Original Article

Effect of nutritional support on clinical outcomes in perioperative malnourished patients: a meta-analysis

Jing-xia Zhong BM[1], Kai Kang MM[2], Xiao-liang Shu PHD[3]

[1]*Department of Pediatrics, Tongji Hospital, Tong Ji University School of Medicine, Shanghai, China*
[2]*Tong Ji University School of Medicine, Shanghai, China*
[3]*Department of Nutrition, Jinshan Hospital, Fudan University, Shanghai, China*

Malnutrition is an independent risk factor for complications, mortality, wound healing, length of hospital stay, and costs. Associations between nutritional support and surgical patients remain controversial. Databases, including Pubmed, EMBASE, Web of Science, CNKI, VIP, and the Cochrane Library, were searched to find randomized controlled trials (RCTs) that assessed the effect of nutritional support on clinical outcomes in perioperative malnourished patients. The methodological quality of each included trial was assessed. A meta-analysis was conducted with Rev Man 5.2. Fifteen RCTs, involving 3831 patients, were included in this meta-analysis. Compared with control group, results showed that nutritional support was more effective in decreasing the incidence of infectious [relative risk (RR): 0.58; 95% CI: 0.50, 0.68; $p<0.01$] and non-infectious complications (RR: 0.74; 95% CI: 0.63, 0.88; $p<0.01$), and shortening the length of hospital stay [weighted mean difference (WMD): -2.64; 95% CI: -5.13, -0.16; $p<0.05$]. Moreover, the incidence of infectious complications in the immune nutrition group was significantly lower than that in the standard nutrition group (RR: 0.75; 95% CI: 0.58, 0.97; $p<0.05$). However, changes in hospital costs (WMD: 894; 95% CI: -1140, 2928; $p>0.05$) and postoperative mortality (RR: 0.77; 95% CI: 0.41, 1.44; $p>0.05$) between the nutritional support group and control group were not significantly different. In conclusion, perioperative nutritional support was superior in improving clinical outcomes in malnourished patients, which could significantly reduce the incidence of complications and effectively shorten the length of hospital stay.

Key Words: malnutrition, perioperative, nutritional support, meta-analysis, prognosis

INTRODUCTION

Malnutrition is a state of energy, protein, or other specific nutrient deficiency that produces a measurable change in body function. It is associated with poor outcomes from illness, but reversible by nutritional support.[1] Malnutrition weakens the body's immunity and stress resistance, so it cannot be effectively compensated in stress, such as trauma, infection, and major surgery.[2,3] Previous studies have demonstrated that malnutrition is an independent risk factor for complications, mortality, wound healing, length of hospital stay, and costs.[4-8] Moreover, surgical stress induces complex modifications in the hemodynamic, metabolic, neurohormonal, and immune responses of the individual,[9] which can cause inflammation, affect wound healing, and even lead to death. Furthermore, the restriction of postoperative oral intake can aggravate the malnutrition of patients.[10] The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on enteral nutrition reported that nutritional support should be initiated without delay even in patients without obvious undernutrition, if the patient is anticipated to be unable to eat for more than 7 d perioperatively.[11] Numerous studies[12-15] have shown that patients undergoing major abdominal surgery with perioperative nutritional support have lower incidence of postoperative mortality and morbidity, particularly for preoperative malnourished patients.[16] However, associations between nutritional support and malnourished surgical patients remain controversial. Pacelli et al conducted a retrospective study, in which they found that weight loss, hypoalbuminemia, and low BMI were not associated with an increased risk of mortality and morbidity in patients who underwent surgery for gastric cancer.[17] Studies have reported that nutritional support is not suitable for all malnourished patients; it has a beneficial effect on clinical outcomes to moderate and severely malnourished patients, but none to mildly malnourished patients.[18,19] The American Gastroenterology Association published a global meta-analysis of parenteral nutrition in 2001, which showed that perioperative parenteral nutrition results in more infections and costs to patients not severely malnourished.[20] Three meta-analyses[21-23] recently investigated the effect of immunonutrition on surgical outcomes, and similarly concluded that preoperative immunonutrition can signifi-

Corresponding Author: Dr Xiao-liang Shu, Department of Nutrition, Jinshan Hospital, Fudan University, No. 1508 Longhang Road, Jinshan District, Shanghai 201508, China.
Tel: +86-13916138269; Fax: +86-21-67226966
Email: shuxiaoliang@vip.sina.com
Manuscript received 14 December 2014. Initial review completed 21 February 2015. Revision accepted 23 April 2015.
doi: 10.6133/apjcn.2015.24.3.20

cantly decrease the total incidence of complications and effectively shorten the length of hospital stay. However, these meta-analyses all lacked preoperative malnutrition assessment, and the patients were either well-nourished or mildly malnourished. Therefore, our meta-analysis aimed to review systematically all randomized controlled trials (RCTs) that investigated the effects of nutritional support on malnourished surgical patients published from 1966 to October 2014. This study will provide further evidence for the clinical application of nutritional support on malnourished surgical patients.

METHODS

Study selection

We systematically searched six databases [PubMed (http://www.pubmed.com), EMBASE (http://www.embase.com), Web of Science (http://apps.webofknowledge.com), CNKI (http://www.cnki.net/), VIP (http://www.cqvip.com/), and the Cochrane Library (http://www.thecochranelibrary.com)] for all RCTs that investigated the effects of nutritional support ["nutritional support," "nutrition supplement," "enteral nutrition (EN)," "parenteral nutrition (PN)," "total parenteral nutrition (TPN)," "immunonutrition," "immune nutrition," "immune nutrition supplement," and their variants] on perioperational ("preoperative," "pre-operation," "perioperative," "perioperation," "postoperative," "post operation," "surgery," "operative," "operation," "resection," "gastrectomy," "enterectomy," and their variants) malnourished ("malnutrition," "mal-nutrition," "dystrophy," and their variants) patients published from 1966 to October 2014. References from the extracted articles and reviews were also consulted to complete the data bank. When multiple articles for a single study were present, we used the latest publication and supplemented it, if necessary, with data from the most complete or updated publication.

Studies were included if they met the following criteria: 1) they were RCTs with a parallel controlled design; 2) the association of malnutrition with nutritional support was specifically evaluated; 3) malnutrition assessment technique was provided; 4) specific outcomes were mentioned, including length of hospital stay, hospital costs, complication (infectious and non-infectious complications) (Table 1), and mortality; and 5) data related to supplementation were available. We excluded studies if they met the following criteria: 1) they were not randomized designs; 2) they did not report an adequate data of specific outcomes; and 3) they were reviews or case reports.

Data extraction

From each study, we extracted information on the first author, publication year, country of origin, sample size, age, sex, type of diseases or surgeries, average study follow-up time, number of subjects, malnutrition assessment technique, type of nutritional support, duration of nutritional support, disease outcome, method of outcome ascertainment, unit of measurement, and corresponding 95% CIs, SES, or exact p values. Given that differences in study populations and design may cause variations in results, study quality scores were used for methodology quality assessment.[24] A study quality score ranging from 0 to 5 was calculated for each included trait. Studies were categorized into those with a high study quality score (3-5 points) and those with a low study quality score (1-2 points), and no RCTs (0 point).

Data analysis

Data pooling was performed using a classical meta-analytical method via RevMan 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration; http://ims.cochrane.org/revman/). Statistical significance was set at $p<0.05$. Data were extracted from the text, tables, and figures of the original published papers. To include data from as many trials as possible, missing SD data for one trial were imputed from the SD data from all other trials using the same measure.[25] When estimating the analysis indexes, relative risk (RR) or OR was used as the effect size of the categorical variable, whereas the weighted mean difference (WMD) was used as the effect size for continuous variables. Subsequently, 95% CIs were calculated for each investigation and for each outcome variable. Before calculating the standardized mean effect for all trials, statistical heterogeneity was evaluated using the I^2 statistic ($\alpha=0.05$), which assessed the appropriateness of pooling the individual study results. The I^2 value provided an estimate of the amount of variance across studies because of heterogeneity rather than chance.[26] The I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high

Table 1. Classification of complications in the included trials

Infectious complications	Non-infectious complications
Pneumonia	Anastomotic leak
Abdominal abscess	Wound dehiscence
Fasciitis	Gastrointestinal bleeding
Bacteremia	Gastrointestinal perforation, obstruction, and ischemia
Septic shock	Pancreatitis
Septic coagulopathy	Myocardial infarction
Wound infections	Cardiogenic shock
Urinary tract infections	Cardiopulmonary arrest
	Stroke
	Pulmonary embolus
	Hemoperitoneum
	Pulmonary failure
	Renal failure
	Pleural effusion
	Hepatic dysfunction

levels of heterogeneity, respectively. If $p \geq 0.05$, heterogeneity was not substantial; that is, low heterogeneity was found between the trials. Thus, a fixed-effects model was used, with the Mantel-Haenszel method weighting for combined statistics. However, if $p<0.05$, heterogeneity was considered substantial; that is, high heterogeneity was present between the trials. In this situation, subgroup analysis was performed. If subgroup analysis could not remove the heterogeneity, combined results were conducted with a random-effects model, which was inversed variance weighting or DerSimonian-Laird method based on the fixed-effects model. A priori potential source of heterogeneity was publication bias. Possible publication bias was investigated by drawing a funnel plot to look for funnel plot asymmetry and meta-regression based on study size.[27]

RESULTS

Characteristics of the studies

The initial search yielded 721 potentially relevant references. After removing duplicates, reviews, animal trials, and papers that were less related according to the titles and abstracts, 53 studies remained. Upon reading the full text of these studies and excluding those that were less related, 15 trials[28-42] met the inclusion criteria and were selected as appropriate for inclusion in this meta-analysis (Figure 1). The included trials were published between 1966 to October 2014. The characteristics of the selected trials are presented in Table 2. The sample size varied from 20 to 1782, reaching a total of 3831. Among the 15 studies that evaluated surgical patients with malnutrition in many countries and regions, ten trials[30,34-42] investigated the effect of nutritional support with gastroenteric cancer surgeries, three trials[29,32,33] with mixed surgery, one trial with cardiac surgery,[28] and one trial with head and neck cancer surgery.[31] In addition to comparing the standard nutritional support group with the control group, we also conducted specific analyses between standard nutritional support and immune nutritional support.[31,32,38-41]

Complications

Infectious complications

Eight studies,[28-30,32,33,35-37] which involved 3821 subjects, evaluated the effect of nutritional support on infectious complications, including wound infections, abdominal abscess, pneumonia, urinary tract infections, and bacteremia. The results suggested that nutritional support was more effective in decreasing the incidence of infectious complications than immune support (RR: 0.58; 95% CI: 0.50, 0.68; $p<0.01$). The heterogeneity of infectious complications (I^2=34%; p=0.14; Chi^2=13.6) was acceptable; therefore, we used the fixed-effects model to analyze the data (Figure 2). Moreover, differences between the standard nutritional support and immune nutritional support groups were determined. The incidence of infectious complications in the immune nutritional support group was significantly lower than that in the standard nutritional support group (RR: 0.75; 95% CI: 0.58, 0.97; $p<0.05$), indicating that immune support was superior in reducing the incidence of infectious complications (Figure 3).

Non-infectious complications

A total of 3549 participants from seven studies[28,30-33,35,36] were enrolled to evaluate the incidence of non-infectious complications, including wound dehiscence, anastomotic leak, intestinal, gastrointestinal bleeding, and hemoperitoneum. The heterogeneity of these studies was acceptable (I^2=21%; p=0.25; Chi^2=11.4), so the fixed-effects model was used. A statistically significant difference was found between the nutrition and control groups (RR: 0.74; 95% CI: 0.63, 0.88; $p<0.01$), suggesting that nutritional support was more effective in reducing the incidence of non-infectious complications (Figure 4). However, no statistically significant difference was observed between the standard nutrition and immune nutrition groups (RR: 0.80; 95% CI: 0.63, 1.03; $p>0.05$). This finding suggests that immune nutrition may be no more different from standard nutrition in changing the incidence of non-infectious complications (Figure 5).

Postoperative mortality

In the analysis of postoperative mortality, five studies[28,30-32,36] with 1296 subjects were included. The fixed-effects model was used because of acceptable heterogeneity (I^2=0%; p=0.50; Chi^2=6.34). No statistically significant difference was found between the nutrition and control groups (RR: 0.77; 95% CI: 0.41, 1.44; $p>0.05$) (Figure 6).

Length of hospital stay

Six studies[28,29,31-33,36] with 3055 subjects mentioned the length of hospital stay. The I^2 value between studies was 96% ($p<0.01$; Chi^2=199); thus, a random-effects model was used. Nutritional support was more effective in shortening the length of hospital stay than immune support (WMD: -2.64; 95% CI: -5.13, -0.16; $p<0.05$) (Figure 7). Moreover, the asymmetry funnel plot suggested possible publication bias between studies that reported changes in the length of hospital stay (Figure 8).

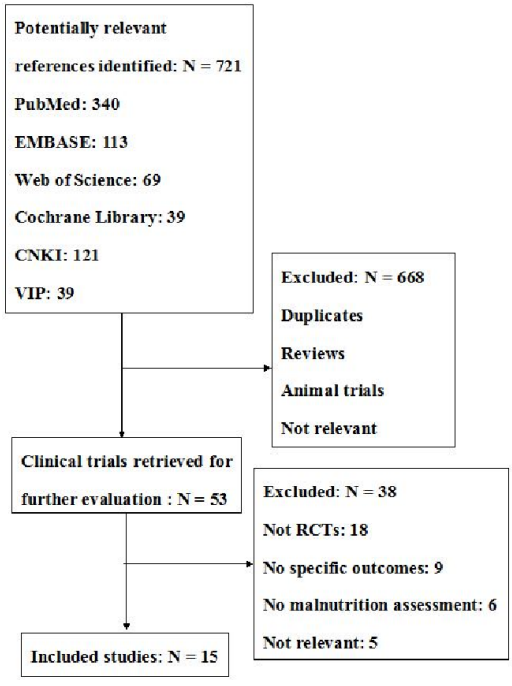

Figure 1. Flow diagram of trial selection process resulting from systematic search

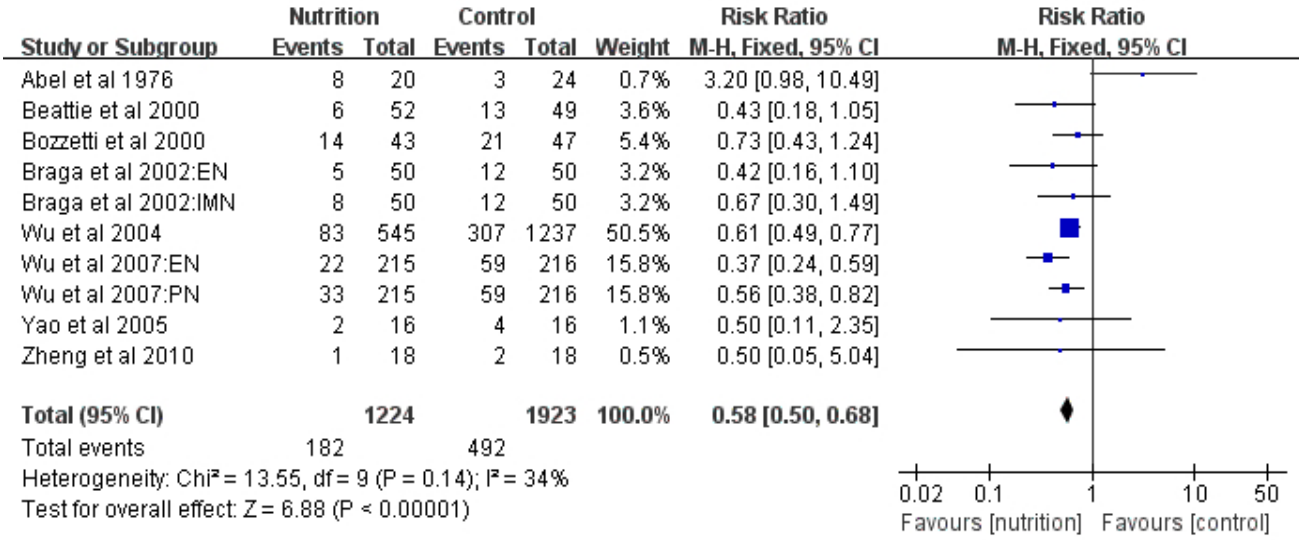

Figure 2. Forest plot of infectious complications between nutritional support and control groups. fixed-effects model. M-H: Mantel-Haenszel test.

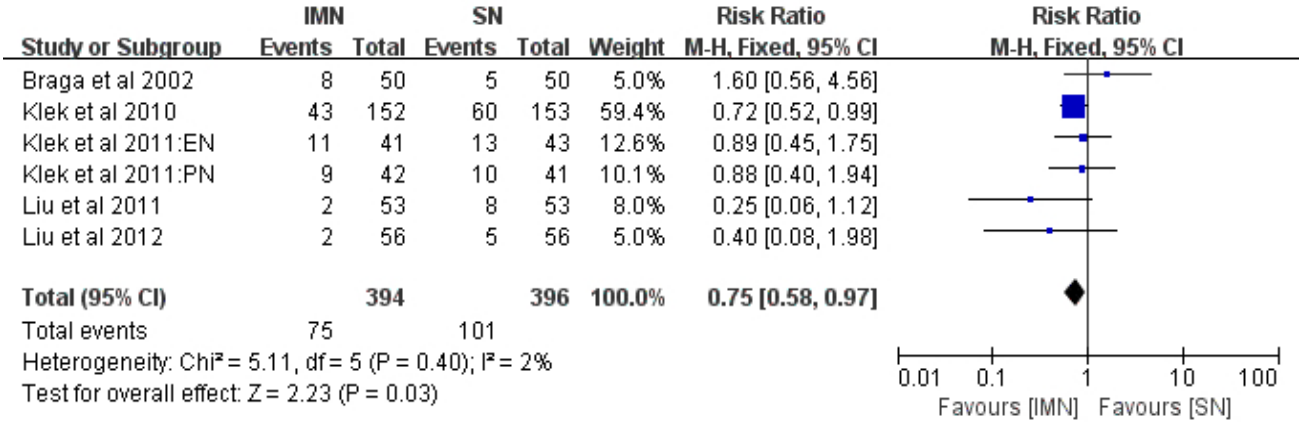

Figure 3. Forest plot of infectious complications between immune nutrition and standard nutrition groups. fixed-effects model. M-H: Mantel-Haenszel test.

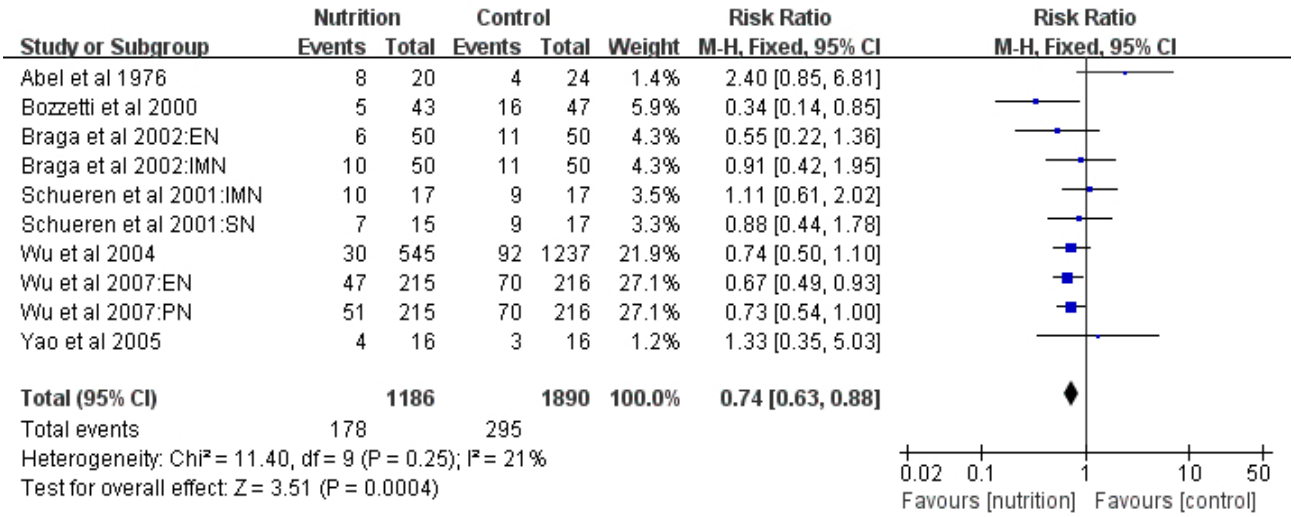

Figure 4. Forest plot of non-infectious complications between nutritional support and control groups. fixed-effects model. M-H: Mantel-Haenszel test.

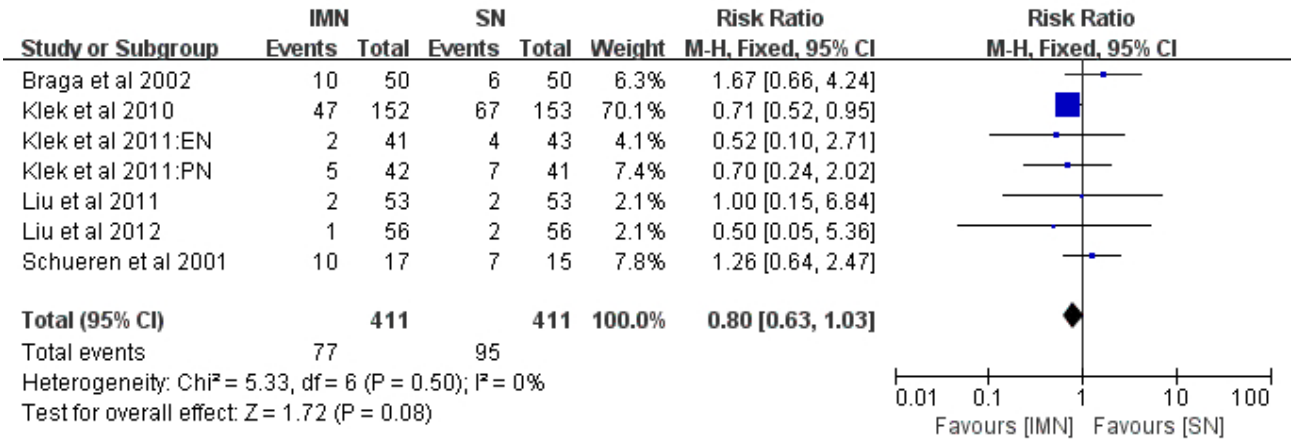

Figure 5. Forest plot of non-infectious complications between immune nutrition and standard nutrition groups. fixed-effects model. M-H: Mantel-Haenszel test.

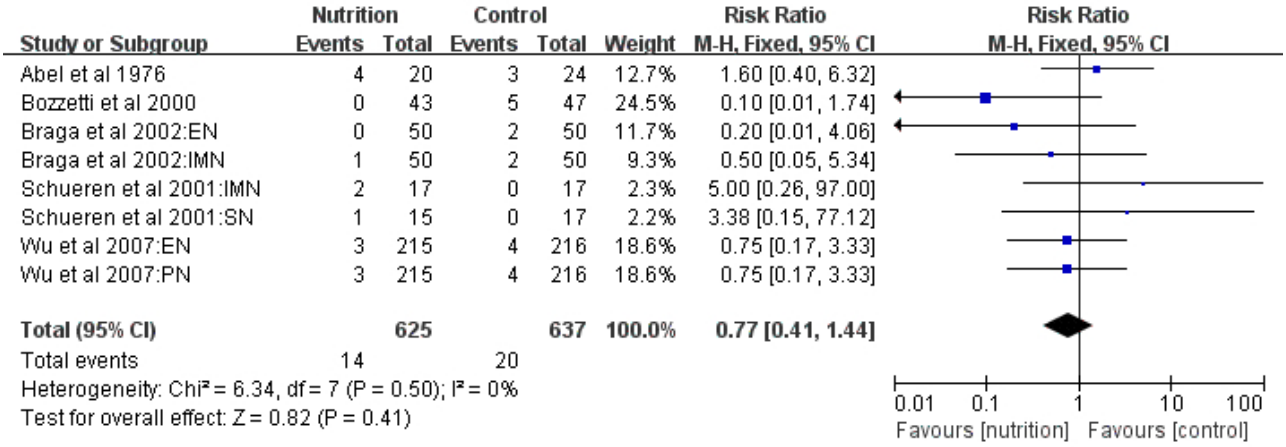

Figure 6. Forest plot of post operation mortality between nutritional support and control groups. fixed-effects model. M-H: Mantel-Haenszel test.

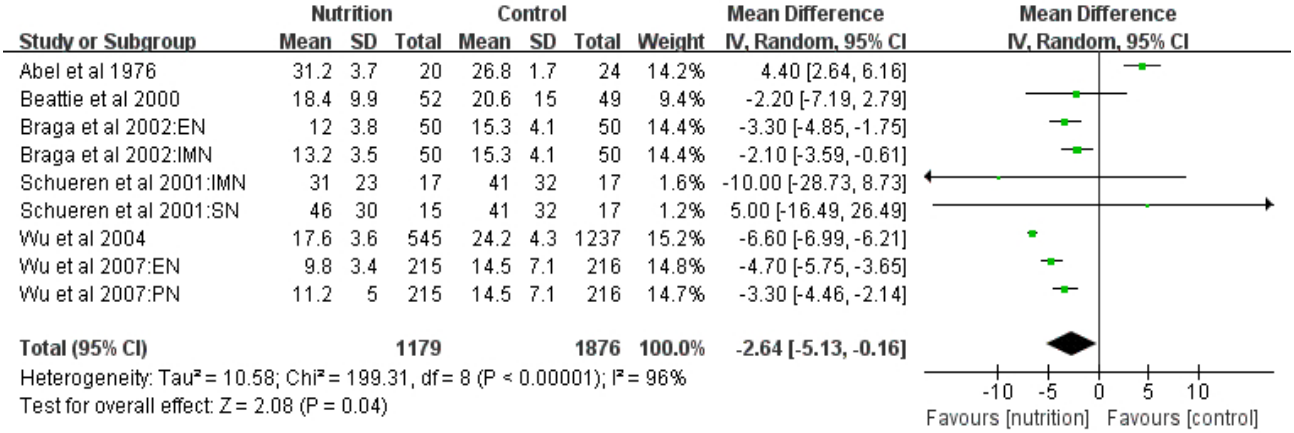

Figure 7. Forest plot of length of hospital stay between nutritional support and control groups: random-effects model.

Hospital costs

Three studies[28,34,42] with 255 subjects described changes in hospital costs (USD) between the nutrition and control groups, but the heterogeneity among them was significant (I^2=95%; p<0.01; Chi^2=40.5). Therefore, we used a random-effects model to analyze the data. No statistically significant difference was detected between the nutrition and control groups (WMD: 894; 95% CI: -1140, 2928; p>0.05), indicating that the relative data were insufficient to draw a conclusion. Moreover, according to the exchange rate, the hospital costs were translated into a unified unit (USD) (Figure 9).

DISCUSSION

Malnutrition can induce weight loss, muscle catabolism, extracellular fluid volume expansion, and lower tolerance of salt and water overload, which can further delay wound healing and increase the incidence of mortality

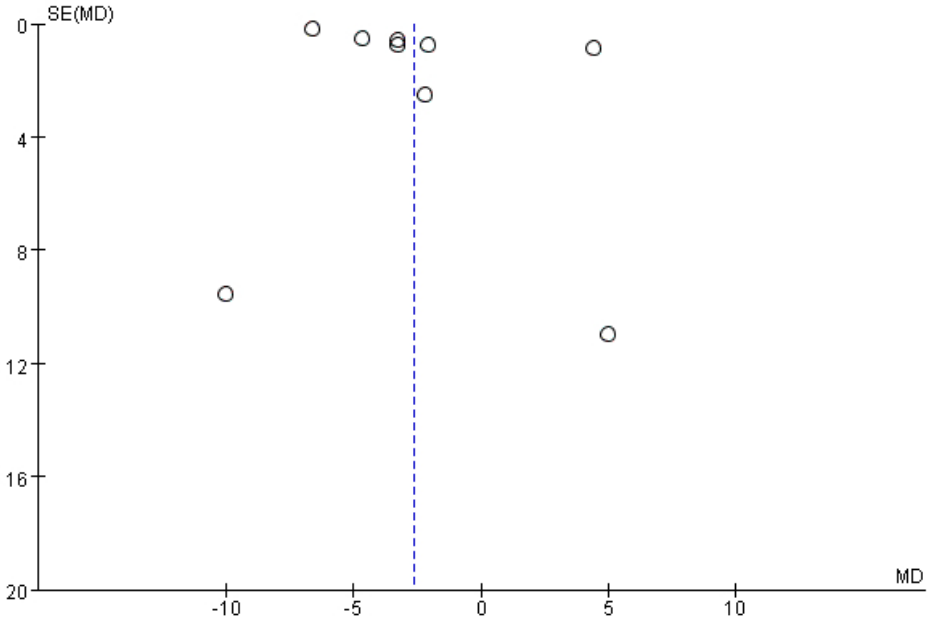

Figure 8. Funnel plot of studies mentioned change of length of hospital stay between nutritional support and control groups. Dotted lines are pseudo 95% CIs. The asymmetry funnel plot suggested possible publication bias existed between studies mentioned change of length of hospital stay, which was associated with the significant heterogeneity.

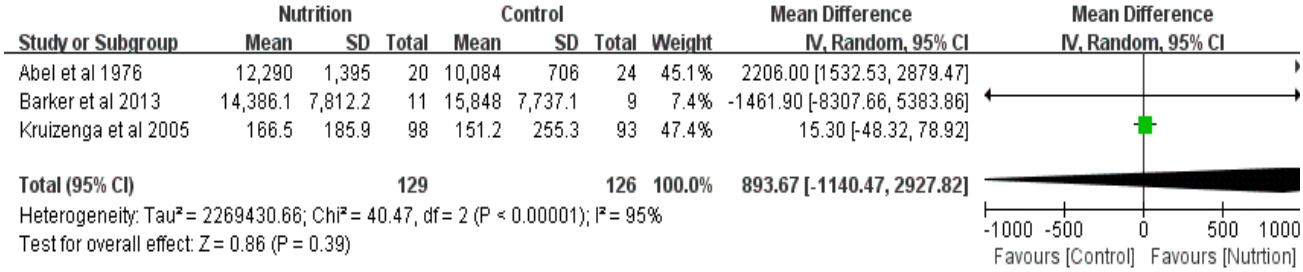

Figure 9. Forest plot of hospital costs between nutritional support and control groups: random-effects model.

and morbidity.[43] Malnutrition is an important factor in increasing postoperative infection and mortality, particularly to malnourished surgical patients.[44] Nutritional support provides comprehensive nutrients for patients through the enteral or parenteral route. Studies suggested that perioperative nutritional support or immune nutrition regulates intestinal flora, reduces bacterial translocation, and maintains normal cell metabolism.[45] In this meta-analysis, data on the effects of nutritional support on malnourished surgical patients were extracted and analyzed, including the incidence of infectious and noninfectious complications, postoperative mortality, length of hospital stay, and hospital costs. A retrospective study[46] demonstrated that preoperative nutritional supplementation with TPN for severely malnourished patients decreased postoperative noninfectious complications from 42.9% to 5.3%. Our results showed that nutritional support significantly reduced the incidence of infectious and noninfectious complications and shortened the length of hospital stay. However, changes in hospital costs between the nutritional support and control groups were not significant. Heterogeneity analysis showed significant heterogeneity among the included trials. Such heterogeneity may be attributed to the differences in national medical standards and the medical insurance system between various countries, which need further verification with more large-sample, multicenter RCTs. In addition, the insignificant change in postoperative mortality was mainly attributed to an impressive improvement of anesthetic and surgical techniques, as well as amelioration of postoperative patient management in the last three decades.[47,48]

Malnutrition plays a major role in the immune dysfunction of cancer patients. As reported in the literature, the sensitivity of lymphocyte response to phytohemagglutinin stimulation and macrophage migration inhibitory factor release in such patients declined.[49] These changes were strongly associated with low cell renewal rate, decreased protein synthesis, thymic atrophy, or enhanced blood mononuclear cells.[50,51] Therefore, aside from standard nutritional support or traditional treatment, the concept of immunonutrition was proposed. Immune-enhancing formulas usually add some pharmacologically active components (e.g., L-arginine, glutamine, omega-3 fatty acids, RNAs, and antioxidant vitamins) to standard formulas, which can improve surgical outcomes by immune regulation, anti-inflammation, and tissue protection.[52,53] In the present meta-analysis, we evaluated the effects of nutritional support on malnourished surgical patients, and de-

Table 2. Characteristics of the trials included in the meta-analysis, by year of publication[†]

Author	Year	Country	Type of disease or surgery	Age (y)	Sex (M/F)	No. of subjects (treatment/ control)	Malnutrition assessment technique	Type of nutrition support	Duration (d)	Design	Study-quality score
Abel et al[28]	1976	USA	Cardiac surgery	57-64	14/30	44 (20/24)	Recent weight loss exceeding 4.5 kg within the past 12 months, an absolute weight of less than 15% below ideal as predicted from life insurance charts, or a clinical impression of malnutrition on the basis of initial physical examination	PN	7	PC, R	3
Beattie et al[29]	2000	UK	Mixed surgery	18-80	60/41	101 (52/49)	BMI <20 kg/m^2, anthropometric measurements <15th percentile on admission, or initiation of oral diet postoperatively and/or a weight loss of 5% or more during the operative period	EN	70	PC, R	3
Bozzetti et al[30]	2000	Italy	Gastric or colo-rectal surgery	>18	45/45	90 (43/47)	Weight loss >10% within 6 months	TPN	19	PC, R	3
Schueren et al[31]	2001	Netherlands	Head and neck cancer	45-71	30/19	49 (15SN/ 17IMN/17)	Preoperative weight loss >10% of body weight over the previous 6 months	EN	7~9	B, PC, R	4
Braga et al [32]	2002	Italy	Mixed surgery	>18	84/66	150 (50IMN/ 50EN/50)	Weight loss ≥10%	EN, IMN	7	DB, PC, R	5
Wu et al[33]	2004	China	Mixed surgery	35±17	959/823	1782 (545/ 1237)	SGA	EN, PN	≥7	PC, R	3
Barker et al[34]	2013	Australia	Gastrointestinal surgery	64.5±15.3	-	20 (11/9)	SGA	EN	5	B, PC, R	4
Yao et al[35]	2005	China	Crohn's disease	18-73	19/13	32 (16/16)	BMI <15 kg/m^2	PN	21	PC, R	3
Wu et al[36]	2007	China	Gastroenteric cancer	62.5±12.2	366/280	646 (215PN/ 215EN/216)	SGA	EN, PN	PN: 7.2±3.2 EN: 7.6±4.0	PC, R	3
Zheng et al[37]	2010	China	Gastrectomy	>18	18/18	36 (18/18)	NRS ≥3	EN, TPN	7	PC, R	3
Klek et al[38]	2010	Poland	Resection for pancreatic or gastric cancer	60.8	182/123	305 (152IMEN/ 153SEN)	Unintentional weight loss by at least 10% or BMI <18	EN, IMN	14	DB, PC, R	5

[†]SN: standard nutrition; IMN: immune nutrition; SEN: standard enteral nutrition; IMEN: immune modulating enteral nutrition; SPN: standard parenteral nutrition; IMPN: immune modulating parenteral nutrition; BMI: body mass index (BMI=weight (kg)/height(m)^2); SGA: subjective global assessment; NRS: nutrition risk screening; EN: enteral nutrition; PN: parenteral nutrition; TPN: total parenteral nutrition; B: blind; DB: double-blind; PC: Parallel-controlled; R: randomized.

Table 2. Characteristics of the trials included in the meta-analysis, by year of publication[†] (cont.)

Author	Year	Country	Type of disease or surgery	Age (y)	Sex (M/F)	No. of subjects (treatment/ control)	Malnutrition assessment technique	Type of nutrition support	Duration (d)	Design	Study-quality score
Klek et al[39]	2011	Poland	Gastrectomy or pancreati-coduodenectomy due to malignancy	61.4	91/76	167 (43SEN/ 41IMEN/ 41SPN/ 42IMPN)	Weight loss >10%-15% within 6 months, BMI <18 kg/m^2, subjective global assessment, Grade C, or serum albumin <30 g/L	EN, PN, IMN	14	PC, R	3
Liu et al[40]	2011	China	Gastrointestinal malignancy	18-70	61/45	106 (53IMEN/53SEN)	SGA	EN, IMN	7	PC, R	3
Liu et al[41]	2012	China	Gastrointestinal malignancy	27-69	64/48	112 (56/56)	SGA	EN, IMN	7	PC, R	3
Barker et al[42]	2013	Australia	Gastrointestinal surgery	64.5±15.3	-	20 (11/9)	SGA	EN	5	B, PC, R	4

[†]SN: standard nutrition; IMN: immune nutrition; SEN: standard enteral nutrition; IMEN: immune modulating enteral nutrition; SPN: standard parenteral nutrition; IMPN: immune modulating parenteral nutrition; BMI: body mass index (BMI=weight (kg)/height(m)^2); SGA: subjective global assessment; NRS: nutrition risk screening; EN: enteral nutrition; PN: parenteral nutrition; TPN: total parenteral nutrition; B: blind; DB: double-blind; PC: Parallel-controlled; R: randomized.

termined the differences between standard nutritional support and immune nutritional support. Our results showed that immune support was superior in terms of reducing the incidence of infectious complications.

A randomized clinical trial conducted by the Veterans Affairs Total Parenteral Nutrition Cooperative Study Group[54] showed that severely malnourished patients who received TPN had fewer infectious complications than controls, whereas patients categorized as either borderline or mildly malnourished had more infectious complications in the TPN group than in the controls. Thus, malnutrition assessment is critical to perioperative nutritional support. It can maximize the effect of perioperative nutritional support and reduce adverse clinical outcomes. Furthermore, in the policy of cost minimization, it prevents unnecessary nutritional supplements and hospital costs. Moreover, according to the recommendations of ESPEN, [55] nutritional support is encouraged to be used on patients with malnutrition assessment. In this meta-analysis, preoperative malnutrition assessment was conducted on all the included trials to overcome deficiencies of previous analyses. However, this meta-analysis also had some limitations. First, the 15 included trials mentioned randomization and parallel control, but did not discuss blinding, which affected the quality score of the included trials. Second, the study quality score of Wu et al[33] was 3 but the number of enrolled subjects was large, which will bring uncertainty biases to the final result of this meta-analysis. Third, the included studies described minimal changes in serum albumin, and this finding should be verified by multicenter RCTs with a large sample size in the future. Finally, the variety of malnutrition assessment technique, type, duration of nutritional support, and dosage of nutritional support could also affect the final results.

In conclusion, perioperative nutritional support was superior in improving malnourished surgical patients prognosis to some degree, which could significantly decrease the incidence of complications and effectively shorten the length of hospital stay.

AUTHOR DISCLOSURES

None of the authors have any conflicts of interest associated with this study. This study was supported by the "Twelfth Five-Year" National Key Technology R&D Program of China (Grant No. 2012BAI35B03).

REFERENCES

1. Allison SP. Malnutrition, disease, and outcome. Nutrition. 2000;16:590-3. doi: 10.1016/S0899-9007(00)00368-3.
2. Cano NJ, Heng AE, Pison C. Multimodal approach to malnutrition in malnourished maintenance hemodialysis patients. J Ren Nutr. 2011;21:23-6. doi: 10.1053/j.jrn.2010.10.016.
3. Sungurtekin H, Sungurtekin U, Balci C, Zencir M, Erdem E. The influence of nutritional status on complications after major intraabdominal surgery. J Am Coll Nutr. 2004;23:227-32. doi: 10.1080/07315724.2004.10719365.
4. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr. 2007;26:698-709. doi: 10.1016/j.clnu.2007.06.009.
5. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr. 2003;22:235-9. doi: 10.1016/S0261-5614(02)00215-7.
6. Gil-Rendo A, Hernandez-Lizoain JL, Martinez-Regueira F, Sierra Martínez A, Rotellar Sastre F, Cervera Delgado M, Valenti Azcarate V, Pastor Idoate C, Alvarez-Cienfuegos J. Risk factors related to operative morbidity in patients undergoing gastrectomy for gastric cancer. Clin Transl Oncol. 2006;8:354-61. doi: 10.1007/s12094-006-0182-x.
7. Putwatana P, Reodecha P, Sirapongam Y, Lertsithichai P, Sumboonnanonda K. Nutrition screening tools and the prediction of postoperative infectious and wound complications: comparison of methods in presence of risk adjustment. Nutrition. 2005;21:691-7. doi: 10.1016/j.nut.2004.10.015.
8. Windsor JA, Hill GL. Risk factors for postoperative pneumonia. The importance of protein depletion. Ann Surg. 1988;208:209-14. doi: 10.1097/00000658-198808000-00013.
9. Cardinale F, Chinellato I, Caimmi S, Peroni DG, Franceschini F, Miraglia Del Giudice M, Bernardini R. Perioperative period: immunological modifications. Int J Immunopathol Pharmacol. 2011;24:S3-12.
10. Meguid M, Laviano A. Malnutrition, outcome, and nutritional support: time to revisit the issues. Ann Thorac Surg. 2001;71:766-8. doi: 10.1016/S0003-4975(00)02481-4.
11. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P et al. ESPEN guidelines on enteral nutrition: Surgery including organ transplantation. Clin Nutr. 2006;25:224-44. doi: 10.1016/j.clnu.2006.01.015.
12. Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A, Eickhoff U, Kemen M. Outcome and cost effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg. 1999;134:1309-16. doi: 10.1001/archsurg.134.12.1309.
13. Brennan MF, Pisters PW, Posner M, Quesada O, Shike M. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. Ann Surg. 1994;220:436-41. doi: 10.1097/00000658-199410000-00003.
14. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med. 1994;331:1547-52. doi: 10.105 6/NEJM199412083312303.
15. Gabor S, Renner H, Matzi V, Ratzenhofer B, Lindenmann J, Sankin O, Pinter H, Maier A, Smolle J, Smolle-JUttner FM. Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction. Br J Nutr. 2005;93:509-13. doi: 10.1079/BJN20041383.
16. Bellantone R, Doglietto G, Bossola M, Pacelli F, Negro F, Sofo L, Crucitti F. Preoperative parenteral nutrition of malnourished surgical patients. Acta Chir Scand. 1988;154:249-51.
17. Pacelli F, Bossola M, Rosa F, Tortorelli AP, Papa V, Doglietto GB. Is malnutrition still a risk factor of postoperative complications in gastric cancer surgery? Clin Nutr. 2008;27:398-407. doi: 10.1016/j.clnu.2008.03.002.
18. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P, Bistrian B, Bothe A, Heitkemper M. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Am J Clin Nutr. 1997;66:683-706.
19. Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW. Total parenteral nutrition in the surgical patient: a meta-analysis. Can J Surg. 2001;44:102-11.
20. Koretz RL, Lipman TO, Klein S. AGA technical review on parenteral nutrition. Gastroenterology. 2001;121:970-1001.

doi: 10.1053/gast.2001.28031.
21. Marimuthu K, Varadhan K, Ljungqvist O, Lobo DN. A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery. Ann Surg. 2012;255: 1060-8. doi: 10.1097/SLA.0b013e318252edf8.
22. Cerantola Y, Hübner M, Grass F, Demartines N, Schäfer M. Immunonutrition in gastrointestinal surgery. Br J Surg. 2011; 98:37-48. doi: 10.1002/bjs.7273.
23. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. Surg Oncol. 2012;21: e87-95. doi: 10.1016/j.suronc.2012.01.002.
24. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12. doi: 10.1016/01972456 (95)00134-4.
25. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol. 2006;59:7-10. doi: 10.1016/j. jclinepi.2005.06.006.
26. Francesco S, Rosanna A, Gian FG, Alessandro C. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010;92:1189-96. doi: 10.3945/ajcn.2010. 29673.
27. Sterne JAC, Egger M, Davey Smith G. Systematic reviews in health care-Investigating and dealing with publication and other biases in meta-analysis. BMJ. 2001;323:101-5. doi: 10. 1136/bmj.323.7304.101.
28. Abel RM, Fischer JE, Buckley MJ, Barnett GO, Austen WG. Malnutrition in cardiac surgical patients. Results of a prospective, randomized evaluation of early postoperative parenteral nutrition. Arch Surg. 1976;111:45-50. doi: 10.100 1/archsurg.1976.01360190047008.
29. Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut. 2000;46:813-8. doi: 10.1136/gut.46.6. 813.
30. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, Bonfanti G, Piacenza S. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr. 2000;24:7-14. doi: 10.1177/014860710002400 107.
31. van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, Kuik DJ, Langendoen SI, Snow GB, Green CJ, van Leeuwen PAM. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. Am J Clin Nutr. 2001;73:323-32.
32. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg. 2002;137:174-80. doi: 10.1001/archsurg.137.2.174.
33. Wu GH, Liu ZH, Zheng LW, Quan YJ, Wu ZH. The effect of perioperative nutritional support on outcome of surgical patients. J Surg Concepts Pract. 2004;9:376-9. (In Chinese)
34. Barker LA, Gray C, Wilson L, Thomson BN, Shedda S, Crowe TC. Preoperative immunonutrition and its effect on postoperative outcomes in well-nourished and malnourished gastrointestinal surgery patients: a randomised controlled trial. Eur J Clin Nutr. 2013;67:802-7. doi: 10.1038/ejcn.2013. 117.
35. Yao GX, Wang XR, Jiang ZM, Zhang SY, Ni AP. Role of perioperative parenteral nutrition in severely malnourished patients with Crohn's disease. World J Gastroenterol. 2005; 11:5732-4.
36. Wu GH, Zhang YW, Pan HT, Zhang B, Liu ZH, Wu ZH. A randomized controlled trial of postoperative artificial nutrition in malnourished patients with gastrointestinal cancer. Chin J Gastrointest Surg. 2007;10:546-9. (In Chinese)
37. Zheng Q, Chen P, Ding GP. Impact of preoperative short-term prophylactic enteral nutrition on malnourished patients with gastric cancer. Mod Pract Med. 2010;22:656-7. (In Chinese)
38. Klek S, Sierzega M, Szybinski P, Szczepanek K, Scislo L, Walewska E, Kulig J. The immunomodulating enteral nutrition in malnourished surgical patients: a prospective, randomized, double-blind clinical trial. Clin Nutr. 2011;30: 282-8. doi: 10.1016/j.clnu.2010.10.001.
39. Klek S, Sierzega M, Szybinski P, Szczepanek K, Scislo L, Walewska E, Kulig, J. Perioperative nutrition in malnourished surgical cancer patients: a prospective, randomized, controlled clinical trial. Clin Nutr. 2011;30: 708-13. doi: 10.1016/j.clnu.2011.07.007.
40. Liu JZ, Lan T, Zhang JS, Chen H, Wang GH, Yuan JL, Sun QS. Use of postoperative enteral immunonutrition in malnutritious patients with gastrointestinal malignant tumor. Chin J Gastrointest Surg. 2011;14:799-802. (In Chinese)
41. Liu JZ, Zhang JS, Lan T, Chen H, Wang CM. Applied Research of Enteral Immune and Nutritional Support in Malnourished Patients with Gastrointestinal Cancer. Med Innov Chin. 2012;9:1-3. (In Chinese)
42. Kruizenga HM, Van Tulder MW, Seidell JC, Thijs A, Ader HJ, Van Bokhorst-de van der Schueren MA. Effectiveness and cost-effectiveness of early screening and treatment of malnourished patients. Am J Clin Nutr. 2005;82:1082-9.
43. Hill GL. Malnutrition and surgical risk: guidelines for nutritional therapy. Ann R Coll Surg Eng. 1987;69:263-5.
44. Aaldriks AA, van der Geest LG, Giltay EJ, le Cessie S, Portielje JE, Tanis BC, Nortier JWR, Maartense E. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. J Geriatr Oncol. 2013;4:218-26. doi: 10.1016/j.jgo.2013.04. 001.
45. Lochs H. Interaction between nutrition, intestinal flora and the gastrointestinal immune system. Nestle Nutr Workshop Ser Clin Perform Programme. 2005;10:179-85. doi: 10. 1159/000083305.
46. Abunnaja S, Cuviello A, Sanchez JA. Enteral and parenteral nutrition in the perioperative period: state of the art. Nutrients. 2013;5:608-23. doi: 10.3390/nu5020608.
47. Bonnet F, Marret E. Influence of anaesthetic and analgesic techniques on outcome after surgery. Br J Anaesth. 2005;95: 52-8. doi: 10.1093/bja/aei038.
48. Leaper D. Effects of local and systemic warming on postoperative infections. Surg Infect (Larchmt). 2006;7: S101-3. doi: 10.1089/sur.2006.7.s-101.
49. Villa ML, Ferrario E, Bergamasco E, Bozzetti F, Cozzaglio L, Clerici E. Reduced natural killer cell activity and IL-2 product ion in malnourished cancer patients. Br J Cancer. 1991;63:1010-4. doi: 10.1038/bjc.1991.219.
50. Savino W. The thymus gland is a target in malnutrition. Eur J Clin Nutr. 2002;56:S46-9. doi: 10.1038/sj.ejcn.1601485.
51. Briet F, Twomey C, Jeejeebhoy KN. Effect of malnutrition and short-term refeeding on peripheral blood mononuclear

cell mitochondrial complex I activity in humans. Am J Clin Nutr. 2003;77:1304-11.
52. Roth E. Immune and cell modulation by amino acids. Clin Nutr. 2007;26:535-44. doi: 10.1016/j.clnu.2007.05.007.
53. Galli C, Calder PC. Effects of fat and fatty acid intake on inflammatory and immune responses: a critical review. Ann Nutr Metab. 2009;55:123-39. doi: 10.1159/000228999.
54. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991;325:525-32. doi: 10.1056/NEJM199108223250801.
55. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M; Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22:415-21. doi: 10.1016/S0261-5614(03)00098-0.

Original Article

Effect of nutritional support on clinical outcomes in perioperative malnourished patients: a meta-analysis

Jing-xia Zhong BM[1], Kai Kang MM[2], Xiao-liang Shu PHD[3]

[1]*Department of Pediatrics, Tongji Hospital, Tong Ji University School of Medicine, Shanghai, China*
[2]*Tong Ji University School of Medicine, Shanghai, China*
[3]*Department of Nutrition, Jinshan Hospital, Fudan University, Shanghai, China*

营养支持对围手术期营养不良患者临床结局的影响：一项 meta 分析

营养不良是增加术后并发症发生率及病死率，延缓创伤愈合，延长住院时间和增加住院费用的独立危险因素。营养支持适用于所有手术患者这一观点仍存在争议。本 meta 分析检索 6 个生物医学数据库（包括 Pubmed、EMBASE、Web of Science、CNKI、VIP、The Cochrane Library) 的文献资料。对纳入的随机对照研究进行方法学质量评定。应用 Rev Man 5.2 软件进行 meta 分析。本 meta 分析共纳入 15 项符合标准的随机对照研究（n=3831）。分析结果显示，与对照组比较，营养支持可明显降低患者术后感染性并发症发生率（RR：0.58；95% CI：0.50，0.68；p<0.01），降低术后非感染性并发症发生率（RR：0.74；95% CI：0.63，0.88；p<0.01），缩短住院时间（WMD：-2.64；95% CI：-5.13，-0.16；p<0.05）。此外，实施免疫营养支持较常规营养支持可以更有效地降低感染并发症发生率（RR：0.75；95% CI：0.58，0.97；p<0.05）。但营养支持组与对照组患者之间住院费用（WMD：894；95% CI：-1140，2928；p>0.05）和病死率（RR：0.77；95% CI：0.41, 1.44；p>0.05）无显著性差异。综上，围手术期营养支持对改善营养不良患者临床结局具有优越性，可显著降低其并发症的发生率，缩短住院时间。

关键词：营养不良、围手术期、营养支持、meta 分析、预后