¬The Effect of Immunomodulatory Diet (Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidants) on clinical outcomes in critically ill patients

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Abstract

Enteral immunomodulatory nutrition is suggested as an adjuvant therapy for patients admitted in intensive care units (ICU), but its effectiveness remains debated. The aim of this systematic review and meta-analysis is to examine the effect of dietary immunomodulatory formula on the clinical outcomes and risk of overall mortality in critically ill patients. PubMed, Scopus and ISI web of Knowledge databases were searched until September 2019. Randomized Controlled Trials (RCTs) that used immunomodulatory diet containing omega-3 fatty acid, γ-linolenic acid and antioxidants in ICU were included. Ten RCTs including 1166 participants were included in the meta-analysis. Immunomodulatory diet containing omega-3 fatty acid, γ-linolenic acid and antioxidants led to significantly reduce the duration of ICU stays (WMD: -2.97 days; 95%CI: -5.59, -0.35), duration of mechanical ventilation (WMD = -2.20 days, 95%CI: -4.29, -0.10), SOFA (sequential organ failure assessment) and MOD (multiple organ dysfunction) score (Hedge's g: -0.42 U/L; 95% CI: -0.74, -0.11). The 28 days' overall mortality was remarkably decreased following Immunomodulatory supplement in critically ill patients (RR = 0.74, 95% CI: 0.58, 0.91) and extended the ICU- free days (WMD: 4.06 days, 95%CI: 0.02, 8.09). However, immunomodulatory formula had no significant effect on length of hospital stays, ventilator- free days and level of oxygenation.Immunomodulatory diet containing omega-3 fatty acid, γ-linolenic acid and antioxidants might have beneficial effects for the patient's residing in ICU; However, further well-designed RCTs with larger sample size are recommended to confirmed its effect.

Introduction

Patient's staying in ICUs with critical condition such as sepsis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) or multiple trauma, excessive inflammation often leads to multiple organ dysfunction syndrome and death (Carcillo et al., 2017). Malnutrition is one of the outcomes of ICU admission which aggravates clinical status including disruption of immune system function, respiratory muscles, ventilation capacity and gastrointestinal tolerance and leads to loss of lean body mass (Lew et al., 2017). As a result of these impairments, complications such as esophagitis, gastroesophageal reflux, pulmonary aspiration and infections can lead to sepsis, multi-organ failure and death (Lew et al., 2017). Supportive nutrition via reducing oxidative stress, modulates inflammatory response, feeding tolerance that could be helpful for critically ill patients (Hegazi and Wischmeyer, 2011). Among the supportive nutrition therapies, fatty acid

based formulas which have considerable role in the mechanism of regulating immune system might have a important role in clinical outcomes in ICU patients.

The influence of fat intake on composition of cell membrane could alter immune inflammatory responses like neutrophils and macrophages function consequently (Hegazi and Wischmeyer, 2011). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most important long chain fatty acid that serves as precursors of anti-inflammatory mediators (Calder, 2006) and suppress the production of cytokines IL-6 and TNF-α, both in vivo and vitro (Das, 2013) whereas arachidonic acid (AA) as an omega-6 fatty acid is precursor to inflammatory eicosanoids and leukotriene mediators (Calder, 2006). However, γ-Linolenic acid (GLA) is an omega-6 fatty acid and unlike arachidonic acid has shown anti-inflammatory properties. Nutritional supplementation with this fatty acid combined with omega-3 fatty acids boosts the immune system (Calder, 2006).

A meta-analysis of 17 clinical trials suggested routine supplementation with omega-3 fatty acids should be avoided because the overall evidence had very low quality and was insufficient to justify the routine use of omega-3 fatty acids in the management of sepsis (Lu et al., 2017). The effects of supplementation with fatty acids on ICU patients showed contradictory findings. Recently Chen et al (Chen et al., 2017) showed that the beneficial effect of omega-3 fatty acids supplementation for treatment of acute lung injury and acute respiratory distress syndrome contributed to the improvement of PaO2/FiO2 ratio, as well as ventilator-free day and decreased ICU-free days; while in another study, supplementation with omega-3 did not cause any significant changes in oxygenation, ventilator free days, ICU free- days and mortality (Stapleton et al., 2011).

Dietary antioxidants such as vitamin C and E act by reducing oxidative stress and as a scavenger of oxidant products to help immune system (Carr and Maggini, 2017, Lewis et al., 2019).

Several Randomized Controlled Trials (RCTs) on this certain formula have been performed for sepsis (Pontes-Arruda, 2005, Pontes-Arruda et al., 2011, Grau-Carmona et al., 2011), ARDS (Elamin et al., 2005, Shirai et al., 2015, Pacht et al., 2003, Nelson et al., 2003), ALI (Schott and Huang, 2012, Rice et al., 2011, Theilla et al., 2007) and multiple trauma (Kagan et al., 2015) reporting contradictory effects. A meta- analysis of 6 clinical trials in critically ill patients showed that immunomodulatory diet containing omega-3 fatty acid, γ-linolenic acid and antioxidants did not have any significant effect on ventilator free- days, ICU free- days and risk of mortality in ALI and ARDS patients, but in subgroup with high mortality it was found to be useful (Li et al., 2015). A number of RCTs about immunomodulatory diet containing omega-3 fatty acid, γ-linolenic acid and antioxidants showed significant reduction in mortality (Gadek et al., 1999, Pontes-Arruda et al., 2006) and improvement in oxygenation (Gadek et al., 1999, Pontes-Arruda et al., 2006, Singer et al., 2006) and ICU free-days (Gadek et al., 1999) and ventilator-free days (Pontes-Arruda et al., 2006, Singer et al., 2006). On the other hand, few RCTs showed no significant change in mortality (Grau-Carmona et al., 2011, Singer et al., 2006), oxygenation (Grau-Carmona et al., 2011, Rice et al., 2011) and ventilator free-days (Grau-Carmona et al., 2011). A meta-analysis (Li et al., 2015) examining the effects of immunomodulatory formula on clinical outcomes excluded the effects on PaO2/FiO2, duration of mechanical ventilation and duration of hospital stays.

Therefore, we conducted a systematic review and meta-analysis for the first time provide a precise estimate of the overall effects of omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation on clinical outcomes and mortality in critically ill patients.

Methods

This systematic review and meta-analysis was performed according to the PRISMA guideline (Liberati et al., 2009). The study protocol was registered in the PROSPERO international prospective register of systematic review.

Search strategy

PubMed, Scopus, and ISI web of knowledge databases were searched for relevant medical literature without language or publication date restrictions up to September 2019. The keywords used in our search strategy were ("Omega-3 Fatty Acid, γ-Linolenic Acid,Antioxidant Supplementation"). Further details about the search strategy in different databases are provided in **Supplementary Table** 1. Reference lists of previous reviews that investigated this immunomodulatory formula were also checked for any additional studies not identified by the database searches. All titles and abstracts were screened by two authors (MM and NP) to identify eligible studies.

Eligibility criteria

Titles, abstracts and full texts of retrieved articles were screened by two reviewers (MM and NP) according to the following inclusion criteria:1) the studies were a RCT with either a parallel or crossover design; 2) Study population were adult patients admitted to a ICU; 3) the mean and SDs, SEMs, or interquartile range or 95% CIs for baseline and final values or change values reported for critically ill parameters (length of hospital stays, duration of ICU stays, ICU- free days, duration of mechanical ventilation, ventilator free-days, level of oxygenation, SOFA (sequential organ failure assessment) and MOD (multiple organ dysfunction) score and overall 28 days mortality); 4) the only difference between the treatment group and control was the immunomodulatory formula containing omega-3 fatty acid, γ-linolenic acid and antioxidants. Studies were excluded as per the following criteria: 1) participants younger than 18 years; 2) pregnant and lactating women; 3) trials designed without concurrent controls; and 4) trials that were not performed in ICU settings and subjects were not critically ill.

Data extraction

Data were extracted from the eligible papers by three independent investigators (SF and NP and SR). Data listed from the eligible studies included: first author's name, country of the study, year of publication, study design underlying diseases, number of participants in the intervention and control group, mean age of the participants and their gender, intervention duration, type of intervention in control and intervention group, before and after measurement of the expected outcomes in the intervention and control group. Outcome included: duration of ICU stays, level of oxygenation (PaO2/FiO2), duration of mechanical ventilation, length of hospital stays, ICU- free days, ventilator- free days, SOFA (sequential organ filure assessment) and MOD (multiple organ disfunction) score, 28 days mortality (for mortality relative risk based on raw data was extracted).

Risk of bias assessment

Two investigators (NP and SR) independently assessed the risk of bias in each included studies on the basis of Cochrane Risk of bias assessment tool (Higgins and Altman, 2008). Disagreements were resolved in consultation with a third investigators (SS). The following criteria were evaluated: random sequence generation, allocation concealment, incomplete data outcome, selective outcome reporting, the blinding of participants and investigators. Each item was classified as yes (low risk of bias), no (high risk of bias) or unclear. The overall quality of included studies was considered as poor if they had less than four points for low risk of bias. They were classified as fair if they had four points and good if they had more than four points for low risk of bias.

Assessment of the quality of meta-evidence

The quality of meta-evidence for this review was evaluated by using the NutriGrade (Grading of Recommendations Assessment, Development, and Evaluation) scoring system (Schwingshackl et al., 2016). This system for systematic review of RCTs has maximum 10 points and includes: 1) risk of bias, study quality,

and study limitations, 2) precision, 3) heterogeneity, 4) directness, 5) publication bias, 6) funding bias, 7) study design [22]. The overall quality of meta-evidence for each outcome was classified: high ([?]8 points), moderate (6–7.99 points), low (4–5.99), and very low (0–3.99).

Data synthesis and analysis

To determine the clinical effect of immunomodulatory supplements containing γ-Linolenic Acid on potential outcome, changes and standard deviations from baseline within intervention and comparator groups were calculated for each trial. The results were expressed as mean differences (MDs) with 95% CIs. Regarding to malnutrition score (SOFA and MOD), Hedges'g and with 95% CIs were calculated because of different questionnaire applied. For 28-days mortality, relative risk (RR) with 95% CIs were considered as an effect size. Meta-analyses were performed using the inverse-variance weighting method with the random-effects model (DerSimonian and Laird, 1986). Heterogeneity of the included trials was assessed using the chi-squared test and the I^2 test (Higgins and Thompson, 2002, Higgins et al., 2011). The substantial heterogeneity was defined as an I^2 value of more than 50%. To detect source of heterogeneity a series of predefined subgroup analyses were performed according to 1) underlying diseases (sepsis, ALI and ARDS), 2) quality of the study (good, poor and fair), 3) type of intervention in control group (standard formula and High fat, low carbohydrate formula), 4) duration of intervention (less than 14 days and equal or more than 14 days), 5) mean age of patients (less than 60 years and more than 60 years). The probability of publication bias was checked by funnel plot if the number of included studies for each outcome were at least 10 studies. The sensitivity analysis was performed to evaluate the robustness of finding using a random-effects model (Borenstein et al., 2010). Analyses were conducted using STATA software, version 13 (Stata Corp, College Station, TX). P values less than 0.05 were considered as statistically significant.

Results

Included studies

In total, 166 articles were initially retrieved, and 144 articles were excluded due to duplication and were irrelevant based on title and abstract screening. After careful screening of the full texts of the 27 trials, 17 articles were excluded for following reasons: article was commentary (n=1) (Schott and Huang, 2012), study was the part of another study (n=1) (Pacht et al., 2003), studies did not have defined outcomes (n=2) (Nelson et al., 2003, Theilla et al., 2007). Full text was not available (n=1) (Tang et al., 2008), studies without sufficient data (n=1) (Elamin et al., 2005), studies conducted in children (n=4) (Al-Biltagi et al., 2017, Covar et al., 2010, Hamilton and Trobaugh, 2011, Jacobs et al., 2013), articles were not RCT (n=4) (Cohen et al., 2013, Gadek et al., 1998, Lev and Singer, 2012, Pontes-Arruda, 2005), or were not conducted on critically ill patients (n=3) (Kalantar-Zadeh et al., 2005, Remans et al., 2004, Matsuda et al., 2017). In total, 10 clinical trials (1166 participants) were eligible to be included in the present systematic review and meta-analysis. The **Figure 1**showed the study screening steps.

Three studies were conducted in USA (Elamin et al., 2012, Rice et al., 2011, Gadek et al., 1999), two in Israel (Kagan et al., 2015, Singer et al., 2006), two in Japan (Shirai et al., 2015, Tsukahara et al., 2014), two in Brazil (Pontes-Arruda et al., 2006, Pontes-Arruda et al., 2011) and one in Spain (Grau-Carmona et al., 2011). The duration of the intervention ranged from 7 to 28 days. The mean age of participants ranged from 42.72-72.5 years. All trials were parallel and conducted in both gender. Underlying diseases included sepsis, ARDS, ALI, severe multiple trauma, head and neck cancer with surgery. In all studies, participants in intervention group received immunomodulatory diet contains omega-3 fatty acid, γ-linolenic acid and antioxidants. In 4 studies, participants in the control group received high- fat, low- carbohydrate formula (Elamin et al., 2012, Kagan et al., 2015, Gadek et al., 1999, Singer et al., 2006) and in 6 studies received standard, iso-caloric formula (Grau-Carmona et al., 2011, Pontes-Arruda et al., 2011, Rice et al.,

2011, Shirai et al., 2015, Tsukahara et al., 2014, Pontes-Arruda et al., 2006). The characteristics of the studies included in the meta-analysis are summarized in **Table 1** .

Assessment of risk of bias

Five studies included in the meta-analysis had a good quality based on Cochrane Collaboration's tool (Grau-Carmona et al., 2011, Kagan et al., 2015, Pontes-Arruda et al., 2011, Rice et al., 2011, Elamin et al., 2012), four were classified as poor (Pontes-Arruda et al., 2006, Singer et al., 2006, Gadek et al., 1999, Shirai et al., 2015) and one study was fair (Tsukahara et al., 2014). In three studies, method of random sequence generation and method to conceal the allocation of participants were unclear (Gadek et al., 1999, Pontes-Arruda et al., 2006, Shirai et al., 2015). In a study by Kagan et al (Kagan et al., 2015) the method to conceal the allocation of participants was not clear. One study did not report blinding (Tsukahara et al., 2014), two studies were not double blind (Shirai et al., 2015, Singer et al., 2006). Blinding of outcome assessment were not reported for three studies (Pontes-Arruda et al., 2006, Pontes-Arruda et al., 2011, Tsukahara et al., 2014). Two studies did not mention incomplete outcome data (Pontes-Arruda et al., 2006, Gadek et al., 1998) and one had bias in this section (Singer et al., 2006). No studies reported selective outcome bias (**Supplementary Table 2**).

Meta-analysis

3.3.1 Level of oxygenation, duration of mechanical ventilation and ventilator free-days and

Six studies with 709 participants reported the effect of the immunomodulatory formula on PaO2/FiO2. Meta-analyses comparing this immunomodulatory formula vs control formula showed no differences between groups in the effect on PaO2/FiO2 (WMD = 27.40, 95% CI: -7.84, 62.65, P=0.13). The heterogeneity was high (Q statistic=55.44, Cochrane Q test, P<0.001, I^2 =91.0%)**(Supplementary Figure 1).** In patients with ALI and ARDS, enhancement in level of oxygenation was statistically significant and heterogeneity decreased. Both level of oxygenation and heterogeneity decreased in patients aged <60 years. Heterogeneity in subgroups of good quality RCTs and in [?] 14 days intervention decreased**(Supplementary Table 3)** .

Seven studies with 667 participants reported the effect of the immunomodulatory formula on duration of mechanical ventilation. This immunomodulatory formula significantly shortened the duration of mechanical ventilation in the intervention group compared to control group (mean difference = -2.20 days, 95% CI: -4.29, -0.10, P=0.04)**(Supplementary Figure 2)** . The heterogeneity among the included studies was high (Cochrane Q test=25.86, P<0.001, I^2 =76.8%). In septic and ARDS patients the immunomodulatory formula significantly reduced duration of mechanical ventilation compared to other subjects. Also, in patients older than 60 years and in the studies that control group consumed the standard formula significant reduction of duration of mechanical ventilation was observed. The reduction of duration of mechanical ventilation in poor quality RCTs was significant. Underlying disease, age and duration of intervention were the source of heterogeneity. **(Supplementary Table 4).**

Four studies with 629 participants reported the effect of the immunomodulatory formula on ventilator free-days. There was non-significant pooled effects of omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation on ventilator-free days (WMD = 3.37 days, 95% CI: -2.20, 8.85, P=0.24) with high heterogeneity (Q statistic=31.74, Cochrane Q test, P<0.001, I^2 =90.5%).

3.3.2. Duration of ICU stays and ICU free days

Eight studies with 901 participants reported the effect of the immunomodulatory formula on duration of ICU stays. The immunomodulatory formula shortened the duration of ICU stays by 2.97 days compared to control group (95% CI: -5.59, -0.35, P=0.02) **(Figure 2)** , between-study heterogeneity was significantly

high (Cochrane Q test=62.55, P<0.001, I^2 =88.8%). The reduction in duration of ICU stays was evident in ALI, ARDS and septic patients and heterogeneity decreased in these subgroups. Moreover, the reduced in duration of ICU stays was evident in the studies where control group received standard formula and in patients more than 60 years old. In the subgroup where the duration of the intervention was more [?] 14 days, heterogeneity decreased and the reduction in ICU stays was statistically significant. Underlying diseases and the quality of studies were sources of heterogeneity **(Supplementary Table 5).**

Five studies with 735 participants reported the effect of the immunomodulatory formula on ICU- free days. This immunomodulatory diet extended 4.06 ICU- free days in the intervention group than the control group (95%CI: 0.02, 8.09, P=0.05). The heterogeneity was also high (Cochrane Q test=39.63, P<0.001, I^2 =89.9%)

(Supplementary Figure 3).

3.3.3. Length of hospital stays

Five studies with 534 participants reported the effect of the immunomodulatory formula on hospital stays. There was non-significant pooled effects of the immunomodulatory supplementation on the length of hospital stays (WMD = -2.12 days, 95% CI: -7.56, 3.31, P=0.44) with high heterogeneity (Q statistic=36.96, Cochrane Q test, P<0.001, I^2 =89.2%).

3.3.4. SOFA and MOD score

Three studies with 195 participants showed that the immunomodulatory formula resulted in decreased SOFA and MOD score in the intervention group compared to the control group (Hedge's g =-0.42; 95%CI: -0.74, -0.11, P=0.008); between-study heterogeneity was low (Q statistic=2.24, Cochrane Q test, P=0.33, I^2 =10.8%).

3.3.5. Overall 28 days mortality

Nine studies with 1104 participants showed that immunomodulatory diet was associated with decreased overall 28 days mortality of about 26% (relative risk = 0.74, 95%CI: 0.58, 0.91, P<0.001). The heterogeneity was low (Cochrane Q test=7.77, P=0.46, I^2 =0.0%) **(Figure 3)** . The reduction in ALI and ARDS was more evident compared to other subgroups

(Supplementary Table 6).

NutriGrade

The quality of meta-evidence for the effect of omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation on duration of ICU stays, duration of mechanical ventilation, duration of hospital stays, ICU-free days, ventilator free days, SOFA and MOD score and overall 28 days mortality was rated as "moderate", and on level of oxygenation and was "low" **(Supplementary Table 7).**

Discussion

The meta-analyses from ten RCTs revealed that an enteral immunomodulatory diet (omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation) significantly shortened duration of mechanical ventilation and ICU stays, extended ICU-free days, reduced SOFA and MOD score and overall 28 days mortality in critically ill patients.

Our finding showed that enteral immunomodulatory containing omega-3 fatty acid, γ-linolenic acid and antioxidant improved the respiratory functions in ICU patients. Our results are similar to a review of 6

clinical trials (Lev and Singer, 2012) in ALI/ARDS patients concluding that the use of formula enriched with omega-3 and GLA could improve oxygenation and clinical outcomes. The n-3/n-6 ratio of fatty acids could have important role in the alveolar cytokines release (Lev and Singer, 2012). A mechanisms for a protective effect of omega-3 fatty acids in the lungs might be resulting from the products of EPA and DHA which resolves mediators, including resolvins, protectins and maresins found within the lung and circulation (6). Resolving these mediators regulates neutrophil infiltration, cytokine production, clearance of inflammatory leucocytes and inflammatory response, which ultimately helps to maintain the integrity of the lung membrane (Lemoine et al., 2019).

Evidence support the relationship between imbalanced oxidant homeostasis and lung disease showing a trend for potential benefit of antioxidant supplementation in respiration function (Tashakkor et al., 2011). Actually, antioxidant supplementation increases antioxidant capacity like reduced glutathione levels, which subsequently decreases oxidative stress (Mudway et al., 2004).

The SOAF and MOD score evaluates organ failure in critically ill patients (Zygun et al., 2006). This study showed that immunomodulatory diet reduced organ failure. This finding is consistent with the results of Shirai et al (Shirai et al., 2015) and Elamin et al (Elamin et al., 2012) where these improvements in patient status lead to decreased duration of ICU stays and increased ICU-free days. On the other hand, this study showed significant reduction in duration of mechanical ventilation and increased PaO2/FiO2 and ventilator free days in ARDS patients. These results have been well illustrated in Shirai (Shirai et al., 2015) and Gadek (Gadek et al., 1999) studies.

Another review claimed that the beneficial effect of this immunomodulatory formula related to its omega-3 fatty acids composition and adverse outcome in critically ill patients is due to excess production of proinflammatory cytokines and eicosanoids from other polyunsaturated fatty acids (Das, 2013). When the balance between proinflammatory and anti-inflammatory molecules is upset as in critically ill patients, it would lead to persistence of inflammation and progressive cell/tissue and organ damage (Das, 2013). In sepsis, ARDS, ALI and other systemic inflammatory conditions, not only an extend in proinflammatory molecules such as IL-6, TNFα, but also a decrease in the production and action of anti-inflammatory molecules such as IL-4, IL-10 occurrs (Das, 2013). Therefore, supplementation with formula containing omega-3 fatty acid, γ-linolenic acid and antioxidant may help to maintain the balance between proinflammatory and anti-inflammatory conditions.

According to previous meta-analysis (Li et al., 2015), the enteral immunomodulatory diet did not extend ICU- free days, ventilator- free days and any significant reduction in the risk of all-cause mortality. The beneficial effect of this formula on reducing risk of mortality indicated only in patients with high mortality. Our result is inconsistent with these reports because of addition of 3 more studies (Pontes-Arruda et al., 2011, Shirai et al., 2015, Kagan et al., 2015) compared to the previous meta-analysis. Our study considered all the studies conducted in critically ill patients, while previous meta-analysis was restricted to only ARDS and ALI patients. However, the findings from our subgroup analysis contrary to previous meta-analysis showing a decrease in all cause 28 days mortality in ARDS and ALI patients. The significant impact of this immunomodulatory diet on mortality should be interpreted with caution, because not only a small number of studies have examined the effect of this immunomodulatory formula on mortality but also this reduction is based on estimated raw data and we could not adjust the impact of other important confounders such as age, severity of injury and body weight.

Gastrointestinal dysfunction such as diarrhea, dyspepsia and nausea were reported as the main adverse effects of this formula (Li et al., 2015). However, it may result from intolerance response to the rate of continuous enteral infusions in patients (Li et al., 2015). Rice et al (Rice et al., 2011) solved this problem by using a bolus delivery, namely small-volume approach. Also, the components of this supplement are within the tolerance range and are safe.

To test the robustness of the results, we conducted sensitivity analyses. We excluded each individual study, re-analyzing and comparing with the original results. When excluding the trial conducted by Rice et al (Rice

et al., 2011), the overall effect for ICU-free days and ventilator-free days became significant suggesting that these outcomes increase in non- ALI patients. When excluding other trials, the results were consistent with a previous report (Li et al., 2015).

Some limitations in this report should be mentioned. First, the sample sizes of the included trials were small. Second, there was one study for some critical diseases like multiple trauma and head and neck cancer. Therefore, we cannot conclude with certainty about supplementation in these patients. Third, for mortality there were few studies (n=9 and sample size=1104) and there was not any clinical trial for long- term mortality (more than 3 months). Also, we reported the risk ratio of all cause 28 days mortality and we could not adjust the impact of other important confounders such as age, severity of injury and body weight. However, due to the randomness of all the included studies, many confounding variables were similar between the intervention and control groups. The effect of this formula requires a longer-term follow up to show its effect on mortality. Forth, we did not have enough data for biochemical and hematological markers and these outcomes could be important to judge about the overall effect of this formula. Finally, according to NutriGrade the meta- evidence for all outcomes were moderate and for level of oxygenation (PaO2/FiO2) was low. Therefore more well-designed studies with larger sample size and long term follow-up of mortality are recommended.

The strength of this study was the adoption of comprehensive search strategy without language and time restrictions. We used Nutrigrade tool to evaluate the quality of each outcome. Compared to previous meta-analysis (Li et al., 2015), our study included more studies and variables including length of hospital stays, duration of ICU stays, duration of mechanical ventilation, level of oxygenation, SOFA and MOD score. In addition, we performed several subgroup analyses to identify the source of heterogeneity

Conclusion

In this review, we demonstrated that in critically ill patients enteral immunomodulatory diet might be benefitial compared to standard formula specially in septic and ARDS conditions. However, the long-term benefits of this diet on clinical outcomes and mortality needs to be tested in well-designed trials with longer follow-up.

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Author contribution

The authors' responsibilities were as follows—Malekahmadi M and Soltani S: designed the study; Pahlavani N and Malekahmadi M: screened and selected the trials; Pahlavani N, Firouzi S and Rezaei S: extracted the data; Pahlavani N and Firouzi S assessed the risk of bias; Soltani S: analyzed the data; Malekahmadi M: drafted the manuscript; Soltani S, Moradi Moghaddam O and Islam SMS: modified the final manuscript; and all authors: read and approved the final manuscript.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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Legend of tables

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TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients

Legend of figures

Figure 1 flow diagram for study selection process

Figure 2 Effects of omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation on duration of ICU stay

Figure 3 Relative risk (RR) of 28 mortality days for the effects of omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation

Table

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Study, year	**country**	**design**	**Subjects, n, T/C**	**gender**	**Mean age years**	**Underline diseases**	**Study duration days**	**Type of intervention in intervention group**	**Type of intervention in control group**
(Elamin et al., 2012),	USA	Parallel	11/11	M/F	53.3	Medical- Surgical Patients with ARDS	7	Oxepa® Ross Labs, Chicago, Illinois, USA	Pulmocare® Ross Labs, Chicago, Illinois, USA

TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]
(Gadek et al., 1999)	USA	Parallel	45/43	M/F	63	ARDS patients	7	The lipid blend provides EPA and docosahexaenoic acid from fish oil and GLA from borage oil	high-fat, low-carbohydrat enteral nutrition formula

TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]
(Grau-Carmona et al., 2011)	Spain	Parallel	61/71	M/F	63.5	Septic patients with ALI or ARDS	21	Oxepa Abbott Labs	Ensur Abbott Labs
(Kagan et al., 2015)	Israel	Parallel	62/58	M/F	40.72	severe multiple trauma	8	Oxepa; Ross Laboratories	Pulmocare; Ross laboratories, Chicago, IL

TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]
(Pontes-Arruda et al., 2011)	Brazil	Parallel	53/53	M/F	71	Early sepsis	7	EPA/GLA diet	isocaloric, isonitrogenous control diet
(Pontes-Arruda et al., 2006)	Brazil	Parallel	55/48	M/F	66.1	ventilated patients with severe sepsis and septic shock	7	enteral nutrition enriched with EPA, GLA,	isonitrogeno and isocaloric control diet

TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]
(Rice et al., 2011)	USA	Parallel	143/129	M/F	59	ALI patients	28	enteral supplementation of n-3 fatty acids, GLA, and antioxidants	isocaloric-isovolemic carbohydrat rich control
(Shirai et al., 2015)	Japan	Parallel	23/23	M/F	72.5	sepsis-induced ARDS	14	Oxepa; Abbott Nutrition, Tokyo, Japan	Ensure Liquid; Abbott Nutrition, Tokyo, Japan

TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]	**TABLE 1** Characteristics of included RCTs in the meta-analysis[1]
(Singer et al., 2006)	Israel	Parallel	44/44	M/F	59.6	ventilated patients with ALI	14	Oxepa, Ross Laboratories	high-fat, low-carbohydrat enteral formula (Pulmocare, Ross Laboratories, Chicago, IL)
(Tsukahara et al., 2014)	Japan	Parallel	30/32	M/F	63.8	Head and Neck Cancer Surgery Patients	8	Oxepa®; Abbott Japan	Ensure® H; Abbott Japan, Tokyo, Japan

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1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ	1RCTs, randomized controlled trials; Duration refers to the duration of treatment. T/C, treatment/control; M, male; F, female; ARDS, acute respiratory distress syndrome; ALI , acute lung injury; ICU, intensive care unit; SOFA, sequential organ failure assessment; MOD, multiple organ

TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]	TABLE 1 Characteristics of included RCTs in the meta-analysis[1]

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			Meta-analysis	**Meta-analysis**	**Heterogeneity**	**Heterogeneity**	**Heterogeneit**
Outcomes	**Num. Studies**	**Num. Participants**	**WMD[1] (95%CI)**	**P effect**	**Q statistic**	**P within group**	**I^2 (%)**
Length of hospital stay (day)	\sout 5	534	-2.12 (-7.56, 3.31)	0.44	36.96	< 0.001	89.2
Duration of ICU stay (day)	8	901	-2.97 (-5.60, -0.35)	0.03	62.55	< 0.001	\sout 88.8
ICU- free days (day)	5	735	4.06 (0.02, 8.09)	0.049	39.63	< 0.001	\sout 89.9
Duration of mechanical ventilation (day)	7	667	-2.20 (-4.29, -0.10)	0.04	25.86	< 0.001	\sout 76.8
Ventilator-free days (day)	4	629	3.24 (-2.20, 8.85)	0.24	31.74	< 0.001	\sout 90.5
Level of oxygenation (PaO2/FiO2)	6	709	27.40 (-7.84, 62.65)	0.13	55.44	< 0.001	\sout 91

TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients	TABLE 2 The overall effect of Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation in critically ill patients
SOFA and MOD score	3	190	-0.42 (-0.74, -0.11)*	0.008	2.24	\sout 0.33	\sout 10.8
Overall 28 days mortality	9	1104	0.74 (0.58, 0.91)**	< 0.001	7.77	\sout 0.46	\sout 0.0
[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;	[1]Data are pooled standardized mean differences (95% CIs) by a random-effects model. * For SOFA and MOD score Hedge's g was calculated. ** For overall 28 days mortality effect size is rr(95%CI). ICU, intensive care unit;

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