**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

**RESEARCH QUESTION: Among COVID-19 patients, should colchicine be used for treatment?**

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## RECOMMENDATION

| Recommendation | Certainty of Evidence | Strength of Recommendation |
|---|---|---|
| We recommend against the use of colchicine in the treatment of COVID-19 patients. | Very Low | Strong |

***Consensus Issues***

The consensus panel recommends against the use of colchicine in the treatment of COVID-19 patients despite the certainty of evidence. This is mainly due to its potential harm without benefit in any of the critical outcomes, especially with the background of the local availability of other effective drugs for COVID-19. Most recent evidence showed that colchicine significantly increased risk of adverse events, without benefit in all-cause mortality, need for mechanical ventilation, hospital discharge within 28 days, need for hospitalization, need for ICU admission, need for hemodialysis or hemofiltration, clinical deterioration, and length of hospitalization. Although there were no studies among children, the panel opted to issue a blanket recommendation for adults and children against use of colchicine in COVID-19. Following the principle of "first do no harm," an intervention should not be prescribed without any evidence supporting its use. Although the effect of colchicine on the different variants could not be extracted, the studies were performed from 2020-2022, covering a wide span of time period, during which different variants were predominant.

## KEY FINDINGS

- Nineteen (19) 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, hospital discharge within 28 days, need for hospitalization, need for ICU admission, need for hemodialysis or hemofiltration, clinical deterioration, and length of hospitalization.
- Several 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.

## WHAT'S NEW IN THIS VERSION?

This version includes an additional 16 randomized controlled trials – 14 new studies and 2 studies which were previously included as preprint studies that have published versions available.

**PREVIOUS RECOMMENDATION**
*As of 08 November 2021*

**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.

## 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 2020 good quality systematic review of adverse events associated with colchicine use, colchicine was shown to increase gastrointestinal adverse events specifically diarrhea. However, there was no 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 August 28, 2021 until January 3, 2023 using Medline and Cochrane Library 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[6] 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 and hospitalization status was planned.

## RESULTS

We found 19 RCTs that included a total of 22,921 COVID-19 patients. There were 15 RCTs that involved hospitalized COVID-19 patients [7-15,18,19,21-24], 3 RCTs that involved outpatients [4,16,17], and 1 RCT that involved both hospitalized and ambulatory COVID-19 patients [20]. All 19 RCTs were published studies. Two of the RCTs were suspended early due to futility [11,16]. Standard of care used across these studies varied as they followed their respective local guidelines at the time the studies were conducted. Examples of standard of care used in the various RCTs include azithromycin, hydroxychloroquine, heparin, corticosteroids, remdesivir, tocilizumab, vitamins, faviripavir, inhaled budesonide, and baricitinib. The dose of colchicine varied from 0.5 to 1.2mg/day, while the duration of treatment with colchicine ranged from 5 to 30 days. Outcomes measured included all-cause mortality, need for mechanical ventilation, hospital discharge, clinical improvement (defined as improvement in symptoms), need for hospitalization, duration of hospitalization, and adverse events. No studies were found among children and adolescents. The characteristics of included studies are summarized in Appendix 3.

The overall certainty 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 (duration of hospitalization). Of the 19 included studies, 6 studies had unclear allocation concealment, 14 studies had serious risk of performance bias, 12 studies had serious risk of detection bias, 2 studies had serious risk of attrition bias and 2 studies had unclear risk of attrition bias, 1 study had serious risk of reporting bias and 2 studies had unclear risk of reporting bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

Based on 19 RCTs, colchicine did not show any significant difference compared to standard care in reducing all-cause mortality (RR 0.99, 95% CI 0.93-1.06; $I^2$=0%). Subgroup analysis by hospitalization status showed no difference in all-cause mortality for hospitalized patients (RR 0.99, 95% CI 0.93-1.06, 15 RCTs). Results were inconclusive for non-hospitalized patients (RR 0.82, 95% CI 0.43-1.56, 3 RCTs). Subgroup analysis according to disease severity showed inconclusive results for mild disease (RR 0.82, 95% CI 0.43-1.56), moderate disease (RR 0.39, 95% CI 0.09-1.63), moderate-to-severe disease (RR 0.64, 95% CI 0.32-1.28), severe disease (RR 0.71, 95% CI 0.30-1.66), and critical disease (RR 1.36, 95% CI 0.45-4.11).

Results were inconclusive for the outcome need for mechanical ventilation (RR 0.84, 95% CI 0.67-1.06, 8 RCTs). Subgroup analysis by hospitalization status showed no difference in need for mechanical ventilation for hospitalized patients (RR 0.93, 95% CI 0.86-1.01, 7 RCTs) and inconclusive evidence for non-hospitalized patients (RR 0.53, 95% CI 0.26-1.09, 1 RCT).

There was no difference in hospital discharge within 28 days between the colchicine and control groups (RR 1.00, 95% CI 0.97-1.03, 5 RCTs).

There was no significant reduction in length of hospitalization (MD 1.34 days shorter, 95% CI 2.79 days shorter to 0.12 days longer, 5 RCTs, $I^2$=67%). Five other studies also reported no significant reduction in length of hospitalization, but results could not be pooled due to inadequate data. One study reported length of hospital stay using hazards ratio (HR 1.13, 95% CI 0.76-1.66) [11]. The second study reported a median hospitalization stay of 8 days for colchicine group and 10 days for control group (p=0.60) [12]. The third study reported a mean hospital stay of 10.7 days for the colchicine group, and 8.8 days for control group (p=0.37) [23]. The fourth study reported that the mean hospital stay for both groups was 11.3 days, with no significant difference between the 2 groups (p=0.765) [14]. The fifth study reported median hospital stay of 6.5 days (IQR 5 to 8) for colchicine group and 8 days (IQR 5 to 11.3) for control group [24].

Results are inconclusive for need for ICU admission (RR 0.69, 95% CI 0.40-1.21, 5 RCTs). One study reported that the ICU length of stay did not differ between the colchicine and control groups, with a median stay of 0 days (IQR 0 to 0.75 days) for colchicine group and 0 days (IQR 0 to 1) for control group, p=0.29 [11].

Results are inconclusive for the outcomes need for hemodialysis or hemofiltration (RR 1.07, 95% CI 0.88-1.29, 1 RCT), and clinical deterioration defined as at least 2 grade deterioration in the WHO ordinal scale (RR 0.40, 95% CI 0.14-1.18, 2 RCTs).

One study reported on clinical improvement, defined as improvement of at least 2 points in the WHO scale. There was no significant benefit observed for colchicine (RR 1.23, 95% CI 0.97-1.55) [13]. One study reported no significant difference in change in WHO ordinal scale between the colchicine group and control group (MD 0.60 points, 95% CI -0.30 to 1.50) [23]. Another study reported on the response rate (defined as symptom resolution), with significant benefit for colchicine compared to control (RR 1.32, 95% CI 1.06-1.65) [20].

One study reported that the time to recovery was significantly shorter for the colchicine group compared to control group, both for those with moderate disease (12 days, 95% CI 10.2-13.8 for colchicine group; 14 days, 95% CI 13-15 for control group) and severe disease (14 days, 95% CI 12.5-15.5 for colchicine group;

19 days, 95% CI 15.9-22.1 for control group) [18]. One other study reported no significant difference in time to recovery, with the HR corresponding to an estimated of 1.14 days, 95% Bayesian credible interval -1.86 to 5.21 days) [16]. Results could not be pooled due to inadequate data.

Results are inconclusive for need for hospitalization among non-hospitalized patients given colchicine compared to control (RR 0.89, 95% CI 0.71-1.11, 3 RCTs).

**Adverse events**

Results are inconclusive for serious adverse events (RR 0.83, 95% CI 0.67-1.03, $I^2$=0, 11 RCTs). Subgroup analysis by hospitalization status showed inconclusive results for hospitalized patients (RR 0.56, 95% CI 0.25-1.21, 8 RCTs) and non-hospitalized patients (RR 0.91, 95 % CI 0.65-1.29, 3 RCTs). 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 1.78, 95% CI 1.36-2.32; $I^2$=65%, 13 RCTs), with moderate heterogeneity. The most common reported adverse event was diarrhea while other adverse events included abdominal pain, nausea, and rash. Subgroup analysis by hospitalization status showed significant harm for both hospitalized patients (RR 1.92, 95% CI 1.27-2.90, 11 RCTs) and for non-hospitalized patients (RR 1.56, 95% CI 1.38-1.76, 1 RCT).

## RECOMMENDATIONS FROM OTHER GROUPS

| Regulatory Agency | Recommendation | Strength of Recommendation / Certainty of Evidence |
|---|---|---|
| NIH Covid-19 Guidelines (as of December 28, 2022) | Recommends against the use of colchicine for the treatment of hospitalized patients with COVID-19. | Strong recommendation |
| | Recommends against the use of colchicine for the treatment of non-hospitalized patients with COVID-19 [26]. | Moderate recommendation |
| Australian COVID-19 Guidelines (as of December 20, 2022) | Do not use colchicine for the treatment of COVID-19.<br><br>This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care [27]. | Moderate recommendation |
| Infectious Diseases Society of America (as of November 21, 2022) | In hospitalized patients with COVID-19, the IDSA panel recommends against colchicine for treatment of COVID-19. | Strong recommendation, Moderate certainty of evidence |
| | In ambulatory persons with COVID-19, the IDSA panel suggests against colchicine for treatment of COVID-19 [28]. | Conditional recommendation, Moderate certainty of evidence |
| World Health Organization (WHO) Living Guidelines (as of October 6, 2022) | We recommend against treatment with colchicine [29]. | Strong recommendation against |

### RESEARCH GAPS

There are 8 ongoing trials registered. This review will be updated as soon as full results from these trials become available.

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

Colchicine is a widely used drug for treatment of acute gout. It is also used to treat familial Mediterranean fever, Behcet's syndrome and pericarditis. In the Philippines, colchicine is available in several drug stores and is sold under various brands and as a generic drug. The price of 1 colchicine 500mcg tablet is ₱2.10 based on the 2021 Philippine Drug Reference Index [25].

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Appendix 1: Preliminary Evidence to Decision

**Table 1. Summary of initial judgements prior to the panel discussion (N=12/12)**

| FACTORS | JUDGEMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|---|---|---|
| **Problem** | No | Yes (12) | | | | | • Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity. |
| **Benefits** | Large | Moderate (1) | Small (2) | Trivial (6) | Uncertain (3) | | • Based on 19 RCTs, colchicine did not show any significant difference compared to standard care in reducing all-cause mortality (RR 0.99, 95% CI 0.93-1.06; I2=0%).<br>• There was no difference in hospital discharge within 28 days between the colchicine and control groups (RR 1.00, 95% CI 0.97-1.03, 5 RCTs). There was no significant benefit in reducing length of hospitalization (MD 1.34 days shorter, 95% CI 2.79 days shorter to 0.12 days longer, 5 RCTs).<br>• Results were inconclusive for the outcome need for mechanical ventilation (RR 0.84, 95% CI 0.67-1.06, 8 RCTs), need for ICU admission (RR 0.69, 95% CI 0.40-1.21, 5 RCTs), need for hemodialysis or hemofiltration (RR 1.07, 95% CI 0.88-1.29, 1 RCT), clinical deterioration defined as at least 2 grade deterioration in the WHO ordinal scale (RR 0.40, 95% CI 0.14-1.18, 2 RCTs) and need for hospitalization (RR 0.89, 95% CI 0.71-1.11, 3 RCTs). |
| **Harm** | Large | Moderate (6) | Small (4) | Trivial (1) | Varies (1) | Uncertain | • Results are inconclusive for serious adverse events (RR 0.83, 95% CI 0.67-1.03, I2=0, 11 RCTs).<br>• There were significantly more adverse events among patients who received colchicine (RR 1.78, 95% CI 1.36-2.32; I2=65%, 13 RCTs). The most common was diarrhea. Other adverse events included abdominal pain, nausea, and rash. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Certainty of Evidence** | High | Moderate (1) | Low (3) | Very low (8) | | | • The overall certainty 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 intervention | Probably favors intervention | Does not favor intervention or no intervention (1) | Probably favors no intervention (4) | Favors no intervention (7) | Varies | • Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, hospital discharge within 28 days, need for hospitalization, need for ICU admission, need for hemodialysis or hemofiltration, clinical deterioration, and length of hospitalization. |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability (6) | Probably no important uncertainty or variability (4) | No important uncertainty or variability (2) | | | |
| **Resources Required** | Varies (1) | Large cost | Moderate Cost | Negligible cost or savings (10) | Moderate savings | Large savings (1) | • Colchicine is a widely used drug for treatment of acute gout. In the Philippines, colchicine is available in several drug stores and is sold under various brands and as a generic drug. The price of 1 colchicine 500mcg tablet is ₱2.10. |
| **Certainty of evidence of required resources** | No included studies (3) | Very low (2) | Low (4) | Moderate (1) | High (2) | | • The price of 1 colchicine 500mcg tablet is ₱2.10 based on the 2021 Philippine Drug Reference Index. |
| **Cost effectiveness** | No included studies (9) | Favors using the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison (2) | Probably favors the invention | Varies (1) | |
| **Equity** | Don't know (3) | Varies (3) | Probably reduced | Probably no impact (6) | Probably increased | Increased | |
| **Acceptability** | Uncertain | Varies (1) | No (2) | Probably no (5) | Probably yes (3) | Yes (1) | |
| **Feasibility** | Uncertain | Varies (2) | No (1) | Probably no (4) | Probably yes (4) | Yes (1) | |
| **Recommendation** | For | Against (12) | | | | | |
| **Strength** | Weak (10) | Strong (2) | | | | | |

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})<br><br>Filters: August 29, 2021 to January 3, 2023 | January 3, 2023 11:00PM | 201 | 12 |
| 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<br><br>Filters: August 29, 2021 to January 3, 2023 | January 3, 2023 11:00PM | 48 | 2 |
| COVID-NMA Initiative | Colchicine | January 3, 2023 11:00PM | 13 | 1 |
| | | | | |
| ClinicalTrials.gov | Colchicine and COVID19 | January 3, 2023 11:00PM | 8 | 8 |
| Chinese Clinical Trial Registry | Colchicine | January 3, 2023 11:00PM | 12 | 0 |
| EU Clinical Trials Register | Colchicine and COVID | January 3, 2023 11:00PM | 5 | 3 |
| Republic of Korea - Clinical Research Information Service | Colchicine | January 3, 2023 11:00PM | 1 | 0 |
| Japan Primary Registries Network/ NIPH Clinical Trials Search | Colchicine | January 3, 2023 11:00PM | 28 | 0 |
| CenterWatch | Colchicine and COVID | January 3, 2023 11:00PM | 26 | 0 |
| | | | | |
| chinaxiv.org | Colchicine | January 3, 2023 11:00PM | 1 | 0 |
| Medrxiv.org | Colchicine<br>Filters: August 29, 2021 to January 3, 2023 | January 3, 2023 11:00PM | 55 | 0 |
| Biorxiv.org | Colchicine and COVID<br>Filters: August 29, 2021 to January 3, 2023 | January 3, 2023 11:00PM | 10 | 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<br><br>*Tardif et al. 2021 (Canada, USA, Brazil)* [4] | N = 4488<br><br>**Non-hospitalized** patients with COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria at least 40 years of age<br><br>Duration of follow-up:<br>Approximately 30 days | EXPERIMENTAL:<br>Colchicine (0.5mg twice daily for 3 days and once daily thereafter)<br><br>CONTROL: Placebo | PRIMARY:<br>Composite of death or hospitalization due to COVID-19 infection<br><br>SECONDARY:<br>Components of the composite primary endpoint; need for mechanical ventilation, serious adverse events, and non-serious adverse events | Randomized<br>Parallel<br>Double-blind |
| Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial<br><br>*Lopes et al., 2021 (Brazil)* [7] | N = 75<br><br>Adults **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,<br><br>Duration of follow-up:<br>Up to 26 days | EXPERIMENTAL:<br>Colchicine 0.5mg 3x daily for 5 days, then 0.5mg 2x daily for 5 days plus standard care<br><br>CONTROL: Standard of care (azithromycin, hydroxychloroquine (HCQ), unfractionated heparin, methylprednisolone) | PRIMARY:<br>Time of need for supplemental oxygen, time of hospitalization, need for admission and length of stay in ICU, death rate and causes of mortality<br><br>SECONDARY:<br>Adverse events | Randomized<br>placebo-control<br>double blind |
| Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized with Coronavirus Disease 2019<br>The GRECCO-19 Randomized Clinical Trial<br><br>*Deftereos et al., 2020 (Greece)* [8] | N = 110<br><br>**Hospitalized** adult patients diagnosed with SARS-CoV-2 infection by RT-PCR<br><br>Duration of follow-up:<br>21-25 days | EXPERIMENTAL:<br>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<br><br>CONTROL:<br>Standard medical treatment (azithromycin, HCQ) | PRIMARY:<br>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<br><br>SECONDARY:<br>Need for mechanical ventilation, all-cause mortality, adverse events. | Randomized<br>parallel |
| The Impact of Colchicine on the COVID-19 Patients: A Clinical Trial Study<br><br>*Salehzadeh et al. 2022 (Iran)* [9] | N = 100<br><br>Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19.<br><br>Duration of follow-up:<br>21 to 30 days | EXPERIMENTAL:<br>HCQ + colchicine 1mg OD<br><br>CONTROL:<br>HCQ + placebo | PRIMARY:<br>Length of hospitalization; symptoms and co-existed disease<br><br>SECONDARY<br>Mortality and morbidity, re-admission, and symptoms | Randomized<br>double blind<br>Placebo control |

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| Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial<br><br>*Horby et al. 2021 (UK, Indonesia, Nepal)* [10] | N = 11,340<br><br>Clinically suspected or laboratory confirmed SARS-CoV-2 infection among patients admitted in a **hospital**<br><br><u>Duration of follow-up:</u><br>28 days | EXPERIMENTAL:<br>Colchicine 1mg after randomization followed by 500mcg 12 hours later and then 500mcg twice daily for 10 days in total or until discharge<br><br>CONTROL:<br>Usual care (corticosteroids, remdesivir, and tocilizumab) | PRIMARY:<br>Mortality<br><br>SECONDARY:<br>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 |
| Colchicine Is Safe Though Ineffective in the Treatment of Severe COVID-19: a Randomized Clinical Trial (COLCHIVID)<br><br>Absalón-Aguilar et al. 2021 (Mexico) [11]<br><br>NCT04367168 | N=116<br><br>**Hospitalized** adult patients aged 18 to 70 years positive for at least one of the following: polymerase chain reaction (PCR) for SARS-CoV-2 in nasopharyngeal swab, rapid antigen test, or serum anti- SARS-CoV-2 IgG antibodies.<br><br>All patients were classified as **severe** COVID-19 | EXPERIMENTAL:<br>Colchicine 1.5 mg followed by 500mcg twice daily for 10 days<br><br>CONTROL: Placebo, usual care (dexamethasone) | PRIMARY:<br>Death or progression to critical disease, defined as multiple organ failure, shock, or need for invasive mechanical ventilation.<br><br>SECONDARY:<br>Duration of intensive care unit (ICU) stay, the total length of hospital admission, the type and number of adverse events | Triple-blind parallel non-stratified placebo-controlled clinical trial<br><br>**Suspended early due to futility** |
| Efficacy of Colchicine and Budesonide in Improvement Outcomes of Patients with Coronavirus Infection 2019 in Damascus, Syria: A Randomized Control Trial<br><br>Alsultan et al. 2021 (Syria) [12] | N=49<br><br>Adult patients with positive PCR test or negative PCR test but had clinical signs and symptoms of viral illness accompanied with chest CT scan showing the radiologic findings of viral pneumonia, AND oxygen saturation ≤93% (**severe**) | EXPERIMENTAL:<br>1. colchicine 1.5mg followed by 0.5mg after hour in day 1, then 0.5 mg twice daily for the next 4 days)<br>2. budesonide inhaler<br><br>CONTROL:<br>supportive care (oxygen supplementation, vitamins, anticoagulants, dexamethasone, prone position, noninvasive ventilation, antibiotics, and fluids) | Median hospitalization days, median days on oxygen supplementation, mortality, recovery | Randomized 3-arm trial |
| Efficacy and safety of Ixekizumab vs. low-dose IL-2 vs. Colchicine vs. standard of care on the treatment of patients hospitalized with moderate to | N=60<br><br>Adult **hospitalized** with **moderate to critical** COVID-19, unvaccinated | EXPERIMENTAL<br>Colchicine: 0.5 mg (PO) every 8 hours for three days, then 0.5 mg BID x 4 weeks<br><br>CONTROL | PRIMARY<br>clinical improvement (decrease of two points on the WHO ordinal scale of seven categories)<br><br>SECONDARY | multicenter, open-label, randomized, adaptive study of 4 arms |

| | | | | |
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| critical Covid-19: a pilot randomized clinical trial (STRUCK: Survival Trial Using Cytokine Inhibitors) Running title: Exploring new targets for Covid-19 treatment<br><br>Bonifacio et al. 2021 (Brazil) [13]<br><br>NCT04724629 | | Standard care (oxygen, dexamethasone, anticoagulants) | Duration of hospitalization.<br>Length of stay in the ICU.<br>Duration of mechanical ventilation | |
| Efficacy of short-course colchicine treatment in hospitalized patients with moderate to severe COVID-19 pneumonia and hyperinflammation: a randomized clinical trial<br><br>Cecconi et al. 2022 (Spain) [14] | N=239<br><br>**Hospitalized** adult patients with **moderate to severe** COVID-19 pneumonia with at least 2 of the following 4 inflammatory criteria: C-reactive protein>4 mg/dL, D-dimer>1 mg/L, ferritin>1000 ng/mL or fever≥38 °C in the last 24 h | EXPERIMENTAL: Colchicine (5 days of oral treatment: 1 mg loading dose and then 0.5 mg/day)<br><br>CONTROL: Standard care (steroids, heparin) | PRIMARY<br>Composite: non-invasive mechanical ventilation, admission to the intensive care unit, invasive mechanical ventilation requirement or death<br><br>SECONDARY:<br>hospital stay, adverse events | prospective, randomized controlled, observer-blinded endpoint (PROBE), investigator-initiated trial. |
| Effect of Colchicine vs Usual Care Alone on Intubation and 28-Day Mortality in Patients Hospitalized With COVID-19<br><br>Diaz et al. 2021 (Argentina) [15] | N=1279<br><br>Hospitalized adults (age ≥18 years) with confirmed or suspected COVID-19, **mild to critical** | EXPERIMENTAL: Colchicine 1.5 mg, followed by 0.5 mg orally within 2 hours, and subsequently 0.5 mg orally twice a day for 14 days or discharge<br><br>CONTROL: Standard care | PRIMARY:<br>composite of a new requirement for mechanical ventilation or death evaluated at 28 days<br><br>SECONDARY:<br>new requirement for mechanical ventilation or death from respiratory failure, new requirement for mechanical ventilation or death from nonrespiratory cause, mortality due to respiratory failure and mortality due to nonrespiratory cause, in-hospital death | open-label, multicenter, randomized clinical trial |
| Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial<br><br>Dorward et al. 2022 (UK) [16] | N=4997<br><br>18–65 years with comorbidities or shortness of breath<br><br>**Outpatient** | EXPERIMENTAL colchicine 500 µg daily for 14 days<br><br>CONTROL: Standard care (antipyretics, inhaled budesonide) | PRIMARY:<br>time to first-reported recovery defined as the first instance that a participant reports feeling recovered; admission to hospital or death related to COVID-19.<br><br>SECONDARY | randomised, controlled, adaptive platform trial<br><br>**Suspended early due to futility** |

| | | | | |
|---|---|---|---|---|
| ISRCTN86534580 | | | early, sustained recovery, time to sustained recovery, duration of hospital admission, oxygen administration, intensive care unit admission, mechanical ventilation, World Health Organization (WHO) ordinal scale of clinical progression, serious adverse events, all- cause death or urgent, non-elective hospital admission | |
| Colchicine and aspirin in community patients with COVID-19 (ACT): an open-label, factorial, randomised, controlled trial<br><br>Eikelboom et al. 2022 (Canada) [17] | N=3881<br><br>Symptomatic laboratory-confirmed COVID-19 disease, at least 30 years old and within 7 days of diagnosis or worsening clinically (but not requiring hospitalisation). Patients younger than 70 years had to have at least one additional risk factor for disease progression, including male sex, body-mass index of at least 30 kg/m2, chronic cardio-vascular, respiratory, or renal disease, active cancer, or diabetes.<br><br>**Outpatient** | EXPERIMENTAL<br>Colchicine 0·6 mg twice daily for 3 days and then 0.6 mg once daily for 25 days<br><br>CONTROL:<br>Standard care | PRIMARY<br>hospitalisation or death<br><br>SECONDARY<br>hospitalisation or respiratory death and individual components of composites | outpatient, open-label, 2 × 2 factorial, randomised, controlled trial |
| Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection<br><br>Gorial et al. 2022 (Iraq) [18]<br><br>NCT05151614 | N=160<br><br>adults aged 18 years and above, **hospitalized with moderate to severe** COVID19 | EXPERIMENTAL:<br>colchicine 1 mg daily orally for 7 days then 0.5 mg daily for another 7 days<br><br>CONTROL:<br>Standard care (acetaminophen, vitamin C, zinc, vitamin d3, azithromycin, oxygen, dexamethasone or methylprednisolone) | PRIMARY<br>Death up to 14 days<br><br>SECONDARY<br>time to recovery, adverse events | randomized controlled open label trial |
| Colchicine anti-inflammatory therapy for non-intensive care unit hospitalized covid-19 patients: results from a pilot open-label, randomized controlled clinical trial | N=96<br><br>adults aged 18 years and above, **hospitalized with moderate to severe** COVID19 | EXPERIMENTAL<br>colchicine 1.5 mg followed by 0.5 mg dose every 12 hours for 14 days<br><br>CONTROL<br>Standard care (corticosteroids, | PRIMARY<br>Recovery within 14 days<br><br>SECONDARY<br>Improvement of symptoms, all-cause mortality, need for ICU | randomized controlled open label trial |

| | | | | |
|---|---|---|---|---|
| Haroon et al. 2022 (Pakistan) [19]<br><br>NCT04667780 | | anticoagulants, antibiotics, PPI) | | |
| Effectiveness of Colchicine among Patients with COVID-19 Infection: A Randomized, Open-Labeled, Clinical Trial<br><br>Jalal et al. 2022 (Iraq) [20]<br><br>NCT04867226 | N=80<br><br>patients with mild, moderate, or severe COVID-19 infection; either **hospitalized or at home**, confirmed RTPCR and/or computed tomography scan compatible with COVID-19, between 18 and 70 years old. | EXPERIMENTAL<br>Colchicine 0.5 mg twice a day for 14 days<br><br>CONTROL<br>Standard care (azithromycin, LMWH, remdesivir, faviripavir, corticosteroids) | time of hospitalization, adverse events, | Randomized, Open-Labeled, Clinical Trial |
| Colchicine in Recently Hospitalized Patients with COVID-19: A Randomized Controlled Trial (COL-COVID)<br><br>Pascual-Figal et al. 2021 (Spain) [21] | N=103<br><br>adults aged 18 years and above, **hospitalized** with COVID19 (non-ICU, **moderate to severe**) | EXPERIMENTAL<br>1.5 mg 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<br><br>CONTROL<br>Standard care (dexamethasone, remdesivir, tocilizumab, baracitinib) | PRIMARY<br>change in the WHO 7-points ordinal clinical scale in 28 days<br><br>SECONDARY<br>death, ICU admission, mechanical ventilation (non-invasive and invasive) | randomized Phase III, controlled and open-label clinical trial |
| Treatment with COLchicine in hospitalized patients affected by COVID-19: The COLVID-19 trial<br><br>Perricone et al. 2023 (Italy) [22]<br><br>NCT04375202. | N=152<br><br>**hospitalized adult** COVID-19 patients, **critical** (with ARDS), unvaccinated | EXPERIMENTAL<br>colchicine 0.5 mg three times a day if weight was less than 100 kg or 1 mg twice a day if weight was more than 100 kg for a maximum of 30 days or until hospital discharge<br><br>CONTROL<br>Standard care (dexamethasone) | PRIMARY<br>Composite - respiratory failure requiring mechanical ventilation; patients with other organ failure who needed ICU monitoring and treatment; death.<br><br>SECONDARY<br>Adverse events | interventional, multicenter, randomized, phase 2 study |
| Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients With Coronavirus Disease-19<br><br>Rabbani et al. 2022 (USA) [23]<br><br>NCT04355143 | N=93<br><br>**hospitalized adult** patients with documented COVID-19 and evidence of cardiac injury | EXPERIMENTAL<br>colchicine 0.6 mg twice daily for 30 days<br><br>CONTROL<br>Standard care | PRIMARY<br>Composite - all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days<br><br>SECONDARY<br>individual components of the primary endpoint, time to the primary endpoint, change in the WHO R&D Blueprint Ordinal Scale at 30 days, and at least 2-grade reduction (i.e., | multicenter open-label RCT |

| | | | | |
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| | | | clinical improvement) in the WHO Ordinal Scale at 30 days, re-hospitalization at 90 days | |
| Efficacy of colchicine in patients with moderate COVID-19: A double-blinded, randomized, placebo-controlled trial<br><br>Rahman et al. 2022 (Bangladesh) [24]<br><br>NCT04527562 | N=300<br><br>Adult **hospitalized** with **moderate** COVID-19 based on a positive RT-PCR result | EXPERIMENTAL<br>1.2 mg of colchicine 12 h divided doses on day 1 followed by 0.6 mg for 13 days<br><br>CONTROL<br>Standard care (paracetamol, antihistamines, oxygen, LMWH, antibiotics, remdesivir) | PRIMARY<br>time to clinical deterioration<br><br>SECONDARY<br>length of hospital stay, proportion of participants requiring supplemental oxygen, proportion of participants requiring mechanical ventilation; all-cause mortality days 14 and 28 | double-blinded, randomized, placebo-controlled trial |

Appendix 4: Study Appraisal

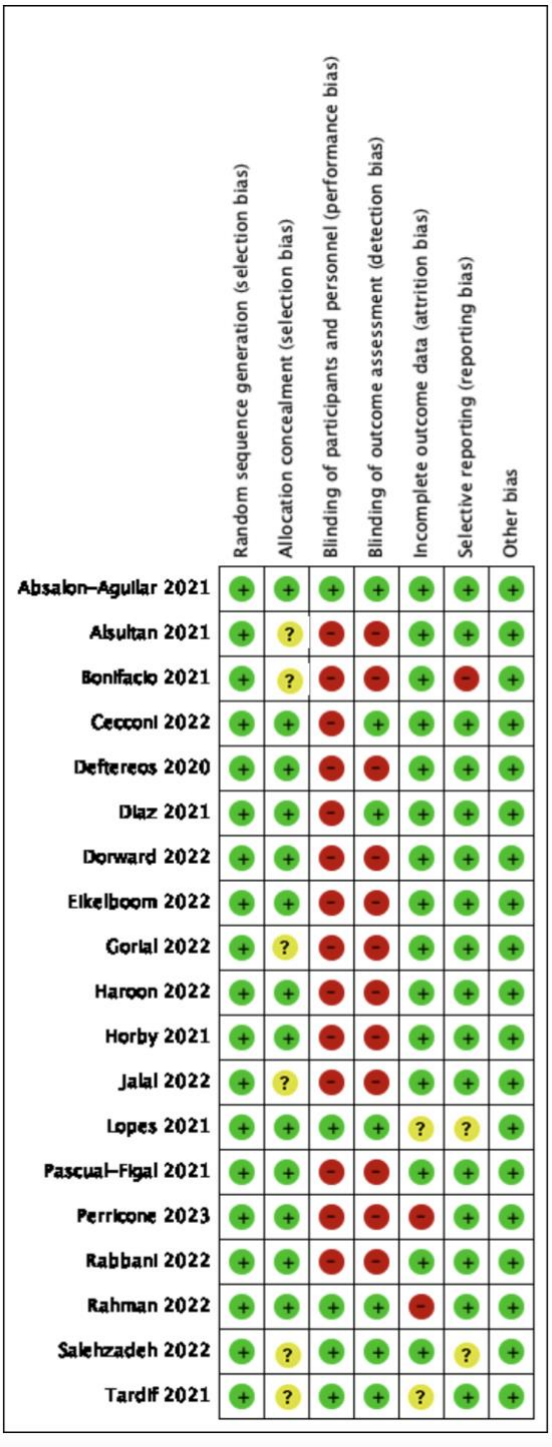


**Figure 1.** Risk of bias summary table

## Appendix 5: GRADE Evidence Profile

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

**Question:** Colchicine for treatment of COVID-19

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | All-cause mortality | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **All-cause mortality** | | | | | | | | | | | | |
| 19 | randomised trials | serious[a] | not serious | not serious | not serious | publication bias strongly suspected[b] | 1358/11402 (11.9%) | 1405/11519 (12.2%) | **RR 0.99** (0.93 to 1.06) | **1 fewer per 1,000** (from 9 fewer to 7 more) | ⊕⊕◯◯ Low | CRITICAL |
| **Need for mechanical ventilation** | | | | | | | | | | | | |
| 8 | randomised trials | serious[c] | not serious | not serious | serious[d] | none | 896/6548 (13.7%) | 1008/6706 (15.0%) | **RR 0.84** (0.67 to 1.06) | **24 fewer per 1,000** (from 50 fewer to 9 more) | ⊕⊕◯◯ Low | CRITICAL |
| **Hospital discharge within 28 days** | | | | | | | | | | | | |
| 5 | randomised trials | serious[e] | not serious | not serious | not serious | none | 4029/5755 (70.0%) | 4156/5877 (70.7%) | **RR 1.00** (0.97 to 1.03) | **0 fewer per 1,000** (from 21 fewer to 21 more) | ⊕⊕⊕◯ Moderate | CRITICAL |
| **Length of hospitalization** | | | | | | | | | | | | |
| 5 | randomised trials | serious[e] | serious[f] | not serious | serious[d] | none | 249 | 248 | - | MD **1.34 lower** (2.79 lower to 0.12 higher) | ⊕◯◯◯ Very low | CRITICAL |
| **Need for ICU admission** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | All-cause mortality | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| 5 | randomised trials | serious [g] | not serious | not serious | serious [d] | none | 20/442 (4.5%) | 30/440 (6.8%) | **RR 0.69** (0.40 to 1.21) | **21 fewer per 1,000** (from 41 fewer to 14 more) | ⊕⊕◯◯ Low | CRITICAL |
| **Clinical deterioration** | | | | | | | | | | | | |
| 2 | randomised trials | serious [h] | not serious | not serious | serious [d] | none | 4/198 (2.0%) | 11/197 (5.6%) | **RR 0.40** (0.14 to 1.18) | **34 fewer per 1,000** (from 48 fewer to 10 more) | ⊕⊕◯◯ Low | CRITICAL |
| **Need for hospitalization** | | | | | | | | | | | | |
| 3 | randomised trials | serious [i] | not serious | not serious | serious [d] | none | 169/4330 (3.9%) | 192/4328 (4.4%) | **RR 0.89** (0.71 to 1.11) | **5 fewer per 1,000** (from 13 fewer to 5 more) | ⊕⊕◯◯ Low | CRITICAL |
| **Serious adverse events** | | | | | | | | | | | | |
| 11 | randomised trials | serious [j] | not serious | not serious | serious [d] | none | 152/4824 (3.2%) | 184/4818 (3.8%) | **RR 0.83** (0.67 to 1.03) | **6 fewer per 1,000** (from 13 fewer to 1 more) | ⊕⊕◯◯ Low | CRITICAL |
| **Adverse events** | | | | | | | | | | | | |
| 13 | randomised trials | serious [k] | serious [f] | not serious | not serious | none | 924/3556 (26.0%) | 630/3625 (17.4%) | **RR 1.78** (1.36 to 2.32) | **136 more per 1,000** (from 63 more to 229 more) | ⊕⊕◯◯ Low | IMPORTANT |

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

## Explanations

a. Lack of blinding in 14 studies, attrition bias in 2 studies, selective reporting bias in 1 study
b. Asymmetric funnel plot
c. Lack of blinding in 6 studies, attrition bias in 3 studies

d. Wide confidence interval
e. Lack of blinding in 4 studies, unclear attrition and selective reporting bias in 1 study
f. I2>50%
g. Lack of blinding in 4 studies, attrition bias in 2 studies
h. Lack of blinding in 1 study, attrition bias in 1 study
i. Lack of blinding in 2 studies, unclear allocation concealment and attrition bias in 1 study
j. Lack of blinding in 8 studies, attrition bias in 3 studies, unclear allocation concealment and selective reporting in 1 study
k. Lack of blinding in 9 studies, attrition bias in 4 studies, unclear allocation concealment in 4 studies, unclear selective reporting in 1 study

## Appendix 6: Forest Plots

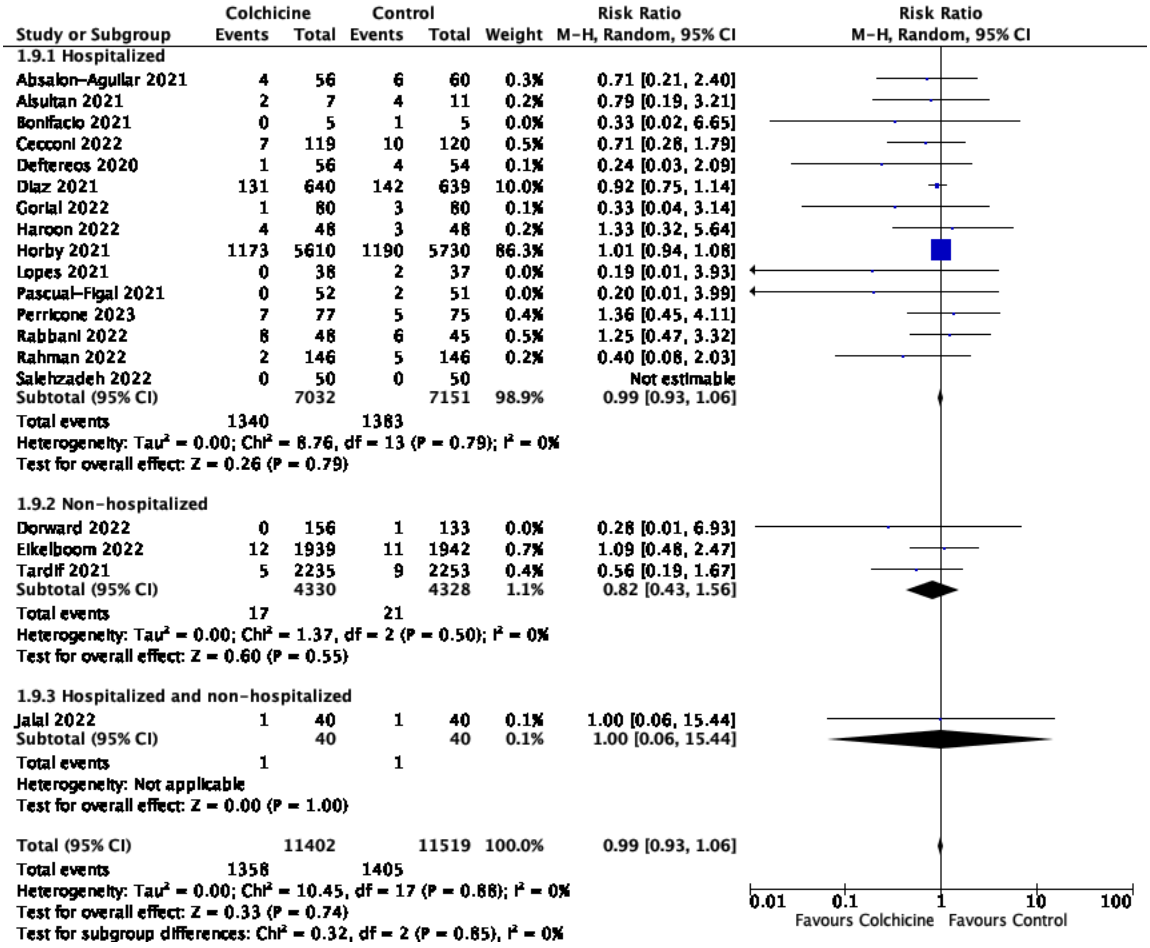


**Figure 2.** All-cause mortality (by hospitalization status)

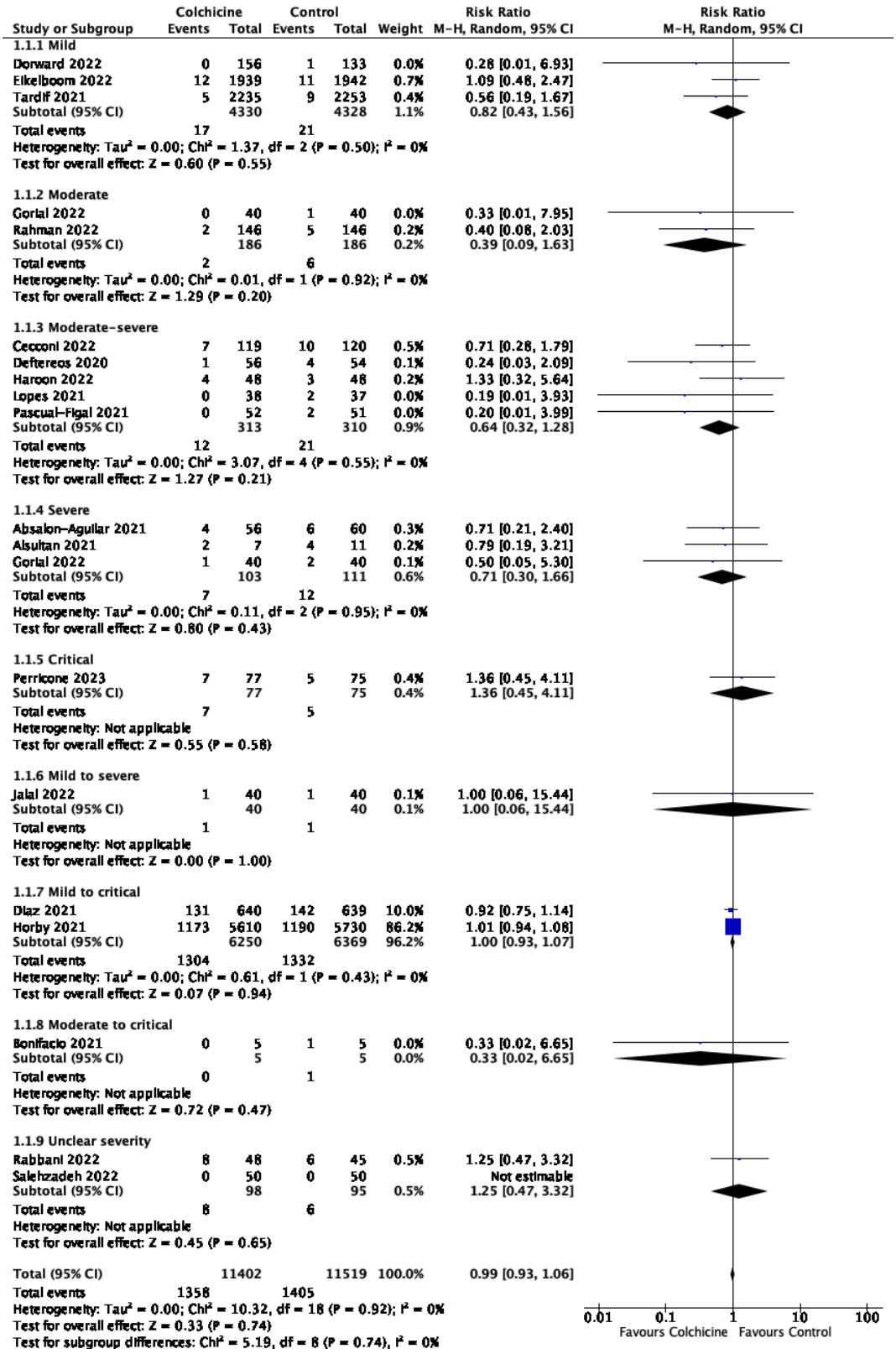


**Figure 3.** All-cause mortality (by severity)

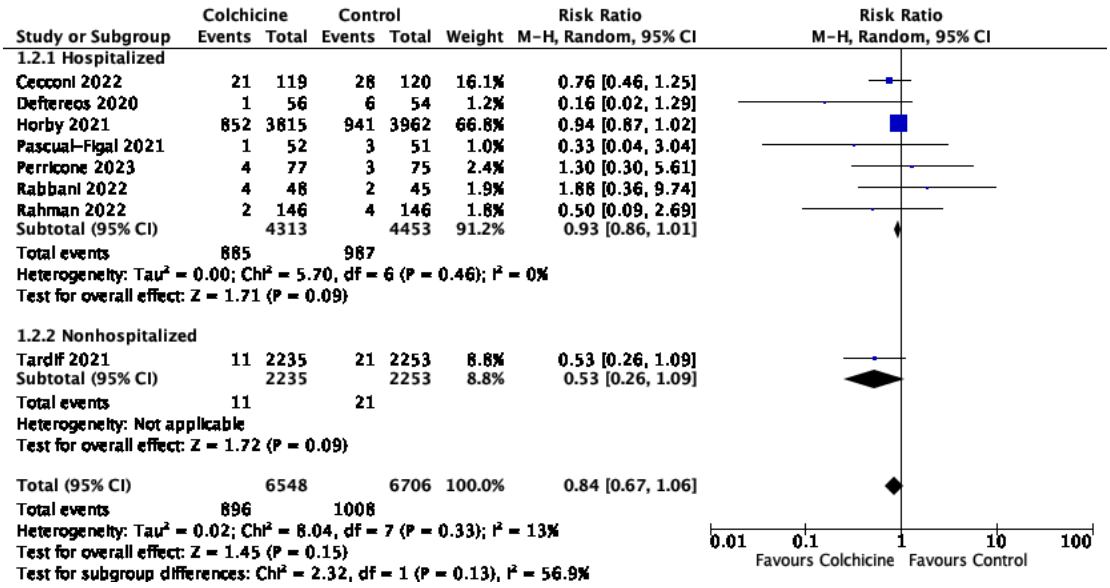


**Figure 4.** Need for Mechanical Ventilation

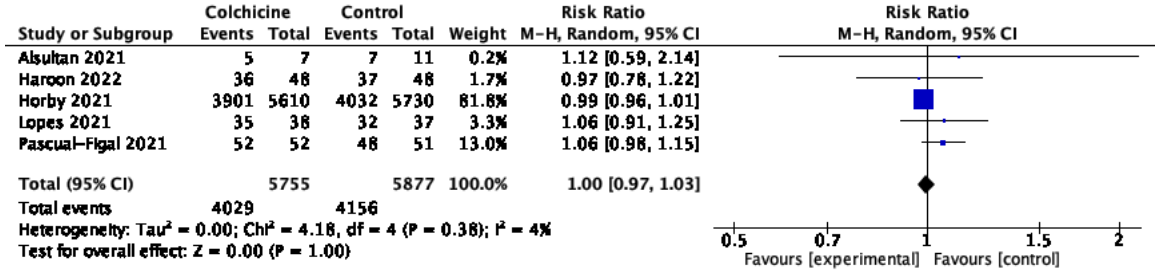


**Figure 5.** Hospital discharge within 28 days

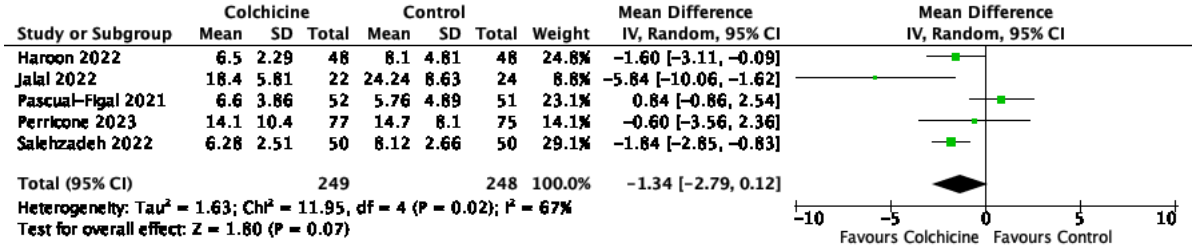


**Figure 6.** Length of hospitalization (in days)

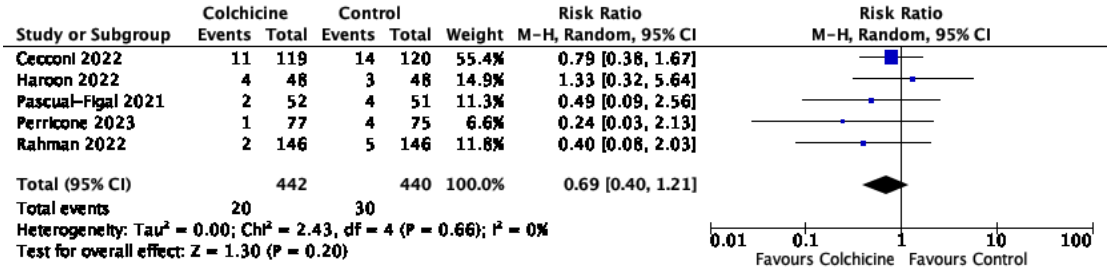


**Figure 7.** Need for ICU admission

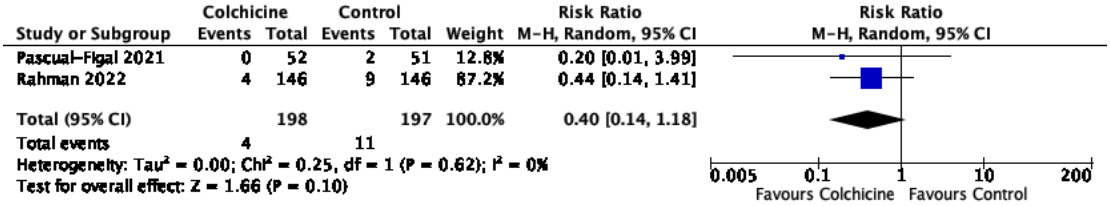


**Figure 8.** Clinical deterioration (at least 2 grade deterioration in WHO ordinal scale)

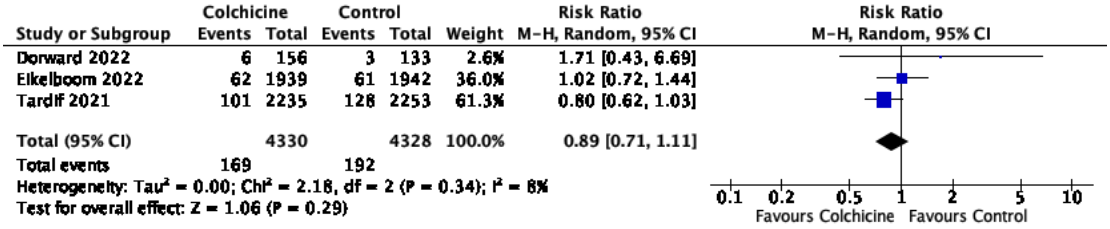


**Figure 9.** Need for hospitalization

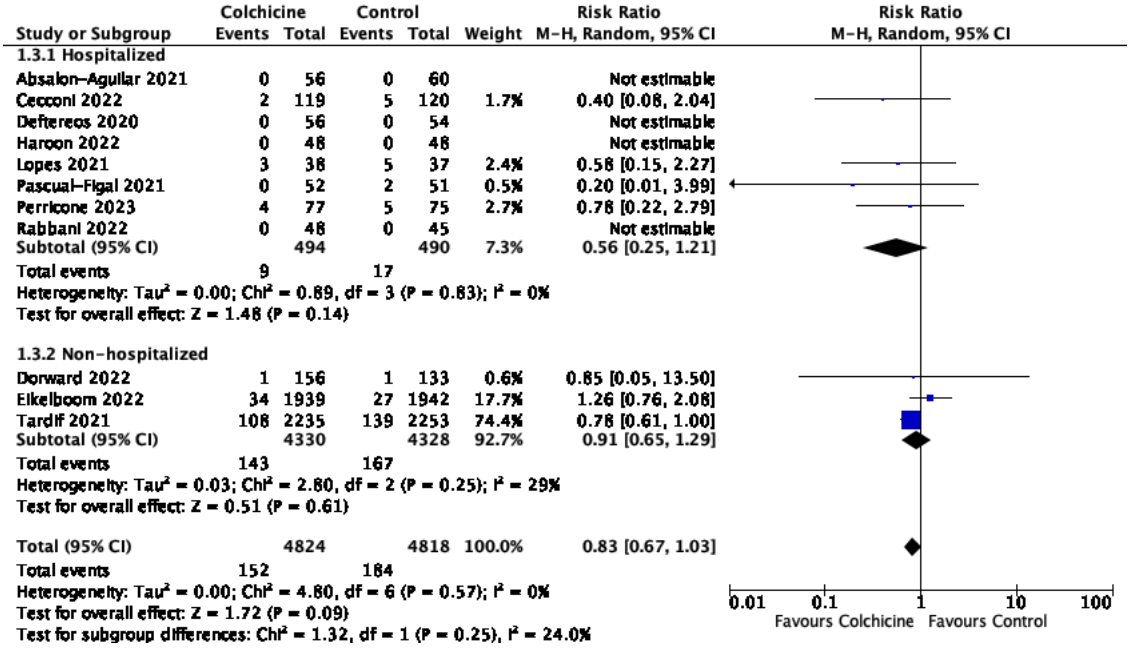


**Figure 10.** Serious adverse events

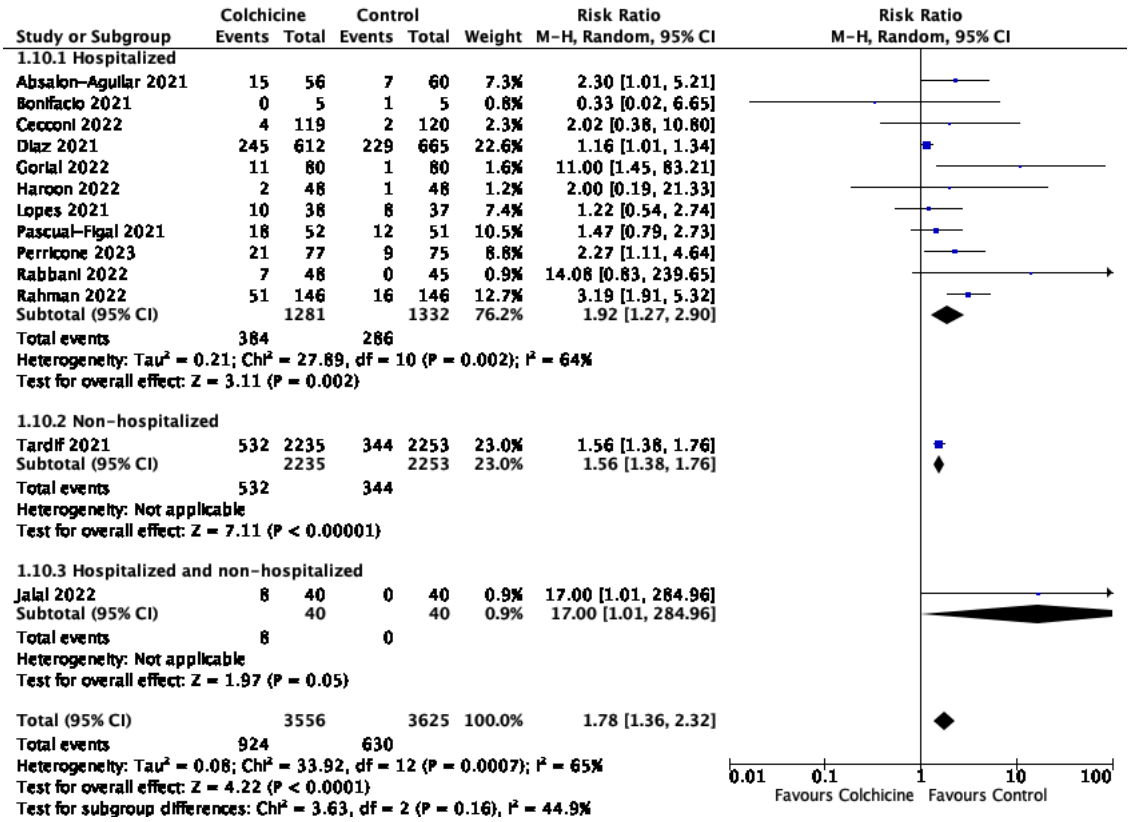


**Figure 11.** Adverse events

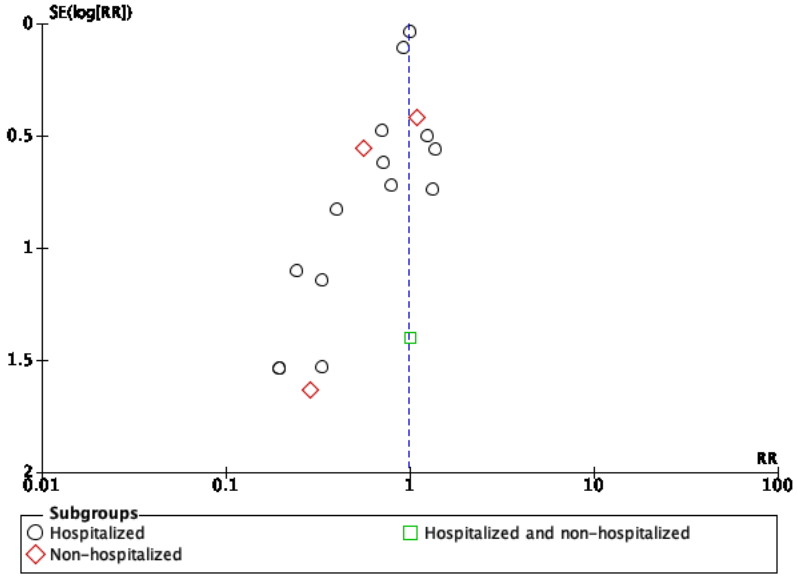


**Figure 12.** Funnel plot (mortality)

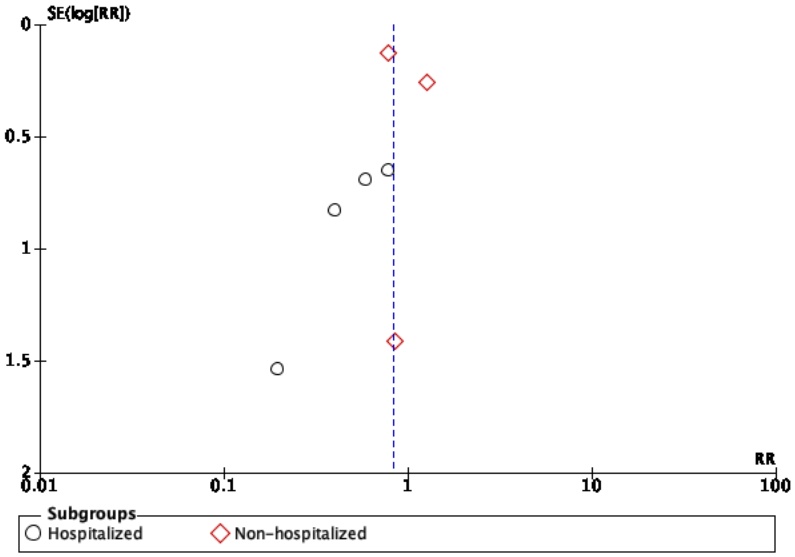


**Figure 13.** Funnel plot (serious adverse events)

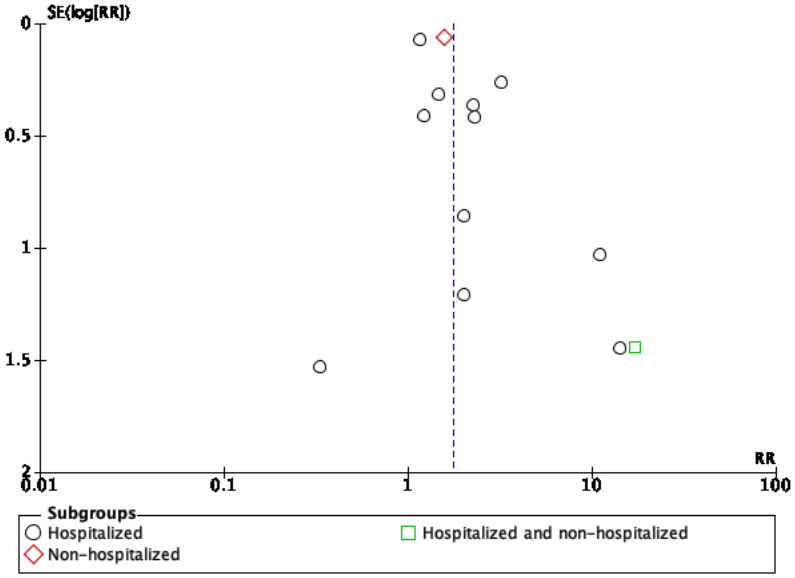


**Figure 14.** Funnel plot (adverse events)

## Appendix 7: Characteristics of Ongoing Studies

| Study Title | Patients (n) | Interventions | Outcomes | Method |
|---|---|---|---|---|
| 1. Study to Evaluate the Efficacy and Safety of Colchicine Tablets in Patients With COVID-19 | 18 to 65 years old, confirmed positive for SARS-CoV-2; symptoms appeared ≤ 5 days before randomization | Experimental: Colchicine plus Standard treatment<br><br>Control: Standard treatment | Primary: Recovery rate of clinical symptoms | Randomized, Single-Center, Open-Lable, Standard Therapy Controlled Study |
| 2. 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<br>Patients in outpatient follow-up or institutionalized in senior centers/residences | Experimental: Colchicine plus symptomatic treatment.<br><br>Control: Symptomatic treatment | Primary:<br>Death, need for hospitalization | Randomized, parallel assignment, open-label |
| 3. Colchicine and Post-COVID-19 Pulmonary Fibrosis | Patients who are confirmed to have COVID-19 clinically, radiologically and PCR<br>Age above 18 years old | Experimental: Colchicine plus Standard treatment<br><br>Control: Standard treatment | Primary:<br>Clinical status, pulmonary fibrosis | Randomized, parallel assignment, Single-masked |
| 4. Double Blind Randomized Clinical Trial of Use of Colchicine Added to Standard Treatment in Hospitalized With Covid-19 | > 18 years.<br><2 weeks from the onset of symptoms.<br>Admitted (with or without pneumonia) and ambulant (with pneumonia demonstrated by X-ray or CT)<br>Microbiologically confirmed infection by SARS-CoV-2 | Experimental: Colchicine plus Standard treatment<br><br>Control: Standard treatment | Primary<br>Proportion of patients who present death, need for mechanical ventilation or respiratory distress | Randomized, parallel assignment, triple-masked |
| 5. Adding Colchicine to Tocilizumab in Patients With Severe COVID-19 Pneumonia. | > 18 years old Severe COVID-19 pneumonia | Experimental: Colchicine plus tocilizumab<br><br>Control: tocilizumab | Primary<br>Rate of invasive mechanical ventilation | Randomized Open Label Trial |
| 6. 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<br><br>Experimental: Colchicine and Naltrexone ("Combined") Arm<br><br>Experimental: Naltrexone-Only Arm<br><br>No Intervention: Standard of Care Arm | Primary: Progression of COVID-19 from "moderate" classification to "severe/critical" | Randomized Open Label Trial |
| 7. 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<br>Clinical diagnosis compatible with COVID-19, moderate to severe | Experimental: Colchicine plus prednisone<br><br>Control: Standard treatment | Primary:<br>Reduction of mortality on day 28 | Randomized Parallel assignment Open label |
| 8. 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.<br>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)<br><br>Experimental 2: Interferon Beta<br><br>Experimental 3: Aspirin (ASA)<br><br>Experimental 4: Rivaroxaban 2.5 mg<br><br>Control: Usual care | Primary:<br>Outpatient trial - hospitalization or death<br><br>Inpatient trial - invasive mechanical ventilation or death | Randomized parallel group factorial Open-label |