

## The impact of immunomodulatory enteral nutrition on patients submitted to elective gastrointestinal cancer surgery: integrative review

O impacto da nutrição enteral imunomodulatória em pacientes submetidos a cirurgia eletiva de câncer gastrointestinal: uma revisão integrativa

El impacto de la nutrición enteral inmunomoduladora en pacientes sometidos a cirugía electiva por cáncer gastrointestinal: una revisión integradora

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### ABSTRACT

**Objective:** To carry out a review about the use of enteral nutrition composed of immunonutrients in cancer patients undergoing elective surgery in the gastrointestinal tract on surgical outcomes. **Methods:** The research was carried out in the Medline, Lilacs and Pubmed databases. **Results:** The administration of enteral diet in both groups was well tolerated, there was no significant difference in the mortality rate and in the Intensive Care Unit or postoperative hospital stay. The immunomodulatory nutritional therapy was favorable to decrease the TNF $\alpha$  values and increase the total lymphocyte count in the postoperative period. Perioperative enteral immunonutrition has no significant effects on mortality rate, length of hospital stay and complications in gastrointestinal tract surgeries. **Final considerations:** Immunonutrition appears to be promising in terms of modulating the immune response. More randomized studies are needed regarding the effects of immunonutrients on abdominal surgical cancer patients.

**Keywords:** Neoplasms, Immunomodulation, Operative surgical procedure, Enteral nutrition.

### RESUMO

**Objetivo:** Realizar uma revisão sobre o uso da nutrição enteral composta por imunonutrientes em pacientes com câncer submetidos a cirurgias eletivas no trato gastrointestinal sobre os resultados cirúrgicos. **Métodos:** A pesquisa foi realizada nas bases de dados Medline, Lilacs e Pubmed. **Resultados:** A administração de dieta enteral em ambos os grupos foi bem tolerada, não houve diferença significativa na taxa de mortalidade e na Unidade de Terapia Intensiva ou internação pós-operatória. A terapia nutricional imunomoduladora foi favorável para diminuir os valores de TNF $\alpha$  e aumentar a contagem total de linfócitos no pós-operatório. A imunonutrição enteral perioperatória não tem efeitos significativos na taxa de mortalidade, tempo de internação e complicações em cirurgias do trato gastrointestinal. **Considerações**

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**finais:** A imunonutrição parece ser promissora em termos de modulação da resposta imune. Mais estudos randomizados são necessários sobre os efeitos dos imunonutrientes em pacientes com câncer cirúrgico abdominal.

**Palavras-chave:** Neoplasias, Imunomodulação, Procedimento cirúrgico operatório, Nutrição enteral.

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## RESUMEN

**Objetivo:** Realizar una revisión sobre el uso de nutrición enteral compuesta por inmunonutrientes en pacientes oncológicos sometidos a cirugía electiva del tracto gastrointestinal sobre los resultados quirúrgicos. **Métodos:** La investigación se realizó en las bases de datos Medline, Lilacs y Pubmed. **Resultados:** La administración de dieta enteral en ambos grupos fue bien tolerada, no hubo diferencia significativa en la tasa de mortalidad y en la estancia hospitalaria en la Unidad de Cuidados Intensivos o postoperatoria. La terapia nutricional inmunomoduladora fue favorable para disminuir los valores de TNF  $\alpha$  y aumentar el recuento total de linfocitos en el postoperatorio. La inmunonutrición enteral perioperatoria no tiene efectos significativos sobre la tasa de mortalidad, la duración de la estancia hospitalaria y las complicaciones en las cirugías del tracto gastrointestinal. **Consideraciones Finales:** La inmunonutrición parece ser prometedora en términos de modular la respuesta inmune. Se necesitan más estudios aleatorios sobre los efectos de los inmunonutrientes en pacientes con cáncer quirúrgico abdominal.

**Palabras-clave:** Neoplasias, Inmunomodulación, Procedimiento quirúrgico operativo, Nutrición enteral.

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## INTRODUCTION

Cancer is the main public health problem in the world and is already among the top four causes of premature death (before the age of 70) in most countries (BRAY F, et al., 2020). For Brazil, the estimate for each year of the 2020-2022 triennium is 625 thousand new cases of cancer. The most frequent stomach cancer is the adenocarcinoma type, responsible for 95% of cases. Stomach adenocarcinoma affects, in most cases, men aged between 60 and 70 years (INCA, 2019).

Cancer is the main public health problem in the world and is already among the top four causes of premature death (before the age of 70) in most countries (BRAY F, et al., 2020). It is estimated 625 thousand new cases of cancer in Brazil for each year from 2020 to 2022. Stomach cancer will be one of the most prevalent (21 thousand cases). The most frequent stomach cancer is the adenocarcinoma type, responsible for 95% of cases. It affects, in most cases, men aged between 60 and 70 years (INCA, 2019).

It is a common tumor of the digestive system and more than 60% of gastric cancer patients are malnourished, due to decreased food intake, impaired digestion and absorption of nutrients and hypermetabolism of neoplastic cells. In addition, they can worsen their nutritional status after undergoing elective surgery (SCHATTNER M, 2003; TORRE LA, et al., 2015). Malnutrition may be related to depression of the immune function, alteration of the inflammatory response and exaggeration of the stress response. Consequently, these patients generally have poor surgical responses, such as infectious complications, delayed or failed wound healing and longer hospital stays (VILHJÁLMSDOTTIR DÖ, et al., 2013).

So, perioperative, oral, enteral or parenteral nutritional support reduce complications associated with malnutrition, such as wound infection and anastomotic dehiscence and improve patient recovery (NATIONAL COLLABORATING CENTER FOR ACUTE CARE, 2006; WEIMANN A, et al., 2006).

It has been seen that enteral immunonutrition (EIN), which contains omega 3 ( $\omega$ -3) fatty acids, glutamine, arginine and nucleotide, is an important treatment to reduce infections and postoperative complications, modulate the immune system and improve the prognosis of patients with gastrointestinal cancer (XU J, et al., 2006; PÉREZ CE, 2015). As well, it may be related to the reduction in hospital stay after gastrointestinal surgery (WONG CS and ALY EH, 2016).

Furthermore, Giger U, et al. 2007 saw a reduction in serum levels of C-Reactive Protein (CRP) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) in patients after undergoing gastrointestinal surgery, in the group that received nutrition immunomodulatory enteral.

However, there is still controversy as to whether immunomodulatory enteral nutrition provides additional clinical benefits and may improve postoperative outcomes for patients with gastric neoplasia compared to standard enteral nutrition. The inconsistency of the results is not clear, but it can be attributed to confounding and heterogeneous factors in the demographic, clinical, nutritional or metabolic status of patients (CERANTOLA Y, et al., 2011; WONG CS and ALY EH, 2016).

Therefore, the aim of this study was to conduct a review about the use of nutrition enteral composed of immunonutrients in cancer patients undergoing elective surgery in the gastrointestinal tract on surgical outcomes, as well as reduction in rates of perioperative complications.

## METHODS

This work consists of an Integrative review, which provides relevant information on a subject, which with methodological rigor facilitates the incorporation of evidence, that is, contributing with new knowledge for clinical practice (SOUSA LMM, et al., 2017).

The present review followed the six steps described by Whittemore R and Knafelz K (2005): 1) selection of the guiding question; 2) definition of the inclusion and exclusion criteria of the sample; 3) selection, by peers, of the researches that comprised the sample; 4) analysis of the findings of the articles included in the review; 5) interpretation of results; and 6) report of the review.

The guiding question elaborated was: "what are the benefits of using immunomodulatory enteral nutrition in surgical cancer patients of the gastrointestinal tract?" The research was conducted in the databases Medline (Medical Literature Analysis and Retrieval System Online), Lilacs (Latin American and Caribbean Literature in Health Sciences) and Pubmed (National Library of Medicine and National Institute of Health - USA). Descriptors in Health Sciences - DeCs in English were combined with Boolean operators: "neoplasms" AND "immunomodulation" AND "operative surgical procedure" AND "enteral nutrition".

The inclusion criteria were original articles, made in humans, available in full, in English and Portuguese, in journals indexed in the databases referred to from 2010 to 2020. The exclusion criteria were studies in which the sample was composed by children under 18, conducted in animals, in vitro, theses and dissertations, literature and editorial reviews, case reports, book chapters, duplicate articles and that were not related to the problem. For the selection of articles, the titles and abstracts were read according to the previously established criteria.

The following inclusion criteria were identified according to the acronym PICOS (participant, intervention, comparison, outcomes of interest and study design): Population (P): all patients scheduled for selective gastrointestinal cancer surgery were included in this study. Intervention (I) and Comparison (C): the trials evaluated the comparative effects of the EIN diet with some immunonutrient (Arg, Glu,  $\omega$ -3-FA and RNA) versus Standard Enteral Nutrition (SEN) (LIBERATI A, et al., 2009).

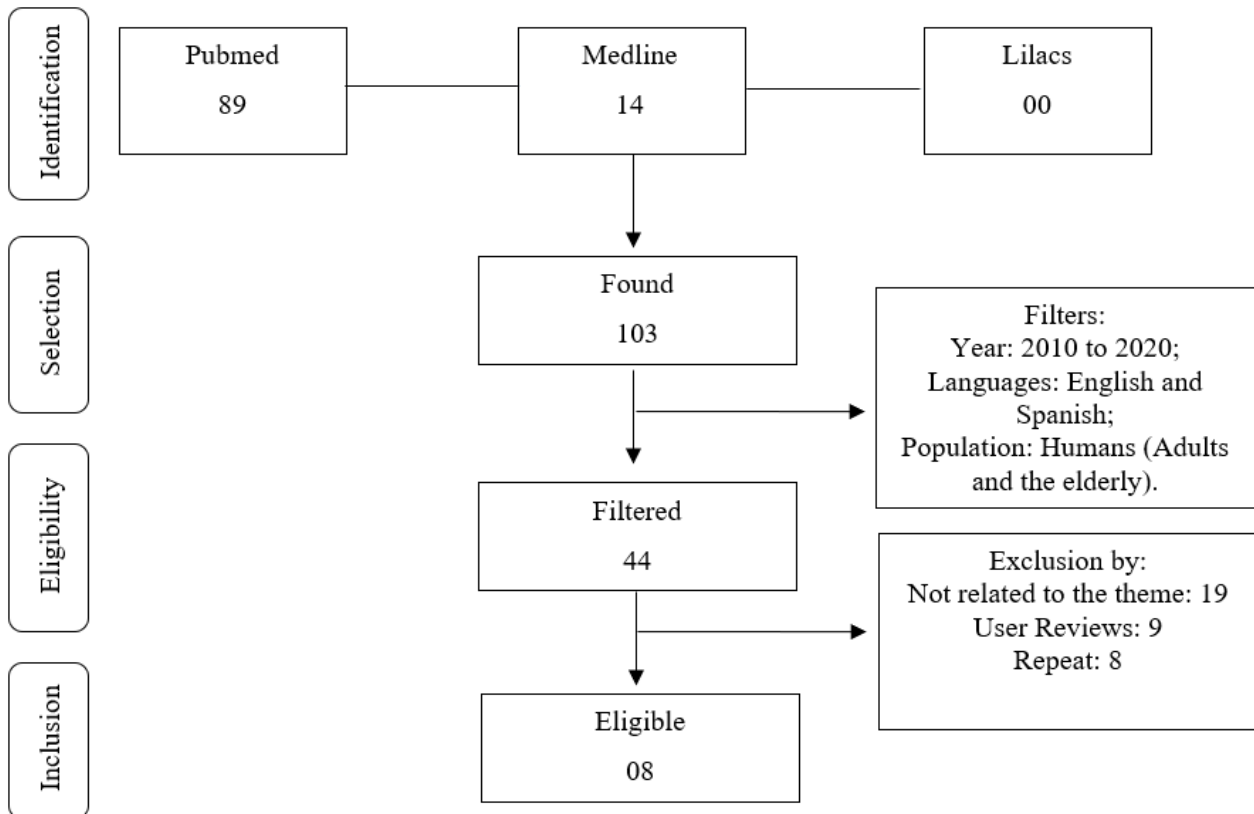
The administration of the EIN diet was performed in the preoperative, postoperative or perioperative period. Outcomes of interest (O): we evaluated the following outcomes: inflammatory cytokines, infectious and non-infectious complications, length of hospital stay or in the Intensive Care Unit (ICU), adverse events and mortality. Study design (S): only RCTs with or without blind method were considered.

## RESULTS

The electronic search resulted in 103 articles, found with the same descriptors, from the different search banks used, of which 59 articles were discarded after using filters related to the period, language and

population, which resulted in 44 articles. Of these, 8 studies were eligible for review and 36 studies were excluded after applying exclusion criteria. The final selection occurred by reading and analyzing the abstracts of the articles, the steps for selecting the articles can be seen in the flowchart (**Figure 1**).

**Figure 1** - Flowchart of the details of the search for articles for integrative review.



**Fonte:** Araripe TSO, et al., 2022.

The selected articles are 100% in English. The period of publication of the articles varied from 2012 to 2019. **Table 1** presents general data on the content of the articles under research, which are analyzed and discussed.

After reading and analyzing the articles, it was observed that all the studies found are in humans, among the outcomes of immunomodulatory enteral nutrition compared to standard enteral nutrition, changes in inflammatory cytokines, postoperative complications, infectious and non-infectious complications, time of hospital stay or in the Intensive Care Unit, adverse events and mortality.

Regarding the characterization of the studies, the research shows high-impact designs, as they are categorized in experimental studies, randomized clinical trials, using human models, investigating the effectiveness of immunomodulatory enteral nutrition. Most of the studies were conducted with individuals of both sexes. The sample size was quite variable, ranging from 34 to 305 participants. Canand follow, it will be Description of the articles selected for review (**Table 1**).

**Table 1 - Description of the articles selected for review.**

Authors e Year	Title	Objective	Results / Conclusion
MA C, et al., (2018).	Combination of arginine, glutamine, and omega-3 fatty acid supplements for perioperative enteral nutrition in surgical patients with gastric adenocarcinoma or gastrointestinal stromal tumor (GIST): A prospective, randomized, double-blind study.	To determine whether an enteral diet with immunomodulatory nutrients can improve nutritional status and reduce postoperative infection and surgery-induced immune suppression in patients with gastric cancer undergoing major surgery.	There were no significant differences between the two groups in laboratory and inflammatory parameters, before and after treatment. AEs and clinical results, including infectious complications, general complications, time to first bowel action and length of hospital stay after surgery, were comparable between treatment groups. That is, patients with NIS had no prominent immunomodulation effect compared to that of SEN.
KANEKIYO S, et al., (2019).	Efficacy of perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy	To investigate the effects of perioperative immunonutritional support on postoperative evolution and long-term survival in patients with esophageal cancer.	Retinol-binding protein levels were significantly higher in the postoperative period (POD). Postoperative infectious complications were significantly lower in the GI group. There was no significant difference in the postoperative ICU or postoperative hospital stay between the two groups. Progression-free survival rates of 5 years and overall survival rates were not significant. Perioperative immunonutrition can improve early postoperative nutritional status and reduce postoperative infectious complications in patients with esophageal cancer undergoing esophagectomy.
MUDGE LA, et al., (2018).	Multicentre factorial randomized clinical trial of perioperative immunonutrition versus standard nutrition for patients undergoing surgical resection of oesophageal cancer.	To compare the effect of the combination of preoperative and postoperative immunonutrition versus standard nutrition on the rate of infectious and non-infectious complications, duration of ICU and hospital stay, mortality and quality of life and nutrition (QoL) and outcomes in patients undergoing esophagectomy for cancer resection.	The incidence of infectious complications was similar for all groups. There were no significant differences in any other clinical or quality of life results. That is, the use of immunonutrition before and / or after surgery did not provide any benefit over standard nutrition in patients undergoing esophagectomy.
LIU H, et al., (2012).	Clinical application of immune-enhanced enteral nutrition in patients with advanced gastric cancer after total gastrectomy.	Determine whether immune enteral nutrition was effective on nutritional status, immune function, surgical results and days of hospitalization after total gastrectomy for patients with advanced gastric cancer (AGC).	The EIN and SEN groups showed a faster onset of flatus and shorter hospital stay than the control group. On the 12th postoperative day, serum levels of total protein, albumin, proalbumin and transferrin in the EIN and SEN groups were significantly higher than those in the control group. The levels of CD4 <sup>+</sup> T cells, NK cells, IgM and IgG of

Authors e Year	Title	Objective	Results / Conclusion
			the EIN group increased prominently and were significantly higher than those before the operation, as well as those in the SEN and control groups. EIN can improve the nutritional status and immune function of patients with AGC after total gastrectomy.
MARANO L, et al., (2013).	Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study.	To evaluate the impact of early postoperative enteral immunonutrition on clinical and immunological outcomes in a homogeneous group of patients with gastric cancer undergoing total gastrectomy.	The incidence of postoperative infectious complications in the EIN group was significantly lower than in the control group, as well as the rate of anastomotic leak. The mortality rate did not show any significant differences; patients in the EIN group had a significantly shorter hospital stay ( $12.7 \pm 2.3$ days) when compared to the standard diet group ( $15.9 \pm 3.4$ days). Cellular immunity data showed that postoperative CD4 (+) T cell counts decreased in both groups, but the reduction in the EIN group was significantly greater. Early postoperative enteral immunonutrition significantly improves clinical and immunological outcomes in patients undergoing gastrectomy for gastric cancer.
FUJITANI K, et al., (2012).	Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer.	To evaluate the clinical effects of preoperative enteral immunonutrition in well-nourished patients with gastric cancer undergoing total gastrectomy.	Preoperative immunonutrition significantly decreased the risk of SSI in patients who had at least 5 percent preoperative weight loss in the 3 months prior to surgery. There was no significant difference between infectious complications, postoperative morbidity, CRP value. Preoperative enteral immunonutrition showed no clear advantage in terms of initial clinical results or modification of the systemic response of the acute phase in well-nourished patients with gastric cancer undergoing elective total gastrectomy.
SCISLO L, et al., (2018).	The Impact of Postoperative Enteral Immunonutrition on Postoperative Complications and Survival in Gastric Cancer Patients - Randomized Clinical Trial.	To evaluate the impact of postoperative immunomodulatory enteral nutrition on postoperative complications and on the survival of patients with gastric cancer.	General postoperative morbidity did not differ between groups. The rate of pulmonary complications (excluding pneumonia) was significantly lower in the immunomodulation group, as well as mortality at 60 days. There was no difference in survival at 6 months and 1 year between groups.

Fonte: Araripe TSO, et al., 2022.

## DISCUSSION

### Relationship of enteral immunomodulation with nutritional status in gastrointestinal (GIT) surgical cancer patients

The impairment of nutritional status is common in cancers of the gastrointestinal tract, where the prevalence of malnutrition varies from 20% to 70% (ARENDS J, et al., 2017; WEIMANN A, et al., 2017). Malnutrition negatively impacts the host's immune response and the tissue healing process and is a factor of risk for postoperative complications (GARTH AK, et al., 2010). In cancers of the gastrointestinal tract the prevalence of malnutrition varies from 20% to 70% (ARENDS J, et al., 2017; WEIMANN A, et al., 2017). Malnutrition negatively impacts the host's immune response and the tissue healing process and is a factor of risk for postoperative complications (GARTH AK, et al., 2010).

Patients with gastric cancer randomized to a standard enteral and immunomodulatory diet group had similar mean of body mass index (BMI) values before the gastrectomy procedure, with a classification for eutrophy. Patients in both groups showed a significant reduction in the average BMI after the surgical procedure, for the immunomodulatory group it was before surgery with a BMI of 24.21 kg / m<sup>2</sup> and after surgery 23.15 kg / m<sup>2</sup>, whereas the control group before the surgery had a BMI of 23.03 kg / m<sup>2</sup> and after the surgery 22.2 kg / m<sup>2</sup> (MA C, et al., 2018).

Contributing, the European Society for Clinical Nutrition and Metabolism (2017), recommends that peri or at least post-operative administration with formulas containing immunomodulatory nutrients should be administered to malnourished patients (ASPEN, 2002; WEIMANN A, et al., 2006).

### Protocols for the use of immunomodulatory supplements in surgical oncology patients of the GIT

Immunomodulatory enteral nutrition enriched with some nutrients (Argine,  $\omega$ -3-FA, Glutamine and RNA) has been recommended to manage the postoperative clinical status since 1990 (WALKER WA, 2012). Several randomized clinical trials (RCTs) have been carried out to investigate the comparative effects of EIN versus SEN in patients undergoing elective abdominal surgery (MA C, et al., 2018; KANEKIYO S, et al., 2019; SCISLO L, et al. 2018; FRUCHTENICHT SLMM, et al., 2018).

The 2006 European Enteral and Parenteral Nutrition Society Enteral Nutrition Guidelines provide a grade A recommendation for preoperative immunonutrition in patients with elective gastrointestinal surgery (WEIMANN A, et al., 2006). There are currently no evidence-based recommendations for the duration of administration or dosage. Most studies administered 500-1000 mL / day of EIN for 5-7 days preoperatively (CERANTOLA Y, et al., 2011).

The articles in this review address similar protocols with pre- and postoperative immunonutrition supply. In the study by Ma C, et al. (2018) patients received 3–5 days before surgery for gastric adenocarcinoma, 400 mL / day (400 kcal / day) from the standard or immunomodulatory diet. On the third postoperative day, enteral nutrition (EN) was started (20 mL / h) of the immunomodulatory or standard diet, on the 4th day they received a semi-liquid diet plus 400 mL / day (400 kcal / day), from days 5 to 14 postoperatively, received 1200 mL / day (1200 kcal / day) and a pasty oral diet.

When evaluating the effectiveness of perioperative immunonutrition in patients undergoing esophagectomy for esophageal cancer. Patients were randomly assigned to receive EIN with IMPACT (n = 20), (1 kcal / mL with 5.6 g / 100 mL of protein) supplemented with arginine (12.8 g / L), w-3 (4, 1 g / L) and RNA (1.29 g / L) or SEN (n = 20), (1.5 kcal / mL with 6.25 g / 100 mL of protein) without immunonutrients. Patients received EN for 7 days before and after surgery. The diet was started at 10 kcal / h and increased gradually each day (KANEKIYO S, et al., 2019).

In the study by Mudge LA, et al. (2018) in patients undergoing esophagectomy. Started feeding on the first postoperative day, with 40 ml / h of their enteral formula designated for 24 hours. The diet was increased in increments of 20 ml / h every 24 h until 100 percent of the expected energy and protein needs were met. The patients were fed with immunonutrition, IMPACT® or an isocaloric / isonitrogen control. They were fed for 7 days after surgery.

Furthermore, in relation to the offer of an immunomodulatory diet only in the postoperative period, it was seen in patients with gastric cancer with a proposal for total gastrectomy that in the groups it was administered 6-48 hours postoperatively for 7 days of standard enteral or immunomodulatory diet. In the study by Liu H et al. (2012), 30 patients in the standard diet group received 500 mL per bottle (20.0 g total protein, 9.5 g fat, 61.5 g carbohydrate, 500 kcal total energy - Nutrison Fiber). The immune group (EN + Gln) patients received the same nutritional product, but enriched with Gln (12.5 g / L) and arginine (9.0 g / L). In the study by Marano L, et al. (2013), a standard enteral diet (Jevity 1 Cal) or immunomodulatory (Impact®) (formulas with 1 kcal / 1 mL) was administered. Post-operative jejunostomy nutrition started with an infusion of 10 mL / h with an increasing rate of 10 mL / h every 12 h, until the maximum feeding rate of 80 mL / h was reached corresponding to the individual of 35 kcal / kg / day.

### **Post-surgical outcomes with the use of immunomodulatory supplements in oncology surgical patients of the GIT**

When assessing the administration of enteral diet in the perioperative period of cancer patients with gastric cancer randomized to receive a standard or immunomodulatory diet (with arginine, omega-3 fatty acids and RNA), it was seen that in relation to adverse events (AEs) there was no significant difference between groups, with only diarrhea being observed in both groups, that is, the offer of perioperative enteral diet is viable and well tolerated (LIU H, et al., 2012; MA C, et al. 2018).

In terms of mortality in patients with gastric or esophageal cancer, receiving perioperative immunomodulatory or standard enteral diet, no deaths were counted and there was no significant difference in the mortality rate between the groups (MA C, et al., 2018; MUDGE LA, et al., 2018; KANEKIYO S, et al., 2019; FUJITANI K, et al., 2012; MARANO L, et al., 2012). Already Scislo L, et al. (2018) observed that all deaths occurred in the standard group. Thus, immunomodulatory nutrition reduced postoperative mortality.

The infectious complications observed were sepsis and intra-abdominal abscess in the control group and no infectious complications developed in the immunomodulator group (MA C, et al., 2018).

When administering perioperative or standard immunonutrition enteral diet in patients undergoing esophagectomy for esophageal cancer. It was assessed that there were no significant differences in operating time, operative blood loss and extubation. However, the number of patients with infectious complications (including pneumonia or surgical site infection) who received therapeutic antibiotics was significantly less in the Impact group (IG) than in the Ensure group (EG). The duration of antibiotic use after surgery was significantly shorter in the IG group ( $p = 0.021$ ) (KANEKIYO S, et al., 2019).

Postoperative immunomodulatory enteral nutrition helped to reduce the duration of the systemic inflammatory response syndrome (SIRS) in the immunomodulatory group ( $1.1 \pm 0.89$  days), as it was significantly lower than in the standard group ( $2.2 \pm 1.02$  days,  $p = 0.036$ ). The incidence of infectious complications and the rate of anastomosis leakage were statistically significantly reduced in the immunoenriched diet group. In the "late postoperative period" a lower rate of complications was recorded in the immunoenriched diet group compared to the standard enteral nutrition diet group (1.8 vs 14.5%,  $p = 0.021$ ) (MARANO L, et al., 2013; SCISLO L, et al., 2018; LIU H, et al., 2012).

There were no significant differences in the length of postoperative hospital stay between the two groups (MA C, et al., 2018; KANEKIYO S, et al., 2019; FUJITANI K, et al., 2012). Likewise, there was no significant difference in the length of stay in the Intensive Care Unit (ICU) (MUDGE LA, et al., 2018). In antagonism, the patients in the group immunomodulators had a significantly shorter hospital stay ( $12.7 \pm 2.3$  days) compared to the standard group ( $15.9 \pm 3.4$  days,  $p = 0.029$ ) (MARANO L, et al., 2013).

Administration of an enteral nutrition formula supplemented with arginine, omega-3 fatty acids and RNA in the initial postoperative period for patients undergoing total gastrectomy for gastric neoplasia significantly improves clinical results, as evidenced by a substantial reduction in healing failures of anastomosis and in postoperative infections, improving cellular immunity (MARANO L, et al., 2013).

Immunomodulatory nutrients have less immunomodulatory effects than expected in gastric cancer patients undergoing elective surgery, where inflammation may be only mild compared to critically ill patients



(MA C, et al., 2018). There is insufficient clinical evidence for the use of immunonutrition in patients with esophageal cancer undergoing elective surgery. Other randomized clinical trials with larger samples are needed to allow the metabolic advantages of this enriched enteral diet to be translated into better results (KANEKIYO S, et al., 2019).

Immunonutrition offers no additional benefits over standard nutrition in patients undergoing esophagectomy for esophageal cancer resection. Research results do not support immunonutrition as a standard for routine treatment in patients undergoing esophagectomy. Currently, there is no evidence of level I or II to support the routine use of immunonutrition in patients before and / or after esophageal cancer surgery (MUDGE LA, et al., 2018).

### **Biochemical tests and use of immunomodulatory supplements in surgical oncology patients of the GIT**

Some studies applied in the methodology the use of laboratory, inflammatory parameters and mediators of systemic immunity, such as blood count, total lymphocyte count, leukocytes, interleukin (IL-6) and tumor necrosis factor alpha (TNF- $\alpha$ ), among others. As a result, they were able to make associations regarding the use of diets supplemented with immunomodulatory nutrients and find results regarding the favorable modulation of the inflammatory response and increased systemic immunity in patients undergoing gastrointestinal tract surgery (MA C, et al., 2018; FUJITANI K, et al., 2021; MARANO L, et al., 2013; LIU H, et al., 2012; HAMZA N, et al., 2015).

Biochemical examinations complement the diagnosis of nutritional status and assist in the specific identification of clinical situations of individuals, contributing to the diagnosis of patients at high nutritional risk (INCA 2016; MARANO L, et al., 2013; HAMZA N, et al., 2015; FRUCHTENICHT SLMM, et al., 2018).

Gastric cancer, a major surgery, has high rates of inflammatory potential, leading the patient to intense catabolism, malnutrition states and preoperative nutritional deficits, causing them to sometimes reach the surgical procedure very depleted of immune reserves. Therefore, an intense nutritional supply is necessary (REIS PF, et al., 2018). In this situation, Ma C, et al. (2018) during their research with the use of immunomodulatory nutrients, sought answers if these nutrients could modulate the immune and inflammatory response of individuals undergoing elective gastric curative surgery.

In contrast, other researchers studied exclusively patients who underwent total gastrectomy surgery, and who had enteral nutrition supplemented with glutamine and arginine compared to a control group without supplementation. Good tolerance to the offered formulas resulted in positive results for the improvement of the nutritional status and modulation of the immune function, bringing as conclusions that the used nutrients can allow a more accelerated recovery of the intestine, the immune system and the protein synthesis (LIU H, et al., 2012).

Patients undergoing pancreaticoduodenectomy surgery were supplemented pre- and postoperatively with immunomodulatory formulas or not and had factors such as IL-1 $\alpha$ , TNF  $\alpha$  and subsets of lymphocytes analyzed. The authors realized that immunomodulatory nutritional therapy was favorable to decrease the values of TNF  $\alpha$  and increase the total lymphocyte count on the 3rd postoperative day and also on the relationship between CD4/ CD8 lymphocyte from the 3rd to the 7th day after -operative compared to patients fed standard substrates. Corroborating that in this group and period of patients, immunonutrients were essential for a better response to the surgical procedure (HAMZA N, et al., 2015).

Marano L, et al. (2013) studied the efficacy of enteral immunonutrition (arginine, omega-3 fatty acids and RNA) early postoperatively in patients undergoing total gastrectomy surgery. They found, when evaluating data related to cellular immunity, such as CD4 T cell count, it was decreased both in the supplemented and in the control group, and in the supplementing group, higher values with a significance level of  $p = 0.032$ . In other parameters evaluated as total leukocytes, CD8 lymphocytes, no significant changes were found. Thus suggesting, despite the benefits found, the need for more clinical trials to be carried out to confirm these findings.

## FINAL CONSIDERATIONS

In view of the analysis of the articles, it was observed that enteral immunonutrition is well tolerated and has been widely used during nutritional support in the perioperative period of patients with cancer in the GIT. Despite its beneficial effects, immunonutrition does not yet have significant effects on reducing the mortality rate and length of hospital stay. Although there is a tendency to reduce infectious and non-infectious complications when using perioperative immunomodulatory enteral diet in GIT surgeries, in most studies there was no significant difference between groups. In addition, the previous nutritional status interferes with the clinical outcome and the precociousness of nutritional therapy, whether immunomodulatory or not, is effective for surgical preparation and its associated outcomes. As for biochemical tests and modulation of the immune response, the results are controversial and are clearer and favorable to the use of immunonutrition when specifying the site and type of surgery. Therefore, it is necessary to carry out more randomized and controlled studies regarding the action of immunomodulators in neoplasms, so that they bring more evidence regarding the effects of immunonutrients in abdominal cancer patients.

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