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Meta-analyses

Parenteral immunonutrition in patients with acute pancreatitis: A systematic review and meta-analysis

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SUMMARY

Background & aims: Acute pancreatitis is a systemic immunoinflammatory response to auto-digestion of the pancrease and peri-pancreatic organs. Patients with acute pancreatitis can rapidly develop nutritional deficiency; hence nutritional support is important and critical. Sometimes parenteral nutrition (PN) is inevitable in acute pancreatitis. Due to immunosuppressive and inflammatory nature of the disease, it seems that immunonutrients like glutamine and omega-3 fatty acids (ω-3 FAs) added to parenteral formulas may improve the conditions. We conducted a meta-analysis to evaluate the effects of parenteral immunonutrition on clinical outcomes (infectious complications, length of hospital stay (LOS) and mortality) in patients with acute pancreatitis.

Methods: A computerized literature search on four databases (PubMed, Cochrane, ISI Web of Science, and Iran Medex) was performed to find all the randomized controlled trials (RCTs) assessed the effects of parenteral immunonutrition in acute pancreatitis. Necessary data were extracted and quality assessment of RCTs was performed with consensus in the study team. Fixed effects model was used to conduct the meta-analysis.

Results: One hundred and ninety four references were found via our search in which 7 articles matched our criteria for enrolling the meta-analysis. Parenteral immunonutrition significantly reduced the risk of infectious complications (RR = 0.59; 95% CI, 0.39–0.88; $p \leq 0.05$) and mortality (RR = 0.26; 95% CI, 0.11–0.59; $p \leq 0.001$). LOS was also shorter in patients who received immunonutrition (MD = −2.93 days; 95% CI, −4.70 to −1.15; $p \leq 0.001$).

Conclusion: Immunonutrients like glutamine and ω-3 FAs added to parenteral formulas can improve prognoses in patients with acute pancreatitis.

1. Introduction

Acute pancreatitis is a systemic immunoinflammatory response to auto-digestion of the pancrease and peri-pancreatic organs. Gallstone and alcohol abuse (usually in men) are the most important causes of acute pancreatitis. The disease is revealed clinically in different patterns ranging from mild forms to severe necrosis of the gland [1].

Patients with acute pancreatitis can rapidly develop nutritional deficiencies due to organs dysfunctions and systemic inflammation; hence nutritional support is very important and even would be critical if the patients had been in malnourished situation before attack [2]. The main predictors of the patients outcomes are: (*i*) severity of the disease, and (*ii*) nutritional status of the patients [3]. There is no specific treatment for acute pancreatitis. In most mild to moderate cases, condition of patients improves spontaneously in a week. During this time, monitoring and supportive treatments such as endoscopic retrograde cholangiopancreatography (ERCP; only in gallstone pancreatitis), intravenous rehydration, and oxygenation may ameliorate the condition [2,4]. Patients with severe acute pancreatitis require more intensive care. Nutritional support is more important and critical due to the significant risk of malnutrition in such patients [5].

Abbreviations: CI, confidence interval; EN, enteral nutrition; ICU, intensive care unit; IMDs, Immunomodulating diets; LOS, length of stay in hospital; MD, mean difference; ω-3 FAs, Omega-3 fatty acids; RCT, randomized controlled trial; RR, relative risk; PN, parenteral nutrition; SE, standard error.

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Until the late 1990s, it was believed that the best way to control the condition of patients with acute pancreatitis is gut rest with or without parenteral nutrition (PN) [5]. Recently, the body of evidence has been increased regarding the use of enteral nutrition (EN) in acute pancreatitis because gut is working [6]. According to the International Consensus Guidelines for Nutrition Therapy in Pancreatitis-2012, EN is preferred over PN in patients with acute pancreatitis. The committee has stated that PN must be restricted to situations in which EN is contraindicated or not feasible (for example when it is difficult to install the feeding tube correctly or when the patients cannot tolerate EN), or as a supplementary therapy when EN cannot provide full nutritional support [7]. In addition to the severity of pancreatitis and presence or absence of necrosis or pseudocysts, conditions like ileus or colonic perforation enforce us to choose PN [8,9].

Owing to immunosuppressive and hyper inflammatory nature of acute pancreatitis, the immune-enhanced products can be useful to improve the immune responses and modulation of inflammation if these products are used enterally or parenterally [6,10,11]. Immunomodulating diets (IMDs) contain immunonutrients such as glutamine or omega-3 fatty acids (ω-3 FAs) that have demonstrated beneficial effects on immune system in experimental models [12]. Glutamine improves lymphocyte functions and contributes to antioxidative defenses. It can also support the intestinal integrity and decrease bacterial translocation; hence reduce systemic inflammatory responses and sepsis, which are important in critical illnesses such as acute pancreatitis [13]. Omega-3 fatty acids may ameliorate the condition of critically ill patients by modulating the production of inflammatory eicosanoids and cytokines; therefore, improve several physiological functions such as immune response, cell proliferation, blood clotting, and inflammation [14]. No adverse effects of the use of ω-3 FAs in parenteral formulas have been reported, but there are few studies in this subject to make a strong deduction. However, there are some evidences asserting that high dosages of ω-3 FAs (≥5 g/d) may increase glucose level, bleeding time, and production of low-density-lipoprotein cholesterol [15,16].

Several meta-analyses failed to produce convincing evidence on the beneficial effects of immunomodulating parenteral nutrition in clinical outcomes of critically ill patients [17–20]. It is important to note that the clinical response depends on the parenteral formula, illness background and severity [5]. Previous meta-analyses grouped different immunomodulating formulas and different types of patients together [18–20]. It may lead to heterogeneity and perhaps masking treatment effects [21]. Therefore, this study aims to evaluate the clinical outcomes of immunoparenteral vs. standard parenteral nutrition in patients with acute pancreatitis by quantitative review of randomized controlled trials (RCTs) published in this field.

2. Materials and methods

2.1. Literature search and selection

The project was registered in PROSPERO, international prospective register of systematic reviews with the registration number: CRD 42013004746. We followed PRISMA criteria to conduct the systematic review and also to report the results of meta-analysis of RCTs [22]. The method and eligibility criteria were documented as a protocol submitted to PROSPERO that was available at the mentioned database. A computerized literature search on four databases (PubMed, Cochrane register of control trials, ISI Web of Science, and Iran Medex) was performed. After achieving consensus within study team on search strategy, RCTs published until June 2013 were identified.

The search strategy for PubMed was: ("acute pancreatitis"[tiab] OR "pancreatitis"[tiab] OR "acute necrotizing pancreatitis"[tiab]) AND ("nutritional support"[tiab] OR" dietary supplementation"[tiab] OR "parenteral nutrition"[tiab] OR "total parenteral nutrition"[tiab] OR "parenteal nutrition solutions"[tiab] OR "immunonutrition"[tiab]) AND ("Fatty Acids, Omega-3"[Mesh] OR "Fish oil"[tiab] OR "glutamine"[tiab] OR "glutamine dipeptides"[tiab] OR "L-glutamine"[tiab] OR "glutamine supplementation"[tiab]). We decided to search other databases with the key words: "parenteral nutrition" AND "acute pancreatitis". Three authors evaluated the total identified articles separately through study of the titles, abstracts, and if necessary, full texts. An additional search was done on the references of the probable related literature to avoid missing articles. The eligibility criteria for articles to be selected were parallel-group RCTs in which a parenteral immunonutrition solution was compared with standard form in patients with acute pancreatitis.

2.2. Inclusion and exclusion criteria

Among the articles with the subject of parenteral nutrition in acute pancreatitis, we selected those consistent with the inclusion and exclusion criteria:

Inclusion criteria:

- RCTs which used parenteral immunonutrition containing glutamine or glutamine dipeptide and compared its effects with standard parenteral nutrition on clinical outcomes of patients with acute pancreatitis.
- RCTs which used parenteral immunonutrition containing ω-3 FAs or fish oil and compared its effects with standard parenteral nutrition on clinical outcomes of patients with acute pancreatitis.
- Both parenteral immunonutrition solution and standard form had to be iso-caloric and also iso-nitrogenus.
- Patients involved were females or males aged 16 or over, with acute pancreatitis whom needed PN therapy, and the parenteral feeding had begun within 72 h after admittance to ICU.
- RCTs that had our desirable clinical outcomes (infectious complications, mortality rate, or LOS).

Trials were included regardless of glutamine or ω-3 FAs doses, and patients could receive additional fluid and electrolytes via supplementation therapy.

Exclusion criteria:

- RCTs evaluated EN, or compared EN with PN.
- RCTs evaluated parenteral immunonutrition in any other condition except acute pancreatitis or gathered all critically illnesses together.

2.3. Quality assessment

Two authors independently assessed the quality of selected articles using modified Jadad score [23]. Intention-to-treat and use of blinded endpoints were added according to Bollhalder et al. [20], with a minor modification in scoring. Each question scored 1 for "Yes", and 0 for "No" answer, thus our new scoring was ranged from 0 to 7. The quality score was not used to exclude the articles; it was used to explain the probable heterogeneity of the results and to achieve a more logical deduction. Final scores were discussed within the study team to consent about doubtful points.

The quality of the evidence for each outcome was assessed according to Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group using GRADE pro software version 3.6. The criteria assessed in each study were consistency and precision of data, directness, the study design and potential

limitations, as well as sample and effect sizes. Finally, the quality of evidence was categorized as high, moderate, low, and very low [24].

2.4. Data extraction

We designed a data extraction table which contained the mentioned information: quality score of the studies, methods of severity assessment, sorts of interventions and dosages, the interval between admittance to ICU and start of PN, duration of PN, and all relevant outcome measures (Table 1).

To extract the data on length of hospital stay, we estimated mean and standard deviation from median and sample size where necessary, according to Hozo et al. [25]. Data extraction process was performed with consensus in the study team.

2.5. Statistical analysis

The association between parenteral immunonutrient-enriched formulas (glutamine or ω-3 FAs) with infectious complications, mortality and LOS, were separately assessed. Main outcome variables were measures of relative risks for the association between parenteral immunonutrition levels and infectious complications and mortality, while for LOS was mean difference ± standard error (SE). Point estimates of relative risks (RRs) or mean ± SE and 95% confidence intervals (CI) were estimated for each study. Within and between-study heterogeneities were assessed using Cochran's Q-statistics [26], and the heterogeneity test was used to assess the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I square (I^2) that provides a measure of the degree of inconsistency between studies and determines whether the percentage of total variation across studies is due to heterogeneity rather than chance [27]. I^2 values range between 0 and 100%, and I^2 values of 25, 50 and 75% are referred to as low, moderate, and high estimates, respectively. We found no evidence of heterogeneity, so the fixed effect method [28] was applied to calculate pooled relative risks (RRs) and 95% confidence intervals (CIs). The funnel plot, Begg and Mazumdar rank correlation test and Egger test were employed to assess the publication bias [29]. Sensitivity analysis was conducted to explore the extent to which inferences might depend on a particular study or number of publications. Statistical analyses were conducted by using Stata version 11.2 (Stata Corp, College Station, TX). P values less than 0.05 were considered statistically significant.

3. Results

3.1. Study identification and selection

We found a total of 194 references via our systematic search. We excluded 130 articles with irrelative topics; the remaining 64 references contained 31 duplications that we had to exclude them. There remained 33 articles about the effects of PN on acute pancreatitis, among them, 7 articles [30–36] were eligible to include in meta-analysis. Figure 1 summarized the process.

3.2. Analysis of outcomes

The results of quality assessment of each outcome are represented in summary of findings table (Table 2). "High" indicated that further research is unlikely to change our confidence in the estimate of the effect. "Moderate" indicated that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. "Low" indicated that

Table 1
Characteristics of RCTs included in meta-analysis.

Study/year	Quality score	Method of severity assessment	Dosage (g/kg BW/d)	AD-PN interval[a] (hours)	Duration of PN (days)		Infectious complication (n/N)		Mortality (n/N)		LOS[b] (days mean ± SD)	
					Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Glutamine												
De Beaux et al. (1998) [30]	4	–	0.22[e]	<72	7	7	0/7	1/7	0/7	0/7	–	–
Ockenga et al. (2002) [31]	5	APACHE[c] CT severity index[d]	0.3[e]	<72	10–18	6–16	5/14	4/14	1/14	0/14	27.25 ± 6.20	22 ± 5.23
Xian-li et al. (2004) [32]	3	–	0.4[e]	24–48	14	14	5/22	0/22	3/22	0/22	28.6 ± 6.9	25.3 ± 7.6
Sahin et al. (2007) [33]	2	Ranson criteria	0.3[e]	<48	7–21	7–15	–	–	6/20	2/20	16.4 ± 3.9	14.2 ± 4.4
Fuentes-Orozco et al. (2008) [34]	5	APACHE[c] CT severity index[d]	0.4[e]	24–48	17.5	19.3	16/22	9/22	5/22	2/22	26.59 ± 13.3	30.18 ± 10.42
ω-3 fatty acids												
Wang et al. (2008) [35]	6	APACHE[c]	0.2	<72	5	5	5/20	3/20	2/20	0/20	70.5 ± 9.1	65.2 ± 7.3
Wang et al. (2009) [36]	5	APACHE[c]	0.2	<72	5	5	9/28	6/28	6/28	0/28	–	–

[a] The interval between admittance to ICU and start of parenteral nutrition.
[b] Length of hospital stay.
[c] Acute physiology and chronic health evaluation.
[d] Computed tomography severity index.
[e] As glutamine dipeptide.

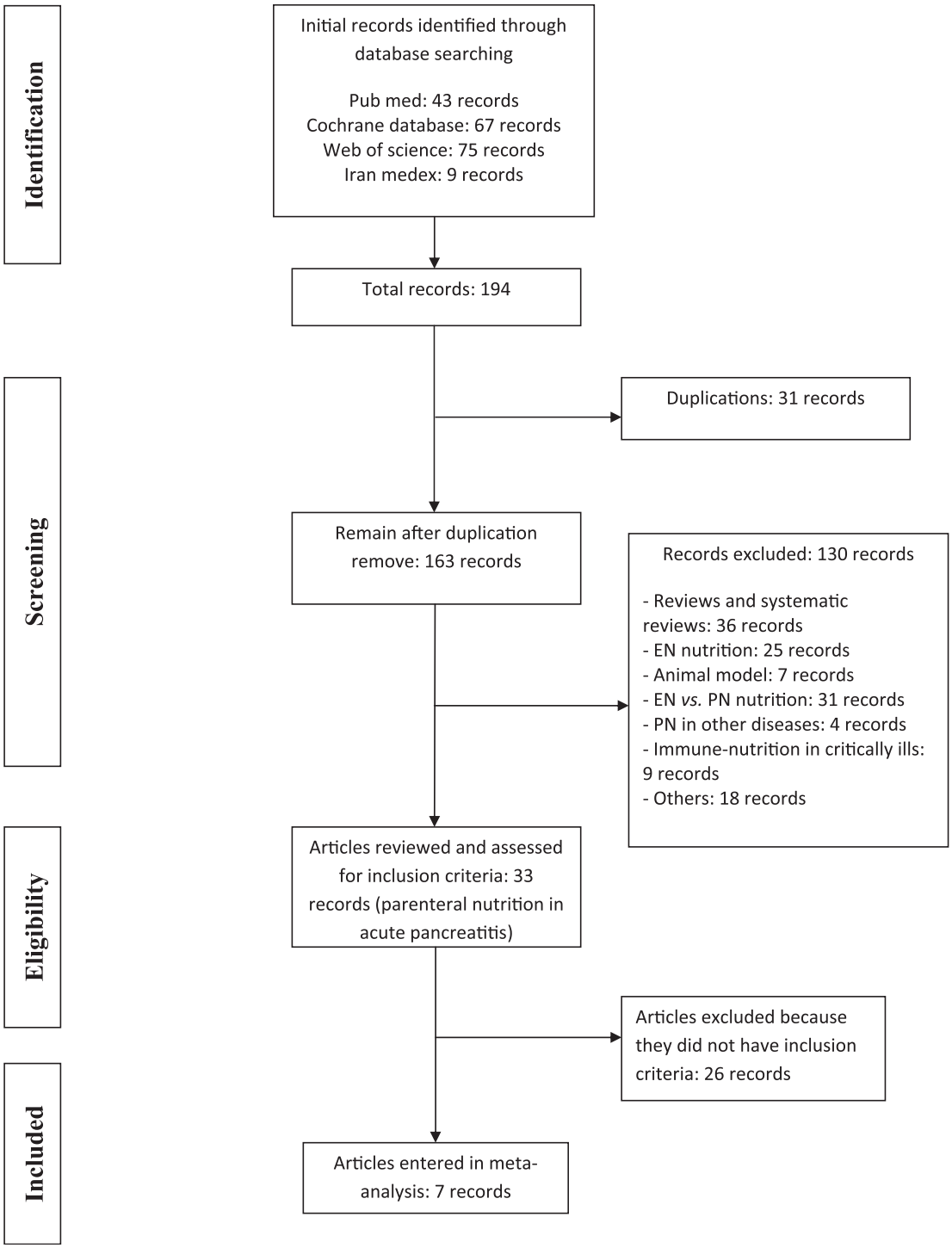

Fig. 1. PRISMA flow diagram of study identification, inclusion, and exclusion.

further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

3.3. Study characteristics

Table 1 shows essential characteristics of 7 mentioned RCTs consisting of 266 participants enrolled in the meta-analysis. The risk of bias for each study was assessed according to the modified Jadad score and is presented in Table 1.

3.4. Effect of parenteral immunonutrition on infectious complications

Infectious complications were indicated in 6 of 7 studies with 226 participants and one study [33] did not report any data in this subject. Pooled analysis of 6 trials represented that parenteral immunonutrition can significantly reduce the risk of infectious complications in patients with acute pancreatitis (Fig. 2; RR = 0.59; 95% CI, 0.39 to 0.88; $p \leq 0.05$). The chi-squared test for heterogeneity was not significant ($p = 0.67$) and I^2 was 0.0%. Moreover, no

Table 2
Summary of findings table: clinical outcomes.

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard parenteral nutrition	Risk difference with parenteral immunonutrition (95% CI)
Parenteral immunonutrition compared to standard parenteral nutrition					
Infectious complications	226 (6 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.59 (0.39–0.88)	354 per 1000	145 fewer per 1000 (from 42 fewer to 216 more)
Mortality	266 (7 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.26 (0.11–0.59)	173 per 1000	128 fewer per 1000 (from 71 fewer to 154 more)
Length of hospital stay	196 (5 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision		The mean length of hospital stay in the control groups was 33.9 days	The mean length of hospital stay in the intervention groups was 2.93 days lower (4.7–1.15 lower)
Glutamin-contained parenteral nutrition compared to standard parenteral nutrition					
Infectious Complication	130 (4 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.56 (0.34–0.91)	400 per 1000	176 fewer per 1000 (from 36 fewer to 264 more)
Mortality	170 (5 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.34 (0.14–0.85)	176 per 1000	116 fewer per 1000 (from 26 fewer to 152 more)
Length of hospital stay	156 (5 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision		The mean length of hospital stay in the control groups was 19.8 days	The mean length of hospital stay in the intervention groups was 2.60 days lower (4.5–0.71 lower)
Omega 3-contained parenteral nutrition compared to standard parenteral nutrition					
Infectious Complication	96 (2 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.64 (0.31–1.34)	292 per 1000	105 fewer per 1000 (from 99 fewer to 201more)
Mortality	96 (2 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.11 (0.01–0.85)	167 per 1000	148 fewer per 1000 (from 25 fewer to 165 more)
Length of stay in hospital	40 (1 study)	⊕⊕⊖⊖ LOW[a,b] due to imprecision, publication bias		The mean length of stay in hospital in the control groups was 70.5 days	The mean length of stay in hospital in the intervention groups was 5.30 days lower (10.41–0.19 lower)

The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.
[a] Low sample size in some studies may make imprecision.
[b] There is only 1 study for this outcome.

evidence of publication bias was found based on funnel plot (Egger test, $p = 0.36$).

Stratified meta-analysis was conducted to show the effect of glutamine- or ω-3 FAs-enriched formulas separately. Results represented that glutamine-contained parenteral formulas significantly attenuated infectious complications in patients with acute pancreatitis (Fig. 2; RR = 0.56; 95% CI, 0.34 to 0.91; $p \leq 0.05$). Regarding ω-3 FAs-enriched formulas, the risk was reduced but the result was not significant (Fig. 2; RR = 0.64; 95% CI, 0.31 to 1.34; $p = 0.23$). No evidence of between study heterogeneity was found in glutamine subgroup ($I^2 = 5.5\%$, $p = 0.36$) and in ω-3 FAs subgroup ($I^2 = 0.0\%$, $p = 0.89$). Also funnel plots did not show evidence of publication bias for glutamine and ω-3 FAs (Egger test, $p = 0.502$ and $p = 0.33$, respectively).

To show the cumulative evidence at the time of each study in included trials from 1998 to 2009, cumulative meta-analysis was also performed. As demonstrated in supplementary data (Fig. S1), the risk for infectious complications reduced significantly by the late of 1998.

3.5. Effect of parenteral immunonutrition on mortality

All 7 studies [30–36] enrolled in meta-analysis (266 participants) had data on mortality. Almost all of these studies had reported a reduction in mortality in intervention group comparing to control, but their results were not significant. After pooling the studies and conducting the meta-analysis, a significant association was found between parenteral immunonutrition therapy and mortality reduction in patients with acute pancreatitis (Fig. 3; $R = 0.26$; 95% CI, 0.11 to 0.59; $p \leq 0.001$). There was not any heterogeneity among the studies (I^2 was 0.0%, $p = 0.92$); also publication bias was not confirmed (Egger test, $p = 0.68$).

Figure 3 also represents the effects of glutamine- and ω-3 FAs-enriched parenteral formulas on mortality separately. In glutamine subgroup, the risk of mortality reduced (RR = 0.34; 95% CI, 0.14 to 0.85; $p \leq 0.05$). The test for heterogeneity was not significant in this subgroup ($I^2 = 0.0\%$, $p = 0.94$). In ω-3 FAs subgroup, mortality incidence was reduced significantly in patients who had received ω-3 FAs parenterally (RR = 0.11; 95% CI, 0.01 to 0.85; $p \leq 0.05$). The test for heterogeneity was also non-significant in this subgroup ($I^2 = 0.0\%$, $p = 0.64$). The funnel plots did not show evidence of publication bias (glutamine subgroup: Egger test, $p = 0.36$; ω-3 FAs subgroup: Egger test, $p = 1$).

Cumulative meta-analysis suggested that the relative risk of mortality has been declined by the late of 1998 (Supplementary data, Fig. S2).

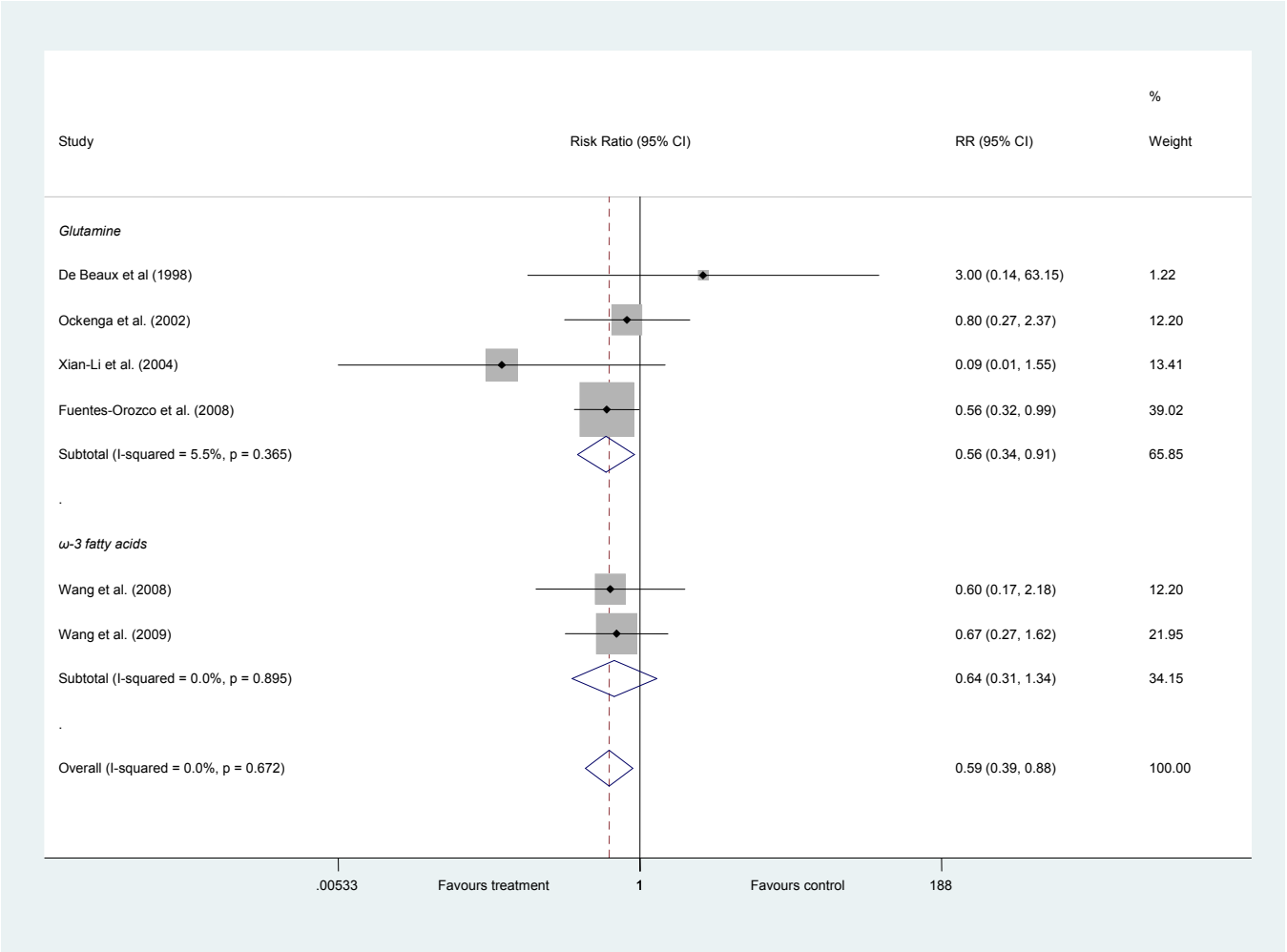

Fig. 2. Forest plot of effect of parenteral immunonutrition on infectious complications.

3.6. Effect of parenteral immunonutrition on LOS

Five records [31–35] (196 participants) among 7 studies had data on LOS for analysis; and 2 studies (De Beaux et al. and Wang et al.) [30,36] did not published information in this field. As represented in Fig. 4, parenteral immunonutrition was significantly associated with reduction in hospitalization in acute pancreatitis (MD = −2.93 days; 95% CI, −4.70 to −1.15; $p \leq 0.001$). The tests for heterogeneity indicated that there were no heterogeneity among the studies ($I^2 = 28.4\%$, $p = 0.23$). Also the funnel plot did not show evidence of publication bias (Egger test, $p = 0.22$).

Stratified meta-analysis in this field demonstrated that both glutamine- and ω-3 FAs-enriched parenteral formulas significantly reduced LOS in patients with acute pancreatitis (Fig. 4; glutamine: MD = −2.60 days; 95% CI, −4.50 to −0.71; $p \leq 0.01$; ω-3 FAs: MD = −5.30 days; 95% CI, −10.41 to −0.19; $p \leq 0.05$). The test for heterogeneity within glutamine supplemented group was not significant ($I^2 = 35.4\%$, $p = 0.20$) and funnel plot represented that no publication bias were existed (Egger test, $p = 0.29$). In the other subgroup comprising one study [35], it was not necessary to check heterogeneity.

Considering the plot of cumulative meta-analysis on effect of parenteral immunonutrition on LOS (Supplementary data, Fig. S3), the most reduction in length of hospitalization was observed in the studies of De Beaux et al. [30] and Ockenga et al. [31], while regarding the two other outcomes (infectious complications and mortality) the trends of relative risks were descending from 1998 to 2009.

4. Discussion

Considering the contradictory results of RCTs comparing parenteral immunonutrition with standard PN, several meta-analyses [18,20,37,38] have been conducted to clarify whether immune-enhanced formulas improve condition of patients. But data from these meta-analyses have failed to make convincing evidence. Most of the quantitative reviews evaluated the effects of parenteral immunonutrition in different types of diseases called critical illnesses. For example, Pradelli et al. apprised the effects of ω-3 FAs-enriched parenteral regimens in elective surgical and ICU patients and concluded that these formulas reduced infectious rate and LOS [19]. In another meta-analysis, Bollhalder et al. evaluated the effects of parenteral glutamine supplementation in different types of diseases [20]. They classified studies to surgery and critical illnesses. The results could not clarify whether parenteral immunonutrition improve the condition of patients. Controversial results are also observed in meta-analyses performed by Chen et al. [18] and Palmer et al. [37]. They grouped the patients with conditions such as trauma, burn, surgery, and ICU admittance as critically ill which may increase heterogeneity and mask the truth. However, in some analyses critically ill patients were subgrouped according to their disease but

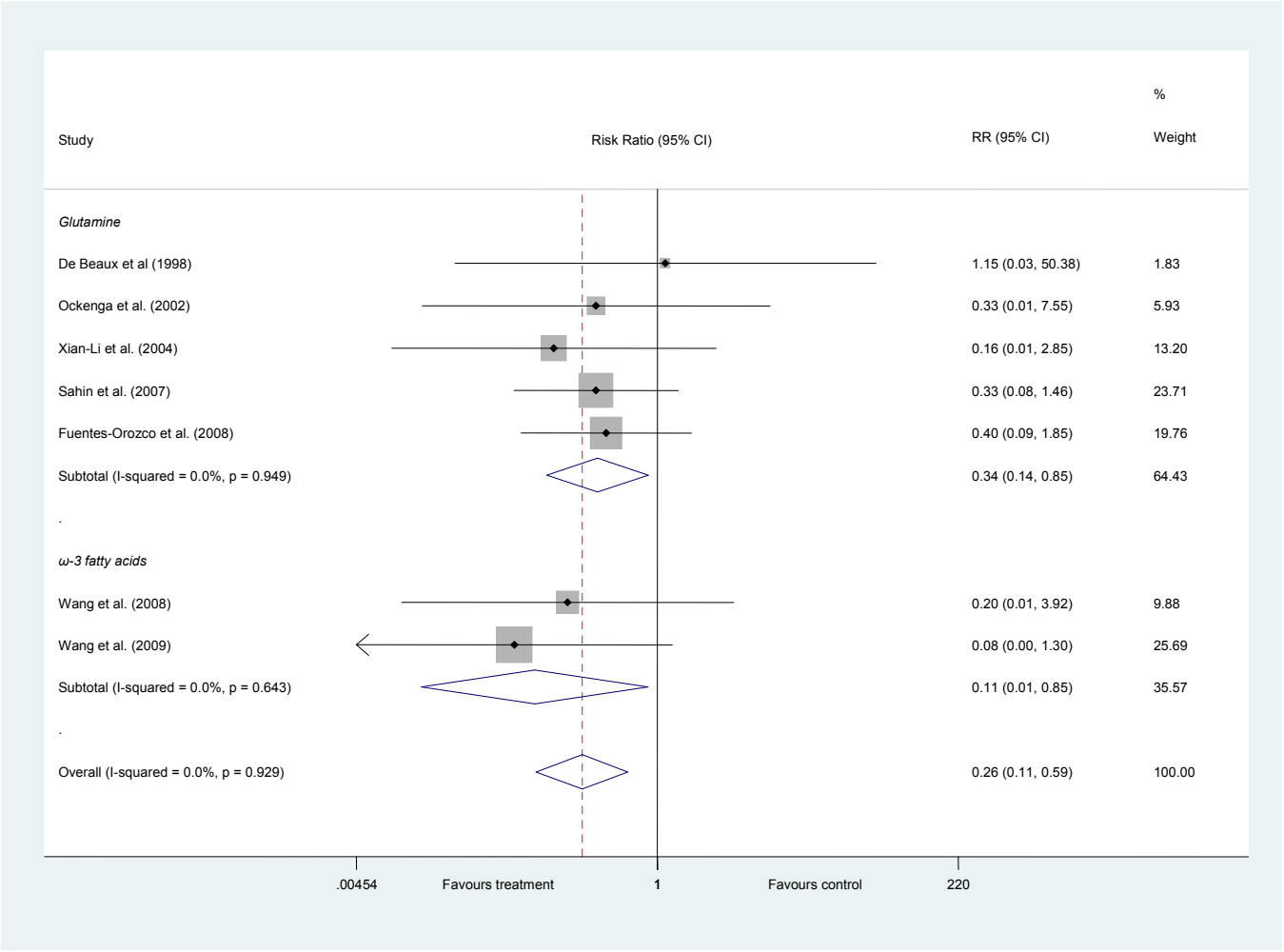

Fig. 3. Forest plot of effect of parenteral immunonutrition on mortality.

patients admitted in ICU were still considered a single group. It seems that subgrouping must be continued because of high heterogeneity of patients in ICU. Most doubt about benefits of immunonutrition (enterally or parenterally) exists in ICU admitted patients [39]. It should be considered that the clinical responses depend on the type of parenteral formula, kind of the disease, and status of patients. These points must be considered before designing a meta-analysis. Considering the scientific literature, this meta-analysis is the first which assessed parenteral immunonutrition in patients with acute pancreatitis specifically. Petrov et al. evaluated enteral immunonutrient-enriched formulas in acute pancreatitis in their meta-analysis and concluded that these formulas did not have any beneficial effect on outcomes of patients [40]. Considering the lack of sufficient RCTs with adequate sample size, they recommended more appropriate trials in patients with acute pancreatitis.

According to our meta-analysis, overall evaluation of the RCTs as well as grouping them according to the type of formula (glutamine or ω-3 FAs) demonstrates reduction in infectious complications via parenteral immunonutrition. Non-significant results in ω-3 FAs group may be due to few scientific evidences performed in the subject (only 2 studies [35,36] conducted by the same authors that might have used the same cohort of patients). McClave et al. designed a meta-analysis with 3 trials existed until 2006 about the effect of glutamine-supplemented parenteral nutrition on complications in patients with acute pancreatitis. They found the trend of reduction only in complications [41]. After that time, 2 more trials were performed [33,34]. Evaluation of the data from 5 trials [30–34] about glutamine demonstrates a significant overall effect in the present meta-analysis. Our meta-analysis clarified that immunonutrient-supplemented PN significantly reduces the mortality rate in patients with acute pancreatitis, while previous meta-analyses which have grouped different types of patients together as critically ill, failed to demonstrate reduction in mortality [19,37,41] or only represented a trend toward reduction [20,42]. Length of hospitalization reduced significantly in groups who received any kind of immuno-nutrients via parenteral pathway according to recent meta-analysis. However, according to GRADE, all 3 outcomes were appraised as moderate quality which means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Considering the trend of the effect of IMDs on LOS (supplementary data, Fig. S3), mean differences between intervention group (who received IMDs) and controls (who did not received IMDs) have declined from 1998 to 2009. It might be due to improvement in treatment strategies of critically ill patients including patients with acute pancreatitis.

The median length of parenteral feeding was significantly lower in glutamine-supplemented group than control [31]. The average ICU stay was lower in patients who received ω-3 FAs than control group

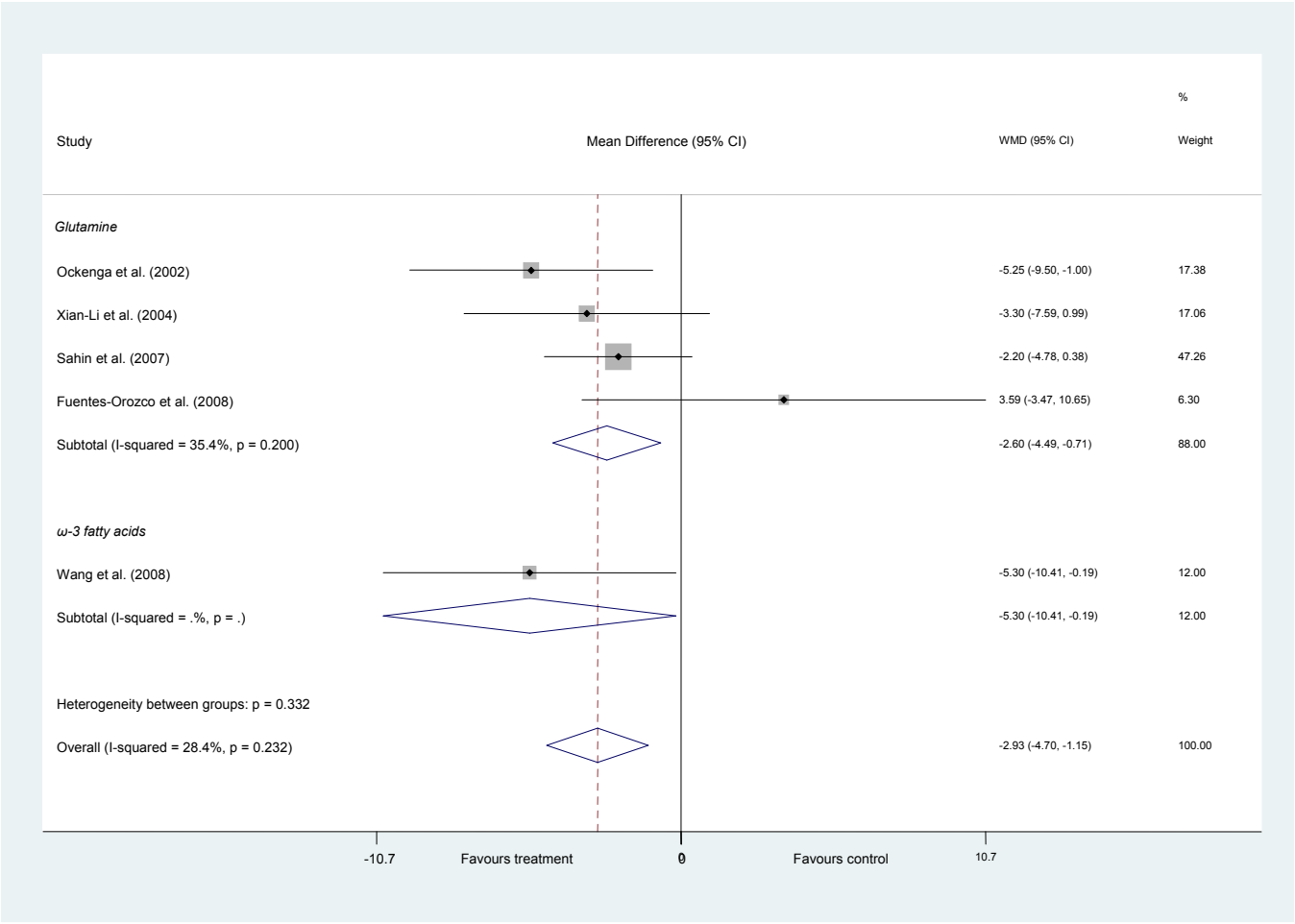

Fig. 4. Forest plot of effect of parenteral immunonutrition on length of stay in hospital.

[35]. It was also reported that despite the increase of daily cost for glutamine-supplemented TPN, the overall related cost for each patient did not differ between glutamine-supplemented and non-glutamine supplemented groups due to the reduction of hospitalization [31].

Some limitations of our meta-analysis are as follows: (*i*) small sample size in most of the studies, (*ii*) few number of studies on the subject specially about ω-3 FAs, (*iii*) possible heterogeneity in the disease severity among the studies due to the application of different methods for severity assessment, (*iv*) absence of accurate data in some studies about antibiotic therapy which may influence the outcomes, specifically the rate of infectious complications, and (*v*) lack of information about probable supplementary therapies such as surgery, drainage, and debridement that may affect the outcomes.

In conclusion, we recommend more precise trials with adequate sample size in this field to make stronger deduction, and also conducting meta-analyses in homogenous patients admitted in ICU to evaluate the effects of IMDs in clinical outcomes.

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Statement of authorship

The author's responsibilities were as follows; TJ was involved in designing, literature search, data extracting, data synthesis, and drafting the manuscript; AAF and GA were involved in literature search, data extracting, and data synthesis; AF was involved in data synthesis and statistical analysis; all authors were involved in quality assessing of the articles. TJ and AAF supervised the study. All authors read and approved the final manuscript.

Conflict of interest

The authors disclose no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.05.008.

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