



Colchicine Against SARS-CoV-2 Infection: What is the Evidence?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a matter of concern worldwide and a huge challenge for rheumatologists. Indeed, several antirheumatic drugs are currently used at different stages of COVID-19, such as several cytokine inhibitors and colchicine. Colchicine is one of the oldest medicines with potent anti-inflammatory properties. In rheumatic diseases it is widely used for the treatment of gout, calcium pyrophosphate deposition disease, and familial

Mediterranean fever. It is also used off-label in cardiology to treat atrial fibrillation, pericarditis, and myocardial infarction. Over the last few years, advances in the understanding of colchicine's mechanism of action and its pharmacology and safety have made colchicine a promising candidate agent for the fight against COVID-19. In this review, we discuss COVID-19 pathophysiology highlighting colchicine's mode of action, its pleiotropic effects on neutrophils, inflammasome inhibition, and its viral activity. Finally, we discuss the main clinical studies dealing with the use of colchicine in COVID-19. Given the large body of evidence that demonstrates its effectiveness, safety, and its simple way of administration, colchicine seems to be a promising drug to reduce the risk of severe COVID-19 disease.

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Key Summary Points

Systemic and uncontrolled inflammation of the innate and adaptive immune system is the hallmark of COVID-19 disease.

In the absence of effective treatment, off-label drugs are used, among them colchicine.

Colchicine interferes with several inflammatory pathways including chemotaxis, adhesion and activation of neutrophils, inflammasome activation, and cytokine release.

Given the fact that colchicine is effective, well tolerated, inexpensive, and has a simple dosage scheme, it seems to be a promising drug to reduce the risk of severe COVID-19 disease.

INTRODUCTION

Systemic inflammation is the hallmark of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The result is an exaggerated inflammatory response of the innate and adaptive immune system known as cytokine release syndrome (CRS). When CRS occurs, several immunological alterations are taking place such as the production and secretion of a plethora of pro-inflammatory cytokines like interleukin (IL)-1 β , IL-6, IL-18, and tumor necrosis factor alpha (TNF α) [1]. COVID-19 is a matter of concern and a huge challenge for the rheumatologists dealing with patients suffering from autoimmune rheumatic diseases (ARD), because several antirheumatic drugs are used at different stages of COVID-19 [2–4]; these drugs include colchicine and cytokine inhibitors against IL-1 β , IL-6, and TNF α [3–5]. However, none of the aforementioned treatment regimens have been proven to be completely

efficacious. Colchicine is an old drug which has been used for many years to treat gout, calcium pyrophosphate deposition disease (CPPD), and familial Mediterranean fever (MMF). Colchicine is used off-label for some heart diseases, like pericarditis, atrial fibrillation, and myocardial infarction [6, 7]. However, over the last few years, advances in the understanding of colchicine's mechanism of action, pharmacology, and safety have changed treatment perspectives for this old drug [8]. Indeed, during the last year it has been used as a potential therapeutic agent against SARS-CoV-2. As physicians gain more experience from its use, there are some contradictory results with encouraging data on one side that favor its use [9] and data that supports its ineffectiveness on the other side [10]. In this review, we discuss COVID-19 pathophysiology highlighting colchicine's mode of action, its pleiotropic effects on neutrophils, inflammasome inhibition, and its viral activity, and we try to give answers to the aforementioned argument, after searching the relevant literature. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

SEARCH STRATEGY

In this narrative review, we searched Medline and Scopus for clinical studies evaluating colchicine for COVID-19. More specifically, we searched for double-blind randomized, open-label randomized, placebo-controlled, cohort, case control, cross-sectional, observational, and retrospective studies.

SARS-COV-2 INFECTION

SARS-CoV-2 is a single-stranded RNA (ssRNA) virus that belongs to the coronavirus family. Coronavirus has an enveloped spherical morphology. The virus affects the host's cells through its receptor-binding domain, which is located in the subunit S1 of the S protein. This receptor can attach to the host's cell receptor angiotensin-converting enzyme 2 (ACE2), located on the cell membrane and invade mostly

the epithelial and alveolar cells of the respiratory system. ACE2 is also frequently present in endothelial cells of many vessels, heart, kidneys, and other tissues [11]. Clinical manifestations of COVID-19 range from asymptomatic to a flu-like syndrome with fever, fatigue, myalgias, and sore throat, to even more severe such as shortness of breath, dry cough, high fever, pneumonia, and hypoxia. In severe cases, the disease progresses rapidly and patients can develop septic shock, multiorgan dysfunction, and thrombotic diathesis. Furthermore, the disease is characterized by the presence, in the peripheral blood, of high acute phase reactants, like C-reactive protein (CRP), high levels of ferritin, fibrinogen, and D-dimers. Leukopenia (especially lymphopenia), anemia, and thrombocytopenia may also occur [12]. The aforementioned clinical manifestations and laboratory abnormalities are the result of an uncontrolled release of pro-inflammatory cytokines like IL-1 β , IL-6, IL-18, TNF α , and chemokines occurring during the COVID-19 disease course. More specifically, once the virus has infected the alveolar cells, it takes over and begins to make copies of itself and multiply. Then, the virus propagation causes tissue injury and thus the host's innate immune system is activated. Indeed, signals driven by SARS-CoV-2 such as the pathogen-associated molecular patterns (PAMPs) (viral RNAs) and damage-associated molecular patterns (DAMPs) (cellular debris) act on resident tissue cells—macrophages (M Φ s) and dendritic cells (DCs)—which activate and try to protect the host against the invader. M Φ s recognize SARS-CoV-2 through ACE2 and other sensors such as the Toll-like receptors (TLRs) and NOD-like receptors (NLRs), leading to further release of pro-inflammatory cytokines and chemokines. M Φ s can also present viral RNA to T cells and mount the adaptive immune response consisting of T cell activation and the generation and release of many cytokines leading to CRS [1, 13, 14]. In addition, B cells can be activated with the production of antibodies against the viral proteins (Fig. 1). M Φ -driven inflammation leads to NLR pyrin protein 3 (NLRP3) inflammasome and caspase-1 activation to generation and release of IL-1 β . Activation of M Φ s leads also to the

production of IL-6, TNF α , and other cytokines. These cytokines cause increased vascular permeability, upregulation of adhesion molecules on endothelial cells (E-selectins) and leukocytes (L-selectins), as well as recruitment of neutrophils and monocytes in the setting of inflammation. Then, neutrophils invade the host tissue through the inflamed endothelium and cause tissue damage, initially in the lung parenchyma and later on to other organs. When neutrophils migrate and invade the inflamed tissue, they degranulate releasing further pro-inflammatory cytokines, proteases, superoxide (oxygen radicals), and α -defensin, which inhibit tissue factor pathway inhibitor with generation of thrombin, platelet activation, and thrombosis (Fig. 2) [11, 14].

COLCHICINE'S MODE OF ACTION

Colchicine is a tricyclic lipid-soluble alkaloid extracted from the plant *colchicum autumn crocus* and it is one of the oldest anti-inflammatory drugs. In rheumatic diseases colchicine is widely used for the treatment of acute gout arthritis, prophylaxis against gout flares, and treatment of CPPD and FMF [6, 7]. In addition, it is used off-label in some heart diseases like pericarditis, myocardial infarction, and others [15]. Its primary mechanism of action is tubulin disruption leading to downregulation of multiple inflammatory pathways and modulation of innate immunity. More specifically, colchicine has the capacity to bind to tubulins, thus blocking the assembly of microtubule polymerization. Microtubules are key components of the cytoskeleton and are involved in many cellular processes (maintaining the cell shape, intracellular trafficking, regulation of ion channels, cell deviation and mitosis, as well as cytokine and chemokine generation and release). At low concentrations, colchicine arrests microtubule growth and at high concentrations it promotes microtubule depolymerization [6–8]. Thus, the main mechanisms of action on innate immune response include the inhibition of neutrophil chemotaxis, neutrophil adhesion, mobilization and recruitment, inhibition of superoxide and α -defensin from

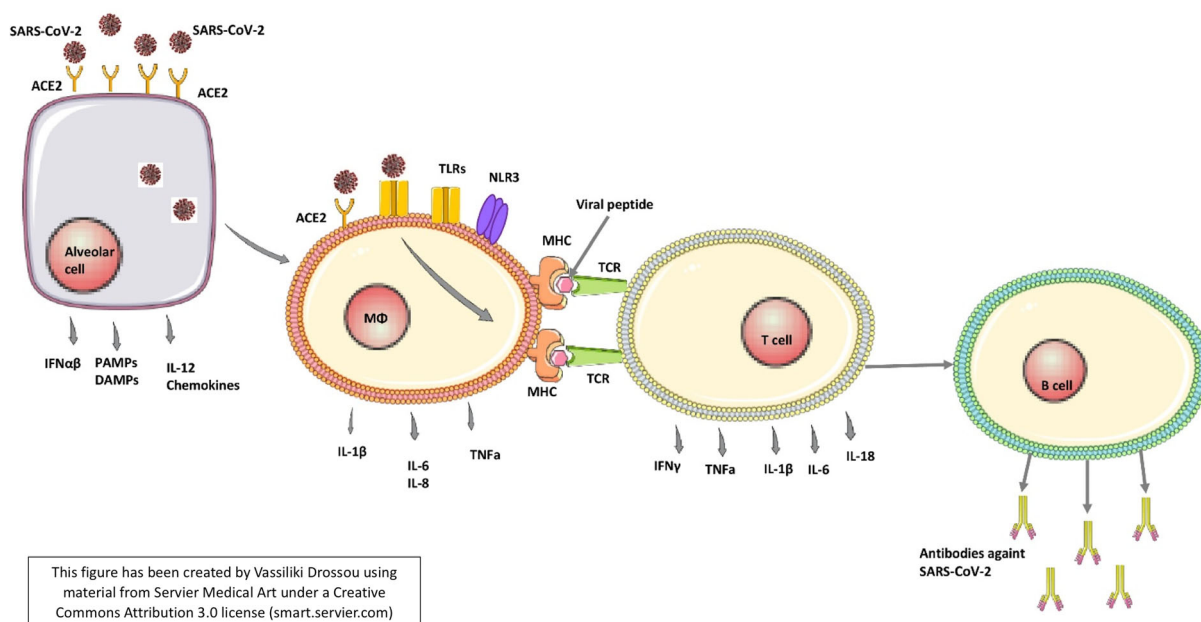


Fig. 1 SARS-CoV-2 infection and exaggerated inflammatory response by innate and adoptive immunity. *ACE2* angiotensin-converting enzyme 2, *IFN- $\alpha\beta$* interferon- $\alpha\beta$, *IL-12* interleukin-12, *PAMPs* pathogen associated molecular patterns, *DAMPs* damage associated molecular

patterns, *IL-1 β* interleukin-1 β , *IL-6* interleukin-6, *IL-8* interleukin-8, *TNF α* tumor necrosis factor alpha, *TLRs* Toll-like receptors, *NLR3* NOD-like receptor 3, *MHC* major histocompatibility complex, *TCR* T cell receptor

neutrophils, and inhibition of NLRP3 inflammasome (Fig. 2). Indeed, it is known that monosodium urate (MSU) and calcium pyrophosphate dehydrate (CPP) crystals potentially stimulate a characteristic protein tyrosine phosphorylation pattern in human neutrophils. Precipitation of MSU and CPP crystals are responsible for the development of gout arthritis and CPPD, respectively. In a study by Roberge et al. the effects of colchicine on protein tyrosine phosphorylation induced by MSU and CPP crystals in human blood neutrophils were investigated. The results showed that colchicine specifically and significantly inhibits the protein tyrosine phosphorylation and suggests that its effects are associated with its intervention with microtubules [16]. This interaction blocks NLRP3 inflammasome formation and activation by inhibiting microtubule polymerization and attenuates M Φ s NLRP3 inflammasome arrangement and activation [17]. Through microtubule depolymerization, colchicine interferes with the recruitment

and adhesion to the inflamed tissue [18] and suppresses superoxide production by neutrophils [19]. Furthermore, in a murine model, it has been shown to inhibit neutrophil release of α -defensin [20].

After a single dose of 0.6 mg of colchicine, its plasma concentration is approximately 3 nmol/L, while neutrophils can contain levels of 40–200 nmol/L [21]. Many experiments performed in vitro used large doses of colchicine that are not feasible for use in humans. On the other hand, a standard low dose of colchicine (0.6 mg) drastically reduced serum levels of inflammasome products and caspase-1 monocyte production [22].

COLCHICINE AND COVID-19

For severe cases of COVID-19, the treatment requires antiviral therapy, dexamethasone, and supportive care. However, in the last year biological therapies and colchicine have been used as potential therapeutic agents against the

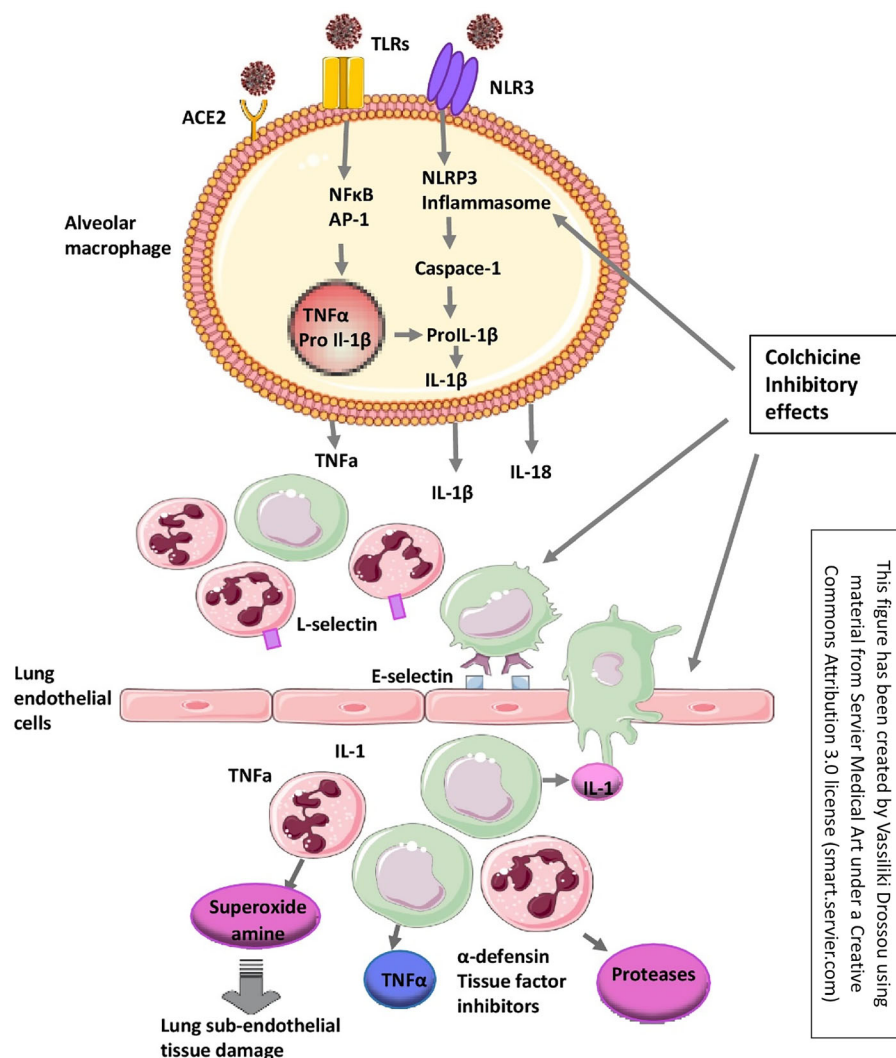


Fig. 2 SARS-CoV-2 disease pathophysiology and colchicine’s inhibitory effects. *ACE2* angiotensin-converting enzyme 2, *TLRs* Toll-like receptors, *NLR3* NOD-like receptor 3, *NFκB* nuclear factor κB, *AP-1* activator

protein 1, *TNFα* tumor necrosis factor alpha, *ProIL-1β* pro-interleukin-1β, *NLRP3* NOD-like receptor protein 3, *IL-1β* interleukin-1β

SARS-CoV-2 infection [4, 8, 9, 17]. Indeed, in patients with ARD who contracted COVID-19 whilst receiving biological therapies (especially cytokine inhibitors), the disease expressed with mild systemic manifestations, less hospitalization, and less severe complications [23–25]. On the other hand, in patients with FMF or gouty arthritis receiving colchicine, the disease manifested without severe respiratory complications and they recovered without additional treatment [26–28]. All the aforementioned results indicate that the chronic use of biological

therapies and colchicine may mitigate the clinical picture and the disease course. The question that arises here is what may biological therapies and colchicine have in common in the setting of SARS-CoV-2 infection? The answer is that both therapeutic strategies target the same pathway leading to IL-1β and IL-6 production—colchicine through its pleiotropic mechanism of action on neutrophils and inflammasome inhibition, while biological therapies through direct inhibition of IL-1β (anakinra) and IL-6 (tocilizumab). Thus, given

the large body of evidence demonstrating the inhibitory effects on neutrophil activity, cytokine generation, inflammation and thrombosis interface, it is rational to investigate colchicine as a potential therapeutic agent against SARS-CoV-2 infection [8, 17].

COLCHICINE STUDIES IN COVID-19

The multicenter, open-label randomized RECOVERY trial in the UK demonstrated a 28-day mortality reduction with the use of dexamethasone ($n = 2104$), versus usual care ($n = 4321$), in hospitalized patients with severe COVID-19 disease [29]. These results supported the idea that an anti-inflammatory therapeutic strategy in COVID-19 may be useful to reduce mortality. In the last few decades, several studies have demonstrated the potent anti-inflammatory effect of colchicine on gout arthritis, FMF, and its cardioprotective effects, in various clinical aspects like pericarditis, atrial fibrillation, and myocardial infarction [30–32]. On the other hand, myocardial injury appears to be a major component in COVID-19. Thus, colchicine was selected as a candidate agent to be used in these patients. The main clinical studies evaluating the effectiveness of colchicine in COVID-19 are depicted in Table 1. The GRECO-19 study from Greece was the first prospective open-label randomized trial that evaluated colchicine use versus standard care (SC) in 105 early hospitalized patients. Patients receiving colchicine had a significant improvement in time to clinical deterioration and suppression of D-dimers versus the control group [9]. A second study from Italy compared 122 hospitalized patients receiving colchicine plus SC and 140 hospitalized patients receiving SC alone. The results showed that colchicine had a significant mortality benefit (84% vs 64% survival), when compared to control group [33]. The third prospective double-blind randomized study evaluated 38 hospitalized patients with COVID-19 receiving colchicine versus 37 receiving placebo. It was demonstrated that colchicine use reduced mortality, supplemental oxygen therapy, and hospitalization [34]. In a large placebo-controlled trial ($n = 4488$) (COLCORONA),

Tardif et al. evaluated the use of colchicine in patients testing positive for SARS-CoV-2 at the time of inclusion, regardless of symptoms, with at least one identified risk factor for COVID-19 complications. This study demonstrated that patients on colchicine had lower rates of death or hospital admission than those in the placebo group [35]. In a small case series, nine outpatients with COVID-19 received colchicine, of whom only one was finally hospitalized. The hospitalized patient received oxygen therapy for 4 days and was discharged without any additional therapy [36]. Brunetti et al.'s matched cohort study evaluated 66 hospitalized patients. Of those, 33 were receiving colchicine plus SC, versus SC only. After 28 days of follow-up, patients on colchicine were five times more likely to be discharged with fewer deaths compared to those receiving the SC alone [37]. In a case control study, Sandhu et al. evaluated 197 patients. Patients were assigned to receive colchicine plus SC or SC only. Patients receiving colchicine had lower rates of intubation (47% vs 87%) and mortality (47% vs 80.8%) compared to the control group [38]. In a retrospective study, Mahale et al. evaluated 134 patients with COVID-19 who were admitted to hospital and received immunomodulatory agents (hydroxychloroquine, methylprednisolone, colchicine, etoricoxib, and tocilizumab) in different combinations. It was shown that patients receiving colchicine had reduced hospital mortality [39]. García-Posada et al.'s observational study of 209 patients with COVID-19 who were admitted to hospital evaluated the effect of (1) antibiotics plus low molecular weight heparin (LMWH) plus corticosteroids and colchicine, (2) antibiotics plus LMWH plus corticosteroids, (3) LMWH plus corticosteroids, (4) LMWH plus corticosteroids and colchicine, (5) tocilizumab. Colchicine combination therapy reduced the mortality rate, compared to other therapeutic strategies [40]. In another observational study, Kevorkian et al. evaluated the effect of a five-drug regimen consisting of a 5-day course of prednisone, furosemide, salicylate, anti-Xa inhibitor, and colchicine in 68 hospitalized patients with COVID-19. This treatment regimen had a beneficial effect on mortality rate in these patients [41]. In a cross-sectional study

Table 1 Clinical trials evaluating the effectiveness of colchicine against SARS-CoV-2 infection

Author, reference, year, country	Study design	Number of patients	Colchicine dose	Setting	Outcome
Deftereos [9], 2020, Greece	Open-label randomized	105	1.5 mg loading dose, then 0.5 mg \times 2	Inpatient	Improvement time to clinical deterioration, D-dimer suppression
Scarsi [33], 2020, Italy	Single-center cohort	272	1 mg/day	Inpatient	Significant mortality benefit (84% vs 64% survival)
Lopez [34], 2021, Brazil	Double-blind randomized	75	0.5 mg \times 3/5 days 0.5 mg \times 2./5 days	Inpatient	Reduced the length of death, oxygen therapy, and hospitalization
Tardif [35], 2021, Canada	Placebo controlled	4488	0.5 mg \times 2/13 days then 0.5 mg daily/27 days	Outpatient	Low rate of composite of death and hospitalization
Brunetti [37], 2020, USA, New Jersey	Matched cohort	66	1.2 mg loading dose, then 0.6 mg \times 2	Inpatient	Five times more likely to be discharged, fewer deaths
Sandhu [38], 2020, USA, New York	Case control	197	0.6 mg \times 2/3 days then 0.6 mg daily/12 days	Inpatient	Low rate of intubation (47% vs 87%), lower mortality (47% vs 80, 8%)
Mahale [39] 2020, India	Retrospective	134	0.5 mg/day for 1 week	Inpatient	Reduced mortality
García-Posada [40], 2021, Colombia	Observational	209	20 days	Inpatient	Reduced mortality
Kevorkian [41], 2021, France	Observational	68	1 mg followed by 0.5/h later, then 0.5/8 h for total 8 mg	Inpatient	Reduced mortality
Pinzón [42], 2021, Colombia	Cross-sectional	301	0.5 mg twice for 7–14 days	Inpatient	Reduced mortality

Pinzón et al. evaluated the use of colchicine in 301 patients with COVID-19 pneumonia. Of these, 145 received corticosteroids plus colchicine 0.5 mg \times 2 for 7–14 days, 95 corticosteroids alone, and 90 patients placebo. Patients receiving corticosteroids plus colchicine had better mortality rates than those receiving steroid alone [42]. Finally, Estebanez et al. proposed a randomized open-label multicenter clinical

trial, in everyday clinical practice, as an early therapeutic intervention with the use of colchicine at 0.5 mg twice for 3 days and then 0.5 mg for 18 days in patients infected with SARS-CoV-2 over 60 years of age with at least one additional comorbidity [43]. In line with the aforementioned results, Dupuis et al. reported that colchicine reduced acute lung injury and respiratory failure in experimental

acute respiratory distress syndrome [44]. A systematic review and meta-analysis showed that colchicine treatment was associated with a significantly lower rate of mortality in patients with COVID-19 [45]. Three more meta-analyses documented the benefit of colchicine in the treatment of patients with COVID-19. More specifically Golpour et al. reported that colchicine therapy was associated with a decreased rate of mortality and decrease in hospitalization time (days) [46]. Moreover, Salah and Mehta's meta-analysis on the effect of colchicine on mortality and mechanical ventilation in COVID-19 showed a possible mortality benefit associated with the use of colchicine in these patients [47]. In another meta-analysis, Vrachatis et al. suggest a definite benefit regarding mortality rates with the addition of colchicine in patients with COVID-19 [48].

CONCLUSIONS

All the discussed studies deal with colchicine and COVID-19, but they differ in many aspects, e.g., timing and dosing of colchicine. Furthermore, some studies measure the clinical improvement, others the laboratory results, whereas others measure a composite outcome. The optimal dose and treatment duration in patients with COVID-19 is not known. However, to prevent gout attacks the daily dose is 1–1.2 mg/day and treatment duration is 3–9 months [6, 7]. Finally, the timing of colchicine initiation is uncertain. Some investigators begin colchicine in the early inpatient setting, others in the outpatient setting. On the other hand, colchicine is an anti-inflammatory agent, which interferes with several inflammatory pathways, including chemotaxis, adhesion and activation of neutrophils, inflammasome activation, and cytokine release and superoxide production. Given the fact that colchicine is well tolerated, inexpensive, and has a simple dosage scheme, it holds particular promise to reduce the risk of severe COVID-19 disease in both the outpatient and inpatient setting. However, further well-designed studies with a large number of patients are needed to answer this thesis.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Owing to the nature of the manuscript and because no sensitive data of the patients are enclosed there was no need to get permission from our university's ethics committee.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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