National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[F] Evidence review for colchicine

NICE guideline NG191

November 2021

Guideline version (Final)

Disclaimer

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Objective

This evidence review aims to review the effectiveness and safety of colchicine for acute symptoms and complications of COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

1. What is the effectiveness and safety of colchicine for acute symptoms and complications of COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The original NICE recommendations were published in May 2021 and used the evidence review that was developed by the Australian Living Guidelines Taskforce. Ongoing surveillance was conducted from publication to identify any new emerging evidence to be considered for inclusion in an update (see below).

Summary of included studies

Continual weekly surveillance searches were used to identify studies for consideration in this update (see appendix B for full details). Relevant references were screened against the protocol using their titles and abstracts and 19 full text references were obtained and assessed for relevance.

17 studies were excluded. Details of excluded studies are in appendix C.

In total, 6 studies are included in this updated evidence review, 4 of which were included in the previous version of the evidence review (the 2 new studies are PRINCIPLE 2021 and RECOVERY 2021 that were identified in surveillance checks). A summary of the included studies and their quality assessment is shown in the Results section and in appendix D. Forest plots are in the Results section.

Study characteristics

Table 1: Hospital setting

COVID severity was not defined in all studies. Where it has been defined, this information has been included in the tables below.

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Deftereos (GRECCO-19) 2020 Greece **No. of participants: 105**	RCT	Clinical status scores: 3/7: 34.0-34.5% 4/7: 60.0-65.5% 5/7: 6.0-0%. The scale ranged from able to resume normal activities to death and was based on the WHO scale.	Adults PCR confirmed COVID-19 Body temperature of 37.5 degrees Celsius or greater and 2 or more of the following: sustained coughing, sustained sore throat, anosmia and/or ageusia, fatigue and/or tiredness and arterial oxygen partial pressure lower than 95 mm Hg on room air. **Median age (years):** Colchicine – 63 (IQR 55 – 70) Standard care – 65 (IQR 54 – 80) **% female:** Colchicine – 40 Standard care – 44	Colchicine plus standard care. Loading dose of 1500 micrograms followed by 500 micrograms colchicine 60 minutes later if no adverse GI effects observed. Reduced to 1000 micrograms for those receiving azithromycin. Maintenance dose of 500 micrograms colchicine twice daily (reduced to one dose in patients <60 kg body weight) for up to 3 weeks. Treatment duration was 30 days.	Standard care. Participants in both arms received 96-100% chloroquine or Hydroxychloroquine, 92.0-92.7% azithromycin, 14-19% lopinavir or ritonavir, 3.6-4.0% tocilizumab.	All-cause mortality Mechanical ventilation Serious adverse events Adverse events Discontinuation due to adverse events Clinical progression (scale)
Lopes 2021 Brazil	RCT	Moderate or severe. The moderate form was defined in	Adults PCR confirmed COVID-19	Colchicine plus standard care. Colchicine 500 micrograms thrice daily for 5 days,	Placebo plus standard care. All participants received the	All-cause mortality Discontinuation due to adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
No. of participants: 75		patients with fever, dyspnoea and imaging findings of pneumonia; the severe form in those with the same findings of moderate form plus respiratory rate ≥30 times per minute or oxygen saturation (SatO2) ≤92%.. These are consistent with how moderate and severe are defined in other studies.	Diagnosed by RT-PCR and lung computed tomography scan involvement compatible with COVID-19 pneumonia; body weight >50 kg, normal levels of serum calcium and potassium, QT interval < 450 ms, negative pregnancy test if woman under 50. **Median age (years):** Colchicine – 54.5 (IQR 42.5 – 64.5) Placebo – 55.0 (IQR 43.0 – 67.0) **% female:** Colchicine – 47 Placebo – 61 **% on methylprednisolone** Colchicine – 69% Placebo – 67%	then 500 micrograms twice daily for 5 days; if body weight was greater than or equal to 80kg, the first dose was 1000 micrograms. Patients with kidney disease (eGFR <30 mL/min/1.73m2) received 250 micrograms thrice daily for 5 days, then 250 micrograms twice daily for 5 days, irrespective of body weight. Treatment duration was 10 days.	institutional treatment for COVID-19 with azithromycin 500000 micrograms once daily for up to 7 days, hydroxychloroquine 400000 micrograms twice daily for 2 days, then 400000 micrograms once daily for up to 8 days and unfractionated heparin 5000 UI thrice daily until the end of hospitalisation.	ICU admission Discharge from hospital (by day 10)
New study: Horby (RECOVERY) 2021 UK **No. of participants: 11340**	RCT	No oxygen support or simple oxygen: 15% Non-invasive ventilation: 31-33% Invasive mechanical ventilation: 45-46%	Adults PCR confirmed or clinically suspected COVID-19. Exclusion criteria: Children and pregnant women were not eligible for randomisation to colchicine. Patients with severe liver impairment, significant cytopaenia, concomitant use of strong CYP3A4 or P-glycoprotein inhibitors, or hypersensitivity to lactose were excluded. Any past medical history that might put a	Colchicine plus standard care. Patients allocated to colchicine were to receive 1000 micrograms after randomisation followed by 500 micrograms 12 hours later. Patients allocated to colchicine then received 500 micrograms twice	Standard care. In each arm, 93% had corticosteroids, and 22% had remdesivir.	All-cause mortality Mechanical ventilation Discharge from hospital within 28 days

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			patient at risk in the opinion of the clinical staff. **Mean age (years):** Colchicine – 63.3 (SD 13.8) Standard care – 64 (SD 13.7) **% female:** Colchicine – 31 Standard care – 30	daily by mouth or nasogastric tube for 10 days in total or until discharge, whichever occurred earlier. Dose frequency was halved for patients receiving a moderate CYP3A4 inhibitor or who had renal impairment (estimated glomerular filtration rate <30 ml/min/1.73m2) or estimated body weight <70 kg. Treatment duration 10 days.		
Salehzadeh 2021 Iran **No of participants: 100**	RCT	Severity and level of oxygen support was not provided	Adults PCR confirmed Exclusion criteria: 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.	Colchicine plus standard care. 1000 micrograms of colchicine daily for 6 days (alongside hydroxychloroquine for 6 days).	Placebo for 6 days plus standard care (alongside hydroxychloroquine for 6 days).	Duration of hospital stay

Table 2: Community setting

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Tardif (COLCORONA) 2021 Brazil, Canada, Greece, South Africa, Spain, and the USA. **No. of participants: 4488**	RCT	Not currently being treated in hospital and not under immediate consideration for hospital treatment or admission.	Adults aged ≥ 40 years and had at least 1 high risk criteria PCR confirmed COVID-19 or clinical criteria **Median age (years):** Colchicine – 53 (IQR 47.0 – 61.0) Placebo – 54.0 (IQR 47.0 – 61.0) **% female:** Colchicine – 55.4 Placebo – 52.5	Colchicine plus standard care. 500 micrograms colchicine orally administered twice per day for the first 3 days. After 3 days: once per day. Duration of treatment was 27 days.	Placebo plus standard care. In each arm, 0.5% had hydroxychloroquine, 2.1-2.9% had an oral anticoagulant, 8.7-10.4% had aspirin, and 1.4-1.9% had other platelet agents.	All-cause mortality All-cause mortality or hospitalisation Mechanical ventilation Serious adverse events Adverse events Hospitalisation for COVID-19 Hospitalisation due to any cause
New study: PRINCIPLE 2021 UK **No. of participants: 276**	RCT	Well-being (WHO5 Questionnaire) mean (SD): 47.5 (25.0) (out of 100).	Adults aged ≥65, or ≥18 years with comorbidities or shortness of breath, and unwell ≤14 days with suspected COVID-19 in the community. PCR confirmed COVID-19 or suspected COVID-19. Comorbidities required for eligibility were: heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problems; weakened immune system (for example, chemotherapy); and self-reported	Colchicine plus standard care. Participants received standard care plus colchicine 500 micrograms daily. Treatment duration was 14 days.	Standard care. Standard care in the NHS for suspected COVID-19 in the community was largely focused on managing symptoms with antipyretics.	All-cause mortality or hospitalisation Mechanical ventilation Serious adverse events ICU admission Participants who experienced alleviation of all symptoms within 28 days of starting treatment

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			obesity or body mass index ≥35 kg/m2. **Age 18-49 years %:** Colchicine – 52.3 Standard care – 29.3 **Age 50-64 years %:** Colchicine – 32.8 Standard care – 46.4 **Age ≥65 years %:** Colchicine – 14.9 Standard care – 24.3 **% female:** Colchicine – 49.4 Standard care – 58.6			Time to alleviation of all symptoms, estimated treatment effect (median days, mean difference) Reported recovery (days) Time to reported recovery (days)

Table 3: Trial funder and status details

Study	Trial registration details/no.	Funder details	Print status
COLCORONA (Tardif) 2021	NCT04322682	Government of Quebec, the National Heart, Lung, and Blood Institute of the US National Institutes of Health (NIH), the Montreal Heart Institute Foundation, the Bill & Melinda Gates Foundation	Full publication
GRECCO-19 (Defereos) 2020	NCT04326790	ELPEN Pharmaceuticals, Acarpia Pharmaceuticals, and Karian Pharmaceuticals	Full publication
Lopes 2021	RBR-8jyhxh	FAPESP grants, CNPq and CAPES grants	Full publication
PRINCIPLE 2021	ISRCTN86534580	UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research	Pre-print
RECOVERY (Horby) 2021	NCT04381936	UK Research and Innovation (Medical Research Council) and National Institute of Health Research. Wellcome Trust.	Full publication
Salehzadeh 2021	IRCT20200418047126N1	Details of funding were not provided.	Pre-print

Results

Hospital setting

In this update we included data from RECOVERY (Horby) 2021 for the following outcomes:

- All-cause mortality within 21-28 days of starting treatment
- Mechanical ventilation within 21-28 days of starting treatment
- Discharge from hospital within 28 days

The following outcomes have not been updated:

- Serious adverse events within 21 days of starting treatment
- Adverse events within 21 days of starting treatment
- Discontinuation due to adverse events within 21 days of starting treatment
- Clinical progression (scale) within 21 days of starting treatment
- ICU admission – follow-up timepoint was not provided
- Discharge from hospital by day 10
- Duration of hospital stay

Findings

There is no evidence that colchicine is more effective than placebo or standard care in treating hospitalised patients with COVID-19.

What is the evidence informing this conclusion?
This is a November 2021 update of the evidence review from May 2021 and includes 1 new study (RECOVERY 2021). Evidence comes from 4 randomised trials that compared colchicine with placebo or standard care in 11620 adults admitted to hospital with COVID-19 (Deftereos 2020, Lopes 2021, Salehzadeh 2020, RECOVERY 2021).

The colchicine arm of the RECOVERY trial stopped recruitment because of futility of the intervention – that is, no effect on mortality was seen for existing participants and recruitment of further participants was not expected to change this finding.

Publication status
Salehzadeh 2020 was only available as a preprint and has therefore not been peer reviewed.

Study characteristics
The median age ranged from 55 to 64 years and the proportion of women ranged from 42% to 59%. The severity of COVID-19 was not clearly reported across studies. In Deftereos 2020, an arterial oxygen partial pressure of lower than 95 mmHg on room air was a key inclusion criterion. Lopes 2021 specified moderate to severe COVID-19 as an inclusion criterion but did not report how many patients of each category of severity were recruited. Salehzadeh 2020 did not define disease severity

other than specifying COVID-19 with confirmed lung involvement. In RECOVERY 2021, 15% of participants had no oxygen support or simple oxygen, 31-33% had non-invasive ventilation, and 45-46% had invasive mechanical ventilation.

The dosage of colchicine differed across the studies. Deftereos 2020, RECOVERY 2021, and Lopes 2021 used a higher initial dose (from 1,000 micrograms daily to 2,000 micrograms daily) for between 1 and 5 days before switching to a lower maintenance dose. The daily dose in the maintenance phase was 1,000 micrograms (Deftereos 2020, RECOVERY 2021, Lopes 2021, Salehzadeh 2020). Duration of treatment ranged from 6 days to 3 weeks across the studies.

Participants in 3 studies received hydroxychloroquine (or chloroquine) and azithromycin as part of standard care (Deftereos 2020, Lopes 2021, Salehzadeh 2020). Deftereos 2020 compared colchicine with standard care which included using hydroxychloroquine (or chloroquine) in 98% of participants and azithromycin in 92% of participants. RECOVERY 2021 compared colchicine with standard care which included using corticosteroids in 93% of participants and remdesivir in 22% of participants.

Follow-up ranged from 2 to 3 weeks; however Lopes 2021 did not clearly report the duration of follow-up.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

What are the main results?

Critical outcomes
There was no statistically significant effect on mortality or need for mechanical ventilation within 21 to 28 days of starting colchicine treatment compared with placebo or standard care.

Important outcomes
There was a statistically significant increase in adverse events with colchicine compared with standard care.
No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes duration of hospital stay.

Our confidence in the results
The certainty of evidence is moderate to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with all studies having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care not including corticosteroids); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). One study was only available as a preprint.

Community setting

In this update we included data from PRINCIPLE 2021 for the following outcomes:

- All-cause mortality or hospitalisation (28 or 30 days)
- Mechanical ventilation within 28-30 days of starting treatment
- Serious adverse events within 28-30 days of starting treatment
- Alleviation of all symptoms, estimated treatment effect (median days) within 28 days of starting treatment
- Time to first reported recovery (days) within 28 days of starting treatment

The following outcomes have not been updated:

- All-cause mortality within 30 days of starting treatment
- Adverse events within 30 days of starting treatment
- Hospitalisation for COVID-19 within 30 days of starting treatment
- Hospitalisation due to any cause (30 days) within 30 days of starting treatment

Findings

There is no evidence that colchicine is more effective than placebo or standard care in treating patients in the community with COVID-19.

What is the evidence informing this conclusion?
This is a November 2021 update of an evidence review from May 2021 and includes 1 new study (PRINCIPLE 2021). Evidence comes from 2 randomised trials that compared colchicine with placebo or standard care in 4764 adults in the community with COVID-19 (Tardiff 2021 (COLCORONA trial), PRINCIPLE 2021).

Publication status
PRINCIPLE 2021 was only available as a preprint and has therefore not been peer reviewed.

Study characteristics
The age of participants ranged from 18 to over 65 years and the proportion of women ranged from 49 to 59%. The studies did not clearly define the severity of COVID-19.

For Tardif 2021, the dosage of colchicine was 500 micrograms twice daily for the first 3 days then once daily for 27 days. For PRINCIPLE 2021, participants received colchicine 500 micrograms daily for 14 days.
As standard care in PRINCIPLE 2021, participants received medications focused on managing symptoms with antipyretics. In Tardif 2021, small percentages of participants were given hydroxychloroquine, oral anticoagulants, aspirin, and/or other platelet agents.

Follow-up after starting treatment was 28 days for PRINCIPLE 2021 and 30 days for Tardif 2021.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

What are the main results?

Critical outcomes

For the critical outcomes of hospitalisation for COVID-19, all-cause mortality, and need for mechanical ventilation, there was no statistically significant effect 28-30 days after starting colchicine treatment compared with control.

Important outcomes

There was a statistically significant increase in adverse events with colchicine compared with standard care. There was a statistically significant increase in serious adverse events with standard care compared with colchicine. This was potentially due to a greater number of cases of pneumonia in the standard care arm.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes time to reported recovery.

Our confidence in the results

The certainty of evidence is high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with one study having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect). One study was only available as a preprint.

Evidence to decision

Benefits and harms

Hospital settings

The panel considered that the results from studies of colchicine for COVID-19 in hospitals showed no benefit of effect on all-cause mortality, mechanical ventilation, discontinuation due to adverse events, clinical progression, ICU admission, or discharge from hospital within 28 days.

The evidence shows that people having colchicine plus standard care have statistically significantly more adverse events compared with people having standard care alone. Known adverse effects such as diarrhoea appear to have been under-reported in the identified evidence in hospital settings. The panel noted that colchicine commonly causes diarrhoea, which can lead to potassium deficiency (hypokalaemia). They advised that, because of the adverse events, colchicine tends to be used (for the treatment of gout) only for 3 to 4 days.

Although one study suggests that colchicine plus standard care reduces duration of hospital stay at a mean follow-up of 21 days compared with placebo plus standard care, this reduction of hospital stay is not statistically significant (a mean difference of 1.84 days (95% CI 0.78 to 2.90)).

Community settings

The panel considered that the results from studies of colchicine for COVID-19 in the community showed no benefit on hospitalisation for COVID-19, all-cause mortality, all-cause mortality or hospitalisation, mechanical ventilation, number of participants who experienced alleviation of all symptoms, or reported recovery time.

The evidence shows that people having colchicine plus standard care have a statistically significant reduction in serious adverse events compared with standard care alone or with placebo. This is possibly because pneumonia was reported less frequently in patients of the colchicine group compared with those in the placebo group. However, people having colchicine plus standard care have a statistically significant increase in adverse events compared with standard care plus placebo.

The adverse event diarrhoea was higher with colchicine than with placebo in Tardif 2021.

Certainty of evidence

The panel agreed that the certainty of evidence on colchicine for people with COVID-19 in hospital and in the community ranges from high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies having some degree of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care in hospitals not including corticosteroids); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Two studies were only available as preprints.

Values and preferences

The panel were not aware of any systematically collected data on preferences and values.

The panel thought that people would not want to take a treatment with no known benefits but well-established side effects such as diarrhoea.

Resources

Cost effectiveness was not assessed as part of the evidence review.

Colchicine costs from £2.54 for 28 tablets (BNF, November 2021). The panel therefore expected a negligible effect on resources.

Equity

Colchicine should not be used in pregnancy and no studies in children were identified. However, because the overall recommendation is not to offer colchicine to anyone, it is not expected to cause inequity among any subgroups.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability.

Colchicine is not licensed in the UK for treating COVID-19. The panel noted that its side effects are unlikely to be acceptable to patients or prescribers, especially diarrhoea and hypokalaemia. The panel noted that diarrhoea is particularly concerning in older people because frequent toilet visits and dehydration could be a risk factor for falls. They also noted that avoidable diarrhoea would not be acceptable in the intensive care setting.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility.

Colchicine is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Appendices

Appendix A: PICO table

PICO table

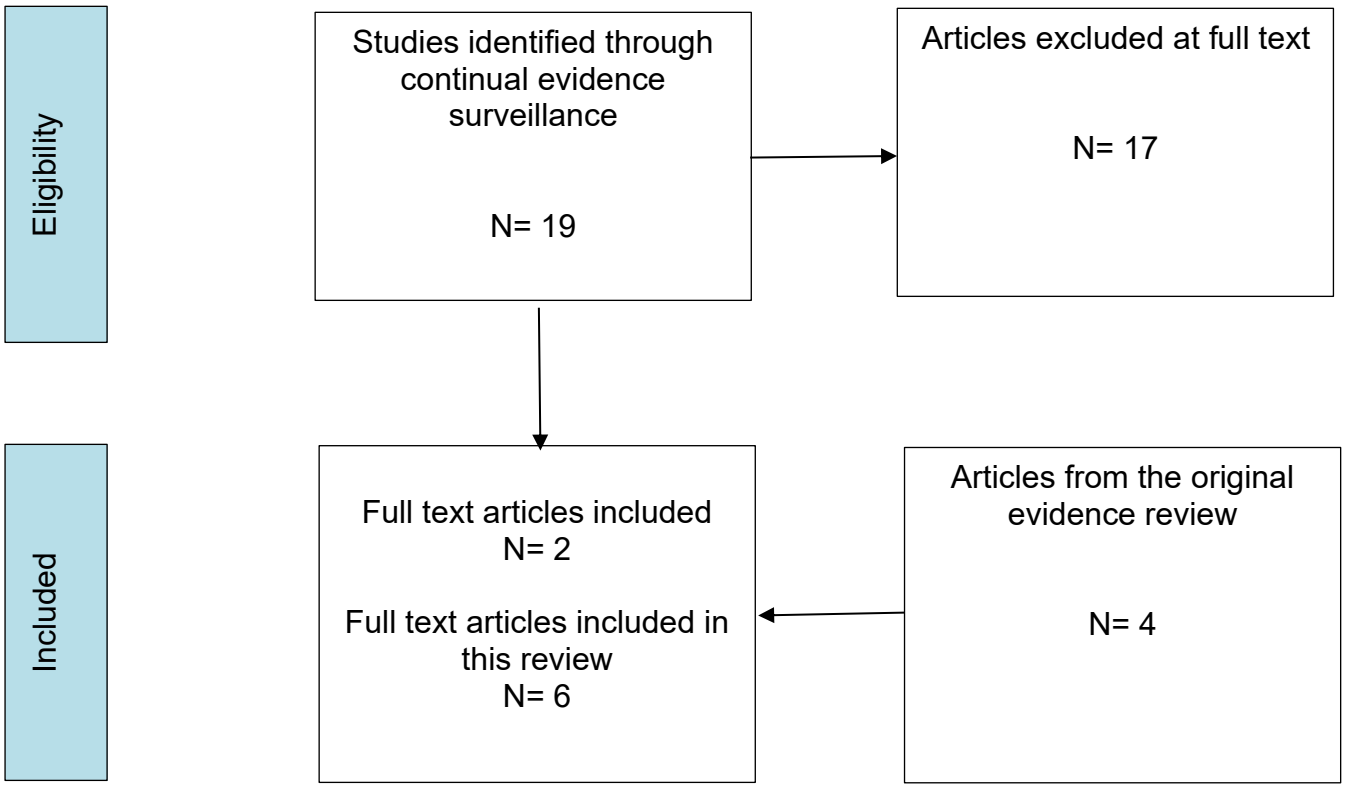
What is the effectiveness and safety of colchicine for acute symptoms and complications of COVID-19?

Criteria	Notes
Population	Adults, young people and children with suspected or confirmed COVID-19.
Interventions	Colchicine
Comparators	Standard care alone, standard care plus placebo, placebo or active comparator Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	Those marked with an * are critical outcomes • Mortality* • Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration)* • Adverse events • Hospitalisation (requirement and duration) • Supplemental oxygen, high-flow oxygen, continuous positive airway pressure or non-invasive ventilation (requirement and duration) • Discontinuation due to adverse events • Symptom resolution or clinical recovery (number and time until) • Virological clearance (negative PCR) • Clinical worsening / deterioration (number and time until) • Sustained recovery (development of long-term effects of COVID) The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway

	pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity (moderate/severe/critical) • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset • Treatment with other therapeutics used for COVID-19
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies

	• editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Study flow diagram



Appendix C: Included studies

Deftereos SG; Giannopoulos G; Vrachatis DA; Siasos GD; Giotaki SG; Gargalianos P; Metallidis S; Sianos G; Baltagiannis S; Panagopoulos P; Dolianitis K; Randou E; Syrigos K; Kotanidou A; Koulouris NG; Milionis H; Sipsas N; Gogos C; Tsoukalas G; Olympios CD; Tsagalou E; Migdalis I; Gerakari S; Angelidis C; Alexopoulos D; Davlouros P; Hahalis G; Kanonidis I; Katritsis D; Kolettis T; Manolis AS; Michalis L; Naka KK; Pyrgakis VN; Toutouzas KP; Triposkiadis F; Tsioufis K; Vavouranakis E; Martinèz-Dolz L; Reimers B; Stefanini GG; Cleman M; Goudevenos J; Tsiodras S; Tousoulis D; Iliodromitis E; Mehran R; Dangas G; Stefanadis C; ; Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial.; JAMA network open; vol. 3 (no. 6)

Horby Peter, W; Campbell, Mark; Spata, Enti; Emberson Jonathan, R; Staplin, Natalie; Amorim Guilherme, Pessoa-Amorim; Peto, Leon; Wiselka, Martin; Wiffen, Laura; Tiberi, Simon; Caplin, Ben; Wroe, Caroline; Green, Christopher; Hine, Paul; Prudon, Benjamin; George, Tina; Wight, Andrew; Baillie J, Kenneth; Basnyat, Buddha; Buch Maya, H; Chappell Lucy, C; Day Jeremy, N; Faust Saul, N; Hamers Raph, L; Jaki, Thomas; Juszczak, Edmund; Jeffery, Katie; Lim Wei, Shen; Montgomery, Alan; Mumford, Andrew; Rowan, Kathryn; Thwaites, Guy; Mafham, Marion; Haynes, Richard; Landray Martin, J; Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial; Lancet

Lopes MI; Bonjorno LP; Giannini MC; Amaral NB; Menezes PI; Dib SM; Gigante SL; Benatti MN; Rezek UC; Emrich-Filho LL; Sousa BAA; Almeida SCL; Luppino Assad R; Veras FP; Schneider A; Rodrigues TS; Leiria LOS; Cunha LD; Alves-Filho JC; Cunha TM; Arruda E; Miranda CH; Pazin-Filho A; Auxiliadora-Martins M; Borges MC; Fonseca BAL; Bollela VR; Del-Ben CM; Cunha FQ; Zamboni DS; Santana RC; Vilar FC; Louzada-Junior P; Oliveira RDR; Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial.; RMD open; 2021; vol. 7 (no. 1)

PRINCIPLE Trial Collaborative Group; Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial; medRxiv; 2021

Salehzadeh, F. Pourfarzi, F. Ataei S; The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study; Research Square; 2021; 1-11

Tardif, Jean-Claude; Bouabdallaoui, Nadia; L'Allier, Philippe L; Gaudet, Daniel; Shah, Binita; Pillinger, Michael H; Lopez-Sendon, Jose; da Luz, Protasio; Verret, Lucie; Audet, Sylvia; Dupuis, Jocelyn; Denault, Andre; Pelletier, Martin; Tessier, Philippe A; Samson, Sarah; Fortin, Denis; Tardif, Jean-Daniel; Busseuil, David; Goulet, Elisabeth; Lacoste, Chantal; Dubois, Anick; Joshi, Avni Y; Waters, David D; Hsue, Priscilla; Lepor, Norman E; Lesage, Frederic; Sainturet, Nicolas; Roy-Clavel, Eve; Bassevitch, Zohar; Orfanos, Andreas; Stamatescu, Gabriela; Gregoire, Jean C; Busque, Lambert; Lavallee, Christian; Hetu, Pierre-Olivier; Paquette, Jean-

Sebastien; Deftereos, Spyridon G; Levesque, Sylvie; Cossette, Marieve; Nozza, Anna; Chabot-Blanchet, Malorie; Dube, Marie-Pierre; Guertin, Marie-Claude; Boivin, Guy; COLCORONA, Investigators; Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial.; The Lancet. Respiratory medicine; 2021

Appendix D: Excluded studies at full text screening

Study	Code [Reason]
Brunetti, L., Diawara, O., Tsai, A. et al. (2020) Impact of colchicine on mortality in severe COVID-19 pneumonia. International Journal of Rheumatic Diseases 23(suppl1): 170	- Non-RCT
Chalmers, James D, Crichton, Megan L, Goeminne, Pieter C et al. (2021) Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. The European respiratory journal 57(4)	- This guideline and systematic review was used to check that we had included all RCTs to date.
Hariyanto, Timotius Ivan, Halim, Devina Adella, Jodhinata, Claudia et al. (2021) Colchicine treatment can improve outcomes of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Clinical and experimental pharmacology & physiology	- This systematic review was used to check that we had included all RCTs to date.
IRCT20190804044429N5 (2021) Colchicine effects on treatment of COVID-19. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20190804044429N5	- This was a study protocol
JPRN-jRCT2071200078 (2021) A randomized double-blind placebo controlled phase 2 clinical trial to assess anti-inflammatory effect of colchicine (DRC3633) in mild to moderately severe COVID-19 patients. - DRC-06C. http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-jRCT2071200078	- Protocol
Karatza, Eleni; Ismailos, George; Karalis, Vangelis (2021) Colchicine for the treatment of COVID-19 patients: efficacy, safety, and model informed dosage regimens. Xenobiotica; the fate of foreign compounds in biological systems: 1-14	- Non-RCT
Lien, Chi-Hone, Lee, Ming-Dar, Weng, Shun-Long et al. (2021) Repurposing Colchicine in Treating Patients with COVID-19: A Systematic Review and Meta-Analysis. Life (Basel, Switzerland) 11(8)	- This systematic review was used to check that we had included all RCTs to date.

Study	Code [Reason]
Madrid-Garcia, A., Perez, I., Colomer, J.I. et al. (2021) Influence of colchicine prescription in COVID-19-related hospital admissions: a survival analysis. Therapeutic Advances in Musculoskeletal Disease 13	- Non-RCT
Manenti, Lucio, Maggiore, Umberto, Fiaccadori, Enrico et al. (2021) Reduced mortality in COVID-19 patients treated with colchicine: Results from a retrospective, observational study. PloS one 16(3): e0248276	- Retrospective, observational study
Mareev, V Yu, Orlova, Ya A, Plisyk, A G et al. (2021) Proactive anti-inflammatory therapy with colchicine in the treatment of advanced stages of new coronavirus infection. The first results of the COLORIT study. Kardiologiia 61(2): 15-27	- Full text in Russian only - abstract indicates RCT design was abandoned early so would be considered a cohort study. Also reported outcomes are physiological, rather than patient-oriented outcomes relevant to NG191
National Institutes of Health (2021) Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: updated 21/04/2021.	- This was a guideline and not a primary study
Nawangsih, Eka Noneng, Kusmala, Yudith Yunia, Rakhmat, Iis Inayati et al. (2021) Colchicine and mortality in patients with coronavirus disease 2019 (COVID-19) pneumonia: A systematic review, meta-analysis, and meta-regression. International Immunopharmacology 96: 107723	- This systematic review was used to check that we had included all RCTs to date.
NCT04756128 (2021) Impact of Colchicine and Low-dose Naltrexone on COVID-19. https://clinicaltrials.gov/show/NCT04756128	- This was a study protocol
Nishimwe, T, Lloyd, V, Muhoza, D et al. (2021) POS-806 LOW DOSE COLCHICINE PROPHYLAXIS FOR SYMPTOMATIC COVID-19 PREVENTION IN PATIENTS ON KIDNEY REPLACEMENT THERAPY: OUTCOMES OF AN OBSERVATIONAL COHORT STUDY. Kidney international reports 6(4): S350	- The patients did not have suspected or confirmed COVID-19 at the start of the study. Colchicine was used as prophylaxis.
Pelechas, Eleftherios, Drossou, Vassiliki, Voulgari, Paraskevi V et al. (2021) COVID-19 in patients with gout on colchicine. Rheumatology international	- Two case studies. The 2 patients had gout and were already on colchicine.
Tuta-Quintero, Eduardo, Vega-Corredor, Maria Camila, Perdomo-Rodriguez, Laura Sofia et al. (2021) Colchicine, an old friend's perspectives for rheumatology in COVID-19: a scoping review. Revista Colombiana de Reumatologia	- Full text is in Spanish only

Appendix E: Evidence tables

COLCORONA (Tardif) 2021

Bibliographic Reference	Tardif, Jean-Claude; Bouabdallaoui, Nadia; L'Allier, Philippe L; Gaudet, Daniel; Shah, Binita; Pillinger, Michael H; Lopez-Sendon, Jose; da Luz, Protasio; Verret, Lucie; Audet, Sylvia; Dupuis, Jocelyn; Denault, Andre; Pelletier, Martin; Tessier, Philippe A; Samson, Sarah; Fortin, Denis; Tardif, Jean-Daniel; Busseuil, David; Goulet, Elisabeth; Lacoste, Chantal; Dubois, Anick; Joshi, Avni Y; Waters, David D; Hsue, Priscilla; Lepor, Norman E; Lesage, Frederic; Sainturet, Nicolas; Roy-Clavel, Eve; Bassevitch, Zohar; Orfanos, Andreas; Stamatescu, Gabriela; Gregoire, Jean C; Busque, Lambert; Lavallee, Christian; Hetu, Pierre-Olivier; Paquette, Jean-Sebastien; Deftereos, Spyridon G; Levesque, Sylvie; Cossette, Marieve; Nozza, Anna; Chabot-Blanchet, Malorie; Dube, Marie-Pierre; Guertin, Marie-Claude; Boivin, Guy; COLCORONA, Investigators; Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial.; The Lancet. Respiratory medicine; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04322682
Study start date	23-Mar-2020
Study end date	22-Dec-2020
Aim of the study	To establish the effects of colchicine on complications, including hospital admission and death, as well as its safety and tolerability.
Country/geographical location	Brazil, Canada, Greece, South Africa, Spain, and the USA.
Study setting	Primary care/Community
Population description	Patients with COVID-19 diagnosed by PCR testing or clinical criteria who were not being treated in hospital were eligible if they were at least 40 years old and had at least one high-risk characteristic: 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 h, dyspnoea at the time of presentation, bicytopenia, pancytopenia, or the combination of high neutrophil and low lymphocyte counts.
Inclusion criteria	Patients were eligible if they were at least 40 years of age, had received a diagnosis of COVID-19 within 24 hours of enrolment, were not currently being treated in hospital and not under immediate consideration for hospital treatment or admission, and presented at least one of the following high-risk criteria: 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, dyspnoea at the time of presentation, bicytopenia, pancytopenia, or the combination of high neutrophil and low lymphocyte counts. The diagnosis of COVID-19 was made by local laboratories using PCR testing on a nasopharyngeal swab specimen. Given the restrictions in laboratory testing early in the pandemic, a diagnosis was also accepted as an epidemiological link with a household member who had a positive nasopharyngeal test result for patients with symptoms compatible with COVID-19, or by a clinical algorithm in a symptomatic patient without an obvious alternative cause, as per official guidelines. Women were either not of childbearing potential or practicing adequate contraception.
Exclusion criteria	Patients were excluded if they had inflammatory bowel disease or chronic diarrhoea or malabsorption, preexistent progressive neuromuscular disease, an estimated glomerular filtration rate of less than 30 mL per min per 1.73 m^2, severe liver disease, current treatment with colchicine, current chemotherapy for cancer, or a history of substantial sensitivity to colchicine.
Intervention dosage (loading)	Patients received 500 micrograms colchicine orally administered twice per day for the first 3 days.
Intervention dosage (maintenance)	After 3 days: once per day.
Intervention scheduled duration	27 days
Intervention actual duration	27 days
Intervention route of administration	Oral
Comparator (where applicable)	Matching placebo.
Methods for population selection/allocation	Masked randomisation was centralised and done electronically through an automated interactive web-response system (IWRS). Participants were randomly assigned (1:1) to either colchicine treatment or placebo, using an allocation sequence that was computer-generated using a blocking schema with block sizes of six. Allocation sequence was not stratified. Eligible patients were randomly assigned by research nurses through the IWRS system that provided the bottle number to send to patients. The randomisation list was computer-generated by an unmasked biostatistician and uploaded to an interactive web response system (Dacima). The database was a validated electronic-datacapture system (eCRF) using InForm 6.0 provided by Oracle. The eCRF was developed by the MHICC as per their internal standard-operating procedures. All eCRF users were trained as per completion guidelines and the data entry was done directly by the study staff during phone calls with the patients. The data cleaning activities were done as per the MHICC data-management plan. All staff involved, including study investigators, nurses, and patients were masked to the treatment received.

Methods of data analysis	Assuming a primary endpoint event rate of 7% in the placebo group, we estimated that a sample size of approximately 6000 patients randomly allocated to treatment with 3000 patients in each treatment group would be required to detect a target 25% relative-risk reduction with colchicine (corresponding to a primary endpoint event rate of 5·25% with colchicine, for an absolute difference of 1·75%) with a power of 80% and a two-sided test at the 0·05 significance level. Because the efficacy interim analyses were done with the conservative O'Brien-Fleming approach, their impact on final significance was deemed to be minimal and no sample size adjustment was done for interim analyses. Efficacy analyses were done according to the intention-to-treat principle. The primary endpoint was compared between the two treatment groups using a χ^2 test, and the odds ratio (OR) along with the 95·1% CI was provided. Secondary endpoints were analysed similarly. Because of potential limitations to the specificity of COVID-19 diagnosis made on clinical or epidemiological criteria alone, a pre-specified subgroup analysis of the primary endpoint examined patients who were enrolled based on a positive PCR test. Pre-specified subgroup analyses of the primary endpoint were done using logistic-regression models including the treatment group, the subgroup factor, and the treatment x subgroup-factor interaction. Investigation of secondary endpoints in subgroups were done as post-hoc analyses. A pre-specified sensitivity analysis of the primary endpoint was done by imputing a primary event in event-free patients who did not complete the study (ie, discontinued before day 30 or for whom no information was available at end of study). Three formal interim efficacy analyses on the primary endpoint were planned after 25%, 50%, and 75% of the primary endpoint events had occurred. The prespecified stopping rule for efficacy was based on the Lan-DeMets procedure with the O'Brien-Fleming α-spending function to determine the significance level. Futility was assessed by computing the conditional power under the original alternative and judged at 15%. Results of the interim analyses were generated by an unmasked biostatistician and were provided only to the data-safety monitoring board members. During the entire duration of the trial, the study team, including the biostatisticians who wrote the statistical analysis plan and generated the final results, remained masked to treatment allocation. Following its review of the first two interim results, the monitoring board recommended that the trial should continue as planned. On Dec 11, 2020, the steering committee chairman informed the data-safety monitoring board that the investigators had decided to terminate the study once 75% of the planned patients were recruited and had completed the 30 day follow-up.

	This decision was made due to substantial logistical, personnel, and budgetary issues related to maintaining the central study call centre active 24 h per day for a prolonged period of time, which were compounded by the inability to reliably model the additional time required to reach the target number of patients through the successive waves of the pandemic. To account for the two interim analyses that were done, the final statistical significance level was calculated as 0·049 for the final analysis of the primary endpoint. No other statistical adjustment for bias was made. All other statistical tests were two-sided and done at the 0.05 significance level. Statistical analyses were done using SAS version 9.4. There was no prespecified plan to adjust for multiple comparisons across the multiple methods used to analyse the primary outcome and secondary endpoints; results of these analyses are reported with point estimates and 95% CI, without p values. 95% CIs are not adjusted for multiple comparisons, and inferences drawn from them might not be reproducible.
Attrition/loss to follow-up	None.
Source of funding	Government of Quebec, the National Heart, Lung, and Blood Institute of the US National Institutes of Health (NIH), the Montreal Heart Institute Foundation, the Bill & Melinda Gates Foundation, Amarin, Esperion, Ionis, Servier, and RegenXBio, along with grants and personal fees from AstraZeneca, Sanofi, and Servier, and grants, personal fees, and minor equity interests from Dalcor.
Study limitations (Author)	The study was stopped when 75% of the planned patients were recruited and had completed the 30 day follow-up. They nevertheless believed that their results were clinically persuasive. The duration of follow-up was relatively short at approximately 30 days. They did not investigate the evolution of persistent COVID-19 symptoms and the effects of longer-term treatment with colchicine. Their results apply to patients who have a proven diagnosis of COVID-19, are at risk of clinical complications, and were not admitted to hospital at the time of treatment initiation.
Study limitations (Reviewer)	Nothing further to add.
Other details	None

Study arms
Colchicine (N = 2235)

Placebo (N = 2253)

Characteristics
Arm-level characteristics

Characteristic	Colchicine (N = 2235)	Placebo (N = 2253)
Age median years (IQR)	53.0 (47.0 – 61.0)	54.0 (47.0 – 61.0)

Characteristic	Colchicine (N = 2235)	Placebo (N = 2253)
Nominal		
Gender % women Nominal	55.4	52.5

Outcomes
Study timepoints
30 day

Outcome	Colchicine (N = 2235)	Placebo (N = 2253)
All-cause mortality	5	9
All-cause mortality or hospitalisation	104	131
Mechanical ventilation	11	21
Serious adverse events	108	139
Adverse events	532	344
Hospitalisation for COVID-19	101	128

Critical appraisal for all outcomes

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

GRECCO-19 (Defereos) 2020

Bibliographic Reference	Deftereos SG; Giannopoulos G; Vrachatis DA; Siasos GD; Giotaki SG; Gargalianos P; Metallidis S; Sianos G; Baltagiannis S; Panagopoulos P; Dolianitis K; Randou E; Syrigos K; Kotanidou A; Koulouris NG; Milionis H; Sipsas N; Gogos C; Tsoukalas G; Olympios CD; Tsagalou E; Migdalis I; Gerakari S; Angelidis C; Alexopoulos D; Davlouros P; Hahalis G;

Kanonidis I; Katritsis D; Kolettis T; Manolis AS; Michalis L; Naka KK; Pyrgakis VN; Toutouzas KP; Triposkiadis F; Tsioufis K; Vavouranakis E; Martinèz-Dolz L; Reimers B; Stefanini GG; Cleman M; Goudevenos J; Tsiodras S; Tousoulis D; Iliodromitis E; Mehran R; Dangas G; Stefanadis C; ; Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial.; JAMA network open; vol. 3 (no. 6)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04326790
Study start date	03-Apr-2020
Study end date	27-Apr-2020
Aim of the study	To evaluate the effect of treatment with colchicine on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019 (COVID-19).
Country/geographical location	Greece
Study setting	Hospital
Population description	Hospitalized adult patients diagnosed with COVID-19.
Inclusion criteria	Adults in hospital with COVID-19, confirmed with reverse transcriptase PCR testing; body temperature of 37.5 degrees Celsius or greater and 2 or more of the following: sustained coughing, sustained sore throat, anosmia and/or ageusia, fatigue and/or tiredness and arterial oxygen partial pressure lower than 95 mm Hg on room air.
Exclusion criteria	Pregnancy or lactation, known hypersensitivity to colchicine, known hepatic failure, estimated glomerular filtration rate under 20 mL/min/1.73m, corrected QT interval of 450 milliseconds or higher (according to the Bazett formula) on a 12-lead surface electrocardiogram, or clinical assessment indicating that ventilatory support would be inevitable in the following 24 hours because of rapidly declining respiratory status.
Intervention dosage (loading)	Loading dose of 1500 micrograms followed by 500 micrograms colchicine 60 minutes later if no adverse GI effects observed. Reduced to 1000 micrograms for those receiving azithromycin.
Intervention dosage (maintenance)	Maintenance dose of 500 micrograms colchicine twice daily (reduced to one dose in patients <60 kg body weight) for up to 3 weeks.
Intervention scheduled duration	30 days
Intervention actual duration	30 days
Intervention route of administration	Not reported

Comparator (where applicable)	Standard care
Methods for population selection/allocation	Hospitalised adult patients diagnosed with COVID-19. The randomization sequence was prepared by a statistician not involved in the trial using R software version 3.6.2 (R Project for Statistical Computing), and the corresponding assignment was provided to site coordinators electronically on each patient enrolment.
Methods of data analysis	The primary efficacy analysis was performed on an intention-to-treat basis. Assuming a median event-free survival of 30 days and an accrual time of 30 days, it was calculated that 180 patients were needed to have a 90% probability to detect a 50% reduction in the primary clinical end point at α = 0.05. For the biochemical analysis, it was estimated 85 patients were needed to have a 90% probability to detect a 30% reduction in peak hs cTn level, assuming a median hs cTn level of 0.00005 micrograms/mL in the control group, at α = 0.05. Continuous parameters were summarized as median and interquartile range (IQR) and compared with nonparametric tests (Mann-Whitney). The Hodges-Lehmann estimate was used to calculate 95%CIs for the difference between medians. Categorical variables are reported as counts and percentages and were compared with the χ2 test. In cases in which the 2 × 2 matrices contained cells with expected values less than 5, the Fisher exact test was used. The Cochran-Armitage test was used to test for trends in 2 × k contingency tables. Odds ratios for the clinical end point were calculated with the Mantel-Haenszel test. Kaplan-Meier analysis was used to assess the time to clinical deterioration, and the log rank test was used to compare end point–free survival between the 2 groups (primary clinical efficacy analysis). No specific statistical handling of missing values was performed. Statistical significance was set at P < .05, and all tests were 2-tailed. SPSS statistical software version 25 was used for all statistical analyses.
Attrition/loss to follow-up	Intervention: 1 withdrew consent before the study Control: 4 withdrew consent before the study
Source of funding	ELPEN Pharmaceuticals, Acarpia Pharmaceuticals, and Karian Pharmaceuticals.
Study limitations (Author)	This was an open-label study. It was decided that the use of a placebo and masking of patients and their clinical caregivers would complicate their treatment, which was already fraught with extreme difficulty, as well as delay study initiation and participant recruitment. However, the clinical events that met the definition of the primary clinical end point of the study were quite clearly defined, considering that the need for mechanical ventilation or death are rather hard clinical end points. Many other laboratory parameters could have been evaluated in this study, including interleukin or tumor-necrosis factor levels, which could elucidate the effect of colchicine on various inflammatory pathways. This could not be realized because of logistical constraints. Furthermore, the most important limitation is probably the fact that, because of the relatively small number of clinical events, the

	statistical robustness of the results is limited, even though the arithmetic difference between the 2 groups was striking. In addition, the study was not powered to detect differences in rare adverse events.
Study limitations (Reviewer)	The open-label nature of the study means that subjective decisions/outcomes maybe prone to bias (the decision to mechanically ventilate, assessment of adverse events, serious adverse events, discontinuation due to adverse events and clinical progression). Mortality should be less prone to bias.
Other details	Nothing further to add.

Study arms
Colchicine (N = 55)

Usual care (N = 50)

Characteristics
Arm-level characteristics

Characteristic	Colchicine (N = 55)	Usual care (N = 50)
Age, median, (IQR) (years) Nominal	63 (55 – 70)	65 (54 – 80)
Gender (% female) (%) Nominal	40	43.6

Study timepoints
3 week

Outcomes

Outcome	Colchicine (N = 55)	Usual care (N = 50)
All-cause mortality	1	4
Mechanical ventilation	1	6
Serious adverse events	0	0
Adverse events	43	15
Discontinuation due to adverse events	2	0
Clinical progression (scale)	1	7

Critical appraisal for all-cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended interventions (effect of	Low

Section	Question	Answer
intended interventions (effect of assignment to intervention)	assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

Critical appraisal for mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

Critical appraisal for serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of	Low

Section	Question	Answer
	assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

Critical appraisal for adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

Critical appraisal for discontinuation due to adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended interventions (effect of	Low

Section	Question	Answer
intended interventions (effect of assignment to intervention)	assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

Critical appraisal Clinical progression (scale)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

Lopes 2021

Bibliographic Reference	Lopes MI; Bonjorno LP; Giannini MC; Amaral NB; Menezes PI; Dib SM; Gigante SL; Benatti MN; Rezek UC; Emrich-Filho LL; Sousa BAA; Almeida SCL; Luppino Assad R; Veras FP; Schneider A; Rodrigues TS; Leiria LOS; Cunha LD; Alves-Filho JC; Cunha TM; Arruda E; Miranda CH;

Pazin-Filho A; Auxiliadora-Martins M; Borges MC; Fonseca BAL; Bollela VR; Del-Ben CM; Cunha FQ; Zamboni DS; Santana RC; Vilar FC; Louzada-Junior P; Oliveira RDR; Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial.; RMD open; 2021; vol. 7 (no. 1)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	RBR-8jyhxh
Study start date	11-Apr-2020
Study end date	31-Aug-2020
Aim of the study	To evaluate whether the addition of colchicine to standard treatment for COVID-19 results in better outcomes.
Country/geographical location	Brazil
Study setting	Hospital
Population description	Individuals hospitalised with moderate or severe forms of COVID-19.
Inclusion criteria	Admitted to hospital with moderate or severe COVID-19, diagnosed by RT-PCR and lung computed tomography scan involvement compatible with COVID-19 pneumonia; older than 18 years; body weight >50 kg, normal levels of serum calcium and potassium, QT interval < 450 ms, negative pregnancy test if woman under 50.
Exclusion criteria	Mild form of COVID-19 or in need of ICU admission, diarrhoea resulting in dehydration, known allergy to colchicine, diagnosis of porphyria, myasthenia gravis or uncontrolled arrhythmia at enrolment, 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 the consent form.
Intervention dosage (loading)	No loading dose
Intervention dosage (maintenance)	Colchicine 500 micrograms thrice daily for 5 days, then 500 micrograms twice daily for 5 days; if body weight was greater than or equal to 80kg, the first dose was 1000 micrograms. Patients with kidney disease (eGFR <30 mL/min/1.73m2) received 250 micrograms thrice daily for 5 days, then 250 micrograms twice daily for 5 days, irrespective of body weight.
Intervention scheduled duration	10 days in total.
Intervention actual duration	10 days
Intervention route of administration	Not reported

Comparator (where applicable)	Placebo
Methods for population selection/allocation	The randomisation was performed 1:1 for placebo or colchicine by using the online tool at https://www. randomizer. org/
Methods of data analysis	Absolute numbers and percentage were compared with Fisher's exact test. Comparisons of clinical and laboratory parameters expressed in median and IQR were done through Mann-Whitney test. Additionally, Kaplan-Meier survival curves were performed, with analysis by Mantel-Haenszel log rank test, to compare the time to abandon supplemental oxygen and time to discharge between the groups. Kruskall-Wallis test was used for comparisons of laboratory exams at the four blood collection times, followed by Dunn's Multiple Comparison test. For all tests, $p<0.05$ was considered for statistical significance.
Attrition/loss to follow-up	Colchicine group: 1 intervention discontinued due to ICU admission. Placebo group: 1 intervention discontinued due to ICU admission.
Source of funding	FAPESP grants, CNPq and CAPES grants
Study limitations (Author)	Small number of participants. The absence of mechanistic investigations, for example, measures of the plasmatic levels of cytokines. Prohibition of some cardiovascular drugs. Much of this concern was related to drugs that could impair colchicine metabolism or excretion, but some concern was also due to the potential hazardous effect of hydroxychloroquine and azithromycin combined use for myocardial fibres. Finally, as patients were discharged, the number of blood samples reduced through the first week of observation and beyond, once it would not be appropriate to summon up the patients for new blood collections due to COVID-19 transmission possibility.
Study limitations (Reviewer)	The follow-up timepoints were not provided.
Other details	Nothing further to add.

Study arms
Colchicine (N = 38)

Placebo (N = 37)

Characteristics
Arm-level characteristics

Characteristic	Colchicine (N = 38)	Placebo (N = 37)
Median age (IQR) (years) Nominal	54.5 (IQR 42.5 – 64.5)	55.0 (42.0 – 67.0)
Gender (% female) (%) Nominal	47	61

Outcomes (follow-up timepoint was not provided)

Outcome	Colchicine (N = 38)	Placebo (N = 37)
All-cause mortality	0	2
Discontinuation due to adverse events	0	0
ICU admission	1	3
Discharge from hospital (by day 10)	33	22

Critical appraisal for all outcomes

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns. No follow-up timepoints were provided.
Overall bias and Directness	Overall Directness	Partially direct The participants receiving standard care in both arms were not using dexamethasone for hospitalised patients on oxygen.

PRINCIPLE 2021

Bibliographic Reference	PRINCIPLE Trial Collaborative Group; Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial; medRxiv; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	ISRCTN86534580
Study start date	02-Aug-2020
Aim of the study	To determine whether colchicine speeds recovery and reduces COVID-19 related hospital admission or death in people in the community.
Country/geographical location	UK
Study setting	Primary care/Community
Population description	Adults aged ≥65, or ≥18 years with comorbidities or shortness of breath, and unwell ≤14 days with suspected COVID-19 in the community.
Inclusion criteria	From the beginning of the trial, people in the community were eligible if they were aged ≥65 years, or 50-65 years with comorbidities, and had ongoing symptoms from polymerase chain reaction (PCR) confirmed or suspected COVID-19 (in accordance with the UK National Health Service definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste) which had started within the previous 14 days. When the colchicine arm opened, eligibility criteria were expanded to allow enrolment of people aged 18-65 years with comorbidities or shortness of breath. Comorbidities required for eligibility were: heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problems; weakened immune system (for example, chemotherapy); and self-reported obesity or body mass index ≥35 kg/m2.
Exclusion criteria	People were ineligible to be randomised to colchicine if they were already taking colchicine or if colchicine was contraindicated according to the British National Formulary.
Intervention dosage (loading)	Colchicine 500 micrograms
Intervention dosage (maintenance)	Participants received usual care plus colchicine 500 micrograms daily.
Intervention scheduled duration	14 days
Intervention actual duration	14 days
Intervention route of administration	Oral

Comparator (where applicable)	Standard care alone.
Methods for population selection/allocation	Eligible, consenting participants were randomised using a secure, in-house, web-based randomisation system. Randomisation was stratified by age (<65 years /≥65 years), and presence of comorbidity (yes/no) and probabilities were determined using response adaptive randomisation via regular interim analyses, which allows allocation of more participants to interventions with better observed time to recovery outcomes. However, between March 31, 2021 and April 08, 2021, only the colchicine and usual care arms were active, with 1:1 allocation between each. The trial team was blinded to randomisation probabilities.
Methods of data analysis	In the Adaptive Design Report the investigators justify sample sizes by simulating the operating characteristics of the adaptive design in multiple scenarios, which explicitly account for response adaptive randomisation, early stopping for futility/success and multiple interventions. In brief, for the primary outcome analyses, assuming a median time to recovery of nine days in the usual care group, approximately 400 participants per group would provide 90% power to detect a 2-day difference in median recovery time. Assuming 5% hospitalisation in the usual care group, approximately 1500 participants per group would provide 90% power to detect a 50% reduction in the relative risk of hospitalisation/death. The first co-primary outcome, time to first self-reported recovery, was analysed using a Bayesian piecewise exponential model. The second co-primary outcome, hospitalisation/death, was analysed using a Bayesian logistic regression model. Both models were regressed on treatment group and stratification covariates (age <65 years /≥65 years and comorbidity yes/no). These primary outcomes were evaluated using a “gate-keeping” strategy to preserve the overall Type I error without additional adjustments for multiple hypotheses. The hypothesis for the time-to-first-recovery endpoint was evaluated first, and if the null hypothesis was rejected, the hypothesis for the second co-primary endpoint of hospitalisation/death was evaluated. In the context of multiple interim analyses, the master protocol specifies that each null hypothesis is rejected if the Bayesian posterior probability of superiority exceeded 0.99 for the time to recovery endpoint and 0.975 (via gate-keeping) for the hospitalisation/death endpoint. For the purposes of defining futility rules, they pre-specified a clinically meaningful hazard ratio for time to first reported recovery as 1.2 or larger (equating to approximately 1.5 days difference in median time to recovery, assuming 9 days recovery in the usual care arm), and a clinically meaningful odds ratio as 0.80 or smaller for hospitalisations/deaths (equating to approximately a 1% decrease in the hospitalisation rate, assuming a rate of 5% in the usual care arm). If there is insufficient evidence of a clinically meaningful benefit in time to recovery, futility is declared and randomisation to that intervention is stopped, meaning other interventions can be evaluated more rapidly in the trial. For each primary outcome endpoint (time to recovery and hospitalisation/death), a model-

based estimate of absolute benefit (days and percent, respectively) was obtained by applying the model-based estimate of treatment benefit (hazard ratio or odds ratio, respectively) to a bootstrap sample of the concurrent and eligible usual care population.

At the beginning of the trial, due to initial difficulties with community SARS-CoV-2 PCR testing in the UK, participants with suspected COVID-19 were included in the primary analysis population, irrespective of confirmatory testing. When testing became more accessible, the Trial Steering Committee recommended restricting the primary analysis population to those with confirmed COVID-19. This change was included in protocol version 7.1 on February 22, 2021 and approved on March 15, 2021, before any interim colchicine results were disclosed to the Trial Management Group. Therefore, the pre-specified primary analysis population includes all eligible SARS-CoV-2 positive participants randomised to colchicine, usual care, and other interventions, from the start of the platform trial until the colchicine arm was closed, on May 26, 2021. This population includes participants randomised to usual care before the colchicine group opened, who may differ from concurrently randomised participants because of changes in the inclusion/exclusion criteria (e.g. participants aged ≥18 years with comorbidity or shortness of breath became eligible when the colchicine group opened), and changes over time in the predominant variant and amount of circulating SARS-CoV-2 or usual care, including increasing availability of vaccinations. Therefore, the primary analysis models include parameters to adjust for potential temporal drift in the trial population, by estimating the primary endpoint in the usual care group across time via Bayesian hierarchical modelling.

They also conducted a key pre-specified sensitivity analysis of the primary outcomes using the concurrent randomised population; defined as all SARS-CoV-2 positive participants randomised during the time period when the colchicine arm was active. To determine the applicability of our results to situations where PCR testing may not be readily available, they also conducted secondary analyses of time to recovery and COVID-19 related hospitalisation/death among the overall study population, irrespective of SARS-CoV-2 status.

Analyses of all secondary outcomes, and pre-specified sub-group analyses, were conducted using SARS-CoV-2 positive participants eligible for colchicine, and concurrently randomised to colchicine or usual care; the concurrently randomised and eligible SARS-CoV-2 positive population. Secondary time-to-event outcomes were analysed using Cox proportional hazard models, and binary outcomes were analysed using logistic regression, adjusting for comorbidity, age, duration of illness and vaccination status. Due to the high proportion contributing to the analysis of primary outcomes (95%), they did not explore the potential impact of missing data. All model assumptions were evaluated

Source of funding	The PRINCIPLE trial is funded by a grant to the University of Oxford from UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research as part of the UK Government's rapid research response fund.
Study limitations (Author)	Although their primary analysis was restricted to SARS-CoV-2 positive patients, they conducted secondary analyses of the co-primary outcomes among patients with suspected COVID-19 but without PCR confirmed SARS-CoV-2 infection, as limited SARS-CoV-2 testing may necessitate early empirical treatment in low resource settings. Furthermore, variation in PCR testing sensitivity, particularly if self-administered, means some participants will have had false negative tests. Time to recovery estimates were similar in the SARS-CoV-2 positive population, all participants irrespective of SARS-CoV-2 status, as well as the concurrent randomisation SARS-CoV-2 positive population (the latter populations are most analogous to those in traditional two arm trials). They used a pragmatic, open label design, similar to other large COVID-19 platform trials to evaluate the addition of colchicine to usual care, rather than to assess benefit of colchicine compared to a placebo. If a positive placebo effect influenced our self-reported time to recovery outcome, it would likely be masking even greater negative effect of colchicine. They used this outcome as it was of greatest interest to their patient and public contributors and is best ascertained by direct patient report, rather than by the use of surrogate measures. They hypothesised that a treatment that does not reduce recovery time is also unlikely to reduce COVID-19 related hospitalisations/death. However, it is possible for a treatment to reduce the likelihood of severe disease without reducing duration of the illness.
Study limitations (Reviewer)	Lack of blinding could lead to bias when outcomes are assessed, with the possible exception of all-cause mortality. There was a drop-out rate of 25% ("Of 184 participants randomised to colchicine who provided medication use information, 138 (75%) reported taking colchicine for at least seven days.") The participants in the standard care arm were on average older than those in the colchicine arm.

Study arms
Colchicine (N = 156)

Standard care (N = 120)

Characteristics
Arm-level characteristics

Characteristic	Colchicine (N = 156)	Standard care (N = 120)
Age 18-49 years (%) Nominal	52.3	29.3

Characteristic	Colchicine (N = 156)	Standard care (N = 120)
Age 50-64 years (%) Nominal	32.8	46.4
Age 65 and over (%) Nominal	14.9	24.3
% Female (%) Nominal	49.4	58.6

Outcomes
Study timepoints
28 day

Outcome	Colchicine (N = 156)	Standard care (N = 120)
All-cause mortality or hospitalisation	7	3
Mechanical ventilation	0	0
Serious adverse events	1	2
Participants who experienced alleviation of all symptoms within 28 days of starting treatment	125	98
Time to alleviation of all symptoms, estimated treatment effect	Hazard ratio 0.94 (0.72 to 1.24)	(comparator, so zero)
Reported recovery (days)	Hazard ratio 0.92 (95% CI 0.72, 1.17)	(comparator, so 1)
Time to reported recovery, median difference in days	Median difference: 1.14 (95% CI -1.86 to 5.21)	(comparator, so zero)

Critical appraisal for all-cause mortality or hospitalisation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. Participants in the usual care arm were on average older.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. There was non-adherence rate of 25% for colchicine
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns. There was non-adherence rate of 25% for colchicine, and participants in the usual care arm were on average older.
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. Participants in the usual care arm were on average older.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. There was non-adherence rate of 25% for colchicine
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. There was no blinding.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High. There was non-adherence rate of 25% for colchicine, and participants in the usual care arm were on average older. There was no blinding, which could have biased measurement of this outcome.
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. Participants in the usual care arm were on average older.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. There was non-adherence rate of 25% for colchicine
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. There was no blinding.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High. There was non-adherence rate of 25% for colchicine, and participants in the usual care arm were on average older. There was no blinding, which could have biased measurement of this outcome.
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for participants who experienced alleviation of all symptoms within 28 days of starting treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. Participants in the usual care arm were on average older.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. There was non-adherence rate of 25% for colchicine
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. There was no blinding.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High. There was non-adherence rate of 25% for colchicine, and participants in the usual care arm were on average older. There was no blinding, which could have biased measurement of this outcome.
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for time to alleviation of all symptoms, estimated treatment effect (median days, mean difference)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. Participants in the usual care arm were on average older.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. There was non-adherence rate of 25% for colchicine
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. There was no blinding.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High. There was non-adherence rate of 25% for colchicine, and participants in the usual care arm were on average older. There was no blinding, which could have biased measurement of this outcome.
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for time to first reported recovery (days)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. Participants in the usual care arm were on average older.

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. There was non-adherence rate of 25% for colchicine
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. There was no blinding.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High. There was non-adherence rate of 25% for colchicine, and participants in the usual care arm were on average older. There was no blinding, which could have biased measurement of this outcome.
Overall bias and Directness	Overall Directness	Directly applicable

RECOVERY (Horby) 2021

Bibliographic Reference	Horby Peter, W; Campbell, Mark; Spata, Enti; Emberson Jonathan, R; Staplin, Natalie; Amorim Guilherme, Pessoa-Amorim; Peto, Leon; Wiselka, Martin; Wiffen, Laura; Tiberi, Simon; Caplin, Ben; Wroe, Caroline; Green, Christopher; Hine, Paul; Prudon, Benjamin; George, Tina; Wight, Andrew; Baillie J, Kenneth; Basnyat, Buddha; Buch Maya, H; Chappell Lucy, C; Day Jeremy, N; Faust Saul, N; Hamers Raph, L; Jaki, Thomas; Juszczak, Edmund; Jeffery, Katie; Lim Wei, Shen; Montgomery, Alan; Mumford, Andrew; Rowan, Kathryn; Thwaites, Guy; Mafham, Marion; Haynes, Richard; Landray Martin, J; Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial; Lancet.

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	ISRCTN (50189673) and clinicaltrials.gov (NCT04381936)
Study start date	Nov-2020
Study end date	01-Mar-2021
Aim of the study	Evaluation of COVID-19 therapy (RECOVERY) trial is an investigator initiated, individually randomised, controlled, open-

	label, platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19
Country/geographical location	UK
Study setting	Hospital
Population description	Hospital - patients with COVID-19
Inclusion criteria	Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.
Exclusion criteria	Children and pregnant women were not eligible for randomisation to colchicine. Patients with severe liver impairment, significant cytopaenia, concomitant use of strong CYP3A4 or P-glycoprotein inhibitors, or hypersensitivity to lactose were excluded
Intervention dosage (loading)	Patients allocated to colchicine were to receive 1000 micrograms after randomisation followed by 500 micrograms 12 hours later
Intervention dosage (maintenance)	Patients allocated to colchicine then received 500 micrograms twice daily by mouth or nasogastric tube for 10 days in total or until discharge, whichever occurred earlier. Dose frequency was halved for patients receiving a moderate CYP3A4 inhibitor or who had renal impairment (estimated glomerular filtration rate <30 ml/min/1.73m2) or estimated body weight <70 kg
Intervention scheduled duration	10 days or until hospital discharge
Intervention actual duration	10 days or until hospital discharge
Intervention route of administration	Oral
Comparator (where applicable)	Usual care
Methods for population selection/allocation	Baseline data collected using a web-based case report form that included demographics, level of respiratory support, major comorbidities, suitability of the study, treatment for a particular patient, and treatment availability at the study site. Patients assigned in a 1:1 ratio to either usual standard of care or usual standard of care plus colchicine or one of the other available RECOVERY treatment arms using web-based simple (unstratified) randomisation with allocation concealed until after randomisation. As a platform trial, and in a factorial design, patients could be simultaneously randomised to other treatment groups: i) convalescent plasma versus monoclonal antibody (REGN CoV2) versus usual care, ii) aspirin versus usual care, and iii) baricitinib versus usual care (appendix pp 31). Until 24 January 2021, the trial also allowed a subsequent randomisation for patients with progressive COVID-19 (evidence of hypoxia and a hyper-inflammatory state) to tocilizumab versus usual care.

Methods of data analysis	Primary analysis for all outcomes was by intention-to-treat comparing colchicine vs usual care. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used to both test the null hypothesis of equal survival curves and to calculate the one-step estimate of the average mortality rate ratio. Same method used to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation. Median time to discharge was derived from Kaplan-Meier estimates. Risk ratio was calculated for all other outcomes where precise dates were not available. At least 90% power at a two-sided significance level of 0.01 required to detect a clinically relevant 189 proportional reduction in 28-day mortality of 12.5% between the two groups.
Attrition/loss to follow-up	5610 patients were randomly allocated to colchicine and 5730 were randomly allocated to usual care. The follow-up form was completed for 5510 (98%) in the colchicine group and 5605 (98%) in the usual care group. Among patients with a completed follow-up form, 5122 (93%) allocated to colchicine received at least one dose. Primary and secondary outcome data are known for >99% of randomly assigned patients.
Source of funding	UK Research and Innovation (Medical Research Council) and National Institute of Health Research (Grant ref: MC_PC_19056). Wellcome Trust (Grant Ref: 54 222406/Z/20/Z) through the COVID-19 Therapeutics Accelerator.
Study limitations (Author)	Detailed information on laboratory markers of inflammation and immune response was not collected, nor was information on radiological or physiological outcomes. Although this randomised trial is open label (i.e., 265 participants and local hospital staff are aware of the assigned treatment), the outcomes are unambiguous and were ascertained without bias through linkage to routine health records.
Study limitations (Reviewer)	The open-label nature of the study means that subjective outcomes/decisions maybe prone to bias (the decision to mechanically ventilate, and discharge from hospital within 28 days). Mortality should be less prone to bias. (Although the investigators were blinded to the outcomes on the database, the clinicians deciding management and recording the outcomes were not.)
Other details	None to add

Study arms
Colchicine (N = 5610)

Usual care (N = 5730)

Characteristics
Arm-level characteristics

Characteristic	Colchicine (N = 5610)	Usual care (N = 5730)
Mean age (SD), years	63.3 (13.8)	63.5 (13.7)

Characteristic	Colchicine (N = 5610)	Usual care (N = 5730)
Gender (% female) (%) Nominal	31	30

Outcomes at 28 days

Outcome	Colchicine (N = 5610)	Usual care (N = 5730)
All-cause mortality	1173	1190
Mechanical ventilation	1344	1343
Discharge from hospital within 28 days	3901	4032

Critical appraisal for all-cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Directly applicable

Critical appraisal for discharge from hospital within 28 days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns because of the lack of blinding.
Overall bias and Directness	Overall Directness	Directly applicable

Salehzadeh 2021

Bibliographic Reference	Salehzadeh, F. Pourfarzi, F. Ataei S; The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study; Research Square; 2021; 1-11

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	IRCT20200418047126N1
Study start date	21-May-2020
Study end date	20-Jun-2020
Aim of the study	To evaluate colchicine anti-inflammatory effect on the symptoms course, duration of hospitalisation, morbidity and mortality rate, of COVID-19 patients.
Country/geographical location	Iran
Study setting	Hospital

Population description	Adults hospitalised with COVID-19.
Inclusion criteria	Adult patients with COVID-19. Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19.
Exclusion criteria	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.
Intervention dosage (loading)	Hydroxychloroquine as a health care system guideline treatment and colchicine regime: 1000 micrograms of colchicine daily alongside hydroxychloroquine for 6 days.
Intervention dosage (maintenance)	Same as above.
Intervention scheduled duration	6 days
Intervention actual duration	6 days
Intervention route of administration	Oral
Comparator (where applicable)	Hydroxychloroquine alone plus placebo. The participants of the placebo group received a similar tablet without therapeutic effects alongside the hydroxychloroquine for 6 days. Hydroxychloroquine was a drug that was included in their healthcare protocol and all of patients in this study received the same treatment such as Azithromycin in their therapy period.
Methods for population selection/allocation	The method of randomisation was not provided.
Methods of data analysis	In this study, SPSS statistical analysis software version 25 was used to analyse the data. The data were first expressed using the frequency command (number, percentage, mean) and then using independent T-test and chi-square test, the relationship between them was examined and the results were presented in tables. To evaluate the significance of the deficiency, foundation was used, which was considered significant less than 0.05.
Attrition/loss to follow-up	None
Source of funding	Not provided
Study limitations (Author)	This study was performed only on the clinical aspects and symptoms of patients and the changes in biomarkers were not evaluated. This study was performed in only non-ICU patients to evaluate their course of disease. On the other hand, the use of hydroxychloroquine in patients due to the health ministry guideline may have a combination medicinal side effects.
Study limitations (Reviewer)	There was no blinding and the outcome reporting was selective (no mortality or adverse events data).

Study arms
Colchicine (N = 50)

Placebo (N = 50)

Characteristics
Arm-level characteristics

Characteristic	Colchicine (N = 50)	Placebo (N = 50)
Mean age (years) Nominal	56.56	55.56
% Female (%) Nominal	62	56

Outcomes at 2-weeks post discharge (total follow-up time was not provided)

Outcome	Colchicine (N = 50)	Placebo (N = 50)
Duration of hospital stay (mean number of days, p-value 0.001)	6.28	8.12

Critical appraisal for duration of hospital stay

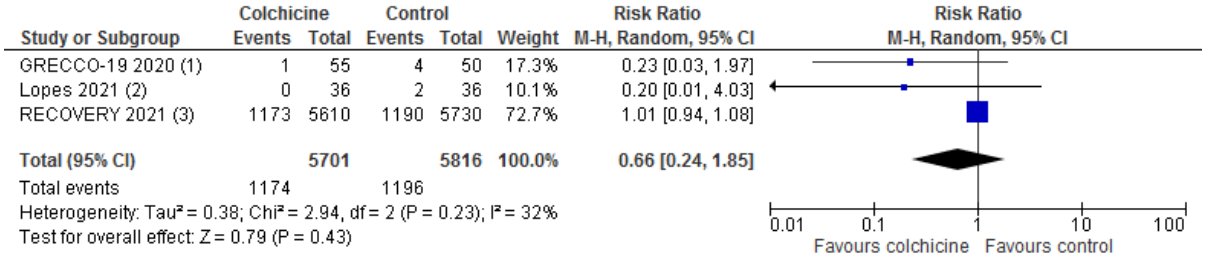
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (The method of randomisation was not provided)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Lack of blinding could have influenced measurement of the outcome.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High (Obvious/essential outcomes were omitted from the publication, such as mortality and adverse events. The methods section did not explain what outcomes the investigators intended to collect.)
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
		(The method of randomisation was not provided. Lack of blinding, which could influence measurement of the outcome and selective reporting of outcomes.)
Overall bias and Directness	Overall Directness	Partially applicable (Corticosteroids were not part of standard care)

Appendix F: Forest plots

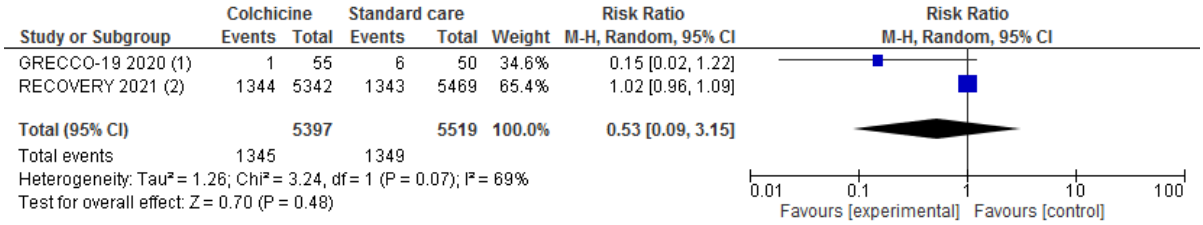
Hospital setting

All-cause mortality within 21-28 days of starting treatment



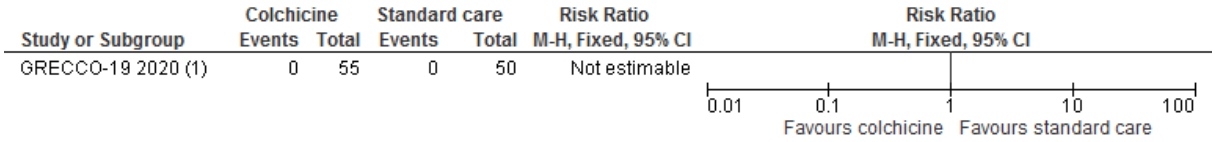
Footnotes
(1) At 3 weeks. Maintenance dose of 500 micrograms colchicine twice a day with standard care versus standard care
(2) Follow-up timepoint not provided. 500 micrograms of colchicine three times a day for 5 days and then for twice a day for 5 days versus...
(3) At 28 days. 500 micrograms colchicine twice a day for 10 days with standard care versus standard care

Mechanical ventilation within 21-28 days of starting treatment



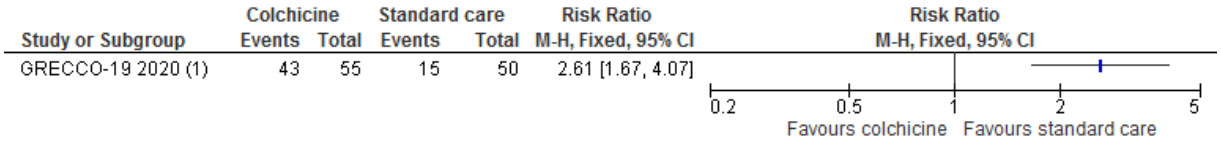
Footnotes
(1) At 3 weeks. Maintenance dose of 500 micrograms colchicine twice a day with standard care versus standard care
(2) At 28 days. 500 micrograms colchicine twice a day for 10 days vs standard care

Serious adverse events within 21 days of starting treatment



Footnotes
(1) At 3 weeks. Maintenance dose of 500 microgram colchicine twice a day with standard care versus standard care. There were no...

Adverse events within 21 days of starting treatment

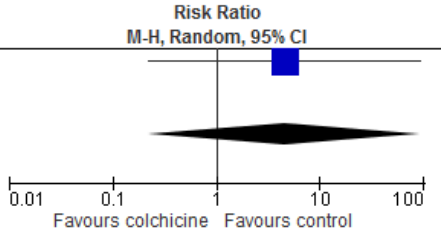


Footnotes
(1) At 3 weeks. Maintenance dose of 500 micrograms colchicine twice a day with standard care versus standard care

Discontinuation due to adverse events within 21 days of starting treatment

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
GRECCO-19 2020 (1)	2	55	0	50	100.0%	4.55 [0.22, 92.62]
Lopes 2021 (2)	0	36	0	36		Not estimable
Total (95% CI)		**91**		**86**	**100.0%**	**4.55 [0.22, 92.62]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

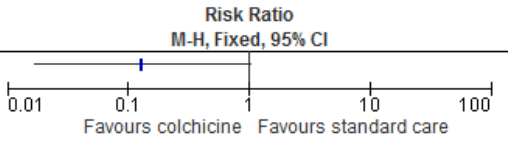


Footnotes
(1) At 3 weeks. Maintenance dose of 500 micrograms colchicine twice a day with standard care versus standard care
(2) Follow-up timepoint not provided. 500 micrograms of colchicine three times a day for 5 days and then for twice a day for 5 days versus...

Clinical progression (scale) within 21 days of starting treatment

Increase of 2 grades on 7-grade scale

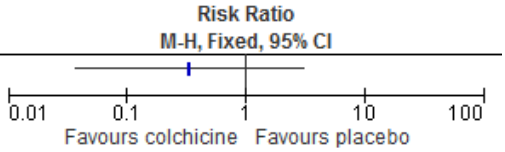
Study or Subgroup	Colchicine Events	Colchicine Total	Standard care Events	Standard care Total	Risk Ratio M-H, Fixed, 95% CI
GRECCO-19 2020 (1)	1	55	7	50	0.13 [0.02, 1.02]



Footnotes
(1) At 3 weeks. Maintenance dose of 500 micrograms colchicine twice a day with colchicine versus standard care

ICU admission – follow-up timepoint was not provided

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Lopes 2021 (1)	1	36	3	36	0.33 [0.04, 3.06]

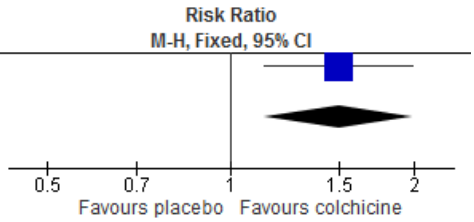


Footnotes
(1) Follow-up timepoint not provided. 500 micrograms of colchicine three times a day for 5 days and then for twice a day for 5...

Discharge from hospital by day 10

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lopes 2021 (1)	33	36	22	36	100.0%	1.50 [1.14, 1.98]
Total (95% CI)		**36**		**36**	**100.0%**	**1.50 [1.14, 1.98]**
Total events	33		22			

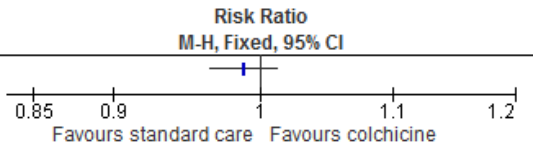
Heterogeneity: Not applicable
Test for overall effect: Z = 2.85 (P = 0.004)



Footnotes
500 micrograms of colchicine three times a day for 5 days and then for twice a day for 5 days versus placebo.

Discharge from hospital within 28 days

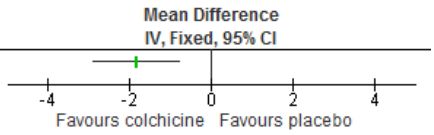
Study or Subgroup	Colchicine Events	Colchicine Total	Standard care Events	Standard care Total	Risk Ratio M-H, Fixed, 95% CI
RECOVERY 2021 (1)	3901	5610	4032	5730	0.99 [0.96, 1.01]



Footnotes
(1) At 28 days. 500 micrograms colchicine twice a day for 10 days with standard care versus standard care

Duration of hospital stay at a mean follow-up of 21 days

Study or Subgroup	Colchicine Mean	Colchicine SD	Colchicine Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Salehzadeh 2020 (1)	6.28	2.711794	50	8.12	2.711794	50	-1.84 [-2.90, -0.78]

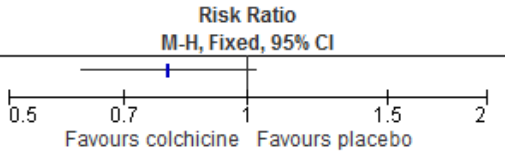


Footnotes
(1) At the 2 week follow-up timepoint. 1000 micrograms colchicine daily. Both arms were given hydroxychloroquine.

Community setting

Hospitalisation for COVID-19 within 30 days of starting treatment

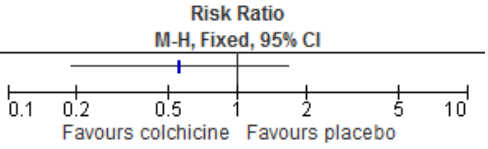
Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
COLCORONA 2021 (1)	101	2235	128	2253	0.80 [0.62, 1.03]



Footnotes
(1) At 30 days. 500 micrograms colchicine once daily for 27 days versus placebo

All-cause mortality within 30 days of starting treatment

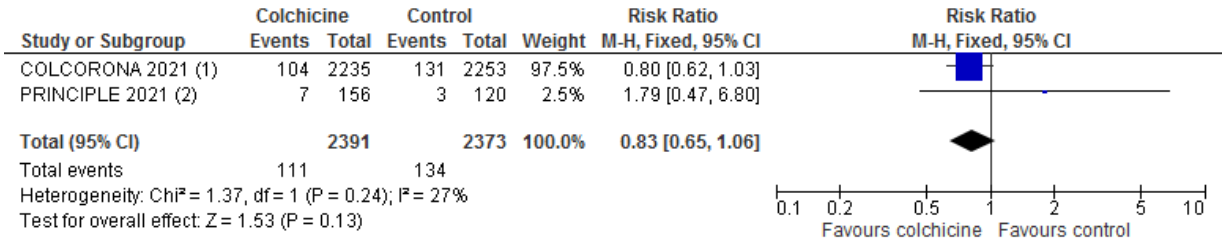
Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
COLCORONA 2021 (1)	5	2235	9	2253	0.56 [0.19, 1.67]



Footnotes
(1) At 30 days. 500 micrograms colchicine once daily for 27 days vs placebo

All-cause mortality or hospitalisation (28 or 30 days)

A person experiencing a hospitalisation and subsequent death was counted as 1 event.

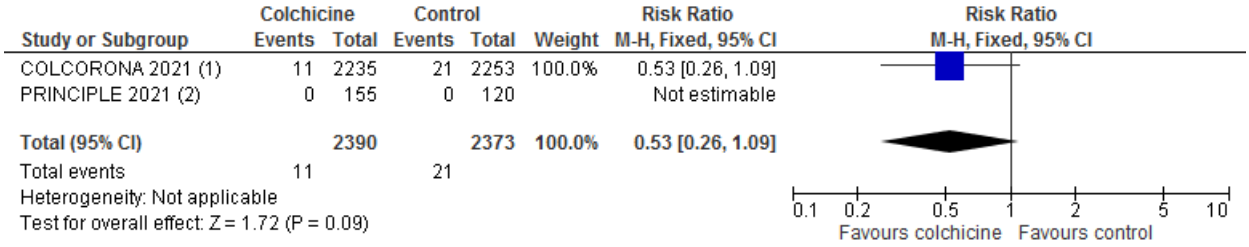


Footnotes

(1) At 30 days. 500 micrograms colchicine once daily for 27 days versus placebo

(2) At 28 days. 500 micrograms colchicine plus usual care for 14 days versus usual care

Mechanical ventilation within 28-30 days of starting treatment



Footnotes

(1) At 30 days. 500 micrograms colchicine once daily for 27 days versus placebo

(2) At 28 days. 500 micrograms colchicine plus usual care for 14 days versus usual care. There were no events in either arm.

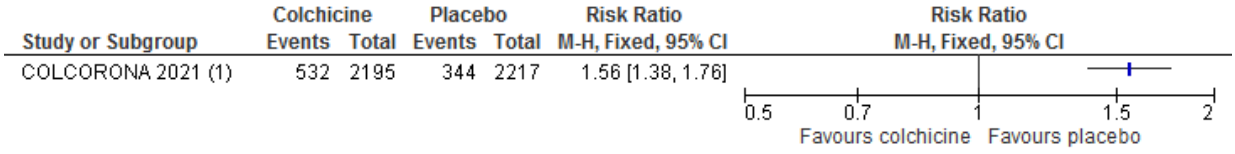
Serious adverse events within 28-30 days of starting treatment

Footnotes

(1) At 30 days. 500 micrograms colchicine once daily for 27 days versus placebo

(2) At 28 days. 500 micrograms colchicine plus usual care for 14 days versus usual care

Adverse events within 30 days of starting treatment

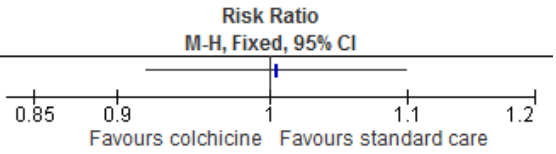


Footnotes

(1) At 30 days. 500 micrograms colchicine once daily for 27 days versus placebo

Participants who experienced alleviation of all symptoms within 28 days of starting treatment

Study or Subgroup	Colchicine Events	Colchicine Total	Standard care Events	Standard care Total	Risk Ratio M-H, Fixed, 95% CI
PRINCIPLE 2021 (1)	125	141	98	111	1.00 [0.92, 1.10]

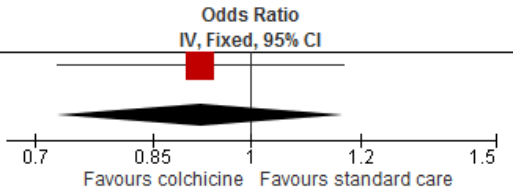


Footnotes
(1) At 28 days. 500 micrograms colchicine plus usual care for 14 days versus standard care

Reported recovery (days) within 28 days of starting treatment

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
PRINCIPLE 2021 (1)	-0.08338161	0.121664	100.0%	0.92 [0.72, 1.17]
Total (95% CI)			**100.0%**	**0.92 [0.72, 1.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

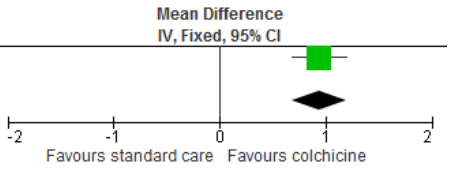


Footnotes
(1) At 28 days. 500 micrograms colchicine plus usual care for 14 days versus usual care

Time to alleviation of all symptoms, estimated treatment effect (median days) within 28 days of starting treatment

Study or Subgroup	Colchicine Mean	Colchicine SD	Colchicine Total	Standard care Mean	Standard care SD	Standard care Total	Weight	Mean Difference IV, Fixed, 95% CI
PRINCIPLE 2021 (1)	0.94	1.045413	141	0	1.045413	111	100.0%	0.94 [0.68, 1.20]
Total (95% CI)			**141**			**111**	**100.0%**	**0.94 [0.68, 1.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.09 (P < 0.00001)



Footnotes
(1) At 28 days. 500 micrograms colchicine plus usual care for 14 days versus standard care

Appendix G: GRADE profiles

Colchicine compared to standard care for COVID-19: Hospitalised

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With colchicine		Risk with standard care	Risk difference with colchicine
All-cause mortality											
11517 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	1196/5816 (20.6%)	1174/5701 (20.6%)	**RR 0.66** (0.24 to 1.85)	206 per 1,000	**70 fewer per 1,000** (from 156 fewer to 175 more)
Mechanical ventilation											
10916 (2 RCTs)	serious[b]	serious[c]	serious[d]	serious[a]	none	Very low	1349/5519 (24.4%)	1345/5397 (24.9%)	**RR 0.53** (0.09 to 3.15)	244 per 1,000	**115 fewer per 1,000** (from 222 fewer to 526 more)
Serious adverse events											
105 (1 RCT)	serious[b]	not serious	serious[d]	not serious	none	Low	0/50 (0.0%)	0/55 (0.0%)	not estimable	0 per 1,000	
Adverse events											
105 (1 RCT)	serious[b]	not serious	serious[d]	not serious	none	Low	15/50 (30.0%)	43/55 (78.2%)	**RR 2.61** (1.67 to 4.07)	300 per 1,000	**483 more per 1,000** (from 201 more to 921 more)

Certainty assessment							Summary of findings				
Discontinuation due to adverse events											
177 (2 RCTs)	serious[b]	not serious	serious[d]	very serious[e]	none	Very low	0/86 (0.0%)	2/91 (2.2%)	**RR 4.55** (0.22 to 92.62)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Clinical progression (scale)											
105 (1 RCT)	serious[b]	not serious	serious[d]	very serious[e]	none	Very low	7/50 (14.0%)	1/55 (1.8%)	**RR 0.13** (0.02 to 1.02)	140 per 1,000	**122 fewer per 1,000** (from 137 fewer to 3 more)
ICU admission											
72 (1 RCT)	serious[f]	not serious	not serious	very serious[e]	none	Very low	3/36 (8.3%)	1/36 (2.8%)	**RR 0.33** (0.04 to 3.06)	83 per 1,000	**56 fewer per 1,000** (from 80 fewer to 172 more)
Discharge from hospital (day 10)											
72 (1 RCT)	serious[f]	not serious	not serious	not serious	none	Moderate	22/36 (61.1%)	33/36 (91.7%)	**RR 1.50** (1.14 to 1.98)	611 per 1,000	**306 more per 1,000** (from 86 more to 599 more)
Discharge from hospital within 28 days											
11340 (1 RCT)	serious[b]	not serious	not serious	serious[a]	none	Low	4032/5730 (70.4%)	3901/5610 (69.5%)	**RR 0.99** (0.96 to 1.01)	704 per 1,000	**7 fewer per 1,000** (from 28 fewer to 7 more)
Duration of hospital stay											

Certainty assessment							Summary of findings				
100 (1 RCT)	very serious[g]	not serious	serious[d]	not serious	none	Very low	50	50	-		MD 1.84 lower (2.9 lower to 0.78 lower)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence intervals
b. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias
c. The magnitude of statistical heterogeneity was high
d. Standard care did not include dexamethasone for hospitalised patients on oxygen
e. Wide confidence intervals, Low number of patients
f. Because of serious bias due to lack of specified follow-up timepoints
g. Due to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes

Colchicine compared to standard care for COVID-19: Community

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With colchicine		Risk with standard care	Risk difference with colchicine
Hospitalisation for COVID-19											
4488 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	128/2253 (5.7%)	101/2235 (4.5%)	**RR 0.80** (0.62 to 1.03)	57 per 1,000	**11 fewer per 1,000** (from 22 fewer to 2 more)
All-cause mortality											
4488 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	9/2253 (0.4%)	5/2235 (0.2%)	**RR 0.56** (0.19 to 1.67)	4 per 1,000	**2 fewer per 1,000** (from 3 fewer to 3 more)
All-cause mortality or hospitalisation											
4764 (2 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	134/2373 (5.6%)	111/2391 (4.6%)	**RR 0.83** (0.65 to 1.06)	56 per 1,000	**10 fewer per 1,000** (from 20 fewer to 3 more)
Mechanical ventilation											
4763 (2 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	21/2373 (0.9%)	11/2390 (0.5%)	**RR 0.53** (0.26 to 1.09)	9 per 1,000	**4 fewer per 1,000** (from 7 fewer to 1 more)
Serious adverse events											

Certainty assessment							Summary of findings				
4688 (2 RCTs)	not serious	not serious	not serious	not serious	none	High	141/2337 (6.0%)	109/2351 (4.6%)	**RR 0.78** (0.61 to 0.99)	60 per 1,000	**13 fewer per 1,000** (from 24 fewer to 1 fewer)

Adverse events

4412 (1 RCT)	not serious	not serious	not serious	not serious	none	High	344/2217 (15.5%)	532/2195 (24.2%)	**RR 1.56** (1.38 to 1.76)	155 per 1,000	**87 more per 1,000** (from 59 more to 118 more)

Participants who experienced alleviation of all symptoms

252 (1 RCT)	very serious[b]	not serious	not serious	serious[a]	none	Very low	98/111 (88.3%)	125/141 (88.7%)	**RR 1.00** (0.92 to 1.10)	883 per 1,000	**0 fewer per 1,000** (from 71 fewer to 88 more)

Time to alleviation of all symptoms

252 (1 RCT)	very serious[b]	not serious	not serious	not serious	none	Low	111	141	-	-	MD 0.94 higher (0.68 higher to 1.2 higher)

Reported recovery (days)

276 (1 RCT)	very serious[b]	not serious	not serious	serious[a]	none	Very low	-	**-**	**OR 0.92** (0.72 to 1.17)	-	-

Time to reported recovery, median difference in days

0 (1 RCT)	very serious[b]	not serious	not serious	serious[a]	none	Very low	Median difference: 1.14 (95 CI -1.86 to 5.21). A positive value in estimated median difference in time to recovery corresponds to an increase in time to recovery in days in colchicine compared with standard care				

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Wide confidence intervals
b. due to a high dropout rate, concerns with randomisation, and lack of blinding