Original Article

Economic value of nutritional support methods in gastrointestinal cancer: A quantitative meta-analysis

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Background and Objectives: Multiple studies of the relative economic value of different nutritional support methods for patients with gastrointestinal cancer have provided inconsistent results. **Methods and Study Design:** The PUBMED and EMBASE databases were systematically searched through September 30, 2018to identify latent studies of the benefits of parenteral nutrition (PN), enteral nutrition (EN) or conventional intervention (CI) in gastrointestinal cancer patients. A fixed-effects model or random-effects model was applied depending on the heterogeneity of the studies. Statistical analysis was conducted using R software. A total of 728 studies were reviewed, and 21 studies published from 1998 to 2018 were included in the final analysis. **Results:** The results showed that the hospitalization expenditure of the EN group was 3938 RMB less than that of the PN group. Similarly, the EN group had a shorter length of hospitalization than the PN and CI groups. The infection rate was lower in the EN group (12%) than in the PN group (16%) and CI group (20%). Subgroup analysis showed that gastrointestinal cancer patients who received oral nutritional supplements had the lowest infection rate (11%) after surgery. **Conclusions:** EN, especially oral nutritional supplements, has a positive economic impact on patients with gastrointestinal cancer, based on reductions in the post-operative infection rate, length of hospitalization, and hospitalization expenditure.

Key Words: nutritional support, economic value, parenteral nutrition, enteral nutrition, meta-analysis

INTRODUCTION

The Global Cancer Statistics 2018 reported that over 1.8 million new colorectal cancer cases and 1,000,000 new stomach cancer cases were estimated to occur in 2018, while the mortality rates for these cancers were also ranked in the top three of all cancers.[1] For all gastric cancer patients with surgical indications, surgical treatment is still the first-line treatment. The operation for gastric cancer itself involves a large area of trauma, requiring reconstruction of the digestive tract and a long fasting time after surgery.[2] Furthermore, patients with malignant tumors undergoing selective gastrointestinal surgery have a high risk of post-operative infection, such as wound infection and respiratory tract infection.[3] These factors not only bring uncertainty regarding the clinical response, but also prolong hospital stays and place additional financial burden on patients. Studies have confirmed that nutritional deficiency will lead to a decrease in the quality of life of patients, an increase in treatment-related adverse reactions, and a decrease in the treatment response rate and survival rate.[4,5] Malnutrition is one indicator of severe illness and poor prognosis.[6]

Therefore, adequate nutritional support is of great significance for the recovery of gastrointestinal cancer patients after surgical treatment. Nutritional support for patients who have undergone surgery for gastrointestinal tumor removal generally involves parenteral nutrition (PN) or enteral nutrition (EN). PN usually achieves a positive nitrogen balance and reduces weight loss, but it may lead to inflammation.[7] Although it has been demonstrated that PN alone is superior to non-nutritional support or

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conventional intervention (CI),[8] EN, especially with oral nutritional supplements (ONS), has been increasingly valued by clinicians in recent years due the advantages of conforming to physiological conditions and contributing to the recovery of gastrointestinal function and morphology.[9]

However, studies evaluating the effectiveness of nutritional support for patients with gastrointestinal cancer have mostly focused on clinical indicators in recent years, while economic evaluation of different nutritional support modes has been neglected, especially a quantitative comparison among different types of nutritional interventions. Therefore, the present study reviewed and quantified economic factors associated with different types of nutritional interventions in patients with gastrointestinal cancer.

METHODS

Search strategy

A systematic review and meta-analysis were conducted in accordance with the Systematic Review and Meta-analysis (PRISMA). The Pubmed and Embase databases were searched for qualifying research from the establishment of each database through September 30, 2108 by applying the following search terms:

Pubmed

((((((((((((((cost[Title/Abstract]) OR effectiveness[Title/Abstract]) OR effective[Title/Abstract]) OR effect[Title/Abstract]) OR efficacy[Title/Abstract]) OR economic[Title/Abstract]) OR expense[Title/Abstract]) OR budget[Title/Abstract]) OR price[Title/Abstract]) OR benefit[Title/Abstract]) OR finance[Title/Abstract])) AND ((((((Nutritional Support[Title/Abstract]) OR Enteral Nutrition[Title/Abstract]) OR Parenteral Nutrition[Title/Abstract]) OR Oral Nutrition[Title/Abstract])) AND (((((Gastrointestinal Neoplasms[MeSH Terms]) OR stomach cancer[Title/Abstract]) OR Colorectal cancer[Title/Abstract]) OR gastric cancer[Title/Abstract]) OR Colon cancer [Title/Abstract]).

Embase

#1.'gastrointestinal neoplasms':ab,ti OR 'stomach cancer':ab,ti OR 'colorectal cancer':ab,ti OR 'gastric cancer':ab,ti OR 'colon cancer':ab,ti

#2.'nutritional support':ab,ti OR 'enteral nutrition':ab,ti OR 'parenteral nutrition':ab,ti OR 'oral nutrition':ab,ti

#3. 'cost':ab,ti OR 'effective':ab,ti OR 'effectiveness':ab,ti OR 'effect':ab,ti OR 'efficacy':ab,ti OR 'economic':ab,ti OR 'expense':ab,ti OR 'budget':ab,ti OR 'price':ab,ti OR 'benefit':ab,ti OR 'finance':ab,ti

#4. #1 and #2 and #3

When we review the Embase, the duplicate databases were removed, in order to reduce the repetition rate. The studies were restricted to the ones which final publications are in English. Study selection began with a review of titles and abstracts, but if the information obtained was insufficient to support the decision, the full text needed to be read. In order to collect as many studies as possible, studies were also identified from citations of other papers and references. All searches were conducted by two independent investigators, and any conflict was resolved through discussion.

Inclusion and exclusion criteria

The eligibility criteria for inclusion of studies in the present analysis were as follows: 1) Patients were pathologically diagnosed with gastrointestinal cancer (limited to gastric and colorectal position); 2) The study compared clinical outcomes between patients who received PN and EN or CI; 3) The patients underwent surgical treatment; and 4) High-quality data could be extracted from the study.

Studies that did not meet the above inclusion criteria were excluded.

Data extraction

The data extraction process was completed by two researchers, with judgement by the third researcher when unclear information was encountered. The main data extracted for the present study were: article title, author, publication time, country, number of subjects, patients' nutritional status, location of disease, nutritional support administered, type of study (e.g., randomized controlled trial [RCT]), use of ONS intervention, hospitalization expenditure (the total cost of the hospitalization, including surgery, nutrition intervention and the treatment of all complications), infection rate (all infection complications, including surgical site infections, sepsis, pneumonia, UTI, and others infections) and other outcome indicators.

In this study, RMB was applied as the currency for comparisons and analyses. When costs in other currencies were given in the studies, we converted them according to the average exchange rate of the year in which the study was conducted.

Statistical analysis

The R software package was used for data analysis in this study, and $p<0.05$ was considered statistically significant. For continuous data, mean and standard deviation (SD) were applied with the 95% confidence intervals (95% CI). Count data were presented as rates. Heterogeneity was estimated using the Q-test and I^2. If $I^2>50\%$, the studies were considered to have homogeneity, and the fixed-effects model was used for analysis. Otherwise, the random-effects model was applied for analysis. In addition, sensitivity analysis was conducted if needed.

RESULTS

Eligible studies

A total of 728 studies were reviewed, and 142 studies were removed due to duplication. Another 500 studies were excluded due to irrelevance to the topic based on a review of the titles and abstracts. The full text of 84 potential studies was read, and of these, 21 met our inclusion criteria for final analysis.[8,10-29] The detailed search steps are presented in the flow diagram in Figure 1.

Basic information of included studies

The basic details of the 21 included studies, which were published from 1998 to 2018, are presented in Table 1. Although most of the research was conducted in Asia, some European studies were included in the analysis. The location of cancer in patients was limited to gastrointestinal cancer (6 studies), gastric cancer (7 studies) and colorectal cancer (8 studies). In terms of nutritional support

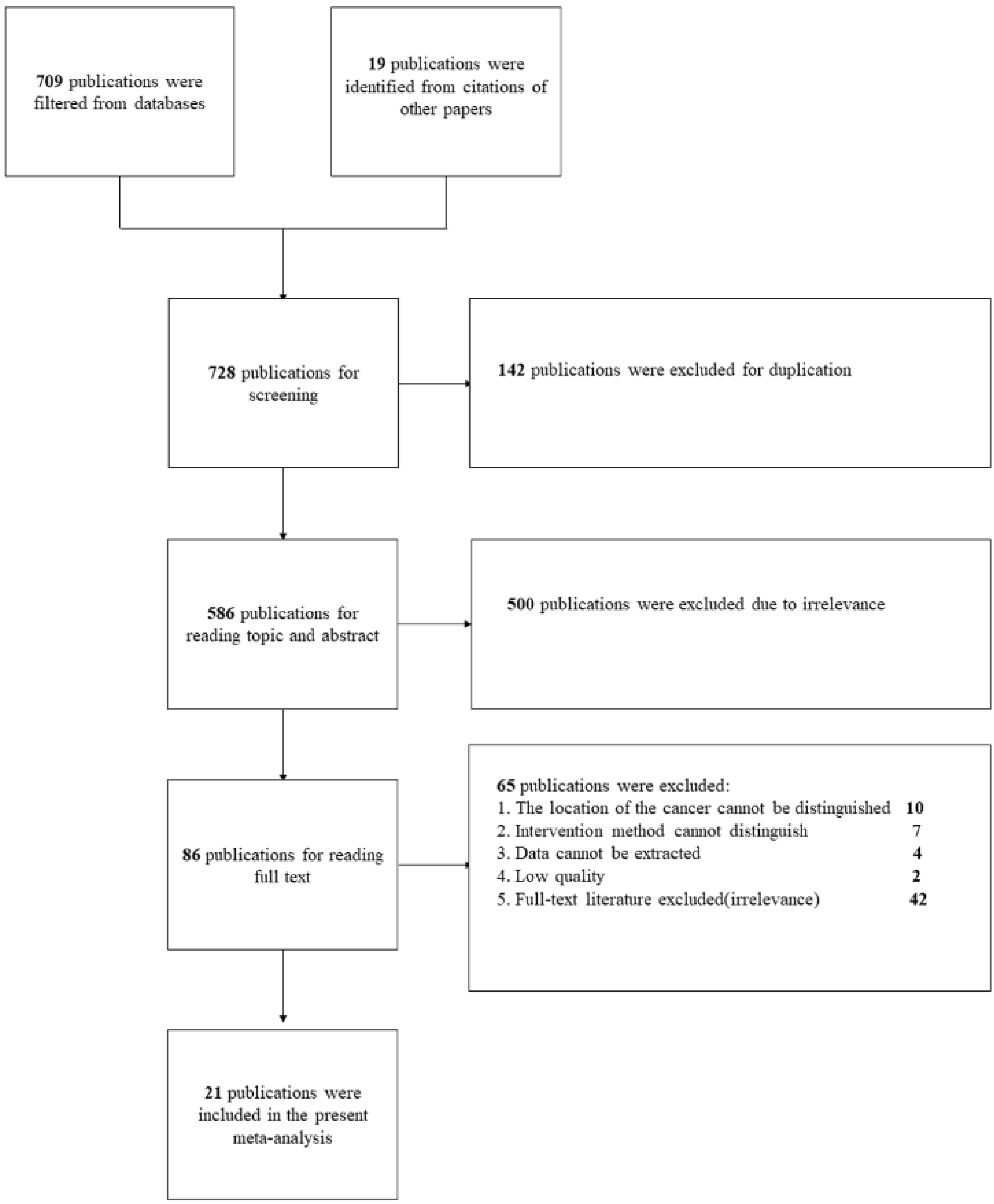

Figure 1. Flow chart of study selection.

interventions, EN was applied in 20 studies, PN in 12 studies, and CI in 6 studies. Only 3 of the 21 studies were designed as non-RCTs.

Comparison of hospitalization expenditure

Hospitalization expenditure was compared between EN and PN groups from three studies. The heterogeneity between the two groups was I^2=86%, with p<0.01. Therefore, a random effects model was used to analyze the heterogeneity. The hospitalization expenditure of the EN group was 3938 RMB less (95% CI -6999, -796) than that in the PN group (Figure 2). Similarly, Figure 3 shows that the cost of hospitalization in the EN group was 3494 RMB less than that in the CI group (95% CI -5871, -1117).

Comparison of length of hospitalization (LOH)

A total of 10 studies were included in the comparative analysis of LOH between EN and PN groups. The heterogeneity between groups was I^2=82%, and the random effects model was used for the analysis. The results showed that the LOH in EN group was 3.09 days (95% CI -3.98, -2.20) shorter than that in the PN group (Figure 4).

Another 10 studies were analyzed to explore the difference in LOH between EN and CI groups. Figure 5 shows

Table 1. Basic characteristics of the studies included in the meta-analysis

Title	Authors	Publication year	Country	No of cases			Nutrition status	Intervention			Location of cancer	Treatment	ONS	RCT
				EN	PN	CI*		EN	PN	CI*				
A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer	Gianotti, L	2002	Italy	102		102	Weight loss <10%	Standard enteral nutrition (preoperative+ postoperative)		Conventional postoperative care	Gastrointestinal cancer	Surgery	YES	RCT
Early enteral nutrition and total parenteral nutrition on the nutritional status and blood glucose in patients with gastric cancer complicated with diabetes mellitus after radical gastrectomy	Wang, J	2018	China	66	63		Not given	Early enteral nutrition (postoperative)	Total parenteral nutrition (postoperative)		Gastric cancer	Surgery	NO	RCT
Effect of preoperative immunonutrition and other nutrition models on cellular immune parameters	Gunerhan, Y	2009	Turkey	13		13	Not given	Standard enteral nutrition (preoperative)		Normal feeding (preoperative)	Gastrointestinal cancer	Surgery	NOT CLEAR	RCT
Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms	Gianotti, L	1997	Italy	86	87		Not given	Standard enteral nutrition (preoperative)	Total parenteral nutrition (preoperative)		Gastrointestinal cancer	Surgery	NO	RCT
Perioperative nutrition in malnourished surgical cancer patients e-A prospective, randomized, controlled clinical trial	Klek, S	2011	Poland	43	41		Malnourished	Standard enteral nutrition (preoperative)	Standard parenteral nutrition (preoperative)		Gastrointestinal tumors	Surgery	NO	RCT
Quick recovery of serum diamine oxidase activity in patients undergoing total gastrectomy by oral enteral nutrition	Kamei, H	2005	Japan	27	21		Not given	Standard enteral nutrition (postoperative)	Total parenteral nutrition (postoperative)		Gastric cancer	Surgery	NO	RCT
The comparison between early enteral nutrition and total parenteral nutrition after total gastrectomy in patients with gastric cancer_ the randomized prospective study	Kim, HU	2012	Korea	17	16		Not given	Early enteral nutrition (preoperative+ postoperative)	Total parenteral nutrition (preoperative+ postoperative)		Gastric cancer	Surgery	NO	RCT

Table 1. Basic characteristics of the studies included in the meta-analysis (cont.)

Title	Authors	Publication year	Country	No of cases			Nutrition status	Intervention			Location of cancer	Treatment	ONS	RCT
				EN	PN	CI*		EN	PN	CI*				
The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial	Klek, S	2008	Poland	53	49		Not given	Standard enteral nutrition (postoperative)	Standard parenteral nutrition (postoperative)		Gastrointestinal cancer	Surgery	NO	RCT
A randomized control study of early oral enteral nutrition after colorectal cancer operation	Wang, D	2014	China	43		45	Not given	Early oral enteral nutrition (preoperative+ postoperative)		Fasting (preoperative+ postoperative)	Colorectal cancer	Surgery	YES	RCT
Effect of early oral enteral nutrition on clinical outcomes after colorectal cancer surgery	Wang, Z	2013	China	24		24	Excessive obesity or malnourished	Early oral enteral nutrition (postoperative)		Conventional postoperative care	Colorectal cancer	Surgery	YES	RCT
Effect of early oral enteral nutrition on clinical outcomes after gastric cancer surgery	Mi, L	2012	China	30		30	Excessive obesity or malnourished	Early oral enteral nutrition (postoperative)		Conventional postoperative care	Gastric cancer	Surgery	YES	RCT
A randomized controlled trial of postoperative artificial nutrition in malnourished patients with gastrointestinal cancer	Wu, GH	2007	China	215	215	216	malnourished	Standard enteral nutrition (postoperative)	Standard parenteral nutrition (postoperative)	Conventional postoperative care	Gastrointestinal cancer	Surgery	NO	RCT
Early enteral nutrition after total gastrectomy for gastric cancer	Chen, W	2014	China	37	35		Not given	Early enteral nutrition (postoperative)	Total parenteral nutrition (postoperative)		Gastric cancer	Surgery	NO	No
Impact of early enteral and parenteral nutrition on prealbumin and high-sensitivity C-reactive protein after gastric surgery	Li, B	2015	China	34	34		Not given	Early enteral nutrition (postoperative)	Standard parenteral nutrition (postoperative)		Gastric cancer	Surgery	NO	RCT

Table 1. Basic characteristics of the studies included in the meta-analysis (cont.)

Title	Authors	Publication year	Country	No of cases			Nutrition status	Intervention			Location of cancer	Treatment	ONS	RCT
				EN	PN	CI*		EN	PN	CI*				
Nutrition support in surgical patients with colorectal cancer	Chen, Y	2011	China	25		174	Not given	Standard enteral nutrition (postoperative)		Conventional postoperative care	Colorectal cancer	Surgery	NOT CLEAR	No
The impact of high protein nutritional support on clinical outcomes and treatment costs of patients with colorectal cancer	Manasek, V	2016	Czech Republic	52		105	Not given	Oral enteral nutrition (preoperative+ postoperative)		Conventional care	Colorectal cancer	Surgery	YES	No
The postoperative clinical outcomes and safety of early enteral nutrition in operated gastric cancer patients	Li, B	2015	China	200	200		Not given	Early enteral nutrition (postoperative)	Standard parenteral nutrition (postoperative)		Gastric cancer	Surgery	NO	RCT
Clinical effects of early enteral nutrition in patients after laparoscopic surgery for colorectal cancer	Niu, WB	2015	China	54	54		Not given	Early enteral nutrition (postoperative)	Standard parenteral nutrition (postoperative)		Colorectal cancer	Surgery	NO	RCT
Effect of early enteral nutrition on postoperative recovery in patients with colon cancer	Yixun, Z	2014	China	30		30	Not given	Early enteral nutrition (postoperative)		Conventional postoperative care	Colorectal cancer	Surgery	NO	RCT
Effect of postoperative early enteral nutrition on the recovery of humoral immune function in patients with colorectal carcinoma undergoing elective resection	Yang, D	2013	China	32		39	Not given	Early oral enteral nutrition (postoperative)		Conventional postoperative care	Colorectal cancer	Surgery	Yes	RCT
Impact of enteral nutrition or parenteral nutrition in postoperative colorectal cancer patients on viscera organ functions and "passing wind" time	Yu, HZ	2009	China	15	15		Not given	Standard enteral nutrition (postoperative)	Standard parenteral nutrition (postoperative)		Colorectal cancer	Surgery	No	RCT

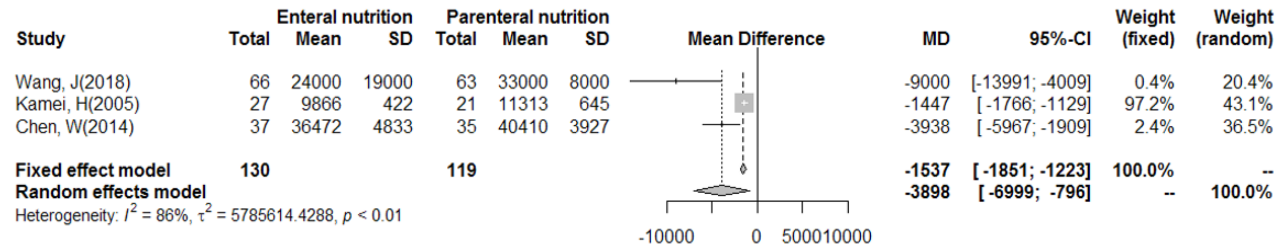

Figure 2. Meta-analysis comparing hospitalization expenditure between the EN and PN groups.

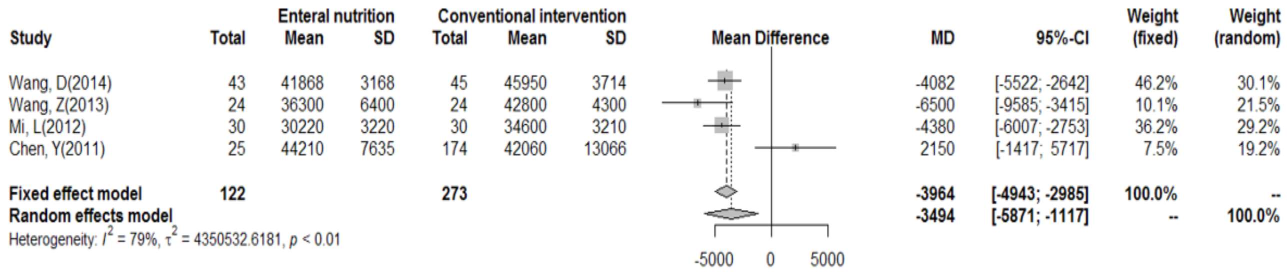

Figure 3. Meta-analysis comparing hospitalization expenditure between the EN and CI groups.

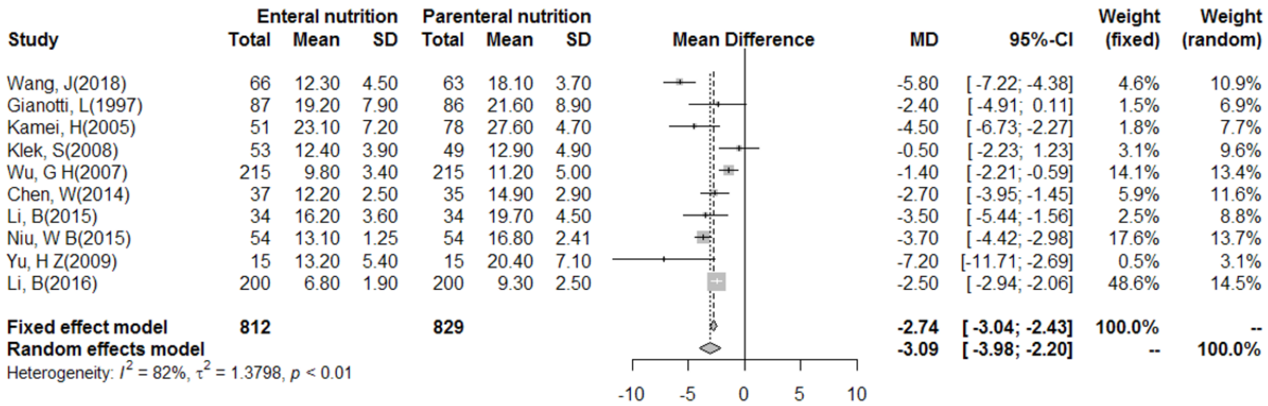

Figure 4. Meta-analysis comparing LOH between the EN and PN groups.

that patients in the CI group were hospitalized for 2.64 days longer than those in EN group. Further subgroup analysis provided consistent results; the LOH of patients who received ONS intervention in the EN group was 2.57 days less than that of patients in the CI group and 2.72 days less than that in the CI group (Figure 5).

Comparison of postoperative infection rates

Infection rate in the EN group

Fourteen studies were included in the analysis (Figure 6). The heterogeneity between groups was I^2=76%, and the results of the random effects model showed that the infection rate of the EN group was 12% (95% CI 0.08, 0.19). At the same time, subgroup analysis showed that the infection rate with ONS was 11% (heterogeneity I^2=5%, fixed effect model was applied), and the infection rate was 13% with other interventions in the EN group.

Infection rate in the PN group

A total of nine studies were included in the analysis. The heterogeneity between groups was I^2=83%, with p<0.01. Therefore, a random effects model was used for analysis. Analysis showed that the postoperative infection rate in the PN group was 16% (95% CI 0.09, 0.26; Figure 7).

Infection rate in the CI group

Data from a total of six studies were included in the random effects model to analyze the postoperative infection rate in the CI group. Figure 8 shows that the postoperative infection rate in the CI group was 20% (95% CI 0.13, 0.30).

Sensitivity analysis

Based on the stability of the results, a sensitivity analysis was conducted. The results indicated that a study should be deleted from the analysis of comparative hospitalization expenditure between EN and PN groups, due to obvious data distortion. With removal of that study, the difference in the hospitalization expenditure was reduced from 3938 RMB to 1717 RMB between the two groups. Therefore, the study conducted by Niu et al (2015) was deleted from the comparison of hospitalization expenditures between EN and PN groups.

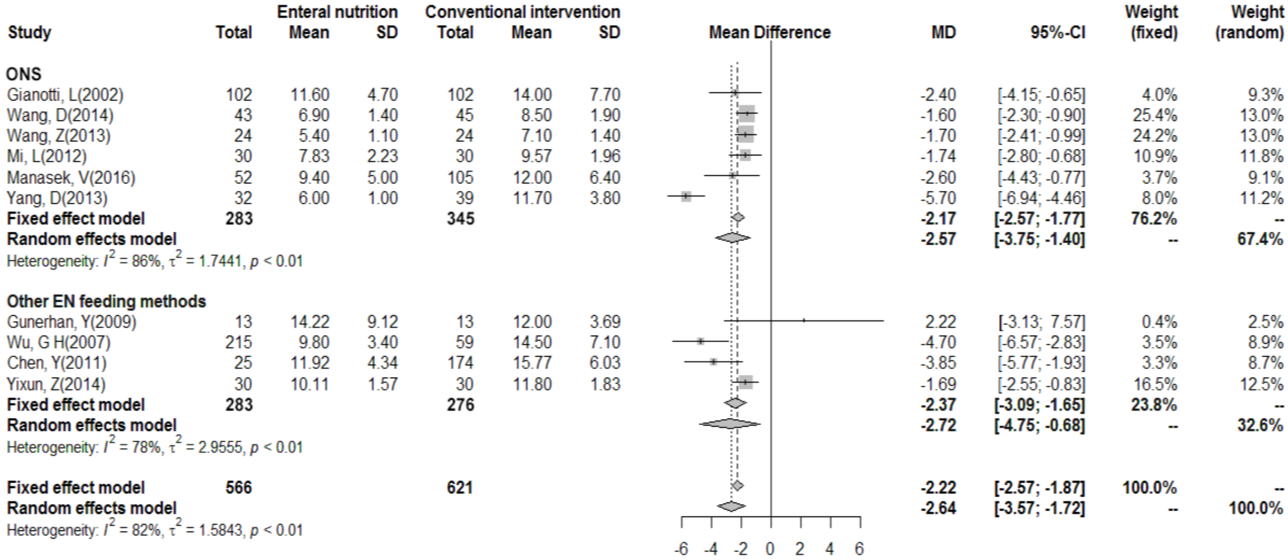

Figure 5. Meta-analysis comparing the LOH between the EN and CI groups.

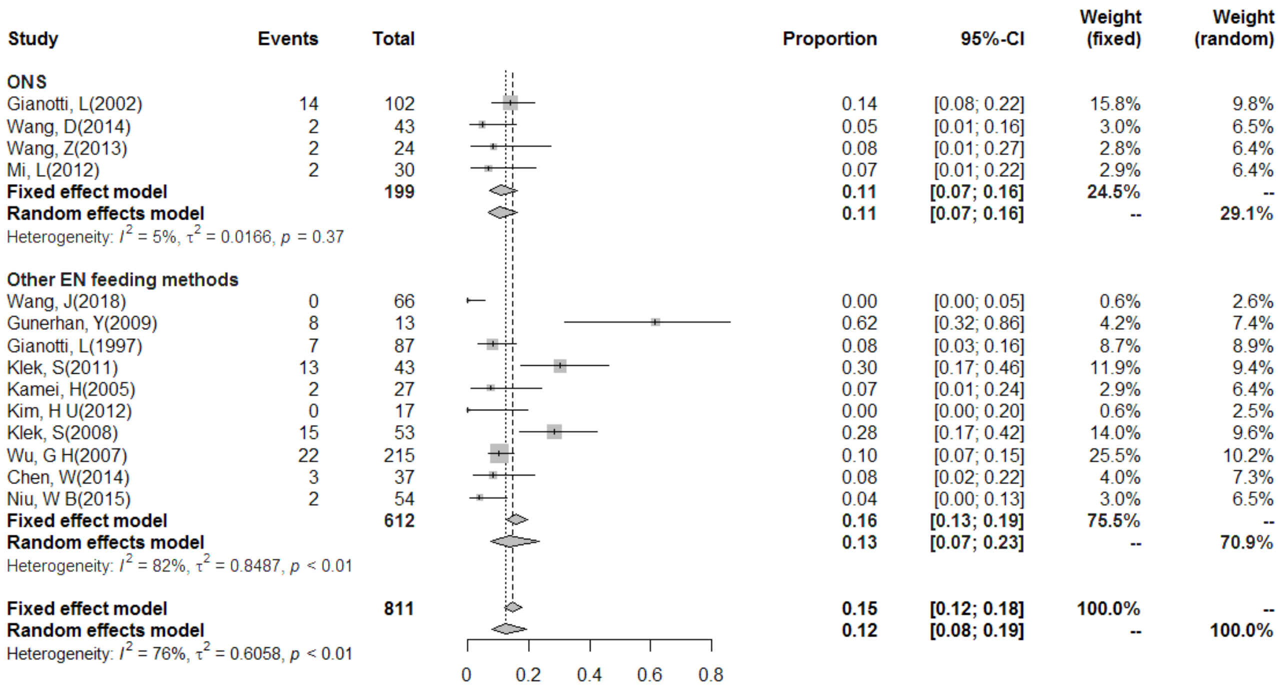

Figure 6. Meta-analysis of the infection rate with EN.

In order to collect as much data as possible, three non-RCT studies were included in the present study. After the sensitivity analysis, the three papers had little influence on the comparisons among the groups. Therefore, the three papers passed the sensitivity analysis.

DISCUSSION

The causes and development of malnutrition in cancer patients is very diverse. A common view is that abnormal metabolism of the tumor leads to malnutrition of patients who suffer from cancer. Tumor cells rapidly proliferate and divide, consuming much glucose, fat and amino acids in patients, and the body's reaction to tumors involves the production of many cytokines such as tumor necrosis factor, interleukin, interferon and prostaglandins,[30] which not only cause a series of metabolic disorders but also play important roles in malnutrition and the production of dyscrasia. Therefore, there is a close relationship between malnutrition, disease and complications.[31]

The poor nutritional status of cancer patients can affect clinical outcomes to some extent, and it will also bring greater economic burden to patients and reduce the efficiency of allocation of medical resources. A Korean study reported that low quality of life and nutritional status are associated with an increased economic burden from cancer treatment.[32] Furthermore, Kernick proposed that combining the output of health intervention resources with the input resources is very important for clinical decision-making, and researchers should provide different interventions as multiple options for clinical decision makers.[33]

At present, the main methods of nutritional intervention for patients with gastrointestinal cancer undergoing surgery are EN and PN. EN is a nutritional support meth-

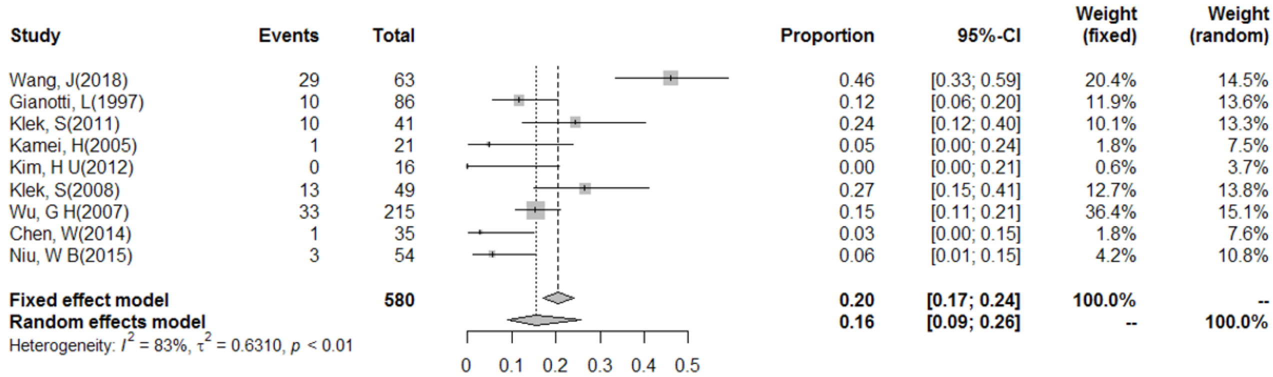

Figure 7. Meta-analysis of infection rate with PN.

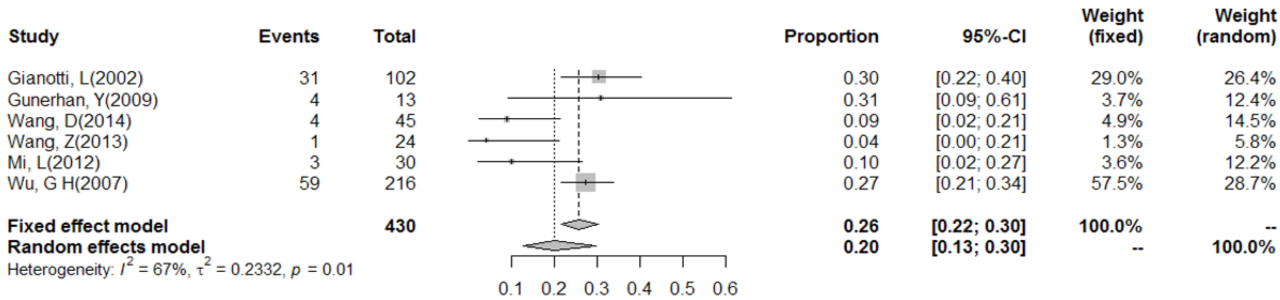

Figure 8. Meta-analysis of the infection rate with CI.

od that provides a metabolic nutrient matrix and other nutrients via oral or tube feeding into the gastrointestinal tract. PN support provides nutrients (including amino acids, fats, carbohydrates, vitamins and minerals) to inhibit catabolism, promote anabolism and maintain the function of structural proteins for patients who are unable to absorb nutrients through the gastrointestinal tract or who cannot meet their own metabolic needs.

In recent years, some studies have shown that although PN costs more than EN, most patients prefer PN, especially elderly patients.[34,35] Similarly, our study also found that the EN group had lower hospitalization costs than the PN group, which may be due to the economics of EN itself. However, lower intra-group infection rates and shorter LOH may also influence the cost of hospitalization.

From the perspective of the LOH, the EN group had a shorter LOH than the PN and CI groups. Timely administration of EN and the lower infection rate are factors that affect the LOH. However, it is worth noting that patients who generally use EN may have better physical status, which could also have some influence. However, the present study is mostly based on RCTs, so the impact in this area may not be significant.

PN treatment is convenient and can provide a high-quality nitrogen source and calories in a short time, which is well-tolerated by patients. Because it is easily absorbed and can quickly and effectively improve the nutritional status of patients, PN support is more appropriate for patients with dietary disorders and impaired digestive tract function. However, PN is prone to complications, with the most common complication being catheter-related infection. Moreover, the intestinal mucosa atrophies due to the long-term idleness of the intestinal tract, resulting in impaired intestinal mucosal immune barrier function and increased intestinal mucosal permeability, which is likely to promote intestinal infection. In our study, the infection rate in the PN group was 16%, which was higher than that in the EN group (12%). However, the infection rate was highest in the CI group, which means the nutritional interventions were beneficial for the prevention of complications during recovery from surgery for gastrointestinal cancer.

ONS, a type of EN support, showed a more meaningful impact in this study. Compared to other types of EN support, ONS resulted in the lowest infection rate (11%) due to the benefits of its non-invasive nutritional support. Unfortunately though, in terms of LOH and hospitalization costs, the data in the literature included in this study were insufficient to permit comparison of other aspects according to use of ONS. We did find that support with ONS can positively impact the LOH, compared with CI.

As other quantitative research studies, this study has some limitations. First, too few countries and regions are represented. However, in order to ensure the quality of the included studies, we balanced the research results from various regions as much as possible. Second, although this study was an economic evaluation study, we performed a meta-analysis to analyze the impact of different nutritional support methods in gastrointestinal cancer patients. Due to the inaccessibility of data, we included three non-RCT studies. These three articles were retained though after sensitivity analysis.

Conclusion

The results of the present study suggest that EN, as a form of nutritional support, has a positive impact on gastrointestinal cancer patients after surgical treatment, including a lower post-operative infection rate, shorter LOH and lower hospitalization expenditure. Although there is still controversy regarding the use of nutritional support treatment in patients with malignant tumors,[36,37] EN, especially ONS, can generate a positive economic impact for patients with gastrointestinal cancer.

AUTHOR DISCLOSURES

Mingwei Zhu, Wei Chen, Hua Jiang, Sainan Zhu and Jingyong Xu were involved in the conduct of the study as investigators. Wenlei Bao, Yan Dang, Michael Yao-Hsien Wang are employees of Abbott Nutrition. The information presented in this article is based on clinical evidence and is not affected by any financial relationship. No additional known conflicts of interests exist and no honoraria were offered or received in the writing of the present report.

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