aspen | LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Nutrition in Clinical Practice
Volume 32 Number 1
February 2017 122–129

DOI: 10.1177/0884533616653807
journals.sagepub.com/home/ncp
SAGE

Nutrition and Immune-Modulatory Intervention in Surgical Patients With Gastric Cancer

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Abstract

This study evaluated the effect of an immune-modulatory diet on patients with gastric cancer and identified the parameters associated with postoperative outcomes. This was a single-arm prospective intervention study. At baseline, patients were assessed for nutrition (Patient-Generated Subjective Global Assessment), inflammatory markers (albumin, C-reactive protein, and interleukin 6 [IL-6]), and immune markers (percentage NK, CD4, CD8, and CD4:CD8 ratio); they also received nutrition counseling and high-calorie/protein supplement. A week before surgery, they were assessed for nutrition and inflammatory/immune markers and started on an immune-modulatory supplement until the day before surgery, when they were evaluated again. On the second postoperative day, patients were assessed for inflammatory/immune parameters, and a final nutrition evaluation was performed until the day of discharge. Complications were recorded daily and up to 30 days after discharge. Thirty-seven patients (60 ± 10 years old) were included, and 57% were classified as malnourished. Maintenance of nutrition and immune parameters occurred throughout the study period, but we found a preoperative increase in C-reactive protein (0.1–1.5 mg/dL) and IL-6 (2.0–14.2 pg/mL) and a postoperative increase in the CD4:CD8 ratio (2.3 ± 1.0). Complications and death were seen in 35%, especially patients with higher preoperative IL-6 (2.2–46 pg/mL), lower CD4:CD8 ratio (1.7 ± 0.5), and lower protein (1.2 ± 0.5 g/kg/d) and calorie intake (1552 ± 584 kcal/kg/d). The high-calorie/protein supplementation with the immune-modulating diet was able to maintain the nutrition and immune status of patients with gastric cancer. (*Nutr Clin Pract*. 2017;32:122-129)

Keywords

stomach neoplasms; immunonutrition; inflammation; gastrectomy; malnutrition; nutrition assessment

According to the World Health Organization, 27 million new cases of cancer, 17 million cancer deaths, and 75 million people living annually with cancer can be expected by the year 2030.[1,2] Among the different types of cancer, gastric cancer (GC) remains the second-most common cause of cancer-related death worldwide. Peak incidence occurs mostly in men, around 70 years old. About 65% of patients diagnosed with GC are >50 years old. In Brazil, regarding incidence, these tumors appear in third place among men and fifth among women. Elsewhere in the world, statistics have shown a decline in incidence, specifically in the United States, United Kingdom, and other developed countries.[2]

Surgical resection is still the main curative treatment; however, patients undergoing gastrectomy are at risk of various serious postoperative complications, usually associated with prior malnutrition, inflammation, and immune function suppression.[3-5] Furthermore, after surgery, weight loss is often associated with poor clinical outcome, cachexia, and lower survival.[6]

Proper nutrition intervention before and after surgery is important to facilitate recovery of patients undergoing gastrectomy. Braga et al showed that the use of an immune-modulatory diet in the preoperative and postoperative period of patients with GC reduced the rate of infection and length of hospital stay.[7,8] The beneficial effects of perioperative administration of immune nutrients, such as arginine, glutamine, omega-3 fatty acids, and ribonucleic acid, in patients with cancer undergoing major surgery was recognized and recommended by the guidelines of ASPEN (American Society of Parenteral and Enteral Nutrition) and ESPEN (European Society of Parenteral and Enteral Nutrition).[9,10] Also, a recent meta-analysis demonstrated that it is effective for enhancing host immunity and relieving the inflammatory response, but better clinical outcomes have been controversial, mainly because of the heterogeneity of studies.[11]

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Financial disclosure: Cytokine kits were purchased by Nestlé Brazil with funds administered by Fundação do Câncer.

Conflicts of interest: None declared.

This article originally appeared online on June 21, 2016.

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Recommendations arising from international consensus should be evaluated in different settings and, in particular, considering each hospital routine. The objective of this prospective observational investigation was to evaluate the effect of a high-protein and immune-modulatory diet on the nutrition status, inflammatory, and immune parameters of patients with GC before and after surgery.

Materials and Methods

This was a prospective observational intervention study on patients with GC from the Cancer Hospital of the National Cancer Institute (INCA, Rio de Janeiro, Brazil). The study was approved by the Local Ethics Committee (177/11), and all patients gave informed consent. The study was conducted from May 2012 to May 2014. The inclusion criteria were as follows: patients with previously untreated GC with exclusive surgical indication who were referred from the surgical outpatient clinic to the nutrition clinic, including both women and men aged 20–75 years. The exclusion criteria were as follows: liver disease with bilirubin >2 mg/dL, HIV-positive status, congestive heart failure class C and D, chronic kidney disease with glomerular filtration rate <60 mL/min/1.73 m^2, focus of infection or noncancer inflammatory diseases, immunosuppressive medication and/or glucocorticoids, and adjuvant chemotherapy or radiotherapy indication. In our hospital, all patients with GC are referred for nutrition counseling and preoperative supplementation. Eighty-one outpatients were included during this period, and 37 were followed up until surgery. Among the 81 patients screened, 44 were excluded because of disease progression and, thus, operation contraindicated (n = 27 patients) and death before surgery (n = 17 patients).

Upon study entry, at the outpatient visit (T0), patients were nutritionally assessed, and the inflammatory and immune markers were measured. Also, all these patients, at this time, received nutrition advice to consume a healthy diet with low lipid content (about 20% of the total calories), since this type of diet is recommended to patients with GC to avoid or decrease symptoms and signs, such as nausea, vomiting, and early satiety, which are very common in this type of tumor, therefore contributing to better acceptance.[12] Also, they were prescribed a high-calorie/protein oral supplement (135 g/d of powder formula with 700 kcal, 34.2 g of protein, dissolved in 600 mL of water; Nutrison, Danone, Brazil) to be taken while waiting for surgical treatment for a median period of 98.2 days. The interval between T0 and T1 was due to the need for extra preoperative complementary tests and because there was an increased demand of patients newly diagnosed with GC in the period. About a week before the surgical procedure was scheduled (T1), they were once again assessed for nutrition, inflammatory, and immune parameters. From this moment on, the patients had the previous oral supplement discontinued, and they were started on an immune-modulatory oral supplement liquid formula—600 mL/d containing 600 kcal, 33.6 g of protein, 7.5 g of arginine, 0.7 g of EPA, 1.1 g of DHA, and 1.2 g of nucleotides (Impact; Nestlé, São Paulo, Brazil)—until the day before the operation, when once again they had their nutrition, inflammatory, and immune data assessed (T2). The immune-modulatory diet was administered for a median of 6.8 days in only the preoperative period, according to international guidelines.[9,10] For analytic purposes, patients were divided according to intake of the immune-modulatory diet: those with <80% or ≥80% intake (<500 or ≥500 mL/d). Patients were encouraged to eat regular food to reach the recommendations; they did not use vitamin/mineral supplements; and they were oriented to drink the high-protein supplement with meals or in between, at their discretion. To monitor the acceptance, patients were contacted by telephone once a week, and they were instructed to bring, at the time of hospitalization for surgery, the supplement packages that had not been used.

Then, on the second postoperative day, patients were assessed for inflammatory and immune parameters, and a final anthropometric evaluation was performed on the day of hospital discharge (T3). Complications were recorded daily, up to the day of discharge, and thereafter up to 30 days (Figure 1). The assessed postoperative complications were infection (sepsis, pneumonia), anastomotic dehiscence/fistula, and death. Infection included the presence of sepsis and pneumonia as confirmed by bacteria culture and radiography (for pneumonia), as well as fever (temperature >38ºC), elevated heart rate (≥90/min), and leukocytosis (≥12,000). Anastomotic dehiscence or gastrointestinal fistula included opening of the surgical incision, abdominal pain, and purulent discharge or leakage of contents through either drains or abdominal incisions.

All patients were diagnosed with adenocarcinoma by clinical diagnosis with histopathology confirmation. Tumor stage was defined as initial and advanced by clinical staging and TNM classification (primary tumor, regional lymph nodes, distant metastasis), depending on the tumor. Initial stage was considered as such: in situ (Tis or stage 0); localized extension; stage I-II; TNM T1-2, N0, and M0; or histologic grade 1 (well differentiated) and 2 (moderately well differentiated). Advanced stage was considered accordingly: regional or distant extension; stage III-IV; TNM T3-4, N1-3, M1; or histologic grade 3 (poorly differentiated) and 4 (undifferentiated).

The PG-SGA was carried out by the main study investigator at the outpatient nutrition clinic (T0 and T1) and at hospital admission (T2). Patients were classified preoperatively according to the PG-SGA as well nourished (A), suspected malnutrition or moderately malnourished (B), and severely malnourished (C).[13] Weight loss was assessed at admission (T0) as part of the PG-SGA. Patients were classified as no weight loss, no significant weight loss (<5% in 1 month or <10% in 6 months), significant weight loss (5% in 1 month or 10% in 6 months), or severe loss (>5% in 1 month or >10% in 6 months).[14]

Anthropometric measurements, including body mass index (BMI), triceps skinfold thickness (TSF), midarm circumference (MAC), and midarm muscle area, were performed by trained dietitians to monitor the nutrition status at each period of the study. BMI was calculated as weight (kg) divided by

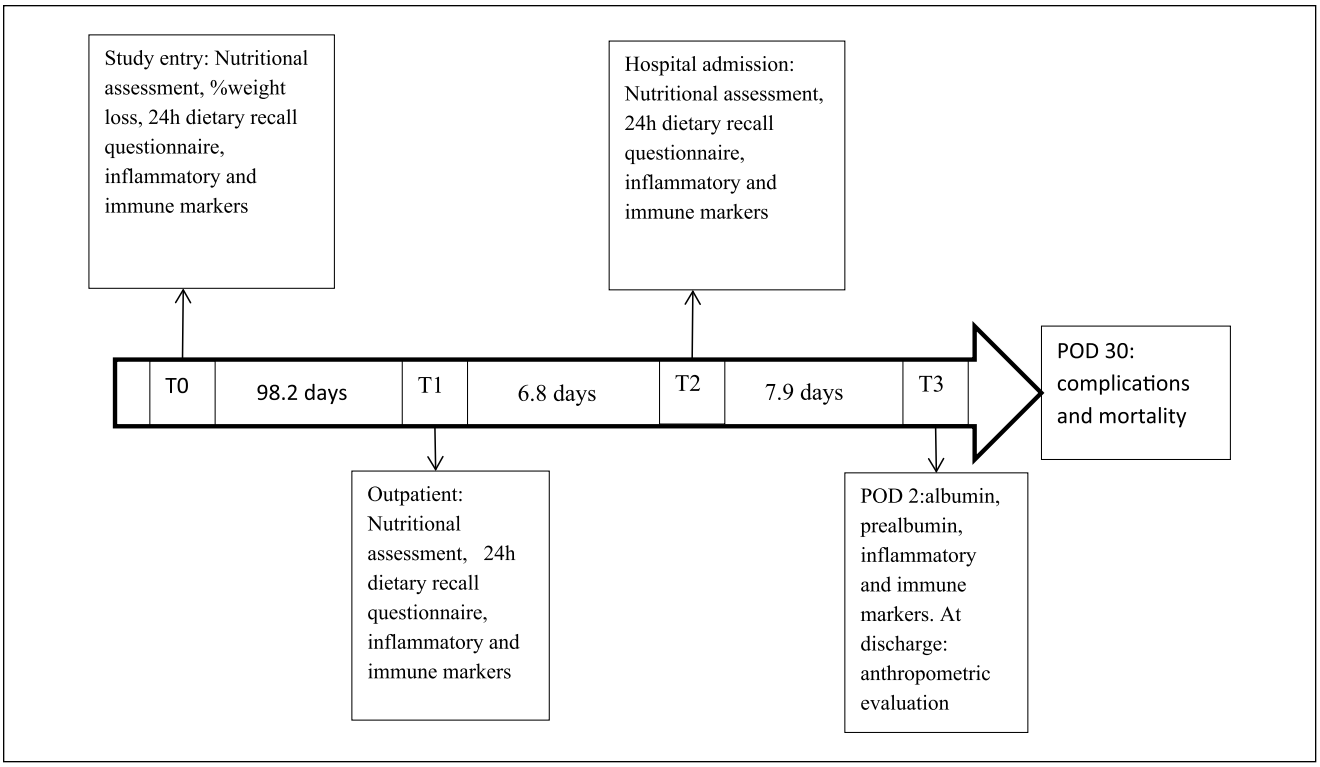

Figure 1. Study flowchart at each time period. POD, postoperative day; T0, study entry; T1, after high caloric and protein supplementation (median 98.2 days); T2, after immune modulatory supplementation and hospital admission (median 6.8 days); T3, postoperatively, at hospital discharge (mean of 7.9 days).

height (m^2) and used as a follow-up marker. MAC was measured in millimeters with a standard measuring tape, and TSF was obtained at the same point as for MAC, with the Lange skinfold caliper (Beta Technology, Santa Cruz, CA), in the nondominant arm. Midarm muscle area was derived from MAC and TSF through standard formulas.[15,16]

Dietary energy (kcal/d) and protein (g/d and g/kg/d) intake were assessed by three 24-hour recall questionnaires in which patients recorded all the food and drinks for (T0) the previous day before study entry, without any supplement intake; (T1) after high-protein supplementation, including food and supplement; and (T2) after the immune-modulatory supplementation, including food and supplement.

Serum IL-6 levels were determined through an enzyme-linked immunosorbent assay kit (Ready Seat-Go; eBioscience, San Diego, CA), according to the manufacturer's instructions. All samples were tested in duplicate wells, and the means of the duplicates were reported. When the concentrations were between the blank and the lower detection limit of the assay, the values of the limit were included in the data analysis (2.0 pg/mL). For those samples with concentrations above the detection limit of the assay, the values were obtained from the standard curve.[17] The cutoff level was arbitrally set from the preoperative median of IL-6, as there are no data in the literature. "High level" was considered when IL-6 >2.1 pg/mL preoperatively. Serum albumin was quantified by the bromocressol green method, and high-sensitivity C-reactive protein (CRP) was measured by the turbidimetric method with specific kits and according to laboratory routine.

The Glasgow prognostic score (GPS) was determined according to the previously described method.[18] In brief, patients exhibiting both an elevated CRP level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were assigned a score of 2. Patients who exhibited only one of these biochemical abnormalities were assigned a score of 1. Patients who did not exhibit either of these abnormalities were assigned a score of 0. The albumin and CRP values were used to determine the CPR:albumin ratio, for which patients whose ratio was ≥2.0 were considered at high risk.[19]

Immune parameters were evaluated as total number of leukocytes (μL), lymphocytes (μL), and lymphocyte subsets (percentage natural killer, CD4, CD8, and CD4:CD8 ratio). At least 1×10^6 cells/mL were evaluated in the flow cytometry device (FACScan; Becton Dickinson, Mountainview, CA) through the Cell Quest program with software Infinicity. Antibodies (CD4-FITC, CD8-PE, CD3 PerCP, CD3-FITC, CD16-Pe) were purchased from BD Biosciences and the CD56-PerCP from Beckman Coulter (Schaumburg, IL).

Statistical Analysis

Categorical variables were expressed as frequency and percentage, and the chi-square test or Fisher's exact test was used when

necessary. The results of continuous variables were expressed as mean ± SD and noncontinuous by median and interquartile range (Q25–Q75). The parametric variables were compared between groups and throughout the study by independent Student's *t* test and analysis of variance with Bonferroni post hoc test, with a 95% confidence interval (95% CI), and were statistically significant when $P < .05$. For nonparametric variables, the Mann-Whitney and Wilcoxon tests were used to compare the groups, with a 95% CI, and were statistically significant when $P < .05$.

Pearson's coefficient was used for the correlation between continuous variables. Inflammatory variables were categorized as IL-6 (<2.1 or ≥2.1 pg/mL), GPS (score, 0–1 or 2), CPR:albumin (<2.0 or ≥2.0). The variables that were statistically significant in the univariate analysis were assessed by multivariate analysis through the logistic regression model and adjusted for continuous variables, as preoperative time and hospital lengh of stay. SPSS 17 (IBM Corp, Chicago, IL) was used for the statistical analysis.

Results

Patients' characteristics are in Table 1. According to PG-SGA, most patients showed some degree of malnutrition (57%). Regarding the clinical stage of the disease, 81% of patients were in an advanced stage (clinical stage III/IV), and malnutrition was present in 57% of this group.

Surgical procedures were as follows: subtotal gastrectomy, 40% (n = 15); total gastrectomy, 49% (n = 18); and palliative surgery, 11% (n = 4). The median hospital stay was 6.0 days (range, 3–23). Complications within 30 days after the operation, including death (n = 4), were seen in 35% of the patients (overall complications). The most frequent complications were anastomotic dehiscence/fistula (24%), death (11.8%), and sepsis in 9%. There was no correlation between (1) parameters (nutrition, immune, and inflammatory), preoperative weight loss, preoperative time (between T0–T1), and stage of disease on study entry and (2) postoperative outcomes.

There was an improvement of the nutrition status according to the PG-SGA throughout the preoperative period, with an increase of patients classified as A—a significant decrease in the PG-SGA score. There was also maintenance of anthropometric parameters throughout the whole study period. The nutrition intervention was important to prevent weight lost and to increase the calorie-protein intake of patients until the time of surgery. During the study, 21 (56,8%) patients did not lose or gain weight; in addition, there was an improvement in food intake, attested by a decrease of 2 points in the PG-SGA score (Table 2).

The majority of patients (65%) were able to eat >80% of the immune-modulatory supplementation. These patients had an increased overall preoperative intake of calories and protein and presented higher preoperative levels of albumin and increased postoperative CD4 (Table 3). There were no differences in hospital length of stay or infectious complications.

Inflammatory parameters increased during the preoperative period but remained stable in the last week after the immune-modulatory supplementation. A reduction of albumin values during the entire period was observed. All the parameters, except albumin, presented a significant increase after the operation. The dosage of IL-6 had a wide variability, ranging from 0–64.12 pg/mL during the preoperative period, so those patients with IL-6 above the median (>2.1 pg/mL) were considered "high level" IL-6 patients (Table 4). Furthermore, natural killer and CD4 were stable throughout the period, although an increase of CD8 and CD4:CD8 ratio after the operation was observed, as shown in Table 5.

Table 1. Baseline Characteristics of Patients With Gastric Cancer (n = 37).

Variable	%
Sex	
Male	59.5
Female	40.5
Age,[a] y	60.2 ± 10
Adult	43.2
Elderly >60 y	56.8
PG-SGA	
A	43.2
B	54.1
C	2.7
Stage	
Initial (I/II)	13.5
Advanced (III/IV)	81.1
No information	5.4
Weight loss	
Without	48.6
Nonsignificant	35.1
Significant	10.8
Severe	5.4
Physical activity (any level)	
Yes	18.9
No	81.1
Drinking alcohol	
Yes	45.9
No	54.1
Smoking	
Yes	43.2
No	56.8
Family cancer history	
Yes	56.8
No	43.2
Diabetes	
Yes	10.8
No	89.2
Hypertension	
Yes	37.8
No	62.2

A, well nourished; B, suspected malnutrition or moderately malnourished; C, severely malnourished; PG-SGA, Patient-Generated Subjective Global Assessment.
[a]Mean ± SD.

Table 2. Nutrition Parameters in Patients With Gastric Cancer Receiving Preoperative Nutrition Supplementation at Different Time Points.[a]

Parameter	T0 (n = 37)	T1 (n = 37)	T2 (n = 37)	T3 (n = 30)
PG-SGA classification,[b] %				ND
A	42.1	43.2	56.8	
B	55.3	56.8	43.2	
C	2.6	0	0	
PG-SGA score[c]				
Mean ± SD	7.4 ± 5.3[d,e]	7.9 ± 5.7[d]	5.9 ± 5.4[e]	ND
Median (min–max)	5 (1–19)	6 (1–19)	3 (1–19)	ND
Weight, kg	68.1 ± 12.1	68.1 ± 11.4	68.1 ± 11.6	67.3 ± 11.3
BMI, kg/m²	25.7 ± 3.7	25.6 ± 3.5	25.6 ± 3.6	25.6 ± 3.2
TSF, mm	17.4 ± 7.6	17.6 ± 6.8	16.1 ± 6.5	16.3 ± 6.1
MAC, cm	24.3 ± 2.8	24.4 ± 2.6	24.4 ± 2.9	24.8 ± 2.3
Dietary				
kcal/d	1497.5 ± 584.6[d]	1708.7 ± 765.5[e]	1772.5 ± 690.6[e]	ND
Protein/d, g	71.4 ± 35.0[d]	90.7 ± 45.7[e]	93.1 ± 36.7[e]	ND
Protein/d, g/kg	1.0 ± 0.5[d]	1.3 ± 0.7[e]	1.4 ± 0.7[e]	ND

BMI, body mass index; MAC, midarm muscle circumference; ND, not determined; PG-SGA, Patient-Generated Subjective Global Assessment; TSF, triceps skinfold.

[a]T0, study entry; T1, after high-protein supplementation; T2, after immune modulatory supplementation; T3, postoperatively. Values are presented as mean ± SD unless noted otherwise.

[b]T0 vs T1 vs T2, $P < .001$ (χ^2 test). A, well nourished; B, suspected malnutrition or moderately malnourished; C, severely malnourished.

[c]PG-SGA score: 0–1, no intervention required at this time and reassessment on routine and regular basis during treatment; 2–3, patient and family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey and laboratory values as appropriate; 4–8, intervention by dietitian in conjunction with nurse or physician as indicated by symptoms; >9 critical need for improved symptom management and/or nutrient intervention options.

[d,e]Values denoted by different superscript letters indicate $P < .05$ (independent Student's *t* test).

Table 3. Nutrition and Immune Parameters of Patients With Gastric Cancer Receiving Preoperative Nutrition Supplementation According to the Intake of the Immunomodulatory Supplement.[a]

	Intake of the Immunomodulatory Supplement	
Parameter	<80% (n = 13)	>80% (n = 24)
Preoperative		
Serum albumin, g/dL[b]	3.6 ± 0.6	4.1 ± 0.5
Dietary		
kcal/d[c]	1318 ± 556	2018 ± 637
Protein g/d[c]	70.8 ± 29.8	105.2 ± 38.8
Protein g/kg/d, 24 h[b]	1.0 ± 0.4	1.6 ± 0.7
Postoperative CD4, % total lymphocytes[b]	28.5 ± 10.2	37.7 ± 8.8

[a]Values are presented as mean ± SD.

[b]$P < .05$ (independent Student's *t* test).

[c]$P < .01$ (independent Student's *t* test).

At hospital admission (T2), there were some significant differences among well-nourished (A) and malnourished patients (B), mainly regarding PG-SGA score, anthropometric parameters, albumin, and CD8 (Table 6). There were negative correlations between the PG-SGA score and BMI ($r = -0.4$; $P < .01$), TSF ($r = -0.4$; $P < .01$), albumin ($r = -0.4$; $P < .01$), and dietary protein (g/d; $r = -0.5$; $P < .01$).

Patients with complications, including death, were those with higher preoperative levels of IL-6, lower CD4:CD8 ratio, and lower protein calorie intake, as shown in Table 7.

In the immediate preoperative period, 61.8% of the patients had a GPS score of 0; 17.6% had a score of 1; and 20.6% had a score of 2. Most patients classified with a score of 0 had no complications or death (n = 15), while 5 patients classified with a score of 2 presented with complications or died. Patients with a GPS score of 2 and a CPR:albumin ratio >2 were also considered "high level" IL-6 cytokine.

According to the logistic regression model, patients considered "high level" IL-6 in the immediate preoperative period had a greater risk of developing complications in the postoperative period (hazard ratio = 11.04; $P = .013$; 95% CI = 1.7–72.8).

Discussion

GC remains one of the most common cancers and the second cause of cancer deaths worldwide. Surgical resection is the only treatment that enables the cure of GC. However, the tendency for local, nodal, and hematogenous spread of this tumor hinders the possibility of early diagnosis and makes curative surgery impossible in around half of the patients. Thus, palliative treatment becomes the only option.[20,21] However, no matter what kind of surgical treatment is adopted, the nutriton status of these patients—influenced by the disease per se and

Table 4. Inflammatory Parameters of Patients With Gastric Cancer Receiving Preoperative Nutrition Supplementation Throughout the Study.[a]

Parameter	T0 (n = 37)	T1 (n = 37)	T2 (n = 37)	T3 (n = 30)
Serum albumin, g/dL	4.3 (4.05–4.60)[b]	4.2 (3.90–4.50)[c]	3.9 (3.50–4.35)[d]	3.2 (2.72–3.60)[e]
CRP, mg/dL	0.27 (0.12–0.61)[b]	0.29 (0.12–1.24)[c]	0.32 (0.12–1.52)[c]	17.2 (9.9–27.9)[d]
CRP:albumin ratio	0.06 (0.02–0.15)[b]	0.06 (0.03–0.29)[c]	0.08 (0.25–0.45)[c]	5.4 (2.9–93)[d]
IL-6, pg/mL	2.0 (2.0–3.9)[b]	2.0 (1.5–15.9)[b,c]	2.1 (2.0–14.2)[c]	14.1 (4.3–45.2)[d]
GPS, Q25–Q75	0–0	0–1	0–1	1–2

CRP, C-reactive protein; GPS, Glasgow prognostic score; IL-6, interleukin 6.
[a]T0, study entry; T1, after high-protein supplementation; T2, after immune modulatory supplementation; T3, postoperatively. Values are presented as median (Q25–Q75) unless noted otherwise.
[b–e]Values denoted by different superscript letters indicate $P < .05$ (Wilcoxon test).

Table 5. Immune Parameters of Patients With Gastric Cancer Receiving Preoperative Nutrition Supplementation Throughout the Study.[a]

Parameter	T0 (n = 37)	T1 (n = 37)	T2 (n = 37)	T3 (n = 30)
Leukocytes, µL	7453 ± 2324[b]	7692 ± 2231[b]	7560 ± 1728[b]	11981 ± 3633[c]
Lymphocytes, µL	1975 ± 603[b,c]	2031 ± 629[b]	1894 ± 640[c]	1163 ± 628[d]
Total lymphocytes, %				
NK[e]	13.4 (10.7–20.8)	15.8 (10.6–19.8)	14.5 (7.8–21.7)	11.9 (8.2–21.8)
CD4	39.2 ± 6.3	39.5 ± 6.9	37.9 ± 8.9	34.5 ± 10.1
CD8[e]	18.7 (14.6–25.3)[b]	20.8 (16.1–28.4)[c]	19.6 (15.1–25.5)[b,c]	16.9 (12.0–23.7)[d]
CD4:CD8 ratio	2.2 ± 0.8[b]	2.0 ± 0.7[b,c]	2.0 ± 0.7[c]	2.3 ± 1.0[d]

NK, natural killer.
[a]T0, study entry; T1, after high-protein supplementation; T2, after immune modulatory supplementation; T3, postoperatively. Values are presented as mean ± SD unless noted otherwise.
[b–d]Values denoted by different superscript letters indicate $P < .05$ (independent Student's *t* test, unless noted otherwise).
[e]Median (Q25–Q75). *P* values based on Mann-Whitney.

the clinical symptoms, such as anorexia and vomiting—has been aknowledged as a determinant of outcomes.[3]

The most prevalent complaints of patients with GC are abdominal pain and dyspepsia; in most cases, however, many patients are asymptomatic in the early stage. According to the studies by Muraro[22] and Campelo and Lima,[23] the most frequent site of GC is the antrum, and due to this, symptoms such as dysphagia, anorexia, weight loss, gastrointestinal bleeding, and vomiting are more frequently present with a proximal lesion and a more advanced-stage disease. The majority of patients in the current study were malnourished and had an advanced presentation of the disease. However, Shim et al evaluated 279 individuals with GC using PG-SGA before surgery and found that only 2.2% were severely malnourished.[24]

Untreated malnutrition is a risk factor for increased complications, mortality, and length of hospital stay (LOS). Ejaz et al—in a study from the multi-institutional US Gastric Cancer Collaborative with 775 patients who underwent gastrectomy between 2000 and 2012—found that 60.9% of patients had GC with advanced stage, 59.6% underwent subtotal gastrectomy, 42% experienced a perioperative complication, and the median LOS was 8 days (range, 7–12).[25]

Therefore, by providing oral supplementation, we attempted to increase protein-calorie intake to affect nutrition status and related outcomes. This treatment contributed to weight stabilization, which certainly represents preservation of the nutrition status, even with patients who have advanced stages of the disease. Our results show that throughout the preoperative period, nutrition and immune parameters remained stable and that after surgery there was an increase in the CD4:CD8 ratio. CD4 and CD8 levels were lower than those reported in the literature for healthy individuals (42%–44% and 24%–32%, respectively).[26,27] However, our results were similar to those seen by others, such as Zhang et al, who assessed the immune profile of 82 patients with GC in different stages of the disease. The authors found that patients with GC had lower levels of CD4 and CD8 (30.7% vs 51.2% and 15.4% vs 31.9%, respectively) when compared with healthy individuals.[28] Also, Xu et al—using a similar protocol (30 patients receiving a immune-modulatory diet for 7 days before surgery vs a control group)—compared the preoperative and postoperative periods and reported a maintenance of CD4 but with a significant increase of the CD4:CD8 ratio in only the group receiving the immune-modulatory diet.[29] Their results of the CD4:CD8 ratio in the supplemented group were similar to those found in the current study, in which all the patients received the immune-modulatory diet.[29] According to the literature, the increase in the CD4:CD8 ratio is beneficial in the postoperative period, as it increases cellular and humoral immunity. Positive effects on immune parameters have been seen when 500–1000 mL/d of

Table 6. Nutrition, Inflammatory, and Immune Parameters of Well-Nourished and Malnourished Patients With Gastric Cancer Receiving Preoperative Nutrition Supplementation at Hospital Admission (T2).[a]

Parameter	Well Nourished (n = 21)	Malnourished (n = 16)
Age, y	58 (53–65)	65.5 (57–69)
PG-SGA score[b]	1.0 (1–2.5)	11.5 (7.5–13.5)
Weight, kg	69.5 (61.7–81.6)	62.2 (58.7–68.5)
BMI,[c] kg/m²	26.3 (24.3–29.3)	24.6 (20.8–26.2)
TSF,[b] mm	18.5 (15.0–23.0)	10.5 (9.0–16.5)
MAC, cm	24.9 (23.6–27.1)	24 (21.3–26.3)
Intake		
kcal/24 h	1712 (1462–2203)	1604 (884–2463)
Protein/24 h, g	90.1 (80.4–125.3)	70.4 (38.3–121.7)
Protein/24 h, g/kg	1.3 (1.0–1.8)	1.0 (0.6–2.0)
Albumin,[c] g/dL	4.2 (3.7–4.6)	3.8 (3.3–4.1)
CRP, mg/dL	0.3 (0.1–1.3)	0.7 (0.1–2.6)
CRP:albumin ratio	0.07 (0.02–0.4)	0.16 (0.03–0.7)
IL-6, pg/mL	2.3 (2–173)	2.1 (2–13.1)
Leukocytes, µL	6732 (6235–8406)	7548 (6763–9502)
Lymphocytes, µL	1919 (1475–2502)	1770 (1455–2084)
Total lymphocytes, %		
NK	14.5 (7–20)	15.2 (8.1–27.3)
CD4	40.3 (35.6–46.8)	35.9 (27.6–42.9)
CD8[c]	22.3 (17.5–28.2)	16.3 (13.2–21.9)
CD4/CD8 ratio	1.9 (1.5–2.3)	2.1 (1.5–2.6)

BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin 6; MAC, midarm muscle circumference; NK, natural killer; PG-SGA, Patient-Generated Subjective Global Assessment; TSF, triceps skinfold.
[a]Values are presented as median (Q25–Q75).
[b]$P < .01$ (Wilcoxon test).
[c]$P < .05$ (Wilcoxon test).

Table 7. Preoperative Parameters of Patients With Gastric Cancer With and Without Surgical Complications.[a]

Parameters	Without Complications	With Complications
IL-6, pg/mL[b]	2.0 (2.0–2.6)	9.1 (2.2–46)
CD4:CD8[c]	2.2 ± 0.7	1.7 ± 0.5
Dietary[c]		
kcal/d	2020 ± 642	1552 ± 584
Protein g/kg/d	1.7 ± 0.7	1.2 ± 0.5

IL-6, interleukin 6.
[a]Complications include anastomotic dehiscence/fistula, sepsis, fever, and death. Values are presented as mean ± SD, unless noted otherwise.
[b]$P < .05$ (Mann-Whitney). Values are presented as median (Q25–Q75).
[c]$P < .05$ (independent Student's *t* test).

the immune-modulatory diet was achieved.[11] It is noteworthy that patients who consumed >80% (≥500 mL/d) of the supplement had higher CD4 postoperatively.

Another aspect of patients with GC is the inflammatory status. In our study, patients classified at the initial stage (I and II) had an IL-6 level of 5.02 ± 6.20 pg/mL, while those patients with advanced stage (III and IV) had an IL-6 level of 7.87 ± 14.50 pg/mL. This was also reported by Kim et al,[30] who assessed 115 patients with GC divided according to the stage of disease. The authors identified an increase of IL-6 and CPR as disease progressed: IL-6 level was 7.36 ± 5.52 pg/mL in those patients with stage I and 13.92 ± 10.76 pg/mL in those classified with stage IV. Also, Ikeguchi et al—who followed 90 patients with GC (47.7% in stage I)—found an IL-6 level of 5.8 pg/mL.[31]

In the present study, complications occurred mainly in patients with higher IL-6 levels, lower levels of CD4:CD8 ratio, and decreased calorie-protein intake. There is evidence that high preoperative or postoperative period levels of cytokines, in particular IL-6, with low albumin levels may be prognostic factors for morbidity.[6,32,33] Also, high CRP is associated with the risk of postoperative complications.[34] It is noteworthy that these variables are closely interrelated, since the increase in CPR is induced by the increase in IL-6.[35,36] Blakely et al, studying 50 patients with cancer who were undergoing palliative elective procedures, found that increased levels of CRP (>0.8 mg/dL) were associated with postoperative complications and shorter survival in 30 days.[35] Even in procedures considered to be low risk such as percutaneous endoscopic gastrostomy, patients with the combination of low albumin levels (<3.0g / dL) and high CRP levels (>1.0 mg/dL) had a mortality rate of 20.5%, compared with 2.6% among those patients with normal values. The risk of death was also increased 7 times (hazard ratio = 7.45; 95% CI = 2.62–21.19).[37] However, the interpretation of CRP levels alone should be taken with caution, since they can be influenced by different preoperative factors, such as leukocytosis, fever, arrhythmia, or cardiovascular events.[38] In this context, the CRP:albumin ratio and the GPS may be an alternative for minimizing the disadvantages of isolated interpretation of CPR. It has been reported that GPS was associated with prognosis in various types of cancer, including GC, and a GPS score of 2 was found to be an independent prognostic indicator of worse prognosis and poor survival in patients with GC.[38,39]

The current study has some limitations, mainly because it is an observational study with no control group. Immune and inflammatory parameters were measured only once postoperatively, and, as expected, inflammatory parameters increased after surgery. Also, a small number of patients were followed due to the difficulty in real clinical practice to assess immune and inflammatory parameters. However, we have carried out a comprehensive assessment, including nutrition, inflammatory, and immune parameters, before and after the operation.

Conclusion

The high-protein/calorie supplementation and the immune-modulating diet, with the regular diet, were able to maintain the nutrition and immune status of patients with GC in the preoperative and postoperative periods, even when the disease was in advanced stages. This suggests that under such conditions,

supplements positively affect nutrition status by providing enough nutrients to reach the nutrition requirements.

Statement of Authorship

V. Dias Rodrigues, N. Barroso de Pinho, and R. Brum Martucci equally contributed to the conception and design of the research and to the acquisition and analysis of the results; E. Abdelhay and J. P. B. Viola equally contributed to the acquisition and analysis of the results; V. Dias Rodrigues, N. Barroso de Pinho, R. Brum Martucci, and M. I. Correia contributed to drafting the manuscript. All authors critically contributed to the interpretation of the results, revised the manuscript, gave final approval, and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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