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The Impact of Preoperative Immune Modulating Nutrition on Outcomes in Patients Undergoing Surgery for Gastrointestinal Cancer

A Systematic Review and Meta-analysis

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Objective: To define the influence of preoperative immune modulating nutrition (IMN) on postoperative outcomes in patients undergoing surgery for gastrointestinal cancer.

Background: Although studies have shown that perioperative IMN may reduce postoperative infectious complications, many of these have included patients with benign and malignant disease, and the optimal timing of such an intervention is not clear.

Methods: The Embase, Medline, and Cochrane databases were searched from 2000 to 2018, for prospective randomized controlled trials evaluating preoperative oral or enteral IMN in patients undergoing surgery for gastrointestinal cancer. The primary endpoint was the development of postoperative infectious complications. Secondary endpoints included postoperative noninfectious complications, length of stay, and up to 30-day mortality. The analysis was performed using RevMan v5.3 software.

Results: Sixteen studies reporting on 1387 patients (715 IMN group, 672 control group) were included. Six of the included studies reported on a mixed population of patients undergoing all gastrointestinal cancer surgery. Of the remaining, 4 investigated IMN in colorectal cancer surgery, 2 in pancreatic surgery, and another 2 in patients undergoing surgery for gastric cancer. There was 1 study each on liver and esophageal cancer. The formulation of nutrition used in all studies in the treated patients was Impact (Novartis/Nestlé), which contains ω-3 fatty acids, arginine, and nucleotides. Preoperative IMN in patients undergoing surgery for gastrointestinal cancer reduced infectious complications [odds ratio (OR) 0.52, 95% confidence interval (CI) 0.38–0.71, $P < 0.0001$, $I^2 = 16\%$, n = 1387] and length of hospital stay (weighted mean difference −1.57 days, 95% CI −2.48 to −0.66, $P = 0.0007$, $I^2 = 34\%$, n = 995) when compared with control (isocaloric isonitrogeneous feed or normal diet). It, however, did not affect noninfectious complications (OR 0.98, 95% CI 0.73–1.33, $P = 0.91$, $I^2 = 0\%$, n = 1303) or mortality (OR 0.55, 95% CI 0.18–1.68, $P = 0.29$, $I^2 = 0\%$, n = 955).

Conclusion: Given the significant impact on infectious complications and a tendency to shorten length of stay, preoperative IMN should be encouraged in routine practice in patients undergoing surgery for gastrointestinal cancer.

Keywords: cancer surgery, gastrointestinal cancer, immune modulating nutrition, infectious complications, postoperative outcomes, preoperative nutrition

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Impairment of nutritional status is common in cancers of the gastrointestinal tract, where the prevalence of malnutrition ranges from 20% to 70%.[1–3] The wide variation in prevalence is, in part, due to the underlying cancer type, stage, and grade, and also the patient-specific factors such as age and comorbidity.[2] Malnutrition impacts negatively on the host immune response and the process of tissue healing,[4,5] and is an independent risk factor for postoperative complications.[6] The high cellular turnover during the process of tumuorigenesis[1,2] also leads to a dysregulation of the immune response in patients with cancer, compounding their risk of developing complications. Definitive treatment of cancers of the gastrointestinal tract invariably involves surgical intervention. However, it is well-documented that the catabolic

response to surgery causes a depletion of essential nutrients and a dysregulation of the immune response resulting in an increased risk of postoperative complications, in particular, infectious complications.[1,7–9] It is, therefore, predictable that patients with gastrointestinal cancer undergoing surgical resection are at a much greater risk of posoperative complications.

It is for these patients, that the concept of preoperative immune modulating nutrition (IMN) or pharmaconutrition, which involves the use of novel nutrients to improve nutritional status and to modulate host immune systems and inflammatory response to stress,[10–12] seems a promising treatment.[13] There is no universally accepted definition of IMN, however, it is characterized by the addition of special nutrients in higher doses than in standard nutritional protocols.[2,3] The generally accepted and most frequently recognized immune-modulating nutrients are various combinations of arginine, fish oil (ω-3 fatty acids), nucleotides, and glutamine.[10] Partial immunonutrients include antioxidants (vitamins E and C, selenium, or beta carotene).[10] Several reviews and meta-analyses[10,14,15] have demonstrated the beneficial effects of IMN by pooling results of randomized control trials (RCTs) in all surgical patients examining the preoperative, perioperative, and postoperative periods of treatment in tandem. However, others have failed to demonstrate any added benefit of IMN over standard supplements using similar methods.[16,17] Therefore, there has been a reluctance to recommend ''immunonutrition'' for routine use.[1–3] Focusing on conditioning the immune system for surgery, administration in the preoperative period may be most reasonable. However, there is still a lack of clarity for the indication, route, timing, and optimal duration of preoperative treatment.[14–16] As the risk of malnutrition and the inflammatory response profiles in cancer surgery are expected to differ from surgery for benign disease, pooling of the results of these patients with benign and malignant disease may yield ambiguous outcomes. Likewise, the evidence from animal studies suggested that a minimum of 72 hours were required for maximal effects of enterally administered IMN to be evident on the composition of macrophage phospholipid.[11] Additionally, in studies that examined IMN in the postoperative period, up to 5 days were required for the full dose of enteral IMN to be delivered.[13] There is no prior systematic review evaluating the preoperative IMN in patients undergoing surgery for gastrointestinal cancer, specifically with due consideration to route and timing of initiation of treatment.

This systematic review and meta-analysis, therefore, investigated the impact of oral or enteral IMN administered a minimum of 3 days and restricted to the preoperative period on postoperative outcomes in patients undergoing surgery for gastrointestinal cancer.

METHODS

Search Strategy

A comprehensive and systematic search of the Embase, Cochrane Collaboration, and Medline databases was undertaken to identify relevant studies published between 2000 and 2018. The terms relating to preoperative, preoperative period, preoperative care, and prehabilitation were combined with terms relating to immunonutrition, immune-enhancing nutrition, IMN, pharmaconutrition, and then to postoperative and postsurgical outcomes.

The following Medical Subject Headings (MeSH) were used: ''Preoperative Period'', ''Preoperative Care'', ''Preoperative'', ''preop'', ''Nutrition(al) Assessment'', ''Parenteral Nutrition'', ''Enteral Nutrition'', Nutrition Disorders'', Nutrition Surveys'', ''Home/ or nutrition'', ''Total/Nutrition Therapy'' combined with ''post-operative outcomes''. (Supplementary document—Supplementary Table 1, http://links.lww.com/SLA/B601). The bibliography of the studies that met the inclusion criteria were searched for additional trials or reports relevant to this meta-analysis.

Criteria for Considering Studies for the Review

All studies on patients undergoing surgery for gastrointestinal cancer were considered. The intervention of interest was IMN defined specifically to include all types and combinations of arginine, glutamine, ω-3 fatty acids, and nucleotides provided as part of oral supplementation or enteral nutrition, and crucially commenced a minimum of 3 days before the intended date of surgery. The primary outcome measure was postoperative infectious complications. Secondary outcomes of interest included length of hospital stay (LOS), noninfectious complications, and mortality up to 30 days postoperatively.

Inclusion Criteria

Prospective RCTs reporting at least 1 relevant clinical outcome were included. The studies had to be in human subjects over the age of 18 years undergoing surgery for gastrointestinal cancer. The control arm was either an isocaloric isonitrogeneous nonimmune-enhancing feed or normal diet with no supplementation. No language limitations were applied.

Exclusion Criteria

Studies which failed to fulfil the inclusion criteria such as nonrandomized or retrospective studies were excluded. This was to reduce the potential risk of bias in such studies. Studies that only used singular components of recognized IMN such as ''only ω-3 fatty acids,'' ''only arginine,'' and so on were also excluded. Additionally, studies that failed to report patient data, duplicated studies, those with restricted access to study report or data, review articles, letters to the editor, editorial reports, case reports, and conference abstracts with no access to the entire study or report were also excluded. Studies that reported perioperative or postoperative administration of IMN were also excluded, along with studies published before the inclusion date. Studies that would have otherwise met inclusion criteria, but reported on both cancer and noncancer gastrointestinal surgery and did not provide data for the cancer patients separately, were also excluded if attempts to get source data failed. The identified studies were screened for relevance to this review independently by 2 reviewers (P.S. and A.A.). All discordant articles were adjudicated by a third reviewer (D.N.L.).

Data Extraction, Collection, and Synthesis

Data were retrieved from the selected study texts using a predetermined data extraction form. Data were collected on publication details, study design, number of participants, type of gastrointestinal surgery, participant age, intervention or treatment investigated, follow-up period, 30-day mortality, readmissions, postoperative nutritional assessments, and LOS. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[18] was adhered to, all studies were appraised critically, and the risk of bias of all included studies assessed. A recent multicenter study from Australia used a 2×2 factorial design randomizing for IMN versus placebo before and after surgery.[19] For our analysis, only the data from the patient groups with IMN before surgery versus control were included.

Statistical Analysis

For the meta-analysis, dichotomous outcome measures were summarized as odds ratios (ORs) or weighted mean differences (WMDs) with 95% confidence intervals (CIs) for continuous variables. The presence of statistical heterogeneity was to some degree expected, given the in-between study variability[20] in type and grade of cancer evaluated, the number of patients per study, the percentage of study

population that were malnourished, the type of IMN given, the choice of controls, and the duration of therapy. Therefore, quantitative synthesis of the pooled data was performed using RevMan v5.3 software[21] assuming a random-effects meta-analysis. Heterogeneity was assessed using the I^2 statistic,[22] and defined as low, moderate, or high corresponding to upper limits of 25%, 50%, and 75%, respectively.[20] The assessment of publication bias was undertaken by assessing symmetry of the funnel plot for the primary outcome. Predetermined separate analyses were performed according to what the "control" group received (ie, isocaloric isonitrogenous feed or standard diet without supplements) and the results were pooled together.

Registration of Systematic Review

The protocol for this systematic review and meta-analysis was registered with the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/), and the registration number assigned was CRD42018079236.

RESULTS

Inclusion of Studies

After screening, 64 full papers were evaluated of which 16 met the inclusion criteria (Fig. 1).[19,23–37] The detailed study characteristics and patient demographics are provided in Tables 1 and 2. Seven studies originated from Japan,[23,27,32–36] 3 from Italy,[24,25,29] and 1 each from Spain,[26] Denmark,[28] Switzerland,[30] Turkey,[31] Australia,[19] and China.[37] Six of the studies included reported on a mixed population of patients undergoing all gastrointestinal cancer surgery.[25,29–31,35,37] Of the remaining, 4 investigated IMN in colorectal cancer surgery,[24,26,32,34] 2 in pancreatic surgery,[23,28] and a further 2

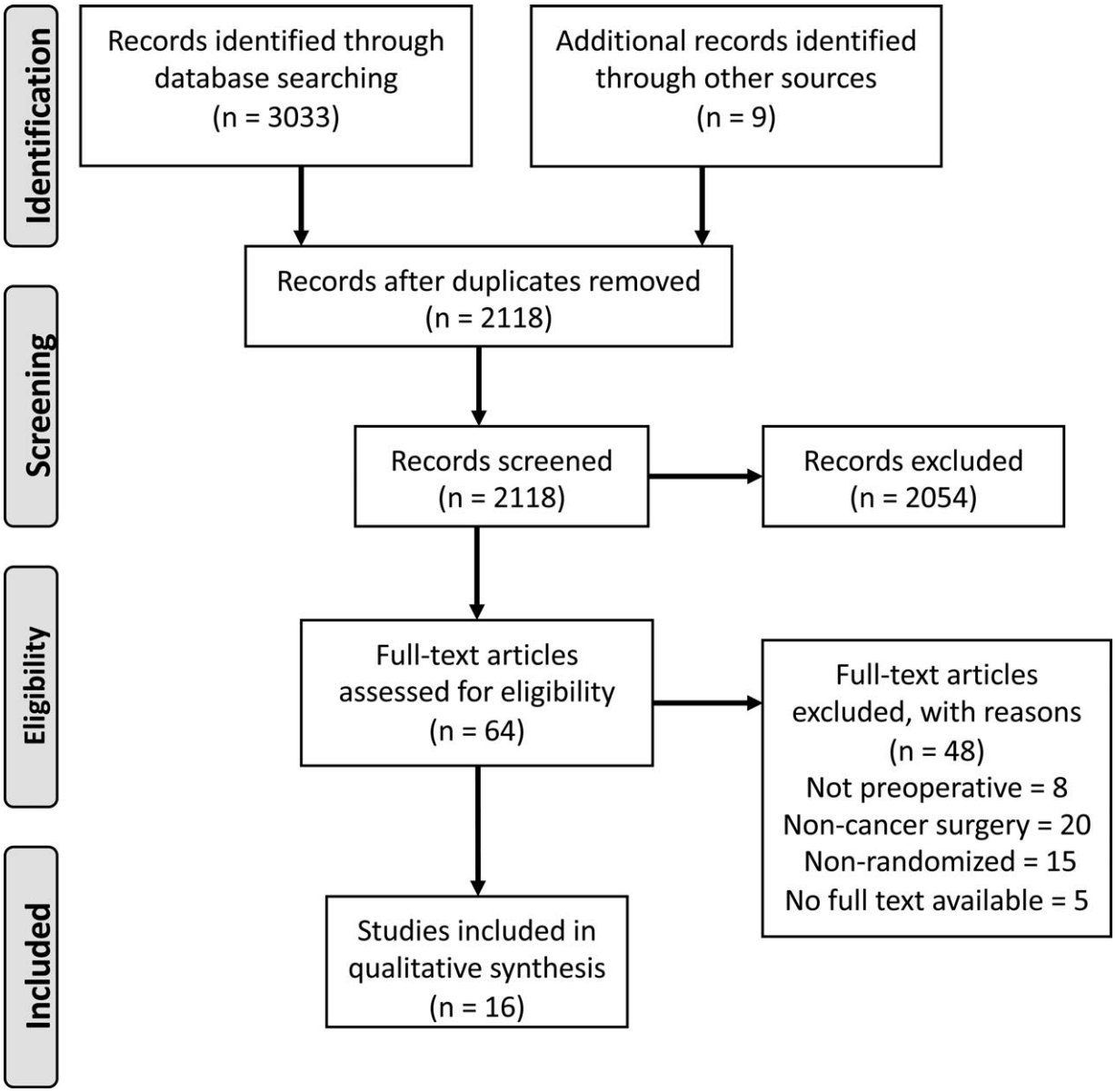


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

TABLE 1. Characteristics of Included Studies

Study, Year	Country	Feeding Protocol	Days	Product in Treatment Group	Dose	Control (Isocal/IsoN)*
Aida et al, 2014[23]	Japan	OS day in addition to standard diet	5	Impact (Novartis Pharma, Tokyo)	1000 mL/d	No supplement
Braga et al, 2002[24]	Italy	OS in addition to standard diet	5	Impact (Novartis, Bern)	1000 mL/d	Yes
Braga et al, 2002[25]	Italy	OS in addition to standard diet	7	Impact (Novartis, Bern)	1000 mL/d	No supplement
Fujitani et al, 2012[27]	Japan	OS in addition to standard diet	5	Oral Impact (Novartis Pharma, Tokyo)	1000 mL/d	No supplement
Gade et al, 2016[28]	Denmark	OS in addition to standard diet	7	Oral Impact (Nestle, Vevey)	1.5 g protein/kg body weight	No supplement
Gianotti et al, 2002[29]	Italy	OS in addition to standard diet	5	Impact (Novartis, Bern)	1000 mL/d	No supplement
Giger-Pabst et al, 2013[30]	Germany	OS in addition to standard diet	3	Impact (Novartis, Bern)	750 mL/d	Yes
Gunerhan et al, 2009[31]	Turkey	Total enteral nutrition	7	Impact (Novartis, Bern)	Harris-Benedict	Yes
Horie et al, 2006[32]	Japan	OS in addition to standard diet	6	Impact (Novartis Pharma, Tokyo)	750 mL/d	No supplement
Manzanares Campillo et al, 2017[26]	Spain	OS in addition to standard l diet	8	Oral Impact (Novartis, Espana)	1000 kcal/d	No supplement
Mikagi et al, 2011[33]	Japan	OS in addition to standard diet	5	Impact (Novartis Ajinomoto Pharma, Tokyo)	750 mL/d	No supplement
Moriya, 2015[34]	Japan	OS in addition to standard diet*	5	Impact (Novartis Pharma, Tokyo)	Low: 250 mL/d† High: 750 mL/d†	No supplement
Mudge et al, 2018[19]	Australia	OS in addition to standard diet‡	7	Oral Impact (Novartis)	909 kcal/d	Yes
Nakamura et al, 2005[35]	Japan	OS in addition to standard diet	5	Impact (Novartis Pharma, Tokyo)	1000 mL/d	No supplement
Okamoto et al, 2009[36]	Japan	OS in addition to standard diet	7	Impact (Novartis, Bern)	750 mL/d	Yes
Xu et al, 2006[37]	China	Enteral nutrition + standard diet	7	Impact (Novartis, Beijing)	25 kcal/d	Yes

*If control was an isocaloric and isonitrogenous supplement—yes (normal diet—no supplement).
†They had a low volume and high volume subgroups receiving 250 mL and 750 mL. Those patient groups are both counted together as treated.
‡For patients with total dysphagia the supplements were dissolved and administered via a nasogastric feeding tube or jejunostomy.
OS indicates oral supplements.

studied patients undergoing surgery for gastric cancer.[27,36] There was 1 study each on hepatic[33] and esophageal cancer.[19] The additional randomized studies evaluated but excluded due to specific data on cancer patients not being available[38,39] or outside study period[40] are presented in the Supplementary Document (Supplementary Table 2, http://links.lww.com/SLA/B601).[38–44]

Patient Characteristics

Sixteen studies 1387 patients (715 IMN group, 672 control group) were included.[19,23–37] Five studies specifically reported patients with and without weight loss.[19,23,24,27,31] Three studies included only well-nourished patients as assessed with Nutritional risk screening 2002[45] or determined to have less than 10% weight loss in a year.[29,30,32] A single study reported a full cohort of malnourished patients undergoing surgery for various types of gastrointestinal cancer.[24] The remaining 7 studies failed to report whether their cohorts were well-nourished, malnourished, or mixed.[26,28,33–37]

Supplemental Nutrition and Administration

In all the studies, the formulation of nutrition was ''Impact'' (Novartis/Nestlé), which contains ω-3 fatty acids, arginine, and nucleotides (Supplementary document—Supplementary Table 3, http://links.lww.com/SLA/B601), but the regimen, dosage, and duration of treatment varied between studies (Table 1). A study from Japan[34] included what they described as high dose (750 mL/d) and low dose (250 mL/d) of IMN. However, for this intention-to-treat-based analysis, their patients are classed as treated irrespective of dosage. The characteristics of the nutrition supplementation are detailed in Table 1. In 6 studies, the control arm was an isocaloric isonitrogeneous feed.[19,24,30,31,36,37] In the remaining 10 studies,[23,25–29,32–35] no supplementation was provided to the control arm and the patients were expected to have a standard diet. Most of the studies evaluated postoperative infectious complications as their primary or secondary outcome measure. The others included length of stay, overall morbidity, and mortality. Some studies also reported variables related to immune response and inflammation such as postoperative interleukin-6 and C-reactive protein.

Results of Meta-analysis

The results of the meta-analysis are summarized in Table 3 and Figs. 2 and 3.

Primary Outcome: Infectious Complications

All 16 studies[19,23–37] provided relevant data for infectious complications. Fig. 2A and Table 3 show the incidence rates of infectious complications in the treated (IMN) versus untreated (isocaloric isonitrogenous supplements, or standard diet groups). The event rate of this outcome was 18.6% (133/715 patients) in the IMN group compared with 29.31% (199/672 patients) in the control group. The pooled OR for infectious complications after preoperative treatment with immune modulating nutrients was 0.52 (95% CI 0.38–0.71, $P < 0.0001$, $I^2 = 16\%$).

The OR for infectious complications was then examined by the choice of control. In the studies where the control arms received an isocaloric isonitrogenous supplement,[19,24,30,31,36,37], the OR was 0.49 (95% CI 0.28–0.85, $P = 0.01$, $I^2 = 0.25\%$), and for those receiving no supplements,[23,25–29,32–35] OR was 0.52 (95% CI 0.35–0.78, $P = 0.001$, $I^2 = 20\%$).

Secondary Outcomes

The secondary outcomes of clinical significance consistently reported in the included studies were LOS, mortality, and noninfectious complications. However, the definition of what constituted noninfectious morbidity varied. The nutritional and immunology variables reported by some studies were not investigated consistently, nor were they reported in a manner that allowed for accurate pooling of their results.

TABLE 2. Nutritional Protocols of Included Studies

Study, Year	No. of Participants	Type of Cancer	Malnutrition Rates, %	Definition of Malnutrition	Primary Endpoint	Secondary Endpoint	Source of Funding
Aida et al, 2014[23]	50	Pancreatic cancer	8%	Loss of >10% body weight	Infectious complications	Immune responses	Grant from Japanese Society for Parenteral and Enteral Nutrition
Braga et al, 2002[24]	100	Colorectal cancer	20%	More than 10% weight loss in 6 months	Delayed hypersensitivity response and IL-6 levels	Infectious complications, noninfectious complications, anastomotic leak, LOS, mortality	Novartis
Braga et al, 2002[25]	100	All gastrointestinal cancer	100%	More than 10% weight loss in 6 months	Postoperative complications	LOS	Novartis
Fujitani et al, 2012[27]	231	Gastric cancer	2.2%	Less than 10% weight loss in 6 months	Surgical site infection	Infection, morbidity, C-reactive protein	Not reported
Gade et al, 2016[28]	35	Pancreatic cancer	Not reported	NRS 2002	Postoperative complications	LOS	Education grant from the University of Copenhagen
Gianotti et al, 2002[29]	204	All gastrointestinal cancer	0	More than 10% loss in 6 months	Infectious complications, length of stay	Gut function, compliance	Novartis
Giger-Pabst et al, 2013[30]	108	All gastrointestinal cancer	0	NRS 2002	Rate of postoperative complications	Infectious complications, noninfectious complications, LOS	Novartis
Gunerhan et al, 2009[31]	24	All gastrointestinal cancer	1%	PG-SGA	Nutritional parameters, blood markers (prealbumin, albumin, lymphocyte count)	Infectious complications, noninfectious complications, LOS	Not reported
Horie et al, 2006[32]	67	Colorectal cancer	0	Not reported	Surgical site infection	Postoperative inflammation and nutrition	Not reported
Manzanares Campillo et al, 2017[26]	84	Colorectal cancer	Not reported	Not reported	Infectious complications	Minor and major complications, length of stay and cost	Not reported
Mikagi et al, 2011[33]	26	Liver cancer	Not reported	Not reported	Indices of inflammatory reaction (interleukin-6, white cell count)	Postoperative complications, length of stay	Not reported
Moriya, 2015[34]	85	Colorectal cancer	Not reported	Not reported	Surgical site infection	Infection, morbidity, LOS	Not reported
Mudge et al, 2018[19]	127	Esophageal cancer	17%	PG-SGA	Infective complications	Noninfective complications, LOS, intensive care unit stay, mortality	Medical Research Council, Australia, Project Grant
Nakamura et al, 2005[35]	26	All gastrointestinal cancer	Not reported	Not reported	Inflammatory mediators, and blood markers and Changes in EPA, DHA, LA, AA	LOS, postoperative complications	Not reported
Okamoto et al, 2009[36]	60	Gastric cancer	Not reported	Not reported	Immunological and nutritional variables	Postoperative complications	Not reported
Xu et al, 2006[37]	60	All gastrointestinal cancer	Not reported	Not reported	Immunological and nutritional variables	Postoperative complications	Not reported

AA indicates arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; NRS 2002, Nutrition Risk Screening 2002; PG-SGA, Scored Patient-Generated Subjective Global Assessment.

TABLE 3. Summary of Pooled Results

Outcome or Subgroup	No. of Studies	Participants	Statistical Method	Effect Estimate
Infectious complications	16	1387	Odds ratio (M-H, random, 95% CI)	0.52 [0.38, 0.71]
Noninfectious complications	15	1303	Odds ratio (M-H, random, 95% CI)	0.98 [0.73, 1.33]
Length of stay	12	995	Mean difference (IV, random, 95% CI)	−1.57 [−2.48, −0.66]
Mortality	8	955	Odds ratio (M-H, random, 95% CI)	0.55 [0.18, 1.68]

Noninfectious Complications. The incidence of noninfectious complications was reported in fifteen studies[19,23–25,27–37] (Fig. 2B, Table 3). The event rate of this outcome was 20.21% (136/673 patients) in the IMN group and 20.79% (131/630 patients) in the control arm. The pooled OR for noninfectious complications was 0.98 (95% CI 0.73–1.33, $P = 0.91$, $I^2 = 0\%$).

Length of Stay. Twelve studies provided complete data on LOS.[19,24–26,28–32,35–37] The pooled WMD was −1.57 (95% CI −2.48 to −0.66, $P = 0.00007$, $I^2 = 34\%$; Fig. 3A). However, subgroup analysis of the group receiving supplements did not reach significance (OR −1.06, 95% CI −2.76 to 0.63, $P = 0.22$, $I^2 = 63\%$).

Mortality. Eight studies reported on perioperative mortality,[19,23–25,27–30] and in 2 studies there were no deaths at up to 30 days.[24,27] In the remainder mortality was a rare event. Mortality rates were 1.03% (5/486 patients) in the IMN group and 2.56% (12/469 patients) in the control group. The pooled OR for mortality was 0.55 (95% CI 0.18–1.68, $P = 0.29$, $I^2 = 0\%$; Fig. 3B, Table 3).

Heterogeneity and Publication Bias

Statistical heterogeneity in this meta-analysis was relatively low, ranging from 0% to 39% (Figs. 2 and 3). The possibility of publication bias was assessed in the funnel plot (Supplementary document—Supplementary Fig. 1, http://links.lww.com/SLA/B601) for the primary outcome of infectious complications, and this was found to show a minor degree of asymmetry, suggesting low risk of publication bias. The risk of bias for the studies included is summarized in Fig. 4.

DISCUSSION

What our Study Found?

The present meta-analysis has shown that the risk of developing infectious complications after surgery for gastrointestinal cancer was reduced significantly by 48% in patients receiving preoperative IMN. The intervention group also had a significant reduction in LOS by 1.5 days, which may be related to the reduction in infectious complications. However, the preoperative administration of IMN did not impact noninfectious complications or mortality.

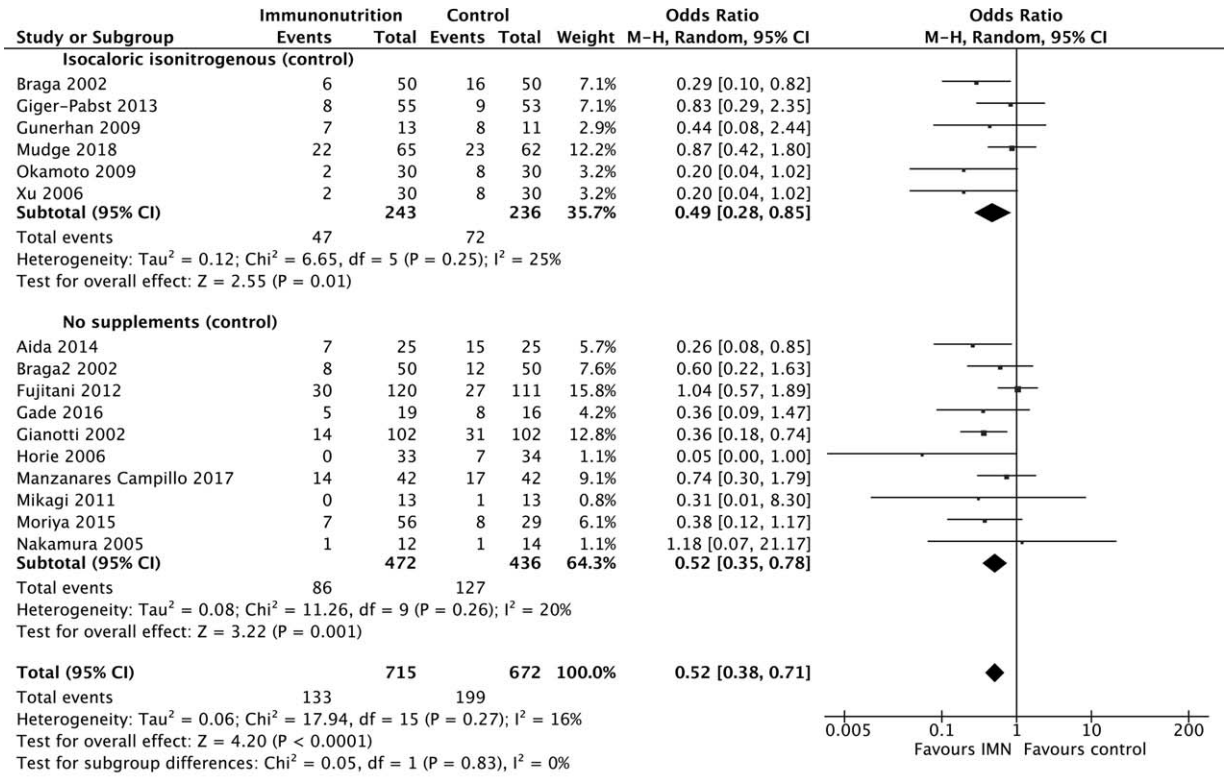
The studies included were from a wide spread of the worldwide population and encompassed patients undergoing surgery for different types of gastrointestinal cancer, each with their own inherent risk of complications and morbidity. However, by encompassing all of gastrointestinal cancer surgery, the results are more likely to be generalizable. Although the IMN product used in all the studies was Impact produced by Novartis/Nestlé (Tokyo, Spain, Switzerland), the volume of the product given and duration of treatment differed ranging from a minimum of 3 days to a maximum of 8 days. These, in part, may account for some of the variability seen in the range of outcomes.

We assessed heterogeneity and found this to be low in the primary outcome of infectious complications, and also the secondary outcomes of noninfectious complications and mortality. The funnel plot assessing publication bias also found a low risk of publication bias.

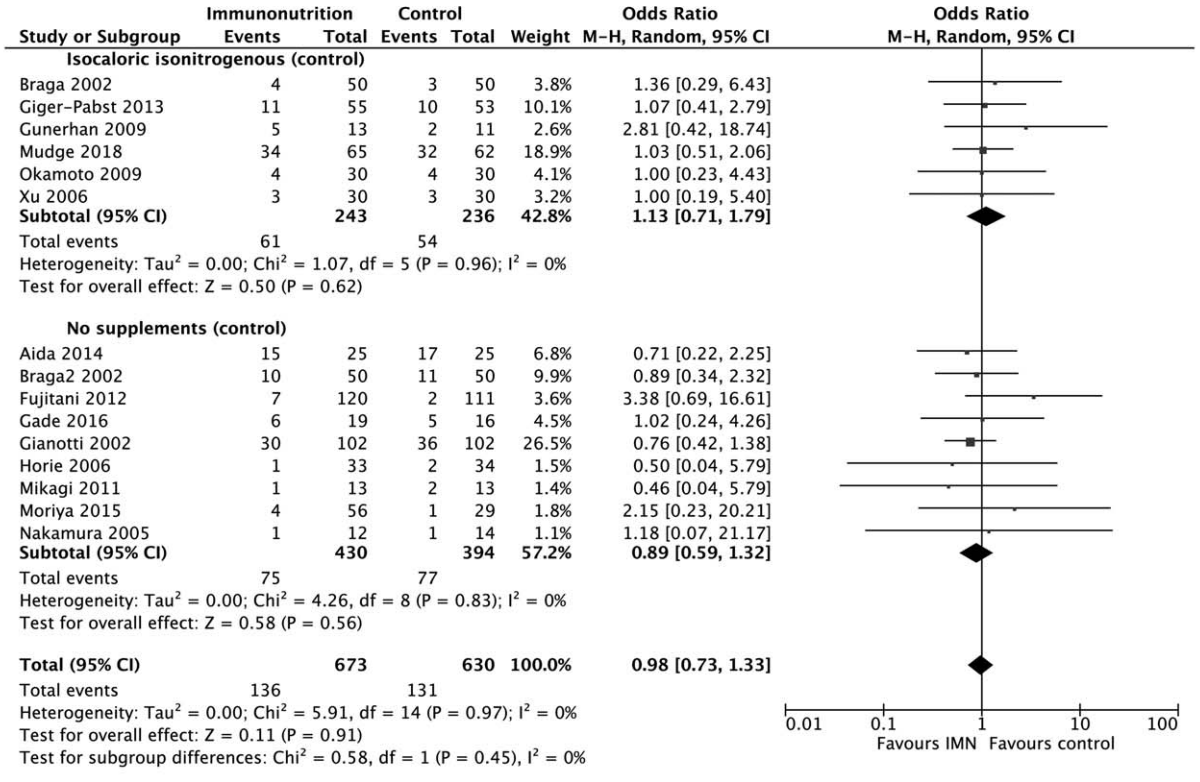
What is Available in the Literature

Over the past 2 decades, several trials, as identified in this systematic review, have been undertaken to investigate potential benefits of IMN regarding postoperative outcome. Systematic reviews have subsequently been carried out, with many of these reporting improvement in postoperative outcomes, especially infectious complications.[10,14,15] IMN was found to reduce the rates of postoperative infection and shorten LOS in another analysis.[46] Studies that evaluated IMN and included a cost-effectiveness analysis also suggested that perioperative IMN in upper gastrointestinal surgery resulted in a decrease in complication rates, and also a substantial decrease in treatment costs.[47,48] The meta-analysis by Marimathu et al[15] concluded that IMN reduced postoperative complications and decreased LOS. However, in their conclusion, they reported that further work was required to evaluate IMN administered preoperatively separate from perioperative and postoperative treatment strategies. Hegazi et al[16] undertook such a preoperative assessment of IMN in patients undergoing gastrointestinal surgery. They showed, in their subgroup analysis, that compared with patients receiving nonsupplemented diets, there was a benefit of IMN in reducing infectious complications and LOS. However, in those studies where controls were given an isocaloric isonitrogenous supplement, there was no additional benefit of IMN.[16] The present meta-analysis, using more contemporary data, has shown the benefit of preoperative IMN in reducing infectious complications in controls with and without isocaloric isonitrogenous supplementation for the primary outcome of infectious complications. LOS was reduced significantly when patients receiving IMN were compared with those receiving a nonsupplemented diet, but not when compared with those receiving isocaloric isonitrogenous supplements—the latter again in line with the results from Hegazi et al.[16] Nevertheless, taking into account a higher heterogeneity ($I^2 = 63\%$) in this subgroup and the clear benefits regarding infectious complications, our results provide arguments for the use of IMN in clinical practice.

The timing of IMN is of importance if it is to be effective in offsetting the impact of postoperative inflammation and immunosuppression. For this effect to be realized, therapeutic levels of the nutrients must be reached in plasma and tissues preoperatively.[13] To date, the evidence derived from animal studies suggests that 72 hours were required for the effects of the enteral administered IMN to be evidenced on macrophage phospholipid profile.[11] In a study of postoperative IMN administered to patients undergoing upper gastrointestinal resections, a total of 5 days was needed for the full dose of IMN to be delivered.[13] Sorensen et al[49] reported a significant uptake of ω-3 fatty acids within 5 to 7 days of commencing oral supplementation in patients undergoing surgery for colorectal cancer.[49] In the present meta-analysis, significant differences in infectious complications were seen mainly in studies in which IMN was given for 5 to 7 days preoperatively, and the only study that gave it for 3 days[30] did not show any difference. It would, therefore, follow that a minimum of 5 to 7 days would be optimal for the intended benefits

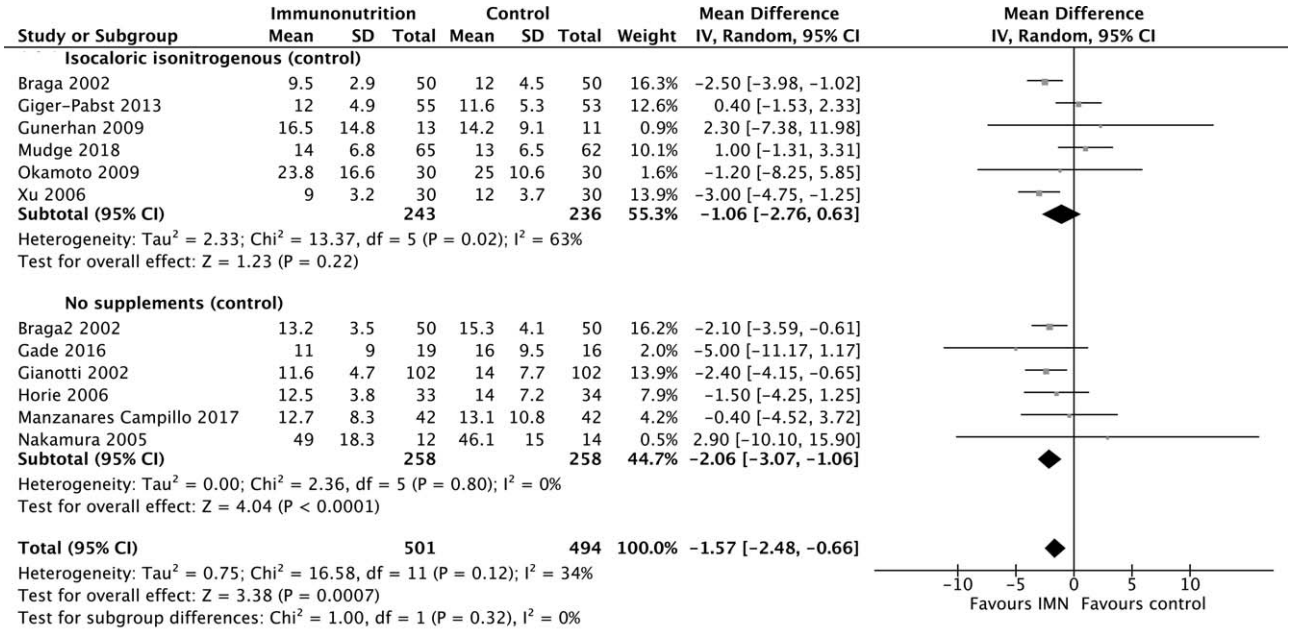


A Infectious complications

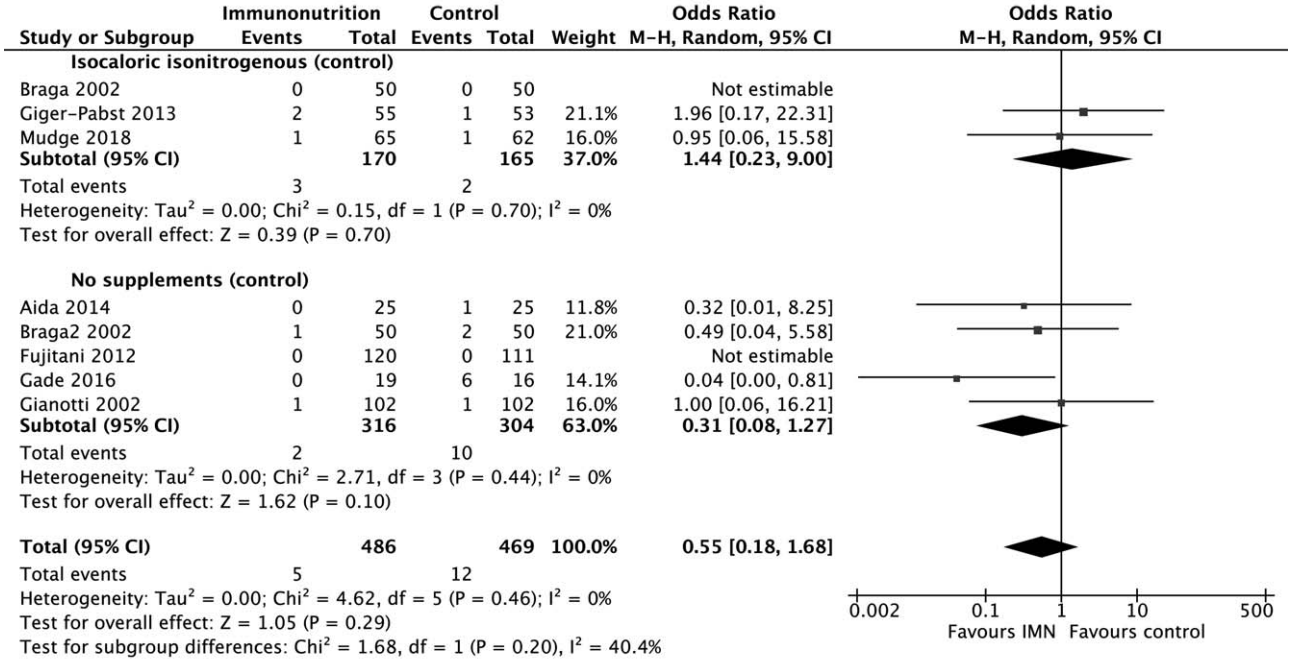


B Non-infectious complications

FIGURE 2. Forest plots showing the pooled odds ratio (Mantel-Haenszel random-effects model) for (A) infectious complications and (B) noninfectious complications. Subgroup analyses are based on controls receiving either ''isocaloric isonitrogeneous supplements'' or ''no supplements''.



A Length of stay



B Mortality

FIGURE 3. Forest plots showing (A) the pooled weighted mean difference (inverse variance, random-effects model) for length of stay and (B) the pooled odds ratio (Mantel-Haenszel random-effects model) for mortality. Subgroup analyses are based on controls receiving either ''isocaloric isonitrogeneous supplements'' or ''no supplements.''

of IMN on outcomes. Incidentally, treatment with IMN for more than 2 weeks did not show a further advantage, supposedly due to a reduction in compliance.[50]

Giger-Pabst et al[30] investigated ''well-nourished'' patients undergoing surgery for all types of abdominal cancer in the only study in which IMN was administered for up to 3 days preoperatively and demonstrated no benefit over isocaloric isonitrogenous control diet. It is possible that the impact of IMN is potentially less in patients who are well-nourished. More importantly, it is likely that treatment duration of 3 days or less was insufficient for the effects of IMN to be

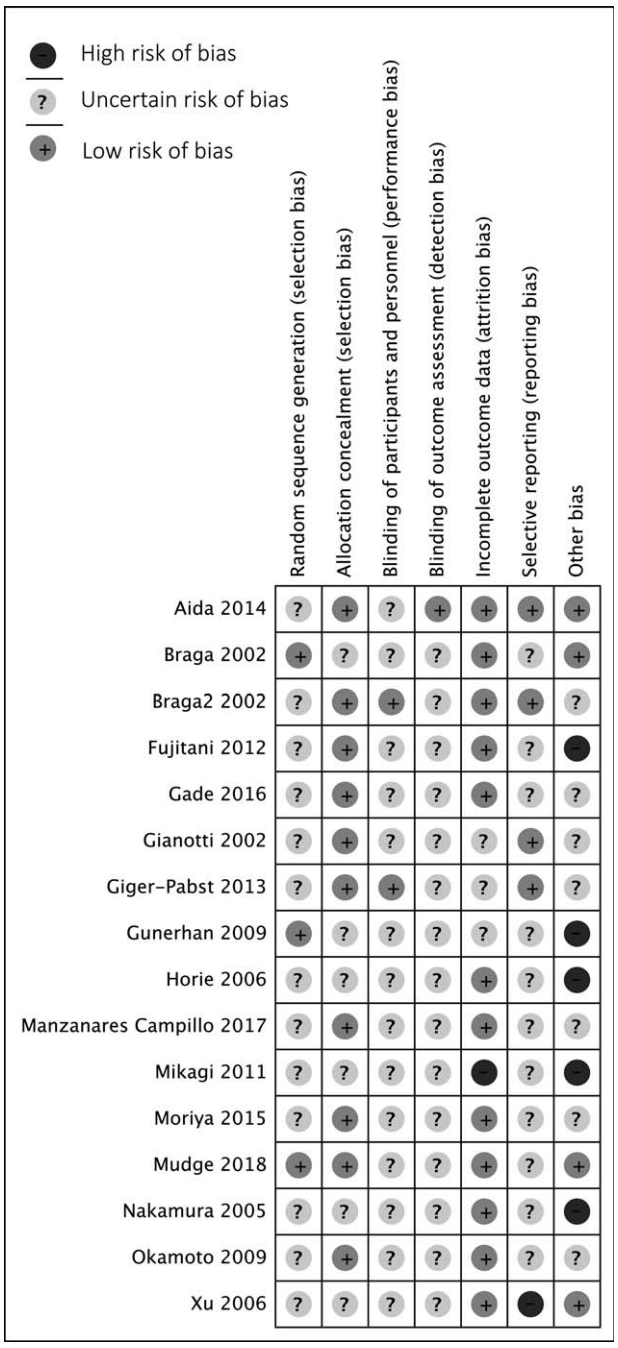


FIGURE 4. Risk of bias of the included studies using the Cochrane Risk of Bias domains.

evident. That study[30] is in direct contrast to the study by Braga et al,[25] where all the study participants were malnourished and were treated for a minimum of 5 days, with a demonstrable reduction in both postoperative complications and LOS. Certain gastrointestinal cancers, especially upper gastrointestinal cancers, place patients at an increased risk of severe malnutrition[2] and the compound effect of surgery causing dysregulation of immune response. IMN, therefore, could be a feasible and beneficial treatment strategy in such patients. The European Society for Clinical Nutrition and Metabolism (ESPEN) Clinical Guidelines, which were published in 2017, recommend IMN in malnourished patients undergoing major cancer surgery.[1,2] However, they accepted there was, at the time, no evidence of benefit over standard oral nutritional supplements in the preoperative period exclusively.[1] This meta-analysis provides new evidence supporting the use of preoperative IMN in patients undergoing surgery for gastrointestinal cancer. A recent study[51] using perioperative IMN in patients undergoing surgery for gastrointestinal cancer and managed with an enhanced recovery after surgery protocol was able to demonstrate the benefit of IMN in reducing infectious complications in that setting.

Strengths and Limitations of Our Study

Evaluating a nutrition-based intervention is always limited by potential confounders such as compliance and potential for the controls to be taking in foods with similar ingredients as is found in IMN (arginine, fish oil, antioxidants). Even where reported, the constituents of the isocaloric isonitrogeneous supplements were not always obvious and may have contained low doses of similar constituents as in IMN. Some smaller studies investigating IMN in all gastrointestinal surgery failed to report if they had equal number of patients undergoing similar procedures in each arm. Some cancer surgery is associated with much longer in-patient stay than others. Hence, in such smaller studies the impact of these variations on LOS may be more pronounced. In addition, no studies had a placebo-controlled arm, and comparisons of IMN were made with isocaloric isonitrogenous supplements or no supplements. Almost all studies provided between 750 and 1000 mL/d of IMN, with the exception of the study by Moriya[34] (who had a subset of patients receiving what they classed as low dose IMN—250 mL/d). Compliance and total amounts of IMN that each patient consumed were not reported adequately to allow calculations of a dose response. It would, therefore, seem reasonable to suggest a dose of 750 to 1000 mL/d of IMN.

That notwithstanding, this meta-analysis has assessed IMN robustly, focusing on preoperative use solely in surgery for gastrointestinal cancer. The results are applicable and generalizable to this population most at risk of malnutrition and its sequalae. There is an expectation of a degree of methodological heterogeneity, given the choice of nutritional supplementation, dosage, route of administration, population, and the varied cancer types and stage of disease evaluated—this was accounted for by undertaking a random-effects analysis. Finding low I^2 values (which is a measure of the quantity of heterogeneity) even when all of this variability is accounted for, confirms the importance of our findings.

CONCLUSIONS

This meta-analysis provides contemporary evidence that preoperative administration of IMN for a minimum of 5 days, either orally or enterally, leads to an appreciable and significant reduction in postoperative infectious complications and a tendency for a shortened LOS. Given the low side effect profile and the limited cost, the results provide arguments to encourage IMN for patients undergoing surgery for gastrointestinal cancer.

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