Letter to the Editor

**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 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 impossible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

**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) and chemokines: |
| TNF-α, monocyte chemotactic protein        | Gastrointestinal bleeding |
| IL-1 receptor, nuclear factor-κB inhibitor, phospholipase A2 inhibitor | 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: |
| Lipocortin 1, B2 IL-10 receptor, IL-1 receptor, nuclear factor-κB inhibitor, phospholipase A2 inhibitor | 60 yr of study without solid evidence in favor of its use in pneumonia |
| Attenuated pulmonary inflammatory response | Decreased duration of bacterial life |
| Decrease in bacterial reproduction         |                |

**Copyright © 2020 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.**
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 I$^2$Events, 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.

The authors have disclosed that they do not have any potential conflicts of interest.

| Study or Subgroup | Corticosteroid | Placebo | Risk Ratio | Risk Ratio |
|-------------------|---------------|---------|------------|------------|
|                   | Events | Total | Events | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% Cl |
| McHardy 1972      | 3      | 40    | 9      | 86    | 1.5%   | 0.72 [0.20, 2.51] | 1972 |
| Weigelt 1985      | 18     | 39    | 13     | 42    | 4.2%   | 1.49 [0.85, 2.62] | 1985 |
| Fowler 1985       | 39     | 53    | 18     | 34    | 5.7%   | 1.39 [0.97, 1.98] | 1985 |
| Bone 1987         | 26     | 50    | 8      | 38    | 3.6%   | 2.47 [1.26, 4.83] | 1987 |
| Lagrue 1987       | 4      | 8     | 4      | 8     | 2.2%   | 1.00 [0.38, 2.66] | 1987 |
| Bernard 1987      | 30     | 50    | 31     | 49    | 6.0%   | 0.95 [0.69, 1.29] | 1987 |
| Luque 1988        | 9      | 13    | 12     | 14    | 5.2%   | 0.81 [0.53, 1.23] | 1988 |
| Headley 1997      | 4      | 9     | 17     | 34    | 2.9%   | 0.89 [0.40, 1.99] | 1997 |
| Keel 1998         | 5      | 13    | 12     | 18    | 3.1%   | 0.58 [0.27, 1.24] | 1998 |
| Meduri 1998       | 0      | 18    | 2      | 8     | 0.3%   | 0.09 [0.01, 1.78] | 1998 |
| Varpula 2000      | 3      | 16    | 3      | 15    | 1.2%   | 0.94 [0.22, 3.94] | 2000 |
| Huh 2002          | 6      | 14    | 25     | 34    | 3.7%   | 0.58 [0.31, 1.10] | 2002 |
| Gu 2003           | 50     | 67    | 31     | 49    | 6.4%   | 1.18 [0.91, 1.52] | 2003 |
| Song 2003         | 43     | 60    | 9      | 17    | 4.8%   | 1.35 [0.84, 2.18] | 2003 |
| Lee 2005          | 1      | 12    | 7      | 8     | 0.8%   | 0.10 [0.01, 0.63] | 2005 |
| Confalonieri 2005  | 0      | 23    | 7      | 23    | 0.4%   | 0.07 [0.00, 1.10] | 2005 |
| Annane 2006       | 45     | 85    | 62     | 92    | 6.5%   | 0.79 [0.61, 1.00] | 2006 |
| Steinberg 2006    | 18     | 89    | 24     | 91    | 4.4%   | 0.77 [0.45, 1.31] | 2006 |
| Meduri 2007       | 15     | 63    | 12     | 28    | 3.9%   | 0.56 [0.30, 1.03] | 2007 |
| Mikami 2007       | 1      | 15    | 0      | 16    | 0.3%   | 3.19 [0.14, 72.69] | 2007 |
| Bajwa 2009        | 16     | 30    | 54     | 147   | 5.4%   | 1.45 [0.98, 2.16] | 2009 |
| Foster 2010       | 13     | 39    | 13     | 42    | 3.8%   | 1.08 [0.57, 2.03] | 2010 |
| Linko 2011        | 7      | 46    | 0      | 12    | 0.4%   | 4.15 [0.25, 67.96] | 2011 |
| Brun-Buisson 2011 | 28     | 83    | 21     | 125   | 4.7%   | 2.01 [1.23, 3.29] | 2011 |
| Wan 2011          | 5      | 38    | 3      | 43    | 1.3%   | 1.89 [0.48, 7.37] | 2011 |
| Schillongowski 2011| 6      | 14    | 1      | 3     | 0.9%   | 1.29 [0.23, 7.11] | 2011 |
| Sabry 2011        | 2      | 40    | 6      | 40    | 1.1%   | 0.33 [0.07, 1.55] | 2011 |
| Seam 2012         | 11     | 55    | 10     | 24    | 3.3%   | 0.48 [0.24, 0.98] | 2012 |
| Liu 2012          | 2      | 12    | 7      | 14    | 1.3%   | 0.33 [0.08, 1.31] | 2012 |
| Rezk 2013         | 0      | 18    | 3      | 9     | 0.4%   | 0.08 [0.00, 1.32] | 2013 |
| Tongyoo 2016      | 22     | 98    | 27     | 99    | 4.7%   | 0.82 [0.50, 1.34] | 2016 |
| Villar 2020       | 33     | 139   | 50     | 138   | 5.6%   | 0.66 [0.45, 0.96] | 2020 |
| Total (95% CI)    | 1349   | 1400  | 100.0% |        | 0.93 [0.78, 1.11] | 2020 |
| Total events      | 465    | 501   |        |        |        |                      | 2020 |

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, 0.78–1.11. $df$ = degrees of freedom.

Eder Iván Zamarrón López, MD, Department of Critical Care, Hospital General Regional #6, Madero City, Mexico

REFERENCES
1. Villar J, Confalonieri M, Pastores SM, et al: Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. Crit Care Expl 2020; 2:e0111
2. Sibila O, Ferrer M, Agustí C, et al: Corticosteroids as adjunctive treatment in community-acquired pneumonia. Minerva Anestesiol 2014; 80:1336–1344
3. Tirapegui F, Díaz O, Saldías F: Clinical efficacy of corticoids treatment in hospitalized adult patients with community-acquired pneumonia. Rev Chil Enferm Respir 2018; 34:236–248
4. Centro Cochrane Iberoamericano: ¿Está justificado el uso de corticoesteroides en el manejo de pacientes con COVID-19? 2020. Manual Cochrane de Revisiones Sistemáticas de Intervenciones, Barcelona, versión 5.1.0. Available at: https://es.cochrane.org/es/¿está-justificado-el-uso-de-corticoesteroides-en-el-manejo-de-pacientes-con-covid-19?. Accessed May 6, 2020
5. Borm GF, Donders AR: Updating meta-analyses leads to larger type I errors than publication bias. J Clin Epidemiol 2009; 62:825–830.e10
6. Thorlund K, Engstrom J, Wetterslev J, et al: User Manual for Trial Sequential Analysis (TSA). Copenhagen, Denmark, Copenhagen Trial
Critical Care Explorations

Letter to the Editor

Unit, Centre for Clinical Intervention Research, 2017, pp 1–115. Available at: http://www.ctu.dk/tsa/files/tsa_manual.pdf. Accessed May 6, 2020

7. Peter JV, John P, Graham PL, et al: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. BMJ 2008; 336:1006–1009

8. Ruan SY, Lin HH, Huang CT, et al: Exploring the heterogeneity of effects of corticosteroids on acute respiratory distress syndrome: A systematic review and meta-analysis. Crit Care 2014; 18:R63

9. Tang BM, Craig JC, Eslick GD, et al: Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. Crit Care Med 2009; 37:1594–1603

10. Lamontagne F, Briel M, Guyatt GH, et al: Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: A meta-analysis of randomized controlled trials. J Crit Care 2010; 25:420–435

DOI: 10.1097/CCE.0000000000000124

Figure 2. Trial sequential analysis of the meta-analysis. The Z value is the test statistic and $|Z| = 1.96$ corresponds to $p = 0.05$; 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.