Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

A reappraisal of corticosteroids use for COVID-19

Dear Editor,

The current evidence suggests that the rapid clinical progression of the Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is closely related to the hyperinflammatory syndrome resulting from a dysregulated host innate immune response [1]. Not surprisingly, aside from active antiretroviral therapy, this has prompted the development of anti-inflammatory therapies for the treatment of patients with COVID-19, and among them the use of corticosteroids in hospitalized patients has been object of numerous clinical investigations, with inconsistent results [2–6]. At the beginning of the SARS-CoV-2 pandemic, the World Health Organization (WHO) advised against systematic use of corticosteroids in COVID-19 patients [2]. However, after the publication of RECOVERY trial [3], the WHO changed its original suggestion and recommended the use of corticosteroids in patients with severe COVID-19 [7]. Since then, a huge number of controlled clinical trials have been conducted in order to evaluate the efficacy and safety of corticosteroids for COVID-19 patients, and others are underway or in development. Because of the great amount of clinical data available, several systematic reviews (SRs) and meta-analysis have been published in the last years. Their conclusions are, however, quite inconsistent and reflect the wide heterogeneity between different studies in terms of design, conduct, and reporting. The current study is an overview of systematic reviews, also called umbrella review [8], and is aimed to reappraise the validity of the conclusions of the SRs and meta-analyses related to corticosteroids use for the treatment of COVID-19.

We considered for inclusion in this umbrella review SRs that included randomized controlled trials (RCTs) and non-RCTs (i.e., prospective, retrospective, cross-sectional, cohort studies and case series) evaluating the safety and efficacy of corticosteroids in COVID-19 patients. We considered SRs on COVID-19 at any stage of disease severity, from asymptomatic/pauci-symptomatic to life-threatening cases, and in any setting (outpatients and hospitalized patients). Treatment with corticosteroids at any dose, timing and frequency was compared to standard of care or placebo. We included the following outcomes: overall mortality, viral clearance, clinical progression, length of hospital stay, adverse reactions. Where available, we reported also results of subgroup analyses based on the severity of COVID-19 and on the design of the studies included in the SRs. Relevant studies in four bibliographic databases (Embase, PubMed, Web of Science, and Cochrane) were searched as of June 2022, using Medical Subjects Heading: ("COVID-19" OR "SARS-CoV-2") AND ("systematic review" OR "meta-analysis").

For the quantitative synthesis, we reported the effect size (odds ratio [OR], risk ratio [RR], risk difference [RD], Hazard ratio [HR] or risk difference [RD] with the 95% confidence intervals (CI), as reported in individual reviews, and the main conclusions of each systematic review/meta-analysis. The quality of evidence was appraised following the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation), applied in its five domains (risk of bias, indirectness, imprecision, inconsistency, and publication bias) [9].

The electronic and manual search retrieved 4202 references After the full texts were scrutinized against the inclusion and exclusion criteria, 35 SRs were included in the umbrella review (references available upon request to corresponding author). The 35 SRs included 307 overlapping reports (98 RCTs and 209 non-RCTs), based on 121 individual primary studies. The primary studies included 25 RCTs, 84 controlled non-RCTs, and 12 uncontrolled studies (single arm studies, including case series and case reports). Thirty-four SRs focused on systemic steroids as treatment of COVID-19, while one review was focused on inhaled use of steroids.

The main findings of this umbrella review can be summarized as follows: (1) In critically ill patients, including those requiring invasive mechanical ventilation and those with ARDS, the use of steroids therapy was found significantly more effective in reducing mortality compared to SOC in 80% of the SRs (12 out of 15 SRs) reporting this outcome, more often with moderate/high level of certainty (7/12). (2) When the comparison included patients with different severity of infection (from severe to critical), the results were more heterogeneous, and a decrease in mortality was reported in only 52% of the SRs. (3) In patients not requiring oxygen supplementation the use of steroids compared to controls increased the overall mortality in 4 out of 6 comparisons (66.6%). (4) Rate of clinical progression of diseases (defined as need for mechanical ventilation, intensive care unit admission, or as a clinical progression composite score) were significantly higher in patients receiving standard of care compared to steroids recipients in 64.2% of the SRs reporting this outcome; the available evidence was graded from very-low to moderate. (5) In more than 80% of the SRs the occurrence of adverse events (serious adverse events, any adverse events, gastrointestinal bleeding, secondary infections and hyperglicemia) was similar among steroids recipients and controls. However, these findings can be biased because adverse events were often not reported in the systematic reviews and, when reported, there was often inconsistency in describing type and severity of adverse events. As expected, the quality of the evidence was on average higher in SRs of RCTs only. Moreover, compared to SRs including RCTs+non-RCTs and non-RCTs, SRs including RCTs only reported more commonly a reduction of mortality in steroids recipients than in controls (Table 1).

Umbrella reviews assemble together several systematic reviews on the same condition, and allow to consider for inclusion the highest level of evidence available, namely other systematic reviews and meta-analyses [10]. Overall, patients receiving corticosteroids with coronavirus diseases in the early phase of the epidemic were more likely to be critically ill; hence, there was a significant selection bias in non-RCTs included in the SRs. In this extremely uncertain and changing context,

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Table 1
Effects of corticosteroids on mortality. Main characteristics and results of the 33 SRs reporting mortality included in the umbrella review.

First Author (journal, year)	No. studies	Covid-19 pts. characteristics, No subjects (steroids/controls)	Effect size (RR, OR, HR or RD) and 95% CIs	GRADE assessment (reason/s for downgrading)	Comment	Effect size direction
Outcome	**Mortality**					
Yousefifard (Iran J Public Health, 2020)	15 studi (1 RCT) in COVID-19, SARS and MERS	5 cohort studies in COVID-19. 428 pts (187/241)	OR 1.08 (0.34/3.50)	Very-low (serious ROB, heterogeneity, imprecision)	It is unclear if corticosteroids reduce mortality of severe COVID-19 compared to control.	
Lee (J Clin Med, 2020)	1 non-RCT in COVID-19 pts with ARDS	201 (pts. with ARDS (62/139); adjusted analysis 84 (50/34)	HR 0.38 (0.20/0.72)	⊕⊕⊕⊖ moderate (imprecision)	After adjustment for time and comorbidity, steroids use reduces mortality compared to controls in ARDS pts	
Li (Int. Immunopharmacol, 2021)	10 non-RCT, 1 RCT	No separate data for Covid-19 pts available	No separate data for COVID-19 pts available			na
Yang (J Infect, 2020)	2 non-RCTs	179 (71/108)	No separate outcome data for Covid-19 pts available		Pts. with severe conditions are more likely to require corticosteroids.	na
Cantini (Drugs., 2020)	1 RCT (Recovery trial) [4]	Pts. with different severity of ilness. 6325 (2104/4321)	-No O_2 need : RR 1.22 (0.93/1.61). - O_2 need: RR 0.80 (0.70/0.92). -Ventilated pts: RR 0.65 (0.51/0.82)	⊕⊕⊕⊖ moderate (ROB due to deviation from intended intervention)	Steroids reduce mortality compared to controls in ventilated pts and in pts requiring O_2 supplementation, but not in pts not requiring O_2 supplementation	
Cheng (Front Pharmacol, 2020)	20 non-RCTs (2840)	mortality data available from 6 reports (2349 pts). Pts with different severity of infection	-RR 1.59 (0.69/3.66) in the overall analysis. - RR 1.80 (0.51/6.33) in severe case	⊕⊖⊖⊖ very low (serious ROB, heterogeneity, imprecision	The use of steroids did not reduce mortality compared to controls	
Wang (Am J Em Med, 2020)	16 (3285) mostly from case series and case reports	mortality data available from 4 reports (495). Pts with different severity of illness	RR 1.38 (0.87/2.18)	⊕⊖⊖⊖ very low (serious ROB, heterogeneity, imprecision)	severe pts. were found to be more likely requiring corticosteroids therapy.	
Sarma (Indian J Pharmacol, 2020)	15 (3 RCTs, 12 cohort studies)	Mortality data in severe/critical pts. from 6 observational studies (5787 pts, and in mild/moderate pts from 2 studies (1566 pts)	-severe/critical pts. RR 0.83 (0.76/0.91) -Mild/moderate, RR 1.27 (1.0/1.61)	⊕⊕⊕⊖ moderate (ROB) -⊕⊕⊖⊖ Low (ROB, imprecision)	Steroids reduce mortality compared to controls in severe/critical ill pts., but not in mild/moderate pts.	
Tlayjek (J Infect Public Health, 2020)	20 (16977 pts), including one RCT (Recovery trial) [4] and 19 non RCTs.	Ten studies (1 RCT, 9 cohorts) evaluated short term mortality in 10278 pts	RR 0.91 (0.71/1.16)	⊕⊖⊖⊖ very low (serious ROB, heterogeneity, imprecision)	The pooled analysis of 1 RCT and 9 observational studies shows that steroids use is not associated with reduction in short-term mortality across all the disease severity groups (critical, severe, and non severe ill pts.)	
Sterne (JAMA, 2020)	7 RCTs (1703 pts)	Mortality data reported in critical ill pts. who were and were not receiving invasive mechanical ventilation at randomization. 1703 pts (678/1025)	OR 0.66 (0.53/0.87)	⊕⊕⊕⊕ High (based on RCTs without important limitations).	In critically ill pts. administration of systemic corticosteroids, compared with usual care or placebo was associated with lower 28-day all-cause mortality.	

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Table 1 (*continued*)

Ye (CMAJ, 2020)	The review included a variety of studies in patients with COVID-19, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), influenza, ARDS, CAP	Data on COVID-19 pts limited to 2 observational studies of 331 pts. with severe COVID-19, and 1 observational study in ARDS pts	-HR 2.30 (1.00/ 5.29) Severe infections -HR 0.41 (0.20 /0.83) ARDS pts	⊕⊖⊖⊖ very low (ROB, serious imprecision)	basing on direct evidence it appears that corticosteroids may increase mortality compared with no corticosteroids in pts with severe infection, and decrease mortality in pts with ARDS	
Van Paassen (Crit Care, 2020)	44 studies (5 RCTs, 39 non-RCTs) for a total of 20.197 pts, with severity of infection ranging from need of hospitalization to admission to ICU,	22 studies (14187 pts) reported mortality data	-OR 0.72 (0.46–0.97) Observational studies -OR 0.89 (0.69/0.99) RCTs	⊕⊕⊖⊖ low (ROB, heterogeneity) ⊕⊕⊕⊖ moderate (ROB)	both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality in pts requiring hospitalization or ICU admission.	
Chauduri (Intensive Care Med, 2021)	18 RCTs (2826 pts) in pts with ARDS of any ethiology.	8 RCTs in 1700 (700/1041) covid-19 pts.	RR 0.82 (0.72 to 0.95)	⊕⊕⊕⊖ moderate (indirectness)	Results from 16 RCTs in ARDS pts show a decrease of mortality in steroids recipients. Subgroup analysis based on COVID-19 status, steroid type, steroid initiation time, steroid dosage, and ROB did not demonstrate any credible subgroup effect, Patients who received a longer course of corticosteroids (over 7 days) had higher rates of survival than those who received a shorter course (<7 days).	
Hasan (Expert Rev Respir Med, 2021)	5 RCTs	pts with various severity of covid-19 (652 pts)	OR 0.64 (0.29/1.43)	⊕⊕⊖⊖ low (ROB, heterogeneity)	Low dose methilprednisolone did not reduce mortality compared to controls.	
Ma (Expert Rev Respir Med, 2021)	7 RCTs.	Mostly pts with severe disease. 6250 pts (2385/3865)	RR: 0.85 (0.73–0.99).	⊕⊕⊖⊖ low (serious ROB, including suspected publication bias)	Steroids reduce mortality compared to controls	
Pasin (J Cardiothorac Vasc Anesth, 2021)	5 RCTs	Pts with different severity of disease. 7692 pts (2835/4837).	-RR 0.39 (0.87/0.96) overall analysis	⊕⊕⊕⊖ moderate (ROB)	mortality in pts. treated with steroids was slightly but significantly lower than mortality of controls. The same beneficial effect was found in the subgroup of patients requiring mechanical ventilation Remarkably, steroids increased mortality in the subgroup of patients not requiring oxygen	
		1417 (529/888) requiring mechanical ventilation.	-RR 0.85 (0.72/1.00) Pts on MV	⊕⊕⊖⊖ low (ROB, inconsistency)		
		1607 (531/1076) not requiring O2 supplementation	-RR 1.28 (1.00/1.62)	⊕⊕⊖⊖ low (ROB, imprecision)		
Pulakulthri (Medicine, 2021)	8 RCTs,	Pts with different severity of disease. 7737 pts (2795/4942)	OR 0.85 (0.76/0.95)	⊕⊕⊖⊖ low (ROB, inconsistency)	steroids reduce the odds for mortality.	

(*continued on next page*)

Table 1 (*continued*)

Sahu (QJM, 2021)	7 trials (4 RCTs, 3 observational) for a total of 2214 pts	Pts. not requiring oxygen supplementation	OR 1.35 (1.01/1.79)	⊕⊕⊖⊖ low (serious ROB)	In pts not requiring oxygen supplementation, steroids increases mortality comparede to SOT	
Tu (Expert Rev Respir Med, 2022)	10 RCTs for a total of 12473 pts	Hospitalized pts, all (4354/8119)	-RR 0,93 (0.82/1.05)	⊕⊕⊖⊖ low (ROB, inconsistency)	Steroids did not reduce mortality compared to control, even in pts requiring mechanical ventilation However, in pts not requiring oxygen supplementation, steroids increases mortality comparede to SOC	
		-pts requiring mechanical ventilation, 5 trials, 2234 pts. (803/1431)	-RR 0.90 (0.79/1.02)			
		-pts not requiring oxygen supplementation. 4 trials, 2769 pts (918/1851)	-RR 1.23 (1.03/1.47)			
Cano (Chest, 2021)	33 studies in the quantitative synthesis	33 studies (1 RCT), 13564 pts (4919/8735) in the overall analysis	OR 2.30 (1.45/3.63)	⊕⊖⊖⊖ very low (serious ROB, inconsistency)	Overall mortality of pts receiving steroids was higher than in patients not receiving steroids, with the caveat that the population studied was too heterogeneous, possibly because of selection bias among studies, with corticosteroids administered to patients with grave prognosis at baseline. On the other hand, there was moderate evidence of mortality benefit in severely ill patients treated with steroids.	
		8 trial, 1404 pts (564/840) in severly ill pts	OR 0.65 (0.51/0.83)	⊕⊕⊕⊖ moderate (ROB)		
Moosazadeh (J Med Virol, 2022)	5 cohort studies comparing steroids + tocilizumab vs standard of care or tocilizumab alone	No information of COVID-19 severity provided. 460 pts received corticosteroids and tocilizumab and 303 tocilizumab alone. In the comparison with standard care group, 567 pts received corticosteroids and tocilizumab, and 890 standard of care.	- steroids+tocilizumab vs tocilizumab alone, 0.74 (0.36/1.50) -steroids+ tocilizumab vs standard of care 0.48 (0.31–0.74.)	⊕⊖⊖⊖ very low (ROB, indirectness, inconsistency)	The risk of death in the group of corticosteroids and tocilizumab was similar to the tocilizumab alone group, But was significantly lower in patients who received corticosteroids and tocilizumab compared to the control group. (continued on next page)	
Nguyen (Clin Infect Dis, 2021)	2 RCT (6818 COVID-19 pts).	Hospitalized pts. with different severity of COVID-19. Data from Recovery and Metcovid trials [4,5]; 6818 pts (2298/4520).	RR 0.90 (0.83/0.98).	⊕⊕⊕⊖ moderate (ROB)	Based on this Bayesian meta-analysis,, steroids reduces the risk of 28-day mortality compared to controls	
Ferreto (Sao Paulo Med J, 2021)	2 RCTs (6724)	Hospitalized pts. with different severity of COVID-19. 6724 pts (2255/4469).	RR 0.89 (0.82/0.97)	⊕⊕⊕⊖ moderate (ROB)	Treatment with dexamethasone had a positive impact on mortality and length of hospitalization among SARS-CoV-2 hospitalized pts.	
Yu (Medicine, 2021)	13 studies (2 RCTs, and 11 cohort/case control studies)	6612 confirmed severe COVID-19 pts.	HR 0.60 (0.45/0.79)	⊕⊕⊖⊖ low (ROB, heterogeneity)	Steroids reduce mortality (and risk of progression to invasive mechanical ventilation) in severe COVID-19 pts.	
Sahilu (Interdiscip Perspect Infect Dis, 2021)	32 studies (5 RCTs and 27 non-RCTs)	14659 pts (5830/8829) with different severity of COVID-19. Pts, with severe conditions were more likely receiving corticosteroids.	-In the overall analysis, RR 0.95 (0.80/1.13). - In critically ill pts, RR 0.89 (0.62/1.27)	⊕⊖⊖⊖ very low (ROB, imprecision, inconsistency)	No significant differences in mortality between the corticosteroid and noncorticosteroid treatment groups were observed in the overall population and critical ill pts.	
Boppana (Monaldi Arch Chest Dis, 2021)	6 RCTs (7707 pts)	7707 pts. (2857/4870) requiring 0_2 supplementation or invasive mechanical ventilation	-In the overall analysis (6 trials), OR 0.76 (0.53/1.00); -In pts. requiring 0_2 or IMV (6 trials), OR 0.74 (0.57/0.97) -In pts. not requiring 0_2	-⊕⊕⊖⊖ low (ROB, heterogeneity) -⊕⊕⊕⊖	Steroids reduce mortality in pts requiring 0_2 supplementation or invasive mechanical ventilation, but not in pts. not requiring 0_2 supplementation	

Table 1 (*continued*)

			or IMV (1 trial), OR 1.32 (0.99/1.77)	moderate (inconsistency) -⊕⊖⊖⊖ very low (ROB, serious imprecision)		
Wagner (Cochrane Database Syst Rev, 2021)	11 RCTs (8075 pts)	8075 pts (3072/5003) with different severity of COVID-19.	RR 0.89 (0.80/1.00(	⊕⊕⊕⊖ moderate (ROB)	Systemic steroids reduces mortality slightly	
Chaharom (Pulm Pharmacol Ther, 2022)	29 studies (18190 pts)	Hospitalized pts with different severity of infections	OR 1.12 (0.83/1.50) -overall analysis	-⊕⊖⊖⊖ very low (serious ROB, inconsistency)	Compared to controls, steroid treatment had no impact on mortality in the overall analysis, but decreased mortality in subgroup analysis of RCTs	
			OR 0.84 (0.75/0.94) In 6 RCTs, 7717 pts	⊕⊕⊕⊖ moderate (ROB)		
Caiazzo (Pharmacol Res, 2022)	11 RCTs (8109 patients)	Pts with different severity of COVID-19	-Mortality at longest follow-up, RR 0.87 (0.74 /1.03). -Mortality at 14 days, RR 0.81 (0.69 /0.85).	-⊕⊕⊖⊖ low (ROB, inconsistency)	systemic glucocorticoids might reduce mortality at 14 days follow-up. With longer follow-up, administration of glucocorticoids was associated with a trend to benefit for those requiring mechanical ventilation but possible harm for those not receiving oxygen at randomisation.	
Mohanty (J Pharm Pharm Sci, 2022)	12 studies (1 RCT, 11 observational studies)	3110 pts from 9 trials (902 received pulse-dose steroids, 756 low-dose steroids, 1452 usual care without steroids); pts. with different severity of covid-19.	-Pulse dose methylprednisolone vs usual care: OR 0.71 (0.51/0.97), -Pulse dose methylprednisolone vs low-dose steroids: OR 0.66(9.44/1.01)	⊕⊕⊕⊖ moderate (ROB) -⊕⊕⊖⊖ low (ROB, imprecision)	The review shows a significant reduction of all cause mortality in pulse-dose steroids compared to usual care, but it is unclear whether pulse-dose steroids reduces mortality compared to low-dose steroids	
Griesel (Cochrane Database Syst Rev, 2022)	3 RCTs	asymptomatic SARS-CoV-2 infection or mild COVID-19; 2132 pts (1057/1075)	-RR 0.61 (0.22/1.67)	-⊕⊕⊖⊖ low (serious imprecision)	it is unclear whether inhaled steroids + standard of care reduces mortality compared to standard of care alone.	
Hong (Steroids, 2022)	33 trials (5 RCTs)	More than half of the studies recruited pts who suffered from severe or critically ill COVID-19	-in the overall analysis (non-RCTs and RCTs), RR 0.73 (0.60/0.89) -in 5 small size RCTs, RR 0.81 (0.50/1.31)	-⊕⊕⊖⊖ low (ROB, inconsystency) -⊕⊕⊖⊖ low (imprecision, inconsystency)	methylprednisolone treatment is associated with reduced short-term mortality, but the benefit is not clear when the analysis is limited to RCTs.	
Thakur (Eur J Pharmacol, 2022)	21 (13 RCTs, 8 non-RCTs))	9922 pts (4018/5904), with different severity of COVID-19	OR 0.52 (0.34, 0.80)	-⊕⊕⊖⊖ low (ROB, inconsystency)	There was a significant reduction in deaths of COVID-19 patients in the steroidal group as compared to the non-steroidal group	

Footnotes. RCT, randomized clinical trial; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; pts, patients; OR, odds ratio; RR, risk ratio; RD, risk difference; HR, hazard ratio; ROB, Risk of bias; SOC, standard of care. ICU, intensive care unit; LOS, length of hospital stay. na, not available.

*Green flag, the effect size favors steroids compared to controls in a significant way; Yellow flag, no significant differences between steroids recipients and control; Red flag, the effect size favors controls compared to steroids in a significant way.

typical of emergency situations such as those of the COVID-19 pandemic, it is evident that even SRs and meta-analyses have produced heterogeneous results. For the outcome most commonly reported, overall mortality, it was possible to perform subgroup analysis of SRs according to study design and severity of COVID-19 at baseline. It was also clear that most of the included studies (both RCTs and non-RCTs) were at risk of bias and showed important clinical, methodological and statistical heterogeneity. Other outcomes (i.e., viral clearance, and length of hospital stay) were addressed by only a minority of SRs with a high level of uncertainty, so that no definitive conclusions can be drawn. Likewise, some of the SRs addressed the issue of the optimal dose (e.g., pulse-dose, high and low-dose steroids) and type of steroids (e.g., dexamethasone, methylprednisolone, hydrocortisone) to be used for the treatment of COVID-19. In this respect the data available from primary studies and SRs are heterogeneous and sparse, so no firm conclusion can be drawn, but the interest in this area of research is timely and relevant, and several clinical trials evaluating the use of corticosteroids for the treatment of COVID-19 are underway or in development.

In conclusion, there is moderate certainty of evidence that corticosteroids reduce mortality and progression of disease in critically ill COVID-19 patients compared to standard of care.

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