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## Letter to Editor

## Comment on "Omega-3 polyunsaturated fatty acids in critically ill patients with acute respiratory distress syndrome: a systematic review and meta-analysis"



To the Editor:

Langlois et al. [1] performed an interesting meta-analysis on 12 randomized control trials to evaluate the clinical benefits of  $\omega$ -3 polyunsaturated fatty acid (PUFA) administration on gas exchange, and clinical outcomes in patients with acute respiratory distress syndrome (ARDS). They concluded that  $\omega$ -3 PUFAs in enteral immunomodulatory diets of critically ill patients with ARDS might decrease the severity of disease by improving early and late ratios of partial pressure of arterial oxygen ( $\text{PaO}_2$ ) to the fraction of inspired oxygen ( $\text{FiO}_2$ ), while marginally significant effects were found for improved intensive care unit length of stay and duration of mechanical ventilation. Although the results are of great importance, several points need to be considered when interpreting these findings.

First, both the title of the article and the aim of the study focused on evaluating the effects of  $\omega$ -3 PUFAs in critically ill patients, whereas 8 of 12 included trials administered an immune-enhancing diet with eicosapentaenoic acid (EPA),  $\gamma$ -linolenic acid (GLA), and antioxidants to the intervention arm. So, these trials have assessed the advantages of an enteral immunomodulatory diet or a combination of EPA, GLA, and antioxidants, not merely  $\omega$ -3 supplementation. Additionally, a comprehensive literature search is an important process in a systematic review and meta-analysis and can affect the findings. An eligible published trial (with a relatively large study sample of 102 participants) [2] was missed by the search in this meta-analysis.

Second, careful data extraction and methodologic considerations are the other key steps in a meta-analysis; however, some issues were not taken into account in these processes in this meta-analysis. In cases of several outcomes of interest, moderate to high between-study heterogeneity was found; however, the authors did not provide information about covariates that could explain the observed heterogeneity. Subgroup analysis based on potential confounders including type of intervention (assigning an immunomodulatory diet versus fish oil), type of secondary outcome (28-d versus hospital mortality), and treatment duration should be performed to determine the sources of heterogeneity. Evaluating dose-response effects could also provide more explanations.

Furthermore, an improvement in early and late  $\text{PaO}_2$ -to- $\text{FiO}_2$  ratio was reported in abstracts and figures, which meant an increment in  $\text{PaO}_2$  along with a decrease in  $\text{FiO}_2$  that resulted in better oxygenation or greater  $\text{PaO}_2$ -to- $\text{FiO}_2$  ratio; however, the authors stated that "the pooled estimate suggests that  $\omega$ -3 PUFAs reduce early  $\text{PaO}_2$ -to- $\text{FiO}_2$  ratio" and "late  $\text{PaO}_2$ -to- $\text{FiO}_2$  ratio had a tendency toward a reduction only in single-center trials" in the results. In the case of mortality outcome, the authors claimed that two trials that reported 60-d mortality were not included in the aggregation; but the forest plot of mortality showed that one of these trials (Rice et al., 2011) was considered in the estimation of overall effect. Additionally, the authors performed stratified analysis by study quality and revealed no significant difference in mortality between subgroups based on the results section; but in the abstract, they reported a significant reduction in mortality ( $P = 0.04$ ) in trials at higher risk for bias.

Another crucial part of an investigation is appropriate citations; however, relevant references were not cited in several cases. For example, the Berlin 2014 criteria for ARDS definition was mentioned in the introduction, however, it is inappropriately referenced to the Berlin 2012 definition. In the discussion, the authors referred to the first meta-analysis in 2008 evaluating the effects of an immune-enhancing diet on mortality and oxygenation in mechanically ventilated patients with ARDS, but they inaccurately cited an original article that was included in their meta-analysis (Pontes-Arruda et al., 2006). Also, the authors reported a negative odds ratio (OR; and 95% confidence intervals [CI]) for overall infections (OR,  $-2.14$ ; 95% CI,  $-3.23$  to  $-1.04$ ), when they reported the tests of asymmetry for this estimate; an OR is a relative measure of effect, which cannot give a negative value [3].

Finally, when the authors evaluated publication bias, tests for asymmetry were significant for overall infections; however, the trim-and-fill method was not applied to identify the effects of unpublished studies on the overall estimate.

In conclusion, identifying the effect of  $\omega$ -3 PUFAs in critically ill patients with ARDS has a great value; however, a comprehensive literature search, careful methodologic, statistical methods and appropriate referencing should be adopted to avoid invalid conclusions.

### Conflict of Interest

None of the authors declared any personal or financial conflicts of interest.

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