European Review for Medical and Pharmacological Sciences 2021; 25: 7151-7161

Can we still consider treatment with colchicine effective in SARS-COV-2 infection? Systematic review, meta-analysis, and trial sequential analysis

E. DE-MIGUEL-BALSA[1,2], R. ESTEVAN-ORTEGA[3], M.-T. SEMPERE-SELVA[2,4], J. LATOUR-PÉREZ[1], A. BAEZA-ROMÁN[1], A. MOYA-MARTINEZ[5], J.-M. RAMOS-RINCON[2,6]

[1]Intensive Care Unit, Elche General University Hospital - Foundation for the Promotion of Health and Biomedical Research of the Valencia Region (FISABIO), Elche, Alicante, Spain
[2]Department of Clinical Medicine, Miguel Hernández University of Elche, Spain
[3]School of Pharmacy, Miguel Hernández University of Elche, Spain
[4]Emergency Department. Short-stay Unit. Elche General University Hospital - Foundation for the Promotion of Health and Biomedical Research of the Valencia Region (FISABIO), Elche, Alicante, Spain
[5]Biostatistics Unit, General University Hospital of Elche, Elche-FISABIO, Alicante, Spain; Center for Operational Research, Miguel Hernández University of Elche, Elche, Alicante, Spain
[6]Department of Internal Medicine, Alicante General University Hospital - Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain

Abstract. – OBJECTIVE: To assess the effectiveness of colchicine, compared with standard of care, for reducing mortality, admission to intensive care, and use of mechanical ventilation.

MATERIALS AND METHODS: We performed a systematic review, meta-analysis, and sequential trial analysis. The terms (SARS-CoV-2 OR COVID-19 OR coronavirus) AND (colchicine) were searched in MEDLINE, Scopus, Embase, Cochrane Central Register of Controlled Trials, and preprint repositories (February 2020 to April 2021, extended to June 2021). Risk of bias for randomised controlled trials and observational studies were assessed using the tools RoB 2.0 and ROBINS-I, respectively. We performed subgroup analyses based on study design and sensitivity analyses based on time of colchicine administration.

RESULTS: We included six observational studies (1329 patients) and five clinical trials (16,048 patients). All studies but one were conducted in the hospital setting. Colchicine treatment was not associated with a significant decrease in mortality (RR 0.93, 95% CI 0.87 to 1; p=0.06, I^2=72%) with a significant subgroup effect (p<0.001) depending on the design of the studies. The drug was effective in observational studies (RR 0.57, 95% CI 0.46 to 0.70, p<0.001, I^2=50%) but not in clinical trials (RR 0.99, 95% CI 0.92 to 1.07, p=0.89, I^2=21%). The effect of colchicine on intensive care admissions and the need for mechanical ventilation could not be confirmed. Trial sequential boundaries for cumulative meta-analyses of randomised controlled trials suggested no significant effect on mortality (p=0.182) beyond the optimal information size (13,107 patients).

CONCLUSIONS: Our results suggest that colchicine treatment has no effect on mortality in hospitalised patients with SARS-CoV-2 infection, and that no further confirmatory clinical trials are needed owing to futility.

Key Words:
COVID-19, Colchicine, Mortality, Systematic review, Meta-analysis, Trial sequential analysis, Futility.

Introduction

The COVID-19 pandemic has entailed 194 million known infections and over 4.15 million deaths worldwide (25 July 2021)[1]. Mortality is high among patients requiring hospitalisation, especially older patients[2,3]. As SARS-CoV-2 infection results in positive regulation of cytokines ("cytokine storm")[4], treatment strategies have included different cytokine-targeted drugs. Steroids are recommended for controlling the immune response in

Corresponding Author: Eva de-Miguel-Balsa, MD; e-mail: eva.miguelb@umh.es

patients with hypoxemia who require oxygen therapy and have become the standard of treatment for hospitalised patients[5]. Tocilizumab (monoclonal antibody directed against the Il-6 receptor) is the most widely used drug for controlling the cytokine storm[6]. Other drugs used for the same purpose are anakinra (IL-1 antagonist), baricitinib and tofacitinib, (Janus kinase inhibitors)[7,8].

Colchicine is an alkaloid obtained from the plant *Colchicum autumnale*. It reduces leukocyte extravasation, leukocyte chemotaxis and TNF-alpha receptor expression on monocytes and endothelial cells, and many researchers have assessed the potential of this drug for treating SARS-CoV infection. Meta-analyses of the initial studies produced favourable results but were limited by sample size and by the quality of the included studies[9-12]. More studies have since been published[13,14] but including them in re-analyses could lead to false positive estimates due to cumulated type 1-error risk[15].

The aim of this systematic review and meta-analysis is to determine whether treatment with colchicine reduces mortality, admission to the intensive care unit (ICU), and use of invasive mechanical ventilation (IMV) in COVID-19 patients; and to determine the limits of sequential significance and the optimal information size (OIS) required.

Materials and Methods

Information Sources and Search Strategy

This systematic review was performed in accordance with PRISMA guidelines[16]. A systematised search strategy was designed to recover articles from PubMed (MEDLINE), Scopus, Embase, Clinicaltrials.gov, and the Cochrane Central Register of Controlled Trials; and unpublished studies from preprint repositories (medRxiv). The last search was undertaken in April 2021. Afterwards, the registered studies were followed up until June 2021. Our search strategy is presented in **Appendix 1**.

Study Selection

Published or forthcoming studies written in English, Spanish or Italian were selected based on the following criteria: (1) Population: adults diagnosed with COVID-19 by PCR (polymerase chain reaction), antigen detection or clinical criteria since December 2019; (2) Intervention: treatment with colchicine; (3) Comparator: standard of care consisting of the prescribed treatment for SARS-CoV-2 infection, which has varied between the successive waves of the pandemic as the scientific evidence has been updated. (4) Outcomes: 28-day all-cause mortality, ICU admission and use of IMV; (5) Study design: observational studies and randomised clinical trials providing data for a 2 × 2 table (exposed/not exposed to treatment vs presence/absence of the outcome under consideration).

In the first stage of screening, two researchers (REO and MTSS) independently screened the titles and abstracts of the recovered records, classifying as potentially eligible all those that mentioned both COVID-19 and colchicine. After retrieving the full text of all potentially eligible papers, the same two researchers independently reviewed each article, selecting those that met the inclusion criteria. Disagreements were resolved by consensus.

Data Extraction and Collection

Two researchers (REO and MTSS) independently extracted and summarised the following data from each included article: first author, country of study, language, study design, sample size, treatment with steroids, hospital admission, mortality, ICU admission, and use of IMV. A third author (JMRR) checked the data.

Risk of Bias of Included Studies

The risk of bias of the studies included in the meta-analysis was evaluated with the Cochrane bias assessment tools RoB-2[17] and ROBINS-I[18] for classification into low, moderate, serious, or critical risk of bias. This process was carried out in duplicate, and divergences were resolved by consensus.

Analysis of Outcomes

We summarised the characteristics and results of the included observational studies[14,19-23] and randomised clinical trials[13,24-27] (Tables I-II). A quantitative synthesis was performed for the outcomes mortality, ICU admission, and use of IMV, where data were available. Relative risks (RR) were calculated together with their confidence intervals (95% CI) using both a random and fixed effects models, considering within-study variability (due to sampling) and between-study variability (differences in context, population, or dose).

In the analysis of mortality, we performed a subgroup study to estimate the effect of study design on the results.

Table I. Characteristics of randomised clinical trials.

Study ID	Country	Colchicine regimen	Patients included	Comparison	Concomitant treatment	Steroid treatment	Mortality	IMV	ICU Admission
Deftereos et al, 2020	Greece	1.5-2 mg loading dose then 0.5 mg maintenance dose 2×/day	105 hospitalized patients from 16 hospitals	Optimal medical treatment (April 2020) according to local requirements	Chloroquine or hydroxychloroquine 98%; Azithromycin 92.4%; Lopinavir/ritonavir 25.5-38%; Tocilizumab 2-4%.	No	Colchicine: 1/55; Control: 7/50	Colchicine: 1/55; Control: 5/50	Not reported
Tardif et al, 2021	Canada; USA; Spain; Brazil.	0.5 mg 2×/day for 3 days; 0.5 mg/day up to 27 days	4488 high-risk outpatients	Placebo	Not reported	No	Colchicine: 5/2235; Control: 9/2253	Colchicine: 10/2235; Control: 20/2253	Not reported
Lopes et al, 2021	Brazil	15 mg/day for 5 days, then 1 mg/day for next 5 days	72 moderate to severe hospitalised patients	Standard of care	Azithromycin; Hydroxychloroquine; Unfractionated heparin.	Yes: 65-70% in both arms	Colchicine: 0/36; Control: 2/36	Not reported	Colchicine: 2/36; Control: 4/36
Horby et al, 2021	UK (177 of 181 hospitals); Indonesia; Nepal.	1 mg followed by 500 mcg 12 hours later, then 500 mcg 2×/day for 10 days or until discharge	11340 hospitalised patients	Standard of care	One of the other available Recovery treatment arms at different stages: Lopinavir/ritonavir; Low-dose corticosteroid; Hydroxychloroquine; Azithromycin; Convalescent plasma; Tocilizumab; Anakinra.	Yes: 95% in both arms	Colchicine 1173/5610; Control: 1190/5730	Colchicine: 268 /5610 Control: 261/5730	Not reported
Mareev et al. 2021	Russia	1 mg colchicine during the first 1-3 days, then 0.5 mg/day	43 hospitalised patients	Standard of care	Two other biological drugs were studied: Secukinumab; Ruxolitinib.	Yes: 10% in colchicine group only	Colchicine: 0/21; Control: 2/22	Not reported	Not reported

IMV: invasive mechanical ventilation; ICU: intensive care unit.

Table II. Characteristics of observational studies.

Study ID	Design	Country	Colchicine regimen	Patients included	Concomitant treatment	Steroid treatment	Mortality	IMV	ICU Admission
Scarsi et al, 2020	Single-centre cohort study	Italy	1 mg/day	262 hospitalised patients	Dexamethasone; Hydroxychloroquine; Lopinavir/Ritonavir.	Yes: Colchicine 58%; Control 32%	Colchicine: 20/122; Control: 52/140	Not reported	Not reported
Brunetti et al, 2020	Single-centre propensity score-matched cohort study Matched patients:	USA	1.2 mg then 0,6 mg 2×/day	303 hospitalised patients	Hydroxychloroquine; Azithromycin; Remdesivir; Tocilizumab.	No Control 2/33	Unmatched patients: Colchicine: 4/41;	Control: 58/262 Colchicine 1/33;	Not reported
Sandhu et al, 2020	Case-control study	USA	0.6 mg 2×/day for 3 days then 0.6 mg/day for 12 days.	254 hospitalised patients	Hydroxychloroquine; Enoxaparin; Apixaban Rivaroxaban;Warfarin; Heparin; Oseltamivir.	Yes: Colchicine; 55.9%; Control 60.3%	Colchicine 26/53; Control 105/144	Colchicine 28/53; Control 106/144	Not reported
Mahale et al, 2020	Observational retrospective study	India	Not reported	134 hospitalised patients	Hydroxychloroquine; Etoricoxib; Tocilizumab.	Yes	Colchicine 11/39; Control 29/95	Colchicine 15/39; Control 25/95	Colchicine 31/39; Control:38/95
Pinzón et al, 2021	Cross-sectional study	Colombia	0 5 mg 2×/day for 7 to 14 days.	301 hospitalised patients with pneumonia	Hydroxychloroquine; Ritonavir/lopinavir; Ceftriaxone; Azithromycin; Tocilizumab.	Yes: 79.7% included patients	Colchicine: 14/145; Control: 23/156	Not reported	Not reported
Manenti et al, 2021	Observational retrospective study	Italy	1 mg/day from day 1 until clinical improvement or up to 21 days.	141 hospitalised patients with pneumonia (CT scan) or outpatients	Hydroxychloroquine; Tocilizumab; Ritonavir or Cobicistat/Lopinavir.	Yes: Colchicine 24.3%; Control 12.7%	Colchicine 7.5%; Control 28.5%	Not reported	Not reported

IMV: invasive mechanical ventilation; ICU: intensive care unit.

Heterogeneity of the included studies was evaluated by calculating the I^2 statistic with its 95% confidence interval. I^2 values above 50% were considered to represent heterogeneous data. The risk of publication bias and/or small studies effect was assessed using the funnel plot and Egger's test. Trial sequential analysis was performed with the O'Brien-Fleming alpha-spending function for estimating group sequential boundaries[28].

The statistical analysis was carried out with Review Manager 5.4 and TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research).

Results

Search Results

Our search yielded a total of 485 records. After screening the titles and abstracts, we retrieved 10 full text articles and assessed them for eligibility. One study[29] was excluded as it contained insufficient data for constructing a 2 × 2 table. Two studies[13,14] were retrieved in the follow-up period (April to June 2021). After this selection process, our review included 11 studies[13,14,19-27] (Figure 1) with an asymmetrical funnel plot (**Supplementary Figure 1**) (Egger's test $p = 0.0017$).

Characteristics and Quality of Included Studies

Tables I and II summarise the characteristics of the included observational studies[14,19-23] (n = 6) and clinical trials[13,24-27] (n = 5). One clinical trial[25] compared the use of colchicine alone *vs.* placebo, while in the remaining studies, colchicine was combined with other drugs (hydroxychloroquine, lopinavir/ritonavir, azithromycin, tocilizumab, convalescent plasma), and in most studies it was combined with steroids. Risk of bias in observational studies and in randomised studies are presented in the ROBINS 1 plot (**Supplementary**

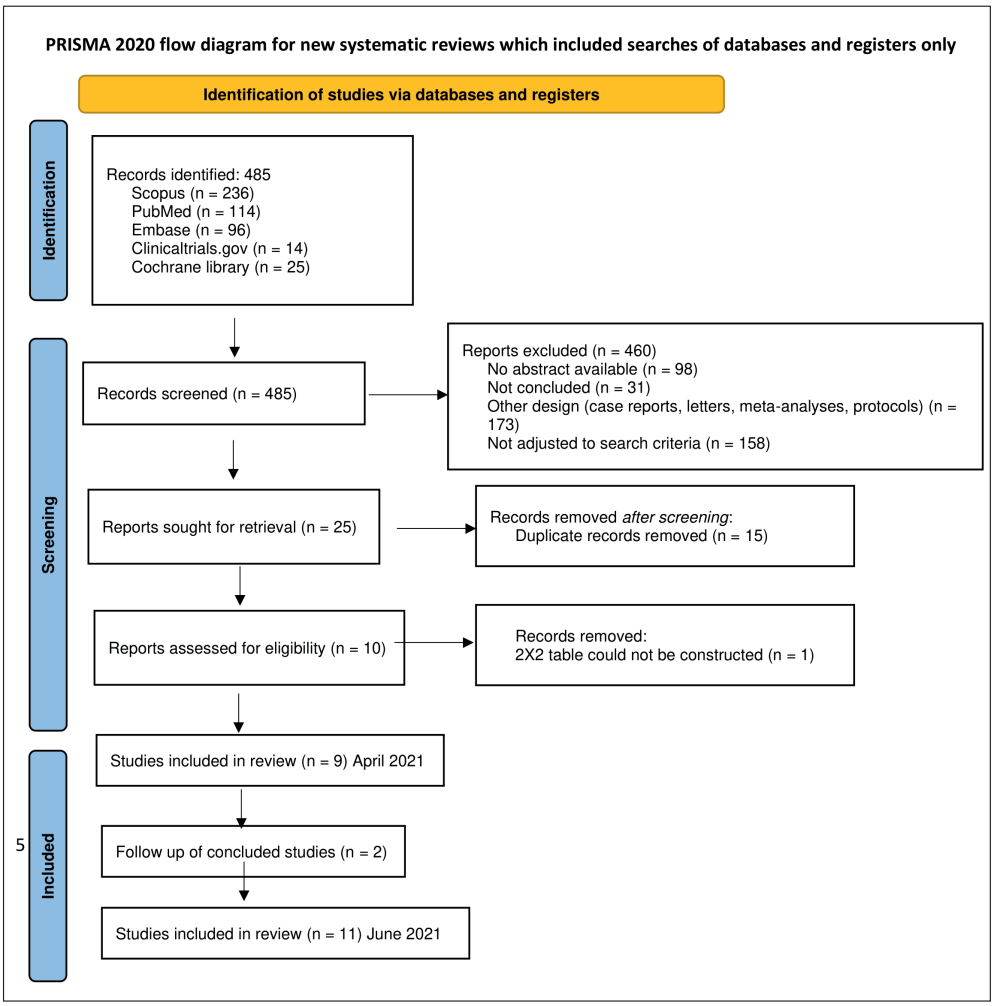

Figure 1. PRISMA flowchart.

Figure 2) and ROB2 plot (Supplementary Figure 3), respectively. One descriptive study[20] and one propensity score-matched cohort study[19] were not evaluated with the ROBINS-I tool.

Analysis of Mortality

A total of 8423 patients in the colchicine group and 8954 patients in the standard treatment group were analysed among the 11 selected studies[13,14,19-27]. In the quantitative synthesis, colchicine treatment did not reduce the risk of 28-day mortality (RR 0.93, 95% CI 0.87 to 1; $p = 0.06$; I2 = 72%) (Figure 2). Subgroup analysis was performed to explore the possible causes of the observed heterogeneity. According to the fixed effect model, the test for subgroup differences gave a statistically significant subgroup effect ($Chi^2 = 24.40$, $p < 0.001$, $I^2 = 95.9\%$), suggesting that study design influenced the results (Figure 2). In observational studies, colchicine treatment was effective (RR 0.57, 95% CI 0.46 to 0.70; $p < 0.001$). We found moderate heterogeneity in these data ($I^2 = 50\%$), probably owing to different patient characteristics, treatments, doses administered, follow-up and other confounding variables. In randomised clinical trials, including the RECOVERY clinical trial[13], treatment with colchicine was not associated with a reduction of mortality (RR 0.99, 95% CI 0.92 to 1.07; $p = 0.89$, I2 = 21%). This subgroup effect could not be demonstrated according to the random effects model (test for subgroup differences: $Chi^2 = 0.63$, $p = 0.43$, $I^2 = 0\%$) (Supplementary Figure 4).

Trial Sequential Analysis

In order to rule out a true effect of the intervention, we calculated sequential significance boundaries, futility boundaries and OIS. Given the high heterogeneity observed in the analysis of all included studies, we analysed observational and randomised studies separately. In clinical trials, OIS based on a prespecified intervention effect with a relative risk reduction of 15% (alpha = 5%, power = 80%) was 13,107 patients, with a non-significant cumulative effect estimate ($p = 0.182$) and a Z curve into the inner wedge of futility area (Figure 3).

For observational studies, we calculated an OIS of 9880 patients, based on the same type 1 and type 2 error assumptions, with inconclusive results (Figure 4).

Analysis of ICU Admission

Two articles[20,27] reported ICU admissions. The effect of colchicine on ICU admissions cannot be

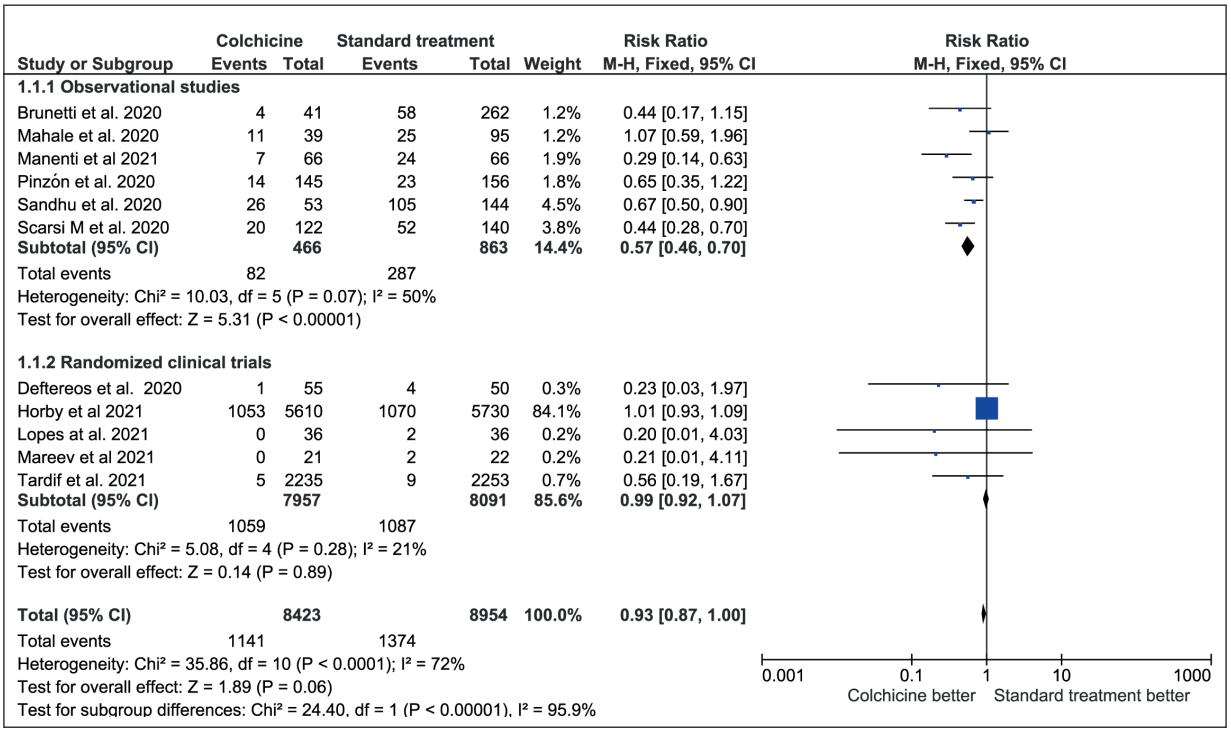

Figure 2. Analysis of mortality divided into randomised clinical trials and observational studies: fixed effect model meta-analysis.

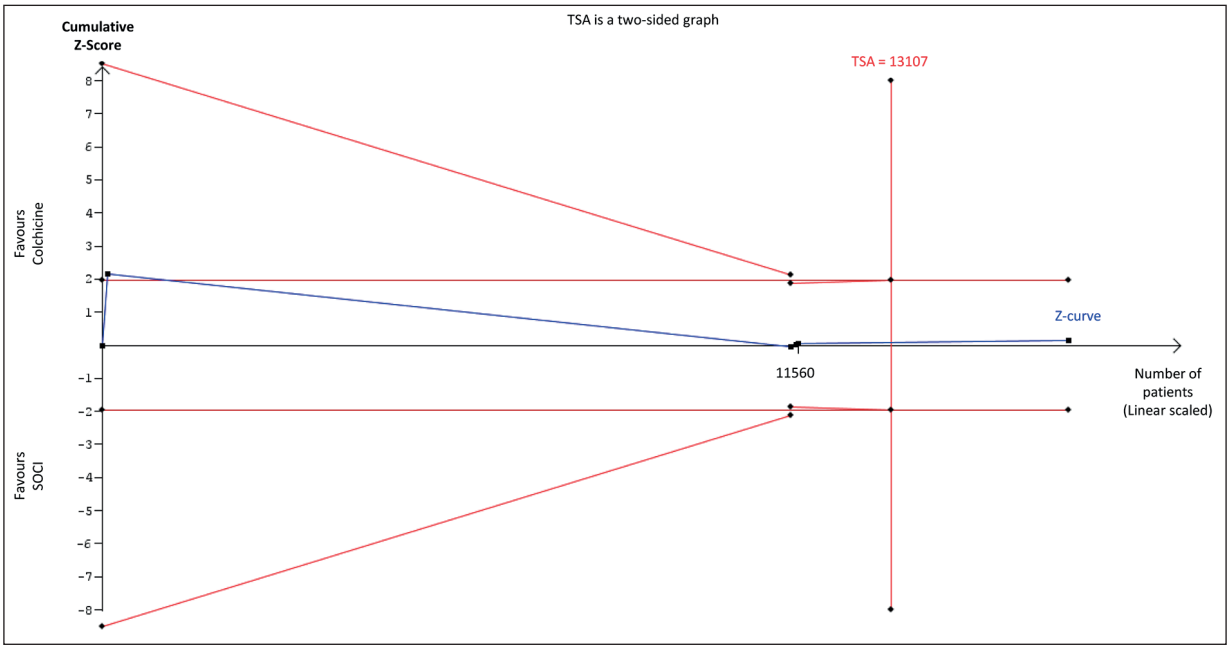

Figure 3. Trial sequential analysis: randomised clinical trials.

demonstrated (RR 1.24, 95% CI 0.32 to 4.78; p = 0.75, I^2 = 66%) (**Supplementary Figure 5**).

Analysis of Need for IMV

Six studies reported on the need for IMV[13,19,20,22,25,26]. The study by Brunetti et al[19] was excluded, as the authors only reported this outcome in the propensity score-matched patients (Table II). As shown in **Supplementary Figure 6** we cannot rule out the possibility that colchicine reduces the need for IMV (RR 0.85, 95% CI 0.59 to 1.23; p= 0.39, I^2 = 72%)

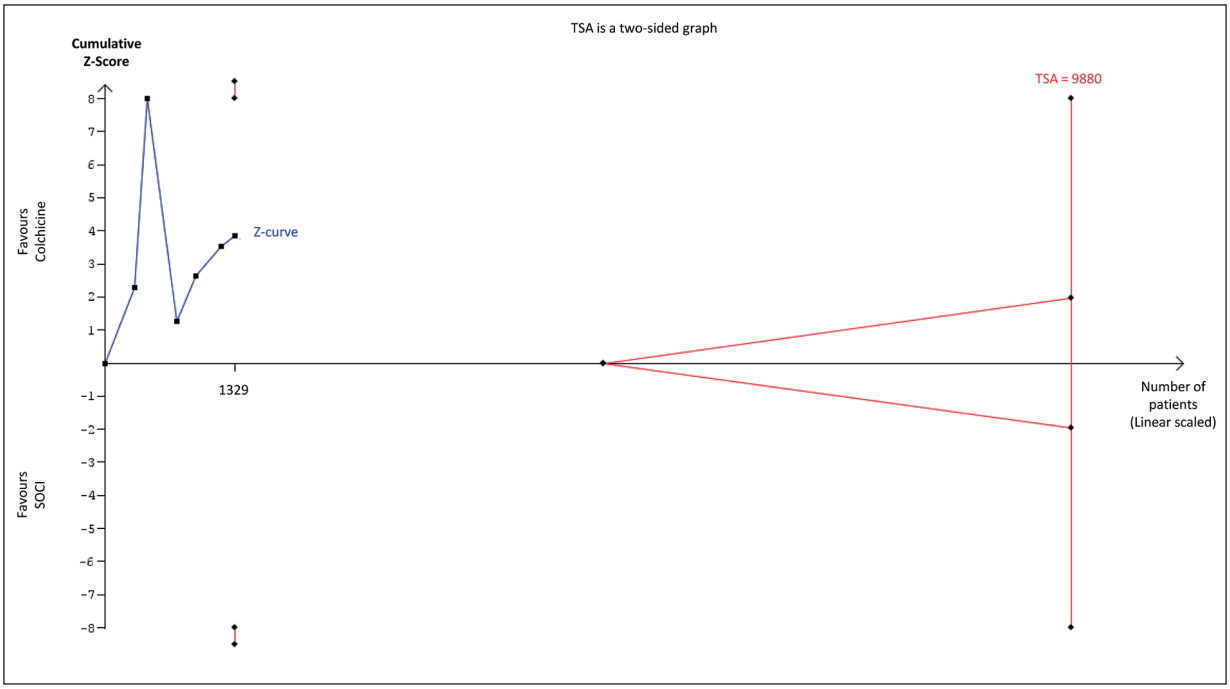

Figure 4. Trial sequential analysis: observational studies.

Discussion

Although the pooled estimate of all the included studies does not rule out a protective effect of colchicine treatment on the mortality of hospitalised patients with SARS-CoV-2 infection, the sequential analysis of the randomised clinical trials indicates no effect once the required information size is exceeded (n = 13,107 patients). With currently available data, a preventive effect on ICU admission and the need for IMV cannot be excluded.

Regarding the discrepancy between fixed and random effects models, it should be noted that the random effects model gives a similar weight to the RECOVERY study[13] (19.2%), with more than 10,000 recruited patients and more than 2000 events, as it does to smaller studies such as Sandhu et al[22] (16.8 %). In a heterogeneous set of studies such as the one we have analysed (I2 = 72%), the random effects model gives relatively more weight than the fixed effects model to smaller studies[30]. We do not consider that the random effects model is the most appropriate for our analysis.

Several meta-analyses[9-12] have assessed the effect of colchicine on COVID-19 outcomes and produced favourable results. Elshafei et al[12] analysed both randomised and non-randomised studies together and did not include the study by Horby et al[13]. In our subgroup analysis, we found that the protective effect of colchicine lost statistical significance in the subgroup of randomised studies. Chiu et al[9] also reported favourable results for the use of colchicine but included fewer patients. None of these meta-analyses included an estimation of the required information size. Our trial sequential analysis showed that the number of patients recruited exceeds the information size necessary for extracting conclusions, suggesting that no further clinical trials are needed. This observation confirms the results of the RECOVERY trial[13] but contradicts the conclusions of other meta-analyses[10]. We have analysed new studies, most notably the trial by Horby et al[13], which has sufficient statistical power and a low risk of bias (Figure 4). These authors ruled out a reduction in mortality from treatment with colchicine.

The successive publication of registered studies reflects the interest that this treatment has aroused. As colchicine is administered orally, has a low cost and tolerable side effects, it can be used in basic as well as sophisticated healthcare infrastructures. Unfortunately, the data from sequential trial analysis show that this drug does not reduce mortality in hospitalised patients.

Our analysis has several limitations. Firstly, most of the included patients were treated with steroids in conjunction with colchicine as part of the standard of care for hospitalised patients[5], but due to lack of individual data, we were unable to analyse this effect. Similarly, we cannot rule out a possible influence of patient age on the efficacy of treatment, as all included patients were considered together. Given that mortality increases incrementally with age, it is possible that colchicine reduced the relative risk of death in older patients. In the published data, the largest increase in mortality risk in COVID-19 patients has been observed in those aged over 60 years compared with those aged 50 to 59 years[2,3,18]. On the other hand, a recent meta-regression analysis suggests that the benefit of colchicine decreases with age[12].

We must consider when interpreting our results that most of the included studies were conducted in hospitalised patients. Although Tardif et al[25] included outpatients with at least one high-risk characteristic (either age, obesity, or comorbidities), their study was completed early owing to logistical issues, with only 75% planned patient recruitment. Therefore, our conclusions are limited to inpatient treatment.

A further concern is the existence of small studies effect and possible publication bias. To our knowledge, all randomised clinical trials published to date were included, and pre-print repositories and evidence summaries were also reviewed. Elshafei[12] et al also produced an asymmetrical funnel plot.

Conclusions

Our results suggest that colchicine treatment has no effect on mortality in hospitalised patients with SARS-CoV-2 infection, and that new clinical trials are not necessary to confirm this result owing to futility.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research received no external funding.

References

1) COVID-19 Map - Johns Hopkins Coronavirus Resource Center [Internet]. [cited 2021 Jul 2]. Available from: https://coronavirus.jhu.edu/map.html
2) Ramos-Rincon JM, Buonaiuto V, Ricci M, Martín-Carmona J, Paredes-Ruíz D, Calderón-Moreno M, Rubio-Rivas M, Beato-Pérez JL, Arnalich-Fernández F, Monge-Monge D, Vargas-Núñez JA, Acebes-Repiso G, Mendez-Bailon M, Perales-Fraile I, García-García GM, Guisado-Vasco P, Abdelhady-Kishta A, Pascual-Pérez MR, Rodríguez-Fernández-Viagas C, Montaño-Martínez A, López-Ruiz A, Gonzalez-Juarez MJ, Pérez-García C, Casas-Rojo JM, Gómez-Huelgas R, for the SEMI-COVID-19 Network. Clinical Characteristics and Risk Factors for Mortality in Very Old Patients Hospitalized With COVID-19 in Spain. J Gerontol A Biol Sci Med Sci 2021; 76: e28-37.
3) Andrés M, Leon-Ramirez JM, Moreno-Perez O, Sánchez-Payá J, Gayá I, Esteban V, Ribes I, Torrus-Tendero D, Gonzalez-de-la-Aleja P, Llorens P, Boix V, Gil J, Merino E, on behalf of COVID19-ALC research group. Fatality and risk features for prognosis in COVID-19 according to the care approach - a retrospective cohort study. PLoS One 2021; 16: e0248869.
4) Olbei M, Hautefort I, Modos D, Treveil A, Poletti M, Gul L, Shannon-Lowe CD, Korcsmaros T. SARS-CoV-2 Causes a Different Cytokine Response Compared to Other Cytokine Storm-Causing Respiratory Viruses in Severely Ill Patients. Frontiers in Immunology. Frontiers Media SA 2021; 12: 629193.
5) RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021; 384: 693-704.
6) RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; 397: 1637-1645.
7) Bahari Z, Jangravi Z, Ghoshooni H, Afarinesh MR, Meftahi GH. Pharmacological mechanism of immunomodulatory agents for the treatment of severe cases of COVID-19 infection. Inflamm Res 2021; 70: 389-405.
8) Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, Kalil Filho R, Junior VM, Soeiro AM, Tognon AP, Veiga VC, Martins PA, Moia DDF, Sampaio BS, Assis SRL, Soares RVP, Piano LPA, Castilho K, Momesso RGRAP, Monfardini F, Guimarães HP, Ponce de Leon D, Dulcine M, Pinheiro MRT, Gunay LM, Deuring JJ, Rizzo LV, Koncz T, Berwanger O; STOP-COVID Trial Investigators. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021; 385: 406-415.
9) Chiu L, Chow R, Chiu N, Lo C-H, Aggarwal R, Lee J, Choi YG, Lam H, Horn Prsic E, Shin HJ. 2021. Colchicine use in patients with COVID-19: a systematic review and meta-analysis. MedRxiv DOI: 10.1101/2021.02.02.21250960.
10) Hariyanto TI, Halim DA, Jodhinata C, Yanto TA, Kurniawan A. Colchicine treatment can improve outcomes of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Clin Exp Pharmacol Physiol 2021; 48: 823-830.
11) Nawangsih EN, Kusmala YY, Rakhmat II, Handayani DR, Juliastuti H, Wibowo A, Lim MA, Pranata R. Colchicine and mortality in patients with coronavirus disease 2019 (COVID-19) pneumonia: A systematic review, meta-analysis, and meta-regression. Int Immunopharmacol 2021; 96. 107723.
12) Elshafei MN, El-Bardissy A, Khalil A, Danjuma M, Mubasher M, Abubeker IY, Mohamed MFH. Colchicine use might be associated with lower mortality in COVID-19 patients: A meta-analysis. Eur J Clin Invest 2021;00: e13645.
13) RECOVERY Collaborative Group, Horby PW, Mark Campbell M, Spata E, Emberson JR, Staplin N, Pessoa-Amorim G, Peto L, Wiselka M, Wiffen L, Tiberi S, Caplin B, Wroe C, Green C, Hine P, Prudon B, George T, Wight A, Baillie JK, Basnyat B, Buch MA, Chappell LC, Day JN, Faust SN, Hamers RL, Jaki T, Juszczak E, Jeffery K, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Mafham M, Haynes R, Landray MJ. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. 2021. MedRxiv DOI 10.1101/2021.05.18.21257267.
14) Manenti L, Maggiore U, Fiaccadori E, Meschi T, Antoni AD, Nouvenne A, Ticinesi A, Cerundolo N, Prati B, Delsante M, Gandoflini I, Donghi L, Gentile M, Farina MT, Oliva V, Zambrano C, Regolisti G, Palmisano A, Caminiti C, Cocchi E, Ferrari C, Riella LV, Cravedi P, Peruzzi L. Reduced mortality in COVID-19 patients treated with colchicine: Results from a retrospective, observational study. PLoS One 2021; 16: e0248276.
15) Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017; 17: 1-18.
16) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, Steve McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: An updated guideline for

reporting systematic reviews. BMJ 2021; 372: n71.

17) Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY,2 Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

18) Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Holger J Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA,Whiting PF, Julian PT Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919.

19) Brunetti L, Diawara O, Tsai A, Firestein BL, Nahass RG, Poiani G, Schlesinger N. Colchicine to Weather the Cytokine Storm in Hospitalized Patients with COVID-19. J Clin Med 2020; 14; 9: 2961.

20) Mahale M, Rajhans P, Godavarthy P, Narasimhan VL, Oak G, Marreddy S, Bedekar A, Dhundi U, Pawar HS, Akole P, Pawar B, Bhurke B, Chavan S, Prayag P, Purandare B, Dalvi P, Telbhare V, Marudwar P, Diwane D, Shahane M, Prayag A, Gugale S, Bhor S, Sameer Jog S. A Retrospective Observational Study of Hypoxic COVID-19 Patients Treated with Immunomodulatory Drugs in a Tertiary Care Hospital. Indian J Crit Care Med 2020; 24: 1020-1027.

21) Pinzón A, Arango DC, Betancur JF, Holguín H, Arias CA, Muñoz BJ, Amarillo M, Llano JF. Clinical outcomes of patients with COVID-19 pneumonia treated with corticosteroids and colchicine in Colombia. 2021, Preprint (posted 22 Jun) available at Research Square DOI. 10.21203/rs.3.rs-94922/v1.

22) 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. 2020; 2020: 8865954. doi: 10.1155/2020/8865954. PMID: 33133323; PMCID: PMC7588830.

23) Scarsi M, Piantoni S, Colombo E, Airó P, Richini D, Miclini M, Bertasi V, Bianchi M, Bottone D, Civelli P, Cotelli MS, Damiolini E, Galbassini G, Gatta D, Ghirardelli ML, Magri R, Malamani P, Mendeni M, Molinari S, Morotti A, Salada L, Turla M, Vender A, Tincani A, Brucato A, Franceschini F, Furloni R, Andreoli L. 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: 1286-1289.

24) Mareev VY, Orlova YA, Pavlikova EP, Akopyan ZA, Matskeplishvili ST, Plisyk AG. Proactive antiinflammatory and anticoagulant therapy in the treatment of advanced stages of novel coronavirus infection (COVID-19). Case Series and Study Design: COLchicine versus ruxolitinib and secukinumab in Open prospective RandomIzed Trial (COLORIT). Kardiologiya 2020; 60: 4-21.

25) Tardif JC, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, Lopez-Sendon J, da Luz P, Verret L, Audet S, Dupuis J, Denault A, Pelletier M, Tessier PA, Samson S, Fortin D, Tardif JD, Busseuil D, Goulet E, Lacoste C, Dubois A, Joshi AY, Waters DD, Hsue P, Lepor NE, Lesage F, Sainturet N, Roy-Clavel E, Bassevitch Z, Orfanos A, Stamatescu G, Grégoire JC, Busque L, Lavallée C, Hétu PO, Paquette JS, Deftereos SG, Levesque S, Cossette M, Nozza A, Chabot-Blanchet M, Dubé MP, Guertin MC, Boivin G; COLCORONA Investigators. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. Lancet Respir Med 2021; 9: 924-932.

26) Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, Metallidis S, Sianos G, Baltagiannis S, Panagopoulos P, Dolianitis K, Randou E, Syrigos K, Kotanidou A, Koulouris NG, Milionis H, Sipsas N, Gogos C, Tsoukalas G, Olympios CD, Tsagalou E, Migdalis I, Gerakari S, Angelidis C, Alexopoulos D, Davlouros P, Hahalis G, Kanonidis I, Katritsis D, Kolettis T, Manolis AS, Michalis L, Naka KK, Pyrgakis VN, Toutouzas KP, Triposkiadis F, Tsioufis K, Vavouranakis E, Martinèz-Dolz L, Reimers B, Stefanini GG, Cleman M, Goudevenos J, Tsiodras S, Tousoulis D, Iliodromitis E, Mehran R, Dangas G, Stefanadis C; GRECCO-19 investigators. 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: e2013136.

27) Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Dib SM, Gigante SL, Benatti MN, Rezek UC, Emrich-Filho LL, Sousa BAA, Almeida SCL, Luppino Assad R, Veras FP, Schneider A, Rodrigues TS, Leiria LOS, Cunha LD, Alves-Filho JC, Cunha TM, Arruda E, Miranda CH, Pazin-Filho A, Auxiliadora-Martins M, Borges MC, Fonseca BAL, Bollela VR, Del-Ben CM, Cunha FQ, Zamboni DS, Santana RC, Vilar FC, Louzada-Junior P, Oliveira RDR. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, pla-

cebo-controlled clinical trial. RMD Open 2021; 7: e001455.

28) Horlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G GC. User Manual for Trial Sequential Analysis (TSA) [pdf]. 2nd ed. Copenhagen: Copenhagen Trial Unit, pp. 1-119. [Internet]. 2017. Available from: https://ctu.dk/

29) Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJ. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care 2020; 24: 429.

30) Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.