Appendix 3 (as supplied by the authors)

GRADE summary of findings on antivirals in COVID-19

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Table 1. GRADE summary of findings: Ribavirin in non-severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Symptomatic anemia	OR 3.00 (95%CI 1.77 to 5.16) Based on data from 306 SARS patients with mixed severity in 1 observational study	296[1]	262 (131 to 388)	Very low ⊕ O O O (Serious indirectness)[2]	Ribavirin may result in a large increase in anemia, but we are very uncertain about the effect of ribavirin on symptomatic anemia.
Symptomatic bradycardia	OR 2.30 (95%CI 1.21 to 4.20) Based on data from 306 SARS patients with mixed severity in 1 observational study	171[1]	151 (29 to 293)	Very low ⊕ O O O (Serious indirectness)[3]	Ribavirin may result in a large increase in bradycardia, but we are very uncertain about the effect of ribavirin on symptomatic bradycardia.

[1]Baseline risk from non-severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Muller MP. doi: 10.1592/phco.27.4.494).
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic anemia). Anemia was defined as decrease in hemoglobin level of 2 g/dl.
[3]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic bradycardia). Bradycardia was defined as heart rate < 55 bpm.

Table 2. GRADE summary of findings: Ribavirin in severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	OR 0.66 (95%CI 0.04 to 12.36) Based on data from 51 MERS patients with mixed severity in 1 observational study	104[1]	-33 (-99 to 485)	Very low ⊕ O O O (Serious imprecision and indirectness)[2]	We are very uncertain of the effect of ribavirin on mortality
Mortality	OR 0.83 (95%CI 0.49 to 1.41) Based on data from 1334 SARS patients with mixed severity in 2 observational studies	104[1]	-16 (-50 to 37)	Very low ⊕ O O O (Very serious indirectness and serious imprecision)[3]	We are very uncertain of the effect of ribavirin on mortality
Symptomatic anemia	OR 3.00 (95%CI 1.77 to 5.16) Based on data from 306 SARS patients with mixed severity in 1 observational study	296[4]	262 (131 to 388)	Very low ⊕ O O O (Serious indirectness)[5]	Ribavirin may result in a large increase in anemia, but we are very uncertain about the effect of ribavirin on symptomatic anemia.
Symptomatic bradycardia	OR 2.30 (95%CI 1.21 to 4.20) Based on data from 306 SARS patients with mixed severity in 1 observational study	171[4]	151 (29 to 293)	Very low ⊕ O O O (Serious indirectness)[6]	Ribavirin may result in a large increase in bradycardia, but we are very uncertain about the effect of ribavirin in symptomatic bradycardia.

[1]We chose the baseline risk from severe COVID-19 patients in: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: indirectness (MERS patients), and imprecision (Wide confidence interval includes no difference).
[3]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: imprecision (Wide confidence interval includes no difference), and for two issues of indirectness (SARS patients. OR was estimated from HR in one study).
[4]Baseline risk from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Muller MP. doi: 10.1592/phco.27.4.494).
[5]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic anemia). Anemia was defined as decrease in hemoglobin level of 2 g/dl.
[6]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic bradycardia). Bradycardia was defined as heart rate < 55 bpm.

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Table 3. GRADE summary of findings: Hydroxychloroquine in non-severe COVID-19, direct evidence from three RCTs of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Viral clearance at day 14	RR 0.98 (95%CI 0.89 to 1.07) Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	714[1]	-14 (-79 to 50)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on viral clearance at day 14.
Duration of fever (day)	Based on data from 39 non-severe patients in 1 RCT	3.2[3]	-1 (-1.64 to -0.36)	Very low ⊕ O O O (Serious risk of bias, imprecision and indirectness)[4]	We are very uncertain of the effect of hydroxychloroquine on duration of fever.
Progressing from non-severe to severe	RR 0.96 (95%CI 0.10 to 9.66) Based on data from 240 non-severe patients in 3 RCTs	143[1]	-6 (-129 to 857)	Very low ⊕ O O O (Serious risk of bias, indirectness and very serious imprecision)[5]	We are very uncertain of the effect of hydroxychloroquine on progressing from non-severe to severe.
Clinical recovery at day 7	RR 1.10 (95%CI 0.44 to 2.77) Based on data from 117 non-severe patients and 2 severe patients in 1 RCT	127[6]	13 (-71 to 225)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[7]	We are very uncertain of the effect of hydroxychloroquine on clinical recovery at day 7.
Diarrhea	Not applicable, no events in control group Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	0[1]	106 (40 to 171)	Low ⊕ ⊕ O O (Serious risk of bias and indirectness)[8]	Hydroxychloroquine may increase diarrhea.
Headache	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[3]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on headache.
Rash	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[10]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on rash.
Nausea	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[10]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on nausea.
Vomiting	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[10]	29 (0 to 68)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on vomiting.
Blurred vision	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[11]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on blurred vision.

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[1]We chose the baseline risk from non-severe COVID-19 patients in the study from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from the referred study were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.

[2]We rated down three levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference), one for indirectness (Both intervention and control patients used other antiviral agents. Possible synergic effect between hydroxychloroquine and other antiviral agents).

[3]We used the control group of the study itself to serve as baseline risk (Chen Z. doi: 10.1101/2020.03.22.20040758).

[4]We rated down three levels: one for risk of bias (No blinding on patients), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), one for imprecision (Wide confidence interval includes very small benefit).

[5]We rated down for the following: risk of bias (No blinding on patients in one study. Open-label in other studies), indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), and imprecision (Very wide confidence interval includes important benefit and harm).

[6]We used the control group of the study itself to serve as baseline risk. Clinical recovery was defined as: resolving from fever to an axillary temperature of ≤ 36.6; normalization of SpO2 (>94% on room air); disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production and shortness of breath.

[7]We rated down three levels: one for risk of bias (open-label study), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), one for imprecision (Wide confidence interval includes no difference).

[8]We rated down two levels: one for risk of bias (open-label study), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents).

[9]We rated down three levels: one for risk of bias (No blinding on patients), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), and one for imprecision (Wide confidence interval includes no difference).

[10]Baseline risk data from non-severe COVID-19 patients is not available. We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe.

[11]We used the control group of the study itself to serve as baseline risk (Tang W. doi: 10.1101/2020.04.10.20060558).

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Table 4. GRADE summary of findings: Hydroxychloroquine in severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	RR 1.48 (95%CI 0.42 to 5.24) Based on data from 181 severe patients and 255 patients with mixed severity in 2 observational studies	104[1]	50 (-60 to 441)	Very low ⊕ O O O (Very serious imprecision, inconsistency and serious indirectness)[2]	We are very uncertain of the effect of hydroxychloroquine on mortality.
Mechanical ventilation	HR 1.43 (95%CI 0.53 to 3.79) Based on data from 255 patients with mixed severity in 1 observational study	387[1]	116 (-159 to 457)	Very low ⊕ O O O (Very serious imprecision and serious indirectness)[3]	We are very uncertain of the effect of hydroxychloroquine on mechanical ventilation.
Viral clearance at day 14	RR 0.98 (95%CI 0.89 to 1.07) Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	563[4]	-11 (-62 to 39)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[5]	We are very uncertain of the effect of hydroxychloroquine on viral clearance at day 14.
Diarrhea	Not applicable, no events in control group Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	0[4]	106 (40 to 171)	Low ⊕ ⊕ O O (Serious risk of bias and indirectness)[6]	Hydroxychloroquine may increase diarrhea.
Headache	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[7]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[8]	We are very uncertain of the effect of hydroxychloroquine on headache.
Rash	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[4]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[8]	We are very uncertain of the effect of hydroxychloroquine on rash.
Nausea	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[4]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on nausea.
Vomiting	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[4]	29 (0 to 68)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on vomiting.
Blurred vision	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[10]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on blurred vision.

[1]We chose the baseline risk from severe COVID-19 patients in the study providing the relative effect estimate: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for imprecision (Very wide confidence interval included important benefit and harm), inconsistency (Two studies reported different directions of mortality), and indirectness (RR was estimated from HR in one study).

[3]Observational studies started at low certainty/quality of evidence. In addition, we rated down for imprecision (Very wide confidence interval included important benefit and harm) and indirectness (Risk difference was estimated from HR).

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[4]We chose the baseline risk from severe COVID-19 patients in the study from Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe.

[5]We rated down for the following: risk of bias (Open-label study), imprecision (Wide confidence interval includes no difference), and for two issues of indirectness (Both intervention and control patients used other antiviral agents. Possible synergic effect between hydroxychloroquine and other antiviral agents. Data came from non-severe COVID-19 patients).

[6]We rated down two levels: one for risk of bias (open-label study), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents).

[7]Baseline risk from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Chen Z. doi: 10.1101/2020.03.22.20040758).

[8]We rated down three levels: one for risk of bias (No blinding on patients), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), and one for imprecision (Wide confidence interval includes no difference).

[9]We rated down three levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference), one for indirectness (Both intervention and control patients used other antiviral agents. Possible synergic effect between hydroxychloroquine and other antiviral agents).

[10]Baseline risk data from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Tang W. doi: 10.1101/2020.04.10.20060558).

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Table 5. GRADE summary of findings: Umifenovir in non-severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Viral clearance at day 14	RR 1.23 (95%CI 0.74 to 2.03) Based on data from 23 non-severe patients in 1 RCT	714[1]	164 (-186 to 286)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on viral clearance at day 14.
Cough alleviation at day 7	RR 1.33 (95%CI 0.35 to 5.13) Based on data from 15 non-severe patients in 1 RCT	333[1]	110 (-216 to 667)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on cough alleviation at day 7.
Fever at day 7	RR 0.66 (95%CI 0.31 to 1.40) Based on data from 11 non-severe patients in 1 RCT	1000[1]	-340 (-690 to 0)	Very low ⊕ O O O (Very serious imprecision)[3]	We are very uncertain of the effect of umifenovir on fever at day 7.
Progressing from non-severe to severe	RR 0.88 (95%CI 0.09 to 8.14) Based on data from 28 non-severe patients in 1 RCT	143[1]	-17 (-130 to 857)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on progressing from non-severe to severe.
Diarrhea	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[1]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on diarrhea.
Decreased appetite	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[1]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on decreased appetite.

[1]We used the baseline risk from non-severe COVID-19 patients from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from Li's study were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.
[2]We rated down three levels for imprecision (Very wide confidence interval includes important benefit and harm).
[3]We rated down three levels for imprecision (Very wide confidence interval includes important benefit).

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Table 6. GRADE summary of findings: Umifenovir in severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	OR 0.18 (95%CI 0.08 to 0.45) Based on data from 504 patients with mixed severity in 1 observational study	104[1]	-84 (-95 to -54)	Very low ⊕ O O O (Serious risk of bias)[2]	We are very uncertain of the effect of umifenovir on mortality.
Viral clearance at day 14	RR 1.23 (95%CI 0.74 to 2.03) Based on data from 23 non-severe patients in 1 RCT	563[3]	129 (-146 to 437)	Very low ⊕ O O O (Very serious imprecision and serious indirectness)[4]	We are very uncertain of the effect of umifenovir on viral clearance at day 14.
Diarrhea	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[3]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[5]	We are very uncertain of the effect of umifenovir on diarrhea.
Decreased appetite	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[3]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[5]	We are very uncertain of the effect of umifenovir on decreased appetite.

[1]We chose the baseline risk from severe COVID-19 patients in: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for risk of bias (Inadequate adjustment for disease severity: failed to adjust for respiratory rate, and cointerventions with oxygen, mechanical ventilation) and ambiguous definition of admission data as a predictor.

[3]We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe.

[4]We rated down three levels: two for imprecision (Very wide confidence interval includes important benefit and harm), one for indirectness (Data came from non-severe COVID-19 patients).

[5]We rated down three levels for imprecision (Very wide confidence interval includes important benefit and harm).

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Table 7. GRADE summary of findings: Favipiravir in non-severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Clinical recovery at day 7	RR 1.18 (95%CI 0.95 to 1.48) Based on data from 236 patients with mixed severity (88.6% non-severe) in 1 RCT comparing favipiravir with umifenovir	517[1]	93 (-26 to 248)	Very low ⊕ O O O (Serious risk of bias, indirectness and very serious imprecision)[2]	We are very uncertain of the effect of favipiravir on clinical recovery at day 7.
Viral clearance at day 7	HR 3.43 (95%CI 1.16 to 10.15) Based on data from 80 non-severe patients in 1 observational study comparing favipiravir with lopinavir/ritonavir	714[3]	272 (52 to 286)	Very low ⊕ O O O (Very serious indirectness)[4]	We are very uncertain of the effect of favipiravir on viral clearance at day 7.

[1]The control group of the study itself serves as baseline risk (Chen C. doi: 10.1101/2020.03.17.20037432).
[2]We rated down for the following: risk of bias (open-label study), indirectness (compared with umifenovir), and imprecision (very wide confidence interval includes important benefit and harm). Clinical recovery was defined as: axillary temperature ≤ 36.6 °C; respiratory frequency ≤ 24 times/min; Oxygen saturation ≥ 98% without oxygen inhalation; mild or no cough.
[3]We used the baseline risk from non-severe COVID-19 patients from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from Li et al. were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.
[4]Observational studies started at low certainty/quality of evidence. In addition, we rated down for three issues of indirectness (Both intervention and control patients used interferon. Possible synergic effect between favipiravir and interferon. Favipiravir was compared with lopinavir/ritonavir. Risk difference was estimated from HR).

Table 8. GRADE summary of findings: Favipiravir in severe COVID-19, direct evidence from one observational study of patients with COVID-19

Outcomes	Relative effects	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Viral clearance at day 7	HR 3.43 (95%CI 1.16 to 10.15) Based on data from 80 non-severe patients in 1 observational study comparing favipiravir with lopinavir/ritonavir	324	415 (41 to 657)	Very low ⊕ O O O (Very serious indirectness)[2]	We are very uncertain of the effect of favipiravir on viral clearance at day 7.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe. The baseline risk was viral clearance at day 5 instead of day 7.
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for four issues of indirectness (Both intervention and control patients used interferon. Possible synergic effect between favipiravir and interferon. Favipiravir was compared with lopinavir/ritonavir. Risk difference was estimated from HR. Data came from non-severe COVID-19 patients).

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Table 9. GRADE summary of findings: Favipiravir in non-severe COVID-19, indirect evidence from one RCT of patients with influenza

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Diarrhea	RR 0.94 (95%CI 0.39 to 2.26) Based on data from 386 influenza patients with unspecified severity in 1 RCT	51	-3 (-31 to 64)	Low ⊕⊕OO (Serious indirectness and imprecision)[2]	Favipiravir may not increase diarrhea.

[1]We used the control group of the study itself to serve as baseline risk (NCT01068912. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01068912?term=FAVIPIRAVIR&rslt=With&draw=2&rank=1).
[2]We rated down two levels: one for indirectness (Influenza patients), one for imprecision (Wide confidence interval includes no difference).

Table 10. GRADE summary of findings: Favipiravir in severe COVID-19, indirect evidence from one RCT of patients with influenza

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Diarrhea	RR 0.94 (95%CI 0.39 to 2.26) Based on data from 386 influenza patients with unspecified severity in 1 RCT	51	-3 (-31 to 64)	Low ⊕⊕OO (Serious indirectness and imprecision)[2]	Favipiravir may not increase diarrhea.

[1]We used the control group of the study itself to serve as baseline risk (NCT01068912. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01068912?term=FAVIPIRAVIR&rslt=With&draw=2&rank=1).
[2]We rated down two levels: one for indirectness (Influenza patients), one for imprecision (Wide confidence interval includes no difference).

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Table 11. GRADE summary of findings: Interferon-α in non-severe COVID-19, direct evidence from one observational study of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Time-to viral clearance (day)	Based on data from 70 patients with mixed severity in 1 observational study	7[1]	-1.1 (-2.32 to 0.11)	Very low ⊕ O O O (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on time-to viral clearance.
Length of hospital stay (day)	Based on data from 70 patients with mixed severity in 1 observational study	11[3]	-2.1 (-4.89 to 0.69)	Very low ⊕ O O O (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on length of hospital stay.

[1]We chose the baseline risk from non-severe COVID-19 patients in the study from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from Li were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe..
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: indirectness (Patients in both groups used umifenovir. Possibe synergic effect between interferon and umifenovir), and imprecision (Wide confidence interval includes no difference).
[3]We chose the baseline risk from non-severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The non-severe patients from the referred study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of non-severe.

Table 12. GRADE summary of findings: Interferon-α in severe COVID-19, direct evidence from one observational study of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Time-to viral clearance (day)	Based on data from 70 patients with mixed severity in 1 observational study	29[1]	-4.60 (-7 to 0.45)	Very low ⊕ O O O (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on time-to viral clearance.
Length of hospital stay (day)	Based on data from 70 patients with mixed severity in 1 observational study	13[3]	-2.48 (-5.78 to 0.82)	Very low ⊕ O O O (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on length of hospital stay.

[1]Baseline risk from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Zhou Q. doi: 2020.04.06.20042580).
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: indirectness (Patients in both groups used umifenovir. Possible synergic effect between interferon and umifenovir), and imprecision (Wide confidence interval includes no difference).
[3]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from the referred study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

Table 13. GRADE summary of findings: Interferon-α in non-severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Leukopenia requiring G-CSF	RR 0.84 (95%CI 0.45 to 1.56) Based on data from 87 SARS patients with mixed severity in 1 observational study	348[1]	-56 (-191 to 195)	Very low ⊕ O O O (Serious risk of bias and very serious imprecision)[2]	We are very uncertain of the effect of interferon-α on leukopenia requiring G-CSF.

[1]Baseline risk from non-severe COVID-19 patients is not available. The control group of the study itself serves as the baseline risk (Li J. doi: 10.3760/cma.j.issn.1008-6315.2005.02.007).

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: risk of bias (Unadjusted outcome value), and imprecision (Very wide confidence interval includes important benefit and harm).

Table 14. GRADE summary of findings: Interferon-α in severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	OR 0.23 (95%CI 0.04 to 1.32) Based on data from 83 MERS patients with mixed severity in 2 observational studies	104[1]	-78 (-99 to 29)	Very Low ⊕ O O O (Serious imprecision and indirectness)[2]	We are very uncertain of the effect of interferon-α on mortality.
Leukopenia requiring G-CSF	RR 0.84 (95%CI 0.45 to 1.56) Based on data from 87 SARS patients with mixed severity in 1 observational study	348[3]	-56 (-191 to 195)	Very low ⊕ O O O (Serious risk of bias and very serious imprecision)[4]	We are very uncertain of the effect of interferon-α on leukopenia requiring G-CSF.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. We rated down two levels: one for indirectness (MERS patients), one for imprecision (Wide confidence interval includes no difference).

[3]Baseline risk from severe COVID-19 patients is not available. The control group of the study itself serves as the baseline risk (Li J. doi: 10.3760/cma.j.issn.1008-6315.2005.02.007).

[4]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: risk of bias (Unadjusted outcome value), and imprecision (Very wide confidence interval includes important benefit and harm).

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Table 15. GRADE summary of findings: Interferon-β in severe COVID-19, indirect evidence from observational studies of patients with MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Mortality	OR 0.37 (95%CI 0.07 to 2.05) Based on data from 83 MERS patients with mixed severity in 2 observational studies	104	-63 (-96 to 88)	Very low ⊕OOO (Serious imprecision and indirectness)[2]	We are very uncertain of the effect of interferon-β on mortality.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down two levels: one for indirectness (MERS patients), one for imprecision (Wide confidence interval includes no difference).

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Table 16. GRADE summary of findings: Lopinavir/ritonavir in non-severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Length of hospital stay (day)	Based on data from 199 severe patients in 1 RCT	11[1]	-0.69 (-1.38 to 0)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of lopinavir/ritonavir on length of hospital stay
Viral clearance at day 14	RR 0.99 (95%CI 0.76 to 1.29) Based on data from 158 patients (130 severe and 28 non-severe) in 2 RCTs	714[3]	-7 (-171 to 207)	Low ⊕ ⊕ O O (Serious risk of bias and imprecision)[4]	Lopinavir/ritonavir may have little or no impact on viral clearance at day 14.
Viral clearance at day 23	OR 2.42 (95%CI 1.10 to 5.36) Based on data from 120 patients with mixed severity in 1 observational study	366[5]	217 (22 to 390)	Very low ⊕ O O O (Serious risk of bias)[6]	We are very uncertain of the effect of lopinavir/ritonavir on viral clearance at day 23.
Cough alleviation at day 7	RR 1.42 (95%CI 0.42 to 4.85) Based on data from 25 non-severe patients in 1 RCT	333[3]	140 (-193 to 667)	Very low ⊕ O O O (Very serious imprecision)[7]	We are very uncertain of the effect of lopinavir/ritonavir on cough alleviation at day 7.
Progressing from non-severe to severe	RR 2.67 (95%CI 0.40 to 17.74) Based on data from 28 non-severe patients in 1 RCT	143[3]	239 (-86 to 857)	Very low ⊕ O O O (Very serious imprecision)[7]	We are very uncertain of the effect of lopinavir/ritonavir on progressing from non-severe to severe.
Fever at day 7	RR 0.85 (95%CI 0.46 to 1.58) Based on data from 13 non-severe patients in 1 RCT	1000[3]	-150 (-540 to 0)	Very low ⊕ O O O (Very serious imprecision)[8]	We are very uncertain of the effect of lopinavir/ritonavir on fever at day 7.
Diarrhea	Not applicable, no events in control group. Based on data from 222 patients (194 severe and 28 non-severe) in 2 RCTs	0[3]	60 (17 to 104)	Moderate ⊕ ⊕ ⊕ O (Serious risk of bias)[9]	Lopinavir/ritonavir probably increases diarrhea.
Stomach ache	RR 4.17 (95%CI 0.47 to 36.62) Based on data from 194 severe patients in 1 RCT	10[10]	32 (-5 to 356)	Very low ⊕ O O O (Serious risk of bias and very serious imprecision)[11]	We are very uncertain of the effect of lopinavir/ritonavir on stomach ache.
Nausea	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[10]	95 (36 to 154)	Moderate ⊕ ⊕ ⊕ O (Serious risk of bias)[9]	Lopinavir/ritonavir probably increases nausea.
Vomiting	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[10]	63 (14 to 112)	Moderate ⊕ ⊕ ⊕ O (Serious risk of bias)[9]	Lopinavir/ritonavir probably increases vomiting.

[1]We chose the baseline risk from non-severe COVID-19 patients from: Guan WJ. doi: 10.1056/NEJMoa2002032. The non-severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of non-severe.
[2]We rated down three levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference), one for indirectness (Data from severe COVID-19 patients).
[3]We used the baseline risk from non-severe COVID-19 patients from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from the referred study were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.

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[4]We rated down two levels: one for risk of bias (One of the study with 83% weight was an open-label study), one for imprecision (Wide confidence interval includes no difference).
[5]Baseline risk from non-severe COVID-19 patients is not available. We used the study itself to serve as baseline risk (Yan D. doi: 10.1101/2020.03.22.20040832).
[6]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for risk of bias (Did not adjust for disease severity).
[7]We rated down three levels for imprecision (Very wide confidence interval includes important benefit and important harm).
[8]We rated down three levels for imprecision (Very wide confidence interval includes important benefit).
[9]We rated down one level for risk of bias (Open-label study).
[10]Baseline risk from non-severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Cao B. doi: 10.1056/NEJMoa2001282). The population of the study from Cao et al. was severe COVID-19 patient.
[11]We rated down three levels: one for risk of bias (Open-label study), two for imprecision (Very wide confidence interval includes important benefit and important harm).

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Table 17. GRADE summary of findings: Lopinavir/ritonavir in severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	RR 0.77 (95%CI 0.45 to 1.30) Based on data from 199 severe patients in 1 RCT	104[1]	-24 (-57 to 31)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may reduce mortality.
Mechanical ventilation	RR 0.83 (95%CI 0.52 to 1.34) Based on data from 199 severe patients in 1 RCT	387[1]	-66 (-186 to 132)	Very low ⊕OOO (Serious risk of bias and very serious imprecision)[3]	We are very uncertain of the effect of lopinavir/ritonavir on mechanical ventilation.
ICU length of stay (day)	Based on data from 199 severe patients in 1 RCT	11[4]	-5 (-9 to 0)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may largely decrease ICU length of stay.
Length of hospital stay (day)	Based on data from 199 severe patients in 1 RCT	13[1]	-0.81 (-1.63 to 0)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may reduce length of hospital stay slightly.
Viral clearance at day 14	RR 0.99 (95%CI 0.76 to 1.29) Based on data from 158 patients (130 severe and 28 non-severe) in 2 RCTs	563[4]	-6 (-135 to 163)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may have little or no impact on viral clearance at day 14.
Viral clearance at day 23	OR 2.42 (95%CI 1.10 to 5.36) Based on data from 120 patients with mixed severity in 1 observational study	577[5]	190 (23 to 303)	Very low ⊕OOO (Serious risk of bias)[6]	We are very uncertain of the effect of lopinavir/ritonavir on viral clearance at day 23.
Diarrhea	Not applicable, no events in control group. Based on data from 222 patients (194 severe and 28 non-severe) in 2 RCTs	0[4]	60 (17 to 104)	Moderate ⊕⊕⊕O (Serious risk of bias)[7]	Lopinavir/ritonavir probably increases diarrhea.
Stomach ache	RR 4.17 (95%CI 0.47 to 36.62) Based on data from 194 severe patients in 1 RCT	10[4]	32 (-5 to 356)	Very low ⊕OOO (Serious risk of bias and very serious imprecision)[8]	We are very uncertain of the effect of lopinavir/ritonavir on stomach ache.
Nausea	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[4]	95 (36 to 154)	Moderate ⊕⊕⊕O (Serious risk of bias)[7]	Lopinavir/ritonavir probably increases nausea.
Vomiting	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[4]	63 (14 to 112)	Moderate ⊕⊕⊕O (Serious risk of bias)[7]	Lopinavir/ritonavir probably increases vomiting.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.
[2]We rated down two levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference).
[3]We rated down three levels: one for risk of bias (Open-label study), two for imprecision (Very wide confidence interval includes important harm).
[4]We used the control group of the study itself to serve as baseline risk (Cao B. doi: 10.1056/NEJMoa2001282).

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[5]We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe. The baseline risk was viral clearance at day 21 instead of day 23.
[6]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for risk of bias (Did not adjust for disease severity).
[7]We rated down one level for risk of bias (Open-label study).
[8]We rated down three levels: one for risk of bias (Open-label study), two for imprecision (Very wide confidence interval includes important benefit and important harm).

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Appendix to: Ye Z, Rochwerg B, Wang Y, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline.
CMAJ 2020. doi: 10.1503/cmaj.200648. Copyright © 2020 Joule Inc. or its licensors