INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Meta-analysis: Total Parenteral Nutrition Versus Total Enteral Nutrition in Predicted Severe Acute Pancreatitis

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Abstract

Background Total parenteral nutrition (TPN) as a traditional mode of treatment in severe acute pancreatitis was still used widely in clinical work. In addition, enteral nutrition treatment methods have developed; early enteral nutrition has already been highlighted for severe acute pancreatitis, but the therapeutic risks versus benefits need to be studied.

Aims and Objective To compare total parenteral nutrition with total enteral nutrition (TEN) in patients with severe acute pancreatitis by performing a meta-analysis.

Materials and Methods Electronic databases including PubMed, EMBASE, Science Citation Index, were searched to find relevant randomized controlled trials. Two reviewers independently identified relevant trials evaluating the effect of total parenteral nutrition and early enteral nutrion. Outcome measures were the mortality, hospital length of stay, infectious complications, duration of nutrition, organ failure and surgical intervention.

Results Eight randomized controlled trials (RCTs) including 381 patients were identified. Meta-analysis demonstrated that TEN was significantly superior to TPN when considering mortality [p=0.001, 95%CI 0.37 (0.21-0.68)], infectious complications [p=0.004, 95%CI 0.46(0.27-0.78)], organ failure [p=0.02, 95%CI 0.44 (0.22-0.88)] and surgical intervention [p=0.003, 95%CI 0.41(0.23-0.74)].While no difference between TEN and TPN when considering the hospital length of stay [p=0.22, 95%CI -14.10(-36.48-8.26)] and as for duration of nutrition [p=0.72, 95%CI -1.50(-9.56-6.56)] there was not enough data to compare the differences.

Conclusion Total enteral nutritional support is associated with lower mortality, fewer infectious complications, decreased organ failure and surgical intervention rate compared to parenteral nutritional support.

Key words: severe acute pancreatitis, total enteral nutrition, total parenteral nutrition

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Introduction

Acute pancreatitis (AP) is an inflammatory disease occurring in the pancreas, nearly 80% of mild to moderate pancreatitis recover spontaneously. However, overall 15%-20% patients progress to severe acute pancreatitis (SAP), which has a high risk of mortality (1, 2). The traditional treatment of AP are as follows: fasting, somatostatin or analogues to inhibit the activity of pancreatin, prophylaxis antibiotics and sufficient intravenous fluids (3). Nutritional support of SAP is an essential part of the disease management (2, 4). Patients with acute pancreatitis are either treated with bowel rest or treated with parenteral nutrition to allow the pancreas to "rest" until the panreatin return to normal (5). The traditional parenteral nutrition (PN) without enteral nutrition (EN) is used because food intake would stimulate pancreatin secretion which may aggravate pancreatic inflammation. However, parenteral nutrition would bring about many complications, such as vasculitis or accompany septemia (6).

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Table 1. Jadad Quality Score of the Trials Included

Study	Randomisation	Blinding	Withdrawals/dropouts	Jadad score
Gupta et al[4]	Sealed envelopes	None	Yes	3
Louie et al[10]	Computer-generated assignment placed in sealed,opaque envelopes	None	Yes	3
Petrov et al[11]	Computerized random number generation	None	Yes	3
Eckerwall et al[12]	Not stated	None	Yes	2
Casas et al [13]	Computerized random number generation placed in sealed envelopes	None	Yes	3
Kalfarentzos et al[14]	Numbered envelopes	None	Yes	3
Doley et al[15]	Not stated	None	Yes	2
Wu et al[16]	Not stated	None	Yes	2

Thus enteral nutrition has already been highlighted for its superior advantage to parenteral nutrition. Enteral nutrition is associated with fewer septic complications, reduced surgical procedures and reduced length of hospital stay (7). It helps maintain the gut barrier, with consequent decreased bacterial translocation, which is in turn a key factor in limiting the complications in SAP (8). The most common technique for nasoenteral intubation is blind passage, as it does not require the use of sophisticated or expensive medical equipment. Unfortunately, blind placement too frequently results in trauma and is a source of significant morbidity and mortality. It is apparent that altered mental status, a preexisting endotracheal tube, and critical illness place a patient in a higher risk group for malposition and complications (9). Parenteral nutrition is still used widely in clinical work.

As a result of the advantages and disadvantages of the enteral nutrition. Numerous randomized controlled trials (RCTs) has been undertaken to compare the two methods of nutrition but the results of RCTs are varied (4, 10-16). The aim of this study was to integrate the latest RCTs to further compare the efficiency of enteral nutrition and parenteral nutrition.

Materials and Methods

Data identification

We searched PubMed, EMBASE, Science Citation Index database from inception to September 2011 using the terms “enteral nutrition”, “pancreatitis” and their analogues. Potentially relevant studies and the reference lists from the identified reports were searched by hand to find relevant trials.

The selection criteria

Studies that were included, fulfilled the following criteria and applied design: (i) RCT fully reported with detailed information available; (ii) population: patients with predicted severe acute pancreatitis; (iii) intervention: total enteral or parenteral nutrition; (iv) outcome measures: primary outcome is the mortality, hospital length of stay (LOS), infectious complications, organ failure and need for surgical intervention.

Quality assessment and statistical analysis

The quality of included trials was assessed by means of Jadad score (17). The reported methodology quality was independently evaluated by two of the reviewers (Yi Fengming and Ge Liuqing).Trials with a low risk of bias were the ones fulfilling the adequacy of three components: generation of the allocation sequence, allocation concealment and binding. Trials with a moderate risk of bias were the ones where one or more of these three criteria partly met, while trials were considered to carry a high risk of bias if only one or more criteria not met. Any disagreement was resolved by discussion between the two reviewers. As shown in Table 1, Jadad scores of RCTs included 5 RCTs with a score of 3, and 3 RCTs with a score of 2.

Two reviewers (Yi Fengming and Ge Liuqing) retrieved data and entered it into Review Manager (Version 4.2 for Windows, Cochrane Collaboration, Oxford, UK) independently. The differences between the total parenteral nutrition group and total enteral nutrition group were expressed as the risk ratio (RR) or mean difference with its 95% confience interval (CI). Statistical heterogeneity among RCTs was assessed with the I^2 Statistics (18). I^2 is the proportion of total variation contributed by between-study variability. In the presence of statistical heterogeneity, a random-effect model was used. In the absence of statistical heterogeneity, the fixed-effect model was used.

Results

Totally 552 trials were retrieved; and the process of selecting relevant trials was described in Fig. 1. In the 552 in-

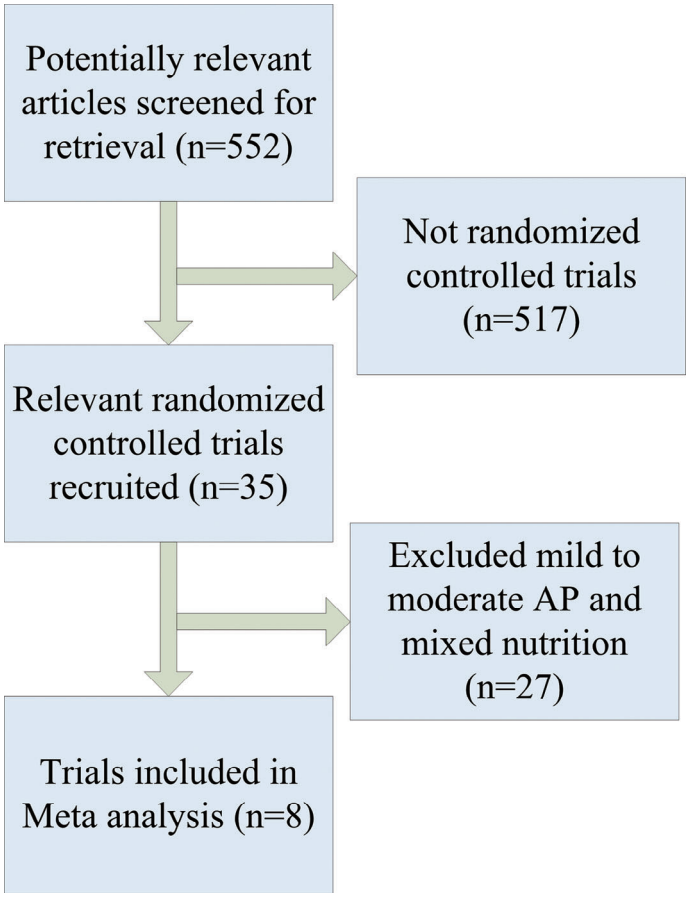

Figure 1. **The study selection process. RCT, randomized clinical trial.**

itially potentially relevant studies, 517were not randomized controlled trials, 27 were RCTs related with moderate AP or mixed nutrition. Finally, 8 RCTs were included (4, 10-16). The general information of the trials is shown in Table 2.

Meta-analysis

In total 381 patients were included in the eight trials which compared TEN with TPN in the therapy of severe acute pancreatitis. The general outcome from randomized studies evaluating TEN versus TPN in severe acute pancreatitis is shown in Table 3. Altogether 184 (48.29%) of the patients with severe acute pancreatitis use TEN, others use TPN. Clinically important outcome parameters of significance were evaluated (mortality, hospital LOS, infectious complications, organ failure and need for surgical intervention).

The results of the meta-analysis are demonstrated in Table 4. No statistical heterogeneity within this group of clinical trials except for the subgroup of infectious complications. Forest plot of meta-analyses of the results caused by TEN or TPN demonstrated that TEN was significantly superior to TPN when considering mortality [p=0.001, 95%CI 0.37(0.21-0.68)], infectious complications [p=0.004, 95%CI 0.46(0.27-0.78)], organ failure [p=0.02, 95%CI 0.44(0.22-0.88)] and surgical intervention (p=0.003, 95%CI 0.41(0.23-0.74)].While no difference between TEN and TPN when considering the hospital length of stay [p=0.22, 95%CI -14.10(-36.48-8.26)] and as for duration of nutrition [p=0.72, 95%CI -1.50(-9.56-6.56)] there was not enough data to compare the differences. (Fig. 2-7,Table 4).

Discussion

According to the summary of the clinical randomized trials, total enteral nutrition was superior to total parenteral nutrition. The lack of difference between hospital LOS and duration of nutrition was because the number of randomized trials recruited was low (n=1 and n=1 respectively).

Severe acute pancreatitis remains a significant clinical challenge. It is associated with a mortality rate of 10-40% (19). The main two etiological factors are gallstones and alcohol abuse (20). The clinical course of an attack of AP varies from a short period of hospitalization with supportive care to prolonged hospitalization and admittance to an intensive care unit (ICU) because of the development of systemic inflammatory response syndrome (SIRS), multiorgan failure (MOF), and septic complications (21). Overall, about 15% to 20% of patients progress to SAP. For these patients, the mortality rate is 10%-40% (19). The length of hospital stay is approximately 1 month (22). Multiorgan failure complicates the course of disease in 16-33% of cases, and infection develops in 30-50% (23, 24) and patients had a high rate of surgical intervention when confronting severe acute pancreatitis (24). Thus we selected mortality, hospital

Table 2. Demographic Data of the Studies Included

Sudy	Year of publication	Country	Patients (TEN/TPN)	Criteria of the study	Definitions of infec--tious complications	Definitions of organ failure
Gupta et al[4]	2003	UK	8/9	APACHE II score ≥ 6)	Defined by the Atlanta criteria	Defined by the Atlanta criteria
Louie et al[10]	2005	Canada	10/18	Ranson's score ≥ 3	N/A	N/A
Petrov et al[11]	2006	Russia	35/34	APACHE II score ≥ 8 and/or CRP ≥ 150mg/L	Pancreatic infectious complications, i.e. infected pancreatic necrosis and pancreatic abscess which were based on micro--biological examination	The Marshall score was used to assess organ failure
Eckerwall et al[12]	2006	Sweden	24/26	APACHE II score ≥ 8 and/or CRP ≥ 150mg/L and/or Peripancreatic liquid shown on CT	N/A	N/A
Casas et al [13]	2007	Spain	11/11	APACHE II score ≥ 8 and or CRP ≥ 150mg/L and or D or E grade shown on CT	N/A	N/A
Kalfarentzos et al[14]	1997	Greece	18/20	APACHE II score ≥ 8 and or CRP ≥ 120mg/L and or D or E grade shown on CT	Blood culture positive sepsis, pneumonia and/or adult respiratory distress syndrome, urinary infections, and infected necrosis or intra-abdominal abscess were recorded as infectious complications	N/A
Doley et al[15]	2009	India	25/25	Severe acute pancreatitis was defined using the Atlanta criteria	Culture of FNA, blood, operative specimens or drain fluid	N/A
Wu et al[16]	2010	China	53/54	Those individuals with pancreatic necrosis, determined by dynamic Spiral CT and confirmed by CRP level (greater than 19.5 mg/dL, 48 hours after the onset of the disease)	Patients with suspected infection underwent FNA. If FNA was negative and sepsis was still suspected, FNA was repeated after 72 hours	N/A

APACHE indicates Acute Physiology And Chronic Health Evaluation; CT indicates computed tomography, CRP indicates C-reactive protein.

Table 3. General Outcome from the Randomized Studies Evaluating TEN vs TPN in Severe Acute Pancreatitis

Study	Mortality		Hospital LOS		Infectious complications		Duration Nutrition		Organ Failure		Surgical intervention	
	TEN	TPN	TEN	TPN	TEN	TPN	TEN	TPN	TEN	TPN	TEN	TPN
Gupta et al[4]	0/8	0/9	7(4-14)	10(7-26)	1/8	2/9	2(2-7)	4(2-7)	0/8	6/9	N/A	N/A
Louie et al[10]	0/10	3/18	26.2 ± 17.4	40.3 ± 42.4	1/10	5/18	13.1 ± 10.5	14.6 ± 10.3	4/10	8/18	N/A	N/A
Petrov et al[11]	2/35	12/34	N/A	N/A	11/35	27/34	N/A	N/A	4/35	10/34	8/35	25/34
Eckerwall et al[12]	1/24	2/26	N/A	N/A	1/24	7/26	N/A	N/A	3/24	2/26	1/24	0/26
Casas et al [13]	0/11	2/11	30.2	30.7	1/11	5/11	N/A	N/A	0/11	2/11	0/11	3/11
Kalfarentzos et al[14]	1/18	2/20	40(25-83)	39(22-73)	5/18	10/20	34.8	32.8	N/A	N/A	N/A	N/A
Doley et al [15]	5/25	4/25	42(15-108)	36(22-77)	16/25	15/25	N/A	N/A	N/A	N/A	7/25	8/25
Wu et al[16]	6/53	23/54	N/A	N/A	12/53	39/54	N/A	N/A	11/53	44/54	12/53	43/54

LOS indicates length of stay

LOS, infectious complications, organ failure and the need for surgical intervention for clinical outcome parameters.

The concept of "pancreatic rest" assumes that pancreatic rest promotes healing, decreases pain, and reduces secretion and leakage of pancreatic juices in pancreas parenchyma and peripancreatic tissue (25, 26). The traditional therapy

Table 4. Results of the Meta-analysis

Outcome	No. of the patients included		RR or WMD	*p* value	Heterogeneity,I^2
	TEN	TPN	(95% Confidence interval)		(%)
Death	184	197	0.37(0.21-0.68)	0.37	7.40
Duration nutrition	10	18	-1.50(-9.56-6.56)	N/A	N/A
Infectious complications	184	197	0.46(0.27-0.78)	0.008	63.50
Hospital LOS	10	18	-14.10(-36.48-8.26)	N/A	N/A
Organ failure	141	152	0.44(0.22-0.88)	0.08	48.70
Surgical intervention	148	150	0.41(0.23-0.74)	0.11	46.4

CI indicates confidence interval; EN, enteral nutrition; PN, parenteral nutrition; RR, relative risk.

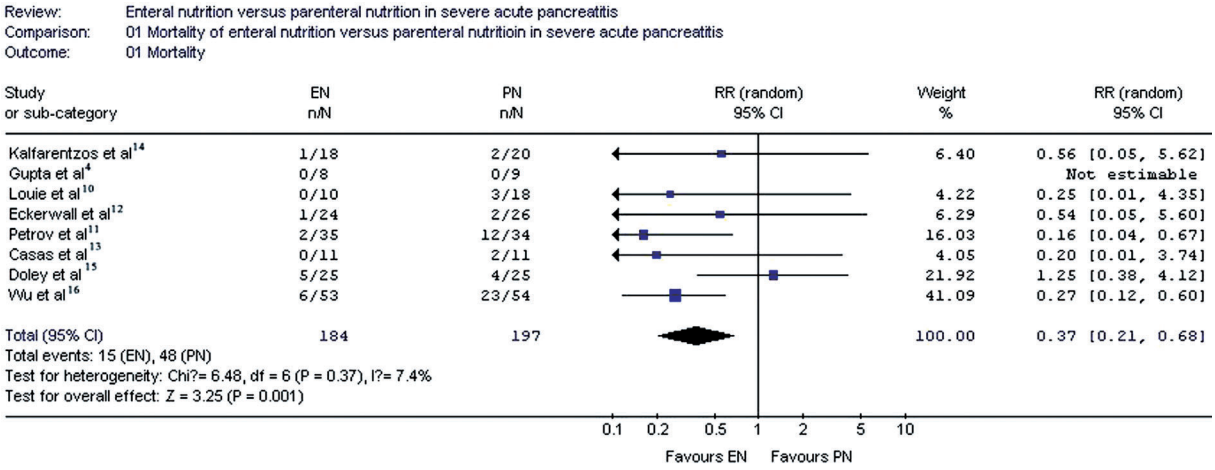

Figure 2. Forest plot for mortality. CI: confidence interval, EN: enteral nutrition, PN: parenteral nutrition, RR: relative risk

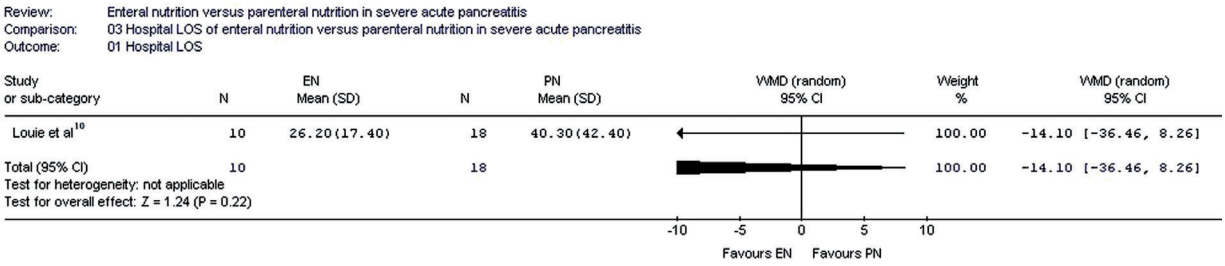

Figure 3. Forest plot for length of hospital stay. CI: confidence interval, EN: enteral nutrition, PN: parenteral nutrition, RR: relative risk

method for SAP are as follows: fasting, somatostatin or analogues to inhibit the activity of pancreatin, prophylaxis antibiotics and sufficient intravenous fluids (3). Total parenteral nutritional support has long been the standard source of exogenous nutrients for these patients, however this is costly and associated with many disadvantages, including dysfunction of the intestinal mucosal barrier, which, in turn, promotes sepsis of intestinal origin (27, 28). While these concepts should now be replaced by the principle that pancreatic stimulation should be maintained and that the stress response should be contained to reduce the likelihood of multiorgan failure, nosocomial infections and mortality (29).

To compare the efficacy of TEN and TPN in severe acute pancreatitis therapy, many randomized clinical trials have already been undertaken to evaluate the different outcomes (4, 8-15). The present meta-analysis, by summarizing all the available data from published RCTs to obtain an overall treatment effect and estimate the relationship between clinical parameters and the different methods of therapy. Forest plot of meta-analyses of the effects of TEN or TPN demonstrated that TEN was significantly superior to TPN when considering mortality [p=0.001,95%CI 0.37(0.21-0.68)], infectious complications [p=0.004, 95%CI 0.46(0.27-0.78)], organ failure [p=0.02,95%CI 0.44(0.22-0.88)] and surgical intervention [p=0.003, 95%CI 0.41(0.23-0.74)]. While there was no difference between TEN and TPN when considering the hospital length of stay [p=0.22, 95%CI -14.10(-36.48-8.26)] and as for duration of nutrition [p=0.72,

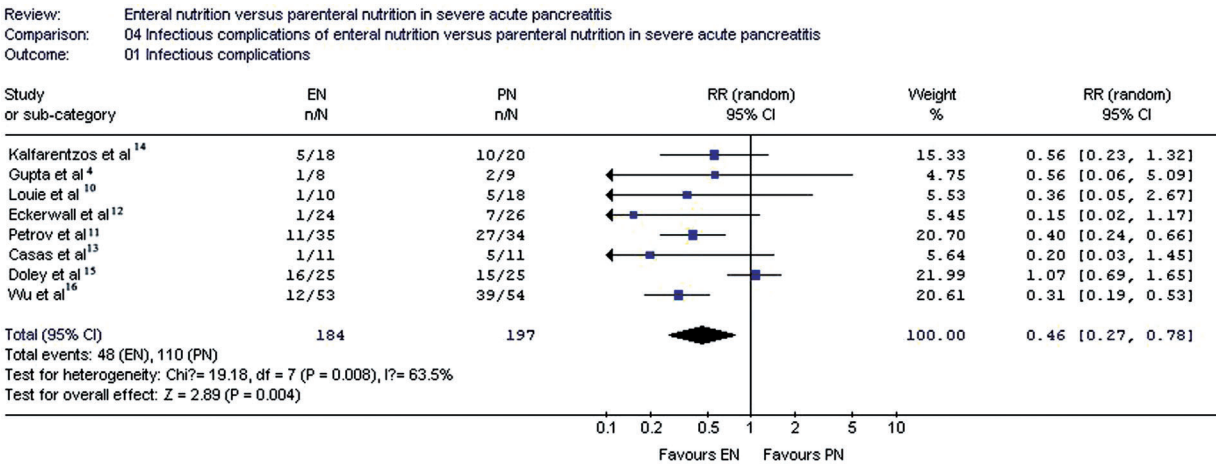

Figure 4. **Forest plot for infectious complications. CI: confidence interval, EN: enteral nutrition, PN: parenteral nutrition, RR: relative risk**

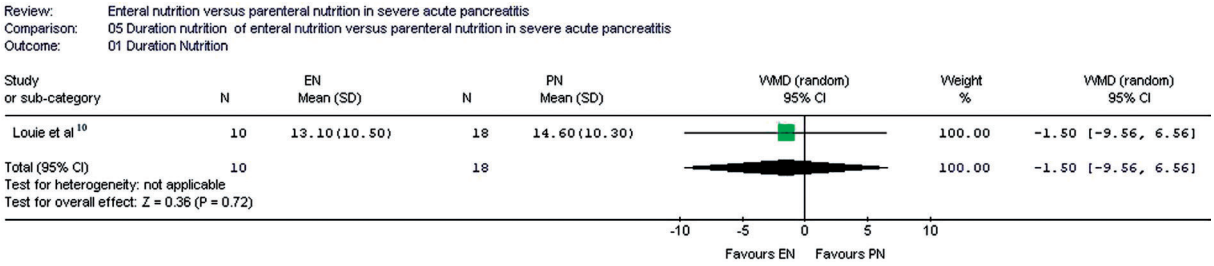

Figure 5. **Forest plot for duration of nutrition. CI: confidence interval, EN: enteral nutrition, PN: parenteral nutrition, RR: relative risk**

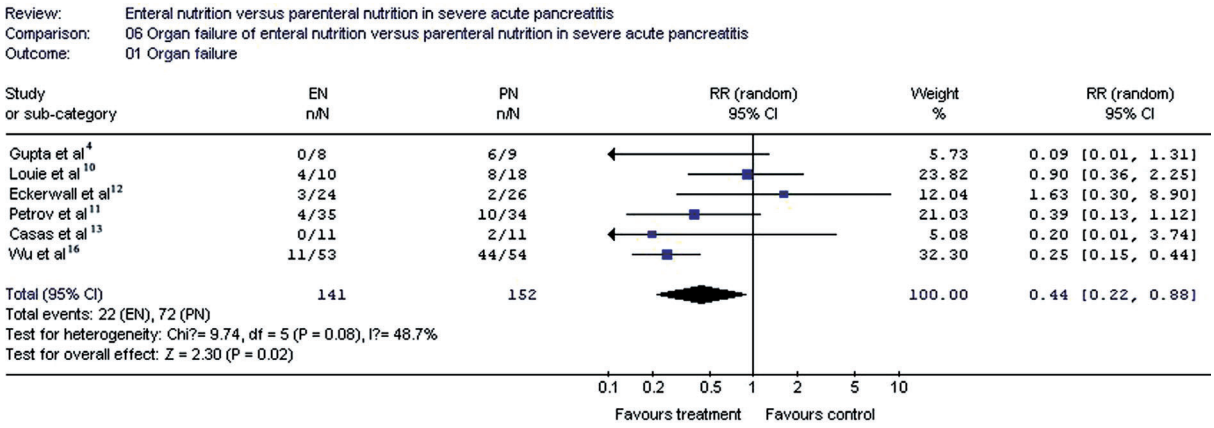

Figure 6. **Forest plot for organ failure. CI: confidence interval, EN: enteral nutrition, PN: parenteral nutrition, RR: relative risk**

95%CI -1.50(-9.56-6.56)] there was not enough data to compare the difference. Which indicated that TEN is superior to TPN when considering the clinical outcomes studied.

As the recruited RCTs have different evaluation standards for the two methods of therapy, we eliminated some parameters. Meanwhile, some biochemical parameters (such as C-reactive protein, cytokine) need to be compared, which may predict the prognosis of the disease. The statistics methods included in the RCTs vary (such as duration nutrition time), which caused the loss of many data in the evaluation. The heterogeneity of the infectious complication is significant, and it may reduce the confidence of this result. Despite the limitations, most of the trials had excellent methodological quality and the pooled number of patients from the eight studies was 381 with reduced type II error.

In conclusion, total enteral nutritional support is associated with lower mortality, fewer infectious complications, a decrease organ failure and surgical intervention rate com-

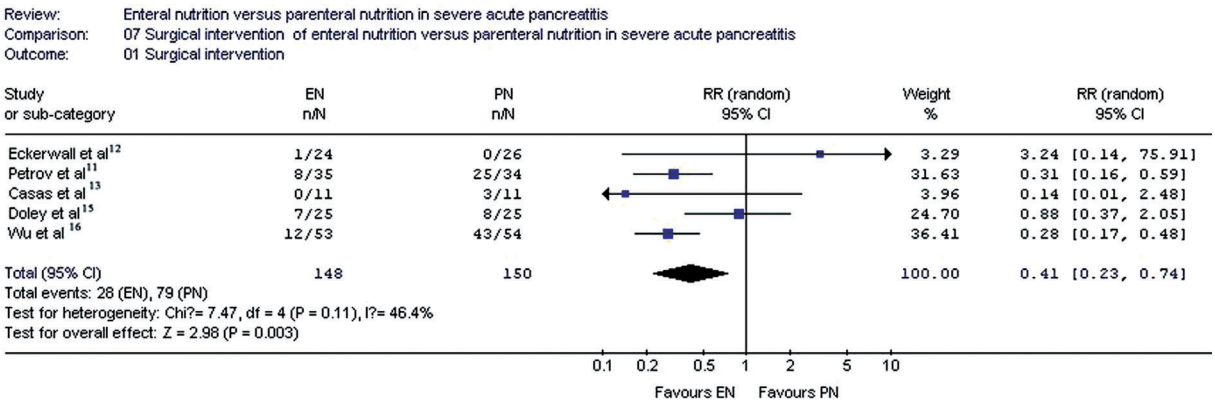

Figure 7. **Forest plot for surgical intervention. CI: confidence interval, EN: enteral nutrition, PN: parenteral nutrition, RR: relative risk**

pared to parenteral nutritional support.

The authors state that they have no Conflict of Interest (COI).

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