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The Potential Role of Colchicine in Reducing Mortality and Mechanical Ventilation Rates in COVID-19 Infection: A Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Colchicine is one of many drugs being repurposed for COVID-19 due to its potential as an anti-inflammatory agent alongside its easy accessibility and oral administration. This study aims to identify the risk reduction in mortality and mechanical ventilation of colchicine-treated COVID-19 patients compared to the standard of care/placebo.

Methods: A systematic search was conducted until December 31, 2021, with keywords including Colchicine, COVID-19, SARS-CoV-2, anti-inflammatory, trials, clinical, mechanical ventilation, death, and mortality. Databases including MEDLINE/PubMed, Scopus, Web of Science, CINAHL Plus, Cochrane, WHO Global Database, and Preprint servers were searched. Using dichotomous data for all values, the risk ratios (RR) were calculated by applying the random-effects model in Review Manager 5.4.

Results: The 12 studies pooled 17,297 participants, with 8,528 patients in the colchicine group and 8,769 in the standard care group. Colchicine treatment led to a statistically significant reduction in the risk of death (RR=0.63, 95% CI=0.48-0.84, P=0.001). Moderately high heterogeneity was present among the included studies (I^2=72%). While insignificant, the risk of mechanical ventilation was decreased by 12% among the colchicine group (RR=0.88, 95% CI=0.64-1.22, P=0.44).

Conclusions: While this meta-analysis finds overall reductions in mortality with colchicine treatment, these findings must be utilized with caution. Placebo-controlled randomized clinical trials are warranted at a large scale to validate the viability of colchicine as an adjuvant treatment for COVID-19. On obtaining more concrete findings, the potential role of colchicine may be better optimized in non-severe patients as well, across in-hospital and outpatient settings.

Keywords: Colchicine; COVID-19; SARS-CoV-2; clinical trials; mortality; adverse outcomes; inflammation.

1. INTRODUCTION

Colchicine is a commonly known anti-inflammatory drug used to treat various conditions, including gout, recurrent pericarditis, and familial Mediterranean fever [1,2]. The drug has recently been utilized for its potential in reducing the risk of cardiovascular events among those with coronary artery disease [3]. Colchicine's mechanism of action includes the chemotaxis of neutrophils, inhibition of the inflammasome signaling, and reduction of the production of cytokines, including interleukin-1-beta [4]. Considering the potential of anti-inflammatory therapies for patients with coronavirus disease 2019 (COVID-19), the use of colchicine in both outpatient and in-hospital patients has been tested to a great extent across randomized clinical trials and observational studies [5]. The purpose of this meta-analysis is to collate solidifying evidence for or against colchicine in reducing mortality and the requirement for mechanical ventilation among patients with COVID-19.

2. METHODS

2.1 Search Strategy and Selection

This meta-analysis was conducted adhering to the PRISMA 2020 statement guidelines (Fig. 1). Databases including MEDLINE/ Pub Med, Scopus, Web of Science, CINAHL Plus, Cochrane, the WHO Global Database, and Preprint servers (i.e., Med Rxiv, Research Square) were utilized. All studies published from December 2019 until December 31, 2021, were included. The following MeSH terms were used by employing a BOOLEAN logic (and/or): colchicine, COVID, SARS-CoV-2, anti-inflammatory, trials, clinical, mechanical ventilation, death, mortality. The reference lists of screened studies were searched as well (umbrella review methodology). All studies were entered into the software Endnote X9 by three reviewers. The final reviewer was present for any disagreements.

2.1.1 Inclusion criteria

Clinical trials and observational studies were included, which comprised an interventional group being treated with Colchicine therapy with control groups receiving either standard care or no treatment.

2.1.2 Exclusion criteria

Case reports, case series with only one group, systematic reviews, meta-analytical studies, and letters were omitted.

2.2 Quality Assessment

For the quality assessment of included studies in this meta-analysis, 7 observational studies and 5 RCTs were assessed using the Newcastle-Ottawa Scale (NOS) and Cochrane's risk of bias 2 (RoB 2) tool respectively. If 10 or more studies reported a common outcome, an assessment of publication bias was conducted using funnel plots.

2.3 Outcomes

The primary outcome to be assessed within the colchicine treatment and control/SoC group was mortality. The secondary outcome was to compare the risk of requiring mechanical ventilation between the two groups.

2.4 Data Analysis

Two investigators extracted the obtained data into a customized and shared spreadsheet for the following variables: author/year, study type, setting, sample size, endpoints, colchicine dosage and regimen, mechanical ventilation outcomes, and death outcomes. The qualitative analysis was conducted and the findings were presented in Table 1. Using a quantitative analytical methodology, and a random-effects model, a meta-analysis was conducted to ascertain the differences in death and mechanical ventilation outcomes among the colchicine treatment and control/SoC groups. The risk ratio was obtained using 95% confidence intervals. The forest plots were presented for the outcomes. P values less than or equal to 0.05 were considered to provide statistical significance. The I^2 index was computed for the outcomes to measure the heterogeneity of the included studies. All data analysis was conducted using Review Manager 5.4 (Cochrane).

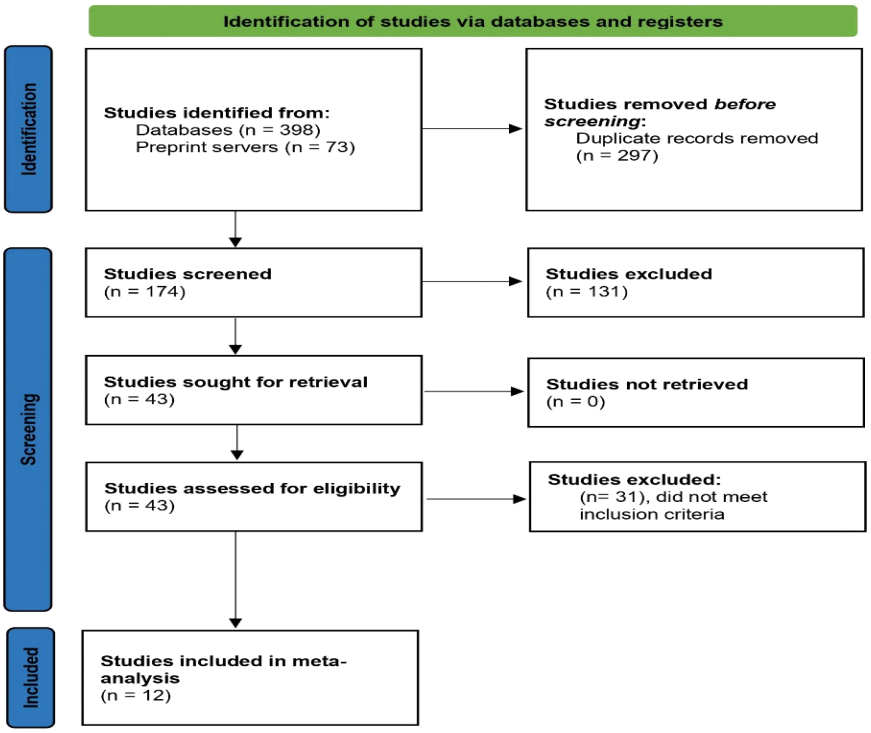

Fig. 1. PRISMA flowchart showing the identification of studies

3. RESULTS

Of the 471 studies initially identified across the databases and preprint servers, 174 studies were screened using abstracts and titles. Of these, 43 studies were sought for retrieval and eligibility. In total, 12 studies were included in the meta-analysis (Fig. 1).

Of the 12 studies included in this analysis, 7 were observational studies, 4 were RCTs, and 1 was a quasi-randomized trial. These studies were all conducted in the inpatient setting, excluding Manenti et al.'s cohort, which was conducted in both the inpatient and outpatient setting, and the COLCORONA trial, which was conducted in a non-hospitalized community-based setting. Our meta-analysis pooled 8,528 patients in the colchicine group and 8,769 in the control/SoC group, yielding a total of 17,297 participants. The characteristics of included studies are listed in Table 1.

All 12 studies reported mortality outcomes as an endpoint of the study, and these were eligible to be included in this meta-analysis. We found that Colchicine treatment led to a statistical reduction in the risk of death in the colchicine group as compared to the control/standard of care group (RR=0.63, 95% CI=0.48-0.84, Z=3.22, P=0.001). There was moderately high heterogeneity present among the included studies despite employing a random-effects model (I^2=72%). A sensitivity analysis was conducted to determine whether the removal of the RECOVERY trial, 2021 (Weight=18.3%) could lead to altered findings. The rerun yielded similar results, with statistically significant associations (RR=0.59, 95% CI=0.46-0.76, Z=4.03, P<0.001), but with a much-lowered heterogeneity (I^2=3.8%) (Fig. 2).

Five of the 12 studies reported group-specific data for the requirement of mechanical ventilation. This analysis found that the risk for mechanical ventilation among the colchicine recipients was decreased as compared to the control/SoC group, albeit with no statistical significance (RR=0.88, 95% CI=0.64-1.22, Z=0.77, P=0.44). In this subset analysis, moderately heterogeneity was present among the included studies (I^2=69%) (Fig. 3).

On visually inspecting the funnel plot, it may be stated that nine of the 12 studies tend to fit the shape of an inverted funnel on the top, with three deviations on the bottom (Lopes et al., 2020; Deftereos et al., 2020; COLORIT, 2021). Based on these findings, it may be inferred that, to some extent, publication bias may have been present in this meta-analysis (Fig. 4).

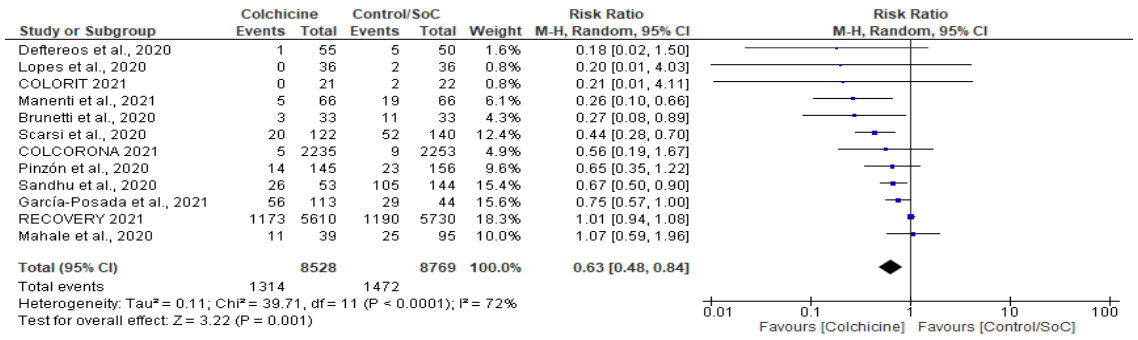

Fig. 2. Forest plot for mortality as the primary endpoint across all 12 included studies (8,528 in the colchicine group versus 8,769 in the control/SoC group)

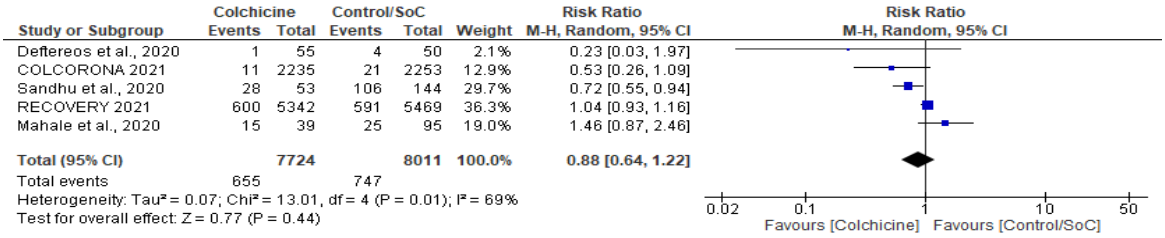

Fig. 3. Forest plot for the requirement of mechanical ventilation across 5 included studies (7,724 in the colchicine group versus 8,011 in the control/SoC group)

Table 1. Characteristics of included studies

Author, year	Study Type	Setting	Sample Size*	Central Endpoints	Colchicine Regimen	Mechanical Ventilation*	Death*
Lopes et al., 20206	RCT	Brazil, Inpatient	36 vs 36	(1) Need for supplemental oxygen, (2) Time of hospitalization, (3) Admission and length of stay in ICU, (4) Death rate	0.5 mg thrice daily for 5 days; then 0.5 mg twice daily for 5 days	NR	0 vs 2
COLCORONA, 20217	RCT, NCT04322682	[Across Brazil, Canada, Greece, South Africa, Spain, and the USA] Non-hospitalized community based	2235 vs 2253	(1) Composite of death, (2) Hospital admission for COVID-19	0.5 mg twice per day for 3 days; then once per day for 27 days	11 vs 21	5 vs 9
GRECCO-19, 20208	RCT, NCT04326790	Greece, Inpatient	55 vs 50	(1) Percentage of participants requiring mechanical ventilation, (2) All-cause mortality, and (3) Number, type, severity, and seriousness of adverse events	1.5-mg loading dose followed by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily for as long as 3 weeks	1 vs 4	1 vs 5
RECOVERY, 2021 [9]	RCT, NCT04381936	UK, Inpatient	5610 vs 5730	(1) 28-day all-cause mortality, (2) Discharge, and (3) Mechanical ventilation	Colchicine twice daily for 10 days or until discharge	600/5342 vs 591/5469	1173 vs 1190
COLORIT 2021 [10]	Quasi-Randomized Trial	Russia, Inpatient	21 vs 22	(1) Clinical state improvement, (2) Degree of lung tissue damage using CT scan, (3) Severity of systemic inflammation (CRP)	1 mg for 1-3 days followed by treatment at a dose of 0.5 mg/day for 14 days	NR	0 vs 2
Pinzón et al., 2020 [11]	Prospective Cohort	Columbia, Inpatient	145 vs 156	(1) Clinical manifestations and (2) Outcomes of patients on treatment	0.5 mg every 12 hours for 7 to 14 days	NR	14 vs 23

Author, year	Study Type	Setting	Sample Size*	Central Endpoints	Colchicine Regimen	Mechanical Ventilation*	Death*
Scarsi et al., 2020 [12]	Prospective Cohort	Italy, Inpatient	122 vs 140	(1) Survival rates and (2) Associations to independent clinical variables	1 mg/day (reduced to 0.5 mg/day, if severe diarrhea	NR	20 vs 52
Brunetti et al., 2020 [13]	Prospective Cohort	USA, Inpatient	33 vs 33	(1) In-hospital death within 28-days and (2) Clinical Improvement on days 14 and 28 versus baseline	Loading dose of 1.2 mg, with a maintenance dose of 0.6 mg twice daily	NR	3 vs 11
Mahale et al., 2020 [14]	Retrospective Cohort	India, Inpatient	39 vs 95	(1) In-hospital mortality, (2) Requirement for mechanical ventilation, and (3) Discharge or present status of the patients	0.5 mg/day for 1 week	15 vs 25	11 vs 25
Manenti et al., 2021 [15]	Retrospective Cohort	Italy, Inpatient, and Outpatient	66 vs 66	(1) Time to death and (2) Clinical prognosis post drug administration	1 mg/day from day 1 up until clinical improvement or up to a maximum of 21 days	NR	5 vs 19
García-Posada et al., 2021 [16]	Retrospective Cohort	Columbia, Inpatient	113 vs 44	(1) Mortality and (2) Adverse outcomes	Standard dose for a period of 20 days	NR	56 vs 29
Sandhu et al., 2020 [17]	Case-Control	USA, Inpatient	53 vs 144	(1) Survival and (2) Need for mechanical ventilation	0.6 mg twice a day for three days and then 0.6 mg once a day for a total of 12 days	28 vs 106	26 vs 105

**Colchicine vs Control/SoC (n), NR: Not reported*

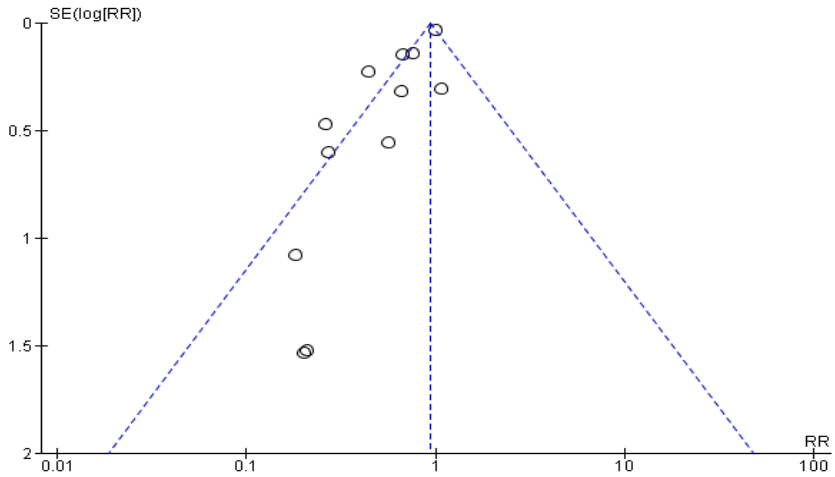

Fig. 4. Funnel plot to assess for publication bias

4. DISCUSSION

Our findings demonstrate a statistically significant reduction in mortality among patients receiving colchicine with a 37% risk reduction compared to the standard of care/placebo group (I^2=72%, p=0.001). To account for high heterogeneity among the included studies, a similar analysis was done after removing the RECOVERY trial, the largest trial contributing to heterogeneity. However, our results were similarly demonstrative of a 41% risk reduction and minimal heterogeneity among included studies (I^2=3.8%, p<0.001). Also, there was a 12% less risk of mechanical ventilation among patients who received colchicine compared to standard of care/placebo. However, these findings were not significant with high levels of heterogeneity (I^2=69%, p=0.44). The lack of significance in reduced mechanical ventilation may be due to a lack of classified severity of infection, probably due to certain patients already having moderate to severe infection. Our funnel plot of included studies suggests a publication bias present in the included studies. In the included studies, no standard dosing regimen and frequency were noted. Colchicine has a narrow therapeutic index with no distinction between toxic and non-toxic doses [18]. The sample represented patients of any severity of COVID-19 infection and the other treatments provided to the patients in the standard of care/placebo group were not considered in these trials.

There has been increased recognition of the cytokine storm syndrome, activating the inflammatory cascade in more severely infected COVID-19 patients. Three distinct phases for systemic hyper inflammation with COVID-19 infection have been identified: 1) early phase, associated with viral replication, 2) pulmonary phase, characterized by respiratory symptoms and activation of adaptive immunity, and 3) hyperinflammatory phase, characterized by systemic production of chemokines and cytokines [19]. Colchicine is known to reduce symptoms among patients with inflammatory responses, which may prevent the occurrence of acute respiratory distress syndrome (ARDS) that contributes to morbidity and mortality of COVID-19 infection [12]. The association of inflammatory response with mortality is strong as there are various implications such as ARDS, distributive shock, myocardial injury, and vascular inflammation [20]. As our findings are strongly suggestive of mortality risk reduction with colchicine treatment, it is pertinent to highlight its potential as a useful agent in COVID-19 infection.

Colchicine is one of many drugs that is being repurposed for COVID-19 due to its modulatory effects on innate immunity and downregulation of inflammatory pathways and the inflammation/thrombosis interface [20]. There have been no major adverse events with colchicine (e.g. gastrointestinal events and myalgias) [21,22]. Other options such as anakinra, tocilizumab, and sarilumab similarly target the inflammatory cascades [23]. However, colchicine has fewer pleiotropic mechanisms with no immunosuppressive effects [24]. It may be expected that the use of colchicine will be beneficial before the inflammatory cascade (e.g. non-hospitalized patients, hospitalized patients

who are not critical). However, there has been no insight into the administration of colchicine before the inflammatory cascade compared with those who are already critical. Therefore, the optimal dosing regimen (dose, duration, and initiation) requires further investigation.

5. CONCLUSION

Our meta-analysis was conducted in 17,297 patients with a significant reduction of mortality among patients receiving colchicine compared to standard of care/placebo (37%). A similar yet insignificant trend of a 12% reduction in mechanical ventilation was observed in the colchicine group. Our study reported insight from double-blinded, placebo-controlled trials, open-label randomized clinical trials, and observational studies. Our subgroup analysis showed a 41% risk reduction when heterogeneity was minimized. To summarize, the use of colchicine as a treatment adjuvant seems promising across all settings of healthcare worldwide, with attention to be paid to dosing regimens in further placebo-controlled trials for optimal efficacy. Finally, our findings must be used with caution as the applicability of colchicine may be subjected to a multitude of contributing factors to adverse outcomes of disease.

6. LIMITATIONS

Certain limitations must be addressed. Many of the studies included in this meta-analysis were observational in nature. In addition, there are many comorbidities and potential confounders that could lead to altered outcomes across the included studies. The data to predict the impact of medications such as colchicine and mortality/ventilatory outcomes are subjected to alter with the different strains of COVID-19 across the world, one of which is the delta variant, which may require healthcare practitioners to account for the risks and benefits of administering anti-inflammatory medications such as colchicine.

7. RECOMMENDATIONS

Given the paucity of data, we recommend considering colchicine as a treatment modality among asymptomatic/mild patients in the clinical trial setting as a measure to collate solidifying evidence of the drug reducing hospitalizations and excess morbidity. Among hospitalized patients, colchicine has strong potential as an adjuvant to other potential therapies. Colchicine is an affordable agent that is administered orally [24]. Such therapy is especially promising in resource-constrained settings such as low- and middle-income countries. Our findings incorporate current evidence obtained from two adequately designed randomized placebo-controlled trials as well as three randomized clinical trials and eight observational studies. We suggest the consideration of further exploration by early vs. late onset presentation in hospital settings as colchicine may not perform as well when the patients are severe. Colchicine also serves as a strong candidate for outpatient settings as an optimal setting. Essentially, it is pertinent to consider standardizing doses in ongoing and future clinical trials to optimize its efficacy.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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