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Effect of colchicine on mortality in patients with COVID-19 – A systematic review and meta-analysis

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ABSTRACT

Background and aim: This systematic review and meta-analysis aimed to evaluate the latest evidence on the association between colchicine and mortality in patients with COVID-19.
Methods: We performed a comprehensive literature search from the PubMed, Scopus, Embase, EuropePMC, and Clinicaltrials.gov up until 02 January 2022. We include randomized controlled trials (RCTs) and observational studies reporting colchicine use in patients with COVID-19 and mortality within 30 days. The intervention group was patients given colchicine during the course of treatment. The control group was patients given placebo or standard of care at the respective institutions. The outcome was mortality. The effect estimate was reported as risk ratio (RR).
Results: There were 12 studies comprising of 6953 patients included in this meta-analysis. Mortality rate was 0.18 [95%CI 0.10, 0.26] in the colchicine group and 0.26 [95%CI 0.15, 0.38] in the control group. Colchicine was associated with reduction in mortality (RR 0.66 [95%CI 0.53, 0.83], $p < 0.001$; I^2: 42%). Sensitivity analysis using fixed-effect model (RR 0.73 [95%CI 0.63, 0.83], $p < 0.001$; I^2: 42%. Subgroup analysis on the four RCTs showed non-significant result (RR 0.81 [95%CI 0.54, 1.20], $p = 0.29$; I^2: 10%). Meta-regression showed that the association between colchicine and reduced mortality was not affected by age ($p = 0.613$) [Fig. 3], sex ($p = 0.915$), diabetes ($p = 0.795$), and hypertension ($p = 0.403$).
Conclusion: Though the meta-analysis showed decreased mortality with colchicine in patients with COVID-19, the meta-analysis of randomized trials did not show any significant effect of colchicine on mortality.

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1. Introduction

COVID-19 contributed to death directly and indirectly [1,2]. The search of effective, safe, and inexpensive drug for improving COVID-19 outcome continues; this usually involve repurposing medications that were widely known. Although most of medications were promising at first, many of them was found to be of no benefit in larger randomized controlled trials (RCTs) [3]. Many drugs were used off-label for treating COVID-19 [4–6], one of them is colchicine, which is a well-known anti-inflammatory agents that is approved by FDA to be used to treat gout arthritis and Familial Mediterranean fever and it is also used as an off-labeled drug against pseudogout, sarcoid and psoriatic arthritis, Bechet's disease and pericarditis [7–9].

The true nature of colchicine remains elusive, however due to its modulatory effect on inflammatory response and its possible antiviral properties, as well as small studies showing promising results [10,11], colchicine is worth to be studied further. This systematic review and meta-analysis aimed to evaluate the latest evidence on the association between colchicine and mortality in patients with COVID-19.

2. Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.

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2.1. Search strategy and study selection

We performed a comprehensive literature search from the PubMed, Scopus, Embase, EuropePMC, and Clinicaltrials.gov for "(2019-nCoV OR COVID-19 OR SARS-CoV-2) AND (colchicine)" from the beginning of time until 02 January 2022. Title/abstract screening and eligibility assessment of the full-text articles were performed by two independent authors. Discrepancies during the process were resolved by discussion.

2.2. Inclusion and exclusion criteria

Studies that fulfil the following criteria were included: 1) RCTs and observational studies reporting colchicine use in patients with COVID-19 and 2) mortality within 30 days.

Studies that fulfil one of the following criteria were excluded: 1) editorial/commentaries, 2) conference papers, 3) review articles, 4) letters, and 5) abstracts. There was no language restriction.

2.3. Intervention and outcome

The intervention group was patients given colchicine during the course of treatment. The control group was patients given placebo or standard of care at the respective institutions. The outcome was mortality. The effect estimate was reported as risk ratio (RR).

2.4. Data extraction

Data from the eligible studies were extracted by two independent authors using standardized extraction form that contain the author of the studies, study design, inclusion criteria, colchicine regimen, control group, sample size, age, sex, comorbidities, and the mortality in the intervention and control groups. Discrepancies during the process were resolved by discussion.

2.5. Risk of Bias Assessment

Risk of bias assessment was performed by two independent authors with two tools, Newcastle-Ottawa Scale (NOS) [12] for non-randomized studies and Cochrane Risk of Bias Assessment for RCTs [13]. Discrepancies during the process were resolved by discussion.

2.6. Statistical analysis

Random-effects meta-analysis using the Mantel-Haenszel statistical method was performed to pool the effect of colchicine on mortality compared to the control group using the dichotomous values. We used random-effects model regardless of heterogeneity considering the variation in doses, and fixed-effects model was performed during the sensitivity analysis. Subgroup analysis was performed for RCTs and published studies. P-values of $\leq$0.05 were considered as statistically significant. Interstudy heterogeneity was evaluated using the I [2] statistics and a value above 50% and p-

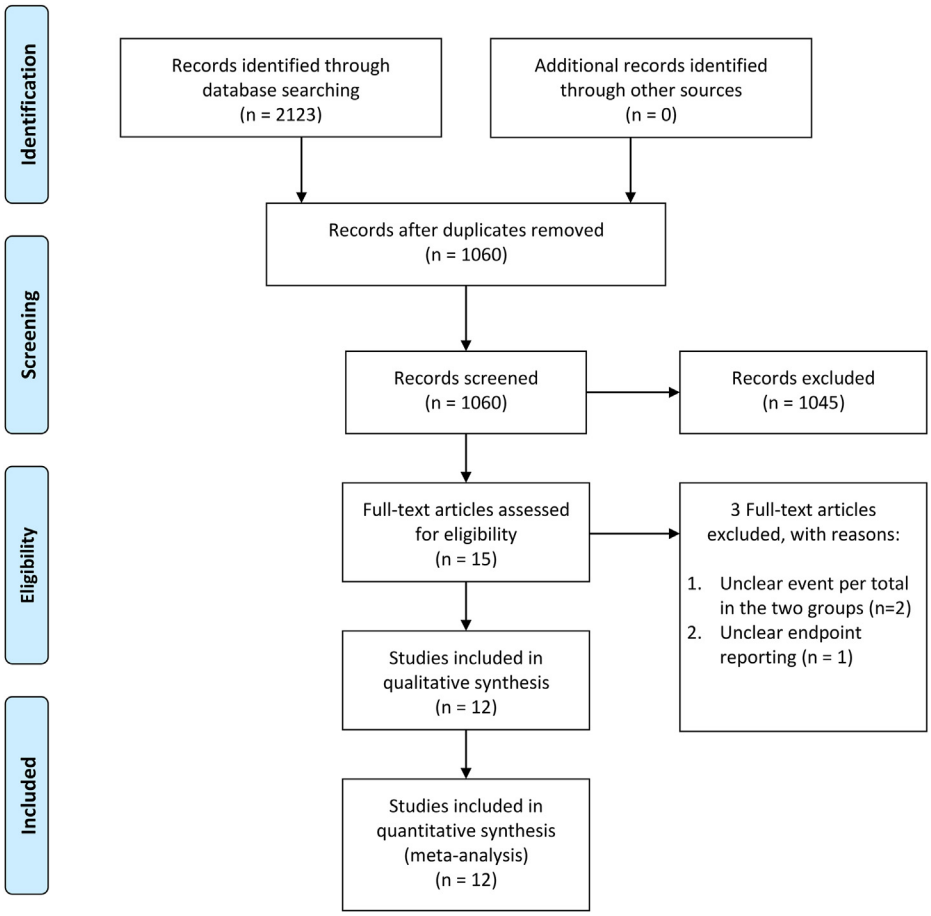

Fig. 1. PRISMA flowchart.

value < 0.10 indicates heterogeneity. Meta-regression analysis was performed using the random-effects restricted maximum likelihood (REML) in order to evaluate whether the effect of colchicine on mortality was influenced by age, sex, diabetes, and hypertension. Review Manager 5.4 and STATA version 16.0 software were used to perform the meta-analysis.

3. Results

3.1. Baseline characteristics

There were 12 studies comprising of 6953 patients included in this meta-analysis [10,11,14–23] [Fig. 1]. There were 4 RCTs and 8 observational studies included in this analysis. García-Posada et al. study reported a group with unclear treatment (treatment: others), which was excluded from our analysis because it may lead to bias. The characteristics of the included studies can be seen in Table 1.

3.2. Colchicine and Mortality

Mortality rate was 0.18 [95%CI 0.10, 0.26] in the colchicine group and 0.26 [95%CI 0.15, 0.38] in the control group. Colchicine was associated with reduction in mortality (RR 0.66 [95%CI 0.53, 0.83], $p < 0.001$; I^2: 42%, $p = 0.06$) [Fig. 2]. Sensitivity analysis using fixed-effect model (RR 0.73 [95%CI 0.63, 0.83], $p < 0.001$; I^2: 42%, $p = 0.06$). Subgroup analysis on the four RCTs showed non-significant result (RR 0.81 [95%CI 0.54, 1.20], $p = 0.29$; I^2: 10%, $p = 0.34$). Subgroup analysis on published studies showed significant reduction in mortality (RR 0.65 [95%CI 0.50, 0.85], $p = 0.001$; I^2: 52%, $p = 0.03$).

3.3. Meta-regression

The association between colchicine and reduced mortality was not affected by age ($p = 0.613$) [Fig. 3], sex ($p = 0.915$), diabetes ($p = 0.795$), and hypertension ($p = 0.403$).

3.4. Publication bias

Risk of bias for RCT is in [Fig. 4] and for observational studies is in Table 1. Funnel-plot was asymmetrical with more studies on the left side (more significant) [Fig. 5]. Egger's test indicated the presence of small-study effects ($p = 0.003$).

4. Discussion

This meta-analysis showed that colchicine was associated with decreased mortality in patients with COVID-19 with low heterogeneity. The benefit was statistically significant with both random-effects and fixed-effect model. Meta-regression analysis was unable to find the cause of heterogeneity. Nevertheless, we note that the doses were different among the studies, which may cause slight heterogeneity in the effect estimate. We note that there was a presence of small-study effects and publication bias, as evident by the funnel-plot analysis that indicate that asymmetry with more studies in the left side of the plot. Studies with positive results are more likely to be reported and published, which is one of the weakness of meta-analysis. Subgroup analysis of RCTs on mortality was not statistically significant, however, it was likely due to small number of events rather than true null result. Although the result remained inconclusive, colchicine is a promising drug that warrants further RCTs to increase the certainty of evidence in order to recommended for routine clinical practice.

Meta-regression analysis was performed to explore potential source of heterogeneity, several comorbidities [24–36] and its associated medications [33,37,38] have been shown to affect mortality in patients with COVID-19, thus may alter the benefit. The meta-regression showed that all covariates we analyzed did not significantly contribute to heterogeneity of the pooled effect estimate.

The history of colchicine itself can be traced back to over 2000 years ago when it was widely used as a poison or as a remedy for gout flares [8]. As a drug that possibly had been discovered in the ancient times and had been used in such an extended period of time, the potential anti-inflammatory and antiviral properties has not been discovered too much. By taking a closer look on the intersection between COVID-19 induced inflammation and colchicine's effect in regulating inflammatory response might shed a light on a potential use of colchicine in COVID-19.

The possible inhibitory effect of colchicine towards COVID-19 might relies on its inhibition on microtubule assembly, and its inflammatory regulation properties. Microtubules, which is a key component of the cytoskeleton, facilitates the movement of adhesion molecules onto the cell surface during inflammation [39]. It also affected by the colchicine which binds to the soluble tubulin heterodimer and it will eventually forms a tubulin-colchicine complex [9]. The interaction between each molecules shows a dose-dependent response which at lower dose, it interferes the microtubule formation and elongation, and in higher dose, it promotes microtubule depolymerization [40]. Consequently, these events might lead to microtubule distortion and leading to possible disruption of cell metabolism such as division, signal transduction, integrity, and transport system [8].

As demonstrated in Dengue virus and Zika virus, Colchicine shows a significant decrease of intracellular viral replication, possibly due to the micro tubule dependence viral replication and the polymerization of microtubule affected by the colchicine [41]. While coronavirus replication in the cell requires a functional microtubule, interference of microtubule and its associated protein might impaired the essential microtubule-associated transport and therefore might interfere viral cell replication [42]. In addition to that, the process of coronavirus cell entry might require an interaction between the cytoplasmic tail of the spike protein and a cytoskeletal protein. It is possibly this process might be interrupted due to the colchicine-tubulin complex, however more evidence is required [43].

The anti-inflammatory effect of colchicine is well demonstrated through various inflammatory pathways in which colchicine exert its effect. It capable of decreasing the expression of adhesion molecules on neutrophil membranes, presumedly due to the colchicine induced neutrophil adhesion molecules shedding, which will leads to a decrease capability of inflammatory cell migration and helps modulate inflammatory cytokine production such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor - α (TNF-α) [9]. In fact, colchicine tends to accumulate in neutrophil, mainly due to the lack of P-glycoprotein membrane efflux pump in neutrophil and therefore reducing the capability of transporting colchicine out from the cell [44]. Due to the accumulation of colchicine in the neutrophil, it causes several disruptions to the neutrophil functions. Intracellular signaling and lysosomal enzyme released during phagocytosis impairment are prominent while it seems colchicine has played a role in the inhibition of calcium influx, which seems also to have an inhibitory effect on platelet activation, and reduce neutrophil response [45]. While it is still under investigation, colchicine seems to be able to decrease cytokine production through the inhibition of nod-like receptor protein 3 (NLRP3) inflammasome activation [46]. This reduces the production of IL-1β which might prevent the induction of other cytokines (IL-6 and TNF) that involve in the process of cytokine storm [47]. COVID-19 was shown to cause endotheliopathy, coagulopathy, hyper-

Table 1
Characteristics of the included studies.

Authors	Design	Inclusion Criteria	Samples	Colchicine Dosing	Control	Age (years)	Male (%)	Diabetes (%)	Hypertension (%)	CAD (%)	Follow-up (days)	NOS
Brunetti 2020	PSM Cohort (1:1)	Severe COVID-19	33 vs. 33	1.2 mg followed by 2 × 0.6 mg per day	SOC	61.7 vs. 64.1	63.6 vs66.7	21.2 vs 21.2	60.6 vs 36.4	21.1 vs 6.1[a]	28	8
COLCORONA 2021	RCT	Age >40 Diagnosed with COVID-19 by PCR within 24 h or direct link with a positive COVID-19 household member or by a clinical algorithm, non-hospitalized patient, at least 1 high risk criteria of: age ≥70, obesity (BMI≥ 30), diabetes, SBP ≥150, history of respiratory disease, heart failure, coronary disease, fever ≥38.4C within 48 h, dyspnea at the time of presentation, bicytopenia, pancytopenia, or the combination of high neutrophil and low lymphocyte counts.	2075 vs. 2084	2 × 0.5 mg per day for 30 days	Placebo	54.4 vs 54.9	44.6 vs 47.5	19.9 vs 20	34.9 vs 20	2.9 vs 3.2[a]	30	See RoB (Fig. 4)
COLORIT 2021	PC	Severe COVID-19	21 vs. 22	1 mg colchicine during the first 1 −3 days followed by 0.5 mg per day	SOC	61.9 vs. 59.9	66.7 vs. 72.7	14.3 vs. 9.09	66.7 vs. 59.1	14.3 vs. 18.2	12	7
ECLA PHRI COLCOVID 2021	RCT	Moderate to Severe COVID-19	640 vs. 639	1.5 mg + 0.5 mg followed by 2 × 0.5 mg per day until discharge or 14 days	SOC	62 vs. 62	65.8 vs. 64	21.8 vs. 23.6	48.8 vs. 46.6	7.7 vs. 6.6	28	See RoB (Fig. 4)
GRECCO-19 2020	RCT	Hospitalized adult COVID-19 patients confirmed with RT-PCR, Body temperature ≥37.5C, ≥ 2 of following: sustained coughing, sore throat, anosmia, and/or ageusia, fatigue and/or tiredness, arterial oxygen partial pressure <95% on room air.	55 vs. 50	1.5 mg + 0.5 mg followed by 2 × 0.5 mg per day until discharge or 21 days	SOC	65 vs 63	60 vs 56.4	24 vs 16.4	50 vs 40	10 vs 16.4	21	See RoB (Fig. 4)
García-Posada 2021[a]	PC	Hospitalized COVID-19	113 vs. 44	Given for 20 days, dose unclear	SOC	NA	NA	NA	NA	NA	NA	5
Lopes 2021	RCT	Age ≥18, Moderate to severe COVID-19 diagnosed by RT-PCR and CT-scan, Body weight >50 kg, normal serum Ca2+ and K+, QT interval <250 ms, negative serum or urinary β-HCG if woman <50 years old	37 vs. 38	1.0 mg followed by 3 × 0.5 mg per day for 5 days	Placebo	55.0 vs 54.5	39 vs 53	42 vs 36	NA	NA	26	See RoB (Fig. 4)
Mahale 2020	RC	Age ≥18 yo, Positive COVID-19 by RT-PCR, SOB at rest or with exercise (6-min walk test), room air saturation <94%	39 vs. 95	0.5 mg per day	SOC	55.6	67.9	44	46	NA	NA	7
Manenti 2021	RC	COVID-19 patients (hospitalized with pneumonia on CT scan or outpatients)	70 vs. 71	1 mg per day up until 21 days	SOC	60.5 vs. 62.5	72.9 vs. 69	15.7 vs. 18.3	55.7 vs. 60.6	NA	21	8
Pinzon 2021	PC	Adult patients with COVID-19 Pneumonia confirmed by Real-Time Polymerase Chain Reaction for SARS-CoV-2 and Radiological Findings	145 vs. 156	2 × 0.5 mg per day for 7−14 days	SOC	57.2	59.1	24.3	45.5	6.0	Until Discharge	7
Sandhu 2020	PC	Age ≥18, Confirmed COVID-19 by PCR, hospitalized,	34 vs. 78	2 × 0.6 mg per day for 12 days	SOC	67.7 vs 66.4	61.8 vs 51.3	32.4 vs 51.3	52.9 vs 71.8	5.9 vs 7.7	Until Discharge	7
Scarsi 2020	PC	Virologically and radiographically confirmed COVID-19 hospitalized patients	122 vs. 140	1.0 mg per day	SOC	69.3 vs 70.5	63 vs 64	NA	NA	NA	21	8

CAD: Coronary Artery Disease, PC: Prospective Cohort, PSM: Propensity-Score Matched; RC: Retrospective Cohort, RCT: Randomized Controlled Trial, RoB: Risk of Bias, NA: Not Available, NOS: Newcastle-Ottawa Scale, COVID-19: Coronavirus Disease-2019, CT-scan: Computed Tomography-Scan, PCR: Polymerase Chain Reaction, SARS-CoV-2: Severe Acute Respiratory Symptoms Coronavirus 2, SOB: Shortness of Breath, β-HCG: β Human Chorionic Gonadotropin, ms: Millisecond, kg: Kilogram, BMI: Body Mass Index, SBP: Systolic Blood Pressure.

[a] Group with unclear treatment (treatment: others) was excluded from the analysis because it may lead to bias.

inflammation, and cytokine storm that may potentially cause end-organ damage [48−55,55−64]. Therefore, the anti-inflammatory and platelet inhibitory properties of colchicine that involved various steps of inflammatory response may potentially alleviate the pathology and improve outcome.

This meta-analysis has several limitations; publication bias is commonly encountered in meta-analysis because positive studies are more likely to be reported compared to negative studies. There were only three RCTs in this pooled analysis, with inconclusive result, to sufficiently conclude additional RCTs are required. The doses were heterogeneous, trials comparing multiple dose are also required to obtain the optimum dosage.

5. Conclusion

Though the meta-analysis showed decreased mortality with colchicine in patients with COVID-19, the meta-analysis of randomized trials did not show any significant effect of colchicine on

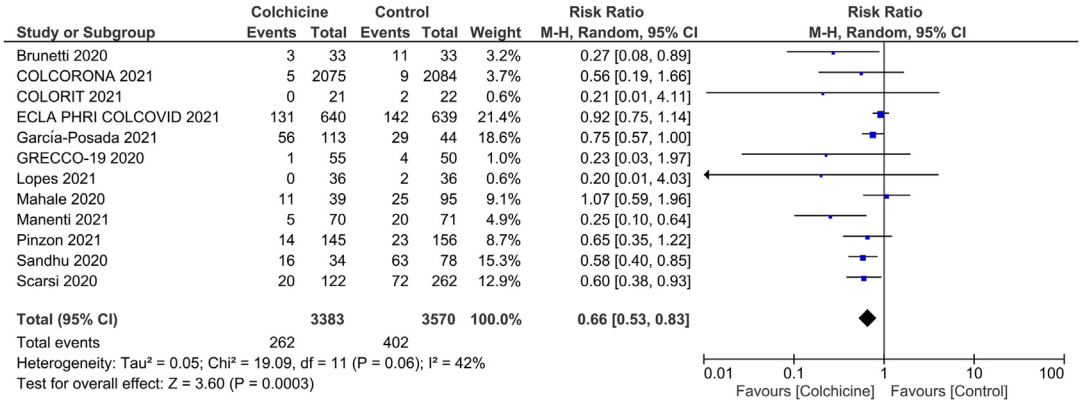

Fig. 2. Colchicine and mortality.

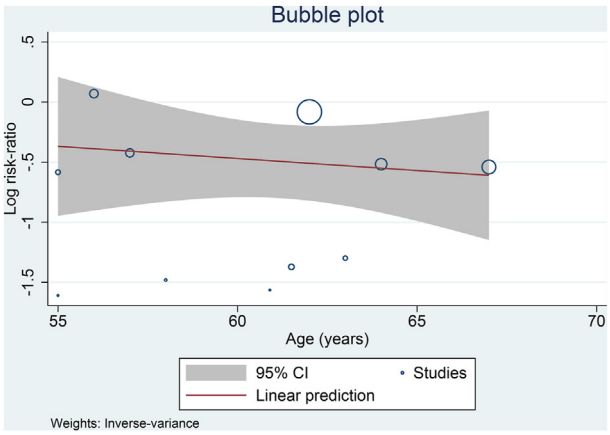

Fig. 3. Meta-regression using age as covariate.

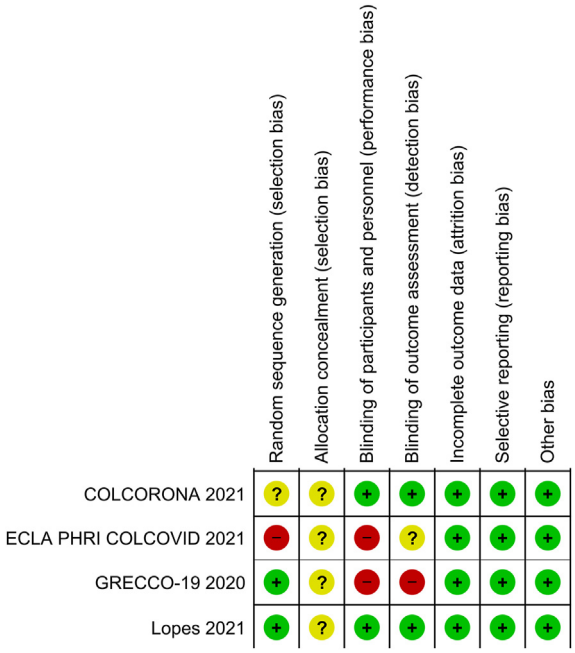

Fig. 4. Risk of bias assessment.

mortality.

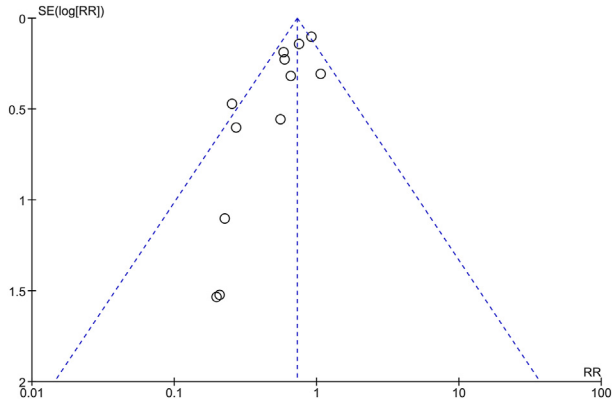

Fig. 5. Funnel-plot analysis.

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Ethical approval

Not Applicable.

Informed consent

Not Applicable.

Data availability

Data are available on reasonable request.

Contributorship statement

AFMZZ was involved in the conceptualization and design of the manuscript. AFMZZ and WMR participated in data curation and investigation. AFMZZ performed formal and statistical analysis. AFMZZ and WMR drafted the manuscript. AFMZZ and WMR review and edited the manuscript.

Declaration of competing interest

None.

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