COLCHICINE

RECOMMENDATION

We suggest against the use of colchicine in the treatment of COVID-19 *(Low quality of evidence; Conditional recommendation)*

Consensus Issues

Current evidence showed significantly more adverse events (e.g., pulmonary embolism, gastrointestinal effects, nausea, rash, and most commonly diarrhea) with no significant clinical benefit in COVID-19 patients treated with colchicine compared to those receiving placebo or standard of care. Results from ongoing studies such as the ACT Trial are needed to better assess the effectiveness of colchicine as a treatment for COVID-19.

EVIDENCE SUMMARY

Should Colchicine be used for Treatment of COVID-19?

Evidence Reviewers: Maria Vanessa V. Sulit, RN, MSc (clinical epidemiology), Namnama P. Villarta-De Dios, MD, MSc (clinical epidemiology), Howell Henrian G. Bayona, CSP-PASP

Key Findings

We found 4 randomized controlled trials (RCTs) that investigated the effect of colchicine compared to standard of care as treatment for patients with COVID-19. Colchicine did not show significant effect in terms of reducing all-cause mortality, need for mechanical ventilation, clinical deterioration. However, low quality evidence suggested that colchicine significantly shortened duration of hospitalization and duration of oxygen supplementation among patients with moderate to severe disease. Although adverse events, particularly diarrhea, were more frequently observed among participants treated with colchicine, the number of serious adverse events were comparable to those who received standard of care. All of the studies had risk of bias issues as there were concerns in allocation concealment, blinding, attrition and selective reporting of outcome. The moderate risk of bias and imprecision in clinical outcomes such as all-cause mortality, mechanical ventilation, clinical deterioration and need for hospitalization contributed to downgrading of evidence to low certainty.

It is important to note that the effect estimates of important clinical outcomes were close to 1.0 for efficacy (no clear or appreciable benefit) among mild and moderate to severe COVID-19, and for serious adverse events (no clear harm) among patients with mild COVID-19. However, among patients with any severity of COVID-19, colchicine may cause more harm.

Introduction

Colchicine is an anti-inflammatory agent currently being used for gout, familial Mediterranean fever, Behcet's syndrome as well as pericarditis [1,2]. Colchicine has a unique anti-inflammatory property with a prolonged anti-inflammatory effect even after discontinuation [1]. Its primary mechanism is tubulin disruption leading to subsequent down regulation of multiple inflammatory pathways and modulation of innate immunity [3]. It is this anti-inflammatory mechanism that may potentially have an effect on the clinical course of the patient with COVID-19 in terms of developing pneumonia and other lung complications [4]. In a recent, good quality systematic review on colchicine and adverse events, colchicine was shown to increase gastrointestinal adverse events specifically diarrhea, but was not shown to increase rate of liver, sensory, muscle, infectious or hemoatologic adverse events or death [5].

Review Methods

A systematic search was done on March 26, 2021 using Medline, Cochrane Library, Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and colchicine. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov*. Only randomized controlled trials that compared colchicine against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy of colchicine. Subgrouping by severity was planned.

Results

We found four (4) RCTs that included a total of 4,773 COVID-19 patients. These RCTs were also included in the COVID-NMA Living Data (The COVID-NMA Initiative 2021). One RCT from Canada (pre-print) recruited out-patients (non-hospitalized) with mild disease [4], 2 RCTs from Brazil [7] and Greece [8] recruited hospitalized patients with moderate to severe disease, 1 RCT from Iran (pre-print) [9] had patients with unclear disease severity. Standard of care used across these studies varied as they followed their respective local guidelines at the time the studies were conducted, namely placebo [4,9], azithromycin and hydroxychloroquine (HCQ) [7], and HCQ [9]. The dose of colchicine varied from 0.5 to 1 mg/day, while the duration of treatment with colchicine ranged from 6 to 27 days. Outcomes measured during the follow-up period of approximately 21-30 days included all-cause mortality [4,7,8,9] need for mechanical ventilation [4,8], need for hospitalization [4], duration of hospitalization [7,9] and adverse events [4,8,7]. The characteristics of included studies are summarized in Appendix 1.

None of the studies were of low risk of bias. All showed some concerns in the risk of bias related to allocation concealment [4,9], blinding from open-labeled trials [8,9], high attrition [4,7], and selective reporting [7,9]. Further downgrading was done because of imprecision in some of the outcomes as seen in the wide confidence intervals and insufficient sample size. For these reasons, overall quality of the evidence was rated as low.

Based on 4 RCTs, colchicine did not show any significant benefit in terms of reducing all-cause mortality (RR 0.43 [95% CI 0.17, 1.10], I^2=0%). Subgroup analysis according to disease severity showed similar non-significant results, with an RR of 0.56 (95% CI 0.19, 1.67) for mild disease [4] and RR of 0.22 (95% CI 0.04, 1.29) for moderate-to-severe disease [7,8]. There were no deaths reported in the subgroup of unclear severity, as none were observed in the follow-up period for this study [9].

Colchicine did not significantly reduce the number of patients needing mechanical ventilation (RR 0.44 [95% CI 0.19, 1.03] I^2=12%) [4,8]. Clinical deterioriation or WHO progression to level 7 or above on the 28th day was reported by Deftereos (2020) and the RR was not significant at 0.14 (95% CI 0.02, 1.08).

In terms of post-discharge findings, one RCT with high risk of bias showed that colchicine was associated with a significantly shorter duration of hospitalization (6.3 vs 8.1 days; MD -1.84 days; p=0.001) [9]). No standard deviation was provided for this value. Another RCT, also with high risk of bias reported significantly shorter duration of hospitalization (median 7 days [IQR 5-9] vs. 9 days [IQR 7-12], p=.003) and time needed to discontinue oxygen supplementation (median 4 [IQR 2-6] vs 6.5 [IQR 4-9], p<.001) among patients treated with colchicine [7]. Both Salehzadeh (2020) and Lopes (2020) were only small studies of 100 and 38 included patients, respectively, and the serious risk of bias in the studies suggests that we approach interpretation of these results with caution.

A significant effect favoring colchicine in terms of reducing the need for hospitalization among out-patients with mild disease (confirmed with PCR) was reported in 1 study (4.6% vs 6.0%, n=4,159) (RR 0.77 [95% CI 0.59, 0.99]). Though this result was from a pre-specified per protocol analysis and the confidence intervals did not cross the value of 1.0, the study had moderate risk of bias. Further, on intention-to-treat analysis of results from both PCR-confirmed and suspect cases (n=4,470), the significant difference in reducing the need for hospitalization was no longer evident (RR 0.80 [95% CI 0.62, 1.03]). Hence, the results need to be interpreted with caution.

Adverse events

More adverse events were observed in patients who received colchicine (24% vs. 15%, n=4563) (RR 1.55 [95% CI 1.37, 1.75] I^2=0%). These included pulmonary embolism, gastrointestinal effects, nausea, rash and more commonly diarrhea. Subgroup analysis according to severity showed that this effect was more evident among patients with mild disease (RR 1.56 [95% CI 1.38, 1.76]) [4] than those with moderate to severe disease (RR 1.30 [95% CI 0.62, 2.71]) [7]. Looking at diarrhea alone, a significantly greater proportion of patients experienced this adverse effect regardless of disease severity (RR 1.94 [95% CI 1.63, 2.31] I^2=0%) [4,7,8].

Three studies showed that the number of serious adverse events differed significantly between the colchicine and control groups but only by a small margin (RR 0.78 [95% 0.61, 0.99] I^2=0 [4,7,8]. There seems to be less serious adverse events with the use of colchicine, though the result was largely contributed by Tardif (2021) on out-patients with mild severity of disease.

Recommendations from Other Groups

The NIH COVID-19 Guidelines (accessed 26 March 2021) does not mention the use of colchicine for COVID-19 treatment (COVID-19 Treatment Guidelines Panel 2021). The Surviving Sepsis Campaign Guidelines on COVID-19, and the Infectious Disease Society of America on the Treatment and Management of Patients with COVID-19 did not make any recommendation related to colchicine [11,12]. The Australian COVID-19 Guidelines (version 36.1) does not recommend the use of colchicine for the treatment of COVID-19 outside of randomized trials [13]. The Philippine Society for Microbiology and Infectious Diseases, the Philippine College of Chest Physicians, the Philippine College of Physicians, the Philippine Rheumatology Association and the Philippine College of Hematology and Transfusion Medicine in their Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection (version 3.1) did not mention any recommendation on the use of colchicine (PSMID-PCCP-PCP Interim Guidance July 2020).

Research Gaps

As of March 5, 2021, the investigators of the RECOVERY trial announced that the colchicine arm of the trial has been closed. Based on their preliminary analysis of 11,162 patients with COVID-19, no significant difference in 28-day mortality was seen between the colchicine and usual care group (Recovery Trial Chief Investigators 2021). In addition to the RECOVERY trial, there are still 26 ongoing studies on colchicine for the treatment of COVID-19 patients listed in *clinicaltrials.gov* (NIH US National Library of Medicine, ClinicalTrials.Gov 2021). Furthermore, the ACT trial (Anti-Coronavirus Therapies to Prevent Progression of COVID-19, a Randomized Trial) is currently recruiting study subjects in the Philippines. This review will be updated as soon as full results from these trials become available.

References

[1] Tan GM, Yan BP. What's old is new again - a review of the current evidence of colchicine in cardiovascular medicine. Current Cardiology Reviews. 2017. 13:130-138.

[2] Katsanos AH, Palaiodimou L, Price C, Giannopoulos S, Lemmens R, Kosmidou M, Georgakis MK, Weimar C, Kelly PJ, Tsivgoulis G. Colchicine for stroke prevention in patients with coronary artery disease: a systematic review and meta-analysis. Eur J Neurol. 2020 Mar 5. doi: 10.1111/ene.14198. [Epub ahead of print]

[3] Leung YY, Yao Hui LL, Kraus VB. Colchicine — Update on Mechanisms of Action and Therapeutic Uses, Seminars in Arthritis and Rheumatism, http://dx.doi.org/10.1016/j.semarthrit.2015.06.013

[4] Tardif JC, Bouabdallaoui N, L'Allier PL, *et al.* for the COLCORONA Investigators. Efficacy of colchicine in non-hospitalized patients with COVID-19. doi: https://doi.org/10.1101/2021.01.26.21250494

[5] Stewart, S., Yang, K.C.K., Atkins, K. *et al.* Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* **22,** 28 (2020). https://doi.org/10.1186/s13075-020-2120-7

[6] The COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/

[7] Lopes MIF, Bonjorno LP, Giannini MC, *et al.* Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv 2020.doi:10.1101/2020.08.06.20169573

[8] Deftereos SG, Giannopoulos G, Vrachatis DA, *et al.* 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 Netw Open 2020;**3**:e2013136. doi:10.1001/jamanetworkopen.2020.13136

[9] Salehzadeh, Farhad & Pourfarzi, Farhad & Ataei, Sobhan. (2020). The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study. 10.21203/rs.3.rs-69374/v1.

[10] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 3/26/2021.

[11] Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19), Accessed 26 March 2021 https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

[12] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Gallagher J, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America **2021**; Version 4.1.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 26 March 2021.

[13] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v36.1 2021 Mar 25.

[14] The Philippine Society for Microbiology and Infectious Diseases, the Philippine College of Chest Physicians, the Philippine College of Physicians, the Philippine Rheumatology Association and the Philippine College of Hematology and Transfusion Medicine in their Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection (version 3.1). 2020 July 20.

[15] RECOVERY Trial Chief Investigators. 2020 (March 26). *RECOVERY trial closes recruitment to colchicine treatment for patients hospitalised with COVID-19*. RECOVERY: Randomised Evaluation of COVID-19 Therapy. https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19

[1] NIH – U.S. National Library of Medicine, ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/results?recrs=&cond=colchicine&term=covid-19&cntry=&state=&city=&dist=

Appendix 1. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19 *Tardif et al. 2021 (Canada, USA, Brazil)* *Pre-print*	N=4488 at least 40 years of age, had received a diagnosis of COVID-19 within 24 hours of enrollment **non-hospitalized patients with COVID-19** diagnosed by polymerase chain reaction (PCR) testing or clinical criteria <u>Duration of follow-up:</u> Approximately 30 days	EXPERIMENTAL: colchicine (0.5 mg twice daily for 3 days and once daily thereafter) CONTROL: placebo	PRIMARY composite of death or hospitalization due to COVID-19 infection in the 30 days following randomization SECONDARY components of the composite primary endpoint; and the need for mechanical ventilation in the 30 days following randomization. Pneumonias, other serious adverse events, and non-serious adverse events were also collected.	Randomized Parallel Double-blind
Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial *Lopes et al., 2021 (Brazil)*	N=75 **individuals hospitalised with moderate or severe forms of COVID-19 diagnosed by RT-PCR in nasopharyngeal swab specimens and lung CT scan involvement** compatible with COVID-19 pneumonia; older than 18 years; body weight >50 kg; normal serum Ca2+ and K+; QT interval <450 ms at 12 derivations ECG (according to the Bazett formula) negative serum or urinary β-HCG if woman under 50 years. <u>Duration of follow-up:</u> Up to 26 days	EXPERIMENTAL (n_e=36): colchicine 0.5 mg 3x daily for 5 days, then 0.5 mg 2x daily for 5 days; if body weight ≥80 kg, the first dose was 1.0 mg. If with chronic kidney disease, with glomerular filtration rate under 30 mL/min/1.73 m2, colchicine dose was reduced to 0.25 mg 3x daily for 5 days, then 0.25 mg 2x daily for 5 days, no matter the body weight. PLUS INSTITUTIONAL PROTOCOL (STANDARD CARE) azithromycin 500 mg once daily for up to 7 days, hydroxychloroquine 400 mg twice daily for 2 days, then 400 mg once daily for up to 8 days and unfractionated heparin 5000 UI thrice daily until the end of hospitalisation methylprednisolone 0.5 mg/kg/day for 5 days CONTROL(n_c=36): INSTITUTIONAL PROTOCOL(STANDARD CARE)	PRIMARY time of need for supplemental oxygen time of Hospitalization need for admission and length of stay in ICU death rate and causes of mortality SECONDARY measures of serum CRP, serum lactate dehydrogenase (LDH) and relation neutrophil to lymphocyte of peripheral blood samples from day 0 to day 7 adverse events - number, type and severity frequency of interruption of the study protocol due to adverse events frequency of QT interval above 450 ms	randomized placebo-control double blind

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 *Deftereos et al., 2020* *(Greece)*	N=110 **Hospitalized adult patients diagnosed with SARS-CoV-2 infection by RT-PCR** body temperature of 37.5 °C 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 95mmHg on room air <u>Duration of follow-up:</u> 21-25 days	EXPERIMENTAL (n_e=55): Colchicine administration (1.5-mg loading dose followed by 0.5mg after 60 min and maintenance doses of 0.5 mg twice daily) with standard medical treatment CONTROL (n_c=50): standard medical treatment	PRIMARY (1) maximum high-sensitivity cardiac troponin level; (2) time for C-reactive protein to reach more than 3 times the upper reference limit; and (3) time to deterioration by 2 points on a 7-grade clinical status scale (WHO R&D Blueprint Ordinal Clinical Scale), ranging from able to resume normal activities to death. SECONDARY (1) the percentage of participants requiring mechanical ventilation, (2) all-cause mortality, and (3) number, type, severity, and seriousness of adverse events.	randomized parallel
The Impact of Colchicine on the COVID-19 Patients: A Clinical Trial Study *Salehzadeh et al. 2021* *(Iran)* *Pre-print*	N= 100 Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19. <u>Duration of follow-up:</u> Up to 2 weeks post discharge; around 21 to 30 days	EXPERIMENTAL: HCQ + colchicine 1mg OD CONTROL: HCQ + placebo	PRIMARY (1) Length of hospitalization; (2) symptoms and (3) Co-existed disease. SECONDARY (1) mortality and morbidity (2) re-admission and (3) symptoms.	Randomized double blind Placebo control

Appendix 2. GRADE Evidence Profile

Author(s): Sulit, Maria Vanessa; Villarta-de Dios, Namnama
Question: Colchicine compared to Placebo or Standard Care for COVID-19
Setting: out-patient and in-hospital
Bibliography:

1. Tardif JC, Bouabdallaoui N, L'Allier PL, *et al.* for the COLCORONA Investigators. Efficacy of colchicine in non-hospitalized patients with COVID-19. doi: https://doi.org/10.1101/2021.01.26.21250494
2. Lopes MIF, Bonjorno LP, Giannini MC, *et al.* Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv 2020.doi:10.1101/2020.08.06.20169573
3. Deftereos SG, Giannopoulos G, Vrachatis DA, *et al.* 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 Netw Open 2020;**3**:e2013136. doi:10.1001/jamanetworkopen.2020.13136
4. Salehzadeh, Farhad & Pourfarzi, Farhad & Ataei, Sobhan. (2020). The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study. 10.21203/rs.3.rs-69374/v1.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo or Standard Care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 1 to 30 days)												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	none	6/2379 (0.3%)	15/2394 (0.6%)	**RR 0.43** (0.17 to 1.10)	**4 fewer per 1,000** (from 5 fewer to 1 more)	⨁⨁◯◯ LOW	
Need for Mechanical Ventilation (follow up: range 1 to 30 days)												
2	randomised trials	serious [c]	not serious	not serious	serious [b]	none	12/2291 (0.5%)	27/2307 (1.2%)	**RR 0.44** (0.19 to 1.03)	**7 fewer per 1,000** (from 9 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Clinical Deterioration / WHO progression to level 7 or above (28 days)												
1	randomised trials	serious [d]	not serious	not serious	serious [b]	none	1/56 (1.8%)	7/54 (13.0%)	**RR 0.14** (0.02 to 1.08)	**111 fewer per 1,000** (from 127 fewer to 10 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Issues on allocation (Salehzadeh 2020, Tardif 2021), blinding (Deftereos 2020, Salehzadeh 2020), attrition (Lopes 2020, Tardif 2021) and selective reporting (Lopes 2020, Salehzadeh 2020)
b. Wide confidence interval of overall estimate
c. Issues on allocation (Tardif 2021), blinding (Deftereos 2020)
d. Issues on blinding (Deftereos 2020)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo or Standard Care	Relative (95% CI)	Absolute (95% CI)		
Need for hospitalization (follow up: range 1 to 30 days)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	93/2075 (4.5%)	123/2084 (5.9%)	**RR 0.77** (0.59 to 0.99)	**14 fewer per 1,000** (from 24 fewer to 1 fewer)	⨁⨁◯◯ LOW	
Duration of hospitalization (follow up: range 1 to 30 days)												
2	randomised trials	serious [c]	not serious	not serious	serious [d]	none	Colchicine was associated with a significantly shorter duration of hospitalization (n=100) 6.3 vs 8.1 days; MD -1.84 days; p=0.001 (Salehzadeh (2020). There was significantly shorter duration of hospitalization (n=38) (median 7 days [IQR 5-9] vs. 9 days [IQR 7-12], p=.003) in patients treated with colchicine (Lopes 2020).				⨁⨁◯◯ LOW	
Time of supplemental oxygen (follow up: 7 days)												
1	randomised trials	serious [e]	not serious	not serious	very serious [f]	none	Time of supplemental oxygen (n=38) (days; median IQR) Placebo 7 (3.0-8.5) Colchicine 3 (1.5-6.5) p=0.02				⨁◯◯◯ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Issues on allocation, attrition (Tardif 2021)
b. Wide confidence interval, no appreciable benefit
c. Issues on allocation, blinding, selective reporting (Salehzadeh 2020); issues on attrition and selective reporting (Lopes 2020)
d. Information may not translate to real effect due to small sample size and continuous nature of the outcome
e. Issues on attrition and selective reporting (Lopes 2020)
f. Information may not translate to real effect due to small sample size, continuous nature of the outcome and evidence from one study

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo or Standard Care	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: range 1 to 30 days)												
3	randomised trials	serious [b]	not serious	not serious	serious [a]	none	111/2329 (4.8%)	144/2344 (6.1%)	**RR 0.78** (0.61 to 0.99)	**14 fewer per 1,000** (from 24 fewer to 1 fewer)	⨁⨁◯◯ LOW	
Adverse events (follow up: range 1 to 30 days)												
2	randomised trials	serious [c]	not serious	not serious	not serious	none	542/2254 (24.0%)	352/2272 (15.5%)	**RR 1.55** (1.37 to 1.75)	**85 more per 1,000** (from 57 more to 116 more)	⨁⨁⨁◯ MODERATE	
Diarrhea (follow up: range 1 to 30 days)												
3	randomised trials	serious [b]	not serious	not serious	not serious	none	331/2329 (14.2%)	172/2344 (7.3%)	**RR 1.94** (1.62 to 2.31)	**69 more per 1,000** (from 45 more to 96 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Wide confidence interval of overall estimate
b. Issues on allocation (Tardif 2021), blinding (Deftereos 2020), attrition (Lopes 2020, Tardif 2021) and selective reporting (Lopes 2020)
c. Issues on allocation (Tardif 2021), attrition (Lopes 2020, Tardif 2021) and selective reporting (Lopes 2020)

Appendix 3. Forest Plots

Primary Outcomes for the Study by Lopes (2020)

	Placebo Group (n=18)	Colchicine Group (n=17)	p-value
Time of supplemental O_2 [days; median (IQR)]	7.0 (3.0 – 8.5)	3.0 (1.5 – 6.5)	0.02
Time of hospitalization [days; median (IQR)]	8.5 (5.5 – 11.0)	6.0 (4.0 – 8.5)	0.03

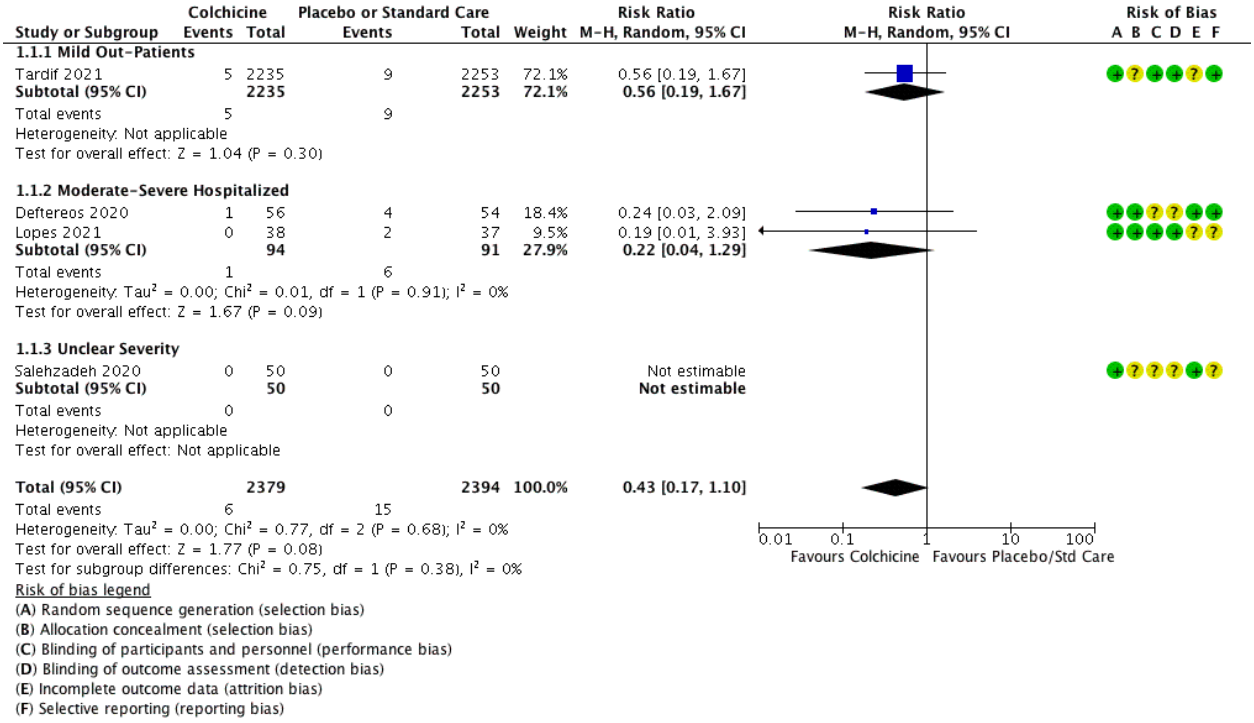

Figure 1. All-cause mortality

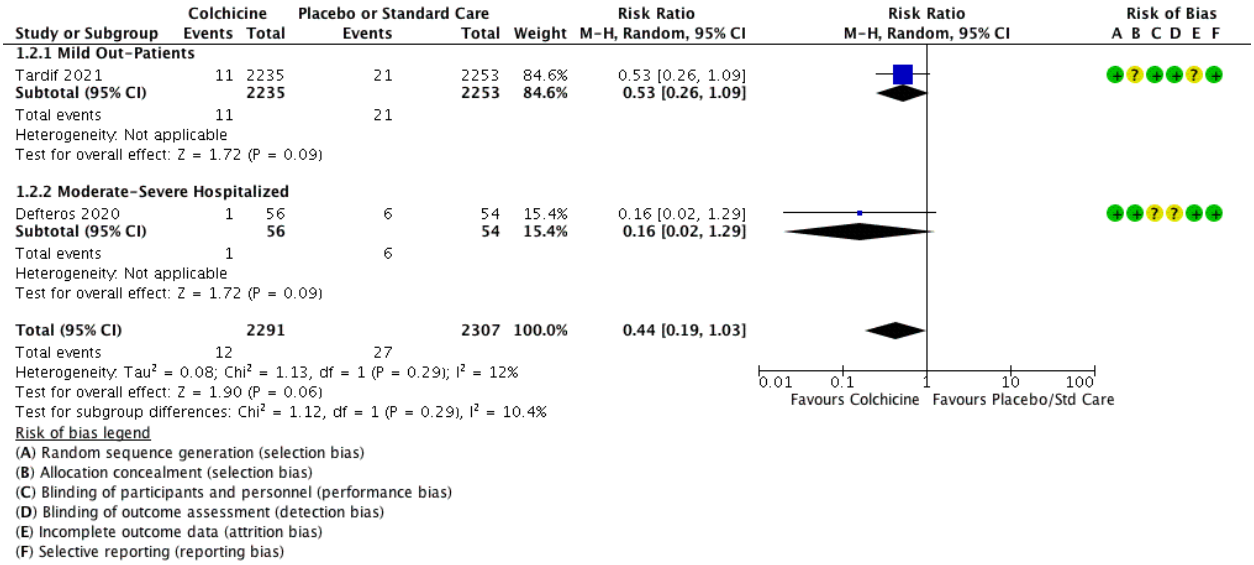

Figure 2. Need for Mechanical Ventilation

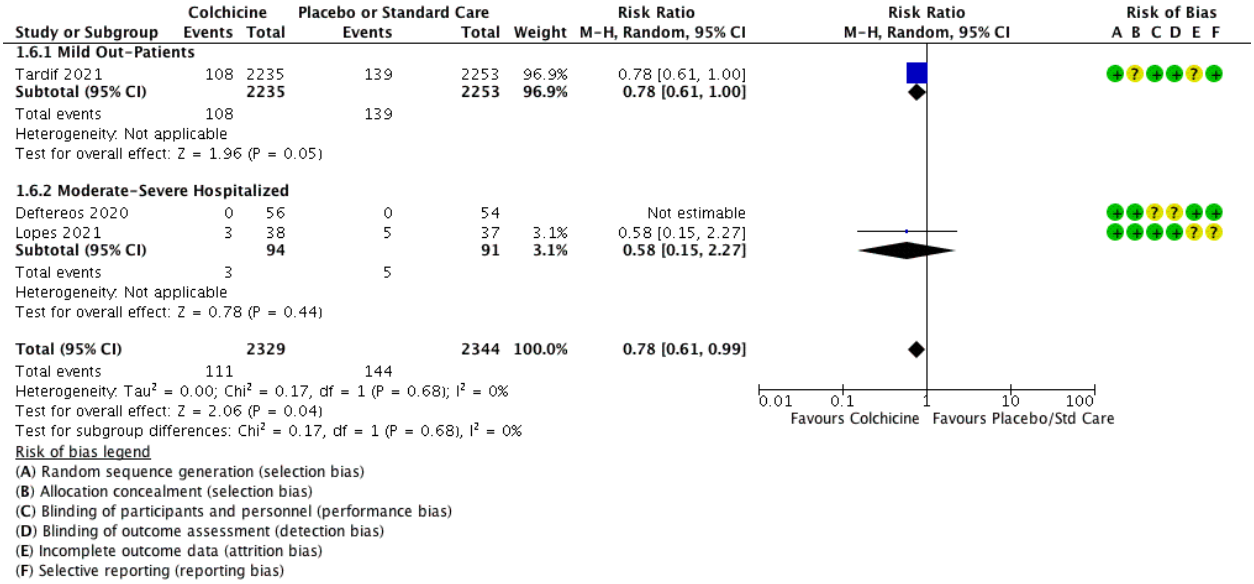

Figure 3. Serious Adverse Events

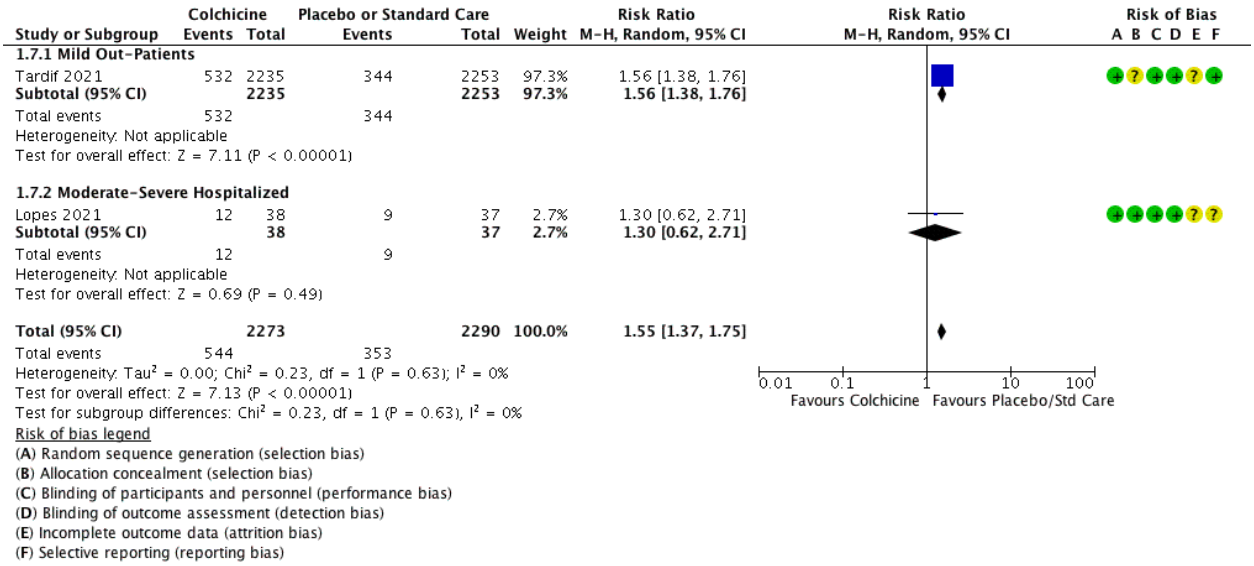

Figure 4. Adverse events

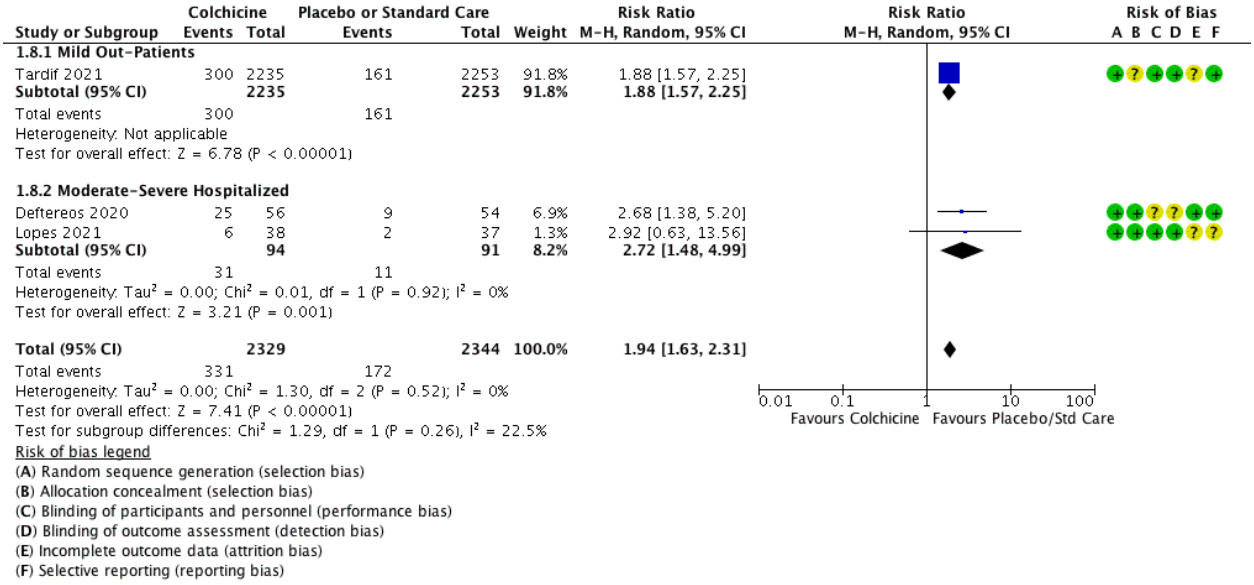

Figure 5. Diarrhea

Appendix 4. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Colchicine / Statins for the Prevention of COVID-19 Complications (COLSTAT) Trial	18 years and older with clinical or definitive diagnosis of COVID-19 by PCR test. Admitted to the hospital (non-ICU) within 48h to hospital admission	Experimental: Standard of Care (SOC) and Colchicine + Rosuvastatin Rosuvastatin 40mg daily and Colchicine 0.6mg twice for 3 days and then 0.6mg daily during hospitalization Control: SOC during hospitalization determined by the primary care team during hospitalization.	As defined by World Health Organization Ordinal Scale, which ranges from 1 to 8. Severity of COVID measured by WHO Scores 5-8: Defined as 5= Hospitalized requiring including CPAP, face mask, high flow nasal cannula (Excludes regular nasal cannula) 6= Hospitalized requiring intubation and mechanical ventilation 7= Hospitalized requiring mechanical ventilation and additional organ support (vasopressors, renal replacement therapy, ECMO) 8= Death	Randomized; parallel assignment, open label
2. Application of Colchicine Plus Herbal Phenolic Monoterpene Fractions to Treat COVID-19	10 years and older Defined cases of COVID-19 based on laboratory and/or radiological and clinical manifestationfs	Experimental: Colchicine and Herbal Phenolic Monoterpene Fractions Control: Standard treatment national guideline	All-cause mortality (up to 30 days) Change in patients' clinical manifestation Length of hospitalization (days) C-reactive protein (mg/L), lymphocyte count (cell/mL), serum LDH (U/L), serum IL-6 (pg/mL), ESR (mm/h)	Randomized; parallel assignment, double blind
3. Treatment With COLchicine of Patients Affected by COVID-19: a Pilot Study	18 years or older Virological diagnosis of SARS-CoV-2 infection (real-time PCR), hospitalized due to clinical/instrumental diagnosis of pneumonia; Oxygen saturation at rest in ambient air ≤94%; PaO2/FiO2 ratio of 350 to 200	Experimental: Colchicine plus Current care Colchicine 0.5 mg three times a day if weight is less than 100 kg; 1 mg twice a day if weight is more than 100 kg for 30 days or up to discharge. Reduce based on gastrointestinal symptoms appearance at discretion of the Investigator. Control: Current care	Primary: Rate of entering critical stage (respiratory failure requiring mechanical ventilation; Patients combined with other organ failure need ICU monitoring and treatment; death)	Randomized; parallel assignment, open label
4. Study to Investigate the Treatment Effect of Colchicine in Patients With COVID-19	18 to 65 years SARS-CoV-2 infection confirmed by PCR. Admitted in the hospital in the previous 48 hours, with clinical status 3, 4 or 5 of WHO classification.	Experimental: SOC plus Colchicine The Colchicine treatment includes an initial dose of 1.5 mg (1 mg and 0.5 mg two hours after), followed by 0.5 mg every 12 hours during the next 7 days and 0.5 mg every 24 hours until the completion of 14 days of total treatment. In patients receiving ritonavir or lopinavir or with reduced renal clearance (<50 ml/min/1.37m2), weight <70 kg or age >75 years old, the dose will be adjusted to the half. Control: SOC	Primary: Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D Blueprint expert group; changes in IL-6 concentrations	Randomized, controlled, open-label

5. Randomized, Open-Label, Controlled Trial of Colchicine to Reduce Cardiac Injury in Hospitalized COVID-19 Patients (COLHEART-19)	Age above 18 years old Confirmed COVID-19 infection by polymerase chain reaction Cardiac injury, including any of the following: Elevated troponin level Elevated B-type natriuretic peptide (BNP) level New ischemic or arrhythmogenic changes on ECG/telemetry New decrease in left ventricular ejection fraction (LVEF) or new pericardial effusion on echocardiogram	Experimental: Colchicine plus current care Colchicine 0.6 mg po BID x 30 days plus current care per UCLA treating physicians Control: current care alone per UCLA treating physicians	Primary: Composite of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support	Randomized, parallel assignment, open-label
6. Preemptive Therapy with Colchicine in Patients Older Than 60 Years with High Risk of Severe Pneumoniae Due to Coronavirus SARS-Cov2 (COVID-19)	At least two of the following high-risk criteria: -60 years of age or older AND -any of the following: Diabetes mellitus, high blood pressure, known pulmonary disease (including asthma or chronic obstructive pulmonary disease), known heart failure, known coronary disease, bicytopenia, pancytopenia, or the existence of simultaneous neutrophilia and lymphopenia Diagnosis of COVID-19 infection in the last 72 hours and confirmed by PCR Patient in outpatient follow-up (not hospitalized or under consideration) or institutionalized in senior centers/residences	Experimental: Colchicine plus symptomatic treatment. Patients in this arm will receive study medication colchicines 0.5 mg orally (PO) twice daily for the first 3 days and then once daily for the last 18 days. If a dose is missed, it should not be replaced. Control: Symptomatic treatment (paracetamol or best symptomatic treatment based on doctor recommendations)	Primary: Number of participants who die due to COVID-19 infection Number of participants who require hospitalization due to COVID-19 infection	Randomized, parallel assignment, open-label
7. Effects of Standard Protocol Therapy With or Without Colchicine in Covid-19 Infection: A Randomized Double Blind Clinical Trial	Patients >18 years old with nasopharyngeal swab confirmed COVID-19 PCR, CT involvement compatible with COVID, Fever and Dyspnea without hypoxemia.	Experimental: colchicine plus SOC 1.5 mg loading then 0.5 mg BID P.O Control: SOC vitamin C 3grams daily , 400 mg Tiamine, Selenium , Omega-3 500 mg daily, Vit A , Vit D, Azithromycine, Ceftriaxone, Kaletra 400 BID 10 days	Primary: increasing inflammatory status (CRPxN/R ratio change); Clinical deterioration by the WHO definition including change in fever or O2 Saturation; RT-PCR viral load; change in CT severity involvement index	Randomized Parallel assignment Double blind

8. Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia: A Pragmatic Randomized Controlled Trial	Age 18 years or over Positive RT-PCR for COVID-19 or high suspicion of SARS covid 19 *Moderate pneumonia-confirmed pneumonia with chest X-Rays and either *Severe pneumonia, sepsis or septic shock-confirmed pneumonia with chest X-Rays and either criteria for in-hospital management according to the simplified CRB-65 scale (score greater than 1) or oxygen saturation lower than 90 percent without supplementary oxygen Multiple organ failure Acute Respiratory Distress Syndrome (radiological findings compatible with bilateral infiltrates and oxygenation deficit	Experimental 1: Emtricitabine (200 mg) + tenofovir (300 mg): 500 mg once a day for 10 days Experimental 2: Colchicine: 0.5 mg every 12 hours for 14 days + Rosuvatatin: 40 mg / day for 14 days Experimental 3: Emtricitabine (200 mg) + tenofovir (300 mg): 500 mg once a day for 10 days + Colchicine: 0.5 mg every 12 hours for 14 days + Rosuvatatin: 40 mg / day for 14 days Control: Standard treatment	Primary: Mortality, cumulative incidence on day 28 Number of participants that develop severe adverse events related to the treatment	Randomized Parallel assignment Open label
9. Phase 2/3, Randomized, Open Study to Compare the Efficacy and Safety of Colchicine and Glucocorticoids Compared With the Standard of Treatment for Moderate/Severe COVID-19 in a Fragile and Vulnerable Population, Admitted to a Geriatric Hospital Unit or in a Transicional Care Center	At least 65 years old and admitted to the Geriatrics Unit of the Internal Medicine Service (Hospital Clínic de Barcelona) or to a transicional care center Clinical diagnosis compatible with COVID-19 (in a favourable epidemiological context), with a disease considered moderate (grade 3-4) or severe (grade 5) according to the WHO 8-point ordinal scale for assessing clinical severity	Experimental: colchicine plus prednisone Colchicine: ideal dose of 0.3 mg/kg/day (or the dose that approximates that adjusted for age, weight and kidney function, and 0.5 mg and 1 mg tablets) Prednisone 60 mg/day, in a single dose, during 3 days Control: Standard treatment	Primary: Reduction of mortality on day 28	Randomized Parallel assignment Open label
10. Efficacy and Safety of Edoxaban and or Colchicine for Patients With SARS-CoV-2 Infection Managed in the Out of Hospital Setting	18 years and older Patients with laboratory confirmed SARS-CoV-2 infection (under RT PCR) who are managed at home or in another out-of-hospital setting.	Experimental 1: Edoxaban 60 mg q.d., or 30 mg q.d. in patients with CrCl = or <50 ml/min or body weight equal or less than 60 kg from randomization to end of study visit at day 25 (+/-3) Experimental 2: Colchicine at 0.5 mg per os (PO) twice daily for the first 3 days and then once daily from randomization to day 14 (+/-3) days. Treatment could be continued to day 25 (+3/-3 days) Experimental 3:	Primary: colchicine versus no active treatment on the SARS-CoV-2 clearance rates under RT PCR or freedom from death or hospitalisation at day 14 (+/-3) after randomization.	Randomized Factorial assignment Open label

		Edoxaban and Colchicine Control: No Edoxaban and No Colchicine		
11. The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients. (COLCOVID)	age ≥18 years COVID-19 suspicious Admitted to hospital or already in hospital COVID-19 suggestive symptoms (fever or febrile equivalent, loss of smell and taste, fatigue, etc.) that may be present or absent at randomization time SARS (severe acute respiratory syndrome) - shortness of breath (dyspnea); or image of typical or atypical pneumonia; or oxygen desaturation (SpO2 ≤ 93)	Experimental: colchicine Control: standard of care	Primary: Number of participants who require new intubation for mechanical ventilation or die on day 28 Number of participants who die on day 28	Randomized Parallel assignment Open label
12. Prospective-randomized Adaptive Study, With Active Control to Evaluate the Efficacy and Safety of Interleukin (IL)-17 Inhibitor Treatment Versus Low Doses of IL-2 Versus Indirect IL-6 Inhibitor in Hospitalized Patients With Severe Forms of COVID-19 (STRUCK Trial)	18 Years and older Positive result in the quantitative real-time PCR (qPCR) test for SARS-CoV-2 in the respiratory tract; Pneumonia confirmed by chest imaging and - Respiratory rate ≥ 24 IRPM (for adults) or - O2 saturation <93% or - No improvement in O2 saturation, despite oxygen supply or - Arterial hypotension; or - Changes in capillary filling time; or - Changes in the level of consciousness; or - Oliguria;	Experimental 1: 80 mg of IL-17 inhibitor (Ixekizumab) Experimental 2: 1.5 million IU (low-dose) of IL-2 (aldesleukin) Experimental 3: colchicine 0.5 mg every 8 hours for 3 days (PO), followed by 4 weeks (+/-7 days) 0.5 mg twice daily. If a dose is missed, it should not be replaced. Control:Standard treatment (including O2 ventilation, antiretrovirals, glucocorticoids)	Primary: Ordinal scale of seven World Health Organization (WHO) categories of IL-17 inhibitor versus low dose IL-2 versus indirect IL-6 inhibitor (colchicine) versus standard treatment in the treatment of severe COVID-19 on day 21	Randomized Parallel assignment Open label
13. Open-label (Unblinded) Randomization to Treatment of Colchicine Plus Current Care Per Institution Treating Physicians vs. Current Care Per Institution Treating Physicians (Control Arm)	18 Years to 99 Years Covid-19 Positive Hospitalized patients able to provide informed consent Cardiac injury (as evidenced by any of the following) - Elevated troponin level - Elevated BNP level - New ischemic or arrhythmogenic ECG/telemetry changes - New decrease in LVEF or new pericardial effusion	Experimental: colchicine plus current care Colchicine dosing = 0.6 mg bid x 30 days Decrease dose to 0.3-0.6 mg daily or every other day in setting of gastrointestinal intolerance (nausea, diarrhea, emesis, abdominal discomfort) Decrease dose to 0.6 mg daily in the setting of weak or moderate CYP3A4 inhibitor Decrease dose to 0.3 mg daily in the setting of	Primary: Composite of all-cause mortality; need for mechanical ventilation; Need for mechanical circulatory support	Randomized Parallel assignment Open label

	on echocardiogram	strong CYP3A4, P-glycoprotein inhibitors, or protease inhibitors Decrease dose to 0.3 mg daily in the setting of CKD stage ≥ 4 (CrCl ≤ 30 ml/min) or liver failure (AST/ALT > 3x normal). Decrease dose to 0.6 mg every 14 days in patients with end stage renal disease (ESRD) or requiring dialysis Route of Administration: oral Control: no intervention		
14. Double-blind, Placebo-controlled Clinical Trial of the Use of Colchicine for the Management of Patients With Mild and Severe SARS-Cov2 Infection	18 Years to 70 Years Diagnosed with COVID-19 with mild or severe disease Must receive in-hospital care at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran fsAble to take pills PO	Experimental: Colchicine 1mg, 1 ½ pill in day 1 and ½ pill BID during 10 days in both mild and severe COVID-19 Control:placebo	Primary: Number of patients with improvement in body temperature, myalgia, arthralgia, total lymphocyte count, D-dimer, fibrinogen and ferritin levels	Randomized Parallel assignment Double blind Placebo controlled Quadruple masking
15. Colchicine to Counteract Inflammatory Response in COVID-19 Pneumonia (ColCOVID-19)	Positive nasopharyngeal swab for COVID-19, asymptomatic or pauci-symptomatic, aged ≥70 years and/or with clinical risk factors for poor outcome (clinically relevant chronic lung disease, diabetes and/or heart disease) or symptomatic with respiratory or systemic symptoms, however clinically stable (MEWS<3) Positive swab for COVID-19 with respiratory symptoms	Experimental: Colchicine 1mg (or 0.5 mg in CKD)/day + standard of care Control: standard care	Primary: Time to clinical improvement Or Live discharge from the hospital (whatever comes first)	Randomized Parallel assignment Open label
16. COLchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial	18 Years and older COVID 19 with the mild and severe course. The diagnosis could be made with positive polymerase chain reaction (PCR) (International Statistical Classification (ICD-10) code - U07.1) and/or virus pneumonia in computer tomography (ICD 10 code - U07.2) Lung exposure on CT more than 25% Sp02 without supportive oxygen ≤ 93% C-reactive protein > 60	Experimental 1: Colchicine 0.5mg twice a day per os during the first three days and then 0.5mg daily per os if weight < 86 kg or 0.5mg twice a day per os if weight > 85kg for seven days Experimental 2: Ruxolitinib - 5mg twice a day per os for ten days Experimental 3: Secukinumab - 300mg subcutaneously as the first dose and then 150mg twice a day subcutaneously for ten days Control: standard therapy	Primary: CAS COVID 19 measures clinical and laboratory parameters in 7 domains: respiratory rate (< 18 - 0 point; 18-22 - 1 point; 23-26 - 2 point; >26 - 3 point) body temperature (35.5 - 37.0 - 0 point; < 35.5 - 1 point; 37.1 - 38.5 - 1 point; > 38.5 - 2 point) Sp02 without support oxygen (> 93% - 0 point; 90-93% - 1 point; < 90% - 2 point) ventilation (not required - 0 point; low-flow ventilation - 1 point; Non-invasive positive pressure ventilation - 2 point;	Randomized Parallel assignment Open label

	mg/l or elevation of C reactive protein 3 times in 8-14 days after first symptoms		mechanical ventilation - 3 point) C-reactive protein (> 10 - 0 point; 10-59 - 1 point; 60-120 - 2 point; > 120 - 3 point) d - dimer (< 0.51 - 0 point; 0.51 - 2.0 - 1 point; 2.01 - 5.0 - 2, > 5.0 - 3 point) exposure area on lung CT (no pneumonia - 0; 1-24% - 1 point; 25-50% - 2; 51-75% - 3, > 75% - 4). Minimal number of points - 0; max - 20. Lower the score-better health	
17. Impact of Colchicine in Hospitalized Colombian Patients With COVID-19	18 Years and older Laboratory-confirmed SARS-CoV-2 infection: infection confirmed with nasopharyngeal swab by positive RT PCR in the last 48 hours. Hospital admission for COVID-19 in the previous 48 hours.	Experimental: Colchicine plus standard treatment colchicine 1,5 orally on the first day (initially two pills of 0,5 mg and 0.5 mg at 2 hours), followed by 0.5 mg every 12 hours on days 2 to 7, and continuing with 0.5 mg per day until completing 14 ± 1 days. The duration of treatment will be 14 ± 1 days, depending on the clinical judgment of the investigator. Control: standard treatment	Primary: Number of participants who die or require transfer to intensive care unit	Randomized Parallel assignment Open label
18. COlchicine in Moderate-severe Hospitalized Patients Before ARDS to Treat COVID-19 (the COMBAT-COVID-19 Pilot Study)	18 years to 100 years Currently hospitalized and requiring medical care for COVID-19 Significant COVID-19 symptom, or judged by the treating provider to be at high risk of progression to severe COVID-19 infection	Experimental: colchicine Control: usual care	Primary: Percentage of Patients requiring supplemental oxygen beyond 8L nasal cannula	Randomized Parallel assignment Open label
19. Anti-Coronavirus Therapies to Prevent Progression of COVID-19, a Randomized Trial	Outpatient trial: Symptomatic and laboratory-confirmed diagnosis of COVID-19 Age ≥18 years. High risk: either age ≥70 or one of the following: male; obesity (BMI ≥30); chronic cardiovascular, respiratory or renal disease; active cancer; diabetes.	Experimental 1: Colchicine 0.6 mg twice daily for 3 days, then 0.6 mg once daily for 25 days (total 28 days) Experimental 2: Interferon Beta 0.25 mg by subcutaneous injection on days 1, 3, 5 & 7 Experimental 3: Aspirin (ASA) 75 to 100 mg once daily for 28 days Experimental 4: Rivaroxaban 2.5 mg twice daily for 28 days Control: usual care	Primary: Outpatient trial - Colchicine vs. control and Aspirin vs. control - composite of hospitalization or death Inpatient trial - Interferon-β vs. control and Colchicine vs. control - invasive mechanical ventilation or death Inpatient trial - Aspirin and rivaroxaban vs. control - invasive mechanical ventilation or death	randomized parallel group factorial Open-label
20. Randomised Evaluation of COVID-19 Therapy (RECOVERY)	Child, Adult, Older Adult (i) Hospitalised (ii) SARS-CoV-2 infection	Experimental: 1 mg after randomisation followed by 500mcg 12 hours later and then 500 mcg twice daily by mouth or nasogastric tube	Primary: All-cause mortality on day 28	randomized factorial Open-label

	(clinically suspected or laboratory confirmed) (iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial	for 10 days in total, for men ≥18 years old and women ≥55 years old only Other experimental arms: Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, IV Immunoglobulin (children only), Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2), Tocilizumab, Aspirin, Baricitinib or Anakinra (children only)		
21. Colchicine in Moderate Symptomatic COVID-19 Patients: Double Blind, Randomized, Placebo Controlled Trial to Observe the Efficacy (COLCOVIDBD) (MARKED AS COMPLETED; RESULTS STILL FOR POSTING)	18 years and older (+) RT-PCR for SARS CoV-2 within the last 3 days moderate symptoms COVID- 19 - Fever or history of fever; Cough and /or Shortness of breath; Oxygen saturation 94% or more; Pneumonia -pulmonary consolidations on chest imaging (chest x ray or CT scan of chest) involving less than 50%of lungs; CRB 65 score 0	Experimental: Colchicine tarting dose of 1.2 mg of Colchicine (2 tablets of 0.6 mg)single or 12 hourly divided dose. After that, they will take colchicine 0.6mg daily for 13 days. If they develop gastro intestinal side effects e.g abdominal pain, burning, vomiting, diarrhea, omeprazole and antiemetic will be prescribed. Control:placebo plus standard care	Primary: Time to develop clinical deterioration, defined as the time from randomization to a deterioration of two points (from the status at randomization) on a Seven-category ordinal scale.	randomized parallel assignment triple blind
22. Clinical Outcome of Patients With COVID-19 Pneumonia Treated With Corticosteroids and Colchicine in Colombia (MARKED AS COMPLETED; RESULTS STILL FOR POSTING)	18 years and older hospitalized for Covid-19 Pneumonia, confirmed positive by nasopharyngeal RT-PCR SARS-Cov2 radiological confirmation of pneumonia, mostly chest tomography or chest X-rays	Experimental 1: Dexamethasone 6mg intravenous OD for seven to ten days Experimental 2: Patients treated with colchicine at a dose of 0.5 mg every 12 hours for 7 to 14 days.	Primary: death	Observational Case-crossover
23. Administration of Colchicine Plus Standard Treatment vs. Standard Therapy, in Hospitalized Patients With COVID-19, Within the First 48 Hours, and no Severity Criteria (MARKED AS COMPLETED; RESULTS STILL FOR POSTING)	18 years and older SARS-CoV-2 infection confirmed by PCR Admitted in the hospital in the previous 48 hours, with clinical status 3, 4 or 5 of WHO classification.	Experimental: colchicine plus standard care (1 mg and 0.5 mg two hours after), followed by 0.5 mg every 12 hours during the next 7 days and 0.5 mg every 24 hours until the completion of 28 days of total treatment. In patients receiving ritonavir or lopinavir or with reduced renal clearance (<50 ml/min/1.37m2), weight <70 kg or age >75 years old, the dose will be adjusted to the half. Control: standard care	Primary: Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D Blueprint expert group; Changes in IL-6 concentrations	randomized parallel assignment open label
24. Colchicine for the Treatment of Hyperinflammation associated with	Patient hospitalized for COVID pneumonia19 (microbiological confirmation and chest X-ray compatible with	Experimental: colchicine 0.5-1 mg Control:other medicinal products	Primary: . Support compound with CPAP / BiPAP, ICU admission, invasive ventilation or death.	Randomized Open label controlled

Pneumonia due to COVID-19	pneumonia are required); Hyperinflammation Including pregnant and nursing women		2. Cytokine levels (IL-6) and inflammatory parameters (PCR, ESR, ferritin, fibrinogen, blood count) at recruitment, at 48 hours and on the fifth day of treatment. 3. Ultrasensitive troponin on the fifth day of treatment.	
25. Randomized clinical trial for the treatment of moderate to severe cases of COVID-19 with Chloroquine and Colchicine	Moderate or severe forms of COVID-19; 18 years or older; body weight of 50 kg or more; serum Ca2+ and K+ normal; QT interval lower than 450 ms at 12 derivations electrocardiogram; beta-HCG (serum or urine) negative (if woman under 50).	Experimental: Chloroquine and colchicine Chloroquine-hydroxychloroquine 400 mg bid for 1 or 2 (if body weight greater than 80 kg) days, followed by 400 mg daily until 10 days of treatment colchicine 0,5 mg tid for 5 days, followed by 0,5 mg bid for 5 days. If body weight greater than 80 kg, a loading dose of 1 mg will be used Control:chloroquine and placebo 1 placebo tablet every 8 hours for 5 days, followed by 1 tablet every 12 hours for 5 days	Primary: number of days of need of supplemental oxygen by catheter or masks; number of days from the admission to the discharge; ICU admission due to clinical deterioration; death	Randomized controlled, parallel double-blind
26. Randomized open-blind controlled trial to study the benefit of Colchicine in Patients with COVID-19	Infection confirmed by SARS-CoV-2 by RT-PCR. Hospital admission in the previous 48 hours for clinical involvement in groups 3, 4 or 5 of the WHO clinical scale. Age over 18 years	Experimental: Colchicine 0.5 mg plus standard care Control: standard care	Primary: 1. Ordinal 7-point clinical evaluation scale (WHO R&D Blueprint expert group. 2. IL-6	Randomized open-blind controlled
27. Adding Colchicine to the Antiretroviral Medication - Lopinavir/ Ritonavir (Kaletra) in Hospitalized Patients with Non-Severe Covid-19 Pneumonia: A Structured Summary of a Study Protocol for a Randomized Controlled Trial	Hospitalized patients with positive nasopharyngeal swab for COVID-19 infection (RT -PCR) and lung Computed tomography scan involvement compatible with COVID-19 pneumonia. The patients are not severely hypoxic, do not need intubation or invasive oxygenation.	Experimental: Lopinavir/Ritonavir (Kaletra) + Colchicine 1.5 mg loading then 0.5 mg twice daily orally Control: Lopinavir/Ritonavir (Kaletra)	Primary: Time for clinical improvement and lung CT score changes 14 days after treatment	Randomized Double blind