

Review Article

Pre-operative immunomodulatory nutrition and post-operative outcomes of surgical treatment of gastrointestinal surgery: a systematic review

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ABSTRACT

Malnutrition is a major health problem in cancer evident in up to 80% of patients. It was associated with high mortality and morbidity, especially with surgical treatment of cancer. That is why many studies are investigating efficient treatment for this problem. One of these treatments is immunomodulatory nutrition. Immunomodulatory nutrition has shown efficacy towards malnutrition, immune status, and other comorbidities. However, there is still a debate about whether it is efficient or not. Five databases were searched using specific search terms. We only included randomized controlled trials that studied the efficacy of preoperative immunomodulatory nutrition before surgical treatment of gastrointestinal carcinoma. The studies were assessed for the quality of evidence. Twenty-three studies were included for the systematic review. Most studies had a low risk of bias. We assessed the efficacy of immunomodulatory nutrition regarding immune markers, infectious complications, non-infectious complications, biological markers, the length of stay, and mortality. Immunomodulatory nutrition has significantly enhanced immune status, biological markers, and post-operative complications. However, it does not have a significant improvement in the mortality rate or hospitalization duration. The immunomodulatory nutrition has promising results in enhancing immune status, and biological markers. However, its effect on post-operative infectious and non-infectious complications is still under debate. Immunomodulatory nutrition had no effect on mortality rates among cancer patients.

Keywords: Malnutrition, Immunomodulatory nutrition, Gastrointestinal tumors, Gastric cancer, Colorectal carcinoma, Glutamine, Arginine, Omega-3

INTRODUCTION

Malnutrition is a well-evident phenomenon in cancer patients, specifically gastrointestinal cancers.¹ It is also associated with an undeniable high risk of morbidity and mortality. The overall incidence of malnutrition in cancer patients is 40 to 80%, 20% of them die due to malnutrition-related causes.²⁻⁴

The cause of malnutrition in cancer patients is multifactorial. Treatment modality largely influences the nutritional status of the patients. The prevalence of malnutrition differs among different groups of patients of the same type of cancer-based on their treatment modality. This is mainly due to side effects related to the treatment including nausea, vomiting, diarrhea, stress esophagitis, stress gastritis, and dysphagia.²⁻⁴

The type of cancer is also a determining cause of malnutrition. A study found that the highest prevalence of malnutrition was in pancreatic cancer (85%) followed by stomach (65-85%).² The high prevalence in gastrointestinal tumors is also caused by the tumor itself rather than the other factors; the gastrointestinal tumors interfere with the eating process.^{1,2}

Malnutrition in the gastrointestinal tumor was associated with decreased quality of life, increased resistance to treatment, increased risk of toxicity from chemotherapy, high morbidity, and mortality rates.^{3,5-7} Malnutrition also affects immunity against tumors causing a decreased immune response to mitogens, dysfunction of phagocytes, cell-mediated immunity, decreased cytotoxic T-cell activity, and impaired inflammatory response.⁸

Moreover, malnutrition was associated with decreased wound healing and increased postoperative complications. It is mainly due to an increased catabolic process after surgical treatment. That was evident in many studies that found that malnutrition was associated with worse outcomes after surgical treatment.⁹ That is why the concept of immunomodulatory nutrition has gained worldwide recognition recently.

Immunomodulatory nutrition is specific nutrition containing nutrition components that increase the immunity of cancer patients.^{8,10} It acts through modulation of immune cells and inflammatory response increasing the healing power after surgery.^{4,7,8,10} Despite no specific determination of the ingredients of the immunomodulatory nutritional diet, it is usually composed of omega-3, arginine, glutamine, and nucleotides.¹⁰

Other constituents that may be added or not are vitamin C, E, selenium, or beta carotene.¹⁰ The choice of Arginine among other amino acids is mainly due to its effect on wound healing and growth. The nucleotides are essential as usual diet would be deficient in essential nucleotide components for the salvage pathway of nucleotide

synthesis. This addition enhanced the production of IL-2 and increased T-cell response.^{3,8,10} Based on animal studies, the effect of immunomodulatory nutrition is only evident when it is given three days before the surgery.¹¹ Furthermore, to obtain the full effect, it should be administered up to five days post-operative.¹¹

The effect of immunomodulatory nutrition on the postoperative outcome is still under debate. More research is needed to understand its effect and whether it should be recommended or not for preoperative preparation of gastrointestinal tumors surgery.

METHODS

Database search

A comprehensive search approach was used to identify randomized controlled trials from five databases PubMed, Google Scholar, SCOPUS, ISI web of science, and Cochrane Collaboration. The keywords used were ('pre-operative' or 'pre-op' or 'peri-operative') and ('immunomodulatory nutrition' or 'pharmaconutrition' or 'immune nutrients' or 'immune modulating nutrients' or 'dietary supplements' or 'oral supplement' or 'enteral nutrition' or 'nutritional support' or 'arginine' or 'omega-3 fatty acid' or 'glutamine' or 'enteric feeding' or 'diet therapy' or 'nutrition feed' or 'nutrition disorders') and ('gastrointestinal surgery' or 'surgeries' or 'post-operative'). We restricted our search to human studies.

Inclusion and exclusion criteria for screening

Specific inclusion criteria were used to identify high quality and studies that fulfill the goals of this study. Inclusion criteria were (i) randomized controlled studies that assess the efficacy of pre-operative immune modulating nutrition on mortality rates of patients; (ii) all enrolled patients should be aged 18 years or more undergoing gastrointestinal surgery.

We excluded any studies that assessed the efficacy of pre-operative immune modulating nutrition against diet with supplements. The pre-operative immune modulating nutrition includes combinations of arginine, glutamine, ω -3 fatty acids, and nucleotides provided as part of oral supplementation or enteral nutrition and should be given pre-operatively at least three days before surgery to be fully effective.

Books, review articles, letters to the editor, editorial reports, case reports, and conference abstracts and duplicates were excluded.

Screening for studies

The retrieved studies from each database were screened based on inclusion and exclusion criteria. First, title/abstract screening was conducted by three

independent reviewers. The included studies were then screened thoroughly to make sure it fulfills the target of this review. Each study was reviewed thoroughly to extract and build a qualitative review.

Quality assessment of the included papers

The quality of included studies was evaluated by three reviewers using 'The Cochrane Collaboration's tool for assessing the risk of bias'.¹² It has seven specific domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.²⁷ The answers were categorized as 'low risk,' 'high risk,' or 'unclear risk' of bias.

RESULTS

Search results and risk of bias

The search performed on five databases yielded 2582 studies, of which only 23 fulfilled the inclusion criteria and were used for qualitative evidence synthesis (Figure 1).

Nine studies have a low risk of bias, six studies had a high risk of bias, and the remaining studies had high risk in some domains Figure 2. Most studies had high risk in the allocation domains Figure 2. Only three studies had an unknown bias in the first domain.¹³⁻¹⁵

Patient characteristics

Two studies investigated the effect of immunomodulatory diet in esophageal carcinoma, three studies for gastric cancer, five studies for colorectal carcinoma, two studies for pancreatic cancer and liver cancer.^{13-18,20-24,26} The remaining studies had non-specific gastrointestinal tumors (Table 1). The patients' age ranged from 55 to 65 years old. There were only eleven studies that assessed the malnutrition status of the patients preoperative. All studies administered the treatment seven days before the surgery except thirteen studies.^{13-15,19,22-24,26-31}

Efficacy of pre-operative immune-modulating nutrition in patients undergoing surgery for gastrointestinal cancer

Immune markers

Many studies measured the efficacy of immunomodulatory nutrition on the immune status of the patients. There were no unified immune markers, and each study used specific markers. Aida et al measured the immune response by measuring the rate of Th1/Th2 differentiation.¹⁴ It was measured through the measurement of the expression level of the mRNA of T-bet. T-bet is a T-box protein expressed in T cells; it has a modulatory effect for enhancing the development of T-

cells.³² In addition, it modulates the action of IL-2 and Th-2 cytokines.³²

In this study, they found that T-bet expression was increased in the immunomodulatory groups indicating enhancement of the immune response.¹⁴ Moreover, they measured the PGE2, which was significantly lower in the treatment group indicating a less inflammatory response. PGE2 is one of the proinflammatory cytokines and has an important role in T helper cell differentiation. It is synthesized from arachidonic acid, which is found to be inhibited by the action of the immunomodulatory diet.³³

Another study found that in contrast to the control group, the treatment group has significantly higher polymorphonuclear cells phagocytic capability indicating higher innate immunity. Furthermore, IL-6 was significantly less in the treatment group and returned to normal earlier than the control group. They also measured the delayed hyperimmune response and found it less in the treatment group.^{24,34}

Ding et al measured the immune response in the form of the level of IgG, IgA, CD4+T cell/ CD8+T cell, which is significantly increased in the treatment group. They also assessed the IL-6 level in the treatment group and was significantly decreased; it also rapidly decreased back to normal than the control group.¹⁸ Gade et al discovered significantly less TNF-alpha postoperative indicating the immunomodulatory effect of the diet. In the same context, Huang et al found significantly higher immune markers e.g. lymphocytes, CD3, CD4, CD8, and natural killer cells in the treatment group.³⁵

Nakamura et al measured the level of polymorphonuclear leukocyte-elastase and interleukin-8 and found a significant decrease in the treatment group. They also found a decrease in inflammatory markers and downregulation of cytokine receptors in the treatment group.³¹ These results are consistent with Okamoto et al and Migaki et al who also proved that there was decreased inflammatory markers in treatment group.^{20,26}

On the contrary, Russel et al found no significant change of the white cell count and total lymphocytes or markers of inflammation like C-reactive protein, tumor necrosis factor- α , IL-8, and IL-10.¹³ Other studies measured CRP as an indication of the inflammatory status of the patients. Fujitani et al found no significant difference in CRP.

Meanwhile, Gade et al found that there was a significant decrease of endotoxin and CRP in the treatment group implying better immune response. Xu et al also proved that cellular immunity was activated in the immunomodulatory nutrition group as evidenced by an increased CD4/CD8 ratio in the treatment group.

In addition, they found decreased complement 3, complement 4 in the treatment group indicating decreased inflammatory conditions.³⁶ Post-operative

immunoglobulin G (IgG) was significantly higher in the treatment group.

Infectious complications

Infectious complications are very common after gastrointestinal surgery. Four studies found there was a decrease in the number of wound abscess, peritoneal abscess, sepsis, enteritis, and pneumonia in the treatment group.

However, it was non-significant.^{14,19,22,25} Notwithstanding, subgroup analysis in Campillo et al found that patients with rectal cancer have a significantly lesser infectious rate in the immunomodulatory nutritional diet. Two studies showed that both treatment and control groups had the same rate of infectious complications.^{17,27} In contrast to the previous finding, Horie et al and Moriya et al implied that it only significantly decreased surgical site infections, specifically superficial incisional surgical site infections.^{15,23} In addition, four studies found that there was a significant decrease in infectious complications, including sepsis, abdominal abscess, and enteritis. It also decreased the dosage and duration of antibiotics.^{16,24,30,36} Okamoto et al proved also that there is not only decreased the risk of infectious diseases, but also the duration of the infections.²⁰

Non-infectious complications

Non-infectious complications were assessed in many studies. The non-infectious complications comprise a wide range of diseases. It was defined clearly in Xu et al, and we explained it in Table 2. Other reported non-infectious complications included pancreatic fistula, delayed gastric emptying, chylous ascites, intra-abdominal bleeding, sterile pancreatic fistula, presacral sterile hematoma, heart failure, myocardial infarction, pulmonary embolism, pleural effusion, transient renal failure, anastomotic rectal bleeding, delayed gastric emptying, anastomotic insufficiency, and aspiration/ARDS.

Most studies revealed that these complications were not decreased in the treatment group and were approximately the same as the standard care group. On the contrary, Braga et al reported a significantly less anastomotic leak in the treatment group.^{24,34} In addition, Gade et al found that there was significant weight gain in the treatment group.²⁵ Another study found that there was a higher rate of diarrhea in the control group.³⁵

However, three studies found that post-operative non-infectious complications decreased in the treatment group more than the control group, yet non-significant decrease.^{17,23,26} Xu et al found that there was a significantly higher weight loss in the control group than the treatment group. Furthermore, the incidence of stoma fistula was significantly decreased in the treatment group.³⁶

Length of stay

Most studies did not find any significant difference between the immunomodulatory nutrition group and the control group, which was explained by the non-significant difference of infectious and non-infectious complications between the two groups.

However, five studies found that the group that received a preoperative immunomodulatory diet had a significantly less post-operative length of stay.^{22,24,25,30,34} These five studies showed significantly better outcomes in the treatment groups, which may explain their significant beneficial effect of the immunomodulatory diet on the length of stay. Notwithstanding, more investigations are needed to understand the difference in these results.

Biochemical markers

Some studies measured different biochemical markers for more accurate identification of the efficacy of the immunomodulatory diet. Aida et al. measured the serum eicosapentaenoic acid and eicosapentaenoic acid/arachidonic acid ratios and found it was significantly higher in the treatment group.¹⁴ This corresponds to findings by Russel et al, who found the plasma ratio of (eicosapentaenoic acid plus docosahexaenoic acid) to arachidonic acid was higher in the immunomodulatory group. Ding et al found a significant increase in pre-albumin and albumin in the treatment group compared to the control group indicating better nutritional value status.¹⁸ However, they did not find a significant difference between the treatment and control group regarding blood sugar, hepatic and renal functions, and electrolytes.

Similarly, Okamoto et al measured the serum concentrations of prealbumin, and transferrin, albumin, choline-esterase, and total cholesterol did not show any significant differences.²⁰ On the contrary, Huang et al found that liver enzymes returned to normal rapidly compared to control.³⁵ Another biochemical process that was measured was protein turn-over. Two studies measured retinol-binding protein as an example of rapid protein turnover.^{16,31} It was higher in the treatment group indicating rapid protein turnover. This phenomenon was not explained and why it happened in treatment groups. Seven days after the surgery, Xu et al found that there was increased prealbumin and transferrin in the treatment group.³⁶

Gastrointestinal microperfusion

Braga et al measured intra-operative colonic microperfusion and found that treatment groups who received pre-operative or peri-operative immunomodulatory diet had significantly better microperfusion as also evidenced by higher O₂ tension. They considered this as a good sign for anastomotic leak healing.²⁴

Mortality

All studies assessed the death rate in the treatment group compared to the control group. There was no significant

difference between the treatment and control groups. There was also no significant difference between peri-operative and pre-operative treatment.

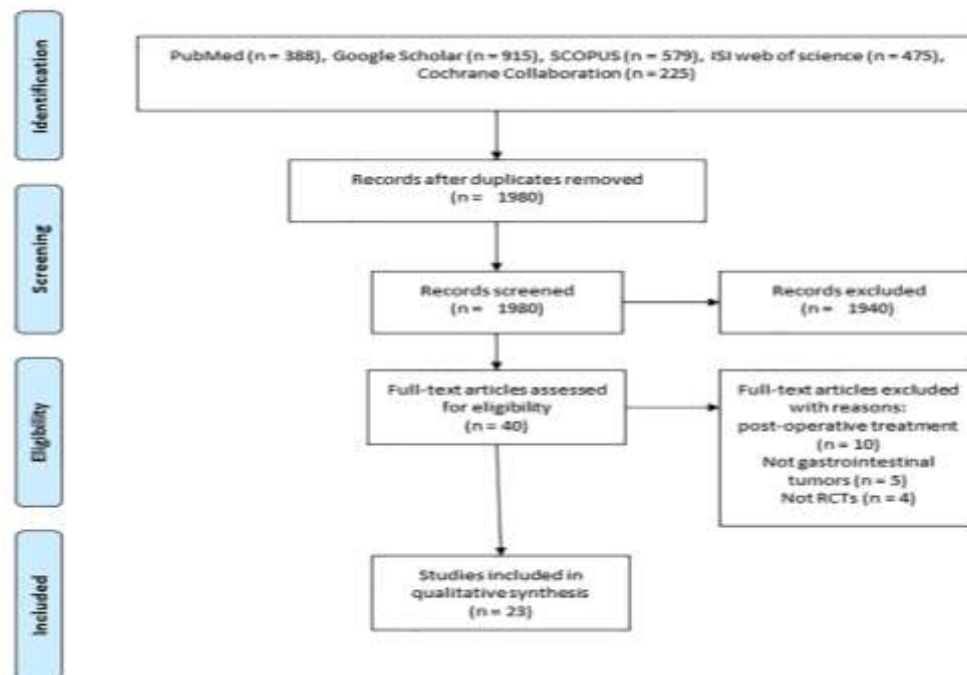


Figure 1: PRISMA flowchart of the search and screening process.

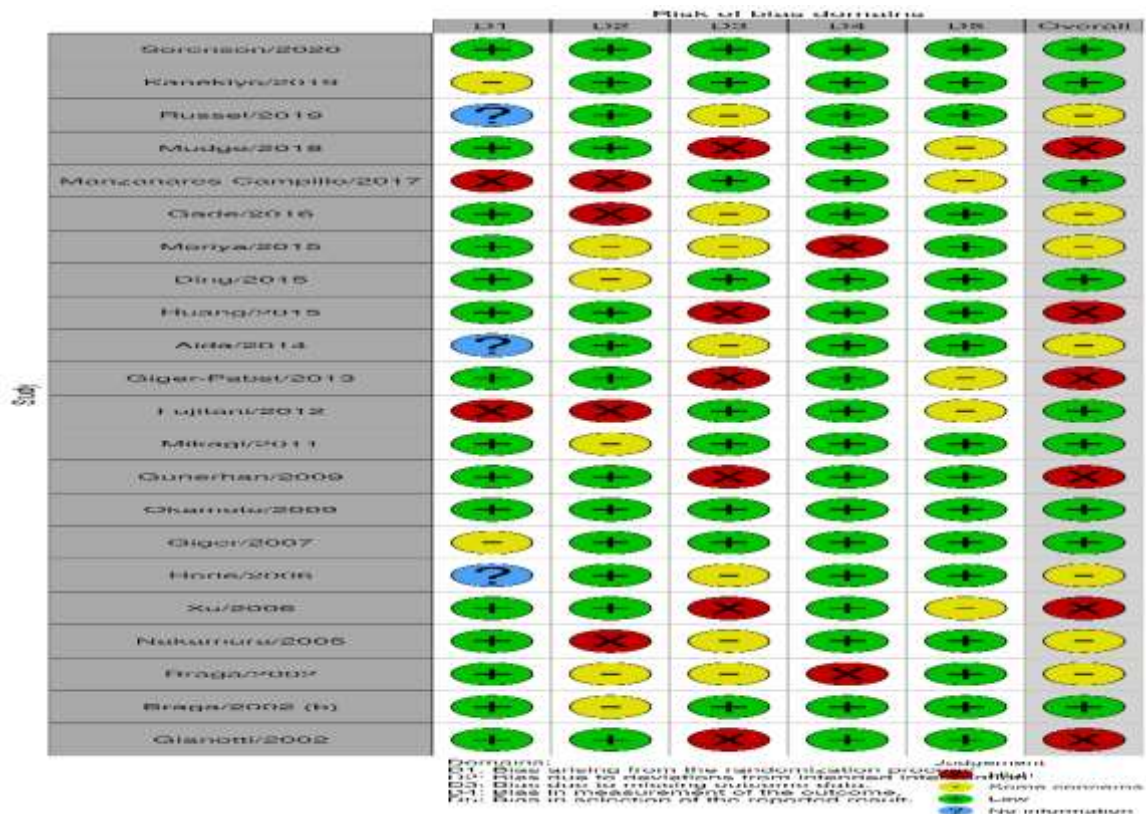


Figure 2: Quality assessment of the included studies.

Table 1: Characteristics table of included patients.

Study	Country	Age (mean)	Type of cancer	Days before surgery	Treatment arm (N)	Energy intake or dose	Control arm (N)	Reported outcomes	Mal nutrition incidence in patient
Sorensen et al ¹	UK	68.3 case 70.6 control	Colorectal cancer	7	isocaloric (1.5 kcal/ml) and isonitrogenous (Supportan®; Fresenius Kabi, Bad Homburg, Germany).	1.5 kcal/ml	The same but no omega-3	Mortality and disease recurrence	NA
Kanekiyo et al ²	Japan	65 case 62 control (median)	Esophageal cancer	7	IMPACT a liquid diet supplemented with arginine, omega-3, RNA (N=20)	1 kcal/ml with 5.6 g/100 ml protein	Standard EN with Ensure (N=20)	Operative time, blood loss, length of stay and mortality	Five patients
Russell et al ³	New Zealand	61 case 63 control (median)	Liver cancer	5	IMPACT Advanced Recovery® (Nestle)	1020 kcal/d	Standard care (Fortisip®, Nutricia)	Plasma phosphatidyl choline fatty acids, Immune and inflammatory markers, Nutritional and functional status, Infective complications, Noninfective complications, LOS, intensive care unit stay, mortality	NA
Mudge et al	Australia	64.6 case 62.5 control	Esophageal cancer	7	Oral impact (Novartis)	909 kcal/d	Standard care	Infective complications non-infective complications, LOS, intensive care unit stay, mortality	8% of patients were affected by malnutrition

Continued.

Study	Cou- n- try	Age (mean)	Type of cancer	Days befo- re surg- ery	Treatment arm (N)	Energy intake or dose	Control arm (N)	Reported outcomes	Mal nutrition incidence in patient
Campi- llo et al ³	Spa- in	50	Color- ectal cancer	8	Oral impact (Novartis, Espana)	1000 kcal/d	Standard care	Infectious complicati- ons minor and major complicati- ons, length of stay and cost	NA
Gade et al ⁶	Den mark	68 case 69 control (median)	Pancr- eatic cancer	7	Oral Impact (Nestle, Vevey)	1.5 g protein/k g body weight	Standard care	Post- operative complicati- ons LOS	NA
Moriya et al ⁷	Jap- an	61.6 case 63.5 control	Color- ectal cancer	5	Impact (Novartis Pharma, Tokyo)	Low: 250 ml/day High: 750 ml/day	Standard care	Surgical site infection, morbidity, LOS	NA
Ding et al ⁸	Chin a		Gastric cancer	7	Intact protein EN powders on the base of semi-liquid diets (Germany Milupa GmbH and Co.KG, model: 320 g/tank, each packet was prepared into a 500 ml solution with the energy density of 1 kcal/m)	1000 kcal/d	Standard care	Immune marker, clinical status and mortality	NA
Huang et al ⁹	Chi- na	66.7	Gastro- - intesti- nal cancer	7	Oral Peptisorb (Nutricia, Netherlands)	30 kcal/kg/d	Standard care	Immune marker, clinical status, biochemical parameters and mortality	NA
Aida et al ¹⁰	Japa n	66.4 case 65.1 control	Pancr- eatic cancer	5	Impact (Novartis Pharma, Tokyo)	1000 ml/d	Standard care	Infectious complicatio ns Immune responses	8%
Klek et al ¹¹	Pola nd	61.1	Gastro- - intesti- nal cancer	3	Reconvan (immunodiet)	150 kcal/ g	Standard care	Infectious and non- infectious complicati- ons	NA
Giger et al ¹²	Ger man	64.9 case 63.2	All gastro-	3	Impact (Novartis,	750 ml/day	Standard care	Rate of post- operative	0%

Continued.

Study	Cou- n- try	Age (mean)	Type of cancer	Days befo- re surg- ery	Treatment arm (N)	Energy intake or dose	Control arm (N)	Reported outcomes	Mal nutrition incidence in patient
	y	control	intesti- nal cancer		Bern)			complicatio ns infectious complicati- ons, non- infectious complicati- ons, LOS	
Fujita- ni et al ¹³	Japa n	64 case 65 control (median)	Gastric cancer	5	Oral Impact (Novartis Pharma, Tokyo)	1000 ml/day	Standard care	Surgical site infection Infection, morbidity, C-reactive protein	2.2%
Mikagi et al ¹⁴	Jap- an	67.5 case 61.5 control (median)	Liver cancer	5	Impact (Novartis Ajinomoto Pharma, Tokyo)	750 ml/d	Standard care	Indices of inflammator y reaction (interleukin- 6, white cell count) post- operative complicatio ns, length of stay	NA
Gune- rhan et al ¹⁵	Tur- key	64.5	All gastro- intesti- nal cancer	7	Impact (Novartis, Bern)	750 ml/d	Standard care	Nutritional parameters, blood markers (prealbumin, albumin, lymphocyte count) Infectious complicati- ons, non- infectious complicatio ns, LOS	1%
Okamo to et al ¹⁶	Jap- an	66.9	Gastric cancer	7	Impact (Novartis, Bern)	750 ml/d	NA	Immunologi cal and nutritional post- operative complicat- ions	NA
Giger et al ¹⁷	Ge- rma- ny	60.1	Upper gastro- intesti- nal tumor	5	Immune- enriched formula (Impact)	750 ml/day	Standard care	Surgical site infection post- operative inflammati- on and nutrition	NA

Continued.

Study	Cou- n- try	Age (mean)	Type of cancer	Days befo- re surg- ery	Treatment arm (N)	Energy intake or dose	Control arm (N)	Reported outcomes	Mal nutrition incidence in patient
Horie et al ¹⁸	Jap- an	69 case 63 control	Colo- rectal cancer	6	IMPACT Japanese version (Ajinomoto, Tokyo, Japan)	1000 ml/day	Standard care	Surgical site infection post- operative inflammati- on and nutrition	0%
Xu et al ¹⁹	Chi- na	57.68 case 60.05 control	All gastro- intestinal cancer	7	Impact (Novartis, Bern)	25 kcal/d	Standard care	Immunologi- cal and nutritional variables post- operative complicati- ons	NA
Nakam- ura et al ²⁰	Jap- an	64	All gastro- intestinal cancer	5	Impact (Novartis, Bern)	1000 ml/d	Standard care	Inflammator- y mediators, and blood markers and Changes in EPA, DHA, LA, AA LOS, post- operative complicati- ons	26%
Braga et al ²¹	Italy	55	Colo- rectal cancer	5	Impact (Novartis, Bern)	1000 ml/d	Standard care	Delayed hypersensit- ivity response and IL-6 levels Infectious complicati- ons, non- infectious complicati- ons, anastomotic leak, LOS, mortality	20%
Braga et al ²²	Italy	63	All gastro- intestinal cancer	7	Impact (Novartis, Bern)	1000 ml/d	Standard care	Post- operative complicati- ons LOS	100%
Gianot- ti et al ²³	Italy	63.4 case 62.3 control	All gastro- intestinal cancer	5	Impact (Novartis, Bern)	1000 ml/d	Standard care	Infectious complicati- ons, length of stay gut function, compliance	0%

Table 2: The definition of post-operative complications of commonly assessed post-operative complications based on suggestion proposed by Xu et al.

Definition	Complications
Wound infection	Any redness or tenderness of the surgical wound, with discharge of pus
Abdominal abscess	Deep collection of pus
Pulmonary tract infection	Abnormal chest radiograph, with fever (temperature>38°C) and white blood cell count >12.103/11 and positive sputum or bronchoalveolar lavage
Urinary tract infection	>107 microorganisms per 1 ml of urine
Bacteremia	Two consecutive positive blood cultures without shock
Wound dehiscence	Any dehiscence of the fascia >3 cm
Bleeding	Necessity of blood transfusion (≥ 2 U)
Anastomotic leak	Any dehiscence with clinical or radiological evidence
Respiratory tract failure	Presence of dyspnea and respiratory rate >35 breaths/minute PaO ₂ <70 mmHg
Circulatory insufficiency	Unstable blood pressure requiring use of extra fluid or cardiac stimulants
Renal dysfunction	Increased serum urea or creatinine level (50% above baseline)
Renal failure	Necessity of hemodialysis
Hepatic dysfunction	Increasing serum bilirubin or hepatic enzyme level (50% above base line)
Multiple organ dysfunction syndrome	A state of physiological derangement in which organ function is not capable of maintaining homeostasis

CONCLUSION

Based on the systematic review of the randomized-controlled trials investigating the efficacy of immunomodulatory nutrition on the outcome of the surgery, immunomodulatory nutrition had enhanced the immune status of the patients and enhanced renal and liver functions. Furthermore, they decreased weight loss and inflammatory biomarkers. However, its effect on the infectious and non-infectious complications are still under debate. The length of postoperative hospitalization was decreased in some cases, but not in all cases. For mortality, immunomodulatory nutrition showed no significant difference from the control group. Despite its failure to prove any favorable outcome on the survival rate, it must be taken seriously for its immune-stimulant effect.

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