Original Article

Peri-operative immunonutrition in patients undergoing liver transplantation: a meta-analysis of randomized controlled trials

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Background and Objectives: No consensus has been reached concerning the effects of peri-operative immunonutrition in patients undergoing liver transplantation. We conducted a meta-analysis to evaluate the effects of peri-operative immunonutrition on clinical outcomes and liver function in patients undergoing liver transplantation. **Methods and Study Design:** The Pubmed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and google scholar were searched to identify all available randomized controlled studies which compared peri-operative immunonutrition support (glutamine, ω-3 polyunsaturated fatty acids, arginine and ribonucleic acids) with standard nutrition. The data analysis was performed using Revman 5.2 software. **Results:** A total of 7 randomized controlled trials (RCTs) involving 501 patients were included. Peri-operative immunonutrition significantly reduced the risk of infectious complications (RR: 0.51; 95% CI: 0.27 to 0.98, *p*=0.04) and shortened the postoperative hospital stay [weighted mean difference (WMD): -3.89; 95% CI: -7.42 to -0.36; *p*=0.03]. Furthermore, peri-operative immunonutrition improved liver function by decreasing the levels of aspartate aminotransferase (AST) in the blood (WMD: -25.4; 95% CI: -39.9 to -10.9, *p*=0.0006). However, we did not find statistically significant differences in serum alanine aminotransferase (ALT), total bilirubin (TB) and direct bilirubin (DB) levels. There were no statistically significant differences in mortality and rejection reaction. **Conclusions:** Peri-operative nutrition support adding immunonutrients like glutamine, ω-3 polyunsaturated fatty acids, arginine and ribonucleic acids may improve outcomes in patients undergoing liver transplantation. Due to the limited sample size of the included trials, further large-scale and rigorously designed RCTs are needed.

Key Words: immunonutrition, ω-3 polyunsaturated fatty acids, glutamine, liver transplantation, meta-analysis

INTRODUCTION

Liver transplantation is a major surgical procedure conducted on end-stage liver disease. With the development of transplantation technology and peri-operative treatment, the 5-year survival rate after liver transplantation is 70%-80%.[1] Malnutrition is a common problem for patients undergoing liver transplantation and is associated with a higher risk of complications and mortality,[2] owing to depressed cellular immunity and humoral immunity. In addition, immune response also worsen rapidly in the post-transplant period because of ischemia reperfusion injury,[3] immunosuppressive therapy[4] and liver or kidney dysfunction. Appropriate supplementation with immunonutrition may be beneficial for the patients following liver transplantation.

The immunonutrition supplements, including glutamine (Gln), ω-3 polyunsaturated fatty acids (ω-3 FAs), arginine (Arg) and ribonucleic acids (RNA), are specially designed to modulate patient's immune response. All had been proved to improve immune function in vitro and animal experiments. In the recent years, a number of meta-analysis have been conducted to clarify whether supplementation with immunonutrition improves the condition of patients. For example, Jafari et al apprised the effects of parenteral immunonutrition in patients with acute pancreatitis and concluded that these formulations reduced infectious complications, mortality and hospital

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stay.[5] In another meta-analysis, Chen et al evaluated the safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery. They found that fish oil treatment can reduce length of hospital stay, ICU stay and the risk of postoperative infection in these patients.[6]

In the context of liver transplantation, the use of immunonutrition was first described in 1995,[7] and it was found that fish oil could improve renal function in patients with liver transplantation. However, due to the complexity and particularity of liver transplantation, the effects of immunonutrition in patients following liver transplantation have not been studied extensively. In addition, the decision to initiate nutrition and its timing in liver transplantation is still debated.[8] So far, there is no meta-analysis about the effects of peri-operative immunonutrition in patients with liver transplantation.

The purpose of this present meta-analysis was to examine the high-level evidence of safety and efficacy in liver transplantation comparing peri-operative immunonutrition (including one or more of Arg, Gln, ω-3 FAs and RNA) with standard nutrition.

METHODS
Literature search
The Pubmed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and google scholar were searched to identify all RCTs of interest from inception to July 2014. The following terms were used: "liver transplantation", "hepatic transplantation", "liver transplant surgery", "ω-3 polyunsaturated fatty acids", "glutamine", "arginine", "ribonucleic acids", "immunonutrition", "postoperative", "preoperative" and "peri-operative". Two authors evaluated the all identified articles separately through study of the titles, abstracts, and if necessary, full texts. Conference articles and review articles were used to identify additional relevant studies. No language restrictions were placed on the searches.

Inclusion and exclusion criteria
The inclusion criteria were as follows: (1) Patients involved were females or males aged 18 or over, with liver transplantation on enteral or parenteral nutrition therapy; (2) Comparing peri-operative immunonutrition support with standard enteral or parenteral nutrition, and immunonutrition supplemented one or more of nutrients including ω-3 FAs, Gln, Arg and RNA; (3) Studies reporting at least one of the following outcome measures; (4) When some studies were reported by the same institution and/or authors, they were selected only if there was no overlap between the results of their researches; (5) RCTs. The exclusion criteria were as follows: (1) Reviews and case reports; (2) Non-comparative articles; (3) Studies reporting the same patient cohorts evaluated in the published literature.

Methodological quality
The quality of all the included RCTs was assessed by two authors using the Cochrane risk of bias tool,[9] which includes seven specific items such as random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete out-

come data, selective outcome reporting and others.

Data extraction
We designed a data extraction form to capture primary data. Data were extracted on the following basis of study characteristics (including the first author, language, country, and year of publication), patient characteristics (including age, sex, clinical setting), Intervention strategies (supplemental immunonutrition or standard nutrition) and outcome variables (including infection complication, postoperative hospital stay, 1-year mortality, rejection reaction, liver function). We used one and half years mortality instead if 1-year of mortality was not reported. The liver function assessment was made on the day 7 or 9 after surgery, which included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and direct bilirubin (DB). To extract the data on hospital stay, we estimated mean and standard deviation from median and sample size where necessary, according to Hozo et al.[10] Two authors independently performed the data extraction, and discrepancies were resolved by consensus in the study team. In the case of studies in which data were published in conference abstract, we contacted the authors to request the full text. Where the information was unavailable due to nonresponse, we reported the available results as stated in the conference abstract.

Statistical analysis
The data analysis was performed using Revman 5.2 software (Cochrane IMS, Oxford, UK). Heterogeneity was assessed using chi-square test and I^2 with a p value <0.10 considered to be significant. Regardless of the presence or absence of heterogeneity, the pooled effect size was calculated using a random effects model. The outcomes for categorical variables were aggregated to obtain a pooled risk ratio (RR) with the 95% confidence interval (CI). For continuous variables, the pooled effect was reported as weighted mean difference (WMD) with the corresponding 95% CI. A subgroup analyses was conducted according to immunonutrition formulation (ω-3 FAs vs Gln). Statistical significance was defined as a p value <0.05.

RESULTS
Search results
A total of 437 records were identified through the database search, and 416 were excluded because of the irrelevant objectives and duplicates of the available literature. Of the 21 potentially relevant records screened, twelve met the selection criteria for the current meta-analysis. Nine out of 21 studies were non-RCTs, reviews or case series. Five studies were excluded because of the overlap of centers, authors, and possibly patient cohorts. Finally, seven RCTs were included for the meta-analysis.

Study characteristics and methodological quality
Characteristics of the 7 RCTs[11-17] included in the present meta-analysis were presented in Table 1. Two of the studies used formulas supplemented with Gln,[11,15] one with Gln and Arg,[17] one with Arg, nucleotides and fish oil[13] and three with fish oil alone.[12,14,16] All studies were published between 2009 and 2013 and investigated a total

Table 1. Characteristics of studies included in meta-analysis of peri-operative immunonutrition in patients with liver transplantation

Trials	Publishing date (year)	Study design	No. of patients (IN/Con)	Mean age (IN/Con)	Clinical diagnosis before surgery	The type of LT	Child-Pugh classification: A/B/C (n)	The regimens of immunosuppressive (n)	Type of immunonutrition	Route of nutrition	Dosage
Qiu[11]	2009	RCT Full text	22/22	50.8/45.9	Post-type B hepatitis liver cirrhosis; Hepatic cell carcinoma; Post-type C hepatitis liver cirrhosis; Alcoholic liver cirrhosis; Primary biliary liver cirrhosis; Wilson's disease; Drug-induced hepatic dysfunction; Congenital poly-cystic liver	NR	IN: 5/8/9 Con: 7/6/9	FK506+P/ CSA+P/ CSA+P+MMF (IN: 8/13/1; Con: 7/13/2)	Glutamine dipep-tide	PN	Dipeptide 20% (NR)
Wei[12]	2010	RCT Full text	32/32	41.6/42.0	Post-type B hepatitis liver cirrhosis; Post-type C hepatitis liver cirrhosis; Hepatic cell carci-noma; Biliary carcinoma; Primary biliary liver cirrhosis; Polycystic liver and kidney disease	Deceased donor LT	NR	MP+CTX/ FK506+MMF+P	ω-3 fish oil	PN	100 mL/d
Plank[13]	2010	Double-blind RCT Abstract	52/49	NR	NR	NR	NR	NR	ω-3 fatty acids, arginine, nucleo-tides (IMPACT)	Oral	0.6 L/d
Jiang[14]	2011	RCT Full text	18/18	46.7/45.8	Post-hepatitis liver cirrhosis; Hepatic cell carcinoma; Serious hepatitis; Biliary liver cirrhosis; Biliary carcinoma	NR	IN: 4/9/5 Con: 3/11/4	NR	ω-3 fish oil (Omegaven, 10%)	PN	100 mL/d
Jiang[15]	2011	RCT Full text	30/30	48.7/50.2	Post-type B hepatitis liver cirrhosis; Post-type C hepatitis liver cirrhosis; Hepatic cell carci-noma; Autoimmune liver cirrhosis; Primary biliary liver cirrhosis; Wilson's disease; Bili-ary carcinoma	NR	IN: 8/13/9 Con: 7/15/8	FK506/CSA+P+MMF	Glutamine dipep-tide	PN	100 mL/d
Zhu[16]	2012	RCT Full text	33/33	51.5/48.6	Hepatic cell carcinoma; post-hepatitis B liver cirrhosis; Alcoholic liver cirrhosis; Primary biliary liver cirrhosis; Congenital polycystic liver	NR	IN: 13/10/10 Con: 14/10/9	FK506+P/CSA+P /CSA+P+MMF (IN: 21/11/1; Con: 22/11/0)	ω-3 fish oil (Omegaven, 10%)	PN	2 mL/kg /d
Huang[17]	2013	RCT Full text	23/23	42.9/45.3	Post-type B hepatitis liver cirrhosis; Hepatic cell carcinoma; Chronic severe hepatitis B; Alcoholic liver cirrhosis; Primary biliary liver cirrhosis	Deceased donor LT	IN: 12/6/5 Con: 11/8/4	FK506+MMP+MP	Glutamine dipep-tide, arginine	PN	20 g/d, respectively

RCT: randomized controlled trial; IN: immunonutrition group; Con: control group; n: number; NR: not reported; LT: liver transplantation; P: prednisone; CSA: cyclosporine; MMF: mycophenolate mofetil; FK506: tacrolimus; MP: methylprednisolone; CTX: cyclophosphamide; PN: parenteral nutrition; EN: enteral nutrition

of 501 patients, the average sample size of each study was 62 subjects (rang: 36-101 subjects). 252 patients were randomized into immunonutrition supplementation and 249 patients into the control group. Child-Pugh classification of hepatic function and the regimens of immunosuppressive drugs were no different between the two groups.

Figure 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure1 summarizes the risks of bias on the included studies, most of which were of moderate to good quality.

Infection complications
Six trials[12-17] (373 patients) reported the rate of infectious complications following liver transplantation. 25.5% patients (48/188) in the immunonutrition group and 38.4% patients (71/185) in the standard nutrition group developed complications, respectively. The pooled results detected statistical significant difference between both two groups (RR: 0.51; 95% CI: 0.27 to 0.98, $p=0.04$; Figure 2). There were some significant heterogeneities in these studies ($I^2=64\%$). In the subgroup analyses, a statistically significant decrease in infectious complications was seen in patients who received Gln (RR: 0.30; 95% CI: 0.12 to 0.75, $p=0.01$), but not those patients who received ω-3 FAs (RR: 0.63; 95% CI: 0.32 to 1.26, $p=0.19$).

Postoperative hospital stay
A pooled analysis of 4 articles[13-16] enrolling 263 patients observed the postoperative hospital stay. A significant reduction in the immunonutrition group was found when compared with standard nutrition group (WMD: -3.89; 95% CI: -7.42 to -0.36; $p=0.03$; Table 2). There were some heterogeneities among these studies ($I^2=52\%$).

Mortality
Four out of 8 RCTs (234 patients)[11,12,15,16] reported the mortality. The mortality rate in included studies was 2.56% (3/117) in immunonutrition group, while 5.98% (7/117) in standard nutrition group. However, no significant difference was found between both two groups (RR: 0.50; 95% CI: 0.14 to 1.80; $p=0.29$; Table 2). There was no significant heterogeneity between these studies ($I^2=0\%$).
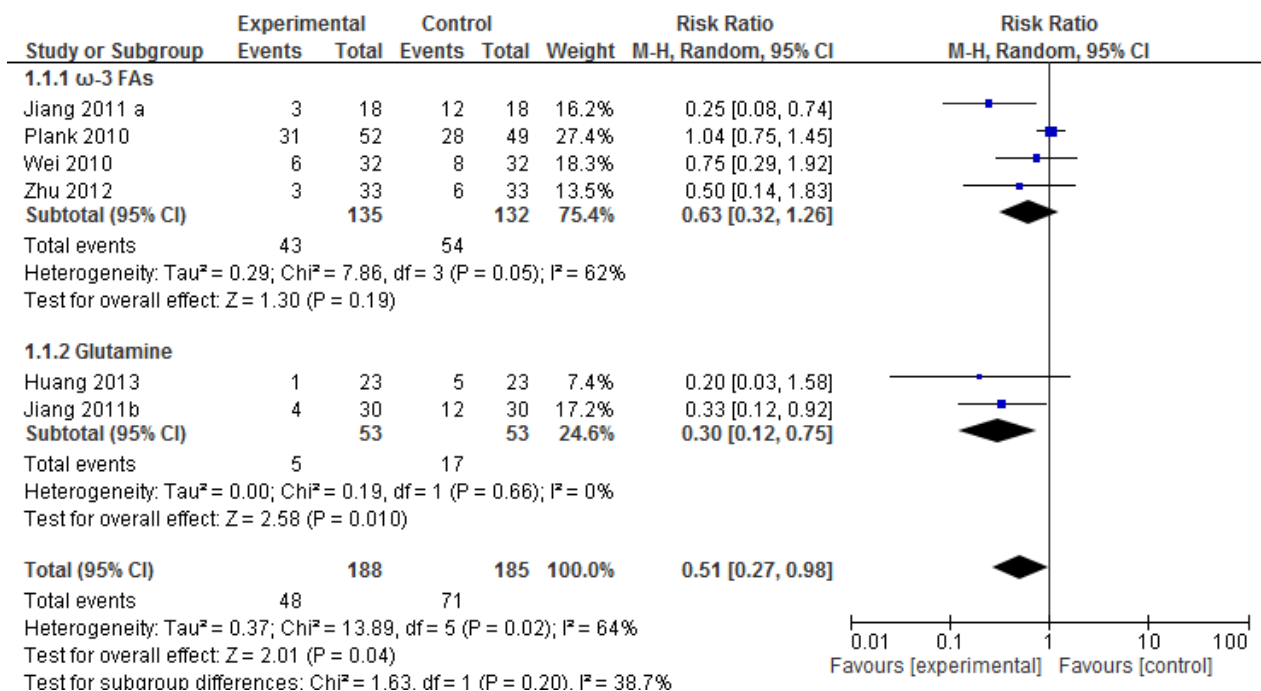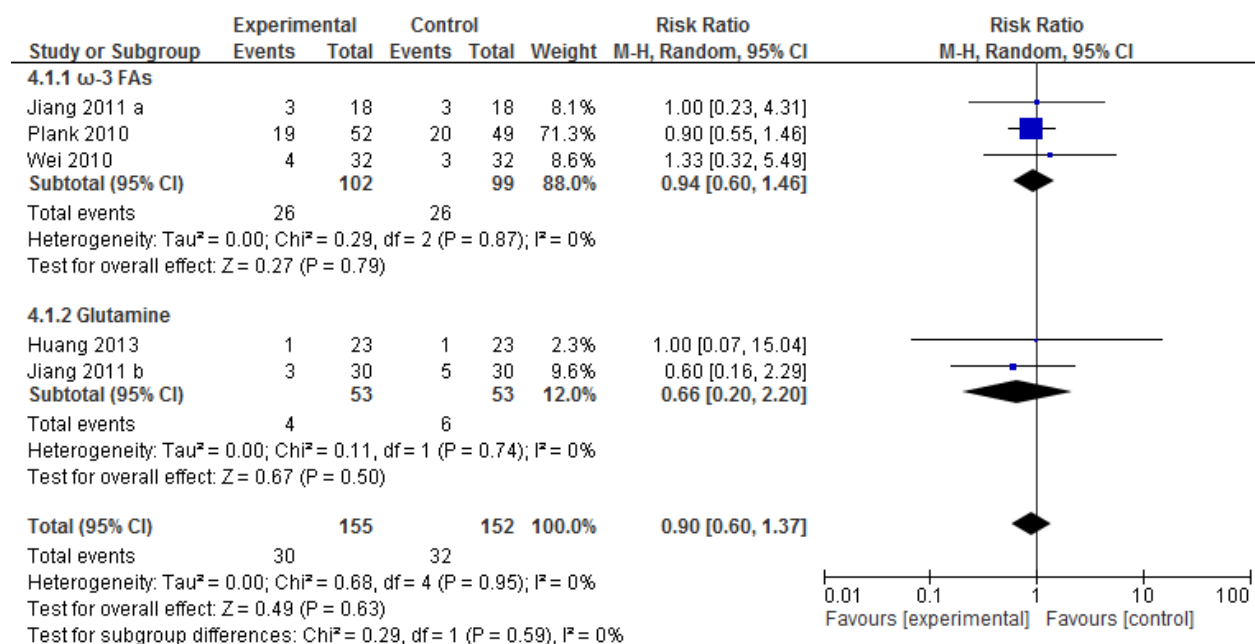

Figure 2. Forest plot of pooled data on infectious complication. CI: confidence interval; df: degrees of freedom; MH: Mantel-Haenszel (statistical method).

Table 2. Results from meta-analysis of peri-operative immunonutrition in patients with liver transplantation

Outcomes	Studies (reference number)	No. of Participants	Statistical method	Effect size (95% CI)	Test for overall Effect (p value)
Postoperative hospital stay	4[13-15,16]	263	WMD (Random)	-3.89 (-7.42, -0.36)	0.03
Mortality	4[11,12,15,16]	234	RR (Random)	0.50 (0.14,1.80]	0.29
ALT levels	5[11,12,14,16,17]	256	WMD (Random)	-38.1 (-76.3,0.09)	0.05
AST levels	4[11,14,16,17]	192	WMD (Random)	-25.4 (-39.9,-10.9)	0.0006
TB levels	4[11,12,14,16]	210	WMD (Random)	-9.25 (-19.8,1.25)	0.08
DB levels	3[11,14,16]	146	WMD (Random)	-7.81 (-17.0,1.33)	0.09

CI: confidence intervals; WMD: weighted mean difference; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TB: total bilirubin; DB: direct bilirubin.

Figure 3. Forest plots of pooled data on rejection reaction. CI: confidence interval; df: degrees of freedom; MH: Mantel-Haenszel (statistical method).

The rate of rejection reaction

Five studies[12-15,17] (307 patients) reported the rejection reaction. Thirty patients from the immunonutrition group and 32 patients in the standard nutrition group had to be readmitted, and the pooled results detected no statistical difference between the two groups (RR: 0.90; 95% CI: 0.60 to 1.37, p=0.63, Figure 3). There was no significant heterogeneity among these studies (I^2=0%). In the subgroup analyses, the rate of rejection reaction was not statistically significant between patients who received ω-3 FAs (RR: 0.94; 95% CI: 0.60 to 1.46, p=0.94) and in patients who received Gln (RR: 0.66; 95% CI: 0.20 to 2.20, p=0.50).

Liver function assessment

Five RCTs[11,12,14,16,17] (256 patients) reporting the levels of ALT and 4 RCTs[11,14,16,17] (192 patients) reporting the levels of AST were pooled, respectively. A significant decrease of AST (WMD: -25.4; 95% CI: -39.9 to -10.9, p=0.0006, Table 2) was seen in the immunonutrition group compared with standard nutrition group. There was no significant difference in the levels of ALT between the two groups (WMD: -38.1; 95% CI: -76.3 to 0.09, p=0.05, Table 2). Four RCTs[11,12,14,16] (210 patients) reporting the

levels of TB and 3 RCTs[11,14,16] (146 patients) reporting the levels of DB were pooled. Pooling the results indicated that there were no statistically significant differences for the levels of TB (WMD: -9.25; 95% CI: -19.8 to 1.25, p=0.08, Table 2) and DB (WMD: -7.81; 95% CI: -17.0 to 1.33, p=0.09, Table 2) between the two groups, respectively. There was no significant heterogeneity among these studies, respectively.

DISCUSSION

In the last decade, with the development of clinical nutrition, the conception of immunonutrition or nutritional pharmacology has been put forward by many scholars.[18] Immunonutrition involves the use of special kinds of nutrients based on the traditional nutrition. Certain appropriate key nutrients can modulate a variety of metabolic, inflammatory and immune processes,[19] for example: (1) ω-3 FAs play anti-inflammatory and immunomodulatory by modulating the synthesis of different eicosanoids;[20-22] (2) Gln is a most abundant free amino acid in the body and plays a role in maintaining the integrity of the intestinal barrier function and preventing the translocation of bacteria;[23] (3) Arg not only can improve nitrogen balance in catabolic states,[24] but also stimulate T-cell proliferation,

IL-2 production and natural killer cell cytotoxic effects;[25] (4) RNA can improve immunosuppression through effects on T lymphocytes in animal experiment,[26] and it also enhance many host defenses in patients with cancer.[27] The above immuno-nutritionials have the potential to improve mortality, reduce infectious complications and shorten hospital stay in some clinical scenarios, such as acute pancreatitis,[5] critical illness,[28] gastrointestinal surgery[29] and kidney transplantation.[6] Some researches demonstrated that appropriate nutrition treatment can improve the patients' tolerance to liver transplantation and the functional recovery of transplanted liver.[30,31] However, it is still controversial if peri-operative immunonutrition could offer substantial benefits to patients undergoing liver transplantation.

The present meta-analysis is the first which assesses peri-operative immunonutrition in patients with liver transplantation. According to our study, we demonstrated that immunonutrient-supplement significantly reduced the infectious complication rate and postoperative hospital stay in patients with liver transplantation. It is well known that both ω-3 FAs and Gln can down-regulate proinflammatory cytokine production and enhance immunity. So the infectious complications in the immunonutrition group may be due to these two effects of the 2 nutritional intervention. Frequent complications are associated with longer hospital stay.[32] In our study, decreased infectious complications may lead to shorten the postoperative hospital stay. Liver function improved significantly in the groups who received any kind of immune-nutrients via standard nutrition pathway according to our meta-analysis. Similar results were also observed in a randomized controlled trial performed by Mikagi et al.[33] They apprised the effects of immunonutrition on patients undergoing hepatectomy and concluded that these formulas reduced inflammantion and protected against liver dysfunction. The protective effect on liver function might be considered to have been derived from the suppression of thromboxane A2 production because of supplement of fish oil.[33] Additionally, supplemental Arg is another one of the reasons that it can improve the microcirculation of organs.[34] With respect to the levels of AST, ALT, TB and DB in our study, there was a trend toward lower levels of ALT, TB and DB for the immunonutrition group. However, pooling the data from these trials failed to show any statistical difference in these three outcomes. The reasons might be that the number of patients in all these studies was relatively small, which might mask the true difference in the outcomes. In our meta-analysis, immunonutrition did not change 1-year mortality. A previous meta-analysis which compared the effect of immunonutrition with standard enteral nutrition in surgical and critically ill patients, failed to show advantages in overall mortality.[35] Similar results are also observed in a meta-analysis performed by Palmer et al.[36] As far as the rate of rejection reaction was concerned, our analysis indicated the rate of rejection reaction was not different between the two groups. The number of included studies was small, and it might mask the real situation. A randomized, double-blind trial reported less rejection episodes for kidney transplant recipients who received fish oil treatment at 12 months.[37] On the contrary, a meta-analysis which assessed fish oil treatment for kidney transplant patients, demonstrated pooling the data from 8 trials (482 patients) failed to show any difference in the acute rejection rate for treatment and control groups.[38] Perhaps future studies should focus more on how to improve the rejection reaction in the long-term using fish oil treatment.

Some limitations of our meta-analysis are as follows. First, there was a small sample size in most of the trials, and this may be a threat to internal validity. Second, only one trial available for present meta-analysis was blinded. Third, surgeons with varying technical proficiency were from different clinical centers, and there are some possible heterogeneities in the peri-operative care. Fourth, absence of accurate data in some studies about antibiotic treatment which may influence the outcomes, specifically the rate of infectious complications.

In conclusion, our meta-analysis showed that peri-operative immunonutrition can reduce the infectious complications, postoperative hospital stays and improve the liver function. There was no significant difference with respect to 1-year mortality and rejection reaction. However, the number of patients included in present meta-analysis was small. Further additional large, well-constructed RCTs need to be conducted to ensure more robust conclusions.

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Original Article

Peri-operative immunonutrition in patients undergoing liver transplantation: a meta-analysis of randomized controlled trials

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肝移植患者围手术期的免疫营养支持：一项随机对照试验的 meta 分析

背景与目的：关于肝移植患者围手术期免疫营养支持的疗效还没有达到共识。我们进行一项 meta 分析来评价围手术期应用免疫营养支持对肝移植患者临床结局和肝功能的影响。**方法与研究设计：**我们通过 Pubmed, Embase, Cochrane Central Register of Controlled Trials, Web of Science 和 google scholar 数据库来检索所有有关肝移植患者围手期免疫营养支持（谷胺酰氨、ω-3 多不饱和脂肪酸、精氨酸与核糖核酸）与标准营养支持比较的随机对照试验。数据分析采用 Revman 5.2 软件。**结果：**总共有 7 项随机对照试验包括 501 例患者纳入研究。围手术期免疫营养支持可明显降低感染并发症风险（RR 0.51；95% CI 0.27 to 0.98，p=0.04）与缩短术后住院时间（WMD -3.89；95% CI -7.42 to -0.36，p=0.03）。此外，围手术期免疫营养支持可以通过减少血中天冬氨酸转氨酶水平（AST）来改善患者肝功能（WMD -25.4；95% CI -39.9 to -10.9，p=0.0006）。同时，我们没有发现两组患者的血清丙氨酸转氨酶、总胆红素及直接胆红素水平有统计学差异。两组患者的死亡率和排斥反应发生率也没有统计学差异。**结论：**围手术期营养支持添加免疫营养素，如谷胺酰氨、ω-3 多不饱和脂肪酸、精氨酸和核糖核酸可能会改善肝移植患者的临床结局。由于纳入研究的样本量小，这个结论需要大规模的、设计严谨的随机对照试验来进一步证实。

關鍵字： 免疫营养、ω-3多不饱和脂肪酸、谷胺酰氨、肝移植、meta分析