

Meta-analysis of High-frequency Oscillation in Acute Respiratory Distress Syndrome and Accuracy of Results

To the Editor:

We read with interest the recent meta-analysis of Maitra *et al.*,¹ which included our randomized clinical study of intermittent recruitment with combined high-frequency oscillation (HFO) and tracheal gas insufflations (TGI) in severe acute respiratory distress syndrome.² As clearly mentioned/described in the Abstract and Results sections of our article,² and pages 7 and 8 of the Supplement² (eMethods section), our study was conducted in two periods (first period, $n = 54$; second period, $n = 71$; total participants, $n = 125$), primarily for reasons of feasibility; the study protocol can be accessed through the webpage of our hospital's scientific society.³ As also (again) clearly stated in the Acknowledgments section of our article,² the results of our study's first period were partly presented in international congresses and published in abstract form and also summarized in the preceding HFO meta-analysis of Sud *et al.*⁴

In the main analysis with respect to mortality presented in figure 3, Maitra *et al.*¹ included the results of the first period ($n = 54$; control, $n = 27$) as reported in the meta-analysis of Sud *et al.*⁴ in addition to the results of the whole study (corresponding to both study periods, $n = 125$; control, $n = 64$).² This inevitably resulted in a duplicate inclusion of the results of the first period. Furthermore, first period results do not correspond to reference 25 of the article by Maitra *et al.*¹ The cited article reports the results of our prior physiological study that compared the short-term gas exchange and hemodynamic effects of HFO-TGI, standard HFO, and lung-protective conventional mechanical ventilation.⁵ This study included 14 patients as also correctly reported in table 2 of the article by Maitra *et al.*,¹ thereby contrasting the wrong number of 54 patients reported in figure 3.

An additional, potential source of inaccuracy pertains to the inclusion of the study of Demory *et al.*^{1,6} This study had physiological endpoints and reported solely on intensive care unit (ICU) mortality, which does not necessarily coincide with either 30-day or in-hospital mortality.² Consequently, the actual primary outcome of the meta-analysis was "30-day, or ICU, or in-hospital mortality" and not "30-day, or in-hospital mortality." Lastly, another point requiring correction was that the 30-day mortality rate of the HFO arm of the study of Young *et al.*⁷ was 166 of 398 and not 165 of 398 as reported in figure 3 in the article by Maitra *et al.*¹

A corrected forest plot of 30-day, or ICU, or in-hospital mortality is presented in figure 1. Notably, the pooled risk ratio is quite close to that reported by Maitra *et al.*¹ However, the 95% CI and the I^2 value differ, and additional data corrections, including the elimination of the above-mentioned first period² data duplication, are required in figures 4, 6, and 7.¹ In addition, the refractory hypoxemia rates reported

by Maitra *et al.* in figure 8 are again inaccurate with respect to our study.² Indeed, refractory hypoxemia (as defined in the first paragraph of page 7 of the Supplement²) occurred in one patient of the HFO-TGI group (third paragraph of page 13 and eTable 11 of the Supplement²) and four patients of the control group (subsection Rescue Oxygenation Therapies of page 14 and eTable 11 of the Supplement²).

An additional, controversial issue pertains to the inclusion of our study.^{1,2} This contrasts the study selections of the authors of another two, very recently published, meta-analyses of HFO in acute respiratory distress syndrome.^{8,9} The HFO treatment we used had substantial differences from the HFO treatments of other clinical studies.^{7,10–13} These studies used continuous, standard HFO, without a mandatory cuff leak or TGI, as a lung-protective ventilatory strategy.^{7,10–13} In contrast, we applied intermittent, low-frequency HFO with short-lasting (*i.e.*, approximately 40 s) recruitment maneuvers, a tracheal tube cuff leak, and superimposed TGI as a lung recruitment protocol that was repeated daily for an average of 11.2 h. HFO-TGI was used according to prespecified oxygenation criteria for a median (interquartile range) of 4 days (2 to 5 days) during the first 10 days postrandomization.² The HFO-TGI recruitment strategy was aimed at reducing the ventilation pressures of the subsequent conventional mechanical ventilation and thus render it less traumatic to the lungs.^{2,14} The potential advantages of the HFO-TGI strategy relative to other HFO strategies, especially with respect to carbon dioxide elimination and hemodynamics, are shown and discussed in detail elsewhere.^{10,14}

A major advantage of meta-analyses is the reliable comparison of treatment effects, achieved mainly through a large, pooled sample size. This leads to improved external validity relative to included, independent studies, and generalizable results. Although it is perfectly understandable that errors can occur, the pooled results of meta-analyses must be accurate, and this can only be ensured through their repeated checking and verification before publication. Also, studies with methodologies exhibiting unique characteristics and clinical targets² should be considered for inclusion mainly in sensitivity rather than in primary analyses to prevent potentially excessive increases in the heterogeneity of the pooled results (fig. 1).

Competing Interests

The authors declare no competing interests.

Spyros D. Mentzelopoulos, M.D., Ph.D., Sotirios Malachias, M.D., Ph.D., Charikleia Vrettou, M.D., Ph.D., Spyros G. Zakyntinos, M.D., Ph.D. University of Athens Medical School, Athens, Greece (S.D.M.). sdmentzelopoulos@yahoo.com

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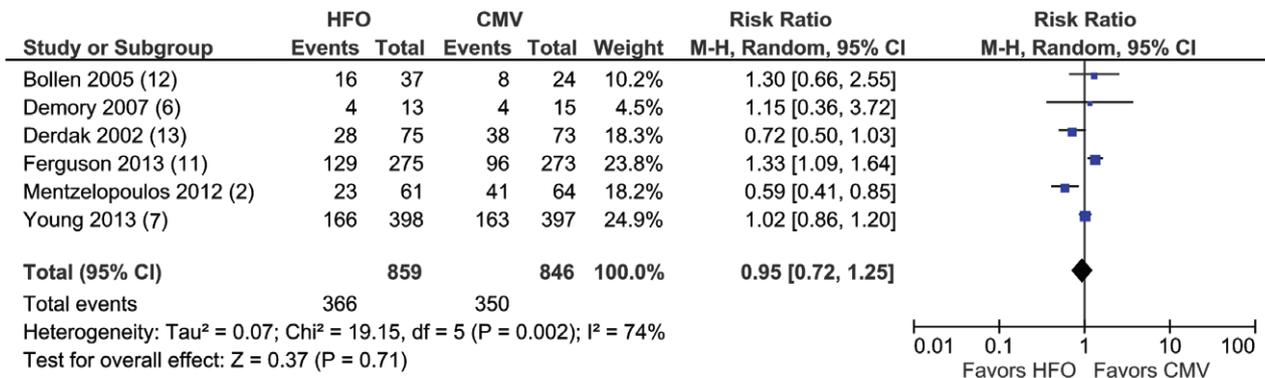


Fig. 1. Corrected forest plot of the risk ratio of 30-day, or intensive care unit, or in-hospital mortality in the studies included in the meta-analysis of Maitra *et al.*¹ Numbers in parentheses correspond to current article references. CMV = conventional mechanical ventilation (corresponding to standard treatment); HFO = high-frequency oscillation (corresponding to experimental treatment); M-H = Mantel-Haenszel.

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In Reply:

We have read the letter by Mentzelopoulos *et al.* regarding the possible inaccuracy in a few outcomes of our analysis.¹ We sincerely apologize for the possible duplication of a few patients from inclusion of a previous study.² Although this error is purely unintentional, we are sorry to say that we were unable to find a statement regarding overlapping of the patients in the Methods section of the later study.³ However, a reanalysis of our primary outcome did not change the primary finding of our meta-analysis (fig. 1). Mentzelopoulos *et al.* correctly reported that I^2 , which is the heterogeneity value, and CI, are different. We have already used a random effect model in all our analysis even if the I^2 value is low due to possible clinical heterogeneity in the included studies. The 95% CI is used to estimate the precision of the odds ratio.⁴ If a 95% CI for the odds ratio does not include 1 (the null value), then the odd ratios are said to be statistically significantly different. We also accept the possibility of biases from inclusion of the randomized controlled trial by Demory *et al.*⁵ However, reanalyzing in-hospital/30-day/intensive care unit