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Correspondence

Impact of colchicine on mortality in patients with COVID-19: A meta-analysis

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has urged clinicians to utilize traditional and novel drugs in a struggle against the virus and its complications.[1] Inflammatory over-reaction and cytokine storm are postulated to play a deleterious role in COVID-19 affecting not only the pulmonary but the cardiovascular system as well.[2] As expected, laboratory evidence of myocardial injury has been reported to be adversely related to short-term mortality in COVID-19 patients and therefore could be utilized in patient risk stratification.[3] However, while a wide range of myocardial injury patterns in COVID-19 patients has been reported (e.g. supply-demand imbalance, acute coronary syndromes, microvascular thrombosis, stress cardiomyopathy, inflammation, myocarditis), it is not yet clear (a) whether there is a prominent mechanism and (b) if and which long-term consequences exist.[4,5] In this context, colchicine – along with other drugs with anti-inflammatory properties – has been proposed to have a beneficial effect in terms of clinical outcomes COVID-19.[6,7] Colchicine's potential COVID-19 is speculated to be mainly mediated by its inhibitory effect on the activation, destabilization, and degradation of inflammasomes, while a potential antiviral effect could be exerted through microtubule polymerization inhibition.[1,8] Published studies suggest a clinical benefit of colchicine therapy including mortality. We aimed to provide a quantitative assessment of the effect of colchicine on mortality in patients with COVID-19.

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines. On November 6th 2020, we searched PubMed, Medrxiv.org using the following query: "colchicine AND ("COVID" OR "COVID-19" OR "SARS-COV-2" OR "CORONAVIRUS DISEASE" OR "CORONAVIRUS DISEASE-19" OR "CORONOVIRUS DISEASE" OR "CORONOVIRUS DISEASE 19" OR "CORONOVIRUS" OR "CORONAVIRUS")", further we searched researchsquare.com using the query "colchicine". Eligible studies had to satisfy the following criteria: 1) study population including patients with COVID-19, 2) studies evaluating the effect of colchicine on clinical outcomes, 3) written in English. The primary outcome of interest was the absolute number of patients who died/survived in each arm (colchicine plus standard-of-care versus standard-of-care alone) at the end of the follow up period. For pooling the primary outcome of interest, we performed a meta-analysis based on the logarithmic transformation (to allow for a more symmetric scale) of odds ratios and

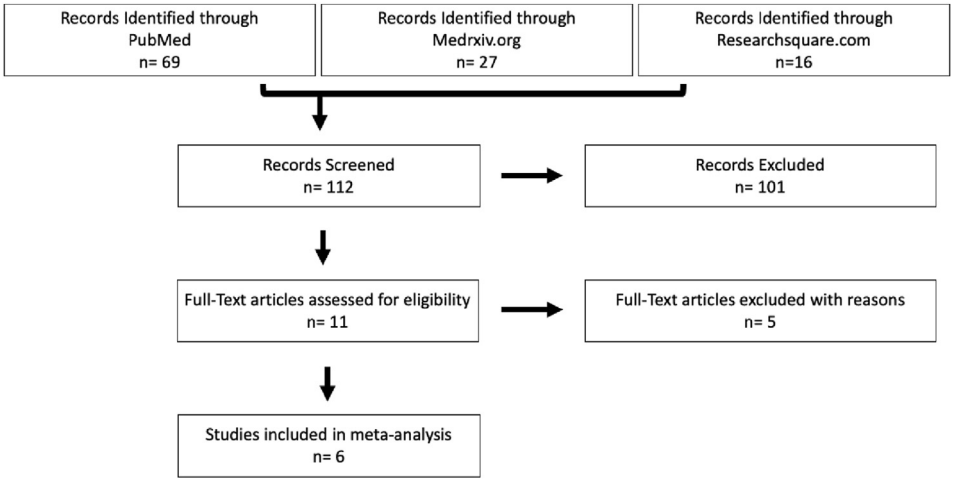

Fig. 1. Flow diagram of search and selection strategy.

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Table
Studies evaluating impact of colchicine on mortality in patients with COVID-19.

Study	Country	Colchicine/Control Group					
		Patients, N	Age (years)	Males (%)	DM (%)	HTN (%)	Known CAD (%)
Studies Published after Peer-Review							
Deftereos et al.[7]	Greece	55/50	63/65	56/60	16/24	40/50	16/10
Scarsi et al.[9]	Italy	122/140	10/14	64/64		––––– 64/74*–––––	
Brunetti et al.[10]	USA	33/33	62/64	64/67	21/21	61/36	12/6#
Sandhu et al.[11]	USA	34/78	68/66	62/51	32/51	53/72	6/8
Pre-prints							
Lopes et al.[12]	Brazil	17/18	48/54	53/28	29/33	––––– 47/33§–––––	
Pinzón et al.[13]	Colombia	145/156	NR	NR	NR	NR	NR
Overall		406/475					

CAD: Coronary Artery Disease, DM = Diabetes Mellitus, HTN= Hypertension, NR=Not Reported.
* Reported as any cardiovascular comorbidity.
§ Reported as cardiovascular diseases.
# Reported as previous myocardial infarction.

their corresponding 95% confidence intervals (CI). Because of the expected effect size dispersion between studies due to differences in interventions in the standard-of-care arm and variations in disease severity, a random effects (DerSimonian-Laird) model was adopted. Heterogeneity was assessed using I^2, with values between 50% and 90% representing substantial heterogeneity. All analyses were performed using STATA/MP version 16.0, Texas, USA software.

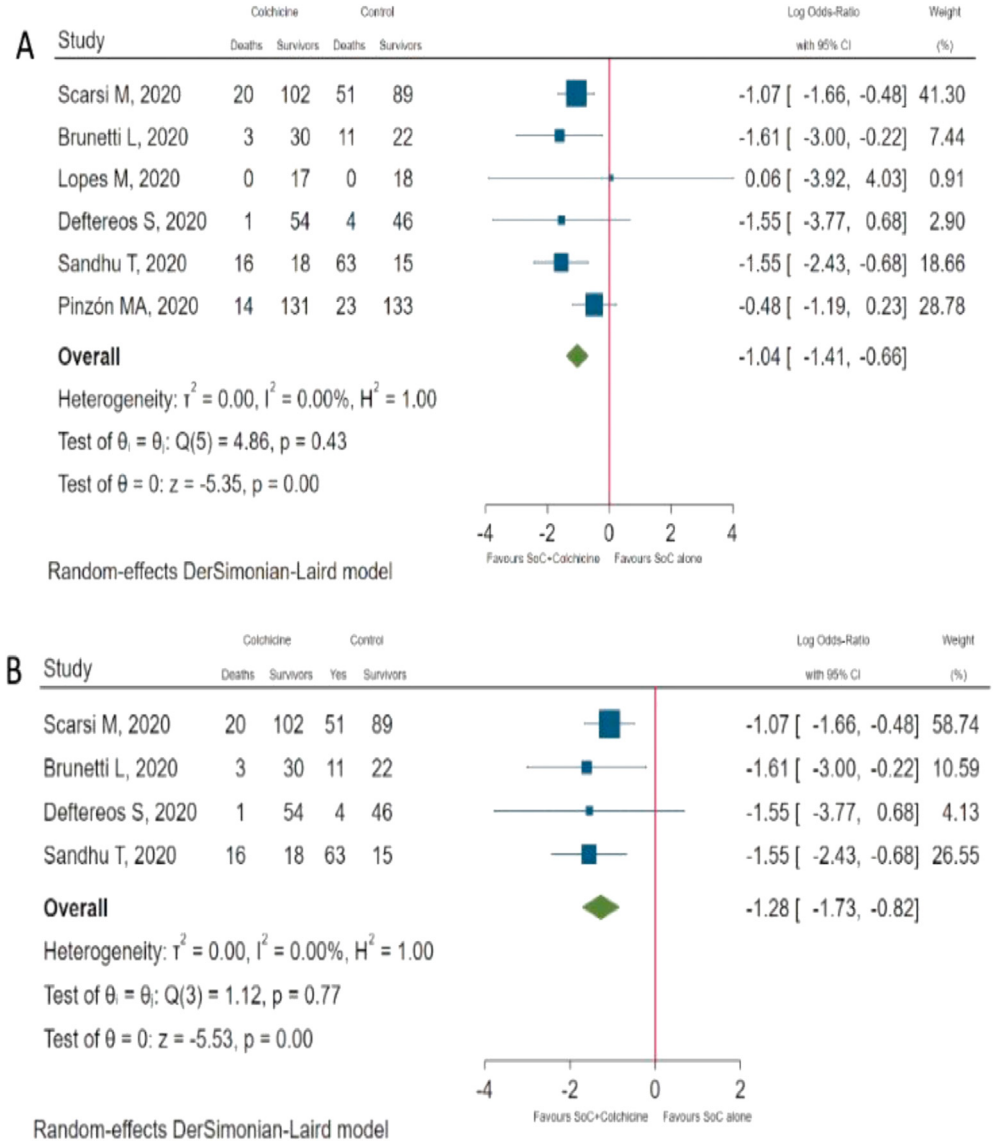

Fig. 2. Log-odds ratios for mortality between colchicine on top of standard-of-care and standard-of-care. Negative values suggest superiority of colchicine. (A) for all studies (peer-reviewed and preprints) (B) for only peer-reviewed studies.

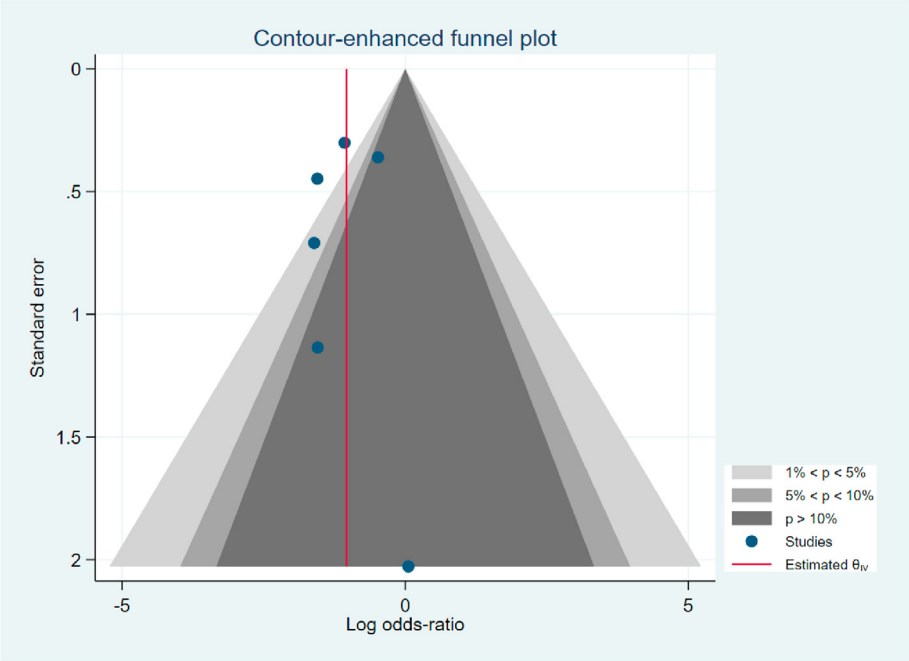

Fig. 3. Contour-enhanced funnel plot, centered at 0.

A total of 112 articles were screened, 106 were excluded since they did not meet inclusion criteria (Figure 1). A total of six studies, four published after peer-review[7,9-11] and two pre-prints[12,13] including 881 patients with confirmed COVID-19 were evaluated, 406 of whom were treated with colchicine in addition to standard-of-care (Table). To address one study[12] that reported no events in both arms, a value of 0.5 was added to the respective cells.[14] The pooled odds ratio for mortality was 0.35 (95% confidence interval 0.24-0.52) and a similar significant trend was observed in terms of the risk difference (Figure 2A). The analysis was also conducted including only peer-reviewed articles (i.e. excluding pre-prints) and the pooled odds ratio for mortality was 0.28 (95% confidence interval 0.18-0.44) (Figure 2B). Heterogeneity was low in the odds ratio analysis (Figure 2). Further, a contour-enhanced funnel plot, centered at 0 is provided in Figure 3. Although the small number of studies does not allow for safe conclusions, the plot does not suggest significant publication bias.

The findings of the present meta-analysis suggest a definite signal of benefit of mortality with the addition of colchicine in patients with COVID-19. The small number of studies and the relatively small absolute number of patients included certainly warrant caution as to any definitive conclusion, but this signal cannot be ignored, considering the scarcity of effective treatments for COVID-19. The need for randomized controlled trials (RCTs) involving adequately numbered populations has been well stressed during this pandemic. On the other hand, a year after the first COVID-19 cases, current standards-of-care is not based upon such evidence. Study limitations include the lack of patient-level data which did not allow to assess or control for possible differences in baseline or procedural variables.

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References

1. Deftereos SG, Siasos G, Giannopoulos G, et al. The GReek study in the Effects of Colchicine in COvid-19 complications prevention (GRECCO-19 study): rationale and study design. *Hellenic J Cardiol*. April 2020. https://doi.org/10.1016/j.hjc.2020.03.002.
2. Amirfakhryan H, Safari F. Outbreak of SARS-CoV2: Pathogenesis of infection and cardiovascular involvement. *Hellenic J Cardiol*. June 2020. https://doi.org/10.1016/j.hjc.2020.05.007.
3. Sanz-Sánchez J, Vrachatis DA, Reimers B, et al. Impact of myocardial injury on mortality in patients with COVID-19: a meta-analysis. *Hellenic J Cardiol*. August 2020. https://doi.org/10.1016/j.hjc.2020.07.004.
4. Vrachatis DA, Giotaki SG, Giannopoulos G. COVID-19 myocardial injury: We have much more to discover. *Int J Cardiol*. 2020;314:96. https://doi.org/10.1016/j.ijcard.2020.05.003.
5. Frangogiannis NG. The significance of COVID-19-associated myocardial injury: how overinterpretation of scientific findings can fuel media sensationalism and spread misinformation. *Eur Heart J*. 2020;41(39). https://doi.org/10.1093/eurheartj/ehaa727.
6. Deftereos S, Giannopoulos G, Vrachatis DA, et al. Colchicine as a potent anti-inflammatory treatment in COVID-19: can we teach an old dog new tricks? *Eur Hear journal Cardiovasc Pharmacother*. 2020;(6):255. https://doi.org/10.1093/ehjcvp/pvaa033.
7. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. *JAMA Netw open*. 2020;3(6), e2013136. https://doi.org/10.1001/jamanetworkopen.2020.13136.
8. Schlesinger N, Firestein BL, Brunetti L. Colchicine in COVID-19: an Old Drug, New Use. *Curr Pharmacol Reports*. 2020;6(4):137–145. https://doi.org/10.1007/s40495-020-00225-6.
9. Scarsi M, Piantoni S, Colombo E, et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. *Ann Rheum Dis*. 2020;79(10):1286–1289. https://doi.org/10.1136/annrheumdis-2020-217712.
10. Brunetti L, Diawara O, Tsai A, et al. Colchicine to Weather the Cytokine Storm in Hospitalized Patients with COVID-19. *J Clin Med*. 2020;9(9):2961. https://doi.org/10.3390/jcm9092961.
11. Sandhu T, Tieng A, Chilimuri S, Franchin G. A Case Control Study to Evaluate the Impact of Colchicine on Patients Admitted to the Hospital with Moderate to

Severe COVID-19 Infection. *Can J Infect Dis Med Microbiol = J Can des Mal Infect la Microbiol medicale*. 2020;2020:8865954. https://doi.org/10.1155/2020/8865954.

12. Lopes MIF, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. *medRxiv*. January 2020. https://doi.org/10.1101/2020.08.06.20169573, 2020.08.06.20169573.
13. Alejandro Pinzón M, Medellin Doris Cardona Arango C, Felipe Betancur J, Arias Arias C, Javier Muñoz B, Felipe Llano Clínica Medellín Pablo Montoya J. *Clinical Outcome of Patients with COVID-19 Pneumonia Treated with Corticosteroids and Colchicine in Colombia*. October 2020. https://doi.org/10.21203/rs.3.rs-94922/v1.
14. Bradburn MJ, Deeks JJ, Berlin JA, Localio AR. Much ado about nothing: A comparison of the performance of meta-analytical methods with rare events. *Stat Med*. 2007;26(1):53–77. https://doi.org/10.1002/sim.2528.

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