**South African National Department of Health**
**Brief Report of Rapid Review**
**Component: COVID-19**

# TITLE: COLCHICINE FOR COVID-19: RAPID REVIEW OF THE EVIDENCE FOR CLINICAL BENEFIT AND HARM

**Date: 19 November 2021** *(third update of original 6 August 2020 rapid review report)*

## Key findings

- We conducted a rapid review of available clinical evidence regarding the efficacy and safety of colchicine in the treatment of patients with COVID-19, regardless of whether they require hospitalisation or not.
- A comprehensive search on 28 January 2021 identified nine published reports (relating to four randomised controlled trials and one systematic review), as well as 25 planned or ongoing studies. The November 2021 (third update) of this review was triggered by the publication of a Cochrane review and the results of the largest colchicine trial to date (RECOVERY trial). The Cochrane review included the RECOVERY results and most records included in previous versions of this rapid review.
- The Cochrane review included 11 525 hospitalised and 4 488 non-hospitalised participants, and showed that colchicine results in little to no difference (no significant effect) in all-cause mortality up to 28 days in hospitalised patients with moderate to severe disease (risk ratio [RR] 1.00; 95% confidence interval [CI] 0.93 to 1.08; 2 RCTs; n=11 445; moderate certainty evidence) or in non-hospitalised patients with asymptomatic or mild disease (Peto odds ratio [OR] 0.57; 95% CI 0.20 to 1.62; 1 RCT; n=4 488; low certainty evidence).
- Colchicine did not significantly reduce the need for invasive mechanical ventilation in hospitalised patients with moderate to severe disease (RR 1.04; 95% CI 0.93 to 1.16; 1 RCT; n=10 811, moderate certainty evidence).
- Colchicine may reduce hospitalisation in previously non-hospitalised patients with PCR-confirmed or clinically suspected COVID-19 (OR 0.79; 95% CI 0.60 to 1.03; 1 RCT; low certainty evidence).
- Only one trial reported on serious adverse events (SAEs) in hospitalised patients, but showed zero events in both the colchicine and placebo arms. Colchicine was not associated with an increased risk of any adverse events (AE) in hospitalised patients (RR 1.00; 95% CI 0.56 to 1.78; 1 RCT; n=72; very low certainty). In non-hospitalised patients, colchicine was associated with a slightly lower rate of SAEs than placebo (RR 0.78; 95% CI 0.61 to 1.00; 1 RCT; n=4 412; moderate certainty evidence). One trial in non-hospitalised patients reported that colchicine was associated with an increased risk of diarrhoea, compared to placebo (RR 1.88; 95% CI 1.57 to 2.26; 1 RCT; n=4 412; low certainty).

## NEMLC MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

| Type of recommendation | We recommend against the option and for the alternative **(strong)** | We suggest not to use the option or to use the alternative **(conditional)** | We suggest using either the option or the alternative **(conditional)** | We suggest using the option **(conditional)** | We recommend the option **(strong)** |
|---|---|---|---|---|---|
| | **X** | | | | |

**Recommendation:** The use of colchicine for the treatment of COVID-19, in either hospitalised or ambulatory patients, is not recommended.
*Rationale:* Colchicine use did not result in clinically important benefits (in terms of reduced risk of mortality, admission to hospital, or progression to invasive mechanical ventilation) in hospitalised or non-hospitalised patients, but was associated with an increased risk of diarrhoea in non-hospitalised patients.
**Level of Evidence:** Moderate certainty of evidence
**Review indicator:** New evidence of safety and efficacy

*(Refer to Appendix 2 for the evidence to decision framework and Appendix 3 for version history)*

**NEMLC MAC ON COVID-19 THERAPEUTICS:** Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*.

**Note:** Due to the continuous emergence of new evidence, the rapid review will be updated if, and when, more relevant evidence becomes available.

**PROSPERO registration:** CRD42021286710

## BACKGROUND

Colchicine, an oral anti-inflammatory drug used to treat gout, has been proposed as a potential treatment for COVID-19. Its mechanisms of action include inhibition of neutrophil and monocyte recruitment, and inhibition of pro-inflammatory cytokines, both of which are thought to be important mediators of COVID-19 disease severity.[1,2]

This third update of the rapid review was triggered by the publication of the Cochrane review by Mikolajewska *et al*. (2021)[3] and the RECOVERY trial by Horby *et al*. (2021)[4,5].

**RESEARCH QUESTION:** Should colchicine be used to treat patients with COVID-19, with or without other medicines?

## METHODS

We previously conducted a rapid review of the evidence relating to colchicine through the systematic searching of three electronic databases (Epistemonikos[6], the Cochrane COVID Register[7] and www.covid-nma.com[8]) on 17 July 2020, and updated the search on 7 October 2020 and 28 January 2021. The search strategy is shown in Appendix 1. Screening of records was done independently and in duplicate (MM and AB for the updates), with arbitration by a third reviewer where necessary, using Covidence systematic review software[9].

**November 2021 update**

We did not perform a new search for this update. AB and MM evaluated studies included in the recently published Cochrane systematic review by Mikolajewska *et al*. 2021[3] against records included in previous versions of this rapid review. AB and MM also compared the results of the pre-print of the RECOVERY trial[5], included in the Cochrane systematic review, with those in the published version (Horby *et al*. 2021[4]) to ensure that the systematic review summarised the latest available evidence.

Relevant study data were extracted in a narrative table of results (MM for the update); results were reviewed, checked and reported by another reviewer (AB). Where outcomes were not obtained from the Cochrane systematic review[3], we used appraisals from previous versions of the rapid review; either obtained by appraising evidence with GRADEpro GDT software[10] (MM and AB), or from existing MAGICapp[11] appraisals. RdW and AG reviewed the overall report.

## Eligibility criteria for review

***Population:*** Patients with confirmed COVID-19, no restriction to age or co-morbidity.

***Intervention:*** Colchicine, either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

***Comparators:*** Any (standard of care/placebo or active comparator).

***Outcomes:*** Mortality; hospitalisation; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV-2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; progression to requiring oxygen; duration of ICU stay; adverse reactions and adverse events; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement.

***Study designs:*** Systematic reviews of randomised controlled trials; individual randomised controlled trials.

## RESULTS

***Description of included studies***

In the previous version of this rapid review, we identified four RCTs. Tardif *et al.* 2021[12] randomised 4 488 non-hospitalised adult patients aged ≥40 years with COVID-19 and at least one 'high-risk' criterion to treatment with colchicine or placebo. This was the largest trial at that point, but had not been published in peer-reviewed form. In addition, the trial was terminated early due to logistical issues, and consequently did not reach the planned sample size of 6 000. The RCT by Deftereos *et al.* 2020[13] initially aimed to recruit 180 patients (which would provide 90% power to detect a 50% reduction in the primary clinical end point: time to a 2-point deterioration on a 7-point modified ordinal scale, at α=0.05), but only included 110 patients due to declining incidence of COVID-19 in Greece. The 7-point modified ordinal scale used by the authors of the trial is shown in Appendix 2. The authors reported that the trial was not powered to detect differences in rare adverse events. Of note, almost all of the included patients received concomitant treatment thought at the time to have an effect on SARS-CoV-2, mostly chloroquine or hydroxychloroquine (98%) and azithromycin (92%). Lopes *et al.* 2021[14] reported on a study that achieved the target sample size (n=30 per trial arm). The primary endpoints were clinical parameters, such as the time of need for supplemental oxygen; time of hospitalisation; need for admission and length of stay in ICU; and death rate and causes of mortality. Salehzadeh *et al.* 2020[15] included 100 patients and the planned outcomes included duration of hospitalisation; cessation of fever; mortality; transfer to ICU and discharge. However, the authors only reported duration of hospitalisation and inflammatory biomarkers.

**November 2021 update**

The Cochrane systematic review by Mikolajewska *et al*. 2021[3] included three of the RCTs included in the previous rapid review (Tardif *et al*. 2020[12], Deftereos *et al*. 2020[13], Lopes *et al*. 2020[14]); including updated records of two of them (a second publication of Deftereos *et al*. in the *Hellenic Journal of Cardiology* and the published version of the COLCORONA study by Tardif *et al*. in *Lancet Respiratory Medicine*). In addition, the Cochrane systematic review included the pre-print of the RECOVERY trial[5]. The included RECOVERY data were identical to those presented in the final publication (Horby *et al*. 2021[4]). The pre-print by Salehzadeh *et al*. 2020[15] was placed under awaiting classification in the Cochrane systematic review, and was retained in this rapid review.

The Cochrane systematic review by Mikolajewska *et al*. 2021[3] included 11 525 hospitalised and 4 488 non-hospitalised participants. The authors pre-specified the following as the most important outcomes in hospitalised patients with moderate to severe disease: all-cause mortality, worsening and improvement of clinical status, quality of life, adverse events and serious adverse events. They pre-specified the following as the most important outcomes in non-hospitalised participants with asymptomatic or mild disease: all-cause mortality, admission to hospital or death, symptom resolution, duration to symptom resolution, quality of life, adverse events and serious adverse events.

The RECOVERY trial[4,5] is multi-centered and described as 'well powered'; recruiting 19 423 participants, 11 340 of whom were eligible to receive colchicine. Planned primary and secondary outcomes were all-cause mortality, time to discharge from hospital alive within 28 days, receipt of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or death in patients not on invasive mechanical ventilation at baseline. Pre-specified subsidiary clinical outcomes were use of non-invasive respiratory support, time to successful cessation of invasive mechanical ventilation, use of haemodialysis or –filtration, cause-specific mortality, bleeding and thrombotic events, and major cardiac arrhythmias.

***Effects of the intervention***

The currently available evidence on the safety and effectiveness of colchicine for the treatment of people with COVID-19 requiring hospitalisation is of low to moderate certainty. However, the certainty of evidence has improved since earlier reviews in 2020; evolving from very low certainty.

The evidence profiles for results in hospitalised patients with moderate to severe disease are presented in Table 4; evidence profiles for results in non-hospitalised patients with asymptomatic or mild disease are found in Table 5. Certainty of evidence for outcomes not formally assessed with GRADE in the systematic review by Mikolajewska *et al*. 2021[3] is reported narratively in the text. The quality appraisal of studies included in the systematic review (Mikolajewska *et al*. 2021[3]) are presented in the meta-analysis figures; the GRADE assessment for the outcome of hospitalisation in non-hospitalised patients, reported by Tardif *et al.* 2021[12], is shown in Table 6; the quality appraisal of Salehzadeh *et al*. 2020[15] from covid-nma.com[8] can be found in Table 7.

***Mortality***

The meta-analysis, conducted by Mikolajewska *et al*. 2021[3] (Figure 1) showed that colchicine results in little to no difference in all-cause mortality (no significant difference/effect) up to 28 days in hospitalised patients with moderate to severe disease (risk ratio [RR] 1.00; 95% confidence interval [CI] 0.93 to 1.08; 2 RCTs; n=11 445; moderate certainty evidence).

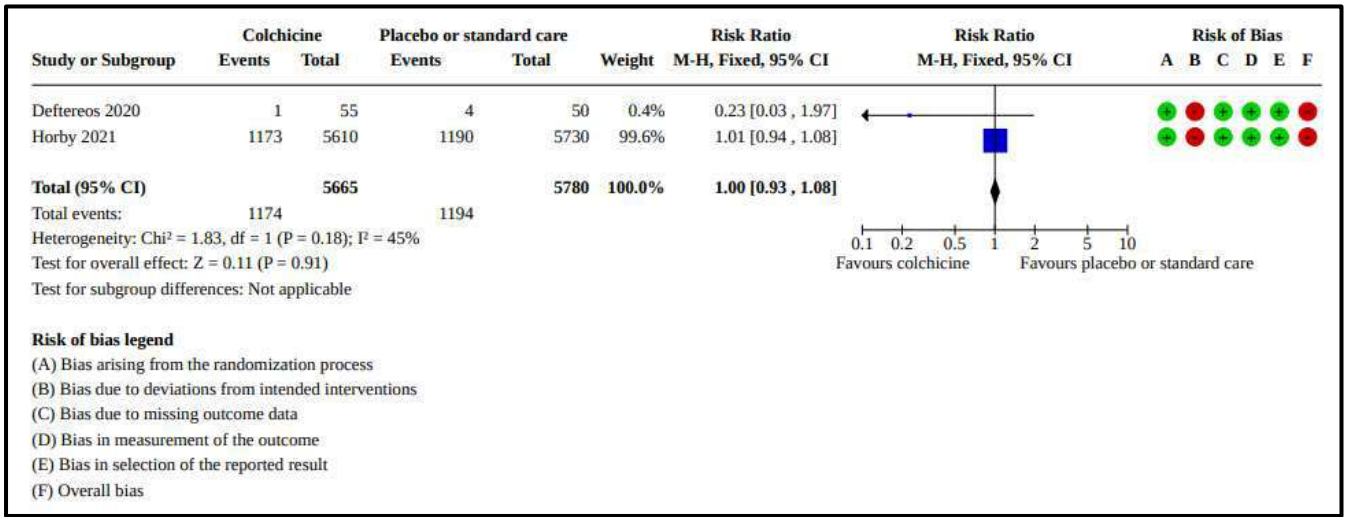


**Figure 1. Forest plot for all-cause mortality at up to day 28 in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

A second meta-analysis[3] presents the all-cause mortality at hospital discharge for one small study[14] (RR 0.14; 95% CI 0.01 to 2.60; 1 RCT; n=75), and is shown in Figure 2. This outcome was not formally assessed using GRADE, as it was not an important pre-specified outcome of the Cochrane systematic review[3]. This is likely to be very low certainty evidence, due to some concerns around bias arising in the randomisation process, small numbers of events and an imprecise 95% CI around the point estimate.

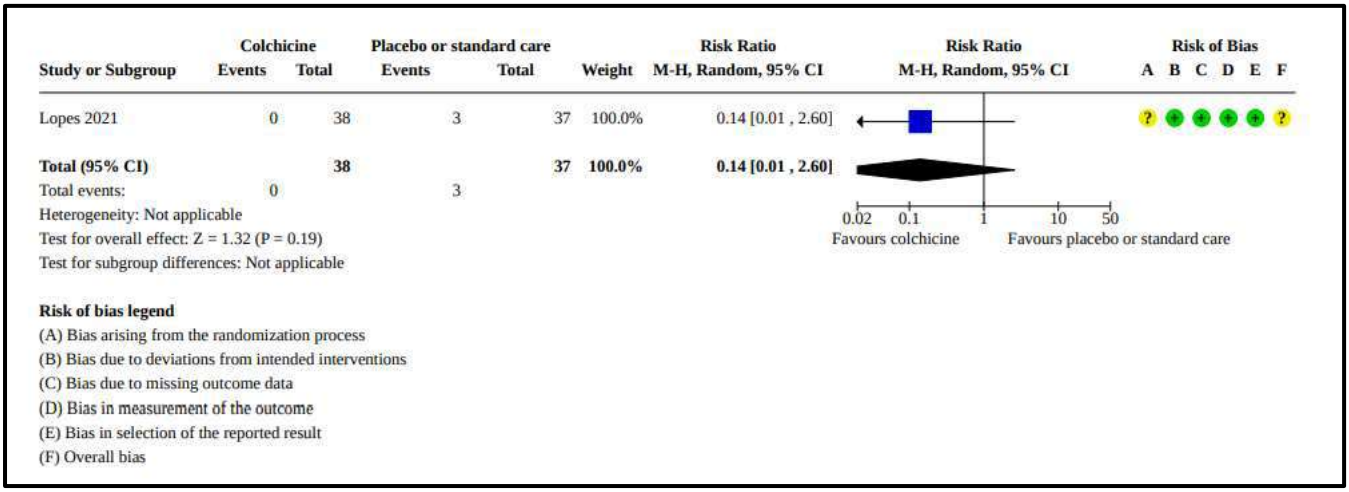


**Figure 2. Forest plot for all-cause mortality at hospital discharge in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

The meta-analysis by Mikolajewska *et al*. 2021[3] (Figure 3) showed that the evidence is uncertain about the effect of colchicine on all-cause mortality at 28 days in non-hospitalised patients with asymptomatic or mild COVID-19 (Peto odds ratio [OR] 0.57; 95% CI 0.20 to 1.62; 1 RCT; n=4 488; low certainty evidence).

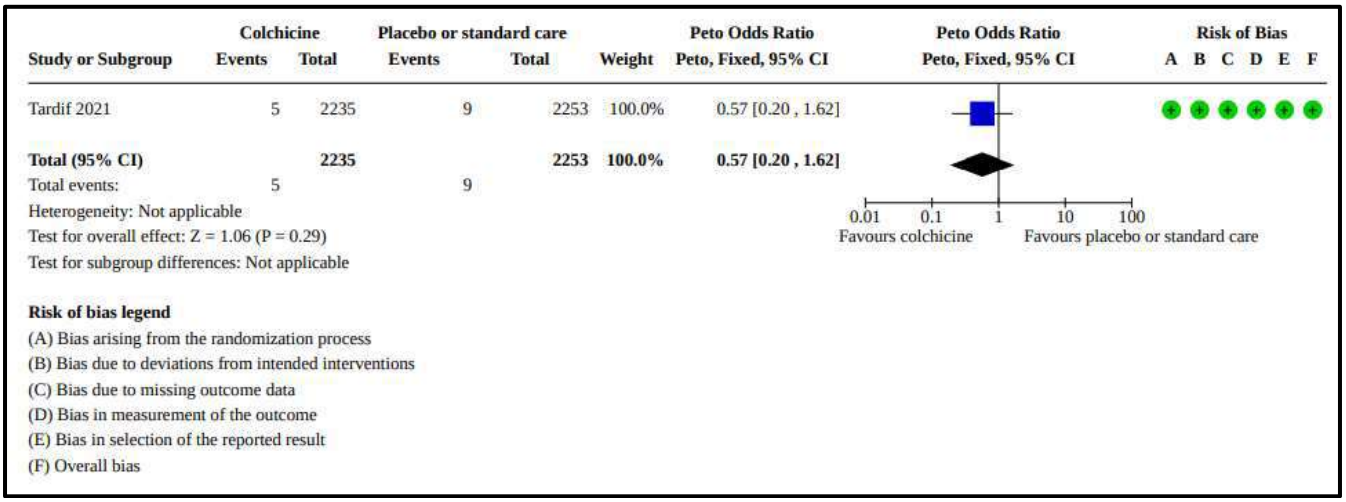


**Figure 3. Forest plot for all-cause mortality at day 28 in non-hospitalised patients with asymptomatic or mild disease (Mikolajewska *et al*. 2021[3])**

***Hospitalisation***

Tardif *et al.* (2021)[12] reported a reduced odds of hospitalisation (OR 0.79; 95% CI 0.60 to 1.03) in the intention-to-treat analysis (including both PCR-confirmed and clinically suspected COVID-19), and in the per protocol analysis (PCR-confirmed COVID-19 only) (OR 0.75; 95% CI 0.57 to 0.99). This is assessed with GRADEpro GDT[10] as low certainty evidence in the previous version of the review (Table 6).

***Duration of hospitalisation***

The Cochrane systematic review (Mikolajewska *et al*. 2021[3]) reported on the duration of hospitalisation in hospitalised participants with moderate to severe disease (mean difference [MD] -2.00; 95% CI -3.32 to -0.68; 1 RCT; n=72), as shown in Figure 4. This outcome was not formally assessed using GRADE, as it was not an important pre-specified outcome of the Cochrane systematic review[3]. This is likely to be very low certainty evidence, due to some concerns around bias arising in the randomisation process and high risk of bias due to missing outcome data, low sample numbers and an imprecise 95% CI around the point estimate.

Deftereos *et al.* 2020[13] reported the median (IQR) duration of hospitalisation to be 12 days (9 to 22) in the colchicine group and 13 days (9 to 18) in the control group, with no significant difference between the two groups (p=0.91). Salehzadeh *et al.* 2020[15] reported a mean duration of hospitalisation of 8.12 days in the placebo group and 6.28 days

in the colchicine group; assessed as very low certainty evidence due to very serious risk of bias and very serious imprecision by MAGICapp[11].

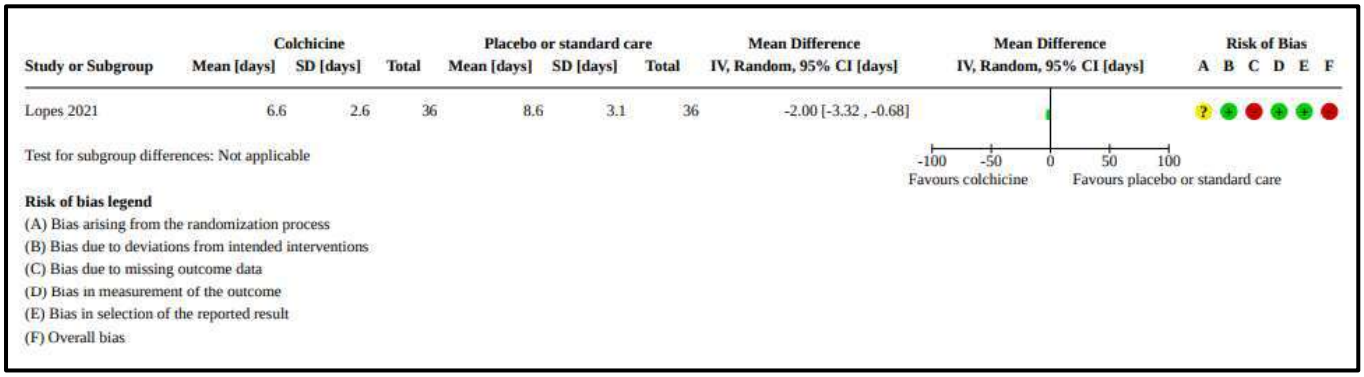


**Figure 4. Forest plot for duration of hospitalisation in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

***Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab***

None of the included studies reported on this outcome.

***Time to negative SARS-CoV-2 PCR on nasopharyngeal swab***

None of the included studies reported on this outcome.

***Progression to ICU admission***

Figure 5 presents the findings for admission of hospitalised patients with moderate to severe disease to the intensive care unit for one small study[14] included in Mikolajewska *et al*. 2021[3] (RR 0.73; 95% CI 0.18 to 3.04; 1 RCT; n=75). This outcome was not formally assessed using GRADE, as it was not an important pre-specified outcome of the Cochrane systematic review[3]. This is likely to be very low certainty evidence, due to some concerns around bias arising in the randomisation process, small numbers of events and an imprecise 95% CI around the point estimate.

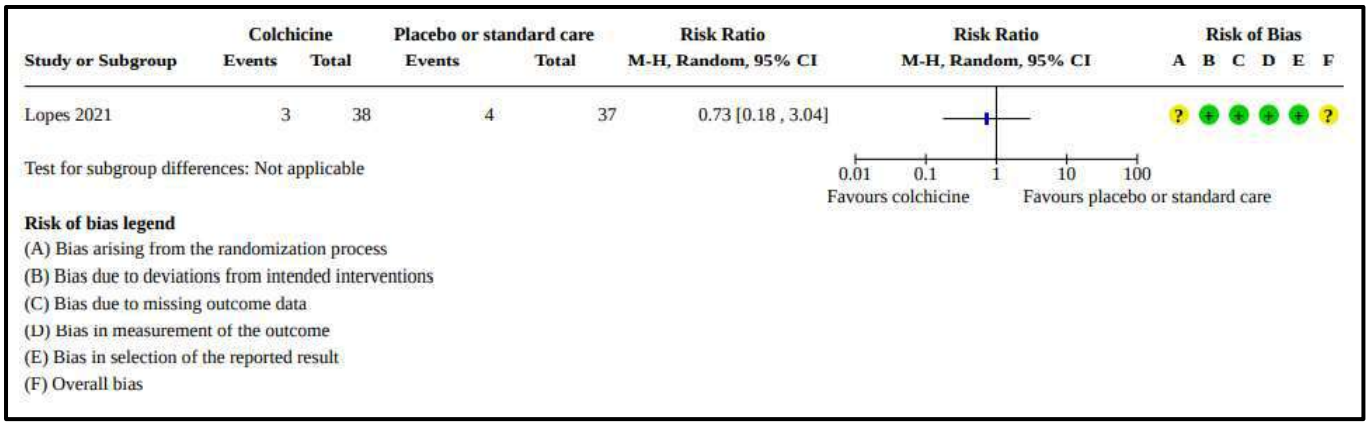


**Figure 5. Forest plot for admission to intensive care unit in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

***Mechanical ventilation***

The need for invasive mechanical ventilation in hospitalised patients was reported in the systematic review by Mikolajewska *et al*. 2021[3], including results from two RCTs. The evidence was not pooled and is presented in Figure 6.

Deftereos *et al*. 2020[13] showed a protective effect of colchicine, but this was not statistically significant (RR 0.18; 95% CI 0.02 to 1.50; 1 RCT; n=105). This result was not formally assessed with GRADE in the systematic review, but is likely to represent very low certainty evidence, due to some concerns around bias in the measurement of the outcome as well as a high risk of bias for deviations from intended interventions and missing outcome data; small numbers of events and an imprecise 95% CI around the point estimate additionally lower the certainty of this evidence.

Horby *et al*. 2021[4] showed no significant effect of colchicine on this outcome (RR 1.04; 95% CI 0.93 to 1.16; 1 RCT; n=10 811). This evidence was also not formally assessed with GRADE, but is likely to represent moderate certainty due to some concerns around bias in the measurement of the outcome, as well as a high risk of bias for deviations from intended interventions and missing outcome data.

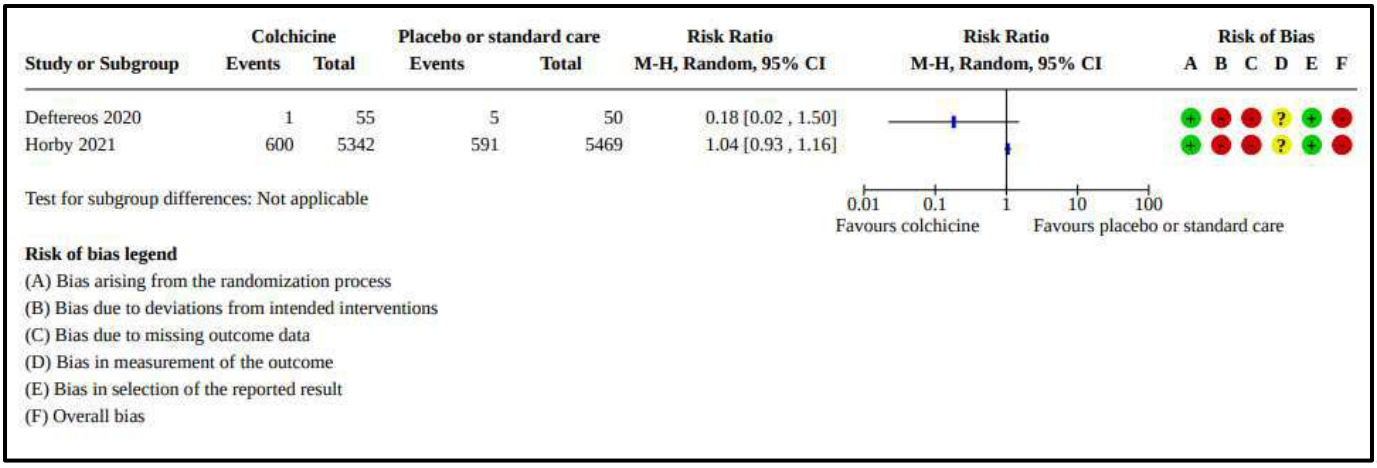


**Figure 6. Forest plot for new need for invasive mechanical ventilation in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

The need for invasive mechanical ventilation in non-hospitalised patients with asymptomatic or mild disease was reported in the systematic review by Mikolajewska *et al*. 2021[3], including evidence from a single RCT[12] (Figure 7). The results indicated a non-significant effect of colchicine (Peto OR 0.54; 95% CI 0.27 to 1.08; 1 RCT; n=4 488), but the evidence is likely of very low certainty due to a high risk of bias due missing outcome data, small numbers of events and an imprecise 95% CI around the point estimate.

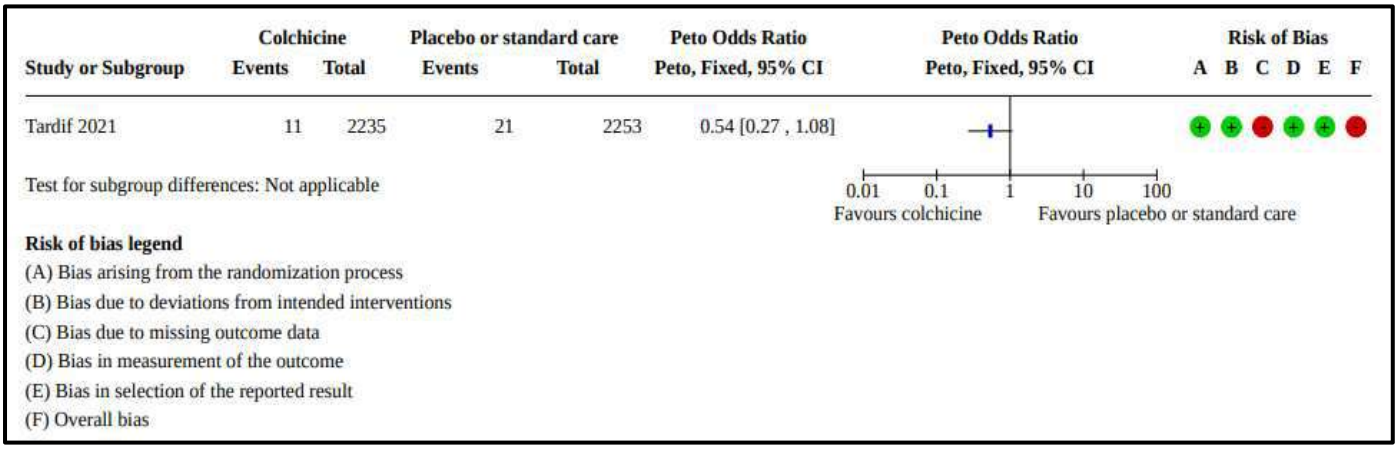


**Figure 7. Forest plot for worsening of clinical status: clinical deterioration, defined as need for invasive mechanical ventilation non-hospitalised patients with asymptomatic or mild disease (Mikolajewska *et al*. 2021[3])**

***Progression to requiring oxygen***

None of the included studies reported on this outcome.

***Duration of ICU stay***

Lopes *et al.* 2021[14] reported no difference in duration of ICU stay, but only 4 patients in the control group and 2 patients in the colchicine group required ICU admission. The durations of ICU stay were 11 days for the control patients and 12 days for the patients treated with colchicine. The evidence is likely of very low certainty due to some concerns related to bias arising in the randomisation process, low numbers of events and small sample numbers resulting in imprecise findings.

***Serious adverse events (SAEs)***

Mikolajewska *et al*. 2021[3] reported on serious adverse events in hospitalised participants with moderate to severe disease (Figure 8). The evidence was from one trial with zero events in both arms, and was considered to be very uncertain (not estimable; 1 RCT; n=105; very low certainty).

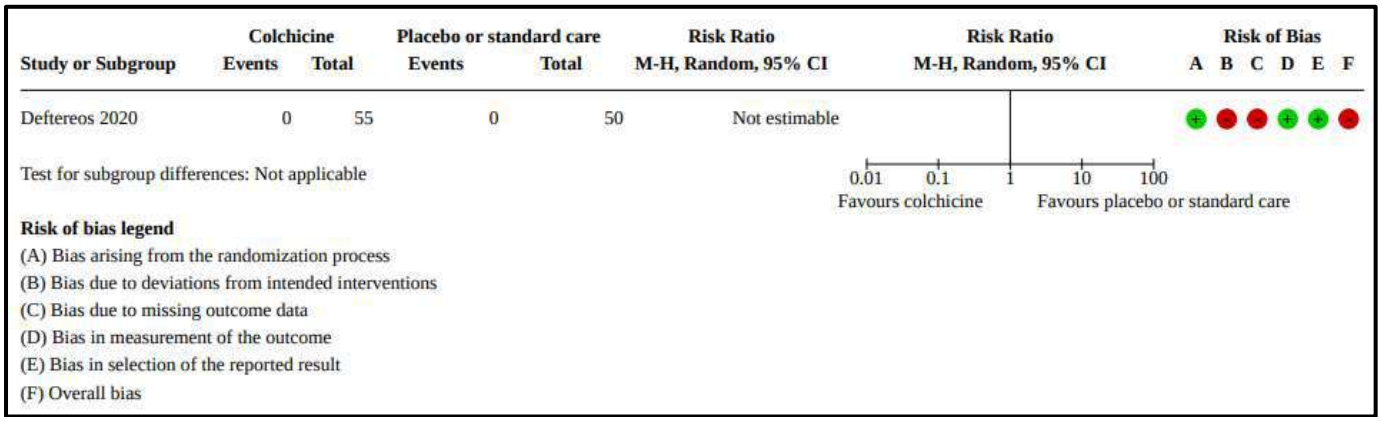


**Figure 8. Forest plot for serious adverse events until discharge in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

In non-hospitalised patients, Mikolajewska *et al*. 2021[3] reported on serious adverse events within 28 days from one RCT (Figure 9). These results indicated that colchicine results in a slight reduction of serious adverse events (RR 0.78; 95% CI 0.61 to 1.00; 1 RCT; n=4 412; moderate certainty evidence).

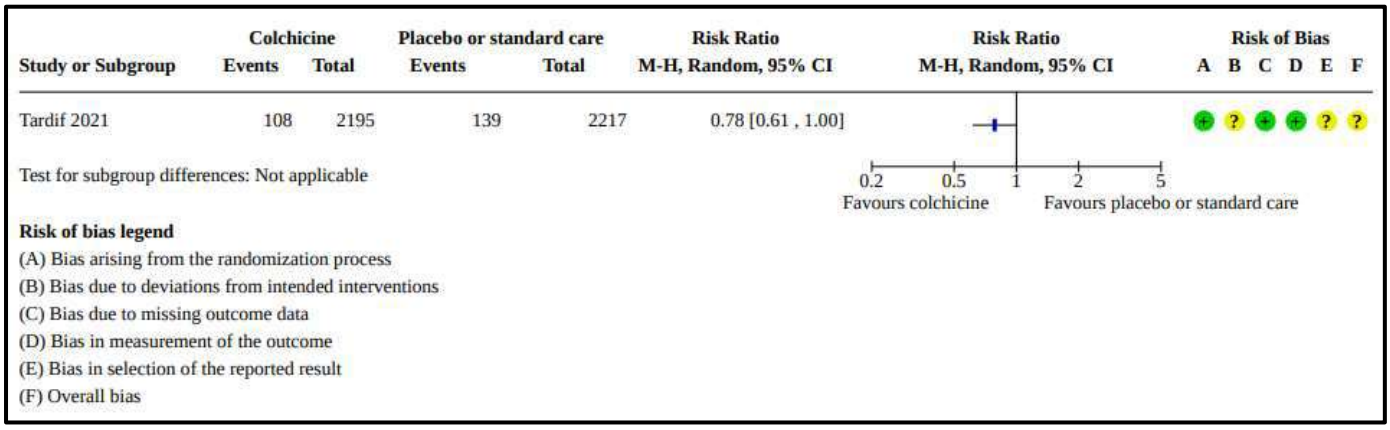


**Figure 9. Forest plot for serious adverse events within 28 days in non-hospitalised patients with asymptomatic or mild disease (Mikolajewska *et al*. 2021[3])**

***Adverse reactions and adverse events (AEs)***

Mikolajewska *et al*. 2021[3] reported on various adverse events in hospitalised patients with moderate to severe disease; including adverse events of any grade (Figure 10), the incidence of abdominal pain (Figure 11), the incidence of diarrhoea (Figure 12) and the incidence of nausea and vomiting (Figure 13).

These results indicated that the evidence is very uncertain about the effect of colchicine on any adverse events (RR 1.00; 95% CI 0.56 to 1.78; 1 RCT; n=72; very low certainty).


**Figure 10. Forest plot for adverse events (any grade) in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

Two RCTs included in Mikolajewska *et al*. 2021[3] provided evidence for the incidence of abdominal pain, but these data were not pooled. Deftereos *et al*. 2020[13] showed a strong, highly imprecise effect in favour of placebo or standard care (RR 10.02; 95% CI 0.57 to 176.70; 1 RCT; n=105); likely of very low certainty due to various methodological limitations, small numbers of events and a very wide 95% CI around the point estimate. Lopes *et al*. 2021[14] showed no difference between the two treatments (RR 1.00; 95% CI 0.27 to 3.69; 1 RCT; n=72); likely also very low certainty owing to various methodological limitations, small numbers of events and an imprecise 95% CI around the point estimate.

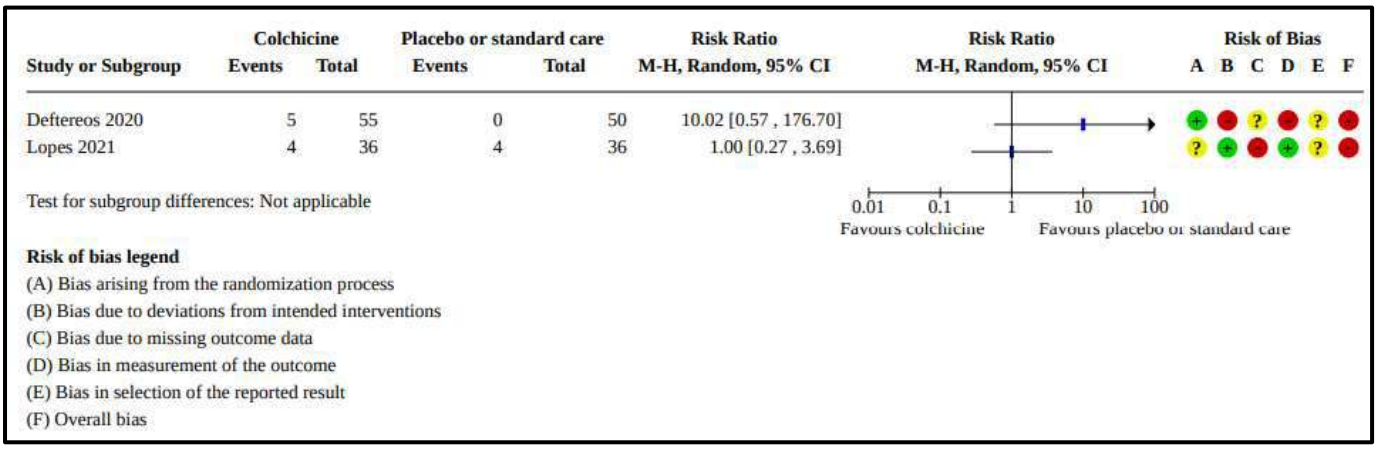


**Figure 11. Forest plot for incidence of abdominal pain events during the study period in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

Two RCTs included in Mikolajewska *et al*. 2021[3] provided evidence for the incidence of diarrhoea; these data were also not pooled. Both Deftereos *et al*. 2020[13] (RR 2.53; 95% CI 1.31 to 4.88; 1 RCT; n=105) and Lopes *et al*. 2021[14] (RR 3.00; 95% CI 0.65 to 13.88; 1 RCT; n=72) showed effects in favour of placebo or standard care; both are likely very low certainty due to various methodological limitations, low numbers of events and an imprecise 95% CI around both point estimates.

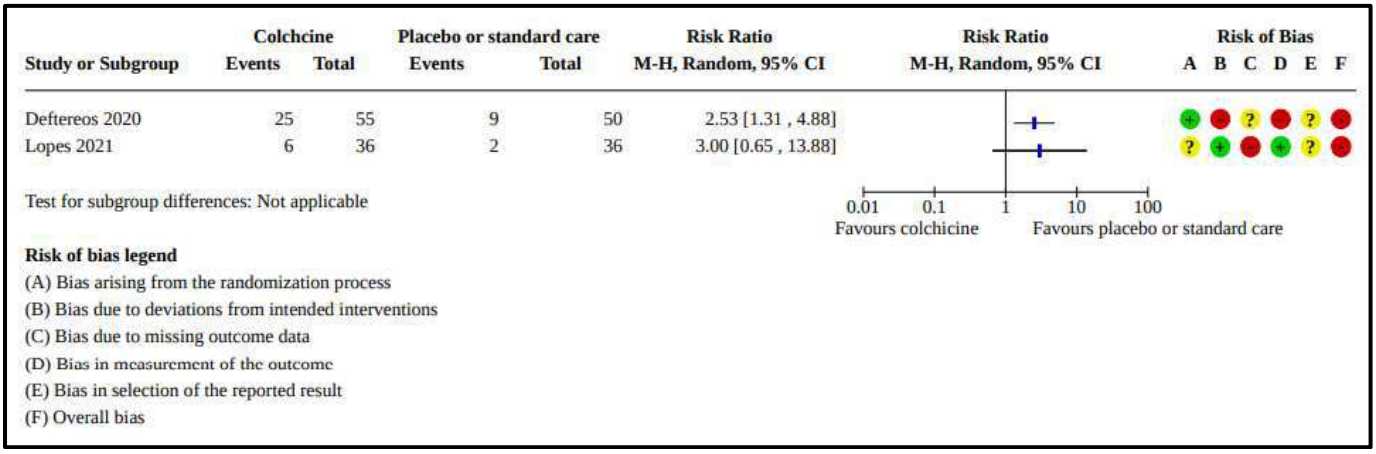


**Figure 12. Forest plot for incidence of diarrhoea events during the study period in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

One RCT included in Mikolajewska *et al*. 2021[3] provided evidence for the incidence of nausea and vomiting, showing an effect in favour of placebo or standard care (RR 2.00; 95% CI 0.39 to 10.24; 1 RCT; n=72). This evidence is likely of very low certainty due to various methodological limitations, low numbers of events and a wide 95% CI around the point estimate.

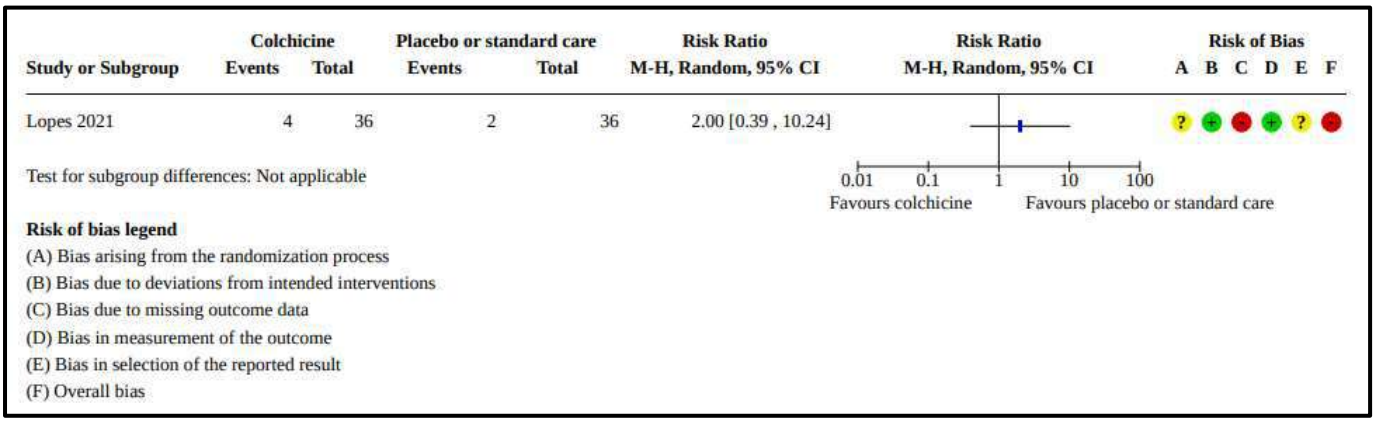


**Figure 13. Forest plot for incidence of nausea and vomiting events during the study period in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

Mikolajewska *et al*. 2021[3] did not find any studies reporting on adverse events in general in non-hospitalised patients. However, the authors did report on diarrhoea as a specific adverse event in non-hospitalised patients with asymptomatic or mild disease; these results are shown in Figure 14. Tardif *et al*. 2021[12] showed a significant effect in favour of placebo or standard care (RR 1.88; 95% CI 1.57 to 2.26; 1 RCT; n=4 412; low certainty), but the evidence is uncertain.

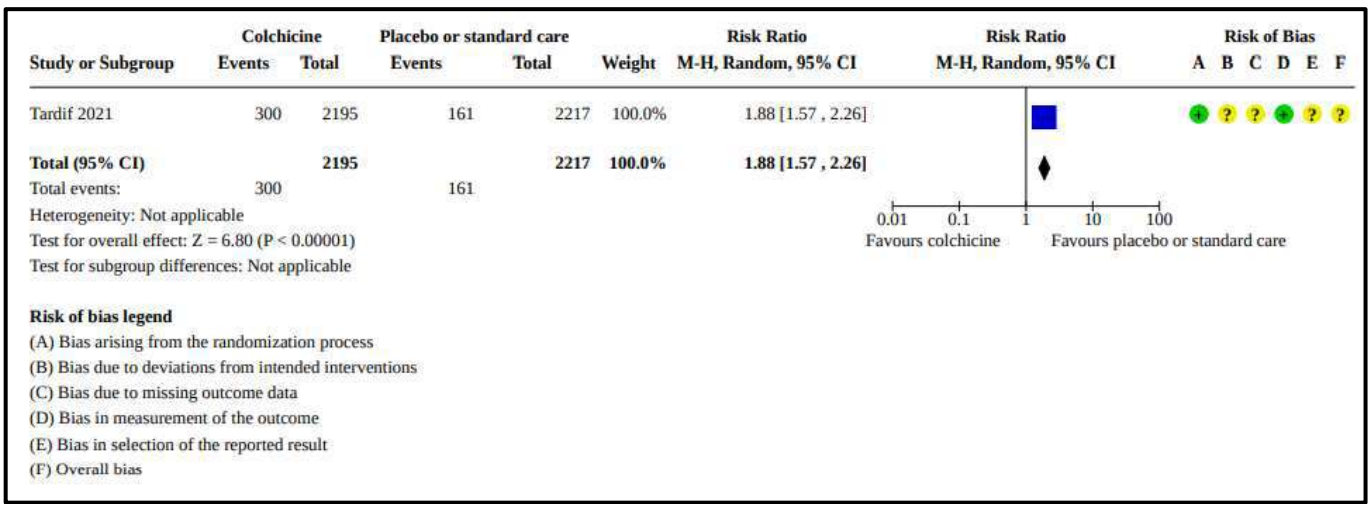

**Figure 14. Forest plot for incidence of diarrhoea events during the study period in non-hospitalised patients with asymptomatic or mild disease (Mikolajewska *et al*. 2021[3])**

***Clinical improvement or deterioration on an ordinal scale at chosen time points***

The systematic review by Mikolajewska *et al*. 2021[3] reported on clinical deterioration and clinical improvement outcomes in hospitalised patients. The results shown in Figure 15 indicate that colchicine has little to no impact on clinical deterioration, defined as the new need for invasive mechanical ventilation or death up to day 28 (RR 1.02; 95% CI 0.96 to 1.09; 2 RCTs; n=10 916; moderate certainty).

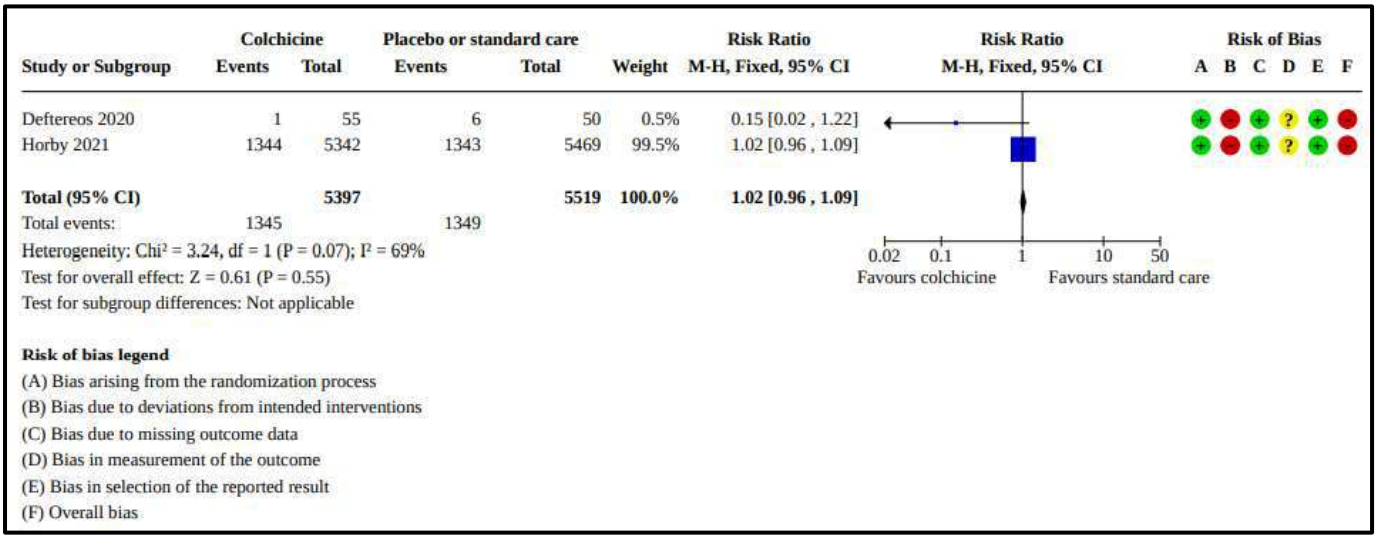


**Figure 15. Forest plot for clinical deterioration, defined as new need for invasive mechanical ventilation or death up to day 28, in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

Clinical improvement, defined as participants discharged alive up to day 28, is shown in Figure 16. The evidence in Figure 16 indicated that colchicine results in little to no difference in improvement of clinical status using this definition (RR 0.99; 95% CI 0.96 to 1.01; 1 RCT; n=11 340; moderate certainty).

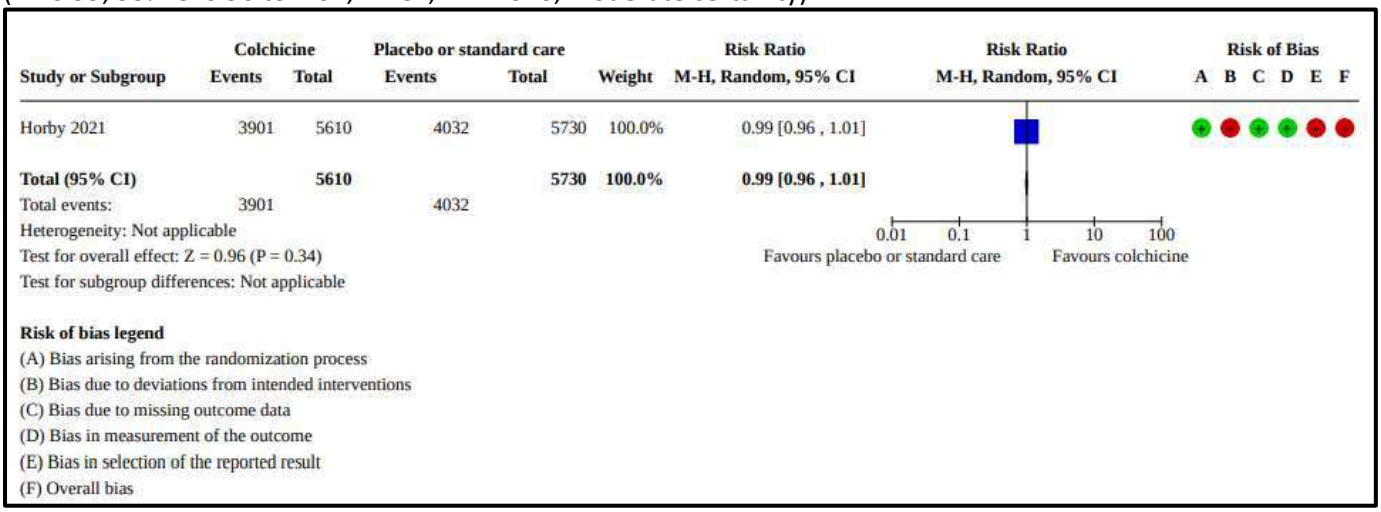


**Figure 16. Forest plot for clinical improvement, defined as participants discharged alive up to day 28, in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

Clinical improvement, defined as participants discharged alive at longest follow-up, is shown in Figure 17. The evidence in Figure 17 showed no significant effect (RR 1.09; 95% CI 0.98 to 1.21; 1 RCT; n=75). Although this evidence was not formally assessed using GRADE, it is likely of low certainty due to some concerns with bias arising from the randomisation process as well as low numbers of events.

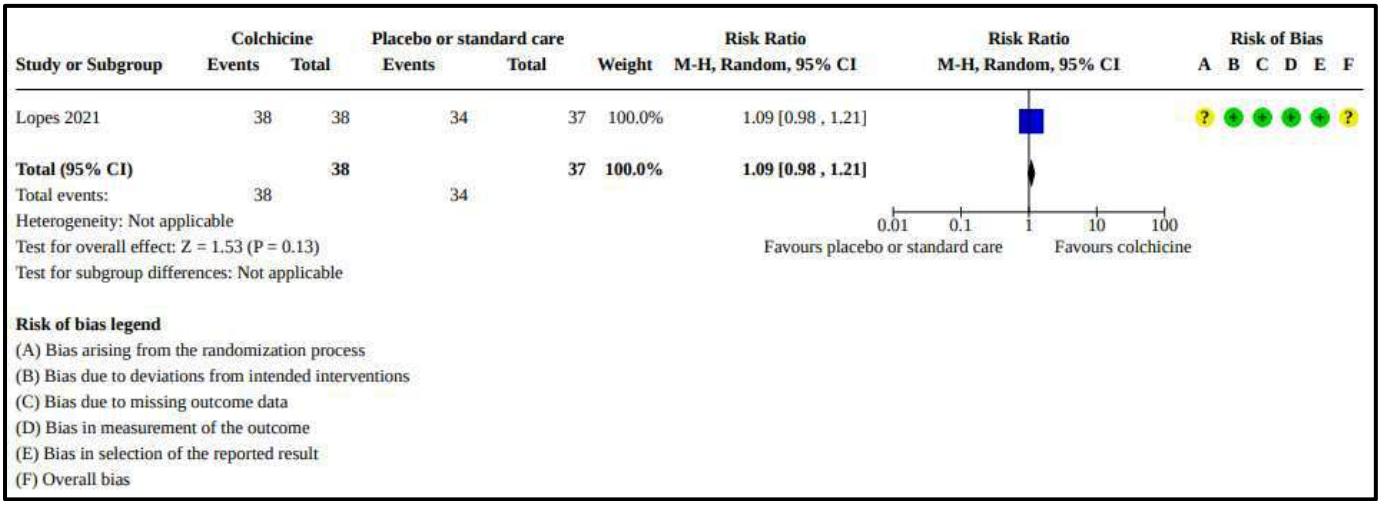


**Figure 17. Forest plot for clinical improvement, defined as participants discharged alive at longest follow-up, in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

The results shown in Figure 18, indicated a non-significant effect (RR 1.06; 95% CI 0.82 to 1.36; 1 RCT; n=529) on weaning from ventilation and surviving, but the evidence is likely of very low certainty. There were some concerns related to the measurement of the outcome, a high risk of bias due to deviations from intended interventions and selection of the reported result, small numbers of events and an imprecise 95% CI around the point estimate.

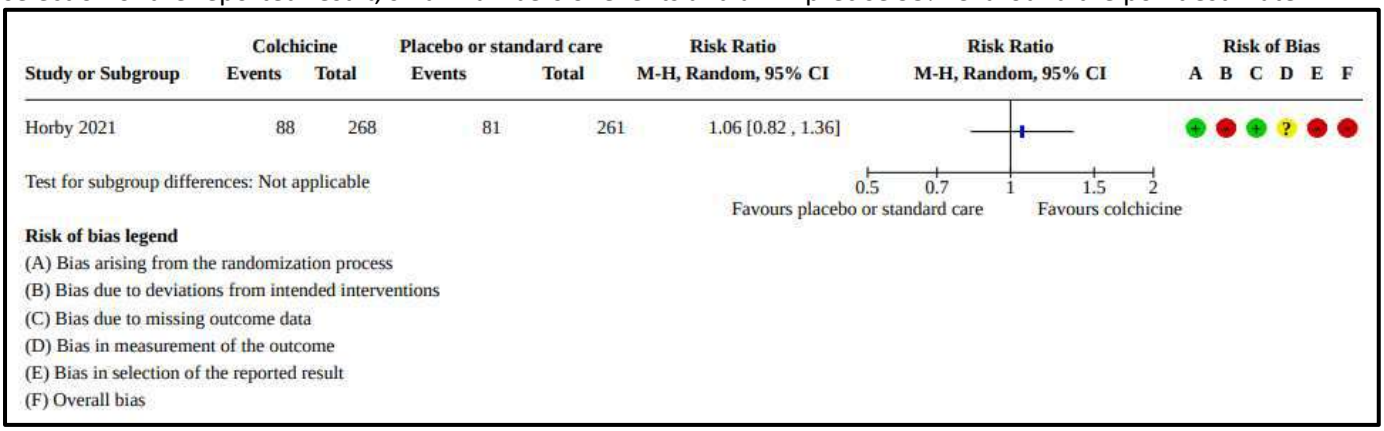


**Figure 18. Forest plot for weaned from mechanical ventilation, and surviving, in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

***Time to clinical improvement***

The time to cessation of supplemental oxygen provision in hospitalised patients with moderate to severe disease was reported in the systematic review by Mikolajewska *et al*. 2021[3], including evidence from a single RCT (Figure 19). The results indicated a shorter time to cessation of oxygen support in the colchicine group (MD -2.50; 95% CI -3.70 to -1.30; 1 RCT; n=72), but the evidence is likely of low certainty due to some concerns related to bias arising in the randomisation process and small sample numbers.

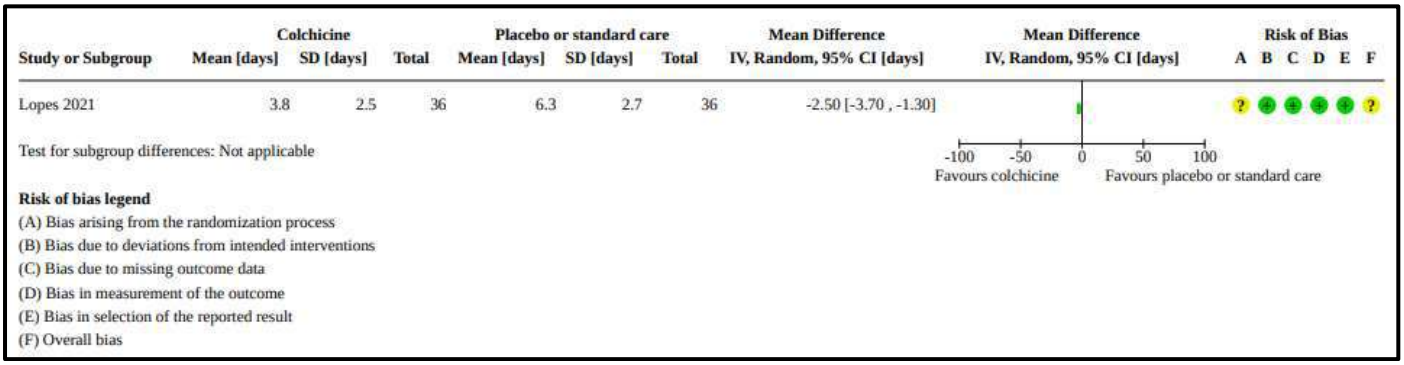


**Figure 19. Forest plot for duration to liberation from supplemental oxygen in hospitalised patients with moderate to severe disease (Mikolajewska *et al*. 2021[3])**

## CONCLUSION

Colchicine has no significant effect on clinically important outcomes such as mortality, hospitalisation, or need for oxygen or mechanical ventilation, and is associated with an increased risk of diarrhoea. The current evidence does not support the inclusion of colchicine in treatment guidelines for hospitalised and non-hospitalised COVID-19 patients in South Africa.

**Reviewers:** Updated review: Michael McCaul, Amanda Brand, Renee de Waal, Andy Gray.

**Declaration of interests:** MM (Centre for Evidence-based Health Care, Stellenbosch University and SA GRADE Network), AB (Centre for Evidence-based Health Care, Stellenbosch University and SA GRADE Network), RdW (School of Public Health and Family Medicine, University of Cape Town) and AG (Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal) have no relevant conflicts of interest to declare.

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## Table 1. Characteristics of included studies

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| Mikolajewska, A. *et al*. Cochrane Database of Systematic Reviews 2021[3]<br>Systematic review | Cochrane Systematic Review of RCTs<br><br>Search date 21 May 2021, no restrictions. | Included three RCTs with 11 525 hospitalised participants and one RCT with 4488 non-hospitalised participants. Mean age was 64 yrs and 55 years respectively.<br><br>17 ongoing studies. | | **<u>Hospitalised people with moderate to severe COVID-19</u>**<br><br>***All cause mortality***<br>Colchicine plus standard care results in little to no difference in all-cause mortality up to 28 days compared to standard care alone (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.93 to 1.08; 2 RCTs, 11 445 participants; moderate-certainty evidence)<br><br>***Adverse events:***<br>The evidence is very uncertain about the effect of colchicine on adverse events compared to placebo (RR 1.00, 95% CI 0.56 to 1.78; 1 RCT, 72 participants; very low-certainty evidence).<br><br>***Serious adverse events:***<br>The evidence is very uncertain about the effect of colchicine plus standard care on serious adverse events compared to standard care alone (0 events observed in 1 RCT of 105 participants; very low-certainty evidence).<br><br>***Worsening of clinical status****:*<br>Colchicine plus standard care results in little to no difference in worsening of clinical status, assessed as new need for invasive mechanical ventilation or death compared to standard care alone (RR 1.02, 95% CI 0.96 to 1.09; 2 RCTs, 10 916 participants; moderate-certainty evidence).<br><br>**<u>Non-hospitalised people with asymptomatic SARS-CoV-2 infection or mild COVID-19</u>**<br><br>**All-cause mortality**:<br>The evidence is uncertain about the effect of colchicine on all-cause mortality at 28 days (Peto odds ratio (OR) |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | | | | 0.57, 95% CI 0.20 to 1.62; 1 RCT, 4488 participants; low-certainty evidence). |
| Horby, PW. *et al*. Lancet 2021[4]<br>Journal publication<br><br>*Pre-print[5] included in latest Cochrane review[3] | RCT, multi-centre, multinational, open label<br><br>Nov 27, 2020 to March 4 2021. | Setting: 117 hospitals (UK), 2 hospitals (Indonesia), 2 hospitals (Nepal)<br><br>n= 5610 (Colchicine) in 28 day ITT<br><br>n= 5730 (usual care) in 28 day ITT<br><br>No baseline imbalances between intervention and control groups.<br><br>Male (69 vs 70%)<br><br>Age, years: mean (SD) 63.3 (13.8) vs 63.5 (13.7)<br><br>Eligible: clinically suspected or laboratory confirmed SARS-CoV-2 infection.<br><br>Exclusions: Children and pregnant women. Patients with severe liver impairment, significant cytopaenia, concomitant use of strong CYP3A4 (eg, clarithromycin, erythromycin, systemic azole antifungal, and HIV protease inhibitor) or P-glycoprotein inhibitors (eg, ciclosporin, verapamil, and quinidine), or hypersensitivity to lactose were excluded from the colchicine comparison | Intervention: Colchicine 1mg after randomisation, followed by 500 µg 12 hrs later, and then 500 µg twice a day for 10 days or until discharge.<br><br>Usual care: symptomatic management (although not specified in article) | **28-day mortality**<br>1173 (21%) vs 1190 (21%). RR 1.01 (95% CI 0.93 to 1.10) p=0.77. Results similar across all subgroups, including restricted to confirmed COVID-19 positive.<br><br>**Time to being discharged alive, days**<br>10 (5 to >28) vs 0 (5 to >28)<br><br>**Discharged from hospital within 28 days**<br>3901 (70%) vs 4032 (70%), RR 0.98 (95% CI 0.94 to 1.03).<br><br>**Receipt of invasive mechanical ventilation**<br>1344/5342 (11%) vs 1343/5469 (11%). RR 1.02 (95% CI 0.96 to 1.09) |
| Tardif, J-C *et al.* medRxiv 2021[12]<br>Pre-print<br><br>*Included in latest Cochrane review[3] | Double-blind, randomized controlled trial<br><br>Multi-centre (across 6 countries)<br><br>Trial was terminated early | Setting: Multi-centre trial across 6 countries (Canada, USA, South Africa; and unspecified countries in Europe and South America)<br>n= 2235 (Colchicine)<br>n= 2253 (Placebo)<br><br>Age, mean (sd): 54.4 (9.7) intervention arm; 54.9 (9.9) control arm<br>Gender, Female, n (%): 1238 (55.4) intervention arm; 1183 (52.,5) control arm | **Intervention**<br>Colchicine 0.5mg twice daily for first 3 days and once daily thereafter for 27 days<br><br>**Control**<br>Placebo for 30 days (oral tablets)<br><br>Mean treatment duration for trial medication was 26.2 days. | **<u>ITT population (n=4 488), OR (95% CI), n (%)</u>**<br>**Mortality**<br>OR 0.56 (0.19 to 1.67), 5 (0.2) intervention vs 9 (0.4) control<br><br>**Primary composite endpoint (death or hospitalisation for COVID-19)**<br>OR 0.79 (0.61 to 1.03), 104 (4.7) intervention vs 131 (5.8) control |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | (75% of planned study participants enrolled and completed 30 day follow up) due to logistical issues. | BMI, mean (sd): 30 (6.,2) intervention arm; 30 (6.3) control arm<br>Comorbidities (% intervention; % control):<br>Smoking (9.7; 9.4), Hypertension (34.9; 37.6), DM (19.9; 20.0), Respiratory disease (26.1; 26.9), Prior MI (2.9; 3.2), Prior heart failure (1.1; 0.8).<br><br>Eligibility: **Non-hospitalised** adult patients (>40 years) with COVID-19 within 24hrs of enrollment, presenting with one of the following: age of 70 years or older, obesity (body-mass index of 30 kg/m2 or more), diabetes, uncontrolled hypertension (systolic blood pressure ≥150 mm Hg), known respiratory disease, known heart failure, known coronary disease, fever of at least 38.4°C within the last 48 hours, dyspnea at the time of presentation, bicytopenia, pancytopenia, or the combination of high neutrophil and low lymphocyte counts. | | **Hospitalisation for COVID-19**<br>OR 0.79 (0.6 to 1.03), 101 (4.5) intervention vs 128 (5.7) control<br><br>**Mechanical ventilation**<br>OR 0.53 (0.25 to 1.09), 11 (0.5) intervention vs 21 (0.9) control.<br><br>**<u>Patients with PCR-proven COVID-19 (n=4 159), OR (95% CI), n (%)</u>**<br>**Mortality**<br>OR 0.56 (0.19 to 1.66), 5 (0.2) intervention vs 9 (0.4) control<br><br>**Primary composite endpoint**<br>OR 0.75 (0.57 to 0.99), 96 (4.6) intervention vs 126 (6) control<br><br>**Hospitalisation for COVID-19**<br>OR 0.75 (0.57 to 0.99), 93 (4.5) intervention vs 123 (5.9) control<br><br>**Duration of hospitalisation**<br>Not reported<br><br>**Mechanical ventilation**<br>OR 0.5 (0.23 to 1.07), 10 (0.5) intervention vs 20 (1) control<br><br>**Adverse events/reactions (ITT*)**<br>**Any SAE**, OR 0.77 (0.59 to 1.09),<br>108 (4.9) intervention vs 139 (6.3) control.<br>**Any related AE**, OR 1.78 (1.5 to 2.0),<br>532 (24.2) intervention vs 344 (15.5) control<br>**Pneumonia SAE**, OR 0.68 (0.48 to 0.95), 63 (2.9) intervention vs 92 (4.1) control<br>**Pulmonary embolism**, OR 5.57 (1.2 to 51.8), 11 (0.5) intervention vs 2 (0.1) control<br>**Gastro-intestinal SAE**, OR 2.0 (0.4 to 12.4), 6 (0.3) intervention vs 3 (0.1) control |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | | | | **Gastro-intestinal AE**, OR 1.7 (1.5 to 2.0), 524 (23.9) intervention vs 328 (14.8) control<br>**Diarrhoea AE**, OR 2.0 (1.6 to 2.4), 300 (13.7) intervention vs 161 (7.3) control<br>**Nausea AE**, OR 0.92 (0.59 to 1.4), 43 (2.0) intervention vs 47 (2.1) control<br>**GI haemorrhage AE**, OR not estimable, 1 (0) intervention vs 0 (0) control<br>**Rash AE**, OR 0.3 (0.07 to 1), 4 (0.2) intervention vs 13 (0.6) control*Total randomized as denominator. |
| Deftereos, SG *et al.* JAMA 2020[13]<br>Journal publication<br><br>*Included in latest Cochrane review[3] | Prospective, open-label, randomised clinical trial<br><br>Multicenter (n=16 tertiary care hospitals)<br><br>Trial was terminated early due to slow enrolment in Greece in late April 2020. | Setting: Greece (**in hospital**)<br>n = 54 (Standard treatment)<br>n = 56 (Colchicine, in addition to standard treatment)<br>Severity: Mild: n=0 / Moderate: n=102/ Severe: n=3<br>Critical: n=0<br><br>Age, median (IQR): 65 (54-80) intervention; 63 (55-70) control<br>Gender Male, n (%): 30 (60.0) intervention; 31 (56.4) control<br><br>Eligibility: 1. Subjects ≥18 years old with laboratory confirmed SARS-CoV-2 PCR, who presented with clinical symptoms including body temperature >37.5°C. AND<br>2. At least two of the following criteria: persistent cough, persistent throat pain, anosmia, ageusia, asthenia, arterial blood partial pressure of oxygen ($PaO_2$) <95 mmHg. | **Treatment**<br>Colchicine (loading dose 1.5 mg; followed by 0.5 mg 60 minutes later if no adverse gastrointestinal effects; then 0.5 mg twice daily (reduced to once daily if body weight <60 kg) until hospital discharge or a maximum of 21 days.)<br>Co-Intervention: Standard care<br>Duration: 21 days<br><br>**Control**<br>Standard care: optimal medical treatment according to local protocols, as established by the National Public Health Organization and following the guidance of the European Centre for Disease Prevention and Control<br><br>Concomitant treatment: Most patients received chloroquine or hydroxychloroquine (103; 98.1%) and azithromycin (97; 92.4%). No patients were reported to have received corticosteroids. | **In the report**<br>The primary end points were the difference in maximal high-sensitivity cardiac troponin (hs cTn) levels, the time for C-reactive protein to reach levels > 3 times the upper reference limit, and the time from baseline to clinical deterioration, defined as a 2-grade increase on an ordinal clinical scale, based on the World Health Organization R&D Blueprint Ordinal Clinical Scale within a time frame of 3 weeks after randomisation or until hospital discharge (whichever occurred first).<br><br>**All-cause mortality**<br>Control: 4/54 (7.4%) vs intervention: 1/56 (1.8%).<br><br>**Duration of hospitalisation**<br>Median (IQR) hospitalisation was 12 (9-22) days in the intervention and 13 (9-18) days in the control group (p=0.91).<br><br>**The percentage of participants requiring mechanical ventilation, in those who deteriorated by at least 2 points on the ordinal scale (as defined by Deftereos *et al*. 2020):**<br>Control: 6/7 (85.7%), Intervention= 1/1 (100.0%).<br><br>**Number, type, severity, and seriousness of adverse events.**<br>Adverse events were similar for the two groups, with no significant differences by event. The exception was diarrhoea, which was more frequent in the colchicine |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | | | | group; 25/55 (45.5%) patients in the intervention and 9/50 (18.0%) patients in the control group (P=0.003) experienced this event.<br><br>**Time to deterioration by 2 points on the 7-grade WHO clinical status scale**<br>Control: Mean (SD) 18.6 (0.83) days vs Intervention: 20.7 (0.31) days.<br><br>**Cumulative event-free 10-day survival** Control: 83% vs Intervention: 97%.<br><br>**Maximum high-sensitivity cardiac troponin level**<br>Control: Median (IQR) 0.0112 (0.0043-0.0093) vs Intervention: 0.008 (0.004-0.0135) ng/mL.<br><br>**Maximum C-reactive protein level**<br>Control: Median (IQR) 4.5 (1.4-8.9) mg/dL vs Intervention 3.1 (0.8-9.8) mg/dL. |
| Lopes, MIF *et al.* RMD Open 2021[14]<br>Journal publication<br><br>*Included in latest Cochrane review[3] | RCT, double blind, placebo controlled<br><br>Single centre<br><br>11 April to 30 August 2020 | Setting: Brazil<br><br>n=38 (Colchicine)<br>n=37 (Placebo)<br><br>Age (years, median (IQR)): 54.5 (42.5 to 64.5) in intervention; 55 (42 to 67) in control<br>33 males (19 in intervention and 14 in control)<br>Severity : Mild: n=0 / Moderate: n=12/ Severe: n=23<br>Critical: n=3 (severity from interim analysis)<br><br>Comorbidities (% intervention; % control):<br>Current or former smoking (19; 25), respiratory diseases (11; 14), cardiovascular diseases (47; 44), diabetes mellitus (36; 42), dyslipidemia (28; 33)<br><br>Inclusion criteria:<br>Individuals **hospitalised** with moderate or severe forms of COVID-19 diagnosed by RT-PCR in nasopharyngeal swab specimens and lung | **Treatment**<br>Colchicine (0.5mg thrice daily for 5 days, then 0.5mg twice daily for 5 days) with loading dose of 1.0 mg if body weight was ≥ 80 kg<br>Co-Intervention: Standard care as described for control<br>Duration : 10 days<br><br>**Control**<br>Placebo<br>Duration : 10 days<br><br>All participants received the institutional treatment for COVID-19 with azithromycin<br>500 mg once daily for up to 7 days, hydroxychloroquine 400 mg twice daily for 2 days, then | **All-cause mortality**<br>Control: 2/37 vs Intervention: 0/38<br><br>**Discharge from hospital**<br>Hospitalisation was maintained for 42% versus 72% of patients at day 7; and 9% versus 39% at day 10 in the colchicine and placebo groups, respectively (p=0.002)<br><br>**Duration of hospitalisation**<br>Duration: 23 (Colchicine) vs 26 (Placebo) days<br>Time of hospitalisation, median (IQR) :<br>Intervention: 7 (5-9)<br>Control: 9 (7-12)<br>p-value: 0.03<br><br>**Time to supplemental oxygen, median (IQR), days**<br>Intervention: 4 (2-6)<br>Control: 6.5 (4-9)<br>p-value: <0.001 |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | | computed tomography scan involvement compatible with COVID-19 pneumonia; older than 18 years; body weight > 50 kg; normal levels of serum Ca2+ and K+; QT interval < 450 ms at 12 derivations electrocardiogram (according to the Bazett formula) and negative serum or urinary β-HCG if women under 50.<br><br>Exclusion criteria:<br>Mild form of COVID-19 or in need for ICU admission; diarrhoea resulting in dehydration; known allergy to colchicine; diagnosis of porphyria, myasthenia gravis or uncontrolled arrhythmia at enrollment; pregnancy or lactation; metastatic cancer or immunosuppressive chemotherapy; regular use of digoxin, amiodarone, verapamil or protease inhibitors; chronic liver disease with hepatic failure; inability to understand consent form. | 400 mg once daily for up to 8 days and unfractionated heparin 5000 UI thrice daily until the end of hospitalization.<br>Methylprednisolone 0.5 mg/kg/day for 5 days could be added if the need for supplemental oxygen was 6 L/min or more. | **Need for supplemental oxygen**<br>Day 2, 53% vs 83% (Colchicine vs Placebo)<br>Day 6, 24% vs 56% (Colchicine vs Placebo)<br>Log-rank, p=0,01<br><br>**Adverse events**<br>The majority of adverse events were mild, did not differ significantly between groups and did not lead to patient withdrawal. Diarrhoea was more frequent in the Colchicine group (p = 0.26). Cardiac adverse events were absent.<br><br>**Progression to ICU**<br>Control: 4/37 vs Intervention: 2/38<br><br>**Length of ICU stay**<br>11 (Control, n=4) vs 12 (Intervention, n=2) days<br>No variation |
| Salehzadeh, F *et al.*<br>Research Square 2020[15]<br>Pre-print | RCT, single centre<br><br>21 May to 20 June 2020. | Setting: Iran<br>n= 50 (hydroxychloroquine and colchicine)<br>n= 50 (hydroxychloroquine and placebo)<br><br>100 patients **hospitalised** with COVID-19; median age 56, control 55.56 vs intervention 56.56 years<br>Female 69%, control 56% vs intervention 62%<br><br>Comorbidities (% intervention; % control): diabetes mellitus (10; 12), ischemic heart disease (12; 18), hypertension (6; 16), cancer/neoplastic disorder (2; 2), COPD (0; 8), renal failure (8; 2), hypothyroidism (2; 2)<br><br>Inclusion criteria:<br>Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19<br><br>Exclusion: | Treatment<br>Colchicine (1 mg)<br>Co-Intervention: Standard care<br>Duration : 6 days<br><br>Control<br>Placebo tablet with no therapeutic effects in addition to standard care (hydroxychloroquine)<br>Duration : 6 days | **Length of hospitalisation (mean)**<br>6.28 days (Colchicine) vs 8.12 days (Placebo), p<0.001 |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | | Sensitivity to any medications of regimens, renal failure, heart failure, pregnancy, participating in another clinical study and refusal to participate in the study before or during the follow-up period | | |

## Table 2. Characteristics of excluded studies

| Citation | Type of record | Reason for exclusion |
|---|---|---|
| Brunetti L, Diawara O, Tsai A, *et al.* Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. *Journal of Clinical Medicine* 2020;9(9):2961. | Journal article | Wrong study design (cohort) |
| Cantini F, Goletti D, Petrone L, *et al.* Immune therapy, or antiviral therapy, or both for COVID-19: a systematic review. *Drugs* 2020;80(18):1929-46. | Journal article | Systematic review synthesising previously included RCT(s)[8] and other ineligible study designs |
| Corral P, Corral G, Diaz R. Colchicine and COVID-19. *The Journal of Clinical Pharmacology* 2020;60(8):978. | Journal article (letter) | Wrong study design |
| McEwan T & Robinson PC. A systematic review of the infectious complications of colchicine and the use of colchicine to treat infections. *Seminars in Arthritis and Rheumatism* 2020;51(1):101-12. | Journal article | Systematic review synthesising previously included RCT(s)[8] and other ineligible study designs |
| Papadopoulos C, Teperikidis E, Mouselimis D, *et al.* Colchicine as a potential therapeutic agent against cardiovascular complications of COVID-19: an exploratory review. *SN Comprehensive Clinical Medicine* 2020;2(9):1-11. | Journal article | Wrong study design (hypothesis-generating review) |
| Kobak S. COVID-19 infection in a patient with FMF: does colchicine have a protective effect? *Annals of the Rheumatic Diseases* 2020; 0(0):1-2. | Correspondence in journal | Wrong outcomes |
| Scarsi M, Piantoni S, Colombo E, *et al.* Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. *Annals of the Rheumatic Diseases* 2020;79:1286-9. | Journal article | Wrong study design (cohort) |
| Vrachatis DA, Giannopoulos GV, Giotaki SG, *et al.* Impact of colchicine on mortality in patients with COVID-19. A meta-analysis. *Hellenic Journal of Cardiology* 2021 Jan 6;S1109-9666(20)30285-2. | Journal article | Systematic review synthesising previously included RCT(s)[8,9] and other ineligible study designs |

## Table 3. Characteristics of planned and ongoing studies

| Citation | Study design | Estimated population (n) | Treatment |
|---|---|---|---|
| Azienda Ospedaliero - Universitaria di Parma. EUCTR2020-001258-23-IT, first registered 20 April 2020 | RCT with parallel assignment | 310 | Patients will be randomised to standard of care or **colchicine in tablet form** |
| Dalili N, Kashefizadeh A, Nafar M, *et al*. *Adding colchicine to the antiretroviral medication - lopinavir/ritonavir (Kaletra) in hospitalized patients with non-severe Covid-19 pneumonia: a structured summary of a study protocol for a randomized controlled trial.* Trials 2020;21:489 AND Shahid Beheshti University of Medical Sciences. NCT04360980, first registered 24 April 2020 | RCT with parallel assignment | 80 | Participants will be randomised to standard treatment (3 g vitamin C, 400 mg tiamine, selenium, 500 mg omega-3, vitamins A and D, azithromycin, ceftriaxone and Kaletra 400 twice a day for 10 days) or **standard treatment plus 1.5 mg colchicine (loading dose) followed by 0.5 mg colchicine orally twice daily** |
| Dhaka Medical College. NCT04527562, first registered 26 August 2020 | RCT with parallel assignment | 300 | Participants will be randomised to standard treatment per the national guidelines of Bangladesh plus placebo or **colchicine at a starting dose of 1.2 mg (single or 12 hourly divided dose), and 0.6 mg daily thereafter for 13 days. In the case of gastrointestinal compliants, omeprazole and antiemetic will be prescribed** |
| Estudios Clínicos Latino América. NCT04328480, first registered 31 March 2020 | RCT with parallel assignment | 2500 | Participants will be randomised to local standard of care or **local standard of care plus colchicine, preferentially administered orally (otherwise via nasogastric route, in the case of ventilation or contraindications to oral route) at dosage schedules dependent on concomitant lopinavir/ritonavir treatment** |
| FFIS. EUCTR2020-001511-25-ES, first registered 15 April 2020 | RCT with parallel assignment | 102 | Patients will be randomised to unspecified control or **0.5 mg colchicine** |
| Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia. NCT04350320, first registered 17 April 2020 | RCT with parallel assignment | 102 | Participants will be randomised to standard therapy or **standard therapy plus colchicine at a loading dose of 1.5 mg (1 mg and 0.5 mg two hours later), with 0.5 mg every 12 hours thereafter for seven days and 0.5 mg every 24 hours until the completion of 28 days. Dosage will be adjusted in participants receiving lopinavir/ritonavir** |
| Fundación Universitaria de Ciencias de la Salud. NCT04539873, first registered 7 September 2020 | RCT with parallel assignment | Not provided | Participants will be randomised to standard treatment per the Colombian guidelines or **colchicine 1.5 mg on the first day, followed by 0.5 mg every 12 hours on days 2 to 7 and 0.5 mg per day until completion on day 14 ± 1 days** |
| Indira Gandhi Medical College & Hospital-Shimla, Department of Medicine. CTRI/2020/09/028088, first registered 28 September 2020 | RCT with parallel assignment | 34 | Participants will be randomised to receive standard of care or **standard of care plus colchicine 0.6 mg orally every 12 hours, aspirin 325 mg orally every 6 hours and montelukast 10 mg orally once a day until discharge** |
| Insel Gruppe AG - Bern University Hospital, Department of Cardiology. EudraCT 2020-002234-32, first registered 26 October 2020 | RCT with parallel assignment | 420 | Participants will be randomised to receive edoxaban tablets administered orally or **colchicine tablets administered orally** |

| Citation | Study design | Estimated population (n) | Treatment |
|---|---|---|---|
| Instituto de Investigación Marqués de Valdecilla. NCT04416334, first registered 4 June 2020 | RCT with parallel assignment | 954 | Participants will be randomised to receive symptomatic treatment (paracetamol and treatment based on physician recommendation) or **symptomatic treatment plus colchicine 0.5 mg orally twice daily for three days, then once daily for 18 days** |
| Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. NCT04367168, first registered 29 April 2020 | RCT with parallel assignment | 174 | Participants will be randomised to placebo tablets taken orally, 1.5 tablets on day 1 and half a tablet twice daily for 10 days thereafter, or **colchicine 1 mg at the same dosing frequency** |
| Kermanshah University of Medical Sciences. NCT04392141, first registered 18 May 2020 | RCT with parallel assignment | 200 | Participants will be randomised to standard treatment based on national recommendations or **standard treatment plus colchicine and a herbal extraction containing phenolic monoterpene fractions** |
| Liaquat University of Medical & Health Sciences. NCT04603690, first registered 27 October 2020 | RCT with parallel assignment | Not provided | Participants will be randomised to receive standard care as per hospital guidelines or **colchicine at an initial dose of 1.5 mg (1 mg initially and 0.5 mg two hours later), followed by 0.5 mg every 12 hours for seven days or 0.5 mg every 24 hours for 14 days (dose halved in patients receiving ritonavir or lopinavir, and those with impaired renal clearance)** |
| Lomonosov Moscow State University Medical Research and Educational Center. NCT04403243, first registered 27 May 2020 | RCT with parallel assignment | 70 | Participants will be randomised to ruxolitinib 5 mg taken orally twice daily for 10 days, or **colchicine 0.5 mg taken orally twice daily during the first three days and then 0.5 mg taken orally once daily if weight is < 86 kg, or twice daily if weight is > 86 kg, for seven days** |
| Maimonides Medical Center. NCT04363437, first registered 27 April 2020 | RCT with parallel assignment | 70 | Participants will be randomised to usual care or **1.2 mg colchicine (loading dose) followed by 0.6 mg two hours later, in the absence of severe gastrointestinal symptoms, on the first day; followed by 0.6 mg twice daily for 14 days or until discharge** |
| Maria Joyera Rodríguez. NCT04492358, first registered 30 July 2020 | RCT with parallel assignment | 144 | Participants will be randomised to standard of care or **colchicine 0.3 mg/kg/day (with adjustments for age, weight and kidney function) plus prednisone 60 mg/day for three days, followed by 0.5 mg/day colchicine for a further 14 days** |
| Mashhad University of Medical Sciences. IRCT20200408046990N2, first registered 25 April 2020 | RCT with parallel assignment | 40 | Patients will be randomised to placebo tablets once daily for two weeks or **1 mg colchicine tablets once daily for two weeks** |
| Medical Biology Research Center, Kermanshah University Medical Sciences. IRCT20150623022884N3, first registered 18 November 2020 | RCT with parallel assignment | 120 | Participants are randomised to receive standard care (Kaletra or hydroxychloroquine, naproxen or other accessory drugs) or **standard care plus MAB98 (colchicine, thymoquinone and thymol fractions from Colchicum autumnale, Nigella sativa and Trachyspermum ammi) capsules 125/250 mg two or three times daily, for 6 days (outpatients) or 12 days (inpatients)** |
| Miami Cardiac and Vascular Institute. NCT04510038, first registered 12 August 2020 | RCT with parallel assignment | 75 | Participants will be randomised to standard of care or **standard of care plus colchicine 0.6 mg twice daily for 30 days, with decreased dose of 0.3 to 0.6 mg daily in the case of gastrointestinal intolerance, CYP3A4 or protease inhibitor, chronic kidney disease at stage 4 or above, end stage renal disease, or dialysis** |
| Saghafi, F. IRCT20190810044500N5, first registered 18 May 2020 | RCT with parallel assignment | 200 | Patients will be randomised, in addition to standard treatment of 200 mg hydroxychloroquine daily, to two tablets of placebo for the first to the third day and one daily dose for 12 days thereafter; or **0.5 mg colchicine for the first to the third day and 1 mg daily for 12 days thereafter in addition to 200 mg hydroxychloroquine daily** |
| Sociedad Española de Cardiología. EUCTR2020-001841-38-ES, first registered 26 May 2020 | Clinical trial with single group assignment | 240 | Patients will receive 0.5 to 1 mg colchicine |
| University of California. NCT04355143, first registered 21 April 2020 | RCT with parallel assignment | 150 | Patients will be randomised to current care as determined by treating physician or **current care plus 0.6 mg colchicine tablets taken orally every 12 hours for 30 days** |
| University of Perugia. NCT04375202, first registered 5 May 2020 | RCT with parallel assignment | 308 | Participants will be randomised to current care or **current care plus 1 mg colchicine twice daily (0.5 taken orally every 8 hours) for 30 days, with dosage halved for those weighing < 100 kg** |
| University of Sao Paulo. NCT04724629, first registered 26 January 2021 | RCT with parallel assignment | 60 | Participants will be randomised to receive standard of care (corticosteroids and antivirals), IL-17 inhibitor (ixekizumab) 80 mg/week for four weeks, low-dose IL-2 (aldesleukin) 1.5 million IU/day for seven days or **indirect IL-6 inhibitor (colchicine) 0.5 mg every 8 hours for three days followed by 0.5 mg twice daily for four weeks** |
| Yale University. NCT04472611, first registered 15 July 2020 | RCT with parallel assignment | 824 | Participants will be randomised to standard of care or **standard of care plus rosuvastatin 40 mg daily and colchicine 0.6 mg twice daily for three days, and 0.6 mg once daily thereafter for the duration of hospitalisation** |

## Table 4. Summary of findings for hospitalised patients with moderate to severe COVID-19 (Mikolajewska *et al*. 2021[3])

SUMMARY OF FINDINGS

**Summary of findings 1. Colchicine plus standard care compared to standard care (plus/minus placebo) for hospitalised patients with COVID-19 and moderate to severe disease**

| Colchicine plus standard care compared to standard care (plus/minus placebo) for hospitalised patients with COVID-19 and moderate to severe disease | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient or population:** people with COVID-19 and moderate to severe disease<br>**Settings:** hospitalised<br>**Intervention:** colchicine plus standard care<br>**Comparator:** standard care (plus/minus placebo) | | | | | | | |
| **Outcomes** | **Absolute effects from study(ies)* (95% CI)** | | | **No of participants (studies)** | **Certainty of the evidence (GRADE)** | **Plain language summary** | **Comments** |
| | **Risk with placebo or standard care alone** | **Risk with colchicine** | **Relative risk [risk difference; 95% CI]** | | | | |
| **All-cause mortality** assessed up to day 28 | 207 per 1000 | 207 per 1000 (193 to 224) | **RR 1.00** (95% CI 0.93 to 1.08)[a]<br>[0 more per 1000; 14 fewer to 17 more] | 11,445 (2 studies) | ⊕⊕⊕○<br>**Moderate** [b] | Colchicine probably results in little to no difference in all-cause mortality up to 28 days. | Additionally, one study reported all-cause mortality at hospital discharge for 75 participants (Lopes 2021).<br>One study analysed also reported all-cause mortality over time (time-to-event) for 11,340 participants (Horby 2021), which similarly showed little to no effect on mortality (HR 1.01, 95% CI 0.93 to 1.10). |
| **Worsening of clinical status:** participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death up to day 28 | 244 per 1000 | 249 per 1000 (234 to 266) | **RR 1.02** (95% CI 0.96 to 1.09)[c]<br>[4 more per 1000, 95% CI 10 fewer to 22 more] | 10916 (2 studies) | ⊕⊕⊕○<br>**Moderate** [b] | Colchicine probably has little to no impact on new need for invasive mechanical ventilation or death. | — |
| **Improvement of clinical status:** participants discharged alive up to day 28 without clinical deterioration or death | 704 of 1000 | 697 of 1000 (676 to 711) | **RR 0.99** (95% CI 0.96 to 1.01)<br>[7 fewer per 1000, 95% CI 28 fewer to 7 more] | 11,340 (1 study) | ⊕⊕⊕○<br>**Moderate** [b] | Colchicine probably results in little to no difference in improvement of clinical status, if this is measured with the number of participants discharged alive up to day 28 without clinical deterioration or death. | One study reported participants discharged alive at the longest follow-up and followed all participants until discharge (Lopes 2021) which similarly showed that colchicine may result in little to no difference in the improvement of clinical status assessed as participants discharged alive (RR 1.09, 95% CI 0.98 to 1.21) |
| **Quality of life**, including fatigue and neurological status at longest follow-up available | We identified no studies reporting quality of life. | | | — | — | We do not know whether colchicine has any impact on quality of life. | — |
| **Adverse events** (follow-up: until discharge) | 389 per 1000 | 389 per 1000 (218 to 692) | **RR 1.00** (95% CI 0.56 to 1.78)<br>[0 fewer per 1000, 95% CI 171 fewer to 303 more] | 72 (1 study) | ⊕○○○<br>**Very low** [d,e,f] | The evidence is very uncertain about the effect of colchicine on adverse events | — |
| **Serious adverse events** (follow-up: until hospital discharge or a maximum of 21 days) | 0 events observed | 0 events observed | Not estimable | 105 (1 study) | ⊕○○○<br>**Very low** [e,g,h] | The evidence is very uncertain about the effect of colchicine on adverse events | — |

*The basis for the **control group absolute risks** from the study(ies) is mean risk across study(ies) unless otherwise stated in comments. **The intervention absolute risk and difference** is based on the risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **COVID-19:** coronavirus disease 2019; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working User Group grades of evidence
**High quality:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Table 4 (continued). Explanations to the summary of findings for hospitalised patients with moderate to severe COVID-19 (Mikolajewska *et al*. 2021[3])**

[a]Sensitivity analysis results presented using a fixed-effect model. This was because the random-effects model meta-analysis resulted in very wide confidence intervals (RR 0.72, 95% CI 0.21 to 2.44), due to more weight being given to one small study with few events (Deftereos 2020), and contributing only 105/11,445 participants included in the mortality analysis.
[b]Downgraded one level for serious study limitations due to the unblinded study design.
[c]Sensitivity analysis results presented using a fixed-effect model. This was because the random-effects model meta-analysis resulted in very wide confidence intervals (RR 0.53, 95% CI 0.09 to 3.15), due to more weight being given to one small study with few events (Deftereos 2020), and contributing only 105/10,916 participants included in the analysis of the worsening of clinical status.
[d]Downgraded two levels for very serious imprecision due to only one study with very small number of participants and events.
[e]Downgraded one level for other considerations due to selective reporting of adverse events across studies (e.g. severe treatment-associated events only).
[f]Downgraded one level for serious study limitations due to the high risk of bias because of the competing event 'death.'
[g]Downgraded one level for serious study limitations due to the unblinded study design, and high risk of bias because of the competing event 'death.'
[h]Downgraded two levels for very serious imprecision due to only one study and no events were observed.

## Table 5. Summary of findings for non-hospitalised patients with asymptomatic or mild COVID-19 (Mikolajewska *et al*. 2021[3])

**Colchicine compared to placebo or standard care alone for non-hospitalised patients with SARS-CoV-2 infection and asymptomatic or mild disease**

**Patient or population:** people with SARS-CoV-2 infection and asymptomatic or mild disease

**Settings: non-hospitalised**

**Intervention:** colchicine

**Comparator:** placebo or standard care alone

| Outcomes | Absolute effects from study(ies)* (95% CI) | | | No of participants (studies) | Certainty of the evidence (GRADE) | Plain language summary |
|---|---|---|---|---|---|---|
| | Risk with placebo or standard care alone | Risk with colchicine | Relative risk [risk difference; 95% CI] | | | |
| **All-cause mortality** up to day 28 | 4 per 1000 | 2 per 1000 (0 to 6) | **Peto OR 0.57** (95% CI 0.20 to 1.62) [2 fewer per 1000, 95% CI 4 fewer to 2 more] | 4488 (1 study) | ⊕⊖⊖⊖ **Low** [a] | The evidence is uncertain about the effect of colchicine on all-cause mortality at 28 days. |
| **Admission to hospital or death** within 28 days | 58 per 1000 | 46 per 1000 (36 to 60) | **RR 0.80** (95% CI 0.62 to 1.03) [12 fewer per 1000, 95% CI 22 fewer to 2 more] | 4488 (1 study) | ⊕⊕⊕⊖ **Moderate** [b] | Colchicine probably results in a slight reduction in the risk of admission to hospital or death within 28 days. |
| **Symptom resolution** | We identified no studies reporting symptom resolution, defined as all initial symptoms resolved (asymptomatic) at day 14, day 28, or up to longest follow-up. | | | — | — | We do not know whether colchicine has any impact on symptom resolution. |
| **Duration to symptom resolution** | We identified no studies reporting symptom resolution, defined as all initial symptoms resolved (asymptomatic) at day 14, day 28, or up to longest follow-up. | | | — | — | We do not know whether colchicine has any impact on symptom resolution. |
| **Quality of life** | We identified no studied reporting quality of life. | | | — | — | We do not know whether colchicine has any impact on quality of life. |
| **Adverse events** within 28 days | We identified no study reporting any adverse events. 1 study (4412 participants) reported treatment-related adverse events for 532/2195 (24.2%) participants in the colchicine group and 344/2217 (15.5%) participants in the control group. | | | 4412 (1 study) | ⊕⊖⊖⊖ **Low** [c] | The evidence is uncertain about the effect of colchicine on the risk of adverse events. |
| **Serious adverse events** within 28 days | 63 per 1000 | 49 per 1000 (38 to 63) | **RR 0.78** (95% CI 0.61 to 1.00) [14 fewer per 1000, 95% CI 25 fewer to 0 more] | 4412 (1 study) | ⊕⊕⊕⊖ **Moderate** [b] | Colchicine probably results in a slight reduction of serious adverse events. |

*The basis for the **control group absolute risks** from the study(ies) is mean risk across study(ies) unless otherwise stated in comments. **The intervention absolute risk and difference** is based on the risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **COVID-19:** coronavirus disease 2019; **OR:** odds ratio; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working User Group grades of evidence
**High quality:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** we are very uncertain about the estimate.

[a]Downgraded two levels for very serious imprecision, because of very few events, and wide confidence intervals.
[b]Downgraded one level for imprecision due to data from only one study.
[c]Downgraded two levels for serious indirectness, because definition of outcome differed substantially from definition used in our review (treatment-related adverse events instead of any adverse events).

## Table 6. Summary of findings for outcome: hospitalisation for COVID-19 in non-hospitalised patients with COVID-19 (Tardif *et al.* 2021[12])

**Author(s)**: M.McCaul, A. Brand

**Question**: Colchicine compared to Standard treatment or placebo for non-hospitalised patients with COVID-19

**Setting**: Canada, USA, South Africa; and unspecified countries in Europe and South America

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Colchicine | Standard treatment or placebo | Relative (95% CI) | Absolute (95% CI) | |
| **Hospitalisation for COVID-19** | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 101/2235 (4.5%) | 131/2253 (5.8%) | **OR 0.79** (0.60 to 1.03) | **12 fewer per 1,000** (from 22 fewer to 2 more) | ⊕⊕◯◯ LOW |

**CI:** Confidence interval; **OR:** Odds ratio

### Explanations

a. Downgraded by 1 due to serious risk of bias in randomisation and missing outcome data
b. Downgraded by 1 due to serious imprecision

**Table 7. Quality appraisal: overall risk of bias for the primary outcome (length of hospitalization; symptoms and co-existed disease) from Covid-nma.com[8] (Salehzadeh *et al*. ,2020)[15]**

| Bias | Author's judgment | Support for judgment |
|---|---|---|
| Randomisation | Some concerns | Quote: "Patients were randomized in 1:1 allocation in two groups (group-A and group-B) which contains 50 patients"<br>Comment: No information on allocation sequence. No information on allocation concealment. Allocation sequence probably random. |
| Deviations from intervention | Some concerns | Quote: "prospective, open-label, randomized and double blind clinical trial"; "The participants of the placebo group were received a similar tablet without therapeutic effects"<br>Comment: Blinding unclear as no description provided and contradictory descriptions used in study.<br>No information on cross-over (no flow chart)<br>No information on administration of co-intervention of interest: antivirals, anticoagulants. biologics, corticosteroids.<br>Data analyzed appropriately; participants analyzed according to their intervention assignment. |
| Missing outcome data | Low | Comment: 100 patients randomized; 100 patients analyzed.<br>Risk assessed to be low for the outcome: Mortality. |
| Measurement of the outcome | Low | Comment: Unclear blinding<br>Mortality is observer-reported and not involving judgement.<br>Risk assessed to be low for the outcome: Mortality. |
| Selection of the reported results | Some concerns | Comment: Neither the protocol nor the statistical analysis plan was available.<br>The prospective registry was available. The mortality outcome was not listed.<br>Risk assessed to be some concerns for the outcome: Mortality. |
| Overall risk of bias | **Some concerns** | |

## Appendix 1: Search strategy (current to 28 January 2021)

| |
|---|
| **Epistemonikos**<br><br>(title:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*) OR abstract:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*)) AND (title:(colchicine) OR abstract:(colchicine))<br>**Records retrieved: 36 in initial review; 53 in first update; 82 in second update (20 relevant to PICO question)** |
| **Cochrane COVID Study Register**<br><br>Searched the register for the term "colchicine"<br>**Records retrieved: 31 in initial review; 45 in first update; 68 in second update (15 relevant to PICO question)** |
| **www.covid-nma.com**<br><br>Searched the website for the term "colchicine"<br>**Records retrieved: 3** |

## Appendix 2: Evidence to decision framework

| Desirable Effects | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| **X Trivial**<br>o Small<br>o Moderate<br>o Large<br>o Varies<br>o Don't know | • Colchicine results in a slight reduction (or little to no difference) in the risk of admission to hospital or death within 28 days in non-hospitalised patients with asymptomatic or mild disease (RR 0.80; 95% CI 0.62 to 1.03; 1 RCT; n=4 488; moderate certainty evidence)<br>• The evidence is uncertain about the effect of colchicine on all-cause mortality at 28 days in non-hospitalised patients with asymptomatic or mild COVID-19 (Peto odds ratio [OR] 0.57; 95% CI 0.20 to 1.62; 1 RCT; n=4 488; low certainty evidence) Figure 3<br>• Colchicine plus standard care results in little to no difference in worsening of clinical status assessed as new need for invasive mechanical ventilation or death compared to standard care alone (RR 1.02, 95% CI 0.96 to 1.09; 2 RCTs, 10,916 participants; moderate-certainty evidence).<br>• Colchicine showed a potentially trivial effect in favour of placebo (RR 1.04; 95% CI 0.93 to 1.16; 1 RCT; n=10 811) for the new need for invasive mechanical ventilation in hospitalised patients with moderate to severe disease<br>• Colchicine results in a slight reduction in the risk of admission to hospital or death within 28 days in non-hospitalised patients with asymptomatic or mild disease (RR 0.80; 95% CI 0.62 to 1.03; 1 RCT; n=4 488; moderate certainty evidence). | |

| Undesirable Effects | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o Large<br>o Moderate<br>**X Small**<br>o Trivial<br>o Varies<br>o Don't know | • The extent to which colchicine use is associated with serious adverse events (SAEs) and adverse events (AEs) in hospitalised patients is uncertain. | |

| Certainty of evidence: What is the overall certainty of the evidence of effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o Very low<br>o Low<br>**X Moderate**<br>o High<br>o No included studies | Overall moderate to low certainty for some outcomes | |

| Values: Is there important uncertainty about or variability in how much people value the main outcomes? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o Important uncertainty or variability<br>o Possibly important uncertainty or variability<br>**X Probably no important uncertainty or variability**<br>o No important uncertainty or variability | There are no available local survey data to indicate preferences in relation to colchicine use in COVID-19. | The committee is of the opinion that there might be some support for the use of colchicine, as it is available and relatively inexpensive. |

| **Balance of effects:** Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| **X Favors the comparison**<br>o Probably favors the comparison<br>o Does not favor either the intervention or the comparison<br>o Probably favors the intervention<br>o Favors the intervention<br>o Varies<br>o Don't know | **Benefit:** Moderate certainty of evidence of little to no benefit for colchicine<br><br>**Harm:** Moderate to low certainty of varied harms associated with the use of colchicine (Figure 3) | |
| **Resources required:** How large are the resource requirements (costs)? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o Large costs<br>o Moderate costs<br>o Negligible costs and savings<br>o Moderate savings<br>o Large savings<br>o Varies<br>o Don't know<br>**X Not applicable** | As the recommendation is not to use the intervention, the resource requirements are irrelevant. | |
| **Cost effectiveness:** Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o Favors the comparison<br>o Probably favors the comparison<br>o Does not favor either the intervention or the comparison<br>o Probably favors the intervention<br>o Favors the intervention<br>o Varies<br>**X No included studies** | No studies on cost-effective are possible, as no benefits were identified. | |
| **Equity:** What would be the impact on health equity? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o Reduced<br>o Probably reduced<br>o Probably no impact<br>o Probably increased<br>o Increased<br>o Varies<br>o Don't know<br>**X Not applicable** | As the recommendation is not to use the intervention, no equity considerations have been included. | |
| **Acceptability:** Is the intervention acceptable to key stakeholders? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| o No<br>o Probably no<br>o Probably yes<br>o Yes<br>o Varies<br>**X Don't know** | Although no studies of acceptability have been conducted, the committee is of the opinion that there might be some support for the use of colchicine, as it is available and relatively inexpensive. | |

| Feasibility: Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know<br>**X Not applicable** | The product is registered in South Africa and is procured in the public sector. The current tender price is R22.18 for 12x 0.5mg tablets (HP09-2021SD). However, as the recommendation is against the intervention, the consideration of feasibility is irrelevant. | |

## Appendix 3: Updating of rapid report

| Date | Signal | Rationale |
|---|---|---|
| 26 October 2021 | Publication of RECOVERY trial and Cochrane review | The study results of the RECOVERY trial by Horby *et al*. 2021, evaluating the efficacy of colchicine in hospitalised patients, and synthesised evidence of the Cochrane review by Mikolajewska *et al*. 2021, including both hospitalised and non-hospitalised populations. |

| Version | Date | Reviewer(s) | Recommendation and Rationale |
|---|---|---|---|
| First | 6 August 2020 | OA, AB, AH, RdW, AG | Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects. |
| Second | 20 October 2020 | MM, AB, RdW, AG | Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects. |
| Third | 12 February 2021 | MM, AB, RdW, AG | Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects. |
| Fourth | 19 November 2021 | MM, AB, RdW, AG | Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. No clinically important benefits in the hospitalised or non-hospitalised, with increased risk of diarrhoea amongst ambulatory patients. |

**For internal NDoH use:**
*WHO INN:* Colchicine
*ATC:* M04AC01
*ICD10:* U07.1/U07.2