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Nutritional status efficacy of early nutritional support in gastrointestinal care: A systematic review and meta-analysis

INTRODUCTION

Gastrointestinal diseases (especially tumors) are becoming common yearly, thus seriously threatening the health and quality of life of many patients and burdening families and the whole society^[1,2]. Gastrointestinal surgery is a complicated process used to treat many gastrointestinal diseases and is associated with large trauma. Patients ⁶ have different degrees of malnutrition and immune dysfunction before surgery and are prone to various infectious complications during postoperative recovery, affecting the efficacy of surgical treatment^[3]. However, nutritional support therapy can improve the above problems. Perioperative enteral or parenteral nutritional support provides the necessary nutritional supply and energy demand, thus improving the nutritional status of the patients and promoting early recovery of normal physiological function, especially gastrointestinal function. As a result, nutritional support therapy has received great clinical attention in recent years^[4]. Parenteral nutrition (PN) and enteral nutrition (EN) are the most commonly used nutritional support methods. PN is mostly used in the early stage after gastrointestinal surgery in clinical practice^[5]. However, PN can cause metabolic and functional complications by affecting intestinal mucosal metabolism and function, leading to impairment of the intestinal mucosal barrier, bacterial and endotoxin translocation, and increasing the incidence of enterogenous infections^[6]. The rapid development of fast-track surgical nutrition in recent years can improve postoperative small intestinal peristalsis, digestion, and absorption function after a few hours of abdominal surgery, thus promoting the rapid

development of early postoperative EN and early EN support^[7]. Jordan *et al*^[8] indicated that early EN can improve the reconstruction of the immune barrier, accelerate postoperative recovery, reduce complication incidence, and shorten the length of hospital stay. Besides, early EN is simpler, economical, and free of serious complications. However, no meta-analysis has studied the effect of early EN on nutritional status. Das *et al*^[9] showed that early EN support cannot significantly improve the nutritional status of patients compared with traditional nutritional support. This study aimed to quantitatively investigate the effect of early nutritional support on nutritional status of patients undergoing gastrointestinal surgery based on meta-analysis.

MATERIALS AND METHODS

Database

All articles published before October 2022 were retrieved from PubMed, EMBASE, Scopus, Web of Science, China National Knowledge Infrastructure, and Chinese BioMedical Literature Database, regardless of the language. The clinical study registration website (Clinicaltrials.org) was also checked to avoid missing unpublished literature.

Search strategy

The following keywords were used for literature search: ("early"[All Fields] AND ("nutritional support"[MeSH Terms] OR ("nutritional"[All Fields] AND "support"[All Fields]) OR "nutritional support"[All Fields]) AND ("digestive system surgical procedures"[MeSH Terms] OR ("digestive"[All Fields] AND "system"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "digestive system surgical procedures"[All Fields] OR ("gastrointestinal"[All Fields] AND "surgery"[All Fields]) OR "gastrointestinal surgery"[All Fields])) AND (randomized controlled trial[Filter]).

Inclusion and exclusion criteria

Inclusion criteria: (1) Only single or multi-center randomized controlled trials (RCTs); (2) Patients undergoing gastrointestinal surgery, including esophageal cancer resection, gastric cancer resection, pancreatic cancer resection, acute pancreatitis, colorectal cancer resection and other types of surgery, excluding patients intolerant to early EN support; (3) Good quality studies based on implementation process (randomization process, data deviation, and data measurement). The patients were divided into the experimental group (observation group) and the control group. The possibility of deviation from the established intervention in the study quality was evacuated if there were differences in the basic data, such as age, type, tumor grade, and surgical classification between the two groups. Patients in the two groups underwent surgery *via* the same surgical methods, preoperative preparation, and infection control. However, patients in the experimental group began to receive nutritional support in the early postoperative period, while those in the control group received traditional nutritional support or delayed nutritional support. Early nutritional support was performed 1-3 d after surgery (enteral nutritional support, oral feeding of liquid diet, PN, or a mixture of multiple nutritional support methods), while conventional nutritional support was given using indwelling intestinal nasal tube, conventional intravenous infusion. The patients were gradually given clear water, liquid food, semi-liquid food after the first defecation; and (4) The primary outcome indicators included nutritional status indicators, serum albumin indicators, serum prealbumin indicators, and serum total protein indicators after the intervention, while the secondary outcome indicators included length of hospital stay, first defecation time, and incidence of postoperative complications.

Exclusion criteria: (1) Non-RCT studies (descriptive literature, observational studies, meeting minutes, review studies); (2) studies with stroke patients, joint replacement patients, and other patients undergoing non-gastrointestinal surgery; (3) studies with no nutritional status outcome indicators, or where data on outcome indicators could not

be obtained; and (4) studies comparing different nutritional formulations, or studies comparing EN with PN.

Literature quality evaluation

The quality of the included RCTs was conducted using Cochrane Risk of Bias V2.0^[10]. This process involved five domains (randomization process, implementation bias, data bias, data measurement bias, and selection bias) and 1 overall bias assessment. Three evaluations ("low risk", "some concerns of risk" and "high risk") were used for each domain (or overall bias).

Outcome indicators

No other nutritional indicators, such as postoperative weight loss, muscle loss, hemoglobin, serum sodium, and potassium, were included in this study according to the actual retrieved literature.

Literatures screening

Two researchers screened the retrieved literatures, read the abstract, obtained the remaining literatures after preliminary screening according to the inclusion and exclusion criteria, read the full text and further screened the RCTs, and removed the studies with serious bias and low quality after quality evaluation.

Data extraction and transformation

Data, such as interventions, total number of people, grouping, characteristics of study subjects, and outcome indicators, were extracted and entered Excel sheets. A uniform unit was used to represent the data. For example, g/dL was converted to g/L, 1 g/dL = 10 g/L and hour (h) was converted to day (d).

Statistical analysis

Continuous data (serum albumin, serum prealbumin, serum total protein, length of hospital stay, first defecation time after intervention) were expressed using combined mean difference (MD) and 95%CI as effect size, while discrete data (complication rate) were expressed using odd ratio (OR) as effect size. The combined results were presented as a forest plot using random effects model with $P < 0.05$ considered statistically significant. Tau values were calculated using Q test to ensure literature heterogeneity ($P < 0.05$ indicated heterogeneity). Subgroup analysis and one-by-one exclusion were used to calculate the contribution of each study to the results in case of heterogeneity between the articles. Publication bias was quantified using Egger' test and presented using trim-filled funnel plots.

RESULTS

Literature screening process and results

Literature search and screening (identification, screening involving the three main processes) followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendation. The flow chart is shown in Figure 1. A total of 693 literatures were initially retrieved, and only 14 literatures were included in the final study after de-duplication and screening (Table 1).

Basic characteristics and patient characteristics of included literatures

Fourteen studies with 2145 adult patients (1138 patients (53.1%) who received early postoperative nutritional support and 1007 patients (46.9%) who received traditional nutritional support or delayed nutritional support) were included in this analysis. Seven of the 14 studies adopted early EN, while the other seven studies adopted early oral feeding (Table 1).

Literature bias and quality assessment

Three of the 14 articles (21.4%)^[18-19,23] were retrospective controlled studies and had "some risk of bias" in terms of deviations from established interventions, data

measurement bias, while four articles (28.6%)^(11,16,18,19) had "some risk of bias" in terms of data measurement. Six articles had "some risk of bias" overall while eight articles had "low risk". All articles had good overall quality. The details of the assessment using Cochrane Risk of Bias V2.0 are shown in Figure 2A.

Meta-quantitative analysis results of outcome indicators

Albumin (g/L): Six literatures reported albumin levels after nutritional support intervention in the two groups. The heterogeneity among the literatures was statistically significant ($\chi^2 = 46.55$, $I^2 = 89\%$, $P < 0.01$), including 402 patients who received early nutritional support and 385 patients who received traditional nutritional support. A random-effects model showed that serum albumin levels were slightly higher in patients receiving early nutritional support than in patients receiving traditional nutritional support (MD = 3.51, 95%CI: -0.05, 7.07, $Z = 1.93$, $P = 0.05$, Figure 2A).

Prealbumin and total serum protein (g/L): Only two literatures reported prealbumin and serum total protein levels (Table 3).

Length of stay (d): Twelve literatures compared the length of hospital stay between the two groups. The heterogeneity among the literatures was statistically significant ($\chi^2 = 37.10$, $I^2 = 70\%$, $P < 0.01$) (1011 patients who received early nutritional support and 994 patients who received traditional nutritional support). A random-effects model showed that patients receiving early nutritional support spent significantly less time in the hospital than patients receiving traditional nutritional support (MD = -2.29, 95%CI: -2.89, -1.69, $Z = -7.46$, $P < 0.0001$, Figure 2B).

Time to first defecation: Seven literatures compared the first defecation time between the two groups. The heterogeneity among the literatures was statistically significant ($Chi^2=46.80$, $I^2=87\%$, $P<0.01$) (750 patients receiving early nutritional support and 733 patients receiving traditional nutritional support). A random-effects model showed that

patients receiving early nutritional support took a significantly shorter time to first defecation than patients receiving traditional nutritional support (MD = -1.00, 95%CI: -1.37, -0.64, $Z = -5.42$, $P < 0.0001$, Figure 2C).

Complication rate: Thirteen literatures compared the incidence of complications between the two groups. There was no statistically significant heterogeneity among the literatures ($\chi^2 = 18.74$, $I^2 = 36\%$, $P = 0.09$). A fixed effect model showed that the incidence rate of complications was significantly lower in patients receiving early nutritional support than in patients receiving traditional nutritional support (OR = 0.61, 95%CI: 0.50,0.76, $Z = -4.52$, $P < 0.0001$, Figure 2D).

Heterogeneity investigation: Twelve literatures were divided into two subgroups based on different methods of early nutritional support to analyze the source of literature heterogeneity. Subgroup analysis showed that there was no significant difference between the two groups ($P = 0.55$), indicating that early nutritional support method was not the source of literature heterogeneity (Figure 3).

Influence analysis: The influence analysis on the outcome indicators of postoperative hospital stay was performed by removing the literatures one by one. The results did not find any significant differences, indicating that the overall results were stable and there was no variability in the study results (Figure 4).

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Publication bias analysis: Publication bias in the combined results of postoperative hospital stay outcome indicators was measured using Egger' test ($t = -0.78$, $P = 0.4551$). The P -value was > 0.05 ,
1 indicating that there was no publication bias. The funnel plot after trim-filled is shown in Figure 5.

DISCUSSION

Gastrointestinal surgery can lead to many pathophysiological changes in the human body (acute phase reactions), especially after larger operations, causing significant and persistent metabolic alterations characterized by hypercatabolism and declining total somatic cell counts⁽²⁵⁾. Yuan *et al*⁽²⁶⁾ suggested that early EN may mitigate this endocrine and metabolic response. The recovery of intestinal function takes about three days after abdominal surgery due to anesthesia and surgical trauma, and most recovery markers are anal excretions. However, postoperative gastrointestinal paralysis mainly occurs in the stomach and colon. Besides, most small intestines with normal preoperative function recover from peristalsis a few hours after surgery and thus can absorb nutrients for about 12 h, thus providing a theoretical basis for the implementation of EN in the early postoperative period⁽²⁷⁾.

In this study, serum prealbumin levels were significantly higher in the early nutritional support group than in the traditional nutritional support. However, albumin level and serum total protein levels were not significantly different between the two groups, suggesting that early nutritional support does not significantly improve nutritional status of patients. Also, the combined results showed that early nutritional support shortened the first defecation time and hospital stay, reduced complications (infection), and accelerated postoperative rehabilitation of patients. Postoperative gastrointestinal paralysis only occurs in the stomach and colon. The small intestine can quickly restore peristalsis and absorption function. The intestinal mucosa with intraluminal nutrition is the main way to obtain energy when the body is hungry, fasting, disease process, surgical trauma, and other circumstances. However, the intestinal mucosa cannot obtain the nutritional substrates required for its energy supply from the intestinal lumen. Intestinal mucosal barrier and immune barrier damage may lead to intestinal flora imbalance, intestinal failure, resulting in poor prognosis. Partial nutrient supplementation can promote early recovery of intestinal physiological function after surgery, protect the barrier function of intestinal mucosa, and prevent postoperative infectious complications⁽²⁸⁾. In addition, early EN support ensures the energy supply of immune cells and normal operation of immune cell function while

providing nutrients for the intestinal mucosa, thereby promoting the recovery of immune function after surgery and effectively inhibiting the inflammatory response^[29]. In this study, early nutritional support was consistent with the nutritional formula adopted for delayed nutritional support. The effect of the two nutritional support regimens on patient nutrition was not significantly different. Besides, no theoretical support has indicated whether early nutritional intervention after surgery can improve the nutritional status of patients. The improvement of the nutritional status of patients is mainly determined by the patient's physical condition and the formulation of nutritional preparations. Nonetheless, the clinical value of early nutritional intervention for a better prognosis should not be ignored.

In this meta-analysis, Boscarino *et al*^[30] concluded that EN can improve intestinal mucosal circulation, facilitate epithelial cells to take energy directly from the intestine and improve microecological environment, prevent translocation of intestinal flora, protect intestinal mucosal barrier, reduce bacterial infection, and promote intestinal peristalsis in postoperative patients compared with PN. However, this meta-analysis did not focus on the type of nutritional support.

Early postoperative nutritional support cannot be as early as possible. Notably, EN may only increase the burden of body metabolism when the respiratory, circulatory, water electrolyte, and acid-base balance of critically ill patients are not stable. In addition, EN may cause diarrhea, abdominal distension, vomiting, and other symptoms when intestinal function has not been resuscitated, thus aggravating the physiological dysfunction. Therefore, special attention should be paid to indications when early postoperative enteral nutritional support is applied. Early nutritional support should be discontinued and changed to PN once a patient develops intolerance^[31].

Furthermore, although heterogeneity was significant among literatures, heterogeneity was not detected within subgroups after subgroup analysis according to factors (nutritional support route) that can cause heterogeneity among literatures, suggesting that the source of heterogeneity was independent of nutritional support route.

Therefore, the heterogeneity could have been caused by sample characteristics of subjects in different studies.

Although seven literatures ¹ had "some concerns of risk", the overall quality of the literatures was good, the results were stable, and there was no publication bias. However, only six literatures reported albumin of nutritional indicators, while only two literatures reported preprotein and total protein indicators, indicating that the effect of early nutritional support on the improvement of nutritional status should be further studied. Furthermore, very few reports had analyzed the key nutritional indicators, such as potassium, sodium, hemoglobin, and weight loss in such RCT studies, and thus a meta-analysis synthesis could not be performed. Therefore, more studies of better quality are needed for in-depth analysis of different indicators from different perspectives.

CONCLUSION

Although this study showed that early EN support can shorten the postoperative defecation time, overall hospital stay, reduce the incidence of complications, and accelerate the rehabilitation process in patients undergoing gastrointestinal surgery, the improvement of nutritional status was not significant. Also, this study included a few articles and thus lacked an in-depth analysis for some important nutritional indicators. Therefore, more clinical multicenter, large-sample, high-quality studies are needed to further evaluate the effect of early EN support on patient's nutritional status.

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Figure Legends

Figure 1 PRISMA based literature selection. WOS: Web of Science; CNKI: China National Knowledge Infrastructure; CBM: Chinese BioMedical Literature Database; RCT: Randomized controlled trial.

Figure 2 Effect of early nutrition support and delayed nutrition support on postoperative albumin level, postoperative hospital stay, postoperative time to first defecation, and postoperative complication rate. A: Effect of early nutrition support and delayed nutrition support on postoperative albumin level; B: Effect of early nutrition support and delayed nutrition support on postoperative hospital stay; C: Effect of early nutrition support and delayed nutrition support on postoperative time to first defecation; D: Effect of early nutrition support and delayed nutrition support on postoperative complication rate. IV: Inverse variance; SD: Standard difference.

Figure 3 Subgroup analysis. IV: Inverse variance; SD: Standard difference.

Figure 4 Influence analysis.

Figure 5 Trim-filled funnel plots.

Table 1 Basic characteristics, patient characteristics, and outcome indicators of the included literatures

Ref.	Year	Design	Intention-to-treat total	Sample (E/D)	Surgery type	Age (yr)	Nutrition support mode	Outcomes
Sun <i>et al</i> ^[11]	2017	A prospective, randomized, single-blinded, controlled study	107	53/54	Major abdominal surgery	56 ± 10	Oral feeding	e, f
Pragatheeswarane <i>et al</i> ^[12]	2014	A randomized controlled study	120	60/60	Elective open bowel surgeries	46.5 ± 17.2	Oral feeding	d, e, f
Dag <i>et al</i> ^[13]	2011	A randomized controlled study	199	99/100	Elective open colorectal cancer surgery	62 (35-85)	Oral feeding	d, e, f
Fujii <i>et al</i> ^[14]	2014	A controlled study	120	62/58	Elective colorectal resection surgery	67.4 ± 11.7	Oral feeding	a, d, e, f
Liao <i>et al</i> ^[15]	2020	A randomized controlled study	41	21/20	Esophageal carcinoma surgery	57.2 ± 8.2	Enteral nutrition	d, f
Mi <i>et al</i> ^[16]	2012	A randomized controlled study	60	30/30	Gastrectomy	57.2 ± 9.5	Oral feeding	a, b, d, f

Mahmoodzadeh <i>et al</i> [17]	2015	A	109	54/55	Gastrointestinal surgeries	64.2 ± 8.2	Oral feeding	d, f
Wang <i>et al</i> [18]	2005	A	454	227/227	Colorectal cancer resection surgery	63.5 ± 11.3	Enteral nutrition	d, e, f
Qiu <i>et al</i> [19]	2020	A	26	13/13	Severe acute pancreatitis treatment	33.4 ± 5.7	Enteral nutrition	a, c, d
Wang <i>et al</i> [20]	2015	A	188	101/87	Esophagectomy	59.5 ± 8.4	Enteral nutrition	a, c, d, e, f
Klappenbach <i>et al</i> [21]	2013	A	295	148/147	Abdominal elective surgery	37.3 ± 18.1	Oral feeding	d, e, f
Li <i>et al</i> [22]	2015	A	300	150/150	Gastric cancer surgery	59.2 ± 9.7	Enteral nutrition	a, b, d, f
Zou <i>et al</i> [23]	2014	A	93	46/47	Severe acute pancreatitis treatment	46.5 (34.6-59.3)	Enteral nutrition	a, d, f

Barlow <i>et al</i> [24]	2011	A	121	64/57	Upper gastrointestinal cancer surgery	64.0 ± 15.0	Eternal feeding	f
			randomized controlled study					

a: Albumin (g/L); b: Prealbumin (g/L); c: Total serum protein (g/L); d: Length of stay (d); e: Time to first defecation (h); f: Complications rate; E/D: Early/delayed.

Table 2 Risk of bias and quality assessment based on Cochrane Risk of Bias V2.0

Ref.	Randomization	Bias defined	from Data missing bias	Data measurement offset	Optional reporting	Overall bias	Weight (%)
	Process	interventions	bias	offset	reporting		
Sun <i>et al</i> [11]	Low	Low	Low	Some concerns	Low	Some concerns	8
Pragatheswarane <i>et al</i> [12]	Low	Low	Low	Low	Low	Low	8
Dag <i>et al</i> [13]	3 Low	Low	Low	Low	Low	Low	8
Fujii <i>et al</i> [14]	Low	Low	Low	Low	Low	Low	8
Liao <i>et al</i> [15]	Low	Low	Low	Low	Low	Low	8
Mi <i>et al</i> [16]	Low	Low	Low	Some concerns	Low	Some concerns	8
Mahmoodzadeh <i>et al</i> [17]	Low	Low	Low	Low	Low	Some concerns	8
Wang <i>et al</i> [18]	Low	Some concerns	Low	Some concerns	Low	Some concerns	8
Qiu <i>et al</i> [19]	Low	Some concerns	Low	Some concerns	Low	Some concerns	8
Wang <i>et al</i> [20]	5 Low	Low	Low	Low	Low	Low	8
Klappenbach <i>et al</i>	Low	Low	Low	Low	Low	Low	8

<i>al</i> ^[21]									
Li <i>et al</i> ^[22]	4	Low	Low	Low	Low	Low	Low	Low	8
Zou <i>et al</i> ^[23]		Low	Some concerns	Low	Low	Low	Low	Some concerns	8
Barlow <i>et al</i> ^[24]		Low	Low	Low	Low	Low	Low	Low	8

Table 3 Meta-analysis results of other nutritional indicators

Outcomes	Literature number	Analysis mode	P value	Effect size	Pooling value	Z, P value
Prealbumin	2	Fixed effect mode	0.22	mean difference	12.4776 15.8320)	(9.1231, 7.29, < 0.0001
Serum protein	2	Random mode	0.0002	mean difference	5.2401 15.6635)	(-5.1833, 0.99, 0.3245

8%

SIMILARITY INDEX

PRIMARY SOURCES

- 1** www.researchgate.net 119 words — 3%
Internet
- 2** Jakob Burcharth, Andreas Falkenberg, Anders Schack, Sarah Ekeloef, Ismail Gögenur. "The effects of early enteral nutrition on mortality after major emergency abdominal surgery: a systematic review and meta-analysis with Trial Sequential Analysis", *Clinical Nutrition*, 2021 34 words — 1%
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- 3** research-information.bris.ac.uk 34 words — 1%
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- 4** Zorah Aziz, Weng Kit Huin, Muhammad Danish Badrul Hisham, Jia Xin Ng. "Effects of pomegranate on lipid profiles: A systematic review of randomised controlled trials", *Complementary Therapies in Medicine*, 2020 27 words — 1%
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- 5** www.cancercareontario.ca 24 words — 1%
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- 6** Xinrong Chen, Kun Yang, Xingxia Zhang, Ka Li. "Meta-analysis of preoperative oral nutritional supplements for patients with gastric cancer: East Asian experience", *European Journal of Clinical Nutrition*, 2019 21 words — 1%
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