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Postoperative complication rate and survival of patients with gastric cancer undergoing immunonutrition: A retrospective study

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ABSTRACT

Objectives: This study aimed to evaluate the effect of preoperative immunonutrition on the rate of postoperative complication and survival of patients with gastric cancer.
Methods: A retrospective cohort was formed after data collection of patients hospitalized with gastric cancer. Postoperative complications classified according to the Clavien-Dindo classification system, length of hospital stay, readmissions, and rates of survival at 6 mo, 1 y, and 5 y were analyzed. A χ^2 or Fisher's exact test, Student or Mann-Whitney *t* test, and Kaplan-Meier and Cox regressions were used in the statistical analysis.
Results: A total of 164 patients were included in the study, with 56 patients assigned to the immunonutrition group and 108 to the conventional group. There were no significant differences in postoperative complications between the immunonutrition and conventional groups (51.8% versus 58.3%; $P = 0.423$). The most frequent complications were fistula and surgical wound infection. Length of hospital stay did not differ between the groups (median of 7.0 d: $P = 0.615$) and the presence of readmissions did not differ either (12.5% versus 15.7%; $P = 0.648$). In the multivariate Cox regression, in a pooled model for group, age, sex, body mass index, Charlson comorbidity index, staging, neoadjuvant chemotherapy, and type of surgery, there was a significant difference in survival rates at 6 mo ($P = 0.011$), 1 y ($P = 0.006$), and 5 y ($P < 0.001$).
Conclusions: Preoperative immunonutrition in patients with gastric cancer did not reduce postoperative complications or length of hospital stay. More studies are needed to confirm the benefit of immunonutriton supplementation for overall survival when associated with other protective factors.

Introduction

Cancer represents one of the world's major public health problems, with an increase in overall burden of 18.1 million new cases and 9.6 million deaths in 2018 [1]. Several factors contribute to the occurrence of cancer, such as population growth and development, and social and economic conditions, with a greater impact in less-developed countries [1,2]. Gastric cancer is the third leading cause of cancer death in the world [2]. Patients with this neoplasm often present with anorexia, nausea, vomiting, abdominal discomfort, dysphagia, fatigue, and weight loss, thus presenting with an unfavorable prognosis [3].

Special attention should be given to malnourished patients who are at increased risk for postoperative infections, poor adherence to anticancer treatment, poor quality of life, and higher morbidity and mortality rates [4,5]. In addition to nutritional damage caused by the disease, gastrectomy itself involves metabolic changes that negatively influence nutritional status. Impaired nutritional status may affect postoperative mortality rates as well as age, stage of disease, and tumor location [6]. In this context, measures of nutritional intervention have been sought to optimize the nutritional status of patients with cancer who will undergo some form of treatment. One of these measures is the immune-modulatory diet, which has shown benefits in the improvement or attenuation of immune and inflammatory responses in surgical patients [7–9].

Among the most common immunonutrients, the following stand out: Arginine, omega-3 fatty acids, glutamine, nucleotides, micronutrients, and antioxidant agents [10,11]. Omega-3 fatty acids participate in the response of the immune system [12,13]. Glutamine is important fuel for lymphocytes, macrophages, and neutrophils, as well as a precursor of peptides and proteins, purines, nucleotides, nucleic acids, and glutathione peroxidase,

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which is an important source of energy for the intestinal mucosa [14,15]. Arginine plays an important role in wound healing and reversing or preserving lean mass in surgical patients [10,16].

The European Society of Parenteral and Enteral Nutrition recommends, with a high level of evidence, oral/enteral immunonutrition in patients with upper gastrointestinal cancer undergoing surgical resection in the context of traditional perioperative care, such as stomach cancer [17]. However, the American Society of Parenteral and Enteral Nutrition) recommends the supplementation of immunonutrients for malnourished patients who will undergo major surgery [18]. The National Oncological Nutrition Consensus, which is a compilation of international studies, recommends diets enriched with immunonutrients for 5 to 10 d in the preoperative period of surgery of the digestive tract, regardless of nutritional status [11]. In clinical practice, the use of preoperative immune-modulatory diets promoted benefits such as improvement in healing, weight gain, reduction of postoperative infectious complications, and reduced the length of hospital stay, duration of systemic inflammatory response syndrome, anastomosis complications, and regulation of tumor infiltrative lymphocytes [7–9,19–21,22]. In addition, the possibility exists that immunonutrition improves the survival of patients [23].

However, these findings are still conflicting, and studies have found no benefit from this therapy [24,25]. At the national level, this definition is even more distant owing to the lack of studies in our context in surgical patients with gastric cancer. Therefore, the objective of this study is to evaluate the effect of immune-modulatory diets on the rate of postoperative complications and survival of patients with gastric cancer undergoing surgery at a large Brazilian public hospital.

Methods

Study design

The study included a retrospective cohort with patients who underwent a gastrectomy for stomach neoplasia between April 2012 and April 2014 at the Hospital do Câncer I/National Cancer Institute in Brazil. The study was approved by the local ethics committee (2.685.547, May 30, 2018).

Inclusion and exclusion criteria

We included female or male patients, ages 20 y to 90 y, with gastric adenocarcinoma tumors who did or did not undergo neoadjuvant chemotherapy and who did undergo subtotal or total gastrectomy. The hospital protocol for neoadjuvant chemotherapy started in September 2012. The main indications for neoadjuvant chemotherapy were the presence of type IV Borrmann gastric adenocarcinoma, T3 or T4 size tumor at cardia, or lymph node enlargement identified with computed tomography.

The exclusion criteria were patients with a history of myocardial infarction or cerebrovascular accident within 6 mo before surgery; patients with liver disease with bilirubin >2 mg/dL; carriers of human immunodeficiency virus; congestive heart failure classes C (symptomatic with structural alteration) and D (symptomatic severe with drug optimization); chronic kidney disease with glomerular filtration rate <60 mL/min/1.73^2 according to Levey et al. [26]; patients with some outbreak of infection or inflammatory disease; or patients on immunosuppressive medication or glucocorticoid agents.

Nutritional support

All patients admitted to the institution for gastric cancer surgery were referred to the nutrition clinic and invited to visit the hospital 5 d to 7 d before surgery to receive the immune-modulatory supplement.

The cohort was divided into two groups. The immunonutrition group was composed of patients who received the immune-modulatory diet (oral or enteral, polymeric, hyperprotein diet, enriched with arginine, omega-3 fatty acids, and nucleotides, totaling 600 mL/d and 600 kcal/d), for 5 to 7 d in the preoperative period, with at least 80% adherence (i.e., 500 mL and at least 5 d of supplementation). To assess adherence to supplementation, patients were contacted by telephone and instructed to bring the supplement packages that had not been used at the time of hospitalization for surgery. Patients who consumed <80% were excluded from the study.

The institution itself provided inputs for diet, including enteral dietary materials, without participants' personal expenses. The conventional group comprised patients who did not receive the immune-modulatory diet, mainly owing to transportation costs, but were operated on at the institution.

Clinical and nutritional assessment

Anamnesis data were collected, such as age, sex, presence of comorbidities, alcoholism, smoking status, family history of cancer, staging, functional capacity, laboratory test results, and preoperative nutritional status.

Comorbidities were classified according to Charlson comorbidity index (CCI) score [27], which takes into account the number and severity of comorbidity per the respective relative risks. The scoring system ranges from 1 to 6 in ascending order from lightest to most severe. To this score, age was added with 1 point for each decade >40 y.

Patients who reported current alcohol consumption were classified as alcoholic. With regard to smoking status, patients who reported being current smokers or cessation of smoking in a period of up to 10 y were considered smokers. Patients who reported never having smoked or had stopped smoking over a prior surgery of >10 y were considered nonsmokers.

The functional capacity of patients described in the chart was evaluated using the performance status scale developed by Zubrod et al. [28], which can measure the outcome of anticancer treatment, taking into account the quality of life of the patient based on the evolution of the patient's ability to perform activities of daily living. This scale is graded from 0 to 4, where 0 indicates that the patient maintains normal activities and 4 where the patient is restricted to bed [29].

Nutritional status evaluation was performed using data from the patient-generated subjective global assessment (PG-SGA), weight, height, and body mass index (BMI). A trained hospital nutritionist applied the PG-SGA at the time of hospital admission, and the anthropometric measurements were collected in the physical or electronic hospital records. The assessment could also have been conducted by any other health professional. The PG-SGA is a questionnaire to evaluate patients with cancer that was translated and validated in Brazil by Gonzalez et al. [30].

Postoperative complications, length of hospital stay, and readmissions

Data on postoperative complications, time of hospitalization from surgery, and readmissions recorded both at the hospital and in outpatient care were collected in physical and electronic records up to 90 d after surgery. The classification of surgical complications was performed according to Dindo et al. [31], in which complications are organized by severity, with citations of examples, a description of the total number of complications, and the total number by type of complication and degree of severity.

Survival at 6 mo, 1 y, and 5 y

Information about death or last contact was collected up to 6 mo, 1 y, and 5 y after surgery, with an active search in physical or electronic medical records.

Statistical analysis

A convenience sample was used with all patients at the institution between April 2012 and April 2014 for gastric adenocarcinoma and gastrectomy proposal. The Kolmogorov-Smirnov normality test was performed to consider normal or parametric variables. Categorical variables were presented as frequency and percentage, and the χ^2 or Fisher's exact test was performed (the latter when cells were <5). Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), which were compared between the study groups with a Student's *t* or Mann-Whitney test.

The Kaplan-Meier method was used to determine the 6 mo, 1 y, and 5 y survival rate of each group, and the Log-rank test was used to compare the values obtained. Cox proportional hazards regression was performed to estimate the adjusted hazard ratio with 95% confidence intervals. The significance level of 5% of probability was adopted in all cases ($P < 0.05$). The SPSS program, version 17, was used for the statistical analysis.

The calculation of the post hoc sampling power (https://clincalc.com/Stats/Power.aspx) was performed, considering two independent groups with a dichotomous outcome. With an alpha complication of 0.05, the sample power was 12.3%, and with a 6-mo survival outcome with an alpha of 0.05, the sampling power was 26.8%.

Results

A final sample of 164 patients was obtained (Fig. 1). The clinical and nutritional characteristics of the groups are presented in Table 1. There was a significant difference only in the number of patients who underwent neoadjuvant chemotherapy, which was higher in the conventional group ($P = 0.039$). The number in the conventional

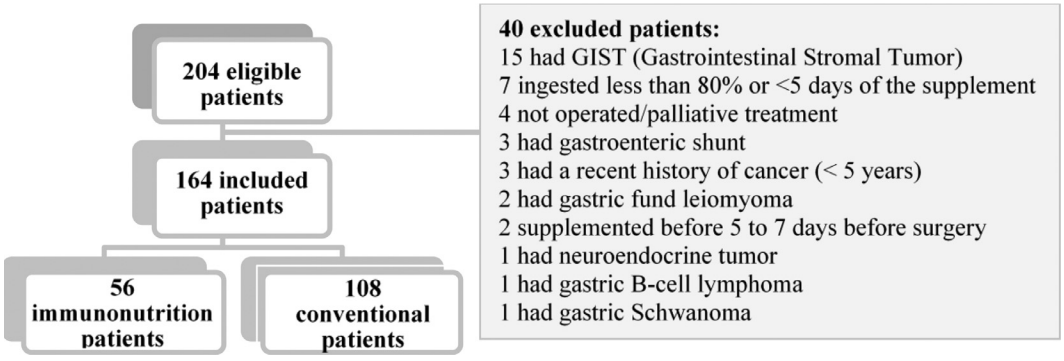

Fig. 1. Flowchart of patient selection.

group was higher because some patients did not visit the hospital before surgery or were advised for surgery with an interval <5 d (mainly patients who underwent neoadjuvant chemotherapy).

Patient characteristics

On the basis of body mass index, the frequency of malnutrition was low (5.4% immunonutrition versus 1.9% conventional group; $P = 0.377$), but the presence of some degree of malnutrition by PG-SGA was elevated (48.2% immunonutrition versus 50.9% conventional group; $P = 0.409$). The majority of patients were classified as advanced TNM grade III (62.5% immunonutrition versus 61.1% conventional group). Arterial hypertension was the greater comorbidity (36%).

Table 1
Clinical and nutritional characteristics

	Immunonutrition n = 56	Conventional n = 108	*P*-value
Age, mean (±SD)	63.7 (±11.8)	61.1 (±13.0)	0.418
Age ≥60 y, n (%)	38 (67.9)	57 (52.8)	0.064
Sex, male, n (%)	32 (57.1)	56 (51.9)	0.519
Female, n (%)	24 (42.9)	52 (48.1)	
CCI score, mean (±SD)	6.6 (±2.4)	6.5 (±2.3)	0.768
Comorbidity Yes, n (%)	24 (42.9)	48 (44.5)	0.846
No, n (%)	32 (57.1)	60 (55.5)	
Smoking (n = 55/107), n (%)	26 (46.4)	40 (37.0)	0.429
Alcoholism (n = 55/107), n (%)	25 (44.6)	43 (39.8)	0.727
Family history of cancer (n = 54/104), n (%)	32 (57.1)	68 (63.0)	0.750
PG-SGA score (n = 56/107), mean (±SD)	6.0 (±5.1)	7.1 (±6.7)	0.235
PG-SGA Moderately malnourished, n (%)	26 (46.4)	48 (44.4)	0.409
Severely malnourished, n (%)	1 (1.8)	7 (6.5)	
Well nourished, n (%)	29 (51.8)	52 (48.1)	
BMI (n = 56/105), mean (±SD)	25.0 (±3.5)	24.7 (±4.1)	0.718
BMI Malnutrition, n (%)	3 (5.4)	2 (1.9)	0.397
Eutrophy, n (%)	27 (48.2)	58 (55.2)	
Overweight and obese, n (%)	26 (46.4)	45 (42.9)	
Albumin g/dL, mean (±SD)	4.1 (±0.5)	4.2 (±0.5)	0.336
CRP mg/dL (n = 52/91), median (min–max)	0.3 (0–3.9)	0.3 (0–19)	0.875
Performance status 0, n (%)	12 (21.4)	23 (21.3)	0.645
1, n (%)	37 (66.1)	76 (70.4)	
2, n (%)	7 (12.5)	8 (7.4)	
3, n (%)	0 (0.0)	1 (0.9)	
TNM I, n (%)	15 (26.8)	22 (20.4)	0.213
II, n (%)	5 (8.9)	20 (17.6)	
III, n (%)	35 (62.5)	66 (61.1)	
IV, n (%)	1 (1.8)	0 (0.0)	
Type of surgery Total, n (%)	19 (33.9)	41 (38.0)	0.611
Subtotal, n (%)	37 (66.1)	67 (62.0)	
Neoadjuvant chemotherapy, n (%)	6 (10.7)	27 (25.0)	0.039
Adjuvant chemotherapy, n (%)	26 (46.4)	44 (40.7)	0.509
Adjuvant radiotherapy, n (%)	1 (1.8)	6 (4.7)	0.424

χ^2 or Fisher's exact test for categorical variables and Student's *t* test for continuous variables.
BMI, body mass index; CCI, Charlson's comorbidity index; CRP, C-reactive protein; PG-SGA, patient generated subjective global assessment; SD, standard deviation.

Postoperative complications

Both the type and degree of severity of complications in the postoperative period were determined. Each patient could present with >1 type of complication; therefore, Table 2 presents the data for only the complication with the greater degree of severity presented by each patient. There were no significant differences in postoperative complications between the immunonutrition and conventional groups. The immunonutrition group had a higher percentage of patients who had no

Table 2
Postoperative complications

Dindo et al. (2004)	Immunonutrition n = 56	Conventional n = 108	*P*-value
No complications, n (%)	27 (48.2)	45 (41.7)	0.423
Grade I, n (%)	3 (5.4)	5 (4.6)	0.837
Fistula	0	1	1.000
Surgical wound complication	1	0	0.341
Ileum	1	1	1.000
Gastric emptying delay	1	1	1.000
Urinary retention	0	2	0.548
Grade II, n (%)	14 (25.0)	31 (28.7)	0.614
Fistula	6	7	0.370
Surgical wound complication	4	13	0.424
Ileum (parenteral nutrition)	1	1	1.000
Fluid collection	1	1	1.000
Hematemesis	0	1	1.000
Urinary infection	1	4	0.662
Pulmonary	1	3	1.000
Deep vein thrombosis	0	1	1.000
Grade IIIa, n (%)	2 (3.6)	1 (0.9)	0.269
Abscess or complicated collection	2	1	0.269
Grade IIIb, n (%)	5 (8.9)	9 (8.3)	1.000
Fistula/Anastomosis dehiscence	0	4	0.300
Abscess or complicated collection	2	2	0.606
Evisceration/drilling	3	2	0.339
Adhesion/bowel obstruction	0	1	1.000
Grade IVa, n (%)	1 (1.8)	3 (2.8)	1.000
Pulmonary	1	3	1.000
Grade IVb, n (%)	0 (0.0)	4 (3.7)	0.300
Pulmonary + renal	0	2	0.548
Cardiovascular + pulmonary + renal	0	2	0.548
Grade V (early mortality), n (%)	4 (7.1)	10 (9.2)	0.774

Consider the highest postoperative complication that occurred up to 90 d. χ^2 or Fisher's exact test was performed.

Table 3
Hospital readmissions

	Immunonutrition n = 56	Conventional n = 108	*P*-value
Presence of readmission, n (%)	7 (12.5)	17 (15.7)	0.648
Days of readmission, median (min–max)	13.0 (1.0–26.0)	8.0 (1.0–54.0)	0.524
Reasons of readmission			0.591
Surgical wound complication	7	11	
Subocclusion/intestinal occlusion	2	2	
Pleural empyema	0	2	
Hematemesis	0	1	
Surgical margin compromised	0	1	
Deep vein thrombosis	0	1	

Patients may have >1 reason for readmission within 90 d. χ^2 or Fisher's exact test for categorical variables and Mann-Whitney test for continuous variable was performed.

complication, although the difference was not significant. Overall, 51.8% of patients in the immunonutrition group and 58.3% of the conventional group had some type of complication. The most frequent complications were those of grade II, which represented approximately one quarter of the complications, including fistula and wound infection.

Postoperative infectious complications were assessed separately. The immunonutrition group had a lower percentage of complications of infectious origin compared with the conventional group, but the differences were not statistically significant (41.1% vs. 48.1%; $P = 0.413$). The most frequent infectious complication was operative wound ($P = 0.864$), followed by respiratory infection ($P = 0.119$) and urinary tract infection ($P = 1{,}000$). Length of hospital stay did not differ between the groups (median of 7.0 d in both groups; $P = 0.615$).

Hospital readmissions

Although the immunonutrition group had a lower percentage of patients who were readmitted for surgical complications than the conventional group, this difference was not significant (Table 3). The most common reason for readmission was surgical wound complication.

Survival at 6 mo, 1 y, and 5 y

There were no significant differences in survival rates at 6 mo (92.6% versus 85.0%; $P = 0.154$), 1 y (87.0% versus 78.5%; $P = 0.153$), and 5 y (69.6% versus 58.3%; $P = 0.137$). Despite this, the immunonutrition group showed a trend of longer survival compared with the conventional group. The survival analyses were adjusted for group (immunonutrition or conventional), age, sex (male or female), BMI, CCI score, staging (initial [TNM I and II] or advanced [TNM III and IV]), neoadjuvant chemotherapy, and type of surgery (total or subtotal gastrectomy). At 6 mo, age ($P = 0.003$) and type of surgery ($P = 0.012$) were predictors of survival, whereas staging ($P = 0.059$) and immunonutrition group ($P = 0.091$) had a trend of increased survival. At 1 y, age ($P = 0.004$), type of surgery ($P = 0.046$), and staging ($P = 0.005$) were predictors of survival, and immunonutrition group ($P = 0.059$) and CCI score ($P = 0.063$) had a tendency to increase survival. At 5 y, age ($P = 0.041$) and staging ($P = 0.001$) were predictors of survival, and neoadjuvant chemotherapy ($P = 0.086$) showed a trend toward increased survival (Table 4). In the multivariate Cox regression, in a pooled model, when divided by immunonutrition or conventional group, there was a significant difference in survival at 6 mo ($P = 0.011$), 1 y ($P = 0.006$), and 5 y ($P < 0.001$; Fig. 2).

Discussion

Immune-modulatory diets have been described in the literature as promising in the reduction of postoperative complications, mainly infectious, as well as the improvement of the immunity of surgical patients with gastric cancer [7–9,19,21]. This fact can be corroborated by randomized and nonrandomized studies, as well as systematic reviews of the literature and recent meta-analyses [20,32,33]. This work followed postoperative complications within 90 d as suggested by specialists in gastrectomy [34]. Despite this, no statistically significant associations were found. One of the hypotheses for this lack of significance between the groups may be the fact that approximately half of patients are classified as normal or overweight and obese according to BMI, and nearly half can be classified as well nourished or moderately malnourished according

Table 4
Multivariate Cox regression with predictors of survival at 6 mo, 1 y, and 5 y

	6 mo		1 y		5 y	
	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Group						
Conventional	1.00 (reference)	0.091	1.00 (reference)	0.059	1.00 (reference)	0.118
Immunonutrition	0.36 (0.11–1.17)		0.41 (0.16–1.03)		0.62 (0.34–1.13)	
Age (y)	1.08 (1.03–1.14)	0.003	1.06 (1.02–1.09)	0.004	1.03 (1.00–1.06)	0.041
Sex						
Male	1.00 (reference)	0.573	1.00 (reference)	0.768	1.00 (reference)	0.135
Female	0.75 (0.28–2.01)		0.89 (0.41–1.94)		0.66 (0.38–1.14)	
BMI (kg/m^2)	0.92 (0.80–1.05)	0.213	0.96 (0.87–1.07)	0.465	0.98 (0.91–1.04)	0.460
CCI (score)	0.77 (0.56–1.07)	0.121	0.78 (0.60–1.01)	0.063	0.92 (0.77–1.11)	0.398
Staging						
Initial (TNM I and II)	1.00 (reference)	0.059	1.00 (reference)	0.005	1.00 (reference)	0.001
Advanced (TNM III and IV)	4.18 (0.95–18.43)		6.54 (1.79–23.89)		5.20 (2.04–13.28)	
Neoadjuvant chemotherapy						
No	1.00 (reference)	0.968	1.00 (reference)	0.416	1.00 (reference)	0.086
Yes	1.02 (0.32–3.25)		0.69 (0.28–1.69)		0.59 (0.32–1.08)	
Type of surgery						
Subtotal gastrectomy	1.00 (reference)	0.012	1.00 (reference)	0.046	1.00 (reference)	0.154
Total gastrectomy	3.78 (1.33–10.75)		2.32 (1.02–5.30)		1.51 (0.86–2.67)	

BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; CT, chemotherapy; HR, hazard ratio.

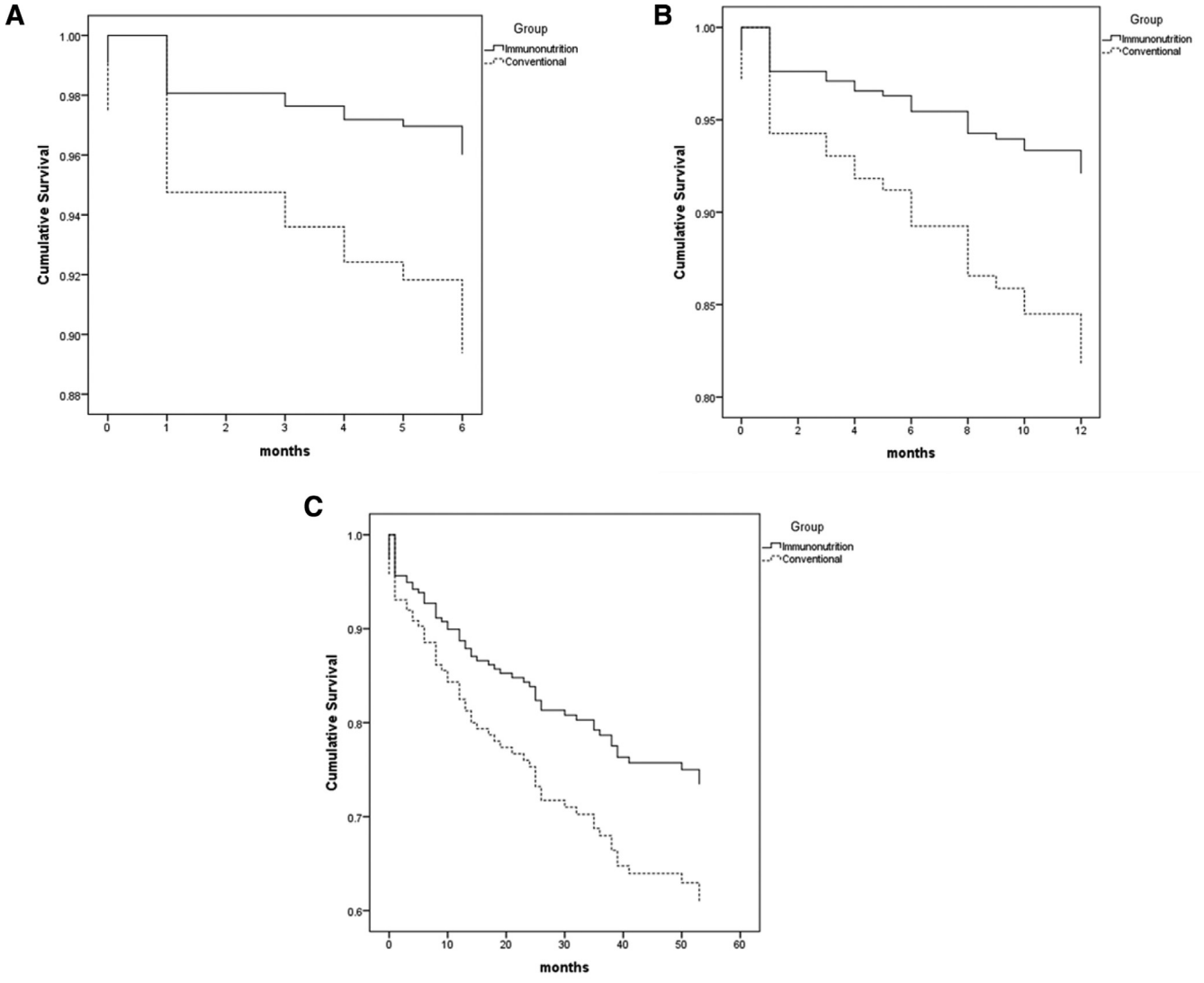

Fig. 2. Kaplan-Meier survival curves with predictors of survival at (A) 6 mo ($P = 0.011$), (B) 1 y ($P = 0.006$), and (C) 5 y ($P < 0.001$).

to the PG-SGA because previous studies have found significant associations in patients with malnutrition [20,33].

In this study, we found a total infectious complication rate of 44.6%, which is higher than the values found in the literature (33.7% [35], 25.5% [25], 24.6% [34], and 24.5% [36]). The degrees of complications found in the present study were higher than the values found by Kim et al. [36]. Grade II complications comprised 53.7% of our population but in the second study, they comprised 25.6% of the complications. Like the present study, other studies have also found no significant results of the benefits of immunonutrition in postoperative complications. In a prospective, randomized study, Fujitani et al. [33] evaluated preoperative enteral nutritional supplementation in well-nourished patients with gastric cancer who underwent total gastrectomy, and found no significant differences in postoperative complications between the groups. Kimura et al. [37] conducted a prospective, randomized, controlled phase III study to evaluate the effect of preoperative immunonutrition on the incidence of infectious complications in nonmalnourished patients after total gastric cancer gastrectomy and did not observe significant results.

The length of hospital stay of 7.0 d for both groups was lower than the time found by Yildiz et al. [20] of 18 d for the control group and 12 d for the immunonutrition group, and this difference was statistically significant. According to Dindo et al. [31], length of hospital stay is not reliable to compare among treatment centers because this parameter is influenced by each institution's discharge policy. Another relevant issue is the number of patients who underwent neoadjuvant chemotherapy, which was higher in the conventional group compared with the immunonutrition group. Neoadjuvant chemotherapy is known to be the most promising treatment for resectable gastric adenocarcinoma [38] and has become the recommended strategy in recent decades to improve the prognosis of patients with gastric cancer per the guidelines of the National Comprehensive Cancer Network [39], European Society of Medical Oncology [40], and Japanese gastric cancer treatment [41]. When comparing patients with resectable gastroesophageal cancer who underwent perioperative chemotherapy versus surgery alone, patients who received chemotherapy had better progression-free and overall survival rates [42]. Despite this, the immunonutrition group showed a trend of better survival when compared with the conventional group.

In the Kaplan-Meier survival analysis, no significant associations were found. A paired analysis was performed with regard to the type of surgery, sex, age, and staging of patients (data not

shown), but also no significant associations were found. When the variables were adjusted by multivariate Cox regression, we found a trend of beneficial effect of the use of the immune-modulatory diet in the 6 mo and 1 y survival rates. Few studies in the literature have evaluated the impact of immunonutrition on the survival of patients with gastric cancer.

In a randomized controlled study, Scislo et al. [35] evaluated the postoperative immune-modulatory diet and found no improvement in 6 mo and 1 y survival rates in patients with gastric cancer. Klek et al. [23] conducted a prospective randomized controlled trial of 5 y overall survival, and the adjusted analyses showed a lower risk of mortality, especially during the first 6 mo after surgery, among the enriched enteral nutrition group only in patients with stage IV gastric cancer, which suggests a short-term benefit and corroborates the results of the present study. However, a prospective double-blind controlled trial conducted by Buijs et al. [43] analyzed the effect of perioperative arginine-enriched enteral nutrition and found an improvement in long-term survival and specific long-term survival in severely malnourished patients with head and neck cancer. These data indicate that the results were not similar in different groups of patients.

The overall 5 y survival rate of the patients in this study was 63.9%, which is lower than the value found by Norero et al. [44] of 85% for patients with gastric cancer submitted to gastrectomy. Several factors may influence the prognosis of these patients. Shi et al. [45] concluded in their study that the immune-inflammatory index represents an independent prognostic factor for patients with gastric cancer in the multivariate analysis, which is an essential factor to predict the survival of these patients. A higher level of inflammatory markers has also been associated with an increase in the rates of complications after gastrectomy [46]. Another study by Feng et al. [47] showed that, after the multivariate analysis, BMI, tumor size, and TNM stage were independent prognostic factors. Malnourished patients are known to present a higher risk of postoperative morbidity, which, in turn, is associated with reoperation, readmission, and mortality, thus minimizing that a nutritional deficit may improve gastrectomy results [48].

To improve the nutritional status of patients, the treatment protocol should be well-defined. The best time for an immune-modulatory diet is still under discussion. A randomized and controlled study observed that the diet during the preoperative period of patients with cancer of the gastrointestinal tract is as effective as perioperative to reduce infectious complications and length of hospital stay [49]. On the other hand, a meta-analysis with 21 studies concluded that perioperative or postoperative administration significantly reduced infectious complications and length of hospital stay, whereas the preoperative period did not present advantages [25]. Another prospective study evaluated the three approaches of the immune-modulatory diet (i.e., pre-, peri-, and postoperative) on the outcomes of postoperative complications and length of hospitalization, and concluded that the perioperative approach is the most effective in malnourished patients with cancer of the gastrointestinal tract [22], but it is more costly to use this diet for a longer period and cannot be performed at all institutions.

In this study, we did not obtain retrospective data on the caloric-protein intake of patients, but an earlier prospective study [46] conducted by our research team with individuals involved in the current study found that before receiving nutritional advice, patients had consumed on average approximately 22 kcal/kg/d and 1.0 g protein/kg/d, which is below the nutritional recommendations for this population. After nutritional advise and immune-modulatory supplements, the caloric intake increased to 26 kcal/kg/d and protein to 1.4 g protein/kg/d before surgery [46]. Therefore, optimizing nutritional status and postoperative results are frequent focuses in clinical practice. This study helps clarify the real benefits of a nutritional intervention used by many institutions, but whether its additional cost is actually offset by the benefits remains unclear. Another strong point of the present work was the use of a standardized classification system for complications, which facilitates the comparison with the scientific literature.

The current analysis is a retrospective study of the immune-modulatory diet in a cohort of 164 patients with gastric cancer. A limiting factor is the lack of comprehensive data on dietary intake, given the nature of the retrospective study. The ideal condition to assess the efficacy of a nutritional intervention would be a controlled, randomized, and double-blinded prospective study. Even with selection bias for a retrospective study with a convenience sample and low sample power according to the post hoc analysis, a tendency was observed for a lower number of infectious complications and better survival in the immunonutrition group.

Conclusions

In the present study, an immune-modulatory diet did not reduce the incidence of postoperative complications and length of hospital stay in patients with gastric cancer. However, this diet may improve survival when associated with other protective factors (e.g., lower age, lower rate of comorbidity, initial staging, neoadjuvant chemotherapy, and subtotal gastrectomy). Probably, other clinical and nutritional variables not evaluated in this study could be involved in the outcome, which makes us reflect on the fact that the improvement of survival may occur even without significant impact on postoperative complications. More studies are needed to confirm the benefit of immunonutriton supplementation on overall survival when associated with other protective factors.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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