Appendix 1 (as supplied by the authors): Summary of findings for corticosteroids

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

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	HR 0.41 (95% CI 0.20 to 0.83) Based on data from 84 COVID-19 patients with ARDS in 1 observational study	61.8%	-29.2% (-44.3% to -6.8%)	Very low (Serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality

Note: ARDS = acute respiratory distress syndrome, HR = hazard ratio, CI = confidence interval.

1Mortality baseline risk from COVID-19 ARDS patients without corticosteroid treatment – Wu C, et al. doi:10.1001/jamainternmed.2020.0994.

2Observational study started at low quality of evidence. Although confidence interval appears narrow the small sample size and implausibly large effect led to rating down for imprecision.

Appendix to: Ye Z, Rochwerg B, Wang Y, et al. Treatment of patients with nonsevere and severe coronarivus disease 2019: an evidence-based guideline.
CMAJ 2020. doi: 10.1503/cmaj.200648.

Table 2: GRADE summary of findings: Corticosteroids in COVID-19 with ARDS, indirect evidence from randomized controlled trials of patients with ARDS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	RR 0.72 (95% CI 0.55 to 0.93) Based on data from 851 ARDS patients in 7 RCTs	61.8%	- 17.3% (-27.8% to - 4.3%)	Low (Very serious indirectness[2])	Corticosteroids may result in a large reduction in mortality
Length of ICU stay	Based on data from 297 patients in 3 RCTs	The median duration of length of ICU was 8.0 days	MD 0.1 days (-3.0 to 3.2)	Very Low (Serious inconsistency, very serious indirectness and serious imprecision[3])	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	The median duration of length of stay was 18.0 days	MD -3.6 days (-7.2 to - 0.02)	Very Low (Very serious indirectness and serious imprecision[4])	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	The median duration of mechanical ventilation was 14.5 days	MD -4.8 days (-7.0 to - 2.6)	Low (Very serious indirectness[2])	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	67.6%	8.1% (0.7% to 16.2%)	Low (Serious indirectness and serious imprecision[5])	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	26.4%	-3.9% (-10% to 4.7%)	Low (Serious indirectness, serious imprecision[6])	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	14.0%	-4.0% (-9.8% to 10.2%)	Low (Serious indirectness, serious imprecision[6])	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	33.0%	-5.9% (-10.8% to 0.6%)	Moderate (Serious indirectness[7])	Corticosteroids probably do not increase superinfection events

Note: RR = risk ratio, CI = confidence interval, RCTs = randomized controlled trials, MD = mean difference, ICU = intensive care unit.

1Mortality baseline risk from COVID-19 ARDS patients without corticosteroid treatment – Wu C, et al. doi:10.1001/jamainternmed.2020.0994. The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events obtained from the median estimate from the control group in the included RCTs.

2We rated down two levels due to indirectness; the ARDS etiology across the studies is inconsistent and might not represent the COVID-19 population.

3We rated down two levels due to indirectness; one for inconsistency (I^2=73%, heterogeneity p-value 0.03) and one for imprecision because effect estimate consistent with benefit or harm.

4We rated down two levels due to indirectness and one for of imprecision due to the confidence interval including a trivial reduction in hospital stay.

5We rated down by one level due to indirectness, as we do not expect the COVID-19 population differs as much from other populations in adverse effects as in benefits; and we rated down by one level for imprecision due to the lower confidence interval, 0.7% representing an unimportant increase in hyperglycemia.

6We rated down by one level due to indirectness as in 4; we rated down by one level for imprecision, effect estimate consistent with benefit or harm.

7We rated down by one level due to indirectness as in 4; we did not rate down due to imprecision because the largest degree of harm consistent with the evidence is 7 in 1,000, which we judge unimportant.

Table 3: GRADE summary of findings: Corticosteroids in severe COVID-19, direct evidence from observational studies of severe COVID-19 patients

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	HR 2.30 (95% CI 1.00 to 5.29) Based on data from 331 severe COVID-19 patients in 2 observational studies	10.4%	11.9% (0 to 33.7%)	Very low (Serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality

Note: HR = hazard ratio, CI = confidence interval.

1Baseline risk from a study of the severe COVID-19 patients without corticosteroids use - Guan W et al. doi: 10.1056/NEJMoa2002032.

2Observational study started at low quality of evidence. We rated down one level due to serious imprecision (wide confidence interval).

Table 4: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from randomized controlled trials and observational studies of patients hospitalized 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 SARS patients in 2 observational studies	10.4%[1]	-1.7% (-6.0% to 6.3%)	Very low (Serious indirectness and serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality
Median time for CoV RNA to become undetectable in plasma	Based on data from 16 SARS patients in 1 RCT	8.0 days[3]	MD 4.0 days (2.0 to 6.0)	Very low (Serious risk of bias, serious indirectness and serious imprecision[4])	We are very uncertain of the effect of corticosteroids on time for CoV RNA to become undetectable in plasma

Note: SARS = severe acute respiratory syndrome, HR = hazard ratio, CI = confidence interval, RNA = ribonucleic acid, RCT = randomized controlled trial, MD = mean difference.

1Baseline risk from a study of the severe COVID-19 patients without corticosteroids use - Guan W et al. doi: 10.1056/NEJMoa2002032.

2Observational studies start as low quality of evidence. We rated down one level due to serious indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from SARS patients) and one level due to serious imprecision (the confidence interval includes both an important benefit and an important harm).

3Baseline risk from the randomized trial which reported median time for SAR-CoV RNA to become undetectable in plasma for no corticosteroids group - Lee N, et al. doi:10.1016/j.jcv.2004.07.006.

4Randomized trial started at high quality of evidence. We rated down due to serious risk of bias, serious indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from SARS patients) and serious imprecision (because of small sample size).

Table 5: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from observational studies of patients hospitalized 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 MERS patients in 1 observational study	10.4%[1]	-2.4% (-4.7% to 0.6%)	Very low (Serious indirectness and serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality
CoV RNA clearance	HR 0.35 (95% CI 0.17 to 0.72) Based on data from 189 MERS patients in 1 observational study	29.8%[3]	-18.2% (-24.0% to -7.3%)	Very low (Serious imprecision[4])	We are very uncertain of the effect of corticosteroids on CoV RNA clearance

Note: MERS = middle east respiratory syndrome, OR = odds ratio, RNA = ribonucleic acid, HR = hazard ratio.

1Baseline risk from a study of the severe COVID-19 patients without corticosteroids use: Guan W et al. doi: 10.1056/NEJMoa2002032.

2Observational studies started at low quality of evidence. We rated down one level due to serious indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from MERS patients), and one level due to serious imprecision (the confidence interval includes both a trivial and an important effect).

3Baseline risk from the observational study which reported MERS-CoV RNA clearance for no corticosteroids group: Arabi YM et al. doi: 10.1164/rccm.201706-1172OC.

4Observational studies started at low quality of evidence. We rated down one level due to serious imprecision because of the small sample size.

Table 6: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from observational studies of patients hospitalized 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 in 11 observational studies	10.4%[3]	6.1% (2.8% to 10.0%)	Very Low (Serious indirectness[1])	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	7.2%[4]	10.3% (3.3% to 20.5%)	Very low (Serious risk of bias and indirectness[2])	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	41.8%[4]	38.1% (15.0% to 50.6%)	Very low (serious risk of bias and indirectness[2])	We are very uncertain of the effect of corticosteroids on need for mechanical ventilation

1Observational studies started at low quality of evidence. Additional concern was indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from hospitalized influenza patients).

2Observational studies started at low quality of evidence. Additional concerns included high risk of indication bias because unadjusted estimates included and indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from hospitalized Influenza patients).

3Baseline risk from a study of the severe COVID-19 patients without corticosteroids use: Guan W et al. doi: 10.1056/NEJMoa2002032.

4Baseline risk comes from median effect of the control group in the included studies.

Table 7: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from randomized controlled trials of patients hospitalized with CAP

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	RR 0.70 (95% CI 0.50 to 0.98) Based on data from 2034 patients in 13 RCTs	10.4%	-3.1% (-0.2% to -5.2%)	Very low (Very serious indirectness[2] 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	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[3])	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	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[4])	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	18.0%	-10.4% (-13.8% to -4.3%)	Low (Very serious indirectness[2])	Corticosteroids may reduce need for mechanical ventilation
Duration of mechanical ventilation	Based on data from 199 patients in 5 RCTs	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[5])	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	9.2%	5.7% (0.18% to 15.3%)	Low (Serious indirectness[6])	Corticosteroids probably 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	3.0%	-0.03% (-1.7% to 3.7%)	Low (Serious indirectness and serious imprecison[6])	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	1.6%	1.4% (-0.5% to 7%)	Low (Serious indirectness and serious imprecison[6])	Corticosteroids may result in a small increase neuropsychiatric events
Superinfection	1.31 (95% CI 0.69 to 2.50) Based on data from 1500 patients in 8 RCTs	3.7%	1.1% (-1.1% to 5.5%)	Low (Serious indirectness and serious imprecison[6])	Corticosteroids may result in a small or no increase superinfection events

Note: RR = risk ratio, CI = confidence interval, RCTs = randomized controlled trials, MD = mean difference.

1Mortality baseline risk was obtained from COVID-19 ARDS patients without corticosteroid treatment – Guan 10.1056/NEJMoa2002032. The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events comes from median effect of the control group in the included RCTs.

2We rated down two levels due to indirectness; the pneumonia etiology 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 restricted to those with severe pneumonia.

3We rated down two levels due to indirectness; one for inconsistency (I^2=76%, heterogeneity p-value 0.0001); and one for of imprecision because the effect estimates are consistent with important benefit and harm.

4We rated down two levels due to indirectness; one for inconsistency (I^2=47%, heterogeneity p-value 0.006) and one for imprecision because the lower confidence interval includes important benefit and important harm.

5We rated down one level due to risk of bias and two levels due to indirectness. We did not rate down due to inconsistency, the effect estimates were in the same direction, despite the I2 54% and the p value of 0.07.

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

.