



# Colchicine as a Potential Therapeutic Agent Against Cardiovascular Complications of COVID-19: an Exploratory Review

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## Abstract

Coronavirus disease-19 (COVID-19) may result in serious complications involving several organ systems, including myocardial tissue. An exaggerated host inflammatory response, described as a cytokine storm, has been linked to play a major role in these complications. Colchicine and other pharmaceutical agents have been proposed to counter the cytokine storm and improve outcomes. In this exploratory review, we utilized a PubMed and Cochrane Database search aiming to identify the biochemical characteristics of the cytokine storm as well as to identify the potential effect of colchicine on these inflammatory biomarkers. The research yielded 30 reports describing the characteristics of the cytokine storm and 44 reports describing the effect of colchicine on various inflammatory biomarkers. According to our research, colchicine may be an agent of interest in the treatment of COVID-19 via its anti-inflammatory properties. However, there are potential drug interactions with cytochrome P450 3A4 inhibitors resulting in acute colchicine toxicities. Additionally, there is scarce evidence regarding the efficacy of colchicine in the acute phase of disease, since most trials evaluated its effect in chronic conditions. In this direction, our team proposes three different hypotheses for evaluating the place of colchicine in the treatment of COVID-19.

**Keywords** COVID-19 · Coronavirus · Virus · Colchicine · Cardiovascular disease · CVD

## Introduction

As of December 2019, a novel coronavirus named severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 has emerged in Wuhan Province in China [1]. Since then, SARS CoV-2 has demonstrated high human to human transmission rates and has developed into a worldwide pandemic

[2]. To date (April 26, 2020), there have been almost 2.8 million confirmed cases as well as over 193,722 deaths attributed to coronavirus disease-19 (COVID-19) according to WHO [3]. Since the original outbreak, a large number of reports have emerged describing all relevant aspects of COVID-19 [4].

The focus of this report is on the exaggerated host inflammatory response, most often described as a cytokine storm that is reported in critically ill patients [5]. This seems to play a major detrimental role in the development of complications and ultimately death associated with COVID-19 [5, 6]. Recent focus has therefore been placed on identifying anti-inflammatory pharmaceutical agents that could be repurposed in an attempt to reduce complications and improve the survival rates of the infection. One such molecule is colchicine, an agent that has been used for several years in the treatment of auto-immune diseases, most relevantly that of post-viral pericarditis [7].

Colchicine is a phytochemical compound that was originally derived from autumn crocus. The use of this plant in the treatment of inflammatory conditions may date back to 1500

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**Table 1** The findings of four retrospective trials from China with regard to the different biomarkers that are elevated in COVID-19

Studies	Methods	Groups	Number	CK (U/L)	LDH (U/L)	Troponin (pg/mL)	NT-proBNP (pg/mL)	D-Dimer ( $\mu$ g/mL)	Procalcitonin (ng/mL)	CRP (mg/L)	CRP (> 100 mg/L)	Ferritin ( $\mu$ g/L)	ESR (mm/h)
Chen et al. 2020 [11]	Retrospective	Deceased vs recovered	113 vs 161	189 vs 84	564.5 vs 268	40.8 vs 3.3 ( $\leq 15.6$ )	800 vs 72	4.6 vs 0.6	99% vs 50% ( $> 0.05$ )	113 vs 26.2	60% vs 14%	1418.3 vs 481.2	38.5 vs 28
Qin et al. 2020 [12]	Retrospective	Severe vs non-severe	286 vs 196						0.1 vs 0.05			800.4 vs 523.7	34 vs 28
Wang et al. 2020 [13]	Retrospective	SpO <sub>2</sub> < 90% vs SpO <sub>2</sub> $\geq$ 90%	55 vs 14		517.5 vs 207				0.13 vs 0.13	81.55 vs 11.30	25% vs 6%		30 vs 17
Peng et al. 2020 [14]	Retrospective	Critical vs non-critical CVD patients	16 vs 96						0.2 vs 0.11	106.98 vs 34.34			

**Abbreviations:** *N* population number, *SpO<sub>2</sub>* peripheral capillary oxygen saturation, *CVD* cardiovascular disease, *CK* creatine kinase, *LDH* lactate dehydrogenase, *NT-proBNP* N-terminal pro-hormone of brain natriuretic peptide, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

BC [7]. In modern medicine, it has been used for several decades in the treatment of gout, Behcet's disease, Mediterranean fever, and pericarditis [7]. Colchicine inhibits microtubule polymerization, thereby affecting a variety of cellular processes, such as the maintenance of shape, signaling, division, migration, and cellular transport [8]. Colchicine has been described to modulate several pro- and anti-inflammatory pathways [9], such as the inhibition of activation and migration of neutrophils as well as interference with the neutrophil inflammasome complex, resulting in inhibition of interleukin-1b (IL-1b) [10].

## Methods

A dual search of PubMed and the Cochrane Database was performed on April 2, 2020. The initial search was aimed at identifying reports describing the cytokine storm induced by COVID-19 and included the terms: "COVID-19," "Coronavirus," "SARS CoV-2," "Inflammation," "Inflammatory response," and "Cytokine storm." The terms were paired in every possible combination using the Boolean operator "AND." The second search was aimed at identifying reports describing the efficacy of colchicine in the treatment of post-viral pericarditis as well as other myocardial conditions related to inflammation. In this search, the search term "Colchicine" was combined using again the Boolean operator "AND" with each one of the terms "Pericarditis," "Myocarditis," and "Viral." The search was limited to the inclusion of keywords within the title and abstract of each report.

## Results

A total of 46 reports were identified in our primary search. After title and abstract review, 16 reports were excluded as irrelevant to the topic, leaving 30 reports for full-text review. A total of 75 reports were identified in our secondary search. After title and abstract review, 31 reports were excluded as irrelevant to the topic, leaving 44 reports for full-text review.

### COVID-19 Cytokine Storm

In severe cases of COVID-19, several laboratory values are elevated indicating an augmented inflammatory response. Table 1 presents the findings of four retrospective trials from China with regard to the different biomarkers that are elevated in COVID-19. Furthermore, these trials reported on the elevations of various inflammatory mediators, which are reported in Table 2. In severe cases, the cytokine storm seems to affect other organs as well. Liver injury was common in 79 non-ICU hospitalized COVID-19 patients [15], but that did not seem to

**Table 2** The elevations of various inflammatory mediators as presented in four retrospective trials from China with regards COVID-19

Studies	Methods	Groups	Number	IgA	IgG	IgM	C 3	C 4	IL-1b	IL 2r	IL-6	IL-8	IL-10	TNF
Chen et al. 2020 [11]	Retrospective	Deceased vs recovered	113 vs 161	NR	NR	NR	NR	NR	NR	81% vs 37%	100% vs 60%	28% vs 8%	70% vs 19%	77% vs 47%
Qin et al. 2020 [12]	Retrospective	Severe vs non-Severe	286 vs 196	NR	NR	NR	NR	NR	NR	757 U/mL vs 663.5 U/mL	25.2 pg/mL vs 13.3 pg/mL	18.4 pg/mL vs 13.7 pg/mL	6.6 pg/mL vs 5 pg/mL	8.7 pg/mL vs 8.4 pg/mL
Wang et al. 2020 [13]	Retrospective	SpO <sub>2</sub> < 90% vs SpO <sub>2</sub> ≥ 90%	55 vs 14	NR	NR	NR	NR	NR	NR	51.69 pg/mL vs 6.69 pg/mL	51.69 pg/mL vs 6.69 pg/mL	6.92 pg/mL vs 4.18 pg/mL		

*Abbreviations:* N population number, SpO<sub>2</sub> peripheral capillary oxygen saturation, Ig immunoglobulin, C complement component, IL interleukin, TNF tumor necrosis factor

be a prominent feature of COVID-19 [16]. Similarly, renal injury was not demonstrated in 116 patients [17]. There are however other reports of patients with COVID-19 with associated renal injury [18]. Acute cardiac injury associated with cardiac dysfunction and arrhythmias however seems to play a detrimental role in mortality [19]. As such, patients with prior cardiovascular disease (CVD) are considered to be at high risk of developing morbid complications [20]. Of particular interest was a case report of an otherwise healthy 53-year-old woman who developed cardiac complications related to COVID-19 without signs and symptoms of interstitial pneumonia [21]. Finally, patients with diabetes have been demonstrated to be at a higher risk of COVID-19 complications [22], which could be at least in part attributed to IL-6, which is already increased in conditions of chronic inflammation [23].

In conclusion, COVID-19 is a disease that seems to target the lungs and the cardiovascular and immune systems [24]. It is worth mentioning that in a report of three post-mortem biopsies, the lungs manifested significant pathological lesions while damages of the heart, vessels, liver, kidney, and other organs were also observed [25]. Interestingly, no evidence of SARS CoV-2 infection was observed in these organs.

The biochemical overview of the cytokine storm in critically ill COVID-19 patients has assisted in the identification of potential targets for anti-inflammatory treatment such as IL-2 receptor, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF). As such, inhibition of these targets along with a large number of different pharmaceutical agents has been hypothesized to be of potential benefit in weathering this cytokine storm. Table 3 lists some of these molecules.

It should be noted that the use of non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen in particular, has been cautioned due to the potential interaction with the angiotensin converting enzyme 2 (ACE 2) receptor [35]. ACE 2 has been previously described as the cellular binding site of the spiked proteins on the SARS CoV-2 surface [36]. However, this theory was highly scrutinized [37], while most authorities have issued statements declaring that there is insufficient evidence to make a recommendation against the use of NSAIDs. Overall, treatment with glucocorticoids, IL-6 antagonists, Janus kinase (JAK) inhibitors, and chloroquine/hydroxychloroquine seems to be the mainstay of treatment, while a vast array of agents are currently being tested in clinical trials across the globe. Colchicine has recently received attention due to its anti-inflammatory mechanism of action that has been successfully utilized in the past in the treatment of pericarditis.

### Colchicine and Biomarkers of Inflammation

We were able to locate 7 trials assessing the anti-inflammatory effect of colchicine in various cardiovascular conditions which are presented in Table 4. Biomarkers of inflammation

**Table 3** Molecules of potential benefit in weathering this cytokine storm

Studies	Investigated molecule
Conti et al. 2020 [26]	IL-2 and IL-2R inhibitors
Conti et al. 2020 [27] B	IL-38
Das et al. 2020 [28]	Arachidonic acid
Li et al. 2020 [29]	Lianhuaqingwen
Phadke et al. 2020 [30]	Angiotensin II receptor blockers and statins
Solaimanzadeh et al. 2020 [31]	Acetazolamide, nifedipine, and phosphodiesterase inhibitors
Stebbing et al. 2020 [32]	Baricitinib, ruxolitinib, and fedratinib
Sun et al. 2020 [33]	ACE and AT1R inhibitors
Zhang et al. 2020 [34]	Melatonin

Abbreviations: *IL* interleukin, *ACE* angiotensin converting enzyme, *AT1R* angiotensin type 1 receptor

such as C-reactive protein (CRP), IL-1b, and IL-6 seem to be reduced by colchicine in chronic auto-immune conditions, while the evidence is somewhat conflicting in the acute phase of inflammatory cardiac disease. In the context of COVID-19, this could indicate a potential role of colchicine in the prevention of myocardial injury related complications. While the reports are inconsistent regarding the acute phase, these trials are always confounded by several factors regarding the nature of medical response, including the necessity for multi-drug treatments and invasive procedures, while placebo control groups are obviously out of the question. It is worth mentioning however that the effect on inflammatory biomarkers can be observed within hours of administration of colchicine. Finally, these results are consistent with data from trials assessing colchicine in non-cardiac auto-immune inflammatory conditions, such as Behcet's disease, where similar reductions have been observed. [45]

### Colchicine and Pericarditis

Ten clinical trials assessing the efficacy of colchicine in the treatment of pericarditis were located and presented in Table 5. It should be noted that only two trials reported on the specific etiology underlying the development of pericarditis [46, 47], while the remaining eight relied on diagnostic

criteria for pericarditis regardless of the pathological condition leading to it.

### Colchicine in the Prevention of Post-operative Complications Related to Inflammation

We located fifteen clinical trials assessing the efficacy of colchicine after several different types of surgery. The primary outcome of these trials was a reduction of post-operative complications related to inflammation. Table 6 presents these trials.

### Systematic Reviews

In a Cochrane Database Systematic Review, the use of colchicine in the treatment of pericarditis was examined [70]. Four clinical trials were included with a total of 564 patients. Colchicine treatment was associated with a lower recurrence of pericarditis while a higher percentage of patients experienced symptom relief.

In a systematic review including 15 trials with 3431 patients and assessing the anti-inflammatory properties of colchicine in various cardiovascular conditions, the authors concluded that colchicine may reduce adverse cardiovascular outcomes in a range of patients with CVD. Furthermore,

**Table 4** Trials assessing the anti-inflammatory effect of colchicine in various cardiovascular conditions

Studies	Disease state	Number	Methods	Follow-up	Outcomes
Akodad et al. 2017 [38]	STEMI	44	Colchicine vs no colchicine	1 month	CRP was not significantly reduced
Deftereos et al. 2014 [39]	HF	267	Colchicine vs placebo	6 months	CRP and IL-6 significantly reduced
Kajikawa et al. 2019 [40]	CAD	28	Colchicine vs placebo (cross-over)	7 days	CRP significantly reduced
Martinez et al. 2015 [41]	ACS	40	Colchicine vs no colchicine	2 doses prior to cardiac catheterization	IL-1b, IL-6, and IL-18 significantly reduced
Nidorf et al. 2007 [42]	CAD	64	Colchicine vs no colchicine	4 weeks	CRP significantly reduced
Raju et al. 2011 [43]	ACS or stroke	80	Colchicine vs placebo	1 month	CRP was not significantly reduced
Robertson et al. 2016 [44]	ACS	30	Colchicine vs no colchicine	2 days	IL-1b significantly reduced

Abbreviations: *N* population number, *STEMI* ST-elevation myocardial infarction, *HF* heart failure, *CAD* coronary artery disease, *ACS* acute coronary syndrome, *CRP* C-reactive protein, *IL* interleukin

**Table 5** Clinical trials assessing the efficacy of colchicine in the treatment of pericarditis

Studies	Disease state	Design	Number	Follow-up	Outcomes
Liebenberg et al. 2016 [46]	Tuberculous pericarditis	Colchicine vs no colchicine	33	16 weeks	No benefit on prevention of pericardial constriction
Sambola et al. 2019 [47]	Acute idiopathic pericarditis	Colchicine vs no colchicine	110	24 months	Colchicine did not reduce the recurrence rate of pericarditis
Imazio et al. 2013 [48]	Acute pericarditis	Colchicine vs placebo	240	18 months	Colchicine significantly reduced the rate of recurrent pericarditis
Imazio et al. 2014 [49]	Recurrent pericarditis	Colchicine vs placebo	240	6 months	Colchicine reduced the rate of subsequent recurrences of pericarditis
Imazio et al. 2005 [50]	Acute pericarditis	Colchicine vs no colchicine	120	3 months	Colchicine reduced the recurrence rate of pericarditis
Brucato et al. 2006 [51]	Acute pericarditis	Colchicine vs no colchicine	58	8 years	Colchicine reduced the recurrence rate of pericarditis
Imazio et al. 2010 [52]	Post-pericardiotomy syndrome (PPS)	Colchicine vs placebo	360	12 months	Colchicine was effective in the prevention of PPS related complications
Imazio et al. 2011 [53]	Recurrent pericarditis	Colchicine vs placebo	120	6 months	Colchicine was safe and effective for secondary prevention of recurrent pericarditis
Imazio et al. 2005 [54]	Recurrent pericarditis	Colchicine vs no colchicine	84	20 months	Colchicine reduced the recurrence rate of pericarditis
Gianni et al. 2012 [55]	Recurrent pericarditis	Colchicine vs placebo	120	6 months	Colchicine reduced the recurrence rate of pericarditis

Abbreviations: *N* population number, *PPS* post-pericardiotomy syndrome

colchicine reduced the rates of recurrent pericarditis, post-pericardiotomy syndrome, and periprocedural atrial fibrillation following cardiac surgery [71].

A third systematic review of the same topic, which included five clinical trials and 795 patients, reached similar conclusions [72]. A fourth systematic review of seven clinical trials and 451 patients reached similar conclusions [73]. In this report, high-dose corticosteroids were associated with a detrimental effect. Finally, a fifth systematic review including seven clinical trials with 1275 patients also demonstrated the efficacy of colchicine in the prevention of both primary and recurrent pericarditis [74].

## Case Reports

In a noteworthy case report, the authors presented a 37-year-old male patient with an acute exacerbation of Crohn's disease [75]. Following 2 weeks of multiple bowel movements associated with abdominal pain, which was not controlled by an increase in mesalamine and corticosteroid dose, the patient presented to the emergency department with a chief complaint of pleuritic chest pain. ST elevations were observed on electrocardiogram (EKG), while troponin I, erythrocyte sedimentation rate (ESR), and CRP were elevated. Cardiac magnetic resonance imaging (CMR) revealed early gadolinium enhancement consistent with myocarditis. The corticosteroid dose was further increased, and colchicine was started, with clinical improvement. The time between initiation of colchicine treatment and clinical improvement was not stated.

A second case report presented a patient with rheumatoid arthritis who developed rheumatoid pericarditis complicated with tamponade [76]. The patient demonstrated resistance to corticosteroid treatment and pericardiocentesis was performed twice. At that point, colchicine was initiated with subsequent clinical improvement, while corticosteroids were tapered down without recurrence of disease exacerbation.

## In vitro Data

It is worth mentioning that in an in vitro experiment assessing colchicine in the treatment in coxsackievirus B3-induced myocarditis, colchicine had a detrimental effect causing complete destruction of the exocrine pancreas and enhancement viral load in both the heart and the pancreas [77]. However, the dose of colchicine used in this experiment was 2 mg/kg, a rather high dose that could be responsible for signs and symptoms of acute toxicity. This was stated by formal correspondence to the authors [78]. It should be noted that the lethal dose (LD) 50 in mice is > 25 mg/kg [79], while lethal doses in humans have been reported with a little as 7 mg [80]. Another trial reported a dose of 0.4 mg/kg on Chagas disease (CD)-induced multifocal myocarditis and extensive fibrosis [81]. The authors reported that colchicine demonstrated a



**Table 6** Clinical trials assessing the efficacy of colchicine after different types of surgeries

Studies	Disease state	Methods	Number	Follow-up	Results
Bessissowa et al. 2017 [56]	Post-lung resection AF	Colchicine vs placebo for 10 days	100	30 days	No difference in rates of AF
Deftereos et al. 2012 [57]	Pulmonary vein isolation	Colchicine vs placebo	161	3 months	Decreased recurrence of AF and reduced CRP and IL-6
Deftereos et al. 2014 [58]	Pulmonary vein isolation	Colchicine vs placebo for 3 months	223	15 months	Decreased recurrence of AF
Finkelstein et al. 2002 [59]	Post-pericardiectomy syndrome	Colchicine vs placebo	163	3 months	Did not decrease post-pericardiectomy syndrome
Imazio et al. 2011 [60]	Post-pericardiectomy syndrome	Colchicine vs placebo	336	1 month	Decreased post-pericardiectomy AF
Imazio et al. 2014 [61]	Post-pericardiectomy syndrome	Colchicine vs placebo	360	1 month	Decreased post-pericardiectomy syndrome but did not decrease postoperative AF or postoperative pericardial/pleural effusion
Tabbalat et al. 2016 [62]	Open heart surgery	Colchicine vs no colchicine	360	Until hospital discharge	Did not decrease post-operative AF
Zarpelon et al. 2016 [63]	Myocardial revascularization	Colchicine vs no colchicine	140	Until hospital discharge	Did not decrease post-operative AF
Giannopoulos et al. 2015 [64]	On-pump coronary artery bypass grafting	Colchicine vs placebo	59	10 days	Reduced hsTnT and CK-MB
Imazio et al. 2011 [65]	Cardiac surgery	Colchicine vs placebo	360	1 month	Reduced post-operative pericardial and pleural effusion
Meurin et al. 2015 [66]	Post-operative pericardial effusion	Colchicine vs placebo	197	14 days	Did not reduce pericardial effusion or prevent late cardiac tamponade
Agzarian et al. 2017 [67]	Post-operative pleural effusion following lung resection	Colchicine vs placebo	100	10 days	Reduced amount of pleural drainage
Izadi Amoli et al. 2015 [68]	Pericardial effusion after open heart surgery	Colchicine vs placebo	149	2 weeks	Did not reduce pericardial effusion
Deftereos et al. 2013 [69]	Post-PCI with bare metal stent decrease in ISR	Colchicine vs placebo	196	6 months	Decreased ISR

*Abbreviations:* N population number, PCI percutaneous coronary intervention, ISR intracoronary stent restenosis, AF atrial fibrillation, CRP C-reactive protein, IL-6 interleukin, hsTnT high sensitivity troponin T, CK-MB creatine kinase myocardial band

cardioprotective effect, as indicated by decreased interstitial myocardial fibrosis, increased intensity of MMP-2, and attenuated myocardial inflammation.

## Discussion

Our results indicate that colchicine could play a role on the prevention as well as the management of the cytokine storm related complications associated with COVID-19. Caution however should be advised in terms of both the safety and efficacy of the medication. For example, 4745 patients were randomized to receive colchicine or placebo within 30 days after a myocardial infarction [82]. The authors reported that colchicine significantly lowered the risk of ischemic cardiovascular events. It should be noted however that pneumonia was reported as a serious adverse event in 0.9% vs 0.4% of treatment vs placebo patients ( $P = 0.03$ ).

Furthermore, the pharmacokinetic profile of colchicine has to be taken into consideration. Colchicine is metabolized in the liver via the cytochrome P450 (CYP) 3A4 isoenzyme and P-glycoprotein (P-gp). While the extent of hepatic metabolism does not seem to exceed 5%, it is listed as a substrate, inhibitor, and inducer of several CYP450 isoforms [83], including 3A4 [84], which could potentially lead to interactions with several medications. Renal and hepatic excretion of colchicine takes place through P-gp-mediated efflux [85]. The two postulated major routes of elimination of colchicine are enterohepatic recirculation and biliary excretion [86].

One trial reported that colchicine exposure was increased after a single dose of colchicine was administered with steady-state atorvastatin [87]. Furthermore, a trial that assessed the co-administration of colchicine with known inhibitors of CYP450 3A4 and P-gp (cyclosporine, ketoconazole, ritonavir, clarithromycin, azithromycin, verapamil extended release [ER], and diltiazem ER) demonstrated threefold increases in colchicine concentrations with all agents except azithromycin [88]. The authors recommended colchicine dose reductions of 33–66% for the treatment of acute gout and 50–75% for prophylaxis when co-administered with CYP450 3A4 and P-gp inhibitors. No dose adjustments were recommended in the combination with azithromycin. Finally, a 50% dose reduction of colchicine when combined with cyclosporin was recommended in another report [89].

In terms of adverse drug reactions (ADRs), colchicine seems to be well tolerated at therapeutic doses. In a recent systematic review of assessing the safety of colchicine, increases in the rate of diarrhea and gastrointestinal adverse events were observed. However, the rate of hepatic, sensory, muscular, infectious or hematological toxicities, or death was not increased [90].

Overall, the drug-drug interaction (DDI) profile of colchicine should be taken into consideration before its initiation in

confirmed COVID-19 cases. That should be done in the context of both medications taken prior to hospital admission and medications administered in-house. In fact, the potential for DDIs in COVID-19 treatments and their possible competitive metabolic destiny should be studied by the application of pharmacogenomics in large scale.

In conclusion, colchicine could offer a viable treatment option in the fight against COVID-19-induced cytokine storm. Its relatively low cost and adequate availability make it a rather attractive option. However, caution should be exercised due to its potential for DDIs. In terms of efficacy, initial reports show limited promise. More specifically, in a trial of 105 patients randomly assigned to either standard treatment or standard treatment plus colchicine [91], the time to clinical deterioration was statistically significant in favor of the colchicine group. However, no differences were observed in high-sensitivity cardiac troponin or C-reactive protein levels. Furthermore, the study was underpowered which led the authors to advise caution in the interpretation of their results. Larger trials are required before safe conclusions can be reached.

## Hypothesis Generation for Clinical Trials

### Safety Hypothesis

The safety of colchicine in COVID-19 patients should be tested first. This will be done to make sure that no unexpected complications arise related to colchicine administration. The potential for opportunistic secondary super-infections, as well as for drug interactions has been previously described, therefore making such a trial of paramount importance. Considering the urgency of the current pandemic, this can be accomplished with an open-label trial of low-risk, symptomatic but not critically ill patients with close clinical and biochemical monitoring. The results of such a trial can then be compared to demographic controls. While a power analysis has not been performed, a reasonable number of 30–50 patients would be sufficient to provide statistically significant results.

### Efficacy Hypothesis 1

The efficacy of colchicine should be assessed as a means of preventing complications related to COVID-19. As such, an open-label trial of hospitalized patients receiving colchicine and measuring the frequency of complications would provide sufficient evidence. The data generated from such a trial could then be compared to demographic controls. Again, a reasonable number of 30–50 patients would be sufficient to provide statistically significant results.

## Efficacy Hypothesis 2

The assessment of the efficacy of colchicine in the treatment of the acute complications related to COVID-19 would be the most challenging. Assuming hypotheses 1 and 2 have been tested with positive results, colchicine could then be added to standard therapy aimed against the cytokine storm. However, there are several challenges that will be difficult to overcome in this setting. Colchicine would have to be administered to critically ill patients, in conjunction with several other medications and invasive procedures. Therefore, measuring the absolute benefit of colchicine in that context would require larger sample sizes and more elaborate trial designs.

**Authors' Contributions** All authors contributed to the research conception and design. Research design, data collection, and interpretation were performed by Christodoulos Papadopoulos, Dimitrios Patoulas, and Eleftherios Teperikidis. Eleftherios Teperikidis and Dimitrios Mouselimis wrote the first draft version of the manuscript. Maria Toumpourleka, Aristi Boulmpou, Constantinos Bakogiannis, Michael Doumas, and Vassilios P. Vassilikos revised and edited it significantly in order to reach its final form. All authors read and approved the final version of manuscript.

**Data Availability** Not applicable.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Code Availability** Not applicable.

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