Preprint

Critical appraisal of multidrug therapy in the ambulatory management of patients with COVID-19 and hypoxemia. Part II: Causal inference using the Bradford Hill criteria

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Abstract: Aim: We continue the critical appraisal of three published case series of 119 COVID-19 patients with hypoxemia, treated in the United States, Zimbabwe, and Nigeria with similar ivermectin-based multidrug treatments, to assess the available evidence supporting a causal relationship between treatment and reduction in hospitalizations and mortality. **Methods:** A narrative review was conducted to assess the Bradford Hill criteria for a causal association. We used a previously proposed refinement of the Bradford Hill criteria that reorganized them into three categories of direct, mechanistic, and parallel evidence. **Results:** The efficacy of the two most aggressive ivermectin-based multidrug protocols is supported by the Bradford Hill criteria for temporality, strength of association, biological gradient, biological plausibility, coherence, consistency, and analogy. **Conclusion:** The causal relation between the treatment of hypoxemic COVID-19 patients using these protocols and the reduction in hospitalizations and mortality is supported as an inference to the best explanation.

Keywords: COVID-19; SARS-CoV-2; ambulatory treatment; early treatment; drug repurposing; biostatistics

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1. Introduction

This paper is the second part in a series of two papers focused on three case series of hypoxemic COVID-19 patients, treated with ivermectin-based multidrug protocols in the United States, Zimbabwe, and Nigeria [**1–5**] during the years 2020 and 2021. The preceding paper [**6**] (hereafter *Paper I*) provided epidemiological quantitative arguments supporting the *strength of association* between these treatment protocols and reduction in hospitalizations and mortality for hypoxemic COVID-19 patients, which was not previously done in a uniform or sufficiently convincing way across all three of the case series.

Paper I has also presented the detailed description of the corresponding ivermectin-based multidrug protocols. The most aggressive protocols were used in the 24 patients treated in the United States by Hazan and colleagues [**2**] (hereafter *Hazan case series*) and the 34 patients treated in Zimbabwe by Stone and colleagues [**1**] (hereafter *Stone case series*). These protocols consisted of a baseline 10-day treatment with ivermectin, doxycycline, zinc, vitamin C, and vitamin D. For the Stone case series, the baseline protocol also included nebulized nanosilver, and additional medications were used on a case by case basis, based on patient presentation and the results of bloodwork. The 61 patients in Nigeria (hereafter *Babalola case series*) were treated with a less aggressive 5-day protocol consisting of ivermectin, zinc, vitamin C, with some patients also receiving a low dose of hydroxychloroquine and azithromycin for 3 days. Rapid recovery of peripheral oxygen saturation (SpO2) was observed in all three case series and all patients survived.

The earliest documented use of ivermectin, as part of a multidrug protocol for treating COVID-19, goes back to April 2020 in Argentina by Carvallo and colleagues [**7**], who proposed a combination therapy of ivermectin, dexamethasone, enoxaparin, and aspirin [**8**]. In the United States, the earliest multidrug protocol used by treating physicians against COVID-19 was Zelenko's multidrug protocol of hydroxychloroquine, azithromycin, and zinc [**9**], which was announced on March 2020 [**10–14**], and was based on preliminary results by Raoult and colleagues [**15**]. By the end of 2020, Zelenko's protocol was expanded into McCullough's protocol [**16–18**], which used a sequenced treatment that included a nutraceutical bundle (quercetin, zinc, vitamin C, vitamin D), an antiviral protocol (hydroxychloroquine or ivermectin combined with azithromycin or doxycycline), an anti-inflammatory protocol (inhaled budesonide, dexamethasone or prednisone, colchicine),

and anticoagulation (aspirin or other anticoagulants), and was later expanded [**19, Fig. 3**] to include virucidal nasal washes and gargles [**20–27**]. Both ivermectin and doxycycline were included in the McCullough protocol because of their antiviral mechanism of action.

The idea of a 10-day combination therapy of ivermectin, doxycycline, zinc, vitamin C, and vitamin D was proposed by Borody and colleagues [**28,29**], and was successfully used by both Hazan [**2**] and Stone [**1**] in the treatment of hypoxemic COVID-19 patients. Stone [**1,30**] expanded Borody's protocol with adaptive dosage of ivermectin, nebulized nanosilver, and, for severe or worse cases, with additional medications, similarly to McCullough's protocol, as discussed in Paper I. It is worth noting, but beyond the scope of this study, that Chetty also reported during early 2020 the rapid recovery of SpO2 in 12 hypoxemic patients, with baseline room air SpO2 between 80% and 85%, by use of an entirely different non-ivermectin based multidrug protocol [**31**].

The goal of this study is to embed the quantitative argument of Paper I, via a narrative review, within a broader causality inference argument based on the Bradford Hill criteria [**32**], as refined by Howick *et al.* [**33**]. In their reorganization, Howick *et al.* [**33**] separated the available evidence into the three categories of direct, mechanistic, and parallel evidence and they also proposed renaming some of the criteria, as shown on Table 1. Howick *et al.* [**33**] also proposed presenting the proposed evidence categories as "guidelines", instead of as "criteria". For the convenience of the reader, we have retained most of the original terminology and note that it may be best to think of the categories of evidence as a *framework* for assessing the strength of the evidence in support of a causality hypothesis. The following three sections of this study are focused on the details of each of these three broad categories of evidence. The combined evidence provide sufficient grounds for a causality inference, with the caveat that, as noted by Ward [**34**], the inference is not a deductive or inductive inference, but an inference to the best explanation [**35**].

2. Direct Evidence

The refinement of the Bradford Hill criteria by Howick *et al.* [**33**] defined Hill's criteria of *strength of association*, *temporality*, and *biological gradient* as *direct evidence*. Direct evidence is the most essential evidence needed for a convincing causality argument, and provides direct support for claiming that an observed association is causal and not coincidental. We argue that temporality, biological gradient, and strength of association are all strongly supported in favor of the ivermectin-based multidrug protocols, used in the Hazan case series and the Stone case series.

2.1. Temporality

In the context of the ivermectin-based multidrug protocols, temporality is clearly satisfied because of the immediate increase in SpO2 levels within 24 to 48 hours observed separately in the case series by Hazan *et al.* [**2**], Stone *et al.* [**1**], and Babalola *et al.* [**3**], shortly after initiating treatment. This rapid response was first noted by Thairu *et al.* [**4**] and Babalola *et al.* [**5**]. Stone *et al.* [**1**] first presented the visualization shown in Fig. 1 where the rapid SpO2 recovery rates observed in the Hazan, Stone, and Babalola case series were compared against a case series of 26 additional patients (hereafter *Thairu case series*) with baseline room air SpO2 $\leq$ 93%, who were treated with a non-ivermectin standard-of-care protocol consisting of a combination of lopinavir, ritonavir, remdesivir, azithromycin, enoxaparin, and vitamin C.

Scheim *et al.* [**36**] used the Mann-Whitney U-test to compare the SpO2 recovery rates of the Hazan, Stone, and Babalola case series against those observed in the Thairu case series and showed that the observed SpO2 recovery rates are statistically significant from Day 1 ($p < 10^{-8}$ for the Hazan and Stone case series and $p = 0.00149$ for the Babalola case series, with baseline room air SpO2 $\leq$ 93% risk stratification). From a qualitative viewpoint, for the patients in the Thairu case series, Fig. 1 shows a decreasing trend in room air SpO2 during the first 3 days, contrasted by the rapidly increasing trend in the Hazan, Stone, and Babalola case series over the same period. Furthermore, Fig. 1 shows that the confidence intervals for the Stone and Hazan case series do not even overlap with the confidence intervals for the Thairu case series, during both Day 1 and Day 2.

Although the patients in the Thairu case series were treated during the delta variant, similar decreasing trends in SpO2 were observed with pre-delta variants over a period of at least 8 days by Annunziata and colleagues [**37, Fig. 4**] (October 2020 to November 2020, despite a 6 day protocol that included azithromycin,

Table 1: Bradford Hill criteria/guidelines as reinterpreted and extended by Howick and colleagues

Bradford Hill criterion/guideline		
Original designation[1]	**Renamed designation**[2]	**Description**
Direct evidence		
strength of association	size of effect	Epidemiological or experimental studies showing that the strength of association between intervention and outcome exceeds the combined effect of plausible confounders.
temporality	temporal and/or spatial proximity	A favorable response to the intervention follows shortly after the intervention. Shorter temporal proximity makes it less likely that confounding has occurred. This evidence is further strengthened when the favorable response reverses, when the intervention is withdrawn, and resumes, when the intervention is repeated (challenge and rechallenge). Howick *et al.* [**33**] extended temporality to include spatial proximity in addition to temporal proximity.
biological gradient	dose responsiveness	The outcome changes when the intensity of the intervention is increased. We have interpreted this to include both an increase in dose/duration of a medication and an expansion of a treatment protocol with additional medications.
Mechanistic evidence		
biological plausibility	plausible mechanism	Evidence of one or more complete causal link chains that connect the intervention with the purported outcome. Howick *et al.* [**33**] broadened this criterion to encompass both biological and non-biological mechanisms of action.
coherence	coherence	The causal hypothesis between intervention and outcome should be coherent with what is known from non-epidemiological studies about the intervention and the underlying condition treated. Included in this category are non-epidemiological studies that corroborate one part of the causal chain between the intervention and outcome, as opposed to corroborating the complete causal chain.
Parallel evidence		
consistency	replicability	Epidemiological studies that replicate the relationship between similar interventions and similar outcomes in similar populations. Replicability reduces the likelihood that the results can be attributed to selection bias.
analogy	similarity	Epidemiological studies that consider the relationship between interventions and outcomes where the intervention may differ either in its details (e.g. dosage, duration, addition or removal of medications) or its circumstances (e.g. different patient demographics, low vs high risk patients, early or late administration of treatment). Causal hypothesis is strongly supported when parallel studies agree on the outcomes, however it is also supported when the pattern of agreement and disagreement on the outcomes is coherent and can be explained.

Note: Howick *et al.* [**33**] have omitted the original Bradford Hill criteria of *specificity* and *experiment*. Evidence under the category of *experiment* can be included under the appropriate category of direct evidence. Evidence under the category of *specificity* can be included under the appropriate category of mechanistic evidence.

[1] These are the original designations given to the Bradford Hill criteria that remain in current use.

[2] These are the designations proposed by Howick *et al.* [**33**] for their redefined criteria/guidelines.

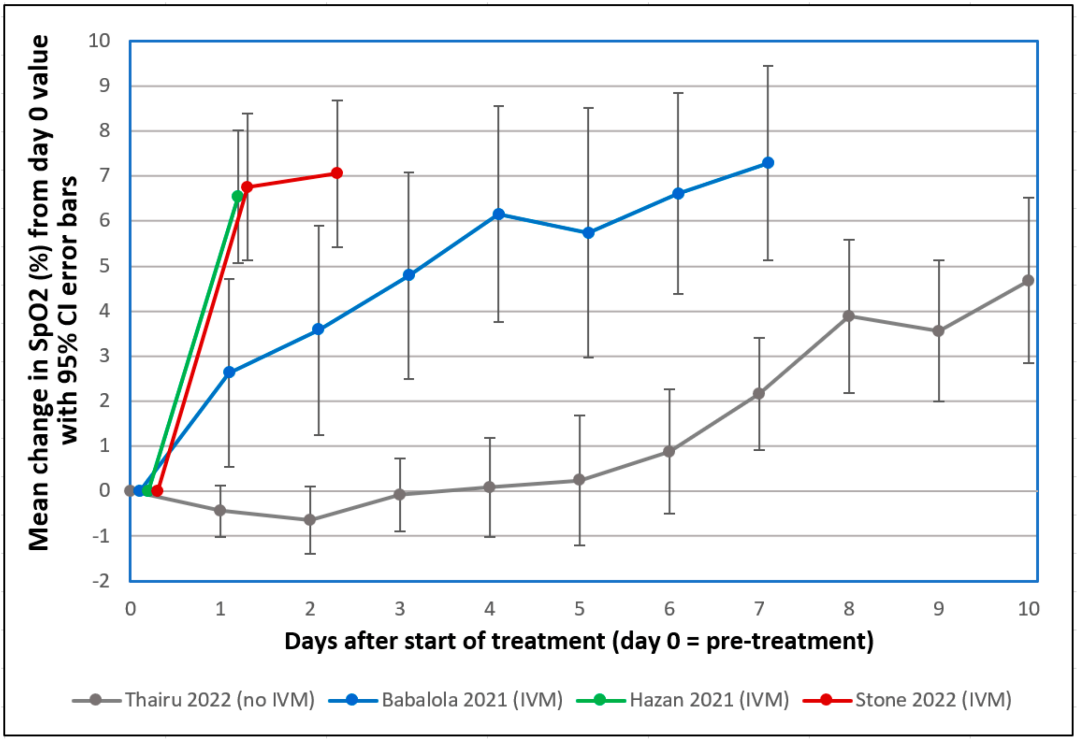

Figure 1: Mean change to room air SpO2 levels from initial value at Day 0 for the patients in the Hazan case series [**2**], the Stone case series [**1**], and the Babalola case series [**3**] with baseline room air SpO2 $\leq$ 93%, with error bars showing 95% confidence intervals. The most rapid increase is observed for the Hazan and Stone case series [**1, 2**]. Slower increase is observed in the Babalola case series [**3**]. The slowest increase is observed under a conventional standard of care (lopinavir/ritonavir, remdesivir, azithromycin, enoxaparin, zinc sulfate, and vitamin C) by 26 patients with median age 45 by Thairu *et al.*[**4**]. Stone *et al.*[**1**] used deidentified data obtained via personal communication from Babalola to be able to extract the patients with baseline room air SpO2 $\leq$ 93% for the curves corresponding to the Babalola case series [**3**] and the Thairu *et al.*[**4**] case series. The figure is reproduced from Stone *et al.*[**1, Fig. 6**] under the terms of the CC-BY-4.0 license.

methylprednisolone, enoxaparin) and even in less severe presentations reported by Osman and colleagues [**38, Fig. 5**] (March 2020 to August 2020; no information provided concerning medications).

The short temporal distance between the onset of treatment and the response, further strengthens the temporality evidence. As was noted by Howick *et al.* [**33**] a short time interval between the onset of treatment and response allows for *"less room for confounders (especially spontaneous remission) to interfere"* [**33**]. Furthermore, the rapid response is consistent with the confluence of possibly multiple mechanisms of action, discussed in the next section on mechanistic evidence, that are responsible for a quick resolution of the microemboli of red blood cells that mediate the decrease of SpO2.

2.2. Strength of association

Prior to Paper I, some evidence in support of the strength of association between the ivermectin-based multidrug protocols and mortality-rate reduction was given by Thairu *et al.* [**4**], where the patients from the Babalola case series with no reported deaths were compared against the Thairu case series of 26 additional patients who were treated with a non-ivermectin standard-of-care protocol, of whom 4 patients died. However, this comparison is not sufficient for establishing mortality rate reduction, because the patients in the Thairu case series were treated during the more deadly Delta variant epidemic wave, whereas the patients in the Babalola case series were treated during the Beta variant. Hazan *et al.* [**2**] also attempted to show both a mortality and a hospitalization rate reduction benefit associated with her protocol, however their mortality rate reduction finding was borderline statistically significant with $p = 0.04$. A similar attempt was made in the preprint of Stone *et al.* [**39**], which was not included in the published paper [**1**].

Given three case series with similar treatment protocols, in Paper I we combined their statistical power by pursuing a unified approach for investigating strength of association. We used a self-controlled technique to establish hospitalization rate reduction, by counting as factual hospitalizations the use of supplemental oxygen or ventilators, despite the attempted treatment, and by counting the number of patients with baseline room air SpO2 $\leq$ 90% as a lower bound for the number of counterfactual hospitalizations that would have occurred under standard hospitalization guidelines. A comparison using the exact Fisher test and the case series threshold analysis technique [**40**] showed clear and convincing hospitalization rate reduction with substantial resilience to confounding by systemic selection bias.

In addition, Paper I compared the three case series, risk-stratified with baseline room air SpO2 $\leq$ 90%, against external control groups of hospitalized patients [**41–48**], noting that the risk stratification only included patients that would have been hospitalized, if standard guidelines for hospitalization had been followed instead of the ivermectin-based multi-drug protocols. For patients in Zimbabwe, we argued that the CFR of hospitalized patients can be lower bounded by at least 20%, from which we inferred mortality rate reduction for the Stone case series by the preponderance of evidence. Furthermore, combining the Hazan and Stone case series, where the most aggressive treatment protocols were used, gives a decisive mortality rate reduction finding by the preponderance of evidence, using comparisons against any of the available external control groups, all of which lower-bound the CFR of hospitalized patients by 10%. In both cases, with a preponderance of evidence finding we can claim that it is more likely than not that the entire mortality rate reduction benefit cannot be attributed solely to confounding [**40**].

Because of the unusual strength of the temporality evidence presented in Fig. 1, it is not unreasonable to suggest that temporality alone provides sufficient direct evidence for justifying the adoption of the ivermectin-based protocols by practicing doctors, even without the strength of association argument presented in Paper I. Clearly, the observed rapid recovery of oxygen levels alleviates patient suffering, and that alone is sufficient to justify the adoption of these protocols under article 37 of the 2013 Helsinki declaration [**49**]. From an epidemiological perspective, the strength of association argument of Paper I complements temporality by showing that the oxygen recovery rate observed in the Hazan and Stone case series and the resolution of the underlying pathogenic mechanisms were both sufficiently rapid and sufficiently sustained to contribute to the ultimate survival of the patients and to reductions in hospitalizations.

2.3. Biological gradient

Biological gradient has been shown by the observation (see Fig. 1) that SpO2 recovery is more rapid in the Hazan case series and the Stone case series, compared to the Babalola case series, noting that Babalola's protocol used mainly ivermectin, zinc sulfate, and vitamin C [**3–5**], but the Hazan and Stone/Gill multidrug protocols [**1, 2, 50, 51**] added Vitamin D3 and doxycycline, and the Stone/Gill protocol also added nebulized nanosilver, corticosteroids, and blood thinners [**1, 50, 51**]. In addition, Stone and colleagues used a variable dosing of ivermectin, dependent on patient response to treatment, and observed that *"higher doses appear to be more effective for the patients with the most severe symptoms"* [**1**]. Indeed, as discussed in Paper I, Stone determined the length of both ivermectin administration and nanosilver nebulizations by continuing treatment until 48 hours past the resolution of symptoms. Furthermore, Stone adjusted the ivermectin dosage based on the severity of the patient presentation [**30, 51**]. Hazan also used an increased dose of ivermectin for patients with the most severe presentation [**2**]. Fig. 1 also shows that the recovery rate of SpO2 in the patients treated with ivermectin-based multidrug protocols is substantially faster than that of 26 patients treated with a non-ivermectin protocol of lopinavir/ritonavir, remdesivir, azithromycin, enoxaparin, and vitamin C; in fact for those patients SpO2 levels were initially declining over a period of several days and did not fully recover after 10 days, a pattern that has also been replicated by other studies conducted during pre-delta variants [**37, 38**].

3. Mechanistic evidence

Howick *et al.* [**33**] categorized the Bradford Hill criteria of *biological plausibility* (renamed to *plausible mechanism*) and *coherence* as mechanistic evidence. This evidence is closely related and purports to explain *how* the ivermectin-based multidrug protocols are connected with mortality and hospitalization rate reduction. We argue that current knowledge supports both biological plausibility and coherence in favor of the ivermectin-based multidrug protocols.

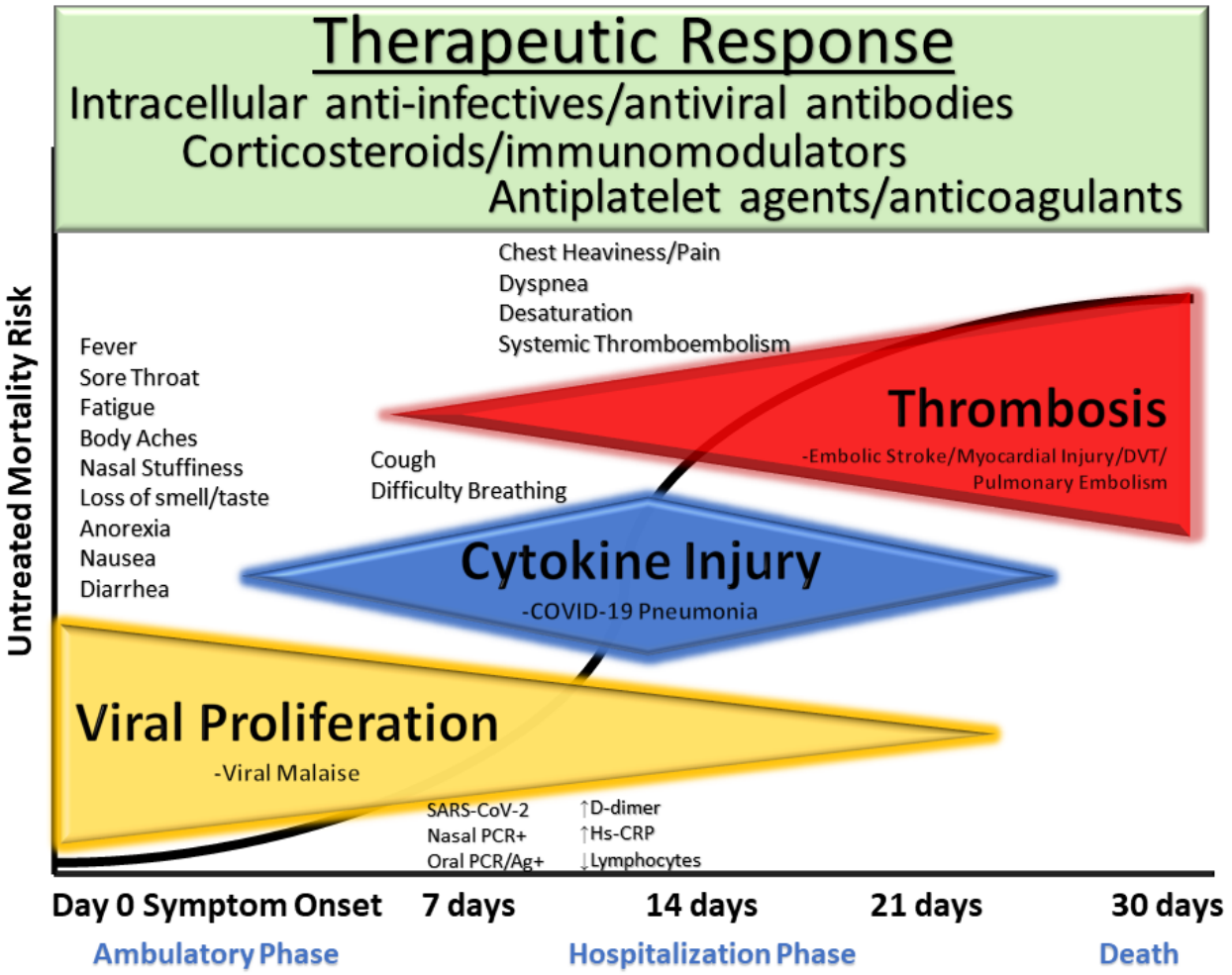

Figure 2: Without treatment, COVID-19 presents as a triphasic illness with three overlapping phases: (1) *viral proliferation*, presenting with flu-like symptoms; (2) *cytokine injury*, caused by immune dysregulation; (3) *thrombosis*, caused by red blood cell microcloting. The baseline combination of ivermectin, nebulized nanosilver, doxycycline, and zinc confers mechanisms of action that mitigate all three phases of COVID-19. This figure is adapted from McCullough *et al.* [**18**] under the terms of the CC-BY-4.0 license.

3.1. Biological Plausibility

Biological plausibility, which was renamed to *plausible mechanism* by Howick *et al.* [**33**], requires evidence that supports a causal connection between the treatment protocol and reduction in mortality and hospitalizations. A causal association is clearly mediated by the rapid recovery of room air SpO2 levels in hypoxemic patients, however it is just as important to eradicate the virus, calm the cytokine storm, and accelerate the disaggregation of microemboli [**18**] (see Fig. 2). In this context, we shall briefly review the known mechanisms of action against COVID-19 of ivermectin, doxycycline, nebulized silver nanoparticles, zinc, vitamin D, and vitamin C, noting that these are the baseline medications and nutraceuticals used in various combinations in the Hazan, Stone, and Babalola case series.

Ivermectin may have several mechanisms of action [**52, 53**] suggesting multiple targets and modes of action against COVID-19, including antiviral, anti-inflammatory, and anticoagulant effects. Ivermectin has anti-inflammatory and immunomodulatory properties because it acts as a positive allosteric modulator of the alpha-7 nicotinic acetylcholine receptor (α7nAChr), which enhances the cholinergic anti-inflammatory pathway, resulting in a balanced response to inflammation triggered by viral particles [**54, 55**]. Ivermectin can inhibit viral attachment to human cells by competitive binding both to the Angiotensin-Converting Enzyme 2 (ACE2) receptor [**56**], used by the virus to enter the cell, and to several sites of the spike glycoprotein of the SARS-

CoV-2 virus, including a glycosylation binding site (site 10, N61) and other sites on the S1-NTD and S1-RBD regions [55]. In addition, ivermectin may interfere with viral replication inside cells by inhibiting the importin (IMP) α/β1-mediated import of viral proteins into the cell nucleus [57]. Spike protein-induced red blood cell and platelet aggregation can trigger blood clot formation and inflammation which causes serious pathologies, including a drop in SpO2 levels to severe hypoxemia [58]. Ivermectin binds competitively to SARS-CoV-2 spike protein glycans, and reverses the bindings with red blood cells thus preventing clumping [36, 55, 58–60]. This mechanism may explain, in part, the rapid recovery of SpO2 levels in hypoxemic COVID-19 patients in response to the ivermectin-based multidrug protocols proposed by Hazan [2] and Stone [1]. Finally, ivermectin may act as a zinc ionophore [61], increasing the intercellular concentration of zinc ions, which may inhibit the RNA Dependent RNA Polymerase (RDRP) protein used by the SARS-CoV-2 virus to replicate [9, 62]. In total, 20 distinct mechanisms of action have been identified that may contribute to the reduction of mortality and hospitalization rates in COVID-19 patients [52].

Prior to the COVID-19 pandemic, doxycycline's antiviral and anti-inflammatory properties were found to be an option for reducing lung damage and dampening the cytokine storm associated with severe diseases [63]. Doxycycline has emerged as a compelling candidate for reducing lung damage and mitigating the cytokine storm in severe COVID-19 [64]. Doxycycline has also demonstrated antiviral activity against various RNA viruses in laboratory settings, which is mediated by targeting host proteases utilized by coronaviruses and inhibiting viral fusion and replication [65]. By impeding viral replication, doxycycline has the potential to alleviate the severity of infection and limit lung damage. It has been shown to inhibit the coreceptors DPP4/CD26 and CD147/EMMPRIN, which are crucial for viral entry into T lymphocytes [65]. Additionally, doxycycline may interfere with viral protein processing, including cleavage of polyproteins and maturation of essential viral proteins [65]. Furthermore, doxycycline acts as a zinc ionophore, enhancing the intracellular concentration of zinc, which has been associated with inhibition of SARS-CoV-2 replication [65]. Severe cases of COVID-19 often exhibit an intense proinflammatory state accompanied by a cytokine storm characterized by elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and doxycycline has been found to reduce these proinflammatory cytokines [66]. In doing so, it may help to quell the excessive inflammatory response by mitigating the cytokine storm, thereby preventing further lung damage. Its anti-inflammatory properties extend to inhibiting nuclear factor kappa B (NF-κB) activation, a transcription factor involved in producing proinflammatory cytokines [64].

Silver nanoparticles (AgNPs) have also shown potential for combating COVID-19 [67]. Jackie Stone pioneered the use of nebulized nanosilver in the treatment of COVID-19 patients in Zimbabwe, which became part of the broader Stone/Gill multidrug protocol [50, 51]. Although the exact mechanisms through which AgNPs impede the infectivity of SARS-CoV-2 require further investigation, numerous studies have proposed compelling theories regarding their potential modes of action [68]. AgNPs reveal a multifaceted approach for managing viral infections. As an immune booster, AgNPs can enhance the immune response [69]. Their anti-inflammatory and antimicrobial properties are effective in treating viruses such as SARS-CoV-2. By reducing inflammation and combating microbial infections, AgNPs aid in managing the progression of viral diseases [70]. AgNPs may inhibit viral entry by interacting with viral envelope proteins, obstruct viral replication by targeting crucial viral RNA or proteins, and induce antiviral immune responses by stimulating the production of key cytokines and activating immune cells [71]. Additionally, AgNPs can generate reactive oxygen species (ROS), which exert an antiviral effect by directly impeding viral proteins and nucleic acids [72]. However, it is important to note that these mechanisms can be sensitive to the size, shape, surface charge, and concentration of the AgNPs employed. One of the serious complications observed in patients with severe COVID-19 is blood clotting. Studies have shown that AgNPs can impede platelet adhesion and disrupt integrin-mediated platelet responses [67]. AgNPs have antiplatelet and anticoagulant effects [73]. Furthermore, AgNPs are electrostatically attracted to the positively charged spike protein of the SARS-CoV-2 virus, and silver nanoparticles with size less than 10 nm can coat free viral particles and prevent their attachment to red blood cells via glycan bindings [58, 74]. This property of AgNPs can potentially prevent the formation of microclots, safeguarding patients from life-threatening complications and contributing to the rapid restoration of SpO2 levels.

Prior to the COVID-19 pandemic, an in vitro study [75] showed that using zinc ionophores to increase intracellular Zn^{2+} ions inhibits the ability of SARS-CoV and equine arteritis virus to replicate by interfering with the function of the RDRP enzyme. It was thus conjectured that a similar mechanism could inhibit the replication of SARS-CoV-2 in the early stages of COVID-19 [76], thus motivating Zelenko's precursor of the McCullough protocol [9]. In the context of the Hazan and Stone/Gill multidrug protocols [1, 2, 50, 51], the

aforementioned combined zinc ionophore properties of ivermectin and doxycycline may act synergistically with zinc supplementation to limit viral replication via the same mechanism. Furthermore, zinc by itself may have additional mechanisms of action which include improving the clearance of viruses and bacteria by mucosal immunity, increasing the immune antiviral response by interferon-α upregulation, and limiting cytokine injury by downregulating the production of proinflammatory cytokines [**77**].

Vitamin D supplementation can be beneficial by a wide range of mechanisms of action which include stimulating the production of antimicrobial peptides by immune cells, protecting the lungs by reducing the production of proinflammatory cytokines, increasing surfactant concentration in the alveoli, and limiting pulmonary vasoconstriction [**78**]. Furthermore, Vitamin D may protect against endothelial dysfunction by reducing oxidative stress, by reducing the proinflammatory cytokines TNF-α and IL-6, and by inhibiting NF-κB activation [**78**]. Vitamin D may reduce the risk of respiratory failure by reducing matrix metalloproteinase-9 (MMP-9) concentration [**78**]. Finally, vitamin D may reduce the risk of Renin Angiotensis System (RAS) mediated bradykinin storm by modulating the RAS and downregulating renin expression and generation, thus reducing the risk of cardiovascular and pulmonary adverse effects from COVID-19, as well as adversely affecting the brain and muscles [**78**].

Finally, high-dose vitamin C supplementation may be beneficial to COVID-19 patients in two ways: (a) it can prevent the depletion of vitamin C levels in patients presenting with severe COVID-19, which may be caused by the metabolic response to the illness; (b) it may also modulate the immune system by increasing α/β interferons, thereby escalating the antiviral immune response, while downregulating proinflammatory cytokines [**79**].

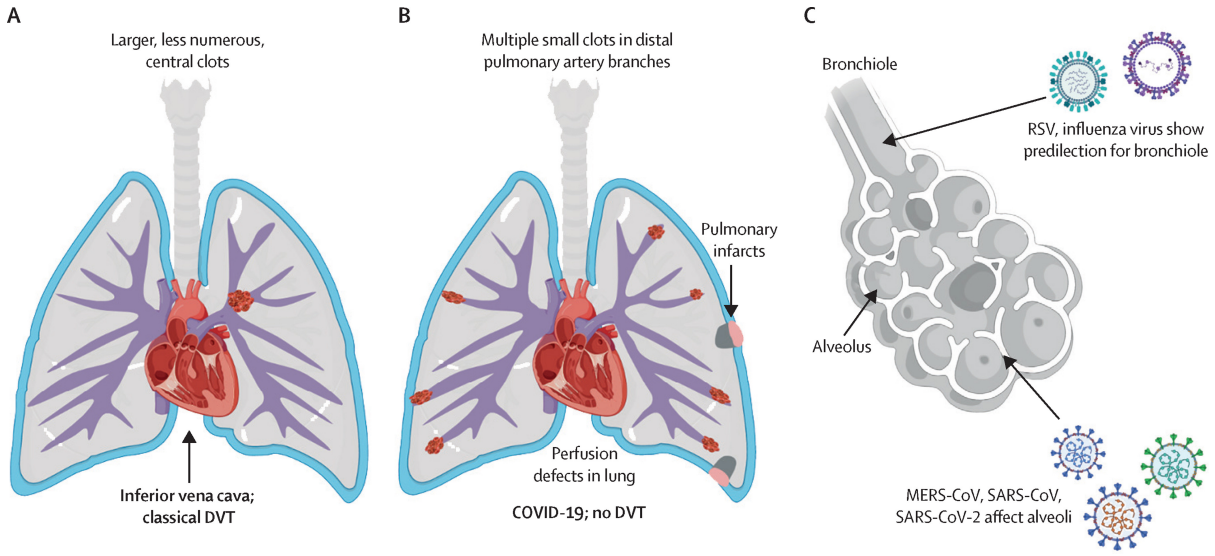

Figure 3: Classic pulmonary venous thromboembolism presents with a preponderance of a smaller number of proximal large emboli. McGonagle *et al.*[**80**] argues that the tendency of the SARS-CoV-2 virus to preferentially attack the alveoli, contrary to RSV and influenza viruses, triggers immunothrombosis, resulting in a larger number of microemboli in the pulmonary and bronchial distal arteries and in the alveoli, which in turn trigger pulmonary infarcts and cause oxygen desaturation. The ambulatory baseline multidrug regimen (ivermectin, doxycycline, nebulized nanosilver) antagonizes the SARS-CoV-2 spike protein [**56**], blocks hemagglutination [**55, 58–60, 67, 73**], and inhibits viral nuclear entry [**57**] and replication [**61, 65, 71, 72**] in the alveoli. Aspirin and anticoagulation can address the accumulated pulmonary microemboli. By resolving the congestion of the alveoli with SARS-CoV-2 viral particles, immunothrombotic production of new microemboli stops, supplemental home oxygen becomes effective and the patient can be kept out of the hospital, provided the work of breathing is tolerable and good support measures are in place. This figure has been reproduced from McGonagle *et al.*[**80, Fig. 1**] with permission from Elsevier.

3.2. Coherence

Coherence requires that the causal hypothesis, that the ivermectin-based multi-drug protocols result in hospitalization and mortality rate reduction in COVID-19 patients should make sense in the context of what we

know about the treatment medications and the COVID-19 disease itself. According to a tricompartmental model, proposed by McGonagle *et al.* [**80**], the rapid decrease of SpO2 levels in COVID-19 patients with hypoxemia can be explained by critically decreased oxygenation, resulting from the combined effect of immunothrombosis in the pulmonary and bronchial distal arteries and in the alveoli, triggered by the SARS-CoV-2 viral invasion of the alveoli (see Fig. 3). Thus, a multidrug treatment regimen with both immunomodulating and anticoagulant mechanisms of action could rapidly restore the ability of the lungs to oxygenate, by addressing the pulmonary microemboli and restoring the oxygenation supply from both the distal bronchial and pulmonary arteries and from the alveoli [**60**]. From the standpoint of biological plausibility, such an approach is most likely to succeed in patients who present with the first of three phenotypes categorized by Robba *et al.* [**81**], showing chest computed tomography with *"multiple, focal, possibly overperfused ground glass opacities"* [**81**], before further deterioration takes hold.

Scheim [**58**] recently explained that the formation of the pulmonary microemboli responsible for this presentation is caused by red blood cell clumping mediated by glycan bindings between the glycans on the SARS-CoV-2 viral spike protein and sialoglycoproteins on the surface of red blood cells. He also noted that the reason why common cold viruses do not cause a similar formation of microemboli is because, unlike the more virulent SARS, SARS-CoV-2, and MERS viruses, common cold viruses express hemagglutinin esterase, which releases these glycan bindings. This hypothesis is supported by an in vitro experiment by Boschi and colleagues [**59**], where they observed that adding viral spike protein from the Wuhan, Alpha, Delta, and Omicron variants to human blood induced red blood cell clumping. The experiment also showed in vitro that ivermectin blocks hemagglutination, if it is added before the spike protein, and reverses hemagglutination when it is added afterwards. Further indirect support for this hypothesis follows from the association between increased propensity for red blood cell aggregation and the risk factors for severe COVID-19 presentation in humans as well as the clinical susceptibility of mammalian species to COVID-19 [**60**]. Furthermore, in vivo animal studies showed that experimentally induced red blood cell clamping causes the same symptomatic presentation that was observed in humans with severe COVID-19 [**60**]. Hydroxychloroquine, ivermectin, fluvoxamine, and resveratrol have been identified as agents that may inhibit the aggregation of red blood cells [**36, 60**]. Conversely, red blood cell disaggregation is the most likely mechanism of action driving the rapid recovery of SpO2 in the patients treated with the Hazan and Stone/Gill Stone/Gill ivermectin-based multidrug protocols [**1, 2, 36**].

Although the antiviral properties of nanosilver against a very broad range of viruses is well-known [**82**], it has not been widely adopted in proposed COVID-19 treatment protocols. Stone observed that nanosilver nebulizations, which were pioneered in treating COVID-19 patients in her clinic, appeared to act synergistically with ivermectin towards rapidly restoring room air SpO2 in hypoxemic patients [**83**]. In particular, Stone observed a pattern of immediate but temporary increase of SpO2 by the administration of nanosilver nebulizations, followed by delayed but more sustained recovery of SpO2 after the administration of ivermectin [**83**]. The anticoagulant effect of nanosilver, observed on an animal model, may be partly responsible for this immediate effect [**73**]. Furthermore, Zachar has proposed that, because of their negative zeta potential, silver nanoparticles, with size less than 10nm, are electrostatically attracted to the positively charged spike glycoproteins on SARS-COV-2 viral particles, which are separated from each other with distances ranging from 10 nm to 20 nm, and they may disable the ability of viral particles to attach to red blood cells, being small enough to coat the viral spike protein [**74**]. Jeremiah *et al.* [**72**] has confirmed in vitro that the viral entry of SARS-CoV-2 to cells can be inhibited by silver nanoparticles, coated with poly (N-vinyl-2-pyrrolidone) (PVP), at sizes ranging from 2 nm to 15 nm at a 2 ppm concentration, which is 10-fold less than the concentration where cytotoxicity was observed. In addition, it is known that silver ions (Ag^{+}) leach off silver nanoparticles under aerobic conditions, and by binding to the genomic viral RNA, they may prevent viral replication inside the cell [**84–86**].

As ivermectin tends to release glycan bindings between viral particles and red blood cells, nanosilver particles may disable the freed viral particles and prevent them from reattaching themselves to red blood cells. Consequently, combining both mechanisms should further accelerate the red blood cell disaggregation. Finally, while the ivermectin/nanosilver combination addresses the existing microclots, the antiviral and anti-inflammatory properties [**64, 65**] of doxycycline may address the immunothrombotic mechanism in the lungs and reduce the production rate of new microclottng. With both ivermectin and doxycycline acting as zinc ionophores [**61, 65**], the antiviral mechanism that results by combining them with zinc may reduce the patient's overall exposure to the cytotoxic viral spike protein [**87, 88**].

4. Parallel evidence

Howick *et al.* [**33**] categorized the Bradford Hill criteria of *consistency* (renamed to *replicability* and *analogy* (renamed to *similarity*) as *parallel evidence*, which assesses whether the causal hypothesis is also supported by other epidemiological studies. It should be noted that Howick *et al.*redefined analogy/similarity to consider epidemiological studies that may differ from this study either in terms of variations in the treatment protocol or variations in the "circumstances in which the intervention is administered" [**33**], or both. This broadens the Bradford Hill definition, which was mainly focused on different but analogous associations involving fundamentally different interventions or illnesses, to include associations using the same or similar interventions but under different circumstances for the same illness. Studies where both intervention and circumstances are sufficiently similar in treating the same disease are categorized by Howick *et al.* [**33**] under consistency/replicability. Otherwise, when there is sufficient difference either with the intervention or with the circumstances of its application, then the evidence is categorized under analogy/similarity.

4.1. Consistency/Replicability

Consistency is satisfied because a rapid increase in SpO2 in hypoxemic patients in response to treatment has been observed in three distinct case series, located in the United States, Zimbabwe, and Nigeria, using similar ivermectin-based multidrug protocols. The consistency in SpO2 recovery rates is most profound between the Hazan case series and the Stone case series, with both using protocols combining ivermectin, doxycycline, zinc, and vitamins C and D. Despite socioeconomic differences between the patients in the Stone and Hazan case series, the immediate response to treatment was very similar. It is therefore unlikely that the immediate response effects were confounded by differences in the demographic characteristics or by selection bias.

4.2. Analogy/Similarity – positive studies

Based on the Howick *et al.* [**33**] definitions, similarity requires that a causality claim should be consistent with and not contradict what is currently known from previous epidemiological studies. This is particularly important, in the context of the ivermectin-based multidrug protocols used in the Hazan, Stone, and Babalola case series, due to conflicting results and controversies concerning the use of ivermectin in treating COVID-19 [**29, 89–92**]. To disentangle these controversies, it is important to remember that evidence of efficacy or of lack of efficacy of single drug monotherapies do not necessarily extrapolate to multidrug protocols that use several medications in combination and studies of inpatients do not extrapolate to studies of outpatients and vice versa [**12, 40**]. Because COVID-19 is a multifaceted triphasic illness [**18**], it is implausible that it can be properly treated with any one particular drug alone; therefore the emphasis of research should be to focus on the validation and incremental improvement of multidrug treatment protocols, rather than investigating drug monotherapies one drug at a time [**93**]. For this reason, observational studies [**9, 28, 31, 40, 94–96**] of multidrug treatment protocols, that have been used by practicing doctors at the frontlines deserve special attention.

In addition to Paper I and this study, other particularly interesting positive evidence include the Procter case series [**94, 95**] of 869 high-risk patients, who were treated early according to the McCullough multidrug protocol [**18**], using hydroxychloroquine and ivermectin in combination with zinc, azithromycin, doxycycline, inhaled budesonide, dexamethasone, folate, thiamine, vitamin B12, and intravenous fluids for a minimum of 5 days. Comparison of outcomes against historical controls, using the case series threshold analysis technique, has shown that the existence of both hospitalization and mortality rate reduction benefits is clear and convincing [**40**], although the patients, for the most part, were treated early as outpatients before the onset of oxygen desaturation. A study on 280 high-risk hospitalized patients by Rajter *et al.* [**97**] showed a signal of benefit with respect to mortality rate reduction, which is statistically significant for severe cases but not for non-severe cases, when adding weekly low-dose ivermectin to the standard of care. This finding is consistent with our finding of a statistically significant reduction in the mortality rate, when using ivermectin at higher dosages and as part of a synergistic multidrug treatment protocol on patients with hypoxemia.

The prospective observational study of prophylactic use of ivermectin conducted in Itaji, Brazil [**98, 99**], and an ecological study on the state-level use of ivermectin in Peru [**100**] both provide additional compelling evidence in support of the efficacy of the prophylactic and pre-hospital early use of ivermectin for reducing the risk of COVID-19 infections and for preventing hospitalizations and deaths in COVID-19 patients. The Itaji studies [**98, 99**] are compelling because they involved more than half of the city population, ensuring negligible risk of confounding by selection bias, and because a dose-response effect was observed with respect

to statistically significant hospitalization and mortality rate reduction. The Peru study [**100**] is a natural experiment that provides evidence of causality between ivermectin use and reduction of excess deaths, since it tracks the variability of excess deaths before the introduction of state-level use of ivermectin, during its use, resulting in 14-fold reduction in excess deaths, and after its use was prohibited, resulting in 13-fold increase in excess deaths. Both studies have been discussed in further detail elsewhere [**92**]. Yagisawa and colleagues [**89, 90**] have conducted extensive reviews of additional evidence in support of using ivermectin in the treatment of COVID-19.

A meta-analysis of ivermectin use in COVID-19 patients by Bryant *et al.* [**101**], which included both observational and randomized controlled trials, showed the association of ivermectin with a statistically significant reduction in all-cause mortality, and confirmed the robustness of their result with an exhaustive sensitivity analysis. Bryant *et al.* [**101**] combined outpatient and inpatient studies and noted that there were very few outpatient trials that used a mortality rate reduction endpoint. Thus, their results tend to support the inpatient use of ivermectin, but do not necessarily extrapolate to outpatient use. A thorough discussion of other ivermectin meta-analysis studies was given by Yagisawa *et al.* [**89, 90**]. Although meta-analysis studies are at the top of the evidence-based medicine pyramid, in terms of design quality, the heterogeneity in the treatment protocols used in the treatment and control arms of the included studies, the variations in dosage and timing, the evolution of the virus into diverging variants with different multiplication rates and lethality throughout the course of the pandemic, and the variability in the prevalence of low-risk vs high-risk patients warrant a very careful qualitative evaluation of the available underlying evidence to draw conclusions supported with a sufficient level of certainty.

A randomized controlled trial from Bangladesh by Mahmud *et al.* [**102**] of a pre-hospital combination therapy (12 mg single dose ivermectin and 100 mg doxycycline twice daily for 5 days) that was a reduced lower-dose variation of the Hazan and Stone/Gill multidrug protocol [**1, 2, 50, 51**], given within the first 3 days from the onset of illness, to a combination of 363 low-risk and high-risk patients that excluded patients with hypoxemia (i.e. SpO2 $\leq$ 90%), showed a statistically significant reduction in mortality rate with $p = 0.016$. Another small randomized controlled trial by Hashim *et al.* [**103**] with a cohort of 84 outpatients (classified as mild or moderate) and 33 inpatients (classified as severe or critical), treated between July 1, 2020 and September 30, 2020, used a similar protocol for the treatment group (ivermectin 0.2 mg/kg for 2 days and an optional third dose a week later, doxycycline for 200 mg per day for 5-10 days; standard of care) and only standard of care for the control group, with the standard of care including daily zinc, Vitamin C, D3, azithromycin (250mg/day for 5 days), and dexamethasone or methylprednisolone as needed. No deaths were reported in either group, for the outpatient cohort, due to an intense standard of care, which was initiated within 3 days from the onset of symptoms, for both the treatment and control groups. However, for inpatients in the severe category, there was some mortality rate reduction benefit (0 deaths out of 11 patients in the treatment group against 6 deaths out of 22 patients in the control group) which gives $p = 0.077$, via two-tailed exact Fisher test, not statistically significant but close to the threshold of 0.05.

In addition to the evidence supporting the use of ivermectin and doxycycline, the following epidemiological evidence support the inclusion of nanosilver, zinc, vitamin D, and vitamin C in the Hazan and/or Stone/Gill protocols. A small randomized case study showed that intravenous injections of nanosilver particles given to COVID-19 pneumonia patients did result in statistically significant mortality rate reduction [**104**], with no observed adverse events. Although this study used injection instead of nebulization as the conduit for administering nanosilver, it corroborates the independent contribution of nanosilver towards reduced mortality in COVID-19 patients. A prospective randomized pilot study on hospitalized COVID-19 patients during 2020 found that zinc deficiency was associated with more complications ($p = 0.009$), prolonged hospital stay ($p = 0.047$), and increased mortality ($p = 0.06$) [**105**]. Subsequent meta-analyses confirmed the association between zinc supplementation and mortality rate reduction in COVID-19 patients [**106, 107**]. Another randomized pilot study on severely ill hospitalized COVID-19 patients found that adding Vitamin D (calcifediol) to the standard of care was associated with reduced ICU admissions and mortality [**108**]; from 50 treated patients there was 1 ICU admission and no deaths, whereas from 26 untreated patients there were 13 ICU admissions and 2 deaths. A later study has confirmed a correlation between vitamin D3 levels and mortality rate reduction in hospitalized COVID-19 patients and recommended raising serum 25-hydroxyvitamin D3 levels above 50 ng/mL [**109**]. Recent meta-analyses have also shown an association between Vitamin C administration and mortality rate reduction in hospitalized COVID-19 patients [**110, 111**].

4.3. Analogy/Similarity – negative studies

Several randomized controlled trials, published in high-impact journals, tend to be cited as evidence against the use of ivermectin in treating COVID-19 [**112–118**]. Among these, the COVID-OUT trial [**112**] used a factorial design that compared a treatment group of patients, that received either a 3-day course of ivermectin (approximately 0.4mg/kg) or a 3-day course of ivermectin combined with a 14-day course of metformin, against a control group, that received placebo or placebo combined with a 14-day course of metformin. Since the study did show a statistically significant signal of efficacy for metformin, including it in both the treatment and control arms of the ivermectin trial strongly biases the results towards the null hypothesis, with respect to establishing any efficacy for ivermectin; therefore, neutral results from this study cannot be used to support a recommendation against the use of ivermectin. Furthermore, the duration of ivermectin treatment was too short compared to the 10-day multidrug treatment used by Hazan *et al.* [**2**], Stone *et al.* [**1**], and Borody *et al.* [**28**]. From the other six cited studies [**113–118**], five tested ivermectin monotherapies against placebo [**114–118**]; therefore their results do not necessarily extrapolate to multidrug protocols [**1, 2, 18, 28**] using ivermectin in combination with other medications.

The most decisive endpoints for recommending or not recommending a treatment regimen for a potentially lethal disease are reduction in hospitalizations and deaths, as opposed to soft endpoints such as duration of illness or time to viral clearance. From this perspective, the most compelling study is the I-Tech RCT [**113**], which recruited high-risk patients, with age ≥ 50 years and at least one comorbidity between May 31, 2021 and October 25, 2021 in Malaysia. The treatment group was administered with a 5-day high-dose course of ivermectin (0.4 mg/kg), initiated within the first 7 days from symptom onset. Both arms of the trial were treated with corticosteroids, antibiotics, and anticoagulants, with each one of these medications given to approximately $1/4$ of the patients of both the treatment and control group, although the number of patients receiving ivermectin monotherapy was not clearly articulated. The paper reported a 4.0% mortality rate in the control group and 1.2% mortality rate in the treatment group with $p = 0.09$, and although there was a signal of mortality rate reduction, it was deemed to be not statistically significant. On the other hand, from 241 patients with 3 deaths in the treatment group, we calculated [**51**] an adjusted efficacy threshold of $y_0 = 3.7\%$, which means that statistical significance can be achieved, if an equivalent control group with an asymptotically infinite size has mortality rate greater than or equal to 3.7%. For untreated high-risk patients with comorbidities, we expect a mortality rate of at least 5% without any treatment for pre-omicron variants [**40**]. Because some treatment was offered to the control group, it had a modest effect in reducing the mortality rate to 4.1%. However, comparison of the treatment arm of the trial against historical controls of high-risk patients with comorbidities, receiving no treatment, suggest that the multidrug treatment that was actually administered to the treatment arm of the trial was more likely than not effective in reducing mortality rate, despite the treatment being initiated within a 7-day window.

The first ACTIV-6 trial [**114**] enrolled patients between June 23, 2021 and February 4, 2022, overlapping with the Delta variant and the Early Omicron variants, and tested ivermectin monotherapy (0.4 mg/kg for 3 consecutive days) against placebo. Subsequently, the second ACTIV-6 trial [**115**] enrolled patients between February 16, 2022 and July 22, 2022, catching the tail end of Early Omicron and overlapping for the most part with Late Omicron in the United States, and tested an ivermectin monotherapy at higher dosage (0.6 mg/kg for 6 consecutive days) against placebo. No deaths were reported in the placebo arm of either trial, suggesting that the patients were low-risk, possibly owing to some combination of low age and low percentage of comorbidities, reduced virulence of the Omicron variants, prior partial natural immunity from previous COVID-19 infections, and prior vaccine-induced immunity. As such, these studies did not prove the absence of a mortality rate reduction benefit for high-risk patients. No statistically significant reduction in hospitalization rates was reported, and none should have been expected because the treatment was monotherapy that, for a substantial proportion of the patients in the treatment group, was not administered within the first 3 days from the onset of symptoms, which is the ideal window of opportunity for preventing hospitalizations [**119**].

The Lopez-Medina *et al.* [**116**] trial was conducted in Colombia between July 15 2020 and December 21 2020, testing ivermectin monotherapy (0.3 mg/kg for 5 consecutive days) against placebo, was not informative with respect to mortality rate reduction, noting that one death was reported out of 198 patients in the control group and zero deaths were reported out of 200 patients in the treatment group. During the study period, the average CFR in Columbia was 2.58% (number of cases increased from 154277 to 1.5 million and number of deaths increased from 5455 to 40268 between July 15 2020 and December 21 2020) [**120**], so the low mortality rate in the control group indicates that the patients were either at very low risk or they accessed ivermectin over the counter as a result of failure of blinding [**121**]. In either case, the study prima facie enrolled low-risk

patients, given the atypically low mortality rate in the control group; therefore, it cannot be used to justify a recommendation against the use of ivermectin in treating high-risk patients.

The TOGETHER ivermectin trial [**117**] tested ivermectin monotherapy (0.4 mg/kg for 3 consecutive days) in Brazil between March 23, 2021 and August 6, 2021 against placebo. The results in the intention-to-treat population from both arms of the trial were as follows: reduction in hospitalizations from 14% (control arm) to 11.6% (treatment arm) and smaller reduction in deaths from 3.5% (control arm) to 3.1% (treatment arm), both not statistically significant. A curious characteristic of the trial was that in the treatment arm, the intention-to-treat population decreased from 679 to a per-protocol population of 624, however, in the control arm, there was a massive decrease from a 679 intention-to-treat population to a 288 per-protocol population, signaling a possible loss of blinding. The authors did not conduct the corresponding per-protocol population analysis for either hospitalization or death reduction. The data have not been made available to research groups interested in conducting the per-protocol reanalysis, even though it was requested for that purpose [**122**]. More than half of the patients initiated treatment 4-7 days after the onset of symptoms. During the study period, Brazil was exposed to the highly lethal Gamma variant. By the beginning of March 2021, the cumulative CFR was 2.4%; however, between March 23, 2021 and August 6, 2021 the average CFR was 3.29% (the number of cases increased from 12.00 million to 20.07 million and the number of deaths increased from 295,042 to 559,607) [**120**]. It is plausible that the ivermectin monotherapy, used in the treatment group, was administered too late, for too short a duration, and at an insufficient dose to make a statistically significant difference with an unusually more lethal variant.

Table 2: Comparison with two-tailed exact Fisher test between the 2157 patient treatment group from the PRINCIPLE trial [**118**] and the United Kingdom population level CFR between June 23, 2021 and July 1, 2022.

Case series	(N, a)	(M, b)	**OR (95% CI)**	p**-value**
PRINCIPLE treatment arm compared against entire UK population				
Principle	(2157, 3)	(265355, 685)	0.54 (0.11 – 1.58)	0.39
Counterfactual comparisons with increased sample size				
Principle $\times$ 2	(4314, 6)	(265355, 685)	0.54 (0.2 – 1.18)	0.168
Principle $\times$ 3	(6471, 9)	(265355, 685)	0.54 (0.24 – 1.03)	0.061
Principle $\times$ 4	(8628, 12)	(265355, 685)	0.54 (0.28 – 0.95)	0.029
Principle $\times$ 5	(10785, 15)	(265355, 685)	0.54 (0.3 – 0.89)	0.014

(N, a) = treatment case series with N cases and a deaths; (M, b) = external control with M cases and b deaths with data obtained from the population level CFR data in the United Kingdom between June 23, 2021 and July 1, 2022 [**120**]; OR = Odds Ratio; CI = Confidence Interval

The PRINCIPLE ivermectin trial [**118**] was conducted in the United Kingdom between June 23, 2021 and July 1, 2022 testing ivermectin (0.3 mg/kg for 3 consecutive days) plus "usual care" against "usual care". According to the authors, "usual care" included the use of monoclonal antibodies and other antiviral medications for *"a minority of extremely clinically vulnerable patients"* [**118**], which may have biased the trial towards the null hypothesis. Otherwise, the study protocol indicates that prior to hospitalization, "usual care" was only supportive care, so for most patients the comparison was between ivermectin monotherapy against placebo. For the first month, the trial recruited high-risk patients (age $\geq$ 65 years or age $\geq$ 18 years with comorbidity or breathlessness) but after July 29, 2021, the trial recruited both low-risk and high-risk patients with positive COVID-19 test and symptomatic infection with up to 14 days since the onset of symptoms. Although the authors reported randomization at 5 days median (IQR 3-7 days) since onset of symptoms, the initiation of treatment was further delayed because the medications were shipped to the patients. The authors reported no statistically significant reduction on the composite hospitalization + mortality endpoint. Considering the late onset of treatment and the short treatment duration of only 3 days, it is not surprising that hospitalizations were not reduced, which is why it is important to also consider the mortality endpoint. The authors did report that the ivermectin group included 2,157 patients with 3 deaths but did not report the number of deaths in the control group and did not compare the treatment arm against the control arm in terms of a mortality endpoint. However, because the trial recruited patients without any risk stratification,

except for the first month, we may compare the ivermectin group against the concurrent mortality rate of the entire population in the United Kingdom (685 deaths out of 265,355 cases between June 23, 2021 and July 1, 2022) [**120**]. There is a two-fold mortality rate decrease (0.13% CFR for ivermectin group vs 0.25% CFR for the entire United Kingdom population), however, Table 2 shows that it is not statistically significant ($p = 0.39$), because the sample size of the ivermectin group is underpowered. Table 2 also shows that to capture a two-fold mortality rate reduction would have required increasing the ivermectin group sample size by a factor of 4. However, the authors terminated the ivermectin treatment arm based on futility criteria using the composite hospitalization + death endpoint. It is worth noting that despite the late administration and short duration of ivermectin treatment, the PRINCIPLE trial showed statistically significant reduction of time to sustained alleviation of symptoms [**118, Figure S6**] and statistically significant reduction of the following long-COVID symptoms at 3 months in the ivermectin group: shortness of breath [**118, Table S7**], inability to concentrate/brain fog [**118, Table S24**], pins and needles or numbness [**118, Table S29**], generalized body pains [**118, Table S31**], joint pains [**118, Table S33**], and fatigue [**118, Table S34**].

Finally, a Cochrane meta-analysis of ivermectin randomized controlled trials [**123**] has also been invoked to justify recommendations against the use of ivermectin in treating COVID-19, even though it excluded two randomized controlled trials with mortality endpoints that used ivermectin in combination with doxycycline (Mahmud *et al.* [**102**] and Hashim *et al.* [**103**], both discussed previously), which reported positive results, solely due to the use of these drugs in combination. In total, the Cochrane meta-analysis [**123**] excluded 11 studies that used ivermectin-based multidrug therapies, with the sole justification that these were combined interventions; therefore the findings of the Cochrane meta-analysis [**123**] do not extrapolate to ivermectin-based multidrug treatments. Unlike the Bryant *et al.* [**101**] meta-analysis, the Cochrane meta-analysis [**123**] also excluded all observational controlled trials, despite known empirical evidence that observational and randomized controlled trials, on average, tend to provide similar effect size estimates [**124–126**]. These exclusions, along with the wide heterogeneity of the treatment protocols used in the underlying studies, account for the divergence in conclusions between the Cochrane meta-analysis [**123**] and Bryant *et al.* [**101**].

The Cochrane meta-analysis selected 11 randomized controlled trials, of which 1 was later retracted, 3 were previously discussed (TOGETHER [**117**], Lopez-Medina *et al.* [**116**], and ITECH [**113**]), and 4 have no mortality reported in either the treatment or control group (Buanfrate *et al.* [**127**], Chaccour *et al.* [**128**], Krolewisky *et al.* [**129**], Mohan *et al.* [**130**]), due to all patients surviving. The remaining 3 studies were Vallejos *et al.* [**131**], Ravikirti *et al.* [**132**], and Gonzalez *et al.* [**133**]. Vallejos *et al.* [**131**] is an outpatient study involving 500 patients that used an ivermectin monotherapy in the treatment group for 2 days (dose staggered by weight, ranging from 0.15 mg/kg to 0.2 mg/kg) that found no hospitalization or mortality rate reduction efficacy. Ravikirti *et al.* [**132**] is an inpatient study of 112 patients with oxygen saturation above 90% using a similar ivermectin monotherapy (12 mg per day, not adjusted by weight, for 2 days) and reported no deaths in the treatment group and a compelling mortality rate reduction signal that is not statistically significant (we calculated $p = 0.11$ using two-tailed exact Fisher test, but the authors reported statistical significance). In both cases, the treatment group received insufficient ivermectin monotherapy for only 2 days.

The remaining study, Gonzalez *et al.* [**133**], is an interesting inpatient randomized controlled trial of 106 patients with very severe hypoxemia (average oxygen saturation reported as $83\% \pm 8\%$ who were seen between May and August 2020 in Mexico. The patients in the treatment group received standard of care and ivermectin (0.15 mg/kg to 0.22 mg/kg dose staggered by weight for 5 days), with the standard of care including thromboprophylaxis for 90% of patients, steroids for approximately half of the patients, and macrolides for approximately 1/5 of patients. The study reported an approximately equal mortality rate in both the treatment and control groups. Although the ivermectin dosage was approximately similar to that used in the Babalola case series [**3**], it did not include zinc, vitamin C, and vitamin D, and although some antibiotics were used for some patients, they did not appear to have included doxycycline, and they were not used across the board in all patients. Our more conservative analysis has not been able to claim a hospitalization or mortality rate reduction benefit for patients in the Babalola case series either, where there were 5 deterioration events, albeit no deaths [**3,134**]. The Gonzalez [**133**] cohort included a large proportion of patients, approximately half of the entire cohort, with oxygen saturation below 80%, for which the Stone/Gill protocol [**50, 51**] recommends a far more aggressive salvage protocol with an initial 0.6 mg/kg stat dose of ivermectin, titrated up to 1-2mg/kg, if SpO2 does not increase, then maintained at 0.3-0.6 mg/kg for up to 10 days or until symptom free for 48 hours, in conjunction with continuous nanosilver nebulizations, while room air SpO2 $\leq$ 90%, doxycycline, corticosteroids, and anticoagulants (see Paper I). In the Babalola case series, only 10 out of 61 patients had room air oxygen saturation below or equal to 90%, so the absence of deaths in the Babalola case series, which

has not been sustained by Gonzalez *et al.* [**133**], is most likely to be attributed to the substantial difference in the risk profile between the two cohorts. From Gonzalez *et al.* [**133**] we infer that a minimal 5-day low-dose ivermectin-based protocol that excludes nanosilver nebulizations, doxycycline, zinc, and vitamins C and D appears to be insufficient for the treatment of the most severe hypoxemic patients.

In summary, from amongst the cited randomized controlled trials on outpatients, the I-Tech trial [**113**], in which a high-dose ivermectin-based multidrug treatment protocol was used relatively early on high-risk outpatients, over a 5-day period in the treatment arm, presents a compelling signal of benefit with respect to mortality rate reduction, with a 3.7% efficacy threshold that compares favorably with the expected mortality rate for such high-risk patients, when they are not offered any early treatment. ACTIV-6 [**114, 115**] and Lopez-Medina *et al.* [**116**] used ivermectin monotherapies on prima facie low-risk patients, and therefore cannot be used to justify a negative recommendation against the use of ivermectin for treating high-risk patients. The TOGETHER trial [**117**] prima-facie shows that ivermectin monotherapy over a short period of 3 days against an unusually tough COVID-19 variant is insufficient for the early treatment of outpatients, however, in light of the totality of evidence, this result is not necessarily generalizable to more aggressive use of ivermectin, as part of a multidrug protocol, over a 10-day duration, as used by Borody *et al.* [**28**], Hazan *et al.* [**2**], and Stone *et al.* [**1**]. The PRINCIPLE trial [**118**] showed that ivermectin use, despite short duration and late administration, resulted in statistically significant reduction of time to sustained recovery of symptoms and prevalence of certain long covid symptoms within a 3-month window; a two-fold mortality rate reduction was also observed relative to the population-level concurrent CFR, but the study was interrupted before reaching statistical significance. Gonzalez *et al.* [**133**] shows that even a 5-day low-dose ivermectin monotherapy with adjunct anticoagulation is insufficient, by itself, in terms of reducing the mortality rate, when treating the most severe hypoxemic COVID-19 patients in a hospital setting. However, the oxygen saturation recovery trend in the Babalola case series (see Fig. 1) shows that even alone, ivermectin does have an active role in driving the normalization of oxygen saturation, which appears to be further intensified by the inclusion of doxycycline and the adaptive variability of ivermectin dosage in the Hazan and Stone case series [**1, 2**]. Mahmud *et al.* [**102**] and Hashim *et al.* [**103**] are the only randomized controlled trials of ivermectin + doxycycline combination (albeit at lower dosages) with a mortality endpoint that have been identified by the Cochrane meta-analysis [**123**]. Both studies showed positive signals of efficacy with respect to mortality rate reduction (Mahmud *et al.* [**102**] for early outpatient treatment and Hashim *et al.* [**103**] for inpatients) despite the low ivermectin dosage, thus corroborating the possible existence of a very important synergistic effect between ivermectin and doxycycline. This synergistic interaction of ivermectin and doxycycline and the variable dosage of ivermectin based on the severity of disease are the most plausible reasons for the rapid normalization of SpO2 levels in hypoxemic patients and for our finding of some hospitalization and mortality rate reduction benefit from the use of the Hazan and Stone/Gill protocols [**1, 2, 50, 51**] on hypoxemic COVID-19 patients.

5. Discussion

The statistical analysis presented in Paper I has shown the strength of association between the Hazan and Stone/Gill ivermectin-based multidrug protocols and the reduction in hospitalization and mortality rates. In this study, we have argued that the Bradford Hill criteria [**32**], as revised by Howick *et al.* [**33**], of temporality, biological gradient, biological plausibility, coherence, consistency/replicability, and analogy/similarity are satisfied, lending support to a claim of causal association. The salient differences resulting from the proposed refinements by Howick *et al.* [**33**] were the following: (a) direct evidence play the decisive role whereas mechanistic and parallel evidence play only supporting roles; (b) for strength of association (renamed to *size of effect*) the key consideration is to show that the magnitude of the association exceeds the magnitude of any plausible confounders; (c) the renaming of *temporality* to *temporal/spatial proximity* highlights that the strength of Bradford Hill's concept of temporality is stronger when the proximal distance between intervention and response is decreased and when it is consistent with the underlying mechanism of action, and the guideline is extended to encompass spatial proximity; (d) the renaming of *biological plausibility* to *plausible mechanism* extends Bradford Hill's biological plausibility to non-biological mechanisms; (e) the definition of *similarity/analogy* has been broadened to include all epidemiological studies on the same disease that are coherent with a causality claim but are not replication studies, because of substantial variability either in the treatment protocol, or in the circumstances of its use, or both; (f) the definition of *coherence* has been thus refocused to the coherence between the causality claim and non-epidemiological studies.

In connection with these refined criteria we note that: (a) the observed SpO2 recovery from the onset

of treatment is indeed remarkably immediate for both the Hazan and Stone case series, occurring within 24 hours; (b) using the case series threshold analysis technique [**40**], we found in Paper I that a claim of the effect size exceeding plausible confounders is clear and convincing with respect to the hospitalization rate reduction endpoint and supported by the preponderance of evidence with respect to the mortality rate reduction endpoint; (c) in addition to good direct evidence, both mechanistic and parallel evidence have been successfully established. A strength of this study is our critical appraisal of the parallel evidence of similarity between this study and previous epidemiological studies that have given rise to controversies [**29, 89–92**]. Our detailed review of these studies outlines the boundary of what works and what does not work in terms of ivermectin-based treatment protocols.

Using the Bradford Hill criteria to infer causality has been controversial [**135**], because one may argue that neither one of the criteria is necessary nor sufficient for establishing causality, with the underlying concern being the strength of the inference that follows once the Bradford Hill criteria have been established. Ward [**34**] highlighted this angle of attack, noting that one may argue that, whereas a causal inference from a randomized controlled trial is an inductive inference, any inference justified via the Bradford Hill criteria is neither a deductive nor inductive argument, because of its qualitative nature, and therefore not legitimate. Ward [**34**] resolved this potential criticism by observing that an inference based on the Bradford Hill criteria is an *inference to the best explanation*.

The concept of "inference to best explanation" was crystallized by Harman [**35**], who defined it as a logical inference that begins with an array of factual evidence and infers the truth of a specific hypothesis by arguing that this specific hypothesis, if true, provides the best explanation for the available evidence relative to any other alternative hypothesis. This method of non-deductive reasoning is distinct from enumerative induction (i.e. if all observed A's are B's then we conclude that all A's are B's, as per Harman [**35**]). It is also distinct from the broader definition of inductive reasoning highlighted by Ward [**34**], according to which *"an inductive inference is any logical inference that is not [a] deductively valid inference where . . . it is improbable, given that the premises are true, that the conclusion is false"* [**34**]. With an inductive inference, the strength of the inference can be quantified probabilistically, whereas an inference to the best explanation argument has either a qualitative nature or a hybrid combination of both quantitative and qualitative considerations.

In the context of the Bradford Hill criteria, Ward [**34**] argued that given a strong association, an argument showing several of the other Bradford Hill criteria constitutes an inference to the best explanation argument in favor of the hypothesis that the association is causal. A properly conducted randomized controlled trial, on the other hand, can establish the internal validity of causality, specifically for the trial sample, by providing an inductive argument, in the broader sense, in support of rejecting the null hypothesis. The internal validity of this inductive causality inference requires sufficiently large sample sizes on both arms of the trial, to ensure sufficient randomization; a requirement that may exceed the sample size requirement needed to achieve statistical significance [**126**].

Although Ward [**34**] argued that inductive inference arguments are generally stronger than inference to the best explanation arguments, Harman [**35**] did argue, in our view convincingly, that the narrower concept of enumerated inductive arguments should be understood as a special case in the broader class of inference to the best explanation arguments. We believe that Harman's argument can be expanded to the epistemology of randomized controlled trials, by noting that it is necessary to be able to argue in favor of the external validity of the trial results, as was highlighted in detail by Deaton and Cartwright [**136**]. Thus, although the internal validity of a causality finding by a randomized controlled trial is supported by inductive reasoning, the additional argumentation that is needed to support the external validity of the trial itself is an inference to the best explanation that may require consideration of qualitative background knowledge that cannot be captured in a strictly inductive reasoning framework. The other side of the argument is that, although Ward acknowledged [**34**] the ongoing debate about whether or not an inference to the best explanation argument can be used to establish the truth of a hypothesis, Howick and colleagues [**33**] proposed several counterexamples where their revised Bradford Hill criteria give strong arguments in favor of causality, that are inference to the best explanation arguments, even in the absence of randomized controlled trials. These considerations lend support to the argument by Aldous and colleagues [**137**] that quality of study design (in the sense of the evidence-based medicine pyramid) does not necessarily imply higher certainty concerning the validity of the study's results, and conversely higher certainty does not necessarily require a study design of higher quality, which is why Aldous *et al.* [**137**] highlighted the need for a paradigm shift towards considering the totality of the available evidence.

We conclude with an important observation by Phillips and Goodman [**135**] who focused on some additional

overlooked insights by Bradford Hill [**32**]. One of them is that policy actions should be informed not only by the strength of the available evidence in favor of a causal inference but also by the *"absolute costs and benefits of potential actions"* [**135**]. With the proposed ivermectin-based multidrug protocols, based on repurposed medicines, the potential absolute cost of using them is a population of overtreated parasite-free COVID-19 patients, however the potential benefits are life-saving. Clearly, the minimum absolute benefit from the observed rapid recovery of oxygen saturations with the onset of treatment, is the alleviation of patient suffering. This consideration alone was just as salient as the strength of the evidence in support of a causal relation with hospitalization and mortality rate reduction, with regards to justifying the emergency adoption of these protocols during 2020 and 2021.

6. Conclusion

The statistical analysis in Paper I combined with the Bradford Hill criteria argument presented in this study lends further support to the adoption of the Hazan and Stone/Gill ivermectin-based protocols by practicing physicians for the treatment of hypoxemic COVID-19 patients, as a community standard of care. The totality of the reviewed evidence indicates that variable dosing of ivermectin, depending on the severity of initial presentation, is essential, and the inclusion of doxycycline, zinc, vitamin C, vitamin D, and nanosilver nebulizations provide important synergistic effects that are necessary for the successful treatment of hypoxemic COVID-19 patients. Given the capability of this combination of medications to rapidly normalize the SpO2 levels of hypoxemic patients, it is a compelling extrapolation to also use these protocols in the treatment of high-risk symptomatic COVID-19 outpatients to prevent red blood cell clumping and/or oxygen desaturation, rather than wait for complications to arise and only then attempt to address them. These protocols remain relevant today for the treatment of high-risk COVID-19 reinfections and may become urgently needed again if a highly lethal strain of COVID-19 re-emerges.

Abbreviations

ACE2, Angiotensin-Converting Enzyme 2; AgNP, silver nanoparticles; CFR, Case Fatality Rate; CD147/EMMPRIN, Cluster of differentiation 147 / extracellular matrix metalloproteinase inducer; COVID-19, Coronavirus Disease 2019; DPP4/CD26, Dipeptidyl peptidase 4 / cluster of differentiation 26; IL-6, Interleukin 6; IMP, importin; MMP-9, matrix metalloproteinase-9; NF-κB, Nuclear factor kappa B; NIH, National Institute of Health; RDRP, RNA Dependent RNA Polymerase; S1-NTD, S1-N-Terminal Domain; S1-RBD, S1 Receptor Binding Domain; PVP, poly (N-vinyl-2-pyrrolidone) ; RAS, Renin Angiotensis System; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO2, Peripheral oxygen saturation; TNF-α, tumor necrosis factor alpha.

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Dedication

This paper is dedicated to the memory of Jacqueline Stone who passed away on October 3, 2024. Jacqueline Stone invented the idea of adding nebulized nanosilver into the ivermectin, doxycycline, zinc, Vitamin D, Vitamin C multidrug protocol for the treatment of COVID-19 patients. Furthermore, she instructed several other outpatient doctors in using her protocol, resulting in a nationwide reduction of COVID-19 mortality throughout the nation of Zimbabwe. An account of Dr. Stone's efforts and of the opposition against herself and colleagues, which contributed to her untimely passing, has been memorialized in a posthumously published book chapter [**138**]

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Ethics approval and consent to participate

Not applicable. The study is an analysis of previously published data.

Conflict of interest

Peter McCullough is the part-time Chief Scientific Office for the Wellness Company, Boca Raton, Florida, United States of America, which had no role in the study or the writing of the manuscript. Eleftherios Gkioulekas is affiliated with the the School of Mathematical and Statistical Sciences at The University of Texas Rio Grande Valley, which regularly invites visiting scholars from other academic institutions and directly receives donations to fund scholarships, however he has not himself hosted any visiting scholars or received a scholarship. Colleen Aldous has no conflicts of interest.

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