Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among patients with COVID-19, should colchicine be used for treatment?

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RECOMMENDATION

We suggest against the use of colchicine in the treatment of COVID-19 patients.
(*Low certainty of evidence; Weak recommendation)*

Consensus Issues
The addition of a large multicenter trial (RECOVERY trial) still showed that colchicine led to net potential harm (significant increase in adverse events) with no significant benefit in terms of all-cause mortality, clinical improvement (defined as hospital discharge) within 28 days, need for hospitalization, need for mechanical ventilation, and need for hemodialysis or hemofiltration. Hence, the consensus panel decided to maintain the previous recommendation against the use of colchicine in patients with COVID-19, regardless of hospitalization status.

PREVIOUS RECOMMENDATION

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

Previous 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.

What's new in this version?

This version includes data from one (1) large multicenter randomized controlled trial (RECOVERY trial).

Key Findings

Five (5) randomized controlled trials (RCTs) investigated the effect of colchicine compared to standard of care as treatment for patients with COVID-19. Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, clinical improvement (defined as hospital discharge) within 28 days, need for hospitalization, and need for hemodialysis or hemofiltration. One large RCT reported that

colchicine did not significantly shorten duration of hospitalization, while 2 smaller RCTs reported significantly shorter duration of hospitalization (data could not be pooled due to inadequate data provided). All studies had risk of bias issues as there were concerns in allocation concealment, blinding, attrition and selective reporting of outcome. The serious risk of bias and issues with inconsistency and imprecision in one critical outcome contributed to the downgrading of evidence to very low certainty of evidence.

Introduction

Colchicine is an anti-inflammatory agent currently being used for gout, familial Mediterranean fever, Behcet's syndrome, and pericarditis.[1,2] Colchicine has a unique anti-inflammatory property with a prolonged anti-inflammatory effect even after discontinuation.[1] Its primary mechanism of action is tubulin disruption leading to subsequent down regulation of multiple inflammatory pathways and modulation of innate immunity.[3] This anti-inflammatory mechanism 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 hematologic adverse events or death.[5]

Review Methods

A systematic search was done from the date of the last search March 26, 2021 until August 28, 2021 using Medline, Cochrane Library, and 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* and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. Only randomized controlled trials that compared colchicine against placebo or standard of 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, hospitalization status, and dosing strategy of colchicine. Subgrouping by severity was planned.

Results

We found five (5) RCTs that included a total of 16,113 COVID-19 patients. These RCTs were also included in the COVID-NMA Living Data (The COVID-NMA Initiative 2021).[6] One RCT from Canada 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, and 1 large multicenter RCT from UK, Indonesia and Nepal that involved hospitalized patients with mild to critical disease severity.[10] 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], azithromycin and hydroxychloroquine (HCQ) [7,8], HCQ [9], and corticosteroids, remdesivir, and tocilizumab which were used in the newly added large multicenter RCT (RECOVERY trial).[10] 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 to 30 days included all-cause mortality [4,7-10], need for mechanical ventilation [4,8,10], clinical improvement (hospital discharge) within 28 days [4,10], need for hospitalization [4], duration of

hospitalization [7,9,10], and adverse events [4,7,8]. The characteristics of included studies are summarized in Appendix 3.

The overall quality of evidence was rated very low because of serious risk of bias in the included studies, as well as issues with inconsistency and imprecision in 1 critical outcome. Of the 5 included studies, 2 studies had serious risk of performance and detection bias due to lack of blinding.[8,10] One study [4] had issues with selection and attrition bias, one study [7] had issues with attrition and reporting bias, and one study [9] had issues with selection, performance, detection and reporting bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

Based on five (5) RCTs, colchicine did not show any significant difference compared to standard care in reducing all-cause mortality (RR 1.00, 95% CI 0.93-1.07; I^2=0%). Subgroup analysis by hospitalization status showed no significant difference in all-cause mortality among hospitalized patients (RR 1.00, 95% CI 0.93-1.08) and non-hospitalized patients (RR 0.56, 95% CI 0.19-1.67) given colchicine compared to control. Subgroup analysis according to disease severity showed no significant results for mild disease (RR 0.56, 95% CI 0.19-1.67), moderate-to-severe disease (RR 0.22, 95% CI 0.04-1.29), and mild to critical disease (RR 1.18, 95% CI 0.99-1.40). Subgroup analysis by age similarly showed no significant results for those <70 years old (RR 1.02, 95% CI 0.91-1.15), 70 to 80 years old (RR 0.98, 95% CI 0.87-1.10), and 80 years and older (RR 1.04, 95% CI 0.93-1.17).

There was no significant difference in clinical improvement, defined as hospital discharge, within 28 days (RR 0.99, 95% CI 0.97-1.01; I^2=0%; 2 RCTs). Colchicine did not significantly reduce the number of patients needing mechanical ventilation (RR 0.68, 95% CI 0.29, 1.60; I^2=74%; 3 RCTs), hospitalization (RR 0.80, 95% CI 0.62-1.03; 1 RCT), and hemodialysis or hemofiltration (RR 1.07, 95% CI 0.88-1.29; 1 RCT).

Three RCTs reported on duration of hospitalization. One large RCT reported no significant benefit in duration of hospitalization with a median of 10 days vs. 10 days, with a range of 5 to >28 for colchicine and control groups (N = 11,340).[10] Two smaller studies reported significantly shorter duration of hospitalization (mean 6.3 vs. 8.1 days, p = 0.001, n =100; median 7 days [IQR 5-9] vs. 9 days [IQR 7-12]; p = 0.003, n = 38).[7,9] Data could not be pooled due to inadequate data provided.

Adverse events

Three (3) studies showed that serious adverse events were reduced among patients given colchicine group compared to control group but only by a small margin (RR 0.78, 95% 0.61-0.99; I^2=0). Subgroup analysis by hospitalization status showed no significant difference for hospitalized patients (RR 0.58, 95% CI 0.15-2.27) and non-hospitalized patients (RR 0.78, 95 % CI 0.61-1.00). The reported serious adverse events included pneumonia, pulmonary embolism, myocardial infarction, and dehydration.

There were significantly more adverse events among patients who received colchicine (RR 1.55, 95% CI 1.37-1.75; I^2=0%; 2 RCTs). The most common was diarrhea. Other adverse events included abdominal pain, nausea, and rash. Subgroup analysis by hospitalization status showed that this effect was more evident among non-hospitalized patients with mild disease (RR 1.56, 95% CI 1.38-1.76) than those hospitalized with moderate to severe disease (RR 1.30, 95% CI 0.62-2.71).

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
NIH Covid-19 Guidelines (as of October 7, 2021)	Recommends against the use of colchicine for the treatment of hospitalized patients with COVID-19. *(Strong recommendation)* No recommendation either for or against the use of colchicine for non-hospitalized patients with COVID-19 was made due to insufficient evidence.[11]
Australian COVID-19 Guidelines (as of September 29, 2021)	Does not recommend the use of colchicine for the treatment of COVID-19 outside of randomized trials.[12]
Surviving Sepsis Campaign Guidelines (as of January 29, 2021)	No statement on the recommendation of colchicine as treatment for COVID-19. (13-15)
Infectious Diseases Society of America (as of October 1, 2021	
World Health Organization (WHO) Living Guidelines (as of September 24, 2021)	

Research Gaps

There are 42 studies registered in various clinical trial registries. Of the 42 studies, 1 was suspended already due to results of the RECOVERY trial [10] showing that further recruitment would not provide conclusive proof of worthwhile benefit, 1 was withdrawn due to lack of funding, 6 are marked as completed but no results have been posted yet, and 34 are still ongoing. 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

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate	Small (5)	Uncertain (3)	Trivial (1)		• Colchicine did not show any significant difference compared to standard care in reducing all-cause mortality (RR 1.00, 95% CI 0.93-1.07; I^2=0%) and clinical improvement, defined as hospital discharge, within 28 days (RR 0.99, 95% CI 0.97-1.01; I2=0%, 2 RCTs). • Colchicine did not significantly reduce the number of patients needing mechanical ventilation (RR 0.68, 95% CI 0.29, 1.60; I^2=74%, 3 RCTs), hospitalization (RR 0.80, 95% CI 0.62-1.03, 1 RCT), and hemodialysis or hemofiltration (RR 1.07, 95% CI 0.88-1.29, 1 RCT).
Harm	Large (4)	Small (3)	Uncertain (1)	Varies (1)			• 3 studies showed that serious adverse events were reduced among patients given colchicine group compared to control group but only by a small margin (RR 0.78, 95% 0.61-0.99; I^2=0). • There were significantly more adverse events among patients who received colchicine (RR 1.55, 95% CI 1.37-1.75; I^2=0%, 2 RCTs).
Certainty of Evidence	High	Moderate (1)	Low (3)	Very low (5)			• The overall quality of evidence was rated very low because of serious risk of bias in the included studies, as well as issues with inconsistency and imprecision in 1 critical outcome.
Balance of effects	Favors drug (2)	Does not favor drug (7)	Uncertain				• Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, clinical improvement
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost	Negligible cost (8)	Moderate savings	Large savings (1)	• 1 colchicine 500 mcg tablet is Php 2.25 • Total cost is around 47.25-56.25

Certainty of evidence of required resources	No included studies (2)	Very low	Low (1)	Moderate (3)	High (3)		• The cost is based on the 2020 Philippine Drug Reference Index
Cost effectiveness	No included studies (6)	Favors the comparison (3)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (2)	Reduced (2)	Probably no impact (4)	Increased (1)			
Acceptability	Uncertain (5)	No (3)	Yes (1)				
Feasibility	Uncertain (2)	No (1)	Yes (6)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (colchicine OR colchicine{Mesh}) Filters: March 26, 2021 to August 28, 2021	August 28, 2021 11:00AM	55	0
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (colchicine OR MeSH descriptor: [Colchicine] explode all trees Filters: March 26, 2021 to August 28, 2021	August 28, 2021 11:30AM	21	0
COVID-NMA Initiative	Colchicine	August 28, 2021 11:30AM	5	1
Google Scholar	Colchicine AND COVID AND randomized trial	August 28, 2021 8:00PM	26	0
ClinicalTrials.gov	Colchicine and COVID19	August 28, 2021 10:00PM	27	5
Chinese Clinical Trial Registry	Colchicine	August 28, 2021 10:30PM	8	0
EU Clinical Trials Register	Colchicine and COVID	August 28, 2021 10:35PM	5	2
Republic of Korea - Clinical Research Information Service	Colchicine	August 28, 2021 10:45PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Colchicine	August 28, 2021 10:50PM	26	0
CenterWatch	Colchicine and COVID	August 28, 2021 11:00PM	3	1
Cochrane COVID-19 study register	Colchicine Filters: March 26, 2021 to August 28, 2021	August 28, 2021 1:00 PM	40	14
chinaxiv.org	Colchicine	August 28, 2021 11:10PM	1	0
Medrxiv.org	Colchicine Filters: March 26, 2021 to August 28, 2021	August 28, 2021 11:12PM	28	1
Biorxiv.org	Colchicine and COVID	August 28, 2021 11:20PM	19	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Colchicine for community-treated patients with COVID-19 (COLCORONA): A phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicenter trial *Tardif et al. 2021 (Canada, USA, Brazil)* [4]	N = 4488 Non-hospitalized patients with COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria at least 40 years of age <u>Duration of follow-up:</u> Approximately 30 days	EXPERIMENTAL: Colchicine (0.5mg twice daily for 3 days and once daily thereafter) CONTROL: Placebo	PRIMARY: Composite of death or hospitalization due to COVID-19 infection SECONDARY: Components of the composite primary endpoint; need for mechanical ventilation, serious adverse events, and non-serious adverse events	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)* [7]	N = 75 Individuals hospitalized 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 <u>Duration of follow-up:</u> Up to 26 days	EXPERIMENTAL: Colchicine 0.5mg 3x daily for 5 days, then 0.5mg 2x daily for 5 days plus standard care CONTROL: Standard of care (azithromycin, hydroxychloroquine (HCQ), unfractionated heparin, methylprednisolone)	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: Adverse events	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)* [8]	N = 110 Hospitalized adult patients diagnosed with SARS-CoV-2 infection by RT-PCR <u>Duration of follow-up:</u> 21-25 days	EXPERIMENTAL: Colchicine administration (1.5-mg loading dose followed by 0.5mg after 60 min and maintenance doses of 0.5mg twice daily) with standard medical treatment CONTROL: Standard medical treatment (azithromycin, HCQ)	PRIMARY: 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: Need for mechanical ventilation, all-cause mortality, adverse events.	Randomized parallel
The Impact of Colchicine on the COVID-19 Patients: A Clinical Trial Study *Salehzadeh et al. 2020 (Iran)* [9] *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> 21 to 30 days	EXPERIMENTAL: HCQ + colchicine 1mg OD CONTROL: HCQ + placebo	PRIMARY: Length of hospitalization; symptoms and co-existed disease SECONDARY Mortality and morbidity, re-admission, and symptoms	Randomized double blind Placebo control

Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial *Horby et al. 2021 (UK, Indonesia, Nepal)* [10] *Preprint*	N = 11,340 Clinically suspected or laboratory confirmed SARS-CoV-2 infection among patients admitted in a hospital <u>Duration of follow-up:</u> 28 days	EXPERIMENTAL: Colchicine 1mg after randomization followed by 500mcg 12 hours later and then 500mcg twice daily for 10 days in total or until discharge CONTROL: Usual care (corticosteroids, remdesivir, and tocilizumab)	PRIMARY: Mortality SECONDARY: Time to discharge from hospital, invasive mechanical ventilation non-invasive respiratory support, time to successful cessation of invasive mechanical ventilation, use of renal dialysis or hemofiltration, cause-specific mortality, and serious adverse reactions	Randomized controlled trial

Appendix 4. Study Appraisal

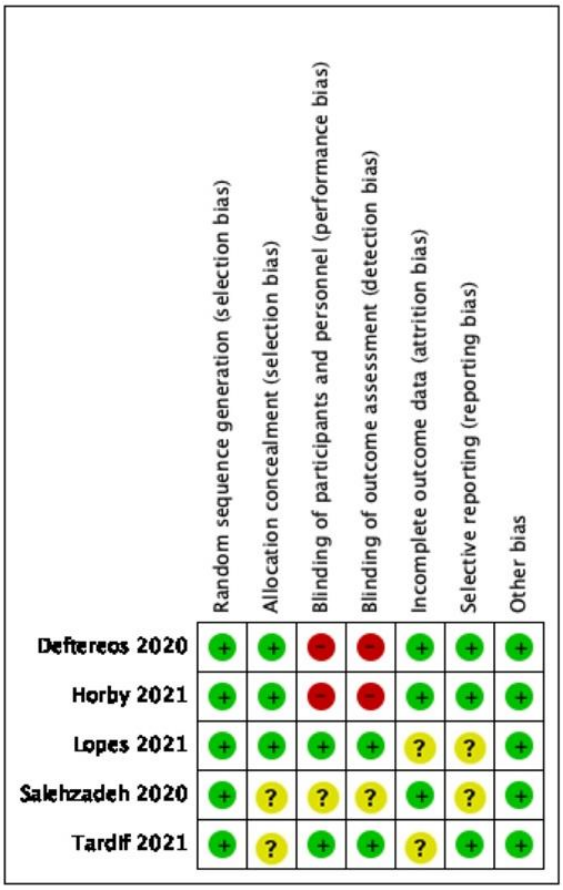

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc

Question: Colchicine compared to Placebo or Standard Care for COVID-19

Setting: out-patient and in-hospital

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo/Standard Care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: 1 month)												
5	randomised trials	serious [a]	not serious	not serious	not serious	none	1180/7989 (14.8%)	1206/8124 (14.8%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation (follow up: 1 month)												
3	randomised trials	serious [b]	serious [c]	not serious	serious [d]	none	271/6106 (4.4%)	255/6269 (4.1%)	**RR 0.68** (0.29 to 1.60)	**13 fewer per 1,000** (from 29 fewer to 24 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical improvement (discharge from hospital) within 28 days												
2	randomised trials	serious [e]	not serious	not serious	not serious	none	3936/5648 (69.7%)	4064/5767 (70.5%)	**RR 0.99** (0.97 to 1.01)	**7 fewer per 1,000** (from 21 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for hospitalization (follow up: 1 month)												
1	randomised trials	serious [f]	not serious	not serious	serious [d]	none	101/2235 (4.5%)	128/2253 (5.7%)	**RR 0.80** (0.62 to 1.03)	**11 fewer per 1,000** (from 22 fewer to 2 more)	⨁⨁◯◯ LOW	CRITICAL
Need for hemodialysis or hemofiltration												
1	randomised trials	serious [g]	not serious	not serious	serious [d]	none	212/5570 (3.8%)	203/5683 (3.6%)	**RR 1.07** (0.88 to 1.29)	**3 more per 1,000** (from 4 fewer to 10 more)	⨁⨁◯◯ LOW	CRITICAL
Duration of hospitalization (follow up: 1 month)												
3	randomised trials	serious [h]	not serious	not serious	not serious	none	Colchicine was not associated with significantly shorter duration of hospitalization with a median of 10 vs 10 days, range 5 to >28 for both groups, n=11,340, Horby 2021). Two studies reported significantly shorter duration of hospitalization (mean 6.3 vs 8.1 days, p=0.001, n=100, Salehzadeh 2020; median 7 days [IQR 5-9] vs 9 days [IQR 7-12], p=0.003, n=38, Lopes 2020)				⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo/Standard Care	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 1 month)												
3	randomised trials	serious [i]	not serious	not serious	serious [d]	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	CRITICAL
Adverse events (follow up: 1 month)												
2	randomised trials	serious [j]	not serious	not serious	not serious	none	554/2273 (24.4%)	353/2290 (15.4%)	**RR 1.55** (1.37 to 1.75)	**85 more per 1,000** (from 57 more to 116 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Explanations

a. Two studies with overall high risk of bias and 3 studies with overall some risk of bias
b. Issues on performance and detection bias (Defteros 2020 and Horby 2021), selection and attrition bias (Tardif 2021)
c. Significant heterogeneity (I2>50%)
d. Wide confidence interval
e. Issues on performance and detection bias (Horby 2021), attrition and reporting bias (Lopes 2021)
f. Issues on selection and attrition bias (Tardif 2021)
g. Issues on performance and detection bias (Horby 2021)
h. Issues on performance and detection bias (Horby 2021), selection, performance, detection and reporting bias (Salehzadeh 2020) and attrition and reporting bias (Lopes 2020)
i. Issues on selection and attrition bias (Tardif 2021), attrition and reporting bias (Lopes 2020), performance and detection bias (Deftereos 2020)
j. Issues on selection and attrition bias (Tardif 2021), attrition and reporting bias (Lopes 2020)

Appendix 6. Forest Plots

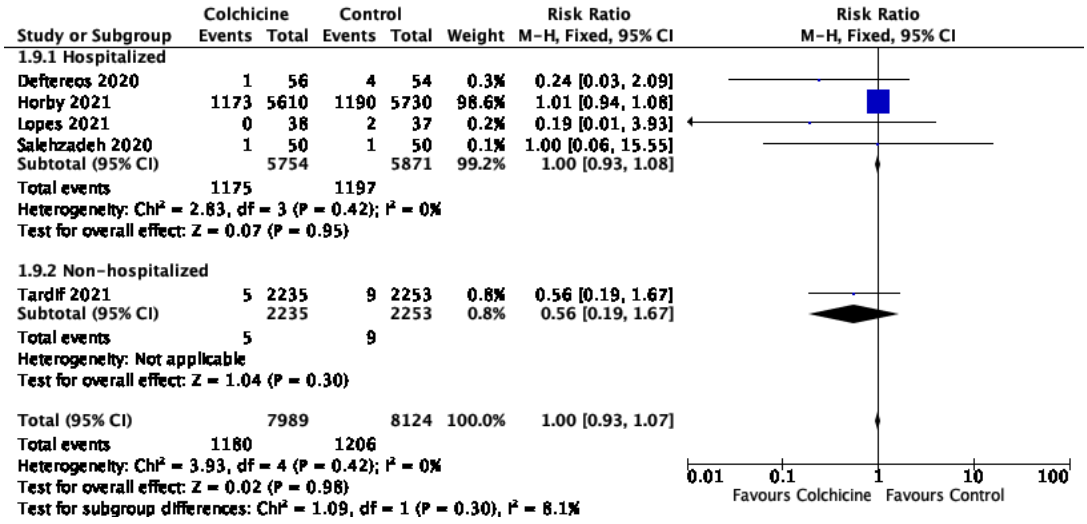

Figure 1. All-cause mortality (by hospitalization status)

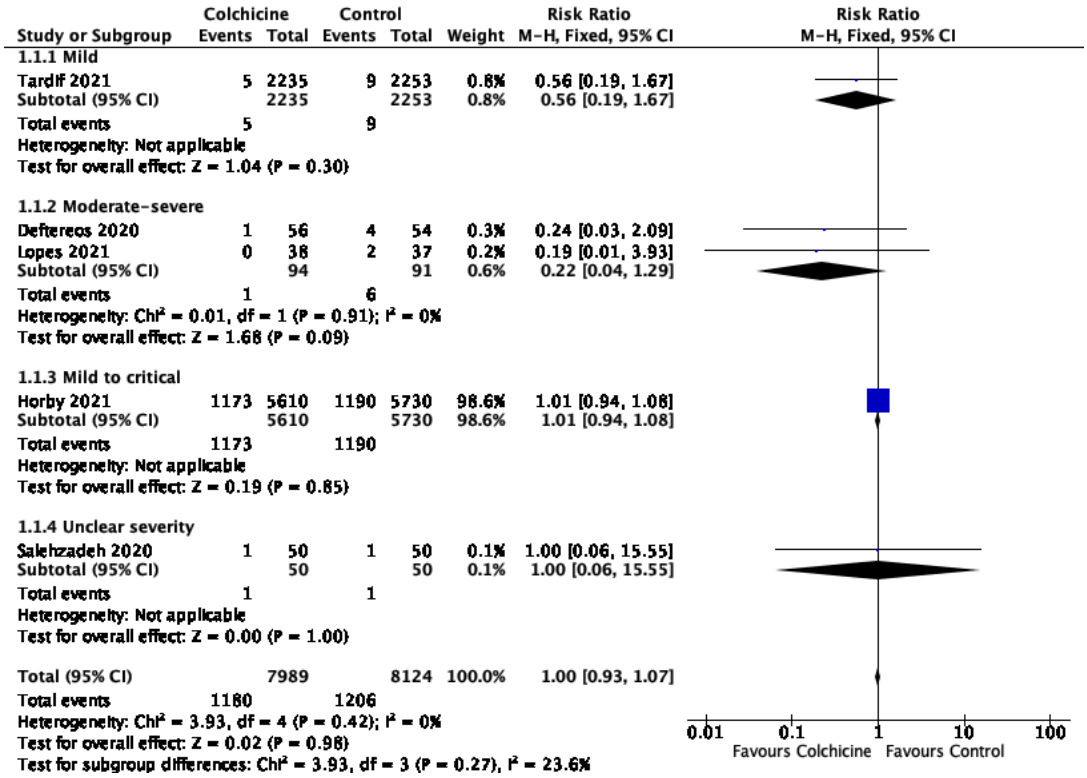

Figure 2. All-cause mortality (by severity)

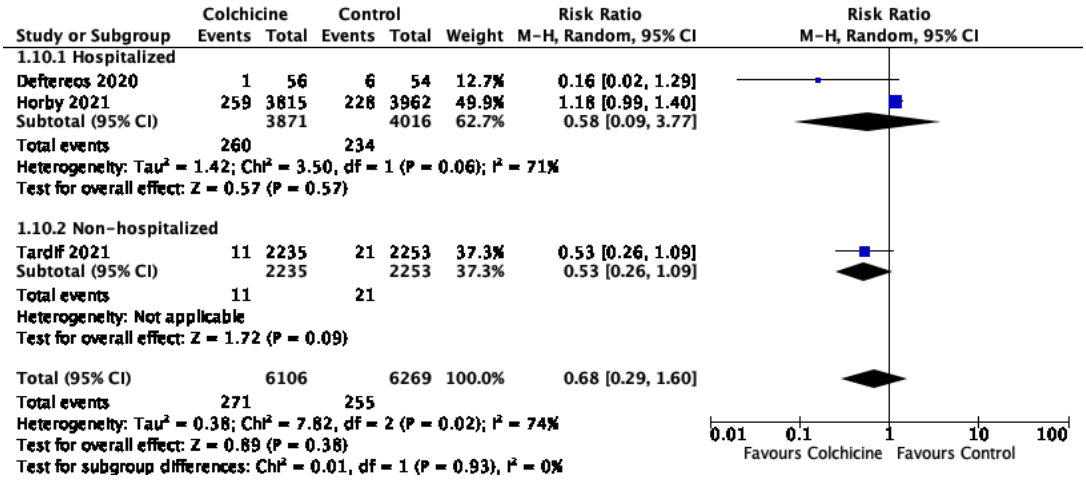

Figure 3. Need for Mechanical Ventilation

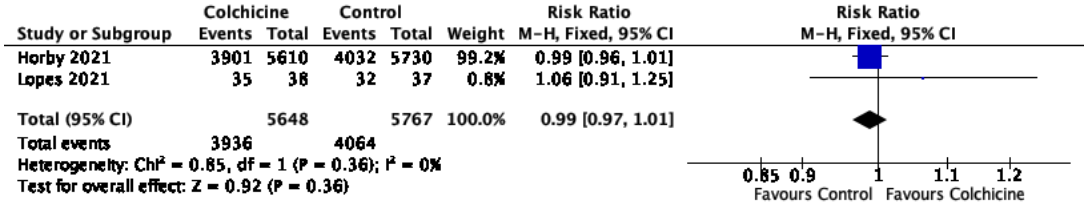

Figure 4. Clinical improvement (hospital discharge) within 28 days

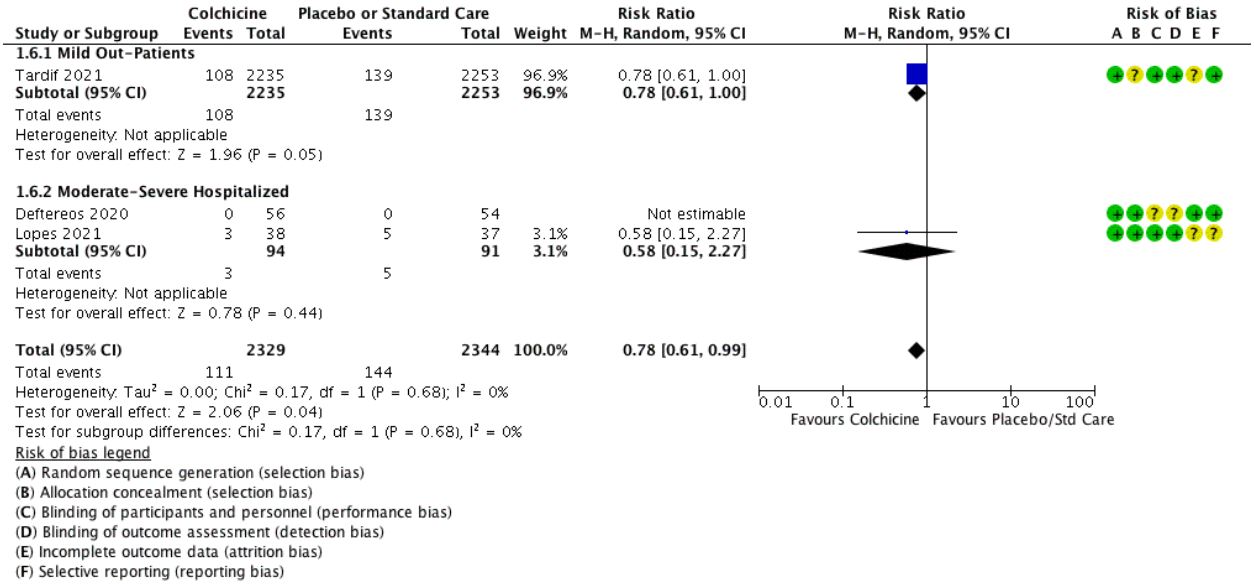

Figure 5. Serious Adverse Events

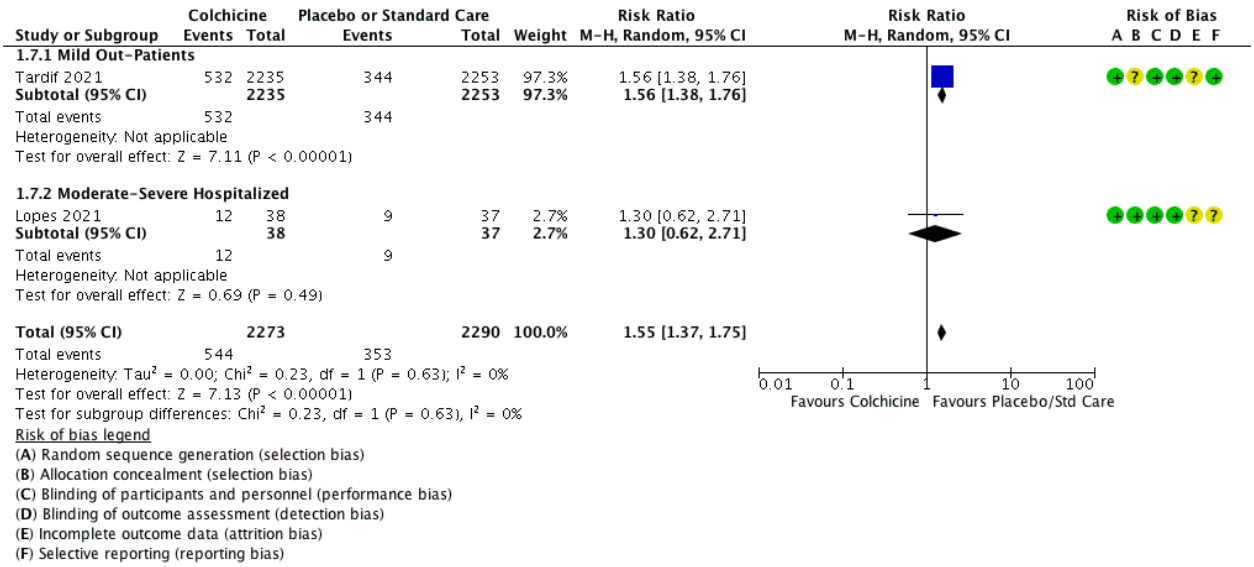

Figure 6. Adverse events

Appendix 7. 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.	Severity of COVID measured by WHO Scores 5-8	Randomized; parallel assignment, open label
2. 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	Experimental: Colchicine plus current care 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
3. Study to Investigate the Treatment Effect of Colchicine in Patients With COVID-19 *Withdrawn due to no funding*	18 to 65 years old 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 Control: SOC	Primary: Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D Blueprint expert group	Randomized, controlled, open-label
4. Randomized, Open-Label, Controlled Trial of Colchicine to Reduce Cardiac Injury in Hospitalized COVID-19 Patients (COLHEART-19) *Suspended due to RECOVERY trial results*	Age above 18 years old Confirmed COVID-19 infection by polymerase chain reaction with cardiac injury	Experimental: colchicine plus current care Control: Current care	Primary: Composite of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support	Randomized, parallel assignment, open-label
5. Preemptive Therapy with Colchicine in Patients Older Than 60 Years with High Risk of Severe Pneumoniae Due to Coronavirus SARS-Cov-2 (COVID-19)	At least two high-risk criteria, diagnosis of COVID-19 infection in the last 72 hours and confirmed by PCR Patients in outpatient follow-up or institutionalized in senior centers/residences	Experimental: Colchicine plus symptomatic treatment. Control: Symptomatic treatment	Primary: Death, need for hospitalization	Randomized, parallel assignment, open-label
6. 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 1.5mg loading then 0.5mg BID plus SOC Control: SOC, vitamin C, thiamine, selenium, omega-3 Vit A, Vit D, azithromycin, ceftriaxone, Kaletra	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

7. 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	Experimental 1: Emtricitabine 200mg + tenofovir 300mg Experimental 2: Colchicine 0.5mg every 12 hours for 14 days + rosuvastatin: 40mg / day for 14 days Experimental 3: Emtricitabine 200mg + tenofovir 300 mg + colchicine: 0.5mg every 12 hours for 14 days + rosuvastatin: 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
8. 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 Transitional 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 transitional care center Clinical diagnosis compatible with COVID-19, moderate to severe	Experimental: Colchicine plus prednisone Control: Standard treatment	Primary: Reduction of mortality on day 28	Randomized Parallel assignment Open label
9. 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 Experimental 2: Colchicine at 0.5mg twice daily for the first 3 days and then once daily to day 14 Experimental 3: Edoxaban and colchicine Control: No edoxaban colchicine	Primary: SARS-CoV-2 clearance rates, death or hospitalization at day 14	Randomized Factorial assignment Open label
10. The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients (COLCOVID) **(Marked as completed; results still for posting)**	Age ≥18 years, suspected COVID-19, admitted in hospital	Experimental: Colchicine Control: Standard of care	Primary: Need for intubation for mechanical ventilation, death	Randomized Parallel assignment Open label
11. 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 PCR test for SARS-CoV-2, with pneumonia confirmed by chest imaging	Experimental 1: IL-17 inhibitor (ixekizumab) Experimental 2: IL-2 (aldesleukin) Experimental 3: Colchicine 0.5mg every 8 hours for 3 days (PO), followed by 4 weeks 0.5mg twice daily. Control: Standard treatment	Primary: Ordinal scale of seven World Health Organization (WHO) categories	Randomized Parallel assignment Open label
12. 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 to 99 years old, Covid-19 positive hospitalized patients with cardiac injury	Experimental: Colchicine (0.6mg BID x 30 days) plus current care	Primary: Composite of all-cause mortality; need for mechanical ventilation; Need for mechanical circulatory support	Randomized Parallel assignment Open label
13. Double-blind, Placebo-controlled Clinical Trial of the Use of Colchicine for the Management of Patients With Mild and Severe SARS-Cov2 Infection	18 to 70 years old, 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	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	Randomized Parallel assignment Double blind Placebo controlled

14. 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 Symptomatic with respiratory or systemic symptoms, however clinically stable	Experimental: Colchicine 1mg (or 0.5mg in CKD)/day + standard of care Control: Standard care	Primary: Time to clinical improvement or live discharge from the hospital (whichever comes first)	Randomized Parallel assignment Open label
15. Colchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial	18 years and older COVID-19 with the mild and severe course	Experimental 1: Colchicine 0.5mg twice a day during the first 3 days and then 0.5mg daily if weight < 86 kg or 0.5mg twice a day if weight > 85kg for 7 days Experimental 2: Ruxolitinib Experimental 3: Secukinumab Control: Standard therapy	Primary: CAS COVID 19 measures clinical and laboratory parameters in 7 domains: respiratory rate, body temperature, Sp02 without support oxygen, ventilation, C-reactive protein, d - dimer	Randomized Parallel assignment Open label
16. 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 1.5mg orally on the first day, followed by 0.5mg every 12 hours on days 2 to 7, and continuing with 0.5mg per day until completing 14 days Control: Standard treatment	Primary: Number of participants who die or require transfer to intensive care unit	Randomized Parallel assignment Open label
17. Colchicine in Moderate-severe Hospitalized Patients Before ARDS to Treat COVID-19 (the COMBAT-COVID-19 Pilot Study)	18 to 100 years old, hospitalized and requiring medical care for COVID-19, with significant COVID-19 symptom or judged 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
18. 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 0.6mg twice daily for 3 days, then 0.6mg once daily for 25 days (total 28 days) Experimental 2: Interferon Beta Experimental 3: Aspirin (ASA) Experimental 4: Rivaroxaban 2.5 mg Control: Usual care	Primary: Outpatient trial - hospitalization or death Inpatient trial - invasive mechanical ventilation or death	Randomized parallel group factorial Open-label
19. 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, moderate symptoms	Experimental: Colchicine Starting dose of 1.2mg of colchicine (2 tablets of 0.6mg) single or 12 hourly divided doses, after that, they will take colchicine 0.6mg daily for 13 days. Control: Placebo plus standard care	Primary: Clinical deterioration, defined as the time from randomization to a deterioration of two points on a Seven-category ordinal scale.	Randomized parallel assignment triple blind
20. 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	Experimental 1: Dexamethasone Experimental 2: Colchicine at a dose of 0.5mg every 12 hours for 7 to 14 days	Primary: death	Case-crossover
21. Administration of Colchicine Plus Standard Treatment vs. Standard Therapy, in Hospitalized	18 years and older SARS-CoV-2 infection confirmed by PCR Admitted in the hospital in the	Experimental: Colchicine plus standard care Control: Standard care	Primary: Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D	Randomized parallel assignment open label

Patients With COVID-19, Within the First 48 Hours, and no Severity Criteria **(Marked as completed; results still for posting)**	previous 48 hours, with clinical status 3, 4 or 5 of WHO classification		Blueprint expert group; Changes in IL-6 concentrations	
22. Colchicine for the Treatment of Hyperinflammation associated with Pneumonia due to COVID-19	Patient hospitalized for COVID pneumonia19 (microbiological confirmation and chest X-ray compatible with pneumonia are required); Hyperinflammation	Experimental: Colchicine 0.5-1mg Control: Other medicinal products	Primary: Support compound with CPAP / BiPAP, ICU admission, invasive ventilation or death	Randomized Open label controlled
23. 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;	Experimental: Chloroquine and colchicine 0.5mg TID for 5 days Control: Chloroquine and placebo	Primary: Number of days needing supplemental oxygen; number of days from the admission to discharge; ICU admission due to clinical deterioration; death	Randomized controlled, parallel double-blind
24. Randomized open-blind controlled trial to study the benefit of Colchicine in Patients with COVID-19 **(Marked as completed; results still for posting)**	Age over 18 years, 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.	Experimental: Colchicine 0.5mg plus standard care Control: Standard care	Primary: Ordinal 7-point clinical evaluation scale (WHO R&D Blueprint expert group)	Randomized open-blind controlled
25. 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	Experimental: Lopinavir/Ritonavir (Kaletra) + colchicine 1.5mg loading then 0.5mg twice daily orally Control: Lopinavir/Ritonavir (Kaletra)	Primary: Time for clinical improvement and lung CT score changes 14 days after treatment	Randomized Double blind
26. Impact of Colchicine on the Clinical Outcome of COVID-19 and the Development of Post-COVID-19 Pulmonary Fibrosis: Randomized Controlled Clinical Trial	Patients who are confirmed to have COVID-19 clinically, radiologically and PCR Age above 18 years old	Experimental: Colchicine group Control: Local standard protocol	Primary: Clinical status, Pulmonary fibrosis at week 2 and day 45	Randomized Controlled Clinical Trial
27. Effectiveness of Colchicine Among Patients With COVID-19 Infection **(Marked as completed; results still for posting)**	Patients diagnosed clinically or by RT-PCR and/ or lung involvement by computed tomography scan compatible with COVID-19 Between 18 year and 70 years, body weight > 50 kg	Experimental: Colchicine group Control: Usual care	Primary: Need for supplemental oxygen, length of hospital stay, need for invasive mechanical ventilation, death rate	Randomized open label clinical trial
28. Investigator initiated study to evaluate the effect of Marketed Colchicine 0.5mg given along marketed Aspirin 75mg with SOC and Marketed aspirin 75mg with SOC on COVID-19 patients	40 to 80 years old Positive oropharyngeal/nasal swab RT-PCR with moderate symptoms	Experimental: Colchicine 0.5mg with aspirin 75mg with SOC Control: Aspirin 75mg with SOC	Primary: Symptomatic improvement through the NEWS score and 8-point ordinal score	Randomized, parallel/crossover trial
29. Evaluation of the colchicine tablet efficacy as an adjuvant therapy for patients with mild to moderate COVID-19	Patients with COVID-19, mild to moderate	Experimental: Colchicine 1mg tablet daily for two weeks. Control: Placebo	Primary: clinical response to treatment, adverse reaction, fever	Randomized, parallel/crossover trial

30. Double Blind Randomized Clinical Trial of Use of Colchicine Added to Standard Treatment in Hospitalized Patients with COVID-19 Infection (CORONACOLCHI)	Acute symptoms compatible with SARS-CoV-2 infection, microbiologically confirmed infection by SARS-CoV-2, .> 18 years, admitted	Experimental: Colchicine for 2 weeks orally added to the standard treatment of COVID-19 Control: Placebo for 2 weeks orally added to standard COVID-19 treatment	Primary: Death, need for mechanical ventilation or respiratory distress	Double Blind Randomized Clinical Trial
31. A Clinical Trial to Assess the Efficacy, Safety and tolerability of Colchicine for COVID-19 Disease Treatment in Indian Patients	40 to 65 years old, confirmed diagnosis of at least moderate COVID-19 symptoms	Experimental: Colchicine 0.5mg tablets plus standard of care Control Standard of care	Primary: Time to clinical improvement of 2-points on WHO 8-point ordinal scale	Randomized, parallel/crossover trial
32. Efficacy of Colchicine in Treatment of COVID-19	Patients with COVID-19 with moderate to severe respiratory failure admitted to ICU wards	Experimental: Methylprednisolone pulse therapy and colchicine (2mg stat then 1mg daily) with standard treatment Control group: Standard treatment (dexamethasone, interferon beta1, remdesivir)	Primary: Respiratory distress	Randomized, parallel/crossover trial
33. Will treatment with a drug named colchicine be useful in treating Corona virus infection in kidney failure patients who are on regular dialysis?	Patients with end stage kidney disease who are on maintenance hemodialysis with SARS-CoV-2 infection	Experimental: Colchicine and Standard of care Control: Standard of care	Primary: Time to deterioration by 2 points on the WHO clinical progression scale	Randomised, parallel/crossover trial
34. Effect of colchicine in treatment of COVID-19	Age 18 to 70 years old with COVID-19 in the last 24 to 48 hours, candidate for hospitalization COVID-19 patients hospitalized with hospital indications according to the guidelines	Experimental: 0.5mg of colchicine until the third day and 12 days later 1mg plus standard treatment Control: Standard treatment	Primary: Clinical symptoms, pulmonary infiltration findings on CT scan.	Randomised, parallel/crossover trial
35. Efficacy and safety of colchicine on clinical improvement in patients with COVID-19: A randomized, double blind clinical trial	Over the age of 18 with a diagnosis of COVID-19 based on clinical criteria or PCR and had clinical symptoms of COVID-19 within two weeks	Experimental: Interferon beta 1 b plus remdesivir with colchicine at 2mg as loading dose then 1 mg daily for 7 days. Control: Interferon beta 1 b and remdesivir	Primary: Blood oxygen saturation, fever recovery, respiratory rate, adverse effects	Randomized, parallel/crossover trial
36. The Effectiveness of Pentoxifylline and Colchicine in the Treatment of COVID-19	Hospitalized patients suspected with COVID-19 infection, SpO2 less than 93%, respiratory symptoms, older than 40 years	Experimental: Pentoxifylline group receiving 400mg every 12 hours plus colchicine ½ mg every day in addition to the standard treatment Control group: Standard treatment	Primary: Duration of hospitalization.	Randomized, parallel/crossover trial
37. Efficacy of colchicine in the treatment of COVID-19 patients	At least 18 years of age, confirmation of COVID-19 with RT-PCR in the last 24 hours, outpatient	Experimental: Colchicine 0.5mg tablets for the first 3 days, twice a day, and then for the next 27 days, once a day, with standard treatment (famotidine, cetirizine, N-acetylcysteine, bromhexine, naproxen, and fluticasone spray) Control: Placebo and standard treatment	Primary: Death, hospitalization, severe illness.	Randomized, parallel/crossover trial
38. Colchicine in combination with infliximab compared with infliximab in the treatment of patients with COVID-19	Patients with the common type of Novel Coronavirus Pneumonia (NCP) (at high risk) and other severe cases of newly diagnosed coronavirus pneumonia between the ages of 18 and 85 with an increase in IL-6 levels	Experimental: Infliximab + standard treatment + colchicine Control group: Infliximab + standard treatment	Primary: Clinical symptoms, pulmonary CT scan changes	Randomized, parallel/crossover trial

39. Impact of Colchicine to Improve long-COVID-19 or ARDS Outcomes	Aged 18 years and older, hospitalized with confirmed COVID-19 respiratory infection by swab-positive PCR with hypoxia	Experimental: Colchicine 0.5mg tablet twice daily + standard of care Control: Standard of care	Primary: Death at 6 months and end of study, maximum oxygen requirement, COVID-19 WHO score	Randomized, parallel/crossover trial
40. Colchicine in COVID-19: a Pilot Study (COLVID-19)	Virological diagnosis of SARS-CoV-2 infection (real-time PCR), Hospitalized due to clinical/instrumental diagnosis of pneumonia	Experimental: Colchicine plus current care Control: Current care alone	Primary Outcome Rate of entering the critical stage with any of the following: respiratory failure and requires mechanical ventilation; organ failure; need ICU admission; death	Randomized, parallel/crossover trial
41. Impact of Colchicine and Low-dose Naltrexone on COVID-19 (COLTREXONE)	Requiring admission to Methodist or Regions Hospital due to laboratory-confirmed COVID-19, only up to moderate COVID-19 disease	Experimental: Colchicine-Only Arm Experimental: Colchicine and Naltrexone ("Combined") Arm Experimental: Naltrexone-Only Arm No Intervention: Standard of Care Arm	Primary: Progression of COVID-19 from "moderate" classification to "severe/critical"	Randomized Open Label Trial
42. A randomization, multicentric, open-label, controlled, clinical trial to investigate the effectiveness of early colchicine administration in patients over 70 years of age with high risk of developing severe pulmonary complications associated with coronavirus sars-cov2 pneumonia (COVID-19) COLCHI-COVID	At least 70 years old, Diagnosis of COVID-19 infection within the last 24 hours and confirmed by PCR, in outpatient follow-up, with at least two high-risk criteria	Experimental: Colchicine Control: Not clearly stated	Primary: Death or requires hospitalization	Randomization, multicentric, open-label, controlled, clinical trial