

RESEARCH

Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis

Zhikang Ye MPharm, Ying Wang MPharm, Luis Enrique Colunga-Lozano MD MSc, Manya Prasad MD MBBS, Wimonchat Tangamornsuksan PharmD PhD, Bram Rochweg MD MSc, Liang Yao MSc, Shahrzad Motaghi MSc, Rachel J. Couban MA MSt, Maryam Ghadimi PharmD BCPS, Malgorzata M. Bala MD PhD, Huda Gomaa MSc, Fang Fang MD, Yingqi Xiao MN, Gordon H. Guyatt MD MSc

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ABSTRACT

BACKGROUND: Very little direct evidence exists on use of corticosteroids in patients with coronavirus disease 2019 (COVID-19). Indirect evidence from related conditions must therefore inform inferences regarding benefits and harms. To support a guideline for managing COVID-19, we conducted systematic reviews examining the impact of corticosteroids in COVID-19 and related severe acute respiratory illnesses.

METHODS: We searched standard international and Chinese biomedical literature databases and prepublication sources for randomized controlled trials (RCTs) and observational studies comparing corticosteroids versus no corticosteroids in patients with COVID-19, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). For

acute respiratory distress syndrome (ARDS), influenza and community-acquired pneumonia (CAP), we updated the most recent rigorous systematic review. We conducted random-effects meta-analyses to pool relative risks and then used baseline risk in patients with COVID-19 to generate absolute effects.

RESULTS: In ARDS, according to 1 small cohort study in patients with COVID-19 and 7 RCTs in non-COVID-19 populations (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.55 to 0.93, mean difference 17.3% fewer; low-quality evidence), corticosteroids may reduce mortality. In patients with severe COVID-19 but without ARDS, direct evidence from 2 observational studies provided very low-quality evidence of an increase in

mortality with corticosteroids (hazard ratio [HR] 2.30, 95% CI 1.00 to 5.29, mean difference 11.9% more), as did observational data from influenza studies. Observational data from SARS and MERS studies provided very low-quality evidence of a small or no reduction in mortality. Randomized controlled trials in CAP suggest that corticosteroids may reduce mortality (RR 0.70, 95% CI 0.50 to 0.98, 3.1% lower; very low-quality evidence), and may increase hyperglycemia.

INTERPRETATION: Corticosteroids may reduce mortality for patients with COVID-19 and ARDS. For patients with severe COVID-19 but without ARDS, evidence regarding benefit from different bodies of evidence is inconsistent and of very low quality.

On Mar. 11, 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic.¹ The worldwide spread of COVID-19 represents a profound threat to human health.

Clinicians frequently treat patients with COVID-19 with corticosteroids.² Their use is controversial: 2 commentaries published recently in *The Lancet* expressed opposing views based partly on

original studies of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and influenza: 1 recommended against using corticosteroids, while the other recommended using corticosteroids in some patients with COVID-19.^{3,4}

Formulating recommendations for clinicians regarding use of corticosteroids in patients with COVID-19 requires systematic summaries of the available evidence. Therefore, to support a clinical

practice guideline addressing management of patients with COVID-19,⁵ we conducted a series of systematic reviews. Because we anticipated a paucity of direct evidence from patients with COVID-19, we included available evidence addressing corticosteroids in the treatment of acute respiratory distress syndrome (ARDS), SARS, MERS, influenza and community-acquired pneumonia (CAP), all providing indirect evidence that informs the efficacy and safety of corticosteroid use in patients with COVID-19.

Methods

For ARDS, we used definitions in eligible studies. For severe COVID-19, we used the World Health Organization definition of severity: fever or suspected respiratory infection, plus 1 of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or peripheral oxygen saturation (SpO₂) ≤ 93% on room air.⁶

For COVID-19, SARS and MERS, we conducted systematic reviews that sought all eligible primary studies. For ARDS, influenza and CAP, we chose the most recent methodologically rigorous systematic reviews and searched for recent eligible primary studies. Choice of outcomes were informed by our preliminary protocol, by guidance from the guideline panel, and from what authors of eligible studies reported.

Search strategies and selection criteria

Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the protocol we developed before launching these systematic reviews, which follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁷

COVID-19, SARS and MERS

With the assistance of a medical librarian (R.J.C.), we searched MEDLINE, Embase, PubMed and the Cochrane Central Register of Controlled Trials from the date of their inception to Apr. 19, 2020, and searched medRxiv until Apr. 25, 2020. For studies of patients with COVID-19, we also searched Chinese databases, including China National Knowledge Infrastructure (CNKI), Wanfang, Chongqing VIP Information (CQVIP), and ChinaXiv. Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the complete search strategy.

We included randomized controlled trials (RCTs), cohort and case-control studies comparing corticosteroids versus no corticosteroids in patients with COVID-19, SARS or MERS. For cohort studies and case-control studies, we included only studies that performed adjusted analysis unless all studies failed to conduct an adjusted analysis, in which case we included unadjusted analyses. For overlapping studies (studies that included patients from the same data sources), we included only the larger unless there was a specific additional helpful analysis in the smaller.

ARDS, influenza and CAP

We conducted separate searches for ARDS, influenza and CAP using a 2-stage process (for search strategy, see Appendix 2). First, to identify systematic reviews that examined the effect of corticosteroids on ARDS, influenza or CAP, we searched MEDLINE, Embase, the Cochrane Database of Systematic Reviews and Epistemonikos, and chose the

most recent methodologically rigorous one. Second, we searched MEDLINE, Embase and ClinicalTrials.gov for ARDS and CAP, and searched MEDLINE, Embase, PubMed and the Cochrane Central Register of Controlled Trials for influenza, for studies published subsequent to the search of the chosen reviews. For ARDS and CAP, we included only RCTs. For influenza, we included RCTs and cohort studies.

For all searches, 2 reviewers independently screened titles and abstracts and, subsequently, full texts of potentially eligible studies to determine final eligibility. Disagreements were resolved by discussion or, if necessary, referral to a third reviewer. We applied no language restriction.

Data analysis

Two reviewers independently extracted study characteristics, with adjudication by a third reviewer if necessary. Outcomes included mortality, length of intensive care unit (ICU) stay, length of hospital stay, duration of mechanical ventilation, need for mechanical ventilation, viral ribonucleic acid (RNA) clearance, viral shedding time, serious hyperglycemia, superinfection, neuromuscular weakness and gastrointestinal bleeding.

We calculated summary estimates using Stata or Review Manager and calculated relative effects (odds ratios [ORs], risk ratios [RRs] or hazard ratios [HRs]) and 95% confidence intervals (95% CIs) for dichotomous outcomes, and mean differences (MDs) and 95% CIs for continuous outcomes using a random-effects model. For continuous outcomes and adjusted estimates, we used the inverse variance (DerSimonian and Laird) method; for dichotomous outcomes from RCTs, we used the Mantel-Haenszel method. We assessed inconsistency among studies by differences in point estimates and overlap of the confidence intervals, and the *I*² statistic. For dichotomous outcomes, we calculated the absolute treatment effects by applying relative effects to risk in patients not receiving corticosteroids in 2 groups: patients with severe COVID-19 and patients with COVID-19 and ARDS. We chose the baseline mortality risk of patients with COVID-19 and ARDS from an observational study of patients with COVID-19 and ARDS,⁸ and the baseline mortality risk of patients with severe COVID-19 from an observational study of patients with severe COVID-19.² For other outcomes, we relied for baseline risks on the medians of the groups not receiving corticosteroids in the included studies.

Risk of bias assessment

We used the ROBIS risk of bias tool⁹ to choose the most methodologically rigorous systematic review to be updated. We used a modified version of the Cochrane risk of bias tool¹⁰ to assess risk of bias in RCTs, and a revised version of the Newcastle-Ottawa Scale^{11,12} for observational studies (details available at www.evidencepartners.com/resources/methodological-resources/). Two reviewers independently assessed risk of bias, resolving disagreements with a third reviewer if necessary.

Rating of evidence quality

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the quality of evidence for each outcome as high, moderate, low or very low.¹³ The assessment included judgments addressing risk of bias,¹⁴ imprecision,¹⁵ inconsistency,¹⁶ indirectness¹⁷ and publication bias.¹⁸ If

there were serious concerns in any of these domains (for instance, in risk of bias), we rated down the quality of the evidence. Because the effect of corticosteroids in these diseases might differ from effects in the COVID-19 population, using the GRADE approach, for benefit outcomes in SARS and MERS, we rated down 1 level for indirectness, and for ARDS, influenza and CAP, we rated down 2 levels. Because we considered estimates of harm to be more likely to apply across populations than benefit outcomes, for all populations we rated down 1 level for harms.

Ethics approval

Ethics approval was not required for this systematic review.

Results

Appendix 3 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the study selection process. Our search for COVID-19, SARS and MERS identified 5120 citations. After removing duplicates, screening titles and abstracts, and reviewing full texts, we ultimately included 1 cohort study⁸ including 84 patients with COVID-19 and ARDS, 5 cohort studies^{19–23} including 679 patients with COVID-19 but without ARDS, 3 studies (2 cohort studies^{24,25} and 1 RCT²⁶) including 7087 patients with SARS, and 2 cohort studies^{27,28} including 623 patients with MERS.

Our search for systematic reviews of ARDS identified 836 citations; we ultimately chose a systematic review published in 2019 as the target for updating.²⁹ Our search for primary studies identified 1 new eligible RCT published in 2020.³⁰ Including 6 RCTs identified from the previous review, we included 7 RCTs^{30–36} with 851 patients.

Our search for systematic reviews for influenza identified 525 citations; we ultimately chose a systematic review published in 2019 as the target for updating.³⁷ Our search for primary studies identified 1 new eligible study published in 2020.³⁸ Including 30 studies identified from the previous review, we identified 31 eligible studies,^{39–69} of which 21 with 9536 patients were included in meta-analyses.^{41,43–47,50,52,53,55–61,63–65,68,69}

Our search for systematic reviews for CAP identified 346 citations. We ultimately chose a systematic review published in 2015 as the target for updating.⁷⁰ Our search for primary studies identified 1 new eligible study published in 2016.⁷¹ With 12 RCTs from the previous review, our systematic review included 13 RCTs^{71–83} including 2095 patients.

Appendix 4 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents characteristics of the included studies. Appendix 5 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the risk of bias assessment for each study. Forest plots of the meta-analysis results are shown in Figures 1–5 for mortality and in Appendix 6 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) for other outcomes.

ARDS

Evidence for patients with COVID-19 and ARDS was available from a single observational study of 84 patients⁹ that suggested corticosteroids may result in a large mortality reduction compared with no corticosteroids (HR 0.41, 95% CI 0.20 to 0.83, MD 29.2% lower; very low-quality evidence) (Table 1).

Evidence for ARDS without COVID-19 was available from 7 RCTs^{30–36} including 851 patients (Table 2). We considered the evidence for most outcomes to be high quality for patients with ARDS in general. After rating down 2 levels for indirectness of populations, we considered the evidence to be low quality for COVID-19. These RCTs suggest that corticosteroids may substantially reduce mortality (RR 0.72, 95% CI 0.55 to 0.93, MD 17.3% lower; low-quality evidence) (Figure 1). Very low-quality evidence raised the possibility that corticosteroids may have little or no impact on length of ICU stay^{32–34} (MD 0.1 days longer, 95% CI 3.0 days shorter to 3.2 days longer) but may reduce length of hospital stay^{33,34,36} (MD 3.6 days shorter, 95% CI 0.02 to 7.2 days shorter). Low-quality evidence shows that corticosteroids may reduce the duration of mechanical ventilation (MD –4.8 days, 95% CI –7.0 to –2.6),^{30,31,33–36} but increase serious hyperglycemia (risk increase 8.1%, 95% CI 0.7% to 16.2%),^{30,33,35} with few or no adverse effects on neuromuscular weakness,^{33,34} gastrointestinal bleeding^{35,36} and superinfection.^{30,33–36}

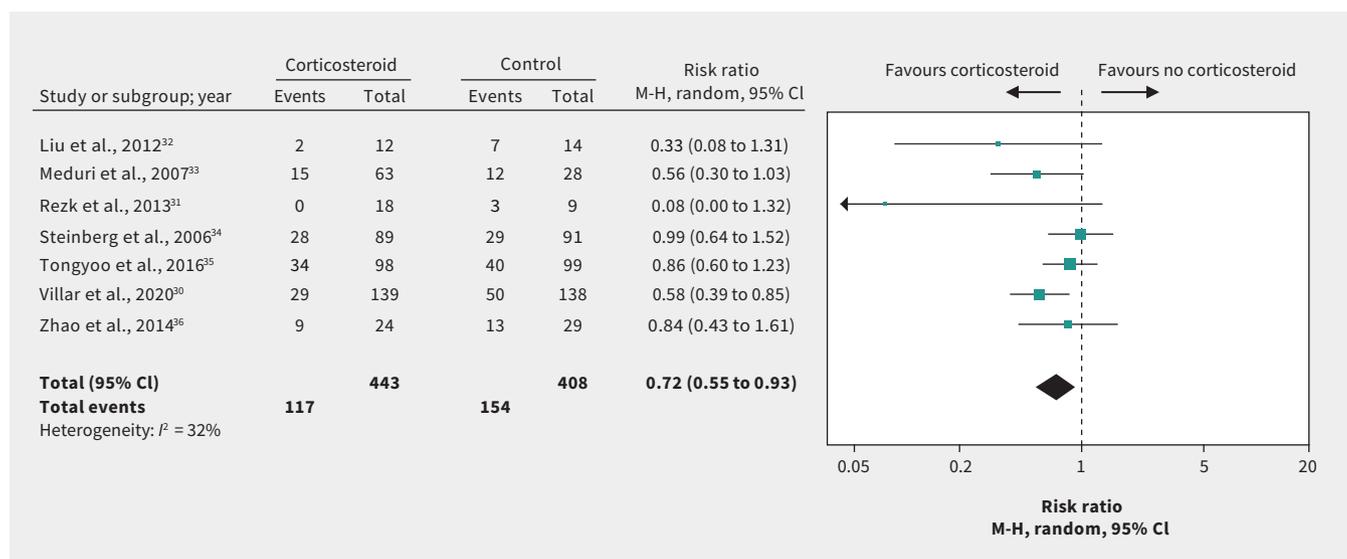


Figure 1: Effect of corticosteroids on mortality in patients with acute respiratory distress syndrome without coronavirus disease 2019. Note: CI = confidence interval, M-H = Mantel–Haenszel.

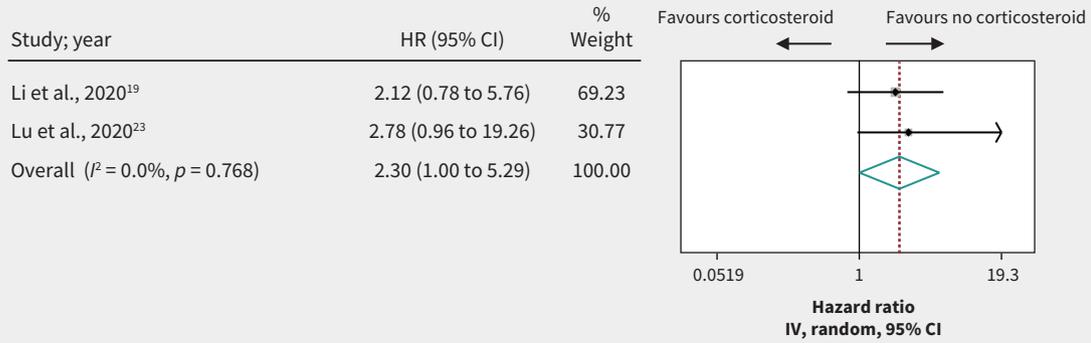


Figure 2: Effect of corticosteroids on mortality in patients with severe coronavirus disease 2019. Weights are from random-effects analysis. Note: CI = confidence interval, HR = hazard ratio, IV = inverse variance.

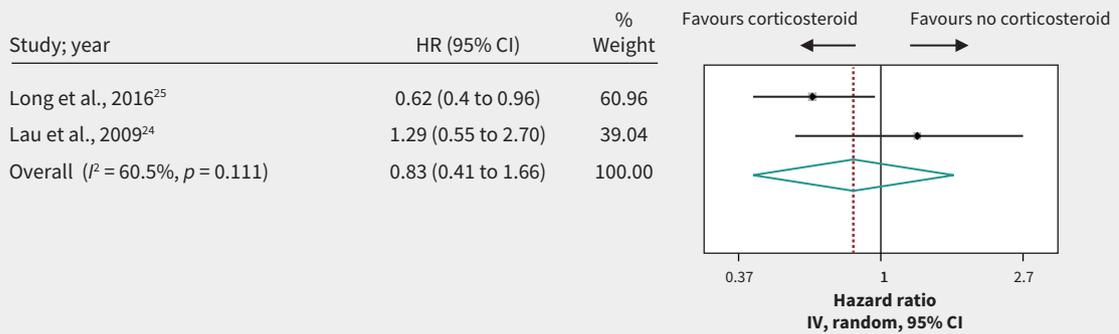


Figure 3: Effect of corticosteroids on mortality in patients with severe acute respiratory syndrome. Weights are from random-effects analysis. Note: CI = confidence interval, HR = hazard ratio, IV = inverse variance.

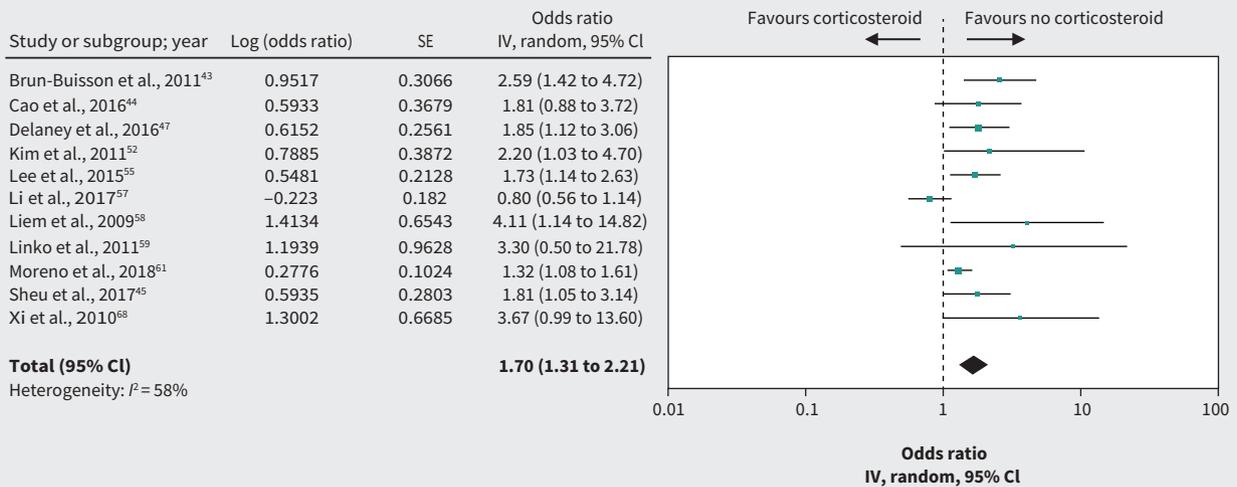


Figure 4: Effect of corticosteroids on mortality in patients with influenza. Note: CI = confidence interval, IV = inverse variance, SE = standard error.

Severe COVID-19: direct evidence from observational studies

Very low-quality evidence from 2 cohort studies^{19,23} including 331 patients with severe COVID-19 raised the possibility that corticosteroids may increase mortality compared with no corticosteroids

(HR 2.30, 95% CI 1.00 to 5.29, MD 11.9% more) (Table 3, Figure 2). One cohort study²⁰ reported an increase in the composite outcome of mortality or ICU admission with steroid use. Two cohort studies^{21,22} suggested that corticosteroids use was associated with prolonged viral shedding (very low-quality evidence).

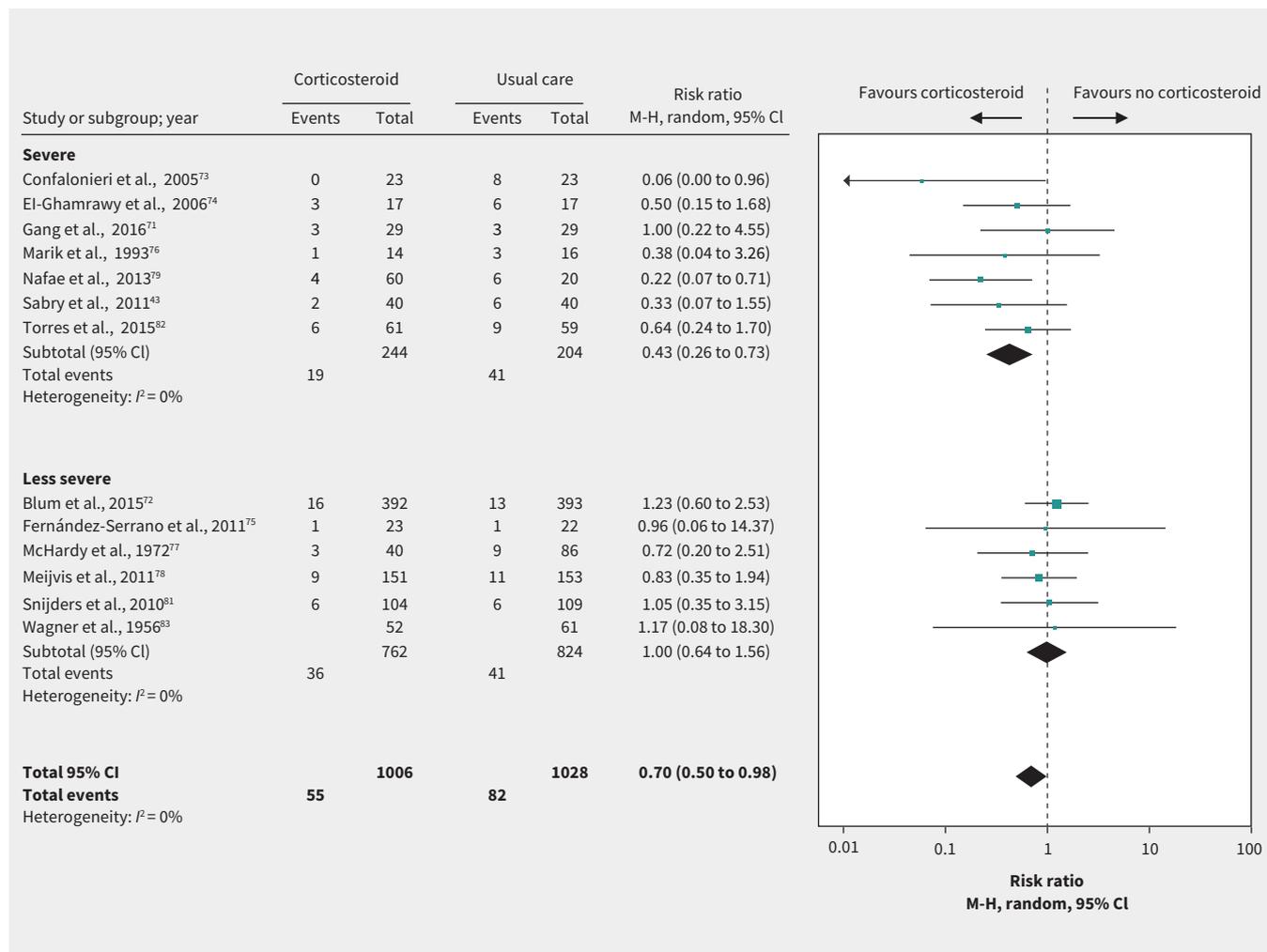


Figure 5: Effect of corticosteroids on mortality in patients with community-acquired pneumonia. Note: CI = confidence interval, M-H = Mantel-Haenszel.

Table 1: GRADE summary of findings: corticosteroids in patients with COVID-19 and ARDS, based on direct evidence from observational studies of patients with COVID-19 and ARDS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group,* %	Difference (95% CI)%		
Mortality	HR 0.41 (95% CI 0.20 to 0.83) Based on data from 84 patients with COVID-19 and ARDS in 1 observational study ⁸	61.8	-29.2 (-44.3 to -6.8)	Very low (serious imprecision†)	We are very uncertain of the effect of corticosteroids on mortality

Note: ARDS = acute respiratory distress syndrome, CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio.

*Mortality baseline risk from patients with COVID-19 and ARDS without corticosteroid treatment.⁸

†Observational study started at low quality of evidence. Although the CI appears narrow, the small sample size and implausibly large effect led to rating down for imprecision.

Severe COVID-19: indirect evidence from observational studies and a randomized trial of SARS

Two cohort studies^{24,25} including 6129 patients with SARS provide low-quality evidence for corticosteroid impact on mortality in these patients, with additional consideration of indirectness in serious COVID-19 pneumonia (HR 0.83, 95% CI 0.41 to 1.66; very low-quality evidence) (Table 4, Figure 3). An RCT²⁶ in which 16 patients with SARS treated with ribavirin were randomized to corticosteroids or no corticosteroids raised the possibility that early (< 7 days of illness) hydrocortisone therapy may increase the median time for SARS-associated

coronavirus (SARS-CoV) RNA to become undetectable in plasma (MD 4.0 days longer, 95% CI 2.0–6.0 days; very low-quality evidence for SARS with additional consideration of indirectness in COVID-19) (Table 4).

Severe COVID-19: indirect evidence from observational studies of MERS

One cohort study²⁸ that enrolled 290 patients with MERS suggests a possible reduction in mortality with administration of corticosteroids (OR 0.75, 95% CI 0.52 to 1.07; very low-quality evidence

Table 2: GRADE summary of findings: corticosteroids in patients with COVID-19 and ARDS, based on indirect evidence from randomized controlled trials of patients with ARDS but without COVID-19

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group*	Difference (95% CI)		
Mortality	RR 0.72 (95% CI 0.55 to 0.93) Based on data from 851 patients and ARDS in 7 RCTs ^{30–36}	61.8%	–17.3% (–27.8% to –4.3%)	Low (very serious indirectness†)	Corticosteroids may result in a large reduction in mortality
Length of ICU stay	Based on data from 297 patients in 3 RCTs ^{32–34}	The median duration of length of ICU stay was 8.0 days	MD 0.1 days (–3.0 to 3.2)	Very low (serious inconsistency, very serious indirectness and serious imprecision‡)	We are very uncertain of the effect of corticosteroids on length of ICU stay
Length of hospital stay	Based on data from 324 patients in 3 RCTs ^{33,34,36}	The median duration of length of hospital stay was 18.0 days	MD –3.6 days (–7.2 to –0.02)	Very low (very serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on length of hospital stay
Duration of mechanical ventilation	Based on data from 888 patients in 6 RCTs ^{30,31,33–36}	The median duration of mechanical ventilation was 14.5 days	MD –4.8 days (–7.0 to –2.6)	Low (very serious indirectness†)	Corticosteroids may reduce duration of mechanical ventilation
Serious hyperglycemia	RR 1.12 (95% CI 1.01 to 1.24) Based on data from 565 patients in 3 RCTs ^{30,33,35}	67.6%	8.1% (0.7% to 16.2%)	Low (serious indirectness and serious imprecision¶)	Corticosteroids may increase serious hyperglycemia events
Neuromuscular weakness	RR 0.85 (95% CI 0.62 to 1.18) Based on data from 271 patients in 2 RCTs ^{33,34}	26.4%	–3.9% (–10% to 4.7%)	Low (serious indirectness, serious imprecision**)	Corticosteroids may not increase neuromuscular weakness
Gastrointestinal bleeding	RR 0.71 (95% CI 0.30 to 1.73) Based on data from 250 patients in 2 RCTs ^{35,36}	14.0%	–4.0% (–9.8% to 10.2%)	Low (serious indirectness, serious imprecision**)	Corticosteroids may not increase gastrointestinal bleeding
Superinfection	RR 0.82 (95% CI 0.67 to 1.02) Based on data from 798 patients in 5 RCTs ^{30,33–36}	33.0%	–5.9% (–10.8% to 0.6%)	Moderate (serious indirectness††)	Corticosteroids probably do not increase superinfection events

Note: ARDS = acute respiratory distress syndrome, CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, ICU = intensive care unit, MD = mean difference, RCTs = randomized controlled trials, RR = risk ratio.

*Mortality baseline risk from patients with COVID-19 and ARDS who do not receive corticosteroid treatment.⁸ The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events was obtained from the median estimate from the control group in the included RCTs.

†We rated down 2 levels owing to indirectness; the cause of ARDS across the studies is inconsistent and might not represent the COVID-19 population.

‡We rated down 2 levels owing to indirectness; 1 for inconsistency ($I^2 = 73%$, heterogeneity p value 0.03) and 1 for imprecision because effect estimate is consistent with benefit or harm.

§We rated down 2 levels owing to indirectness and 1 for imprecision owing to the CI including a trivial reduction in hospital stay.

¶We rated down by 1 level owing to indirectness, as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits; and we rated down by 1 level for imprecision owing to the lower CI, 0.7% representing an unimportant increase in hyperglycemia.

**We rated down by 1 level owing to indirectness as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits; we rated down by 1 level for imprecision, effect estimate consistent with benefit or harm.

††We rated down by 1 level owing to indirectness as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits; we did not rate down owing to imprecision because the largest degree of harm consistent with the evidence is 7 in 1000, which we judge to be unimportant.

for MERS with additional consideration of indirectness in COVID-19) (Table 5). Data from 189 patients in the same study²⁸ suggest that corticosteroid use may be associated with a delay in Middle East respiratory syndrome coronavirus (MERS-CoV) RNA clearance (HR 0.35, 95% CI 0.17 to 0.72; very low-quality evidence for MERS with additional consideration of indirectness for COVID-19) (Table 5).

Severe COVID-19: indirect evidence from observational studies of influenza

Evidence in patients with influenza from 11 cohort studies^{43–45,47,52,55,57–59,61,68} including 8530 patients with adjusted effect estimates for mortality suggests that corticosteroids may increase mortality (OR 1.70, 95% CI 1.31 to 2.21, MD 6.1% higher; low-quality evidence for influenza rated down to very low for indirectness) (Table 6, Figure 4). Very low-quality evidence for influenza with additional consideration of indirectness when applied to COVID-19 from

cohort studies that failed to conduct an adjusted analysis raised the possibility that corticosteroids may increase the rate of superinfection (OR 2.74, 95% CI 1.51 to 4.95)^{43,44,47,52,55,57,65} and increase the number of patients requiring mechanical ventilation (OR 5.54, 95% CI 1.83 to 16.80)^{52,57,59,61} (Table 6).

Severe COVID-19: indirect evidence from randomized trials of CAP

Thirteen RCTs^{71–83} including 2034 patients with CAP addressed a number of important efficacy outcomes. For patients with CAP in general, evidence varied from high to low quality. After we rated down 2 levels for indirectness, all evidence for these outcomes was of low or very low quality. Corticosteroids were associated with reductions in mortality (RR 0.70, 95% CI 0.50 to 0.98, MD 3.1% lower), need for mechanical ventilation^{72,75,76,79,82} (risk difference [RD] 10.4%, 95% CI 4.3% to 13.8%), duration of mechanical ventilation^{71,73,74,79,80} (MD 3.5 days shorter, 95% CI 1.8 to 5.2 days), length of

Table 3: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on direct evidence from observational studies of patients with severe COVID-19

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group,* %	Difference (95% CI), %		
Mortality	HR 2.30 (95% CI 1.00 to 5.29) Based on data from 331 patients with severe COVID-19 in 2 observational studies ^{19,23}	10.4	11.9 (0 to 33.7)	Very low (serious imprecision†)	We are very uncertain of the effect of corticosteroids on mortality

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio.
*Baseline risk from a study of the patients with severe COVID-19 without corticosteroids use.²
†Observational study started at low quality of evidence. We rated down 1 level owing to serious imprecision (wide CI).

Table 4: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from randomized controlled trials and observational studies of patients admitted to hospital with SARS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group	Difference (95% CI)		
Mortality	HR 0.83 (95% CI 0.41 to 1.66) Based on data from 6129 patients with SARS in 2 observational studies ^{24,25}	10.4%*	-1.7% (-6.0% to 6.3%)	Very low (serious indirectness and serious imprecision†)	We are very uncertain of the effect of corticosteroids on mortality
Median time for SARS-CoV RNA to become undetectable in plasma	Based on data from 16 patients with SARS in 1 RCT ²⁶	8.0 days‡	MD 4.0 days (2.0 to 6.0)	Very low (serious risk of bias, serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on time for SARS-CoV RNA to become undetectable in plasma

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio, MD = mean difference, RCT = randomized controlled trial, RNA = ribonucleic acid, SARS = severe acute respiratory syndrome, SARS-CoV = SARS-associated coronavirus.
*Baseline risk from a study of patients with severe COVID-19 without corticosteroid use.²
†Observational studies start as low quality of evidence. We rated down 1 level owing to serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with SARS) and 1 level owing to serious imprecision (the CI includes both an important benefit and an important harm).
‡Baseline risk from the RCT that reported median time for SARS-CoV RNA to become undetectable in plasma for the no corticosteroids group.²⁶
§Randomized controlled trial started at high quality of evidence. We rated down owing to serious risk of bias, serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with SARS) and serious imprecision (because of small sample size).

ICU stay,^{72-76,78,79,82} and length of hospital stay^{71-76,78,79,81,82,84} (Table 7, Figure 5). Meta-analysis of 8 RCTs^{71,72,75,78,79,81,82,84} showed that corticosteroids may increase the rate of serious hyperglycemia (RD 5.7%, 95% CI 0.18% to 15.3%; moderate-quality evidence for CAP, low quality after rating down 1 level for indirectness).

Mortality results suggested a possible subgroup effect of corticosteroids by pneumonia severity (severe pneumonia, RR 0.43, 95% CI 0.26 to 0.73; less severe pneumonia, RR 1.00, 95% CI 0.64

to 1.56; *p* for interaction 0.02). However, the apparent effect is based on differences between rather than within studies, is driven to a considerable extent by a small study⁷³ that was stopped early for benefit, almost certainly represents a large overestimate of effect, and does not appear with any other outcome. Thus, the subgroup effect has low credibility.

For other adverse events (neuropsychiatric events;^{72,81,82,84} superinfection^{71-74,78,81,82,84} and gastrointestinal bleeding^{71-75,79,80,82}),

Table 5: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from observational studies of patients admitted to hospital with MERS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group, %	Difference (95% CI), %		
Mortality	OR 0.75 (95% CI 0.52 to 1.07) Based on data from 290 patients with MERS in 1 observational study ²⁸	10.4*	-2.4 (-4.7 to 0.6)	Very low (serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on mortality
MERS-CoV RNA clearance	HR 0.35 (95% CI 0.17 to 0.72) Based on data from 189 patients with MERS in 1 observational study ²⁸	29.8†	-18.2 (-24.0 to -7.3)	Very low (serious indirectness and serious imprecision¶)	We are very uncertain of the effect of corticosteroids on MERS-CoV RNA clearance

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio, MERS = Middle East respiratory syndrome, MERS-CoV = Middle East respiratory syndrome coronavirus, OR = odds ratio, RNA = ribonucleic acid.

*Baseline risk from a study of patients with severe COVID-19 without corticosteroid use.²

†Baseline risk from the observational study that reported MERS-CoV RNA clearance for no corticosteroids group.²⁸

§Observational studies started at low quality of evidence. We rated down 1 level owing to serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with MERS), and 1 level owing to serious imprecision (the CI includes both a trivial and an important effect).

¶Observational studies started at low quality of evidence. We rated down 1 level owing to serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with MERS), and 1 level owing to serious imprecision because of the small sample size.

Table 6: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from observational studies of patients admitted to hospital with influenza

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group, %	Difference (95% CI), %		
Mortality	OR 1.70 (95% CI 1.31 to 2.21) Based on data from 8530 participants from 11 observational studies ^{43-45,47,52,55,57-59,61,68}	10.4*	6.1 (2.8 to 10.0)	Very low (serious indirectness‡)	We are very uncertain of the effect of corticosteroids on mortality
Superinfection	OR 2.74 (95% CI 1.51 to 4.95) Based on data from 6114 participants from 7 observational studies ^{43,44,47,52,55,57,65}	7.2†	10.3 (3.3 to 20.5)	Very low (serious risk of bias and indirectness§)	We are very uncertain of the effect of corticosteroids on superinfections
Mechanical ventilation	OR 5.54 (95% CI 1.83 to 16.80) Based on data from 4364 participants from 4 observational studies ^{52,57,59,61}	41.8§	38.1 (15.0 to 50.6)	Very low (serious risk of bias and indirectness‡)	We are very uncertain of the effect of corticosteroids on need for mechanical ventilation

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, OR = odds ratio.

*Baseline risk from a study of patients with severe COVID-19 without corticosteroids use.²

†Baseline risk comes from the median effect of the control group in the included studies.

‡Observational studies started at low quality of evidence. Additional concern was indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients admitted to hospital with influenza).

§Observational studies started at low quality of evidence. Additional concerns included high risk of indication bias because unadjusted estimates were included, and indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients admitted to hospital with influenza).

Table 7: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from randomized controlled trials of patients admitted to hospital with community-acquired pneumonia

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group*	Difference (95% CI)		
Mortality	RR 0.70 (95% CI 0.50 to 0.98) Based on data from 2034 patients in 13 RCTs ⁷¹⁻⁸³	10.4%	-3.1% (-0.2% to -5.2%)	Very low (very serious indirectness† and serious inconsistency)	We are very uncertain of the effect of corticosteroids on mortality
Length of ICU stay	Based on data from 1376 patients in 8 RCTs ^{72-76,78,79,82}	The median length of ICU stay was 8.3 days	MD -1.7 days (-3.4 to 0.1)	Very low (serious inconsistency, very serious indirectness and serious imprecision‡)	We are very uncertain of the effect of corticosteroids on length of ICU stay
Length of hospital stay	Based on data from 1636 patients in 10 RCTs ^{71-76,78,79,81,82,84}	The median length of hospital stay was 14.3 days	MD -1.8 days (-2.8 to -0.8)	Very low (serious inconsistency, very serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on length of hospital stay
Need for mechanical ventilation	RR 0.42 (95% CI 0.23 to 0.76) Based on data from 1017 patients in 5 RCTs ^{72,75,76,79,82}	18.0%	-10.4% (-13.8% to -4.3%)	Low (very serious indirectness†)	Corticosteroids may reduce need for mechanical ventilation
Duration of mechanical ventilation	Based on data from 199 patients in 5 RCTs ^{71,73,74,79,80}	The median duration of mechanical ventilation was 11.3 days	MD -3.5 days (-5.2 to -1.8)	Very low (serious risk of bias and very serious indirectness¶)	We are very uncertain of the effect of corticosteroids on duration of mechanical ventilation
Serious hyperglycemia	RR 1.62 (95% CI 1.02 to 2.67) Based on data from 1476 patients in 8 RCTs ^{71,72,75,78,79,81,82,84}	9.2%	5.7% (0.18% to 15.3%)	Low (serious indirectness and serious imprecision**)	Corticosteroids may increase serious hyperglycemia events
Gastrointestinal bleeding	RR 0.99 (95% CI 0.43 to 2.24) Based on data from 1228 patients in 8 RCTs ^{71-75,79,80,82}	3.0%	-0.03% (-1.7% to 3.7%)	Low (serious indirectness and serious imprecision**)	Corticosteroids may have little or no impact on gastrointestinal bleeding
Neuropsychiatric events	RR 1.91 (95% CI 0.68 to 5.39) Based on data from 1142 patients from 4 RCTs ^{72,81,82,84}	1.6%	1.4% (-0.5% to 7%)	Low (serious indirectness and serious imprecision¶)	Corticosteroids may result in a small increase in neuropsychiatric events
Superinfection	RR 1.31 (95% CI 0.69 to 2.50) Based on data from 1500 patients in 8 RCTs ^{71-74,78,81,82,84}	3.7%	1.1% (-1.1% to 5.5%)	Low (serious indirectness and serious imprecision¶)	Corticosteroids may result in a small or no increase in superinfection events

Note: CAP = community-acquired pneumonia, CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, ICU = intensive care unit, MD = mean difference, RCT = randomized controlled trial, RR = risk ratio.

*Mortality baseline risk was obtained from patients with COVID-19 and ARDS without corticosteroid treatment.² The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events comes from the median effect of the control group in the included RCTs.

†We rated down 2 levels owing to indirectness; the cause of pneumonia across the studies is inconsistent and might not represent the COVID-19 population. We also rated down for inconsistency because of a possible subgroup effect that suggests mortality benefit was restricted to those with severe pneumonia.

‡We rated down 2 levels owing to indirectness; 1 for inconsistency ($I^2 = 76%$, heterogeneity p value = 0.0001); and 1 for imprecision because the effect estimates are consistent with important benefit and harm.

§We rated down 2 levels owing to indirectness; 1 for inconsistency ($I^2 = 47%$, heterogeneity p value = 0.006) and 1 for imprecision because the lower CI includes important benefit and important harm.

¶We rated down 1 level owing to risk of bias and 2 levels owing to indirectness. We did not rate down owing to inconsistency; the effect estimates were in the same direction, despite the I^2 54% and the p value of 0.07.

**We rated down by 1 level owing to indirectness, as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits, and 1 for imprecision because effect estimates are not consistent with benefit or harm.

evidence was moderate quality for small, no, or uncertain harms of corticosteroids in patients with CAP, and low quality after rating down once for indirectness (Table 7).

Interpretation

This series of systematic reviews informed a guideline addressing management of patients with COVID-19.⁵ Direct evidence from 1 observational study⁸ of 84 patients with COVID-19 and ARDS was consistent with the findings of our systematic review of RCTs of patients without COVID-19 that suggested corticosteroids may reduce mortality in patients with COVID-19 and ARDS by more than 15% and reduce the duration of mechanical ventilation. The evidence suggested corticosteroids may increase the rate of serious hyperglycemia, although not of other potentially worrisome adverse effects. The evidence for these effects is mostly of low quality.

For patients who have severe COVID-19 but are not critically ill, direct evidence from observational studies provided very low-quality evidence of an increase in mortality with corticosteroids. In SARS and MERS, evidence from observational studies raises the possibility of a modest mortality reduction with corticosteroids, but also of a delay in viral clearance. In CAP, RCT evidence also raises the possibility of a mortality reduction with corticosteroids and other benefits including reduction in length of hospital and ICU stay, and need for and duration of mechanical ventilation. Low-quality evidence suggests a likely increase in hyperglycemia and possible small increases in neuropsychiatric events and superinfection, but not in gastrointestinal bleeding. Observational studies in influenza provide discrepant findings, raising the possibility of substantial increases in mortality, superinfection and mechanical ventilation with corticosteroids.

Strengths of this review include a comprehensive search, independent study selection, data abstraction and risk of bias assessment by 2 reviewers and presentation of absolute effects for dichotomous outcomes. We rated the quality of evidence with the GRADE approach, paying close attention to important methodological issues such as differences in the impact of indirectness of evidence on benefit and harm outcomes. We are more skeptical of making inferences regarding benefits in patients with COVID-19 from other patient populations than we are of making inferences on harms. For observational studies, we included, as far as possible, only those with adjusted analyses. Finally, a particular strength is the presentation of a comprehensive assessment of all the indirect evidence, including from ARDS, SARS, MERS, influenza and CAP, together in a single document.

We compared our review with another published systematic review addressing corticosteroid therapy in COVID-19.⁸⁵ Apart from COVID-19, SARS and MERS, our review included 3 additional populations: ARDS, CAP and influenza. We updated our search until Apr. 19, including evidence published more recently than the previous systematic review, which searched until Mar. 15.^{8,19-23} Third, we included, as far as possible, only cohort and case-control studies with adjusted effect estimates. Finally, we used GRADE to rate the quality of evidence.

For ARDS, our review showed similar results to the 1 other published systematic review²⁹ that included the latest published studies. For CAP, the results on which we focus are similar to those of other recent reviews⁸⁶⁻⁸⁹ that showed that corticosteroids may

reduce mortality and length of hospital stay, and increase hyperglycemia.

The findings for influenza are consistent with other previous systematic reviews⁹⁰⁻⁹² that also found increased mortality associated with corticosteroid use. One review⁹⁰ focused on patients with influenza pneumonia only, excluding those with mild illness or those in the ICU. The results showed that corticosteroids were associated with higher mortality. In contrast, another review⁹² studied severe forms of influenza and reported that among studies with adjusted estimates, results showed no statistically significant difference between the corticosteroid and control groups.

Limitations

The limitations of this study are largely those of the underlying evidence, which is either of low or, for benefits, very low quality for the most part. One could argue that we should have broadened our consideration of indirect evidence. For instance, we could have included *Pneumocystis jiroveci* pneumonia, in which evidence supports corticosteroid use. Our threshold was based on patients with viral pneumonia being included in the population, which is clearly the case for SARS, MERS and influenza, but also true for ARDS and CAP.

Similarly, with respect to harms, consideration of evidence from RCTs of short-term use of corticosteroids in other conditions might have strengthened our findings. We have, however, moderate-quality evidence in patients with ARDS of no important increase in superinfection, and low-quality evidence of an increase in serious hyperglycemia. Low-quality evidence suggests a possible small increase in neuropsychiatric events. For this outcome, evidence from other conditions might have been particularly helpful.

Conclusion

Given the paucity of direct evidence and the limitations of indirect evidence, it is critical for clinicians and researchers to cooperate in conducting high-quality studies, in particular large and rigorous RCTs, to evaluate the effect of corticosteroids in both patients with COVID-19 and ARDS and patients with severe COVID-19 but who are not critically ill. Fortunately, RCTs, including those that address corticosteroid treatment, are ongoing.

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Affiliations: Department of Health Research Methods, Evidence and Impact (Ye, Tangamornsuksan, Rochweg, Guyatt, Colunga-Lozano, Yao, Motaghi, Fang, Xiao), McMaster University, Hamilton, Ont.; Department of Pharmacy (Wang), Beijing Chaoyang Hospital, Capital Medical University, Beijing, China; Department of Clinical Medicine (Colunga-Lozano), Health Science Center, Universidad de Guadalajara, Guadalajara, Mexico; Department of Community Medicine (Prasad), North DMC Medical College, New Delhi, India; Faculty of Medicine and Public Health (Tangamornsuksan), HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand; Department of Medicine (Rochweg); DeGroote Institute for Pain Research and Care (Couban), McMaster University, Hamilton, Ont.; Department of Clinical Pharmacy (Ghadimi), Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; Chair of Epidemiology and Preventive Medicine Jagiellonian (Bala), University Medical College, Krakow, Poland; Biostatistics Department (Gomaa), High institute of Public Health, Alexandria University, Alexandria, Egypt; Drug Information Center (Gomaa), Tanta Chest Hospital, Ministry of Health and Population, Egypt; Clinical Medicine College of Acupuncture, Moxibustion and Rehabilitation (Fang), Guangzhou University of Chinese Medicine, Guangdong, China; West China School of Nursing (Xiao), West China Hospital, Sichuan University, China

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Correspondence to: Gordon Guyatt, guyatt@mcmaster.ca