JAMA Internal Medicine | Original Investigation

Effectiveness of Colchicine for the Treatment of Long COVID
A Randomized Clinical Trial

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IMPORTANCE Long COVID is characterized by persistent symptoms after SARS-CoV-2 infection, with inflammation playing a key role in pathogenesis. Colchicine, an established anti-inflammatory agent, may reduce these symptoms by targeting inflammatory pathways.

OBJECTIVE To evaluate the superiority of colchicine over placebo in improving functional outcome at 52 weeks from baseline.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, 1:1 randomized clinical trial recruited participants with confirmed SARS-CoV-2 infection and persistent symptoms from 8 hospitals in 6 states in India between January 2022 and July 2023. Individuals were eligible if they had functional limitation (Post–COVID-19 Functional Status scale grade 2 or more) and/or elevated inflammatory markers (high-sensitivity C-reactive protein >0.20 mg/dL and/or neutrophil to lymphocyte ratio >5). Outcomes were assessed at 12, 26, and 52 weeks after randomization. Data were analyzed from January to February 2025.

INTERVENTIONS Participants were randomly assigned to receive colchicine, 0.5 mg, once or twice daily, based on body weight, or placebo for 26 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in distance walked during a 6-minute walk test from baseline to 52 weeks. Secondary outcomes included changes in inflammatory markers and patient-reported outcome measures, such as quality of life, anxiety, depression, fatigue, dyspnea, measured using validated instruments.

RESULTS Of 346 participants included in the modified intention-to-treat analysis, 209 (60.4%) were female, 137 (39.6%) were male, and the mean (SD) age was 46 (12) years. At 52 weeks, there was no difference in mean (SD) change in 6-minute walk test distance between the colchicine and placebo groups (colchicine, 35.5 [19.76] m; placebo, 29.96 [19.83] m; mean difference, 5.59 m; 95% CI, −9.00 to 20.18; $P = .45$). Similar null findings were seen across all predefined outcomes, except for a small, nonclinically relevant difference in the mean (SD) ratio of forced expiratory volume in 1 second to forced vital capacity (colchicine, −0.02 [0.03]; placebo, −0.06 [0.03]; mean difference, 0.04; 95% CI, 0.02 to 0.07; $P = .001$).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, among adults with long COVID, colchicine did not improve functional capacity, respiratory function, or inflammatory markers. These findings underscore the need to explore alternative therapeutic approaches for long COVID.

TRIAL REGISTRATION Clinical Trial Registry of India: CTRI/2021/11/038234

Visual Abstract

Supplemental content

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JAMA Intern Med. doi:10.1001/jamainternmed.2025.5408
Published online October 20, 2025.

Long COVID—a complex multisystem disorder affecting an estimated 65 million individuals worldwide—has emerged as an important public health challenge in the post-COVID-19 pandemic era.[1] The syndrome is characterized by persistent fatigue, cardiopulmonary dysfunction, neurocognitive impairment, and debilitating postexertional malaise and affects at least 10% of those infected with the SARS-CoV-2 virus.[1] It has been shown to reduce quality-of-life scores by 40% to 60% compared with preinfection baselines.[2] While acute COVID-19 management strategies have advanced steadily, the absence of approved therapies targeting long COVID's unique pathophysiology leaves clinicians and patients navigating an evidence vacuum.

Several pathophysiological mechanisms, such as persistent inflammation, immune dysregulation, gut dysbiosis, and endothelial dysfunction, have been proposed as causes for symptoms of long COVID.[3] A key role has been proposed for persistent nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation with subsequent downstream activation of IL-1β and IL-6 as a central driver of long COVID's manifestations.[2] Postmortem analyses reveal sustained myeloid cell infiltration in cardiac and neural tissues up to 8 months postinfection, and proteomic studies demonstrate elevated IL-1β and IL-6 levels correlating with symptom severity.[4] This chronic inflammatory milieu creates a self-perpetuating cycle of endothelial dysfunction, mitochondrial impairment, and autonomic dysregulation—processes potentially modifiable through targeted immunomodulation.

Currently, no pharmacological therapy has been recommended for prevention or treatment to address the symptoms of long COVID. Metformin initiated in the acute phase reduced the incidence of long COVID in a randomized clinical trial,[5] and low-dose naltrexone led to an improvement in fatigue scores in uncontrolled trials.[6] Several therapies are under investigation.[7] Colchicine's impact on microtubule disruption and subsequent inhibition of inflammasome assembly positions it as a biologically plausible therapeutic candidate.[8] Preclinical models have demonstrated that colchicine reduces IL-1β production,[9] and some clinical trials in acute COVID-19 have shown 25% to 44% reduction in hospitalization rates when administered early.[10,11] Critical knowledge gaps persist, however, regarding anti-inflammatory strategies in the postacute phase.

While colchicine has been evaluated in acute COVID-19,[12] its potential role in addressing the persistent inflammatory state characteristic of long COVID remains unexplored. We hypothesized that colchicine's anti-inflammatory properties would improve functional capacity, as measured by the 6-minute walk test (6MWT), while reducing systemic inflammation in individuals with long COVID. Positive results would validate NLRP3 inflammasome inhibition as a therapeutic strategy, guiding the development of next-generation therapies. Null findings, conversely, would redirect the focus toward alternative mechanisms, such as viral persistence, autoantibody production, or mitochondrial dysfunction.[13]

Key Points

Question What is the effectiveness of 28-week oral colchicine therapy in improving functional outcomes among individuals with persistent symptoms after acute COVID-19 infection?

Findings In this randomized clinical trial including 346 adults, there was no statistically significant difference in functional capacity, respiratory function, mental states, constitutional symptoms, or inflammatory markers at 52 weeks among those treated with colchicine or placebo.

Meaning This trial provides evidence against colchicine monotherapy as a broadly effective treatment for long COVID.

Methods

Study Design and Participants

This was an investigator-initiated, multicenter, parallel-group, double-blind, 1:1 superiority randomized clinical trial. The trial was approved by The George Institute for Global Health India Ethics Committee and the ethics committees of all participating centers and conducted in accordance with principles consistent with the Declaration of Helsinki. All patients provided written informed consent prior to randomization. Patients and public were not involved in the design, conduct, and reporting of the trial except for membership of an individual with lived experience of long COVID in the trial steering committee to incorporate patient-centered oversight. Even though this individual did not participate in technical determinations regarding study design, they provided important oversight to the assessment of trial progress and tracking recruitment and retention through the lens of patient experience. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

The study protocol has been published previously[14] and can be found in Supplement 1; the statistical analysis plan can be found in Supplement 2. Participants were recruited from 8 sites across 6 states in India (5 private hospitals, 2 public hospitals, and 1 community outreach center). Individuals listed in the COVID-19 registers of the hospital or visiting the outpatient department were screened for eligibility from January 2022; enrollment ended in July 2023. Eligible participants were adults with confirmed SARS-CoV-2 infection at least 22 days ago and with the functional limitation (Post-COVID-19 Functional Status [PCFS] scale grade 2 or more)[15] (eFigure 1 in Supplement 3) and/or elevated inflammatory markers above normal range (high-sensitivity C-reactive protein [CRP] >0.20 mg/dL [to convert to milligrams per liter, multiply by 10] and/or neutrophil to lymphocyte ratio >5). The PCFS scale has shown high correlation with quality of life and functional limitation.[16,17] We excluded those with a definite indication to colchicine, such as arthritis or inflammatory bowel disease, history of any gastrointestinal tract surgery, chronic diarrhea, or any surgical or medical condition that could alter the absorption or distribution of colchicine. Other exclusion criteria were current pregnancy or breast feeding, any known blood dys-

crasias, and estimated glomerular filtration rate less than 15 mL/min/1.73 m^2.

Assessments and Measures

Basic demographic characteristics, current symptoms, comorbidities, and hospitalization at the time of acute COVID-19 infection were collected from all enrolled participants using standardized case report forms at baseline before randomization. Follow-up was done at 12, 26, and 52 weeks with a window period of 2 weeks. Telephonic follow-ups were conducted for those who were unable to visit the hospital within the specified window period. Trial participants, treating physicians, laboratory staff, and all members of the research team at the clinical site and trial coordinating center were unaware of the treatment allocation groups until the end of the trial.

The assessments included physical functional capacity, general and mental health status, respiratory function, inflammatory markers, constitutional symptoms, and cardiovascular outcomes. Physical functional capacity was assessed using the 6MWT. The core outcome set for evaluation of interventions for long COVID recommends physical function and cardiopulmonary function as one of the core outcomes.[18] The 6MWT is a well-established objective measure for cardiopulmonary and physical function. Further, this test was a feasible measure for our study setting involving diverse clinical and community sites. The normal range of 6-minute walk distance in apparently healthy adult population ranges from 400 to 600 m.[19] Other secondary assessments were quality of life (EuroQol 5-Dimension Questionnaire), anxiety scores (Generalized Anxiety Disorder-7 [GAD-7]), depression scores (Patient Health Questionnaire-9), post-6MWT dyspnea score (Borg dyspnea scale), maximal desaturation during 6MWT, high-sensitivity CRP, fatigue score (Chalder Fatigue scale), and self-reported symptom count. Forced vital capacity (FVC) and percentage forced expiratory volume in 1 second (FEV_1) were measured at baseline, week 26, and week 52. Adverse events (AEs), such as diarrhea, nausea, vomiting, abdominal pain, and sore throat, were collected in a case report form alongside other self-reported adverse symptoms. Further details about trial assessments are reported in the protocol.[14]

Randomization and Interventions

Participants were randomly assigned 1:1 to either colchicine or matching placebo tablets. The randomization sequence was generated using block sizes of 4 and 6 stratified by site, hospitalization status at the time of acute infection, and body weight (≤70 kg or >70 kg) by an independent researcher at the trial coordinating center (A.R.). Medication kits of colchicine and matching placebo were packed and labeled identically using a unique alphanumerical kit identifier. Following written informed consent, eligible participants were randomized using a web-based randomization system in REDCap, which revealed the kit identifier to be dispensed to the trial participant. The dosing was colchicine, 0.5 mg, once daily for individuals with body weight of 70 kg or less or colchicine, 0.5 mg, twice daily if body weight was greater than 70 kg for 26 weeks starting from the day of randomization.

Outcomes

The primary outcome was the mean difference in change in distance in meters walked in 6 minutes from baseline at 52 weeks. The secondary outcomes were changes from baseline in distance walked during a 6MWT at 12 and 26 weeks; changes in baseline quality-of-life scores, anxiety scores, and depression scores; post-6MWT dyspnea scores; maximal desaturation during the 6MWT; high-sensitivity CRP levels; fatigue scores; and self-reported symptom counts at 12, 26, and 52 weeks. Other secondary outcomes include the change from baseline at 26 and 52 weeks in percentage FVC, percentage FEV_1, and FEV_1/FVC ratio. Further details about trial outcomes are reported in the protocol.[14]

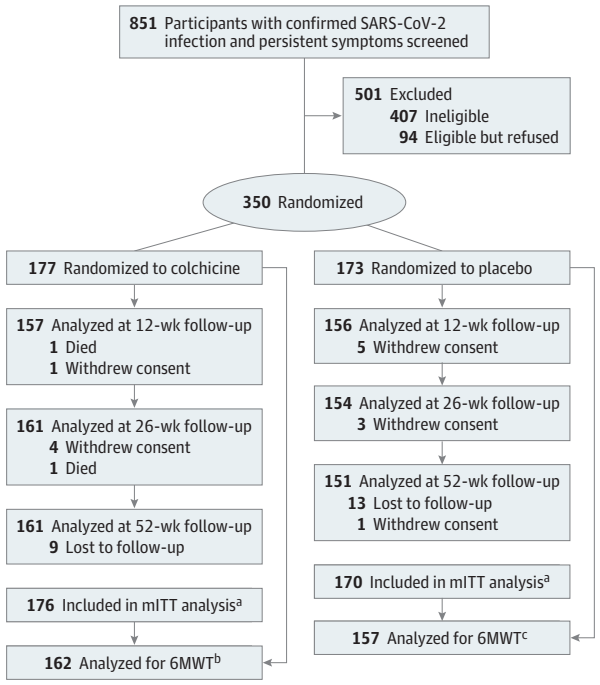
Statistical Analysis

A total of 350 participants were required to detect a difference of 30 m between 2 groups in 6MWT,[20] assuming a dropout of 15% and a common standard deviation of 80 m (90% power at a 2-sided significance level of .05).

Primary and secondary effectiveness outcomes were analyzed using a repeated-measures mixed-effects model following the modified intention-to-treat principle that included all randomized patients eligible as per the protocol and who had taken at least 1 dose of the trial medication. The changes from baseline values at 12, 26, and 52 weeks were the dependent variable. Participants without any follow-up data were excluded from analysis. The main analysis included baseline value, treatment group, visit time, and the variables used for stratified randomization—hospitalization at the time of infection and body weight as fixed effects. A random site effect was included to model within-site correlations, assuming an exchangeable correlation structure, and correlation between repeated measurements from the same participant was modeled using an unstructured covariance matrix. The effect of the intervention was estimated as the adjusted mean difference at 52 weeks, together with its 95% CI. The same model was used to estimate the effect at 12 and 26 weeks. This analysis included all participants with a baseline measurement and at least 1 postbaseline measurement. Subgroup analysis was carried out for the following subgroups: body weight (<70 kg vs ≥70 kg), hospitalization at the time of COVID-19 infection (yes or no), sex (male or female), and any comorbidity (yes or no). The per-protocol population was defined as all randomized participants who were noncompliant to study treatment (compliance <80%), for reasons known to be unrelated to AEs (eg, due to supply or collection issues). No statistical adjustment for multiplicity was made. A detailed statistical analysis plan was published before unblinding and database lock.[21] The statistical analysis plan includes details about adjusted analyses, sensitivity analyses, and per-protocol analyses. There was no planned interim analysis for efficacy when 12-week and 26-week data were complete. However, a blinded interim report was reviewed for safety and data quality by the trial independent data safety monitoring board when 118 participants had completed 12-week follow-up, and the recommendation was to continue the trial as per plan.

All continuous variables were analyzed using repeated-measures linear mixed-effects model. Significance was set at

Figure 1. CONSORT Flowchart



mITT indicates modified intention to treat; 6MWT, 6-minute walk test.

[a]mITT population (defined as all randomized patients who have taken at least 1 dose of randomly assigned treatment).

[b]One died before 12-week visit, 5 withdrew consent and had no visits, 3 had no visits, and 5 had follow-up visits (telephonic) but no 6MWT measures.

[c]Six withdrew consent and had no visits, 4 had no visits, and 3 had follow-up visits (telephonic) but no 6MWT measures.

$P < .05$, and all P values were 2-tailed. Analyses were conducted using R version 4.4.1 (The R Foundation). Data were analyzed from January to February 2025.

Results

A total of 851 patients were screened for eligibility between January 2022 and July 2023, of whom 350 were randomized: 177 to the colchicine group and 173 to the placebo group (**Figure 1**). At 12 weeks, 157 (88.7%) in the colchicine arm and 156 (90.2%) in the placebo arm completed the follow-up. There was no difference in the characteristics of those who visited and those who did not visit the hospital. The modified intention-to-treat analysis included 162 and 157 participants in the colchicine and placebo groups, respectively.

Table 1 presents the baseline characteristics of the overall population and the 2 study groups. Of 346 participants included in the modified intention-to-treat analysis, 209 (60.4%) were female, 137 (39.6%) were male, and the mean (SD) age was 46 (12) years. The mean (SD) weight was 65 (13) kg. The mean (SD) systolic and diastolic blood pressure were 124 (16) mm Hg and 80 (10) mm Hg, respectively, while the mean (SD) resting oxygen saturation was 98% (2%).

Table 1. Baseline Characteristics of Participants Assigned to the Colchicine or Placebo Groups

Characteristic	Participants, No. (%)	
	Colchicine (n = 176)	Placebo (n = 170)
Demographic characteristics		
Age, mean (SD), y	46 (13)	46 (12)
Sex		
Female	109 (62)	100 (59)
Male	67 (38)	70 (41)
Weight, mean (SD), kg	66 (14)	64 (12)
Vital signs		
Blood pressure, mean (SD), mm Hg		
Systolic	125 (17)	122 (15)
Diastolic	81 (10)	80 (10)
Resting oxygen saturation, mean (SD), %	98 (1)	98 (2)
New York Heart Association functional classification		
I	33 (19)	28 (16)
II	139 (79)	137 (81)
III	4 (2)	5 (3)
COVID-19 history and treatment		
Polymerase chain reaction testing	122 (69)	111 (65)
Time since diagnosis, median (IQR), wk	74 (49-93)	78 (54-96)
Required hospitalization	68 (39)	53 (31)
Required intensive care unit admission	4 (2)	11 (7)
Oxygen therapy	28 (16)	24 (14)
Ventilation support required	0	4 (2)
Post-COVID-19 Functional Status scale grade 2 or more	162 (92)	157 (92)
Laboratory results		
Neutrophil to lymphocyte ratio, median (IQR)	1.62 (1.29-2.22)	1.64 (1.30-2.10)
High-sensitivity C-reactive protein, median (IQR), mg/dL	5 (3-9)	5 (3-10)
Comorbidities		
Diabetes	28 (16)	29 (17)
Hypertension	31 (18)	31 (18)
Chronic respiratory illness	5 (3)	5 (3)
Past history of acute coronary event	1 (1)	1 (1)
Chronic kidney disease	2 (1)	1 (1)
Symptoms		
Myalgia	134 (76)	115 (68)
Breathlessness	109 (62)	109 (64)
Insomnia	75 (43)	67 (39)
Headache	71 (40)	60 (35)
Cough	58 (33)	65 (38)
Palpitations	48 (27)	35 (21)
Anorexia	38 (22)	38 (22)
Sore throat	36 (20)	28 (16)
Chest pain	32 (18)	25 (15)
Dizziness	27 (15)	33 (19)
Anosmia	4 (2)	2 (1)
Concomitant medications		
β-Blockers	9 (5)	7 (4)
Angiotensin II receptor blockers	5 (3)	2 (1)
Aspirin	8 (5)	10 (6)
Antidepressants	1 (1)	2 (1)

SI conversion factor: To convert C-reactive protein to mg/L, multiply by 10.

The median (IQR) time since COVID-19 diagnosis was 78 (52-93) weeks, and 319 participants (92.2%) had a PCFS scale grade of 2 or more. The median (IQR) CRP level was 5 (3-9) mg/

dL, and the median (IQR) neutrophil to lymphocyte ratio was 1.63 (1.30-2.12), similar in both groups. Regarding the clinical course of COVID-19, 121 participants (35.0%) had required hospitalization, with a higher proportion in the colchicine group (68 [38.6%]) compared with the placebo group (53 [31.2%]). Intensive care unit admission was reported in 15 participants (4.3%), more often in the placebo group (11 [6.5%]) than in the colchicine group (4 [2.3%]). Ventilation support was required by 4 participants (1.2%), all in the placebo group.

The prevalence of comorbidities was comparable across groups, with diabetes and hypertension affecting 57 participants (16.5%) in the colchicine group and 62 (17.9%) in the placebo group. Persistent symptoms following COVID-19 were common, with myalgia reported by 249 participants (72.0%), breathlessness by 218 (63.0%), and insomnia by 142 (41.0%).

Compliance, defined as consuming at least 80% of the prescribed tablets, was similar between groups (colchicine, 134 [76.1%]; placebo, 131 [77.0%]) (eTable 1 in Supplement 3). The most common reason for discontinuation was the inability to visit the site for follow-up at 12 weeks (39 [66%]).

Primary and Secondary Outcomes

The primary outcome, 6MWT distance, was analyzed using data for 319 participants. At the 52 weeks, the mean change from baseline 6MWT distance between the colchicine and placebo groups was 5.59 m (95% CI, -9.00 to 20.18; P = .45), with no statistically significant difference between the groups (**Table 2**). There were no statistically significant differences in 6MWT distance at 12 and 26 weeks. **Figure 2** presents a composite view of the changes in 6MWT performance from baseline to 12, 26, and 52 weeks in both groups. These estimates are valid under the missing-at-random assumption. The effect of missing data under the assumption that data are not missing at random was not assessed, as there was no evidence of treatment difference at 52 weeks in change in 6MWT distance from baseline.

For all other secondary outcomes—namely, maximal desaturation during the 6MWT, Borg dyspnea score after the 6MWT, high-sensitivity CRP, EuroQol 5-Dimension Questionnaire, Patient Health Questionnaire-9, and GAD-7 scores—changes from baseline assessed at 12, 26, and 52 weeks were not statistically significant between the groups. Adjusted modified intention-to-treat analyses produced similar findings for these outcomes, except that GAD-7 scores at 52 weeks were significantly improved in the colchicine group (eTable 2 in Supplement 3). At 52 weeks, there was a statistically significant difference in the change in the FEV_1/FVC ratio between groups (mean difference, 0.04; 95% CI, 0.02 to 0.07; P = .001); however, changes in FVC and FEV_1 measured at 26 and 52 weeks did not differ significantly between groups.

There was no heterogeneity in treatment effect for the 4 a priori subgroups (body weight, hospitalization at the time of COVID-19 infection, sex, and any comorbidity) (eFigure 2 in Supplement 3). Two exploratory subgroup analyses, tertiles of baseline 6MWT distance and time from infection (<24 weeks vs ≥24 weeks), also indicated no treatment difference.

AEs

The incidence of AEs was similar between groups (eTable 3 in Supplement 3). In the colchicine group, a total of 87 AEs were reported by 35 participants (19.9%); in the placebo group, 91 AEs were reported by 30 participants (17.6%).

Most solicited AEs were mild or moderate in severity. Tingling sensation of the fingers or toes was reported in 17 events (13 participants [7.4%]) in the colchicine group, with 15 events classified as mild (12 participants [6.8%]) and 2 as moderate (2 participants [1.1%]), compared with 36 events (20 participants [11.8%]) in the placebo group, with 32 events classified as mild (19 participants [11.2%]) and 4 as moderate (4 participants [2.4%]). Joint or muscle symptoms were the most common unsolicited AE, occurring in 13 events (9 participants [5.1%]) in the colchicine group and 6 events (5 participants [2.9%]) in the placebo group.

Discontinuation of trial medication due to AEs occurred in 3 participants in the colchicine group (3 events [1.7%]) and 1 participant in the placebo group (1 event [0.6%]). Additionally, the colchicine group experienced 2 deaths—one due to suicide and another due to miliary tuberculosis.

Discussion

This multicenter randomized clinical trial evaluating 52-week colchicine therapy against placebo in 350 individuals with long COVID demonstrated no significant improvement in the primary end point of 6MWT distance. Similarly, secondary outcomes, including inflammatory markers, quality-of-life measures, and respiratory function parameters, demonstrated no meaningful improvement with colchicine. Although a statistically significant difference was observed in the FEV_1/FVC ratio at 52 weeks, the direction and magnitude of the change did not indicate clinical relevance. Finally, the AE rates were comparable between groups, despite known gastrointestinal tract tolerability issues with colchicine. We collected several secondary outcomes to encompass the multitude of symptoms that individuals with long COVID present with, including anxiety and depression that have been linked to post-viral infection neuroinflammation.[22,23] The consistency of null findings across all outcomes with a narrow confidence interval indicates conclusively that colchicine does not show a benefit in improving physical and mental symptoms in long COVID.

The definition of long COVID was evolving at the time we developed the trial protocol. The duration of persistent symptoms in the definitions by the World Health Organization and National Institute for Health and Care Excellence guidelines varied from 4 to 12 weeks postinfection[24] and may last until 3 years.[25] While we used a 3-week cutoff for the diagnosis of long COVID, 99% of enrolled patients had symptoms for at least 4 weeks after the index infection, fulfilling the World Health Organization and National Institute for Health and Care Excellence definitions of long COVID.[24]

This trial examined whether delayed colchicine initiation still modulates established postviral inflammation and whether extended 26-week dosing can overcome the transient anti-inflammatory effects observed in prior studies. The

Table 2. Primary and Secondary Outcomes

Outcome	Participants, No.	Group, mean (SD)		Mean difference (95% CI)[a]
		Colchicine	Placebo	
Primary outcome				
Change in 6MWT distance from baseline to 52 wk, m	319	35.55 (19.76)	29.96 (19.83)	5.59 (−9.00 to 20.18)[b]
Secondary outcomes				
Change in 6MWT distance from baseline, m				
12 wk	319	20.41 (19.70)	23.49 (19.73)	−3.09 (−16.88 to 10.71)
26 wk	319	25.34 (19.68)	17.17 (19.73)	8.16 (−5.55 to 21.88)
Maximal desaturation during 6MWT				
12 wk	318	−0.13 (0.49)	−0.07 (0.49)	−0.06 (−0.42 to 0.30)
26 wk	318	−0.09 (0.49)	0.04 (0.49)	−0.13 (−0.57 to 0.32)
52 wk	318	0.05 (0.47)	0.14 (0.48)	−0.09 (−0.31 to 0.12)
Borg dyspnea score after completion of 6MWT				
12 wk	318	−1.17 (0.33)	−1.14 (0.33)	−0.03 (−0.16 to 0.10)
26 wk	318	−1.24 (0.32)	−1.27 (0.32)	0.02 (−0.07 to 0.12)
52 wk	318	−1.23 (0.33)	−1.18 (0.33)	−0.04 (−0.16 to 0.08)
FEV_1 (% predicted)				
26 wk	297	−0.47 (1.98)	0.18 (2.00)	−0.64 (−4.44 to 3.15)
52 wk	297	4.89 (1.90)	3.15 (1.92)	1.74 (−1.62 to 5.10)
FVC (% predicted)				
26 wk	297	1.82 (2.44)	2.55 (2.45)	−0.73 (−3.98 to 2.52)
52 wk	297	3.95 (2.42)	4.79 (2.43)	−0.85 (−3.85 to 2.16)
FEV_1/FVC ratio				
26 wk	297	−0.05 (0.03)	−0.06 (0.03)	0.01 (−0.02 to 0.04)
52 wk	297	−0.02 (0.03)	−0.06 (0.03)	0.04 (0.02 to 0.07)
High-sensitivity CRP, mg/dL				
12 wk	320	1.06 (1.83)	−0.84 (1.84)	1.89 (−1.35 to 5.14)
26 wk	320	−0.08 (1.71)	−0.59 (1.72)	0.51 (−2.17 to 3.19)
52 wk	320	−2.46 (1.53)	−2.60 (1.53)	0.15 (−1.40 to 1.70)
EQ-5D-5L score				
12 wk	327	0.05 (0.02)	0.06 (0.02)	−0.01 (−0.03 to 0.02)
26 wk	327	0.07 (0.02)	0.08 (0.02)	−0.01 (−0.03 to 0.02)
52 wk	327	0.08 (0.02)	0.06 (0.02)	0.01 (−0.02 to 0.04)
PHQ-9 score				
12 wk	327	−1.29 (0.44)	−1.21 (0.44)	−0.08 (−0.69 to 0.53)
26 wk	327	−2.03 (0.43)	−1.97 (0.43)	−0.06 (−0.59 to 0.47)
52 wk	327	−2.31 (0.44)	−1.90 (0.45)	−0.41 (−1.02 to 0.21)
GAD-7 score				
12 wk	327	−1.01 (0.39)	−1.07 (0.39)	0.06 (−0.51 to 0.64)
26 wk	327	−1.69 (0.37)	−1.57 (0.37)	−0.11 (−0.59 to 0.36)
52 wk	327	−1.88 (0.38)	−1.35 (0.39)	−0.52 (−1.07 to 0.03)
Fatigue score				
12 wk	327	−0.32 (1.43)	−0.24 (1.44)	−0.08 (−0.73 to 0.56)
26 wk	327	−0.70 (1.43)	−1.13 (1.44)	0.43 (−0.21 to 1.08)
52 wk	327	−0.80 (1.4)	−0.46 (1.43)	−0.34 (−0.96 to 0.29)
Self-reported symptom count				
12 wk	327	−1.92 (0.23)	−1.78 (0.23)	−0.15 (−0.46 to 0.16)
26 wk	327	−2.10 (0.24)	−2.32 (0.24)	0.22 (−0.14 to 0.57)
52 wk	327	−2.63 (0.23)	−2.42 (0.23)	−0.21 (−0.50 to 0.09)

Abbreviations: CRP, C-reactive protein; EQ-5D-5L, EuroQol 5-Dimension Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GAD-7, Generalized Anxiety Disorder-7; 6MWT, 6-minute walk test; PHQ-9, Patient Health Questionnaire-9.

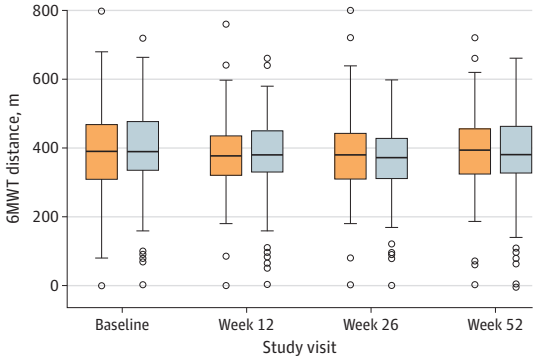
SI conversion factor: To convert C-reactive protein to mg/L, multiply by 10.

[a] All estimates are derived from a repeated-measures linear mixed-effects model, with change from baseline measurements at 12, 26, and 52 weeks as the dependent variables. The model includes fixed effects for treatment group, visit, their interaction, and baseline measurements, as well as random effects for site and repeated measures for visits.

[b] $P = .45$.

26-week treatment duration exceeded prior acute COVID-19 trials yet failed to demonstrate delayed benefits—a finding consistent with recent meta-analyses showing limited efficacy of late immunomodulation.[26] These results contrast with acute

Figure 2. Distribution of 6-Minute Walk Test (6MWT) Distance in the Colchicine and Placebo Groups



Patients, No.				
Colchicine	176	153	152	147
Placebo	170	149	147	140

Midlines indicate medians; boxes, IQRs; whiskers, minimum and maximum values; and data points, outlier observations.

COVID-19 trials where colchicine reduced hospitalizations by 25% when initiated 7 days or less postinfection but align with the PRINCIPLE trial's null findings for community-treated COVID-19.[27] This temporal dichotomy supports emerging pathophysiological models, where early viral replication and late autoimmune/inflammatory mechanisms represent the need for distinct therapeutic targets.

Several factors may help explain these null findings. One potential explanation relates to the characteristics of the study population. The trial's broad enrollment criteria (any persistent symptom ≥3 weeks) likely included multiple long COVID endotypes that could have had differing treatment responsiveness. However, we were unable to demonstrate any heterogeneity in the subgroup analysis. Overall, the high-sensitivity CRP values were marginally elevated, indicating that most participants exhibited only a mild inflammatory state. Although recruitment for this study began in January 2022, most participants were enrolled in the latter half of 2022 and early 2023 —a period dominated by the Omicron variant. Compared with the Delta variant, the Omicron variant was associated with milder disease, a lower inflammatory response, and significantly reduced odds of developing long COVID.[28] In addition, most participants were enrolled a median of over 1 year after their acute SARS-CoV-2 infection; natural recovery processes may have influenced the outcomes, even though complete recovery remains unlikely.[29] Together, these factors may have reduced the potential for observable benefits from the intervention. Moreover, 19% of controls showed a 50 meter or greater improvement in 6MWT distance, potentially obscuring modest treatment benefits.

Furthermore, while no prior studies, to our knowledge, have specifically assessed colchicine for long COVID, findings from other interventions offer useful comparisons. A trial of the antidepressant vortioxetine for post-COVID-19 cognitive dysfunction showed benefits only in participants with elevated high-sensitivity CRP, reinforcing the potential importance of heightened inflammation in driving therapeutic responses.[30] Additionally, a single-arm study involving low-dose naltrexone and nicotinamide adenine dinucleotide reported improvements in fatigue among patients with severe postviral fatigue syndrome, suggesting that targeting subgroups with pronounced symptoms may yield better outcomes.[6] However, an exploratory subgroup analysis of the effect of colchicine across levels of high-sensitivity CRP did not show any difference.

Another possible explanation for the lack of significant benefit is that although colchicine's anti-inflammatory properties were anticipated to be beneficial, targeting systemic inflammation alone may not be sufficient to address the complex symptoms of long COVID fully. Emerging evidence suggests that these symptoms are influenced by a variety of factors, including vascular inflammation, immune dysregulation, mitochondrial dysfunction,[13] impaired cellular bioenergetics, and alterations in the gut microbiome.[31-34] The interplay among these factors likely contributes to the ongoing challenge of identifying effective treatments.

Strengths and Limitations

To our knowledge, this multicenter, placebo-controlled trial represents the first rigorous evaluation of prolonged colchicine therapy targeting long COVID's inflammatory substrate. The study has several strengths. Its multicenter design, which incorporates large hospitals and first-time clinical trial sites in rural India, is a novel feature. The rigorous double-blind design combined with a 52-week follow-up enabled a comprehensive assessment of colchicine's long-term effects. By addressing both functional and patient-centered outcomes, the study provides a comprehensive understanding of the impact of long COVID. Additionally, comparable compliance and attrition rates between arms, as well as consistent null findings across subgroups and sensitivity analyses, bolster confidence in the reliability of the results.

We overcame key limitations of prior observational studies by using a stratified randomization design accounting for hospitalization at the time of the acute infection. The selection of 6MWT distance as the primary end point aligns with US Food and Drug Administration guidance on functional outcomes in postviral syndromes, while serial cytokine profiling enables mechanistic correlations. Further, 6MWT is an objective and inexpensive way of measuring cardiopulmonary and physical function. Future studies with 6MWT distance as the primary outcome should ensure stringent follow-up of all patients until an alternative, more specific tool is developed to capture all symptoms of long COVID that is responsive to change. With a 52-week follow-up that captures relapse patterns and delayed treatment effects, this study addresses the urgent calls from the World Health Organization Long COVID Task Force for therapeutic trials that target the syndrome's fluctuating nature.

However, this study has limitations. Underrepresentation of severe acute COVID-19 survivors (12% hospitalized) and the long interval since participants' acute SARS-CoV-2 infection indicated recruitment of participants with milder symptomatic and inflammatory states at baseline.

Conclusions

In this randomized clinical trial, colchicine did not improve functional capacity or respiratory function or reduce inflammatory markers in individuals with persistent symptoms following long COVID. This rigorous trial provides definitive evidence against colchicine monotherapy as a broadly effective long COVID treatment. The consistently null findings across several outcomes emphasize the need to explore alternative therapeutic strategies for long COVID and underscore the need of disentangling long COVID's biological subtypes through deep phenotyping.

ARTICLE INFORMATION

Accepted for Publication: August 24, 2025.

Published Online: October 20, 2025. doi:10.1001/jamainternmed.2025.5408

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Obtained funding: Rathore, Jha.
Administrative, technical, or material support: Bassi, Thankachen, Rastogi, Bahuleyan, Gummidi, Basheer, Prabhakaran Sreelal, Bangi, Sahu, Rathore, Bhalla, Samita, Moni, Dipu, Jain, Prajapati, Bodhey, Jha.
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Conflict of Interest Disclosures: Dr Bangi reported personal fees from the Jivanrekha Multispeciality Hospital during the conduct of the study. Dr Bhalla reported grants from the George Institute for Global Health during the conduct of the study. Dr Jha reported personal fees from Vera, AstraZeneca, Biogen, Otsuka, Visterra, George Clinical, Boehringer Ingelheim, and Novartis outside the submitted work. No other disclosures were reported.

Funding/Support: This trial was funded by Indian Council of Medical Research grant ECD/CSTPU/Adhoc/COVID-19/13-2021-22.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 4.

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