Colchicine use might be associated with lower mortality in COVID-19 patients: A meta-analysis

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Conflict of Interest

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Dear Editor,

We read with great interest the recently published meta-analysis by Aimo et al. in the European Journal of Clinical Investigation. The analysis encompassing over 5000 patients’ data revealed a significant reduction in adverse cardiovascular events in patients with chronic coronary syndrome receiving colchicine vs. control. These results are promising and suggest a potential role for colchicine in treating thrombogenic conditions. Colchicine is an ancient anti-inflammatory agent with an established safety profile. It inhibits various inflammatory pathways, including neutrophils adhesion, inflammasome activation, microtubule formation, neutrophil extracellular traps (NETs) essential in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogenesis. Coronavirus disease 2019 (COVID-19) is thought to be associated with an exaggerated inflammatory response and thrombogenicity. Thus, studies tested repurposing this medication in the treatment of COVID-19 and yielded promising results.
We performed a rapid systematic review and meta-analysis to examine the mortality effect in patients with COVID-19 receiving colchicine vs. control. We followed our previously published protocol; however, we decided to accept observational studies for this rapid review due to data scarcity. We comprehensively searched PubMed, EMBASE, Google Scholar since their inception till 25/03/2021 for observational or controlled studies that reported mortality as an outcome. On screening, we limited the inclusion to articles written in the English language. We generated the mortality odds ratio with a 95% confidence interval utilizing the random effect models. We performed a subgroup analysis to examine the effect in hospitalized patients, also another analysis limited to peer-reviewed publications. We generated a funnel plot to ascertain publication bias, and we performed a sensitivity analysis to check the results' consistency. MetaXL software was used for statistical analysis.

Nine studies comprising 5522 patients met our inclusion criteria comparing colchicine with control in the treatment of COVID-19. Hence, they were included in the quantitative analysis (Table 1). Three of the studies were randomized controlled trials, one was quasi-experimental, and the remaining were observational. The only included non-peer-reviewed publication by Tardif et al. accounted for the majority of included cases (4488 patients) and consisted of non-hospitalized patients. Patients in the intervention group received colchicine in different dosage regimens and were followed up to 30 days. All studies revealed numerically reduced mortality associated with colchicine use, albeit statistically insignificant in a few instances. The quality of most included studies was moderate. Our meta-analysis revealed significantly lower mortality in the colchicine group (OR 0.35, 95% CI 0.25–0.48, I² 0%) (Figure 1). A subgroup analysis limited to 902 hospitalized patients of which 433 received colchicine (OR 0.35, 95% CI 0.25–0.50, I² 0%) and to peer-reviewed publications including total of 1034 patients (OR 0.33, 95% CI 0.24–0.47, I² 0%) revealed similarly lower mortality in the colchicine group. The exclusion of constituent studies did not affect the results' consistency. There was no evidence of heterogeneity as depicted an I² of 0%. Moreover, sensitivity analysis, including two studies that we have excluded (studied colchicine in a poorly controlled manner), revealed a consistent effect on mortality (OR 0.43, 95% CI 0.31–0.58, I² 13%). The funnel plot revealed asymmetry suggesting a possibility of a publication bias.

Our analysis revealed lower mortality associated with colchicine use. Significant immunosuppressed status and predisposition to infections seen with other immunomodulators are not commonly seen with colchicine. This may have contributed to the mortality benefit seen with colchicine and not with many other immunomodulators. Moreover, endothelial dysfunction and vascular inflammation play an integral role in SARS-CoV-2 pathogenesis. This has led to a significant risk of thrombosis in this patient cohort.
autopsy study by Wichmann et al., deep venous thromboses were found in 58%, and pulmonary embolism was the direct cause of mortality in a third of COVID-19 patients.\textsuperscript{16} Deftereos and Sandhu et al. found a lower rise of d-dimers in COVID-19 patients receiving colchicine compared to the standard of care.\textsuperscript{5,10} These observations may suggest a potential role of colchicine in mitigating COVID-19 thrombogenicity, thereby prevent fatal thrombotic events in COVID-19 patients. Nonetheless, d dimers reduction might be due to the anti-inflammatory properties of colchicine and may not necessarily correlate with thrombotic events. To further explore this effect, prospective related studies should account for venous and arterial thrombotic events as secondary outcomes and correct for these when ascertaining mortality outcomes.

Our review has limitations, including the observational nature of the majority of the included studies, varying severity of included patients, varying follow-up durations, different dosages and durations of colchicine used in the individual studies, mortality was a secondary outcome in most studies, and the inability to rule out a publication bias. Moreover, the large reliance on the preprint of Tardiff et al.’s study is another limitation. All these may have affected the analysis conclusion. Nonetheless, the review encompassed a large number of patients, and the effect was consistent across constituent studies.

In summary, results from this meta-analysis suggest lower mortality in COVID-19 patients treated with colchicine. Colchicine is a low-cost, widely available drug with a known safety profile. Thus, it may play a fundamental role in preventing COVID-19 associated dysregulated inflammatory response and, perhaps, its related thrombogenicity without causing significant immunosuppression. These findings are to be further supported by the results of ongoing RCTs.

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| Study author (country) | Design | Median age (male%) | Patient setting | Intervention | Follow-up duration | Primary outcomes | Mechanical ventilation n/N (%) | Mortality n/N (%) |
|------------------------|--------|--------------------|-----------------|--------------|--------------------|------------------|--------------------------------|-----------------|
| Deftereos et al. 2020 (Greece) | RCT    | 63 (56.4%)/65 (60%) | Inpatient       | Colchicine 1.5 mg × 1 dose > 0.5 mg after 60 min > maintenance of 0.5 mg BID up to 3 weeks | Hospital discharge or up to 21 days | 1-Time to deterioration. 2- Maximum high-sensitivity cardiac troponin level 3-Time for C-reactive protein to reach more than 3 times the upper reference limit. | Colchicine 1/55 (1.8%) Control 5/50 (10%) | Colchicine 1/55 (1.8%) Control 4/50 (8%) |
| Scarsi et al. 2020 (Italy) | Prospective cohort study | 69.3 (63%)/70.5 (64%) | Inpatient       | Colchicine 1mg OD, reduced to 0.5 mg/day if severe diarrhea (duration NS) | Recruitment March 5-April 5, 2020 and patients followed till April 16 The study reported 21 days survival. | Survival rate | NS | Colchicine 20/122 (16%) Control 52/140 (37.1%) |
| Sandhu et al. 2020 10 | Case Control Study | 70 (64.2%)/65 (55.6%) | Inpatient       | Colchicine 0.6 mg BID × 3 days > 0.6 mg OD up to | Follow-up period NS | 1-Hospitalization days 2-Mortality | Colchicine 28/53 (52.8%) | Colchicine 26/53 (49%) |
| Study                        | Design          | Country     | Inpatient/Outpatient | Colchicine Treatment | Follow-up Duration | Primary Outcomes                                                                 |
|------------------------------|-----------------|-------------|----------------------|----------------------|--------------------|----------------------------------------------------------------------------------|
| Brunetti et al 2020          | Prospective cohort study | (United States) | Inpatient (severe COVID-19) | Colchicine 1.2 mg × 1 dose > Maintenance 0.6 mg BID (duration NS) | Up to 28 days | In-hospital mortality within 28 days.                                                |
| Lopes et al 2020             | RCT             | (Brazil)    | Inpatient (moderate to severe COVID-19) | Colchicine 0.5 mg TID × 5 days > 0.5 BID × 5 days. | -Recruitment April 11- July 6, 2020 (follow-up period NS) | 1-Time to need for supplemental oxygen; 2-Time to hospitalization. 3-Need for admission and length of stay in ICU 4-Death rate |
| Tardif et al 2020            | RCT             | (Canada)    | Outpatient (mild to moderate COVID-19) | 0.5 mg BID × 3 days > OD × 27 days | Up to 30 days | Composite of death or hospitalization due to COVID-19 infection                   |
| Manenti et al. 2021          | Retrospective cohort | (Italy)     | Inpatient and outpatient | 1 mg OD till clinical improvement (up to 21 days) | Up to 21 days | 1-Differences in mortality 2- Clinical improvement 3- Inflammatory markers |

| Control 106/144 (73.6%)     | Control 105/144 (72.9%)  |
| 3-Mechanical ventilation    | 4-Discharge rate         |
| NS                          | 3/33 (9.1%)              |
| NS                          | 0/36 (0%)                |
| NS                          | 0.5/2235 (0.5%)          |
| NS                          | 5/2235 (0.2%)            |
| NS                          | 5/66 (7.5%)              |

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| Study | Design | Setting | Inpatient | Dose and duration | Follow-up period | Mortality comparison | Mortality  |
|-------|--------|---------|-----------|-------------------|-----------------|---------------------|-----------|
| García-Posada et al\(^{12}\) (Columbia) | Retrospective cohort | Overall, NS (moderate to severe COVID-19), NS for each group separately | Dose and duration NS | Follow-up period NS | Differences in mortality between treatment groups | NS |
| COLORIT 2021\(^{2}\) (Russia) | Quasi-randomized trial | 61.9 (66.7%) / 59.9 (72.7%) | 1 mg OD ×1-3 days > 0.5 mg OD (up to 14 days) | Up to discharge or 12 days | Changes in the SHOCS-COVID score | NS |

**Figure 1:** Forest plot summarizing the pooled mortality odds in COVID-19 patients receiving colchicine compared to controls.

NS=Non specified, OD= once daily, BID= twice daily, > = followed by, COVID-19= coronavirus disease 2019, SHOCS-COVID= Symptomatic Hospital and Outpatient Clinical Scale for COVID-19, RCT= randomized clinical trial
The diagram shows a forest plot with odds ratios (OR) and 95% confidence intervals (CI) for different studies. The studies included are:
- Deftereos 2020
- Scarsi 2020
- Sandhu 2020
- Brunetti 2020
- Lopes 2020
- Colorit 2021
- García-Posada 2021
- Manenti 2021
- Tardif 2021

The overall effect is calculated with Q=3.90, p=0.87, I²=0%.

The ORs and their weights are as follows:

- Deftereos 2020: OR = 0.21 (0.02, 1.97), Weight = 2.1
- Scarsi 2020: OR = 0.33 (0.18, 0.60), Weight = 29.4
- Sandhu 2020: OR = 0.36 (0.19, 0.69), Weight = 24.0
- Brunetti 2020: OR = 0.20 (0.05, 0.80), Weight = 5.3
- Lopes 2020: OR = 0.19 (0.01, 4.08), Weight = 1.1
- Colorit 2021: OR = 0.19 (0.01, 4.22), Weight = 1.1
- García-Posada 2021: OR = 0.51 (0.25, 1.05), Weight = 19.5
- Manenti 2021: OR = 0.20 (0.07, 0.58), Weight = 9.2
- Tardif 2021: OR = 0.56 (0.19, 1.67), Weight = 8.5

Overall OR: OR = 0.35 (0.25, 0.48), Weight = 100.0