major abdominal surgery, early administration of SPN (starting on POD 3) can reduce hospital-related infection complications compared with late administration of SPN (starting on POD 8), especially in patients with high nutritional risk and poor tolerance to EN after major abdominal surgery [9]. We speculate that starting SPN on POD 3 is the best time for patients because their stress and inflammatory reactions have decreased, and their ability to regulate nutrient metabolism has increased.

Results from previous studies [29, 30] suggested that early SPN (POD 3) was associated with lower mortality than late SPN (POD 8). To the best of our knowledge, this is the first study to report the effect of SPN with different energy intakes in the early postoperative period (i.e., POD 3 to 7) on mortality in patients with gastric cancer. The lack of significant differences in mortality rates observed in this study may be attributed to the

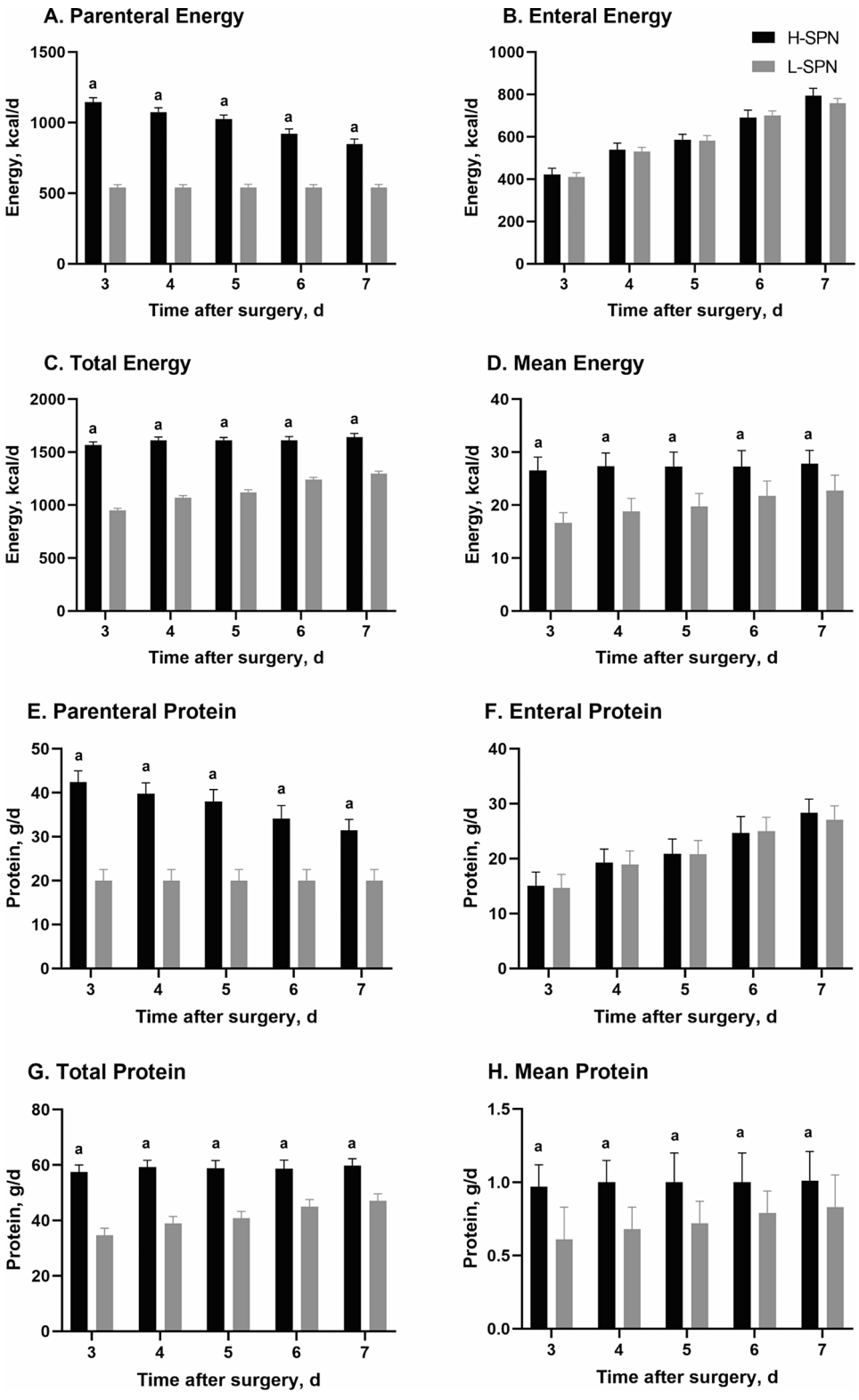

Fig. 2 Daily energy (kilocalories per day) and protein intake (grams per day) during 3–7 days after surgery between high energy intake supplemental parenteral nutrition (H-SPN) group and low energy intake supplemental parenteral nutrition (L-SPN) group. [a] $P < 0.05$

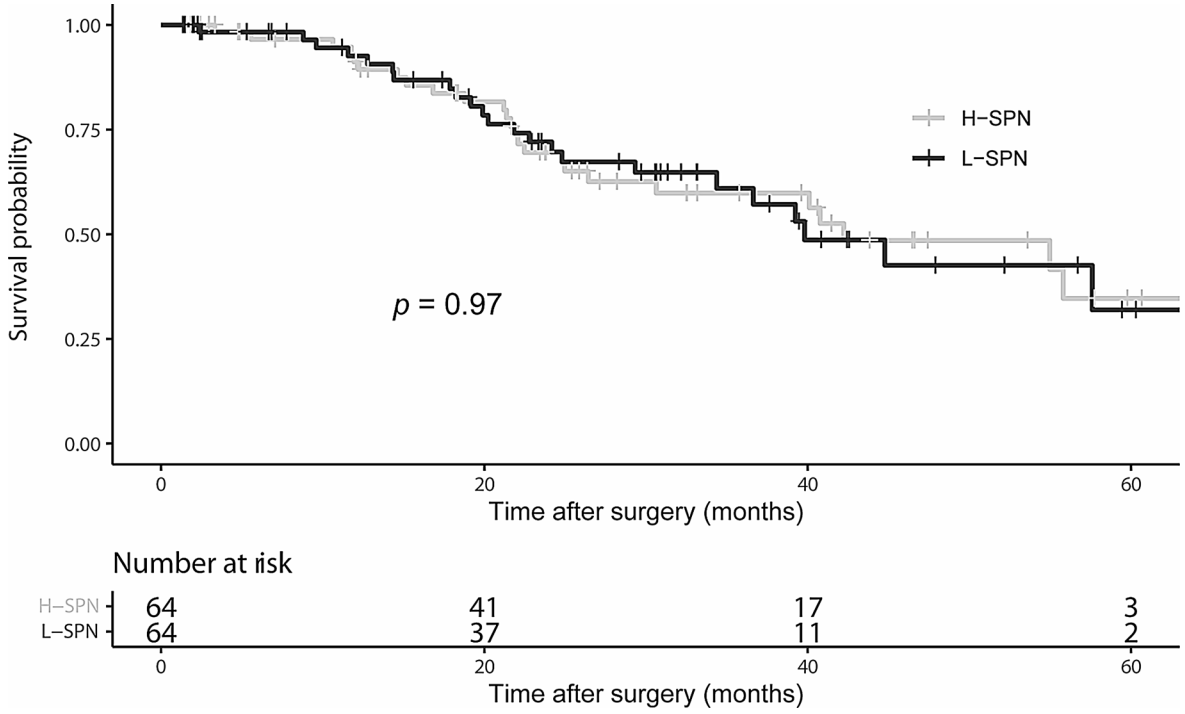

Fig. 3 Kaplan-Meier survival curves for patients with high energy intake supplemental parenteral nutrition (H-SPN) and low energy intake supplemental parenteral nutrition (L-SPN)

Table 3 Postoperative complications by SPN group

Complications	Total number of complications*			Total number of patients suffering from complications**		
	H-SPN (*n* = 64)	L-SPN (*n* = 64)	*P* value	H-SPN (*n* = 64)	L-SPN (*n* = 64)	*P* value
Total complications	36 (56.3%)	60 (93.8%)	< 0.001	19 (29.7%)	29 (45.3%)	0.068
Infectious complications	22 (34.4%)	39 (60.9%)	0.004	14 (21.9%)	25 (39.1%)	0.035
Surgical site infection	5 (7.81%)	7 (10.94%)	0.763	4 (6.25%)	3 (4.69%)	> 0.999
Intra-abdominal infection	4 (6.25%)	12 (18.75%)	0.059	3 (4.69%)	9 (13.8%)	0.069
Pulmonary infection	1 (1.56%)	12 (18.75%)	0.002	1 (1.56%)	9 (13.8%)	0.008
Septic shock	4 (6.25%)	4 (6.25%)	> 0.999	0	0	> 0.999
Anastomotic fistula	1 (1.56%)	1 (1.56%)	> 0.999	1 (1.56%)	1 (1.56%)	> 0.999
Stump fistula	1 (1.56%)	0	> 0.999	1 (1.56%)	0 (%)	> 0.999
Biliary fistula	6 (9.38%)	3 (4.69%)	0.492	4 (6.25%)	3 (4.69%)	> 0.999
Noninfectious complications	14 (21.9%)	21 (32.8%)	0.234	5 (7.81%)	4 (6.25%)	> 0.999
Anastomotic stenosis	1 (1.56%)	0	> 0.999	1 (1.56%)	0	> 0.999
Postoperative bleeding	1 (1.56%)	3 (4.69%)	0.619	0	1 (1.56%)	> 0.999
Intestinal obstruction	1 (1.56%)	5 (7.81%)	0.208	1 (1.56%)	1 (1.56%)	> 0.999
Gastroparesis	0	2 (3.13%)	0.496	0	1 (1.56%)	> 0.999
Venous thrombosis	4 (6.25%)	3 (4.69%)	> 0.999	1 (1.56%)	0	> 0.999
Pleural effusion	2 (3.13%)	5 (7.81%)	0.440	1 (1.56%)	1 (1.56%)	> 0.999
Peritoneal effusion	0	1 (1.56%)	> 0.999	0	0	> 0.999
Cerebral infarction	2 (3.13%)	0	0.496	1 (1.56%)	0	> 0.999
Liver dysfunction	3 (4.69%)	2 (3.13%)	> 0.999	0	0	> 0.999

H-SPN, high calorie SPN; L-SPN, low calorie SPN; SPN, supplementary parenteral nutrition

*As some patients developed more than one postoperative complication, we counted the total number of complications, which was actually greater than that of the patients who suffered complications

**We counted the most serious one, not the total number of complications

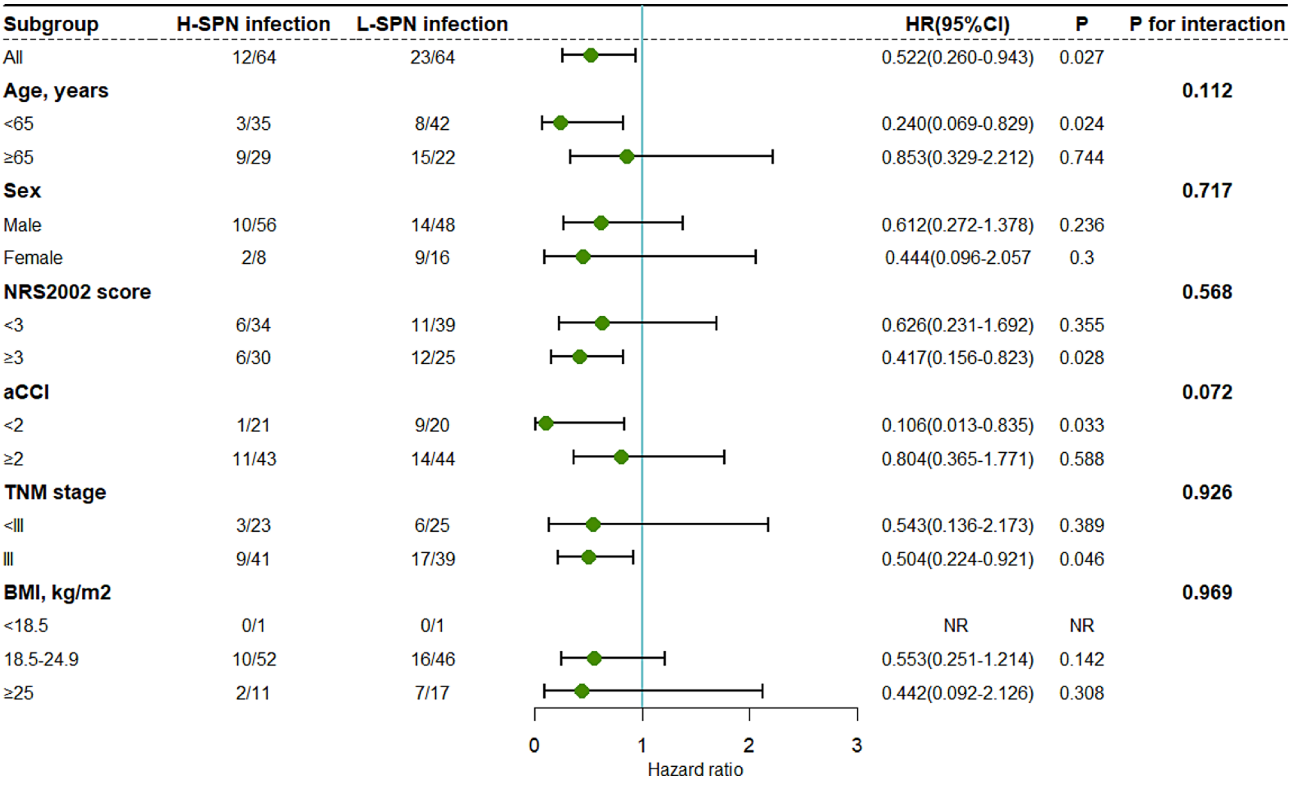

Fig. 4 Hazard ratios of high energy intake supplemental parenteral nutrition (H-SPN) vs. low energy intake supplemental parenteral nutrition (L-SPN) by prespecified subgroups

limitations of its single-center design and small sample size. If randomized controlled trials with multiple sets of gradient energy intakes can be established in the future, the results may be different.

Results of the present study revealed that providing H-SPN after surgery in patients diagnosed with gastric cancer is advantageous in reducing infectious complications. This may be because early H-SPN fulfills the nutritional demands of the body because nutrition affects the maintenance and response of the immune system. Achieving established nutritional demands is an important strategy for optimizing immunity [31]. Nutritional deficiency can also reduce intestinal barrier function, thereby increasing the risk for infection [32, 33]. Nutrient deficiency also alters the intestinal microbiota [34], damages the activation and production of immune cells, and limits the intake of macro- and micronutrients [35]. However, verifying the relationship between malnutrition, microbiome effects, gut susceptibility, and infection severity requires further clinical and basic research, and is also the direction of our future research. In our study, a significant difference in infectious complications was observed only for pulmonary infections. However, this may be because H-SPN enhances patient immune function, especially the defense mechanism(s) of the lungs. On the other hand, it may help maintain the integrity of respiratory mucosa and reduce the decline of respiratory function caused by surgery and anesthesia, thereby reducing the incidence of pulmonary infection. However, there were no statistically significant differences in other infectious complications, which may have been due to the limited sample size. At the same time, the occurrence of surgical site infection, abdominal infection, septic shock, and other complications may be affected by a variety of factors, including——but not limited to——surgical skills of the physicians and underlying disease(s) in the patients. In the future, we will increase the sample size and optimize the study design in attempts to more precisely reveal the relationship between nutritional dose and infectious complications.

Previous studies have shown that ALB levels can be used to evaluate the state of human nutrition [36], and that preoperative and postoperative hypoalbuminemia are risk factors for postoperative complications [37, 38]. The decrease in serum ALB after major abdominal surgery is not only related to systemic inflammatory response syndrome [39] but also to the stress response because stress leads to an increase in the decomposition rate of ALB, while the synthesis rate remains unchanged, ultimately leading to a decrease in overall levels [40]. In our study, there was no significant difference in ALB levels between the 2 groups on POD 7, which may be due

to the shorter postoperative hospital stay and shorter administration of SPN. The circulating half-life of ALB is 19–21 days [41], and its metabolic and production cycles are longer; therefore, there is no difference in its short-term adminstration. In future research, we will attempt to detect prealbumin, which, on average, has a shorter circulating half-life (2.5 days), and may reflect trends in nutritional improvement faster.

Whether postoperative CRP level can be used as a predictive indicator of postoperative complications remains controversial. Although some studies have shown that postoperative CRP levels can be used to predict complications after subtotal gastrectomy [42, 43], others have also pointed out that the use of postoperative CRP as a marker of complications after gastrectomy is not accurate in some cases, and its increase and decrease are not sufficient to identify patients at a high risk for postoperative complications [43, 44]. This also explains the results of our study, in which there were differences in infectious complications between the 2 patient groups, but no significant differences in inflammatory indicators. Previous studies have shown that SPN may lead to a series of PN-related liver damage events such as liver function impairment, liver fat infiltration, and liver fibrosis [6, 45]. This is mainly related to endotoxemia, intestinal injury, nutrient imbalance, and other factors, particularly lipid-related liver damage. In this study, the postoperative ALT and AST levels of patients in both groups did not increase significantly, and there was no difference between the 2 groups, indicating that appropriate and sufficient SPN in the short term after surgery may not necessarily impair liver function.

In terms of postoperative hospitalization days, the H-SPN group was superior to the L-SPN group, which may be explained by a reduction in postoperative infectious complications because sufficient energy supplementation promotes faster and better recovery. Interestingly, there was no significant difference in hospitalization costs between the 2 groups. It is believed that H-SPN, in theory, incurs higher costs, and the hospitalization costs of the H-SPN group should be higher than those of the L-SPN group. However, due to fewer infectious complications and fewer postoperative hospital stays in the H-SPN group, medical expenses were——to some degree——reduced, and there was no significant difference in hospital expenses between the 2 groups.

Results of subgroup analysis revealed that among patients < 65 years of age, aCCI score < 2, NRS 2002 score ≥ 3, and TNM stage III, H-SPN exhibited a more significant advantage. This may be because these subgroups of patients had greater energy needs, which is consistent with previous research findings [46]. Compared with patients > 65 years, those < 65 years of age had faster metabolism of life activities, better metabolic capacity, and higher metabolic needs. High-energy nutritional support can effectively meet these needs, thereby reducing the risk for postoperative infection. However, the immune and metabolic functions of patients > 65 years of age are relatively weak [47], which may affect the potency of high-energy nutrition, leading to a less obvious response to high-energy nutrition than in younger patients. Preoperative NRS 2002 score ≥ 3 indicates that the patient already had insufficient intake before surgery and needed more energy supplementation. Patients with TNM stage III disease also had a significant energy demand due to tumor-related metabolic enhancement and consumption. In summary, we speculate that, among patients with high energy intake demands, such as younger age, malnutrition, and late tumor staging, nutritional support with relatively higher energy intake was more beneficial for patient prognosis.

The present study had several limitations. First, whether the results of our study can be applied to other surgical procedures, such as esophagectomy or hepatectomy, remains uncertain. Second, some confounding factors may have inevitably affected the statistical analysis. Although no significant difference in sex was observed between the 2 groups after PSM, there were still 10% more males in the L-SPN group than in the H-SPN group, which may have influenced the higher incidence of complications in the L-SPN group. Third, this was a single-center retrospective study with a relatively small number of patients. As such, multicenter, larger-sample, and prospective studies are required to validate the conclusions drawn from this study. In the future, we will increase the sample size and further optimize the study design to more accurately reveal the relationship between nutrition dose and complications, and more comprehensively investigate risk factors for postoperative complications to help design and develop the most appropriate postoperative nutritional support programs.

Conclusions

H-SPN administered in the early postoperative period to patients diagnosed with gastric cancer effectively reduced postoperative infectious complications and shortened hospital stays without increasing hospitalization costs or non-infectious complications. Additionally, H-SPN may be more beneficial in reducing the incidence of infectious complications in patients < 65 years of age, and those with a preoperative NRS 2002 score ≥ 3, aCCI score < 2, and TNM stage III. Early postoperative H-SPN may be an advantageous nutritional support strategy for patients diagnosed with gastric cancer.

Abbreviations

SPN	Supplementary parenteral nutrition
PSM	Propensity score matching
EN	Enteral nutrition

ONS	Oral nutritional supplements
PN	Parenteral nutrition
ERAS	Enhanced recovery after surgery
POD	Postoperative day
BMI	Body mass index
NRS	Nutrition risk screening
ASA	Anesthesiologists physical status classification system
aCCI	Adjusted Charlson Complexity Index
TNM	Tumor-Node-Metastasis
ALB	Albumin
HB	Hemoglobin
WBC	White blood cells
NE%	Neutrophil percentage
CRP	C-reactive protein
ALT	Alanine transaminase
AST	Aspartate transaminase
HR	Hazard ratios
CI	Confidence interval

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Author contributions
Study conception and design: S.S., W.S., W.X., Q.H. and H.Z.; Administrative support: X.G., J.Z., Q.H. and H.Z.;Provision of materials and samples: S.S., W.S., W.X. and F.Z.;Acquisition of data: S.S., W.S, W.X. and F.Z.;Analysis and interpretation of data: S.S., W.S., J.Z., Q.H. and H.Z.;Drafting of manuscript: S.S., J.Z. and Q.H.;Critical revision of manuscript: Q.H.

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Data availability
The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethics and consent to participate
This study was approved by the Committee of First Affiliated Hospital of Fujian Medical University (No. MTCA, ECFAH of FMU [2015] 084 – 2) and the work described has been carried out in accordance with Declaration of Helsinki. Written consent was obtained from all subjects involved.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
Sida Sun, Wenxing Sun, Wenhui Xie, Fuya Zhao, Xianzhong Guo, Junfeng Zhou, Qingliang He and Hanfeng Zhou have no conflicts of interest or financial ties to disclose.

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