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

To the Editor:

e 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 metaanalysis, 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:

$$IS_{events} = P_{c} \times IS / 2 + P_{E} \times IS / 2.$$

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

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	Corticost	eroid	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI Yea	r IV, Random, 95% Cl
McHardy 1972	3	40	9	86	1.5%	0.72 [0.20, 2.51] 1972	2
Weigelt 1985	18	39	13	42	4.2%	1.49 [0.85, 2.62] 1985	5 +
Fowler 1985	39	53	18	34	5.7%	1.39 [0.97, 1.98] 1985	5
Bone 1987	26	50	8	38	3.6%	2.47 [1.26, 4.83] 1987	7
Laggner 1987	4	8	4	8	2.2%	1.00 [0.38, 2.66] 1987	7
Bernard 1987	30	50	31	49	6.0%	0.95 [0.69, 1.29] 1987	7 -
Luce 1988	9	13	12	14	5.2%	0.81 [0.53, 1.23] 1988	3
Headley 1997	4	9	17	34	2.9%	0.89 [0.40, 1.99] 1997	7
Keel 1998	5	13	12	18	3.1%	0.58 [0.27, 1.24] 1998	3
Meduri 1998	0	18	2	8	0.3%	0.09 [0.01, 1.78] 1998	3
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	2
Gu 2003	50	67	31	49	6.4%	1.18 [0.91, 1.52] 2003	3 -
Song 2003	43	60	9	17	4.8%	1.35 [0.84, 2.18] 2003	3 +
Lee 2005	1	12	7	8	0.8%	0.10 [0.01, 0.63] 2005	5
Confalonieri 2005	0	23	7	23	0.4%	0.07 [0.00, 1.10] 2005	5
Annane 2006	45	85	62	92	6.5%	0.79 [0.61, 1.00] 2006	5 -
Steinberg 2006	18	89	24	91	4.4%	0.77 [0.45, 1.31] 2006	3
Meduri 2007	15	63	12	28	3.9%	0.56 [0.30, 1.03] 2007	7
Mikami 2007	1	15	0	16	0.3%	3.19 [0.14, 72.69] 2007	7
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] 201 ²	1
Brun-Buisson 2011	28	83	21	125	4.7%	2.01 [1.23, 3.29] 201 ²	1
Wan 2011	5	38	3	43	1.3%	1.89 [0.48, 7.37] 201 ²	1
Schellongowski 2011	6	14	1	3	0.9%	1.29 [0.23, 7.11] 201 ²	1
Sabry 2011	2	40	6	40	1.1%	0.33 [0.07, 1.55] 2012	1
Seam 2012	11	55	10	24	3.3%	0.48 [0.24, 0.98] 2012	2
Liu 2012	2	12	7	14	1.3%	0.33 [0.08, 1.31] 2012	2
Rezk 2013	0	18	3	9	0.4%	0.08 [0.00, 1.32] 2013	3
Tongyoo 2016	22	98	27	99	4.7%	0.82 [0.50, 1.34] 2016	3 −+
Villar 2020	33	139	50	138	5.6%	0.66 [0.45, 0.95] 2020	·
Total (95% CI)		1349		1400	100.0%	0.93 [0.78, 1.11]	•
Total events	465		501				
Heterogeneity: Tau ² = 0.11; Chi ² = 72.24, df = 31 (P < 0.0001); l ² = 57% Test for overall effect: Z = 0.81 (P = 0.42)						0.001 0.1 1 10 1000 Corticosteroid Placebo	

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 (Tau² = 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.

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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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