

## A Systematic Review on the Effectiveness of Enteral Immunonutrition (EIN) on Pre- and Post-Operative Outcomes in Gastric Cancer Patients (Suatu Ulasan Sistematis tentang Keberkesanan Imunonutrisi Enteral (EIN) kepada Hasil Operatif Pra dan Pos pada Pesakit Kanser Gastrik)

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### ABSTRACT

*Gastric cancer is one of the most common upper gastrointestinal malignancies. To date, enteral immunonutrition (EIN) has gained increasing attention as it is found to effectively enhance the host's immunity and improve the metabolic status of gastric cancer patients undergoing gastrectomy. The health-boosting effects of EIN are believed to originate from a number of nutritional elements such as omega-3 fatty acids, glutamine, arginine and nucleic acid precursors that help reduce the incidences of post-operative complications and shorten the length of hospital stay among the aforementioned patients. However, little was known about the consistency of health-boosting benefits conferred by EIN. Hence, according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) protocol, this systematic review was carried out using nine meticulously and specifically selected full-length articles focusing on the pre- and post-operative effects of EIN including physical, biochemical, clinical and immunological outcomes on gastric cancer patients. Among the selected articles, seven of them focused on post-operative EIN while the remaining two concentrated on pre-operative EIN. In most of the selected studies, more than one immunonutritional components (arginine, glutamine, omega-3 fatty acid, RNA) were integrated. Patients receiving EIN showed significantly improved immunity, for example, increase in CD4+ T and NK cell counts that are responsible for fighting pathogens. In addition to that, individuals receiving EIN also showed increased levels of inflammatory biomarkers in their sera such as pre-albumin and transferrin. This results in shorter period of post-operative hospital stay that in turn permits progressive healing process and increases the survival rate due to minimal frequency of post-operative infections. Conclusively, our systematic review acknowledges that regardless of the initiation timing (pre-operative or post-operative) of immunonutrition, EIN can improve the overall health status of gastric cancer patients including infection complications and the length of hospital stay through regulation of immune responses.*

*Keywords: Arginine; enteral immunonutrition; gastric cancer; glutamine; omega-3 fatty acids; RNA*

### ABSTRAK

*Kanser gastrik adalah salah satu kanser yang umum di bahagian atas gastroperut. Kini, imunonutrisi enteral (EIN) semakin mendapat perhatian kerana pendekatan ini didapati dapat meningkatkan keimunan tubuh badan dan memperkukuh fungsi metabolik badan bagi pesakit yang menjalani gastrektomi. Kesan peningkatan kesihatan EIN dipercayai berasal daripada unsur pemakanan seperti asid lemak omega-3, glutamin, arginin dan prekursor asid nukleik yang dapat mengurangkan kejadian komplikasi pasca-operasi dan memendekkan tempoh penginapan di hospital dalam kalangan pesakit tersebut. Namun, konsistensi manfaat EIN dalam meningkatkan kesihatan masih kurang perinci. Oleh itu, dengan berpandukan protokol PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses), kajian tinjauan sistematik ini telah dijalankan dengan teliti dengan menggunakan sembilan artikel penuh spesifik yang memfokuskan kesan pra- dan pasca-operasi EIN yang merangkumi segi fizikal, biokimia, klinikal dan keimunan dalam kalangan pesakit kanser gastrik. Antara artikel yang terpilih, tujuh daripadanya tertumpu pada kesan pasca-operasi EIN manakala dua artikel lagi menumpu pada kesan pra-operasi EIN. Kebanyakan kajian terpilih menggabungkan lebih daripada sejenis komponen imunonutrisi (arginina, glutamina, asid lemak omega-3, RNA). Pesakit yang menerima EIN menunjukkan peningkatan dalam penanda biologi seperti bilangan sel T CD4+ dan NK yang bertanggungjawab untuk melawan patogen. Tambahan pula, individu yang menerima EIN juga menunjukkan peningkatan dalam aras serum penanda inflamasi seperti pra-albumin and transferrin. Hal ini memendekkan tempoh penginapan pasca-operasi di hospital, seterusnya mempercepat proses penyembuhan dan meningkatkan kadar kemandirian akibat penurunan kebarangkalian jangkitan pasca-operasi. Secara konklusi, ulasan sistematik ini mendapati tanpa kira masa permulaan imunonutrisi (pra-operasi atau pasca-operasi), EIN dapat menambah baik status kesihatan pasakit kanser gastrik secara keseluruhan termasuk komplikasi jangkitan dan tempoh penginapan hospital melalui regulasi tindak balas keimunan.*

*Kata kunci: Arginina; asid lemak omega-3; glutamina; imunonutrisi enteral; kanser gastrik; RNA*

## INTRODUCTION

Cancer is a collective term for a large group of diseases characterized by the growth of anomalous cells beyond their usual perimeter that allows them to invade adjoining parts of the body and/or advance to the other organs. Cancer is known to be the second leading cause of death globally and is estimated to account for 9.6 million deaths in 2018 (WHO 2018). Cancers that are most commonly identified in male are lung, prostate, colorectal, stomach and liver cancers whilst breast, colorectal, lung, cervix, and thyroid cancers are the most common among women (Choo et al. 2019; Md Pauzi et al. 2019; Nies et al. 2018; Yap et al. 2018, 2017).

Cancer incidences are hiking up in Malaysia. In 2014, cancers contributed 13.02 % of all deaths in the Ministry of Health (MOH) hospitals compared to 9.23 % in 1994 (Ministry of Health Malaysia 2017). Among the cancer incidences, gastric cancer was the eighth most common cancer in male and tenth in female with the highest incidence rate recorded among Chinese followed by Indian and Malay for both sexes (Azizah et al. 2016).

Patients with gastrointestinal (GI) tract neoplasms usually suffer from malnutrition (Choi & Kim 2016; Liu et al. 2017) and suppressed immune functions (Schattner 2003). This situation might be worsened by major elective surgery. Hence, provision of adequate nutrition becomes an important approach in managing patients with gastric cancer.

Total parenteral nutritional (TPN) and enteral nutritional (EN) supports are sought after in clinical settings to help immune-suppressed gastric cancer patients. The EN is emphasized for patients with GI malignancy during the perioperative period to accelerate bowel function recovery and improve nitrogen balance and immune response while reducing post-operative complications and hospitalization time (Liu et al. 2012). In addition to conventional enteral nutrition, application of immunonutrition (IN) containing arginine, glutamine, omega-3 fatty acids and nucleotides (RNA), either alone or in combination, has gained increasing attention due to various improved health benefits seen among patients following enteral immunonutritional (EIN) support (Fujitani et al. 2012).

Surgery is the key curative treatment for gastric cancer. However, the total gastrectomy is known to be associated with post-operative catabolism, and perturbation in metabolic, endocrinal, neuroendocrinal and immune systems which in turn contribute to high post-operative morbidity among gastric cancer patients (Fujitani et al. 2012). On that account, IN is a promising treatment option for them in order to modify their metabolic status and immune responses, reduce the incidence of post-operative complications and shorten the length of hospital stay. This systematic review on the outcomes of IN among gastric cancer patients receiving enteral IN (EIN) in the pre-and post-operative periods intends to provide reliable empirical evidence to corroborate the aforementioned health-

improving benefits of IN. In this systematic review, the effectiveness of EIN in gastric cancer patients was deliberately reviewed in terms of pre- and post-operative outcomes. The positive outcomes of EIN such as improving the patients' overall health status, reducing post-operative infection complications and the period of hospitalization are greatly attributed to the immune-boosting elements in the EIN.

## METHODS

### PROTOCOLS AND REGISTRATION

The protocol and guidelines for preparing this systematic review were based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.

### ELIGIBILITY CRITERIA AND SELECTION CRITERIA

In the primary screening, all duplicate articles were removed and publications deviating from this review goal were excluded. Reports that described gastric cancer patients receiving pre- or post-operative EIN were included. Reports involving interventional approaches were selected over observational or case-control studies. The selected reports were assessed for the quality and equality of methodology. Finally, according to the objectives and eligibility criteria of this review, we included studies that: described interventions in the form of clinical trials with randomized controlled (blind or non-blind experiment, open-label) and/or non-randomized and/or non-controlled trials; involved adult (>18 years) gastric cancer patients; implicated male and/or female (non-pregnant/lactating) gastric cancer patients; described pre- and post-operative EIN interventions via oral or enteral feeding tubes; described interventions with or without control groups, and control groups with or without placebo or any other interventions. The exclusion criteria were: studies without interventions and non-clinical studies; non-reviewed articles; patients having the other combined cancers; patients on the parenteral nutrition; patients receiving immunosuppressive drugs, and patients undergoing radiotherapy.

Studies were identified and selected through electronic search and article screening from databases such as PubMed (1968 to October 2018), OVID (1980 to October 2018), EBSCOhost (1980 to October 2018) and COCHRANE. According to PICO, the keywords and text terms used in COCHRANE comprising gastric cancer patients (population), clinical trial (study design), pre- and post-operative EIN (intervention), laboratory indices and clinical outcomes (outcome) were used. Laboratory indices included interleukin-2 (IL-2), immunoglobulin-G (IgG), serum albumin whereas clinical outcomes included the length of hospital stay and post-operative complications. In PubMed, OVID and EBSCOhost, medical subject headings (MeSH) defining the PICO, such as 'Gastric

Neoplasm', 'Gastric Cancer', 'Gastric Tumor', 'Gastric Carcinoma', 'Arginine', 'Glutamine', ' $\omega$ -3 Fatty Acids', 'Enteral Immune Nutrition', 'Immune-Enhancing Enteral Nutrition', 'Immunoenhanced Enteral Nutrition' and 'Enteral Immunonutrition' were used to select eligible reports. All studies were limited to full-text articles describing human studies published in the English language. Conference abstracts and proceedings were excluded.

#### INFORMATION SOURCES AND SEARCH STRATEGY

Keywords used for literature search included gastric cancer; gastrectomy, enteral immunonutrition; omega-3 fatty acids; glutamine; arginine; ribonucleic acid (RNA), pre-operative, post-operative. Table 1 summarizes time-frame and chronology of literature search and MeSH used for literature search.

#### DATA COLLECTION AND STUDY CHARACTERISTICS

In this systematic review, characteristics of each selected study were extracted, analysed and cited. Data were pulled out and categorized according to five 'PICOS' components in order to maintain the explicitness of this review: patient population (P); interventions or exposure of interest (I); comparators (comparison between interventions) (C); main outcomes or endpoint of interest (O); and the chosen study design (S). The data were further refined to the following characteristics: study (setting, type of study design, eligibility criteria), patient population (number of participants, age, gender, ethics) and control groups, EIN (duration, dosage/prescription/contents) and control regimen. Post-operative adverse effects observed in intervention groups receiving EIN were also extracted.

#### DATA ANALYSIS AND SUMMARY MEASURES

Measurable outcomes especially laboratory indices were recorded in respective units. The following laboratory indices of the selected studies were compared:

C-reactive protein (CRP) (mg/dl); Serum albumin (g/L); IL-2 and tumour necrosis factor alpha (TNF- $\alpha$ ) (pg/mL); Immunoglobulin-M (IgM) and IgG (g/L); and CD4+ and CD8+ T cells (%).

The eligibility and validity of the selected articles (risk of bias) were analysed using the Cochrane Collaboration's tool adapted from Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Table 2) (Cochrane Back & Neck 2011; Higgin et al. 2011). This is to minimize bias during data extraction from the selected articles.

## RESULTS

#### STUDY CHARACTERISTICS

In this systematic review, 75 studies were initially identified across four electronic databases. After removal

of 8 duplicates and 34 irrelevant studies, 33 articles were eligible for further full-text screening of which 24 articles did not meet the criteria of article selection. Thus, only 9 articles with a total number of 780 subjects were included in the final analysis. The flow of article selection and screening was outlined in Figure 1.

The eligibility of the selected articles was assessed using the Cochrane Collaboration's tool. Due to lack of data, the risk of bias for a few factors could not be completely determined, such as the allocation concealment, blinding of the participants and personnel, blinding of outcome assessors and funding (Table 2). However, two major contributing components of this systematic review were free from risk of bias: outcome data and reporting. This permitted us to proceed with the systematic review of the selected articles.

The characteristics and selection parameters of the selected articles were tabulated in Table 3. Most of the articles reported both laboratory findings and clinical and outcomes, and more than one immune-boosting element like arginine, glutamine, omega-3 fatty acid, RNA and others were incorporated in the IN. The EIN was supplied post-operatively in the majority of the studies whereas two studies supplied pre-operative EIN. Subjects in the studies were mostly elderly aged 60 years old and above, however, in a few studies, subjects aged 37 to 70 years old were involved. The studies were performed in China, USA, Japan, Spain and Italy.

#### IMPROVEMENT OF THE OVERALL HEALTH STATUS

Both pre- and post-operative EIN resulted in positive outcomes especially on the overall health status of the patients. In the majority of the studies, the incidences of post-operative infection complications in the immune-enhancing diet (ID) group were significantly ( $p < 0.05$ ) lower (0 - 7.4 %) than that of the conventional diet (CD) group (9.3 - 28 %). This is in line with the significantly lower number of post-operative infections in the ID group (2 cases) than that of the CD group (8 cases) ( $p = 0.039$ ). In addition to that, the anastomotic leak rate was also lower in the ID group (3.7 % vs 7.3 %,  $p < 0.05$ ) (Marano et al. 2013; Okamoto et al. 2009; Scislo et al. 2018). The duration of Systemic Inflammatory Response Syndrome (SIRS) was therefore significantly ( $p < 0.05$ ) shorter ( $0.77 \pm 0.9$  days) in the ID group than that observed in the CD group ( $1.34 \pm 1.45$  days) (Okamoto et al. 2009). These findings prove that EIN supplemented with arginine, omega-3 fatty acids and RNA in the early post-operative period strengthens the immunity of gastric cancer patients undergoing gastrectomy. They showed increased collagen synthesis and demonstrated improved surgical wound healing which in turn reduced general morbidity (Farreras et al. 2005) omega-3 fatty acids and ribonucleic acid (RNA). A significant reduction of CD4+ T cell count was observed in several reports (Braga et al. 1999; Marano et al. 2013; Okamoto et al. 2009). The CD4+ T cell count of the ID group on day-7 post-operation was significantly lower than that of the standard enteral nutrition group ( $352 \pm 45$  vs

TABLE 1. Database search details and MeSH used for literature search

No.	Item	Explanation
1.	Date of literature search	24 September 2018 - 21 December 2018.
2.	Period cover by the literature search	Multiple databases were systematically searched and the review included all publications in the past 15 years (December 2003 - December 2018).
3.	Literature sources used to identify data	<p>There are various sources of literature used which include the following sources:</p> <ol style="list-style-type: none"> <li>1. Electronic literature search</li> <li>2. Scientific databases</li> <li>3. Citations referenced in scientific literature</li> </ol> <p>A comprehensive search strategy was used to identify and access the relevant literature, involving multiple databases like PubMed, OVID, EBSCOhost and Cochrane library.</p> <p>The search strategy for selection of literature was documented and justified where objective, non-biased and systematic search and review methods were employed. The uses of precise search term were applied to reduce the risk of missing studies.</p> <p>The title, abstract and full text studies were assessed according to eligibility criteria. Then, the data were extracted using a standardized form and being summarized in a descriptive table.</p>
4.	Databases search details	<p>Databases were searched using the following keywords for title and abstract:</p> <ol style="list-style-type: none"> <li>1. Clinical trial AND gastric cancer OR gastrectomy</li> <li>2. Gastric cancer AND pre-operative AND post-operative</li> <li>3. Gastric cancer AND post-operative</li> <li>4. Gastric cancer AND pre-operative AND post-operative</li> <li>5. Enteral immunonutrition and gastric cancer</li> <li>6. Pre-operative enteral immunonutrition AND post-operative enteral immunonutrition</li> <li>7. EffectivenessOR efficacy of enteral immunonutrition AND gastric cancer</li> </ol> <p>Our search strategy identified 75 potential studies through electronic search. Most of the studies (N=66) were excluded following the database search details and exclusion criteria. The remaining studies (N=9) met the eligibility criteria and included in the review.</p>
5.	Selection criteria used to choose articles	<p>Inclusion criteria</p> <ol style="list-style-type: none"> <li>1. Male or female adult gastric cancer patients aged &gt;18 years</li> <li>2. Described pre- and post-operative EIN interventions via oral or enteral feeding tubes</li> <li>3. Described interventions with or without control groups</li> <li>4. Control groups with or without placebo or any other interventions.</li> <li>5. Interventions in the form of clinical trials with randomized controlled (blind or non-blind experiment, open label) and/or non-randomized and/or non-controlled trials</li> </ol> <p>Exclusion criteria</p> <ol style="list-style-type: none"> <li>1. The studies without interventions and non-clinical studies</li> <li>2. Non-reviewed articles</li> <li>3. Patients having other combined cancers</li> <li>4. Patients on parenteral nutrition</li> <li>5. Patients receiving immunosuppressive drugs</li> <li>6. Patients on radiotherapy</li> </ol>

542 ± 53, p=0.032). Such reduction implies EIN is capable of limiting CD4+ T cell-mediated pro-inflammatory responses that are commonly associated with post-operative complications. Furthermore, those receiving EIN also showed improved serum levels of total serum protein, albumin, pro-albumin, transferrin, NK cells, IgM, IgG, inflammatory cytokines such as IL-6 and TNF- $\alpha$  (Chen et

al. 2015; Farreras et al. 2005; Liu et al. 2012; Scisslo et al. 2018; Marano et al. 2013; Zhao et al. 2013). The improved levels of serum proteins might indicate better nutritional status of the individuals whereas the increased levels NK cells, antibodies and cytokines could mean better cell-mediated and humoral responses that protect them from post-operative infections and complications.

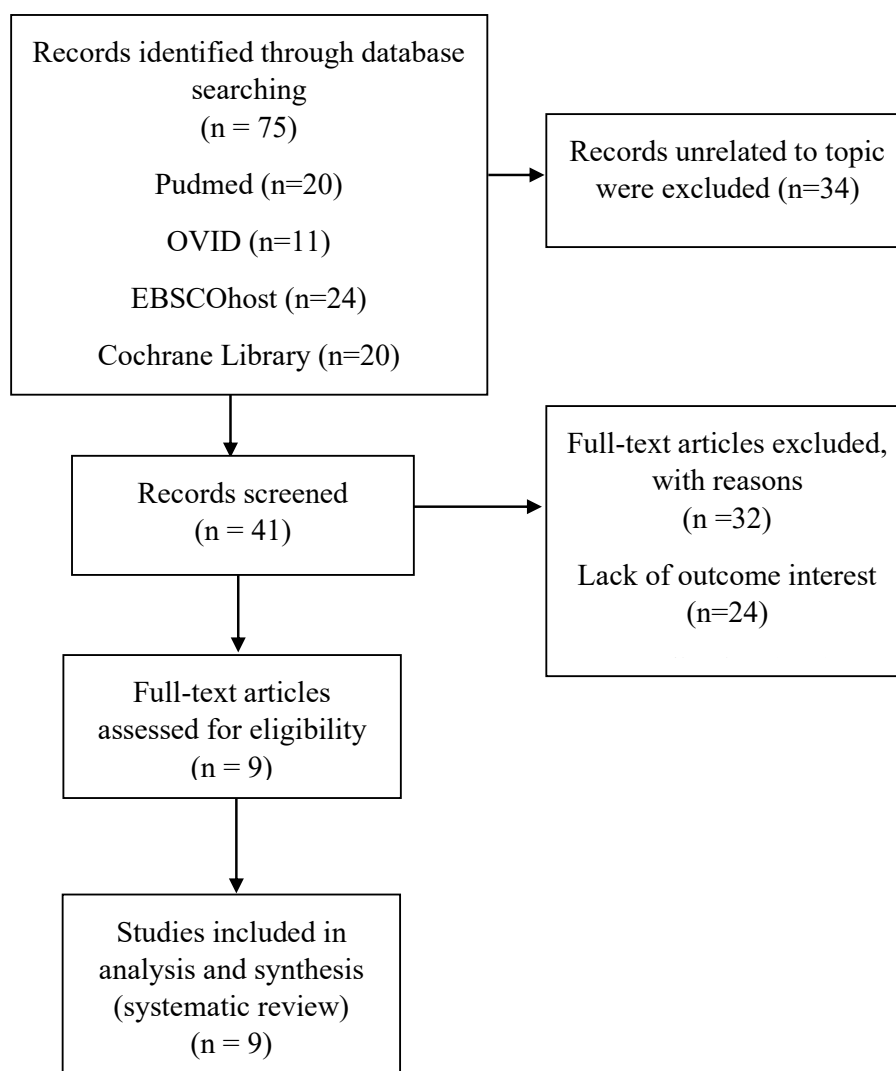


FIGURE 1. The selection of eligible articles for analysis

Despite the benefits of EIN as discussed in the majority of the articles, two studies showed no significant differences in the post-operative pulmonary infections between the immunonutrition group and the control group (Liu et al. 2012; Zhao et al. 2013). Fujitani et al. (2012) also showed that the five-day pre-operative EIN failed to prevent early clinical outcomes of systemic acute-phase responses in well-nourished gastric cancer patients undergoing elective total gastrectomy.

#### OVERALL LENGTH OF HOSPITAL STAY

Generally, the length of hospital stay is used to indicate the efficiency of a treatment. Among the nine chosen randomized controlled trials, four of the studies found the length of hospital stay of those receiving IN was significantly shorter ( $12.7 \pm 2.3$  -  $23.8 \pm 16.6$  days) compared to the control or standard diet group ( $15.9 \pm 3.4$  -  $25 \pm 10.6$  days) (Farreras et al. 2005; Liu et al. 2012; Marano et al. 2013; Okamoto et al. 2009). Zhao et al. (2013) however, reported no significant differences in the

duration of hospital stay ( $P=0.73$ ) between the arginine-supplemented and control groups. The authors hypothesized that such variations could be affected by the relatively small sample size.

Although post-operative EIN is generally beneficial to gastric cancer patients in the context of improving their overall health and reducing the length of hospital stay, certain individuals may not experience the advantages, as do the other patients. This is largely due to some inherent biological factors such as the body metabolism and serum protein levels, and the individual immunity.

#### DISCUSSION

Generally, IN is defined as utilization of specific nutritional elements to modulate the immune system, which in turn improves certain injury or disease states (Chow & Barbul 2014). In IN, supranormal quantities of nutrients are supplied via the enteral or parenteral route to achieve pharmacological effects (Grimble 2005). EIN refers to

TABLE 2. Validity assessment including Risk of Bias Model for reviewed studies

Authors, year (Reference)	Internal validity							
		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other biases
	External validity	Random sequence generation	allocation concealment	Blinding of participants and personnel	Blinding (or masking) of outcome assessors	Incomplete outcome data, fail to follow-up	selective outcome reporting	funding
Okamoto et al. (2009)	/	?	?	?	?	!	!	?
Mochiki et al.(2011)	/	?	?	!	?	!	!	?
Fujitani et al. (2012)	/	!	!	?	?	+	+	?
Liu et al. (2012)	/	!	?	?	?	!	!	?
Marano et al. (2013)	/	!	?	?	?	!	!	?
Zhao et al. (2013)	/	?	?	!	?	!	!	!
Scisslo et al. (2018)	/	!	+	+	?	!	!	!

Low Risk of Bias ; High Risk of Bias ; Unclear Risk of Bias 

standard EN supplemented with specific immune-promoting compounds, such as arginine, glutamine, omega-3 fatty acids and RNA. These compounds are responsible for strengthening immune defense and intestinal barriers, and modulating inflammatory responses (Chen et al. 2005). IN is recommended for patients undergoing abdominal surgery such as cancer and malnourished patients both pre-operatively and post-operatively.

The experimental and clinical findings have proven the benefits of IN particularly in up-regulating the host's immunity, controlling inflammatory responses, modulating the synthesis of acute-phase and constitutive proteins, improving gut oxygenation and barrier functions after injury, and reducing morbidity and mortality due to post-operative infections (Gianotti et al. 2002). This is especially evident in gastric cancer patients undergoing surgery. Their nutritional status deteriorates after gastrectomy. This often leads to decreased food intake and reduced body weight (Shim et al. 2013). As a result, malnutrition in this population causes them more susceptible to infection complications. In addition to that, IN also ensures well-regulated inflammatory responses take place after surgery. Controlled inflammatory responses are essential for wound healing, immune processes and successful recovery from an earlier surgery. This is because any uncontrollable systemic inflammatory events may lead to organ dysfunction and adverse outcomes (Chen et al. 2005).

The nutritional constituents included in an IN formula play an important role in balancing the inflammatory and anti-inflammatory responses. The functions of a few commonly employed immune-boosting nutrients, such as omega-3 fatty acids and amino acids are described as follows:

#### OMEGA-3 FATTY ACIDS

Omega-3 fatty acids (FAs) generally modulate the structural and functional integrity of cell membranes, intercellular signal transduction and synthesis of eicosanoids (important immune mediators) (Alexander 1998; Chan et al. 2005). Fish oil-derived omega-3 fatty acids displace arachidonic acid (AA) of immune cell membranes, thus reduces the production of inflammatory prostaglandins and prostacyclins (Martin & Stapleton 2010), as well as cytotoxicity of inflammatory cells (Hegazi et al. 2014). Fish oil-derived omega-3 FAs such as eicosapentaenoic and docosahexaenoic acids are also precursors of resolvins. They help reduce cellular inflammation through inhibition of inflammatory cell migration and mediators to affected sites (Hegazi et al. 2014).

#### ARGININE

Arginine stimulates secretion of a variety of hormones, such as growth hormones, glucagons and insulin that exert concerted modulatory effects on immune responses (Chen

TABLE 3. Characteristics of eligible studies

No.	Authors & year of publication	Country	Diagnosis	Ages of patients (years)	Sample size (EIN/EN)	Elements of EIN	Nature of EIN	Duration of EIN support (days)	Mode of enteral feeding	Outcomes (Improvement)
<i>Pre-operative administration</i>										
1.	Okamoto et al. (2009)	Japan	Gastric adenocarcinoma	66.9±11.5 (EIN) 70.9±13.2 (EN)	30/30	Arginine, omega-3 fatty acids & RNA	Standard EN	7	Oral	CD4+, CD8+, SIRS, lymphocytes, LHS, post-operative complications, operation time, intra-operative blood loss.
2.	Fujitani et al. (2012)	Japan	Gastric adenocarcinoma	64 (26-78) EIN 65 (30-79) (EN)	120/111	Arginine & RNA	Regular diet	5	Oral	Mortality, pulmonary infections, post-operative complications.
<i>Post-operative administration</i>										
1.	Liu et al. (2012)	China	Advanced gastric cancer	57.3±7.1 (EIN) 58.4±6.3 (EN) 56.2 ± 6.7 (Control)	28/24/26	Arginine & glutamine	Standard EN	7	Nasoenteral	Total protein, albumin, proalbumin, transferrin, CD4+, CD8+, IgM, IgG, LHS, post-operative complications, incision infections, pulmonary infection.
2.	Chen et al. (2005)	China	Gastric carcinoma	NA	20/20	Arginine, glutamine & omega-3 fatty acids	Standard EN	7	Nasoenteral	Proalbumin, albumin, transferrin, CD4+, CD8+, IgM, IgG.
3.	Mochiki et al. (2011)	Japan	Gastric cancer	65±2.6 (EIN) 59±2.1 (EN)	15/16	Glutamine	Oral placebo	NA	Oral	Operation time, intra-operative blood loss.
4.	Farreras et al. (2005)	Spain	Gastric cancer	66.7±8.3(EIN) 69.2±13.8 (EN)	30/30	Arginine, glutamine & omega-3 fatty acids	Standard EN	7	Oral	Total protein, albumin, proalbumin, lymphocytes, incision infections, pulmonary infections, post-operative complications, mortality.
5.	Marano et al. (2013)	Italy	Gastric adenocarcinoma	66.6 (55-78) (EIN) 65.1 (49-83) (EN)	54/55	Arginine, glutamine, omega-3 fatty acids & RNA	Standard EN	7	Oral	Total protein, albumin, transferrin, CD4+, CD8+, lymphocyte, LHS, SIRS, incision infections, post-operative complications, operation time, mortality, intra-operative blood loss.
6.	Scisslo et al. (2018)	USA	Gastric Cancer	62.6 (EIN) 62.9 (Control)	44/54	Arginine, omega-3 fatty acids & RNA	Protein-rich, isocaloric, no-residue diet	6	Naso-jejunal feeding	Infections, wound healing and pneumonia.
7.	Zhao et al. (2013)	China	Gastric cancer	37 - 59 (EIN) 36 -56 (EN)	37/36	Arginine	Standard EN	7	Tube feeding	Incision and pulmonary infections.

LHS: Length of hospital stay; SIRS: systemic inflammatory Response Syndrome

et al. 2005). Therefore, arginine is a crucial immunomodulating nutrient and also a precursor for nitric oxide (NO) synthesis (Hegazi et al. 2014). Clinical studies evaluating the effects of enteral arginine supply demonstrated net nitrogen retention, increased protein synthesis and improved wound healing (Barbul 1986). Arginine, therefore, helps improve systemic inflammatory responses resulted from unbalanced release of NO. An immune-modulating enteral diet containing increased amounts of arginine and fish oil is therefore, advocated in all high-risk patients undergoing major surgery (Hegazi et al. 2014).

#### GLUTAMINE

Glutamine is the most abundant amino acid in the plasma and a primary metabolic fuel for rapidly proliferating cells (Chow & Barbul 2014). It helps maintain gut barrier functions, induces expression of heat shock proteins and stimulates nucleotide synthesis (Wischmeyer 2007). During catabolic stress due to trauma, sepsis and burn, glutamine is rapidly released from muscle stores and serum; this, in turn, reduces the expression of inflammatory cytokines. As a result, the induction of heat shock protein synthesis via glutamine supplementation may promote inflammatory responses that are needed to fight post-operative infections, hence shorter hospital stay and ventilator time among critically ill patients (Singleton et al. 2005). Therefore, glutamine becomes conditionally essential to patients undergoing physiological stress conditions (Lacey & Wilmore 1990).

#### LIMITATIONS

We acknowledge a number of limitations of this systematic review. The non-English studies were not included in this review. Due to the lack of relevant articles, local studies were also excluded. The EIN-related indicators such as cost-effectiveness were not reported due to inconsistent data presentation in the selected articles. Considerable between-study heterogeneity on the biochemical and clinical outcomes was observed. Besides, we also faced difficulties to match the outcomes due to geographical differences. Regardless of the limitations, we still carried out the assessment of Risk of Bias using the Cochrane Collaboration's tool in order to ensure an objective data analysis.

#### CONCLUSION

Regardless of the initiation timing (pre-operative and post-operative) of IN, this systematic review clearly demonstrates that IN comprising various immune-boosting elements is able to improve overall health status of gastric cancer patients especially infection complications and the length of hospital stay through modulation of immune responses. In order to ensure a more consistent reporting of the robust health benefits of IN, more randomized control trials with

a better quality of methods and a larger sample size are warranted. In the nutshell, pre- and post-operative IN supplementation is recommended for gastric cancer patients. An effective immune-modulating diet is suggested to begin at least 5 days prior to a surgery and be continued through the post-operative period whenever such initiation is feasible (Marik & Zaloga 2010). This is believed to provide additional energy and nitrogen supplies for wound healing and to compensate impaired immune responses resulted by the earlier surgery (Gianotti et al. 2002).

There are several practical recommendations made based on McCowen and Bistrain (2003) to maximize the success of EIN such as: arginine should be >12 g/L; duration of EIN should be >3 days, preferably 5-10 days; nasogastric feeding should be executed every 4-6 h, and gastric residuals of  $\approx$  200 mL should be acceptable; and feeding goal should reach 25 kcal/kg, and  $\geq$  800 mL/d should be given for optimum outcomes.

#### ACKNOWLEDGEMENTS

All authors have contributed equally to the design of study and data acquisition, manuscript preparation and writing. We declare no conflict of interest.

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Received: 13 June 2019

Accepted: 11 November 2019