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# Evidence of Steroids in Patients With Acute Respiratory Distress Syndrome in Coronavirus Disease 2019

## To the Editor:

We have read with exceptional interest the article by Villar et al (1) published in the recent issue of *Critical Care Explorations*.

The use of corticosteroids in the critically ill patient should be under a precise indication and not, in response to a question, that we cannot yet perform. The scenarios contemplated in the article by Villar et al (1) are acute respiratory distress syndrome (ARDS) from coronavirus disease 2019, ARDS nonviral and dysregulated systemic inflammation (cytokine storm), in which the World Health Organization does not recommend the use of corticosteroids routinely in viral pneumonia, understanding the pros and cons of the administration of corticosteroids (2, 3) (**Table 1**).

When all available evidence is included, systematic reviews and meta-analyses are considered as the best quality evidence available (4). In the application of some statistical analyses such as meta-analyses, as additional results accumulate (update of studies), increases the probability of observing false positive results (error type 1) or false negative results (error type 2) causing a phenomenon called multiplicity secondary to repeated significance tests (5). The trial sequential analysis (TSA) it is a methodology that combines an information size calculation (cumulative number of patients, number of observations of the event of interest in the included studies or impact of the multiplicity), with an adjusted statistical significance threshold (monitoring limits or test penalty) of a meta-analysis, in order to avoid multiplicity secondary to repeated significance tests (6).

Thirty-two studies from four meta-analyses (7-10) and the study by Villar et al (1) that compared mortality with the use of corticosteroids in ARDS were taken into account (**Fig. 1**), for the construction of a single meta-analysis, using a random-effects model with the Biggerstaff-Tweedie method. Subsequently, based on the results, a TSA was constructed with a statistical significance of 95%, a probability of type 1 error (α) of 5%, a probability of type 2 error (β) of 20%, and a statistical power of 80% (1–α). For the size of the information, the required numbers of events for conclusive and reliable information was calculated with a test of bilateral significance according to the formula:

$$IS_{events} = P_c \times IS / 2 + P_E \times IS / 2.$$

PC is the expected proportion in the control group (no steroid), PE is the expected proportion in the experimental group (steroid), and IS is the information size in each group. Due to the existence of trials reporting zero events in both the experimental and control groups, an empirical continuity correction was applied in the zero event trials.

Thirty-two clinical trials included with a total of 2,749 patients with the naked eye it could be inferred that if there is a possible association in the reduction of mortality with the use of steroids (risk ratio, 0.93; 95% CI, 0.78–1.11), however, when analyzing the CI it is observed that it is short and touches the null value, which translates into an inconclusive association and despite the fact that more studies are carried out, it was not possible to improve the clinical significance. In terms of heterogeneity, there is a high proportion of variability observed in steroid use that is

**TABLE 1. Potential Aspects for and Against the Use of Corticosteroids in Pneumonia**

| Pros | Cons |
|---|---|
| Genetic immunomodulation: | Hyperglycemia |
| Decreased inflammatory mediators: | Muscular weakness |
| Cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-13, tumor necrosis factor-α) and chemokines (eotaxin, macrophage inflammatory protein-1α, monocyte chemotactic protein) | Gastrointestinal bleeding |
| Receptors (IL-2 receptor, neurokinin-1 receptor) | Neuropsychiatric disorders |
| Adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1) | Risk of secondary infections and superinfections |
| Enzymes (nitric oxide synthetase, cyclooxygenase 2, phospholipase A2) increase in anti-inflammatory cytokines: | 60 yr of study without solid evidence in favor of its use in pneumonia |
| Lipocortin 1, B2 IL-10 receptor, IL-1 receptor, nuclear factor-κB inhibitor, phospholipase A2 inhibitor | |
| Attenuated pulmonary inflammatory response | |
| Decreased duration of bacterial life | |
| Decrease in bacterial reproduction | |

IL = interleukin.

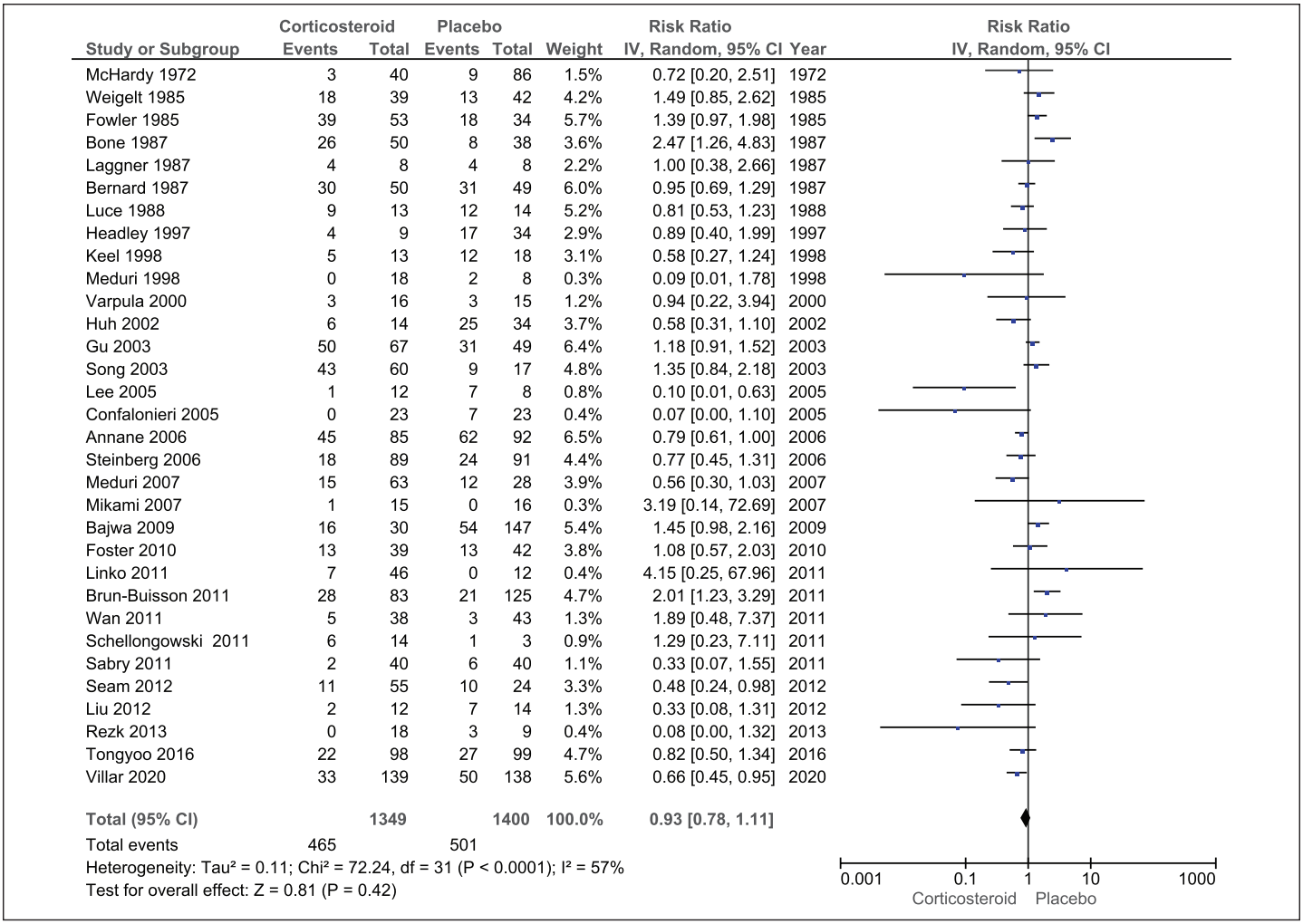


**Figure 1.** Forest plot. Meta-analysis of the effect of corticosteroids on mortality in patients with acute respiratory distress syndrome. Random-effects model of 32 studies with 2,749 patients with a risk ratio (RR), 0.93; 95% CI, 0.78–1.1.1. *df* = degrees of freedom.

due to heterogeneity and not random ($I^2$ = 57%) and little variability in effect size between studies ($Tau^2$ = 0.11) (Fig. 1). For better evidence, a TSA was constructed with the TSA Viewer software Version 0.9.5.10 Beta from the Copenhagen Trial Unit with an adjusted information size of 17,027 patients based on the result of ISevents, the cumulative curve *Z* does not cross statistical limits of significance (**Fig. 2**) creating false positive results. Therefore, with all the available evidence, it is concluded that there is no reason that justifies the use of steroids in ARDS.

Dr. Escarramán-Martínez designed the article. Dr. Guerrero Gutiérrez redacted the article. All the authors read and approved the final version of the article.

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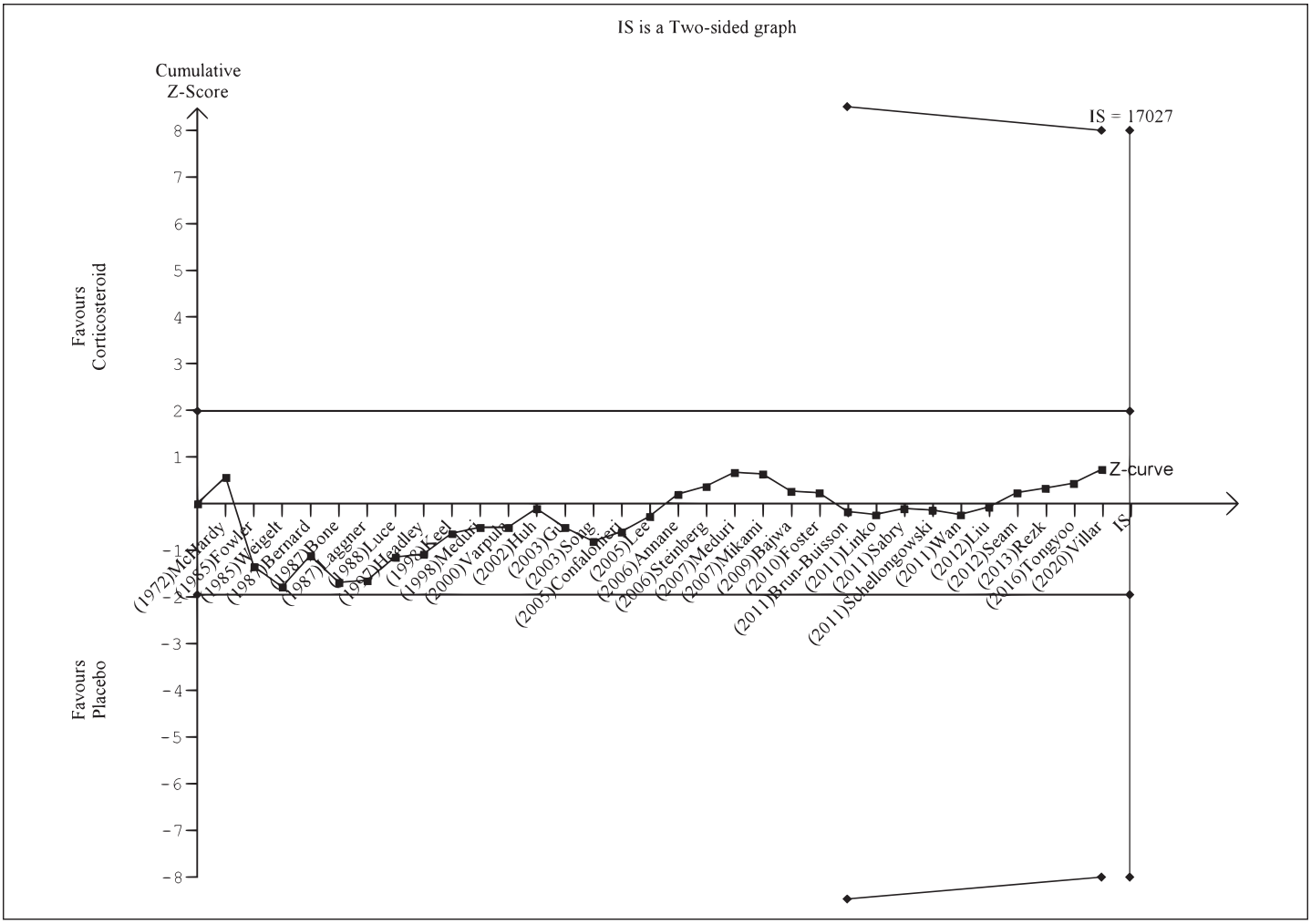


**Figure 2.** Trial sequential analysis of the meta-analysis. The *Z* value is the test statistic and $|Z| = 1.96$ corresponds to a $p = 0.05$; the higher the *Z* value, the lower the *p* value. The size of the information required to accept or reject the reduction in the relative risk of mortality with the use of corticosteroids found in the meta-analysis of the random-effects model was calculated for 17,027 patients using the diversity (D2) of 64% found, significance 95% statistic and 80% power. IS = information size in each group.

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