Critical appraisal of multidrug therapy in the ambulatory management of patients with COVID-19 and hypoxemia

Eleftherios Gkioulekas [1,*], Peter A. McCullough [2,3], and Colleen Aldous [4]

[1] School of Mathematical and Statistical Sciences, University of Texas Rio Grande Valley, Edinburg TX, USA
[2] President, McCullough Foundation, Dallas TX, USA
[3] Chief Medical Officer, Truth for Health Foundation, Tucson, AZ, USA
[4] College of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa
[*] Corresponding author: Eleftherios Gkioulekas; Email: drlf@hushmail.com

Abstract: Aim: This critical appraisal is focused on three published case series of a total of 119 COVID-19 patients with hypoxemia who were successfully treated in the United States, Zimbabwe, and Nigeria with similar off-label multidrug treatments that may include ivermectin, nebulized nanosilver, doxycycline, zinc, and vitamins C and D, resulting in rapid recovery of oxygen levels. We investigate the hypothesis that these treatment protocols were successful in preventing hospitalizations and deaths. **Methods:** We use a simplified self-controlled case series method to investigate the association of treatment with the existence of a hospitalization rate reduction effect. To show the association of treatment with the existence of a mortality rate reduction effect, we make conservative comparisons of the treatment case series with several external control groups using the exact Fisher test. A novel statistical technique, based on the Sterne interval and the Bayesian factor, is used to assess the resilience of these results with respect to selection bias. **Results:** The existence of statistically significant hospitalization rate reduction is shown for two of the three case series with the most aggressive treatments, and it is resilient against both random and systemic selection bias. Combining either all three case series or the two case series with the most aggressive protocols allows us to show the existence of statistically significant mortality rate reduction, and it is more likely than not that random selection bias does not overturn this finding. **Conclusion:** These results, combined with an extensive literature review, show that the efficacy of these multidrug treatments is supported by the Bradford Hill criteria of strength of association, temporality, biological gradient, consistency, and biological plausibility.

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

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1. Introduction

On March 11, 2020, COVID-19, the disease caused by the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) [**1**]. Worldwide, there have been 768,187,096 confirmed cases of COVID-19 and 6,945,714 deaths were reported to WHO as of June 21 2023, amounting to an average CFR of 0.9% [**2**]. During 2020, while several governments and public health agencies were focused on contagion control and in-hospital patient care, several medical doctors from all around the world were forced to innovate and discover early outpatient multidrug treatments using several repurposed medications in combination [**3–15**]. In the United States, several independent efforts coalesced into the formulation of the McCullough sequenced multidrug protocol [**9**], which is based on the pathophysiological understanding of COVID-19 as a triphasic illness with three overlapping phases: (1) viral proliferation; (2) a hyperinflammatory cytokine storm (COVID-19 pneumonia); (3) thrombosis. McCullough's protocol proposed a combination antiviral therapy for treating the viral proliferation phase, immunomodulators for treating the cytokine storm, and antiplatelet agents and antithrombotics for handling the thrombotic stage, based on risk stratification and on how the disease presents on each individual patient. Thus, the McCullough protocol is an algorithmic treatment using sequenced multiple drugs in combination and customized to the individual patient and their response to treatment; no single drug is necessary nor sufficient to achieve treatment efficacy towards reducing hospitalizations and deaths. An updated version of the McCullough protocol [**10,11**] added ivermectin as an option for the combination antiviral therapy, and a more recent update [**16**] introduced some additional adjustments, including virucidal nasal washes and oral gargles [**17–24**].

Although there has been no published randomized controlled study of the entire McCullough protocol, a large case series of 869 high-risk patients [**25,26**], that were treated using an early version of the McCullough protocol, has been compared against population-level and historical controls [**27**], showing the existence of efficacy with respect to reduction of mortality and hospitalizations, that is also resilient with respect to random selection bias, provided that patients are treated early enough within the first 3 to 5 days from the onset of illness. Indeed, an earlier study by Fazio *et al.*[**28**] showed that the ideal window of opportunity

for initiating an effective early outpatient treatment of COVID-19, that can prevent hospitalization, is approximately within the first 3 days. Interestingly, although ivermectin was included in the McCullough protocol as an antiviral agent for early pre-hospital use, the ICON study [**29**] was one of the first to demonstrate that weekly low-dose ivermectin is associated with mortality rate reduction in hospitalized patients with severe presentation.

The focus of the present paper is the hypothesis that an ivermectin-based multidrug treatment protocol can rescue patients with hypoxemia by reversing the formation of microscopic red blood cell clumping in the lungs that causes the sudden declining oxygen saturation in some COVID-19 patients, resulting in the rapid recovery of peripheral oxygen saturation (SpO2) levels upon initiation of treatment [**30–33**]. Thus, the focus is on COVID-19 patients whose condition has deteriorated, either due to lack of early treatment or due to insufficient response to some initial attempt at an early treatment. Our goal is to quantify the strength of the evidence in favor of the hypothesis that these multidrug protocols are ultimately efficacious in reducing hospitalizations and deaths. To that end, we study several case series of high-risk COVID-19 patients with severe hypoxemia, reported by Hazan *et al.*[**34**], Stone *et al.*[**35**], and Babalola *et al.*[**36**], who were treated between August 2020 and June 2021, with respect to showing the existence of mortality and hospitalization rate reduction benefit.

Hazan *et al.*[**34**] reported a case series of 24 patients (hereafter *Hazan case series*) that consisted of patients with severe hypoxemia that enrolled to participate in a clinical trial but were excluded due to very low baseline SpO2 levels [**34**]. Some of these patients declined hospitalization and were treated at home, which limited the options for offering supplemental oxygen, via telemedicine, using off label treatment. Likewise, with the case series of 34 hypoxemic patients reported by Stone *et al.*[**35**] (hereafter *Stone case series*), resource limitations in Zimbabwe constrained the possibility of using supplemental oxygen [**35**]. In both cases, this provided an unusual opportunity to track room air SpO2 throughout the treatment of the recovering COVID-19 patients. In doing so, these physicians acted in accordance with article 37 of the 2013 Helsinki declaration [**37**], as they attempted to meet the needs of their patients with unproven, at the time, multidrug treatments.

Hazan and colleagues treated their patients with a 10-day multidrug protocol consisting of ivermectin, doxycycline, zinc sulfate, and Vitamins C and D3, with adjunct use of hydroxychloroquine and azithromycin in the highest risk cases [**34**]. Stone and colleagues used a more aggressive multidrug protocol [**35, 38**], developed in collaboration with Gill from South Africa, that included ivermectin, doxycycline, zinc, vitamin C, vitamin D, nebulized nanosilver, corticosteroids, and anticoagulants, following the concept of a sequenced multidrug protocol recommended by McCullough [**11**]. This Stone/Gill multidrug protocol [**38**] was used at several urgent care centers in both Zimbabwe and South Africa, and it was designed under the assumption that some patients will be treated at an urgent care setting, while other patients will complete their treatment at home, as opposed to the telemedicine approach that was used in the United States. Furthermore, the Stone/Gill multidrug protocol [**38**] includes a protocol for treating patients with baseline room air SpO2 as low as 80% and an additional protocol for attempting to salvage patients with baseline room air SpO2 below 80%, to prevent them from requiring hospitalization.

Babalola *et al.*[**36**] reported a case series of 61 COVID-19 patients (hereafter *Babalola case series*) who were part of a clinical trial in which 30 patients were treated with ivermectin and the other 31 patients were treated with a combination of ivermectin and a low-dose regimen of hydroxychloroquine and azithromycin. All 61 patients also received zinc and vitamin C, however unlike with the Hazan and Stone case series, they did not receive doxycycline or vitamin D. Thairu *et al.*[**39**] compared the 61 patients from the Babalola case series with 26 additional patients that were treated with a non-ivermectin standard of care protocol (hereafter *Thairu case series*), of which 4 patients died. Babalola *et al.*[**40**] highlighted that SpO2 levels in the 61 patients of the Babalola case series recovered more rapidly than the 26 patients in the Thairu case series. Furthermore, according to Stone *et al.*[**35**], for the Hazan and Stone case series, where the most aggressive multidrug treatment protocols were used, statistically significant normalization trend of SpO2 was observed within 24 hours, followed by a slower rate of recovery by the Babalola case series, where a less aggressive ivermectin-based protocol was used, which was still substantially faster than the recovery rate of the Thairu case series, where a non-ivermectin standard of care protocol was used (see Fig. 1). Compared against the Thairu case series, Fig. 1 also 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.

According to a tricompartmental model, proposed by McGonagle *et al.*[**41**], 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. 2). Scheim *et al.*[**33**] have recently explained that this immunothrombotic process is mediated by glycan bindings between red blood cells and the SARS-CoV-2 viral spike protein, and noted that the reason why common cold strains do not cause a similar formation of microemboli is because common cold viruses, unlike SARS, SARS-CoV-2, and

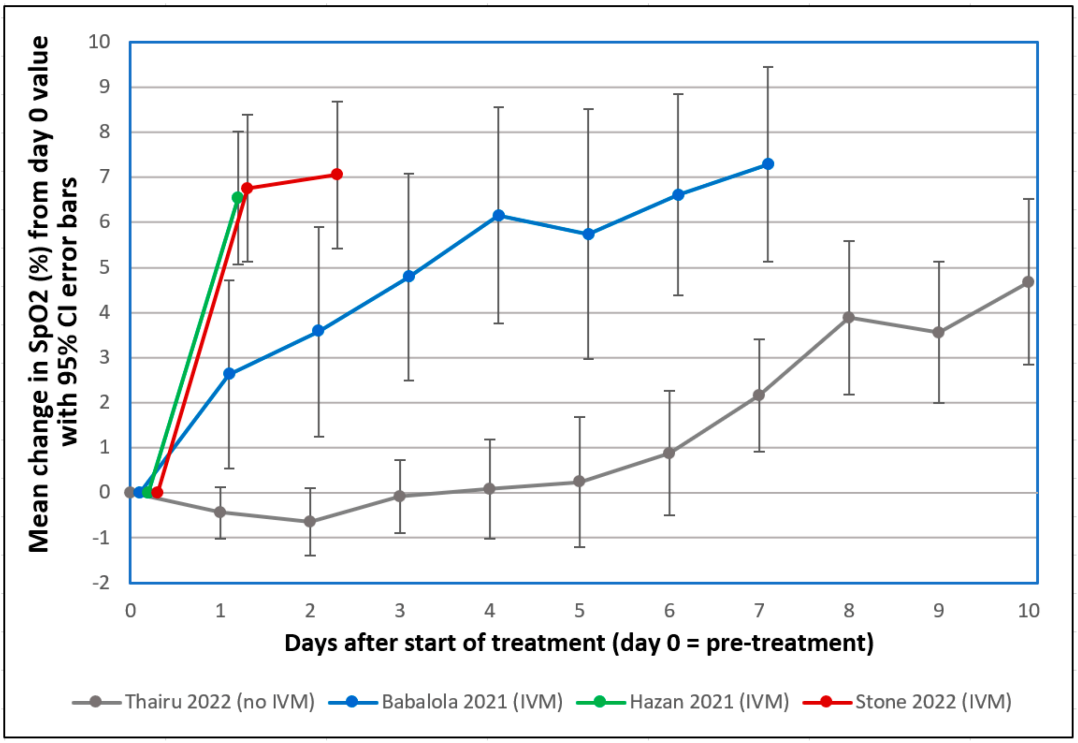

Figure 1: Mean change to room air SpO2 levels from initial value at Day 0 for the patients in the Hazan case series [**34**], the Stone case series [**35**], and the Babalola case series [**36**] with baseline room air SpO2 $\leq$ 93%, with error bars showing 95% confidence intervals. The most rapid increase is observed for the Hazan and Stone case series [**34,35**]. Slower increase is observed in the Babalola case series [**36**]. 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.*[**39**]. Stone *et al.*[**35**] 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 [**36**] and the Thairu *et al.*[**39**] case series. The figure is reproduced from Stone *et al.*[**35**] under the terms of the CC-BY-4.0 license.

MERS, express hemagglutinin esterase which releases these glycan bindings. Thus, a multidrug treatment regimen with both immunomodulating and anticoagulant mechanisms of actions, that can also release the glycan bindings between the viral spike protein and red blood cells, 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 [**33**]. 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.*[**51**], showing chest computed tomography with *"multiple, focal, possibly overperfused ground glass opacities"* [**51**], before further deterioration takes hold. There is a substantial body of literature, reviewed in our discussion section, that supports the biological plausibility of a baseline multidrug therapy, consisting of ivermectin, doxycycline, zinc, and nebulized nanosilver, used in combination with zinc, vitamin C, and vitamin D, to provide antiviral, anti-inflammatory, and anti-clotting effects that can address the three stages of the COVID-19 disease and restore SpO2 levels [**30–32,42,44,45,47–50,52–60**]. Biological plausibility is one important component of the evidence in support of the baseline therapy used by Hazan *et al.*[**34**] and Stone *et al.*[**35**]. Furthermore, the escalating rapid increase in SpO2 levels in severe COVID-19 patients, with escalating itensity of treatment, highlighted by Babalola *et al.*[**40**], Hazan *et al.*[**34**], and Stone *et al.*[**35**], support the temporality and biological gradient components of the Bradford Hill criteria [**61,62**]. However, the most important evidence needed is strength of association with positive outcomes at the relevant endpoints.

From an epidemiological point of view, the most decisive endpoints, for assessing strength of association for any COVID-19 treatment protocol, are hospitalization and death. Although reducing the duration of the illness is desirable, it is conceivable that when using immunomodulators, as part of a multidrug treatment protocol for COVID-19, to suppress the hyperinflammatory cytokine storm and prevent its damaging effects, one could, in theory, even prolong the duration of the illness. However, that would be acceptable, if it also results in more patients surviving the illness and preventing hospitalization. Similar considerations apply to other soft endpoints such as time to viral clearance; showing the existence of an

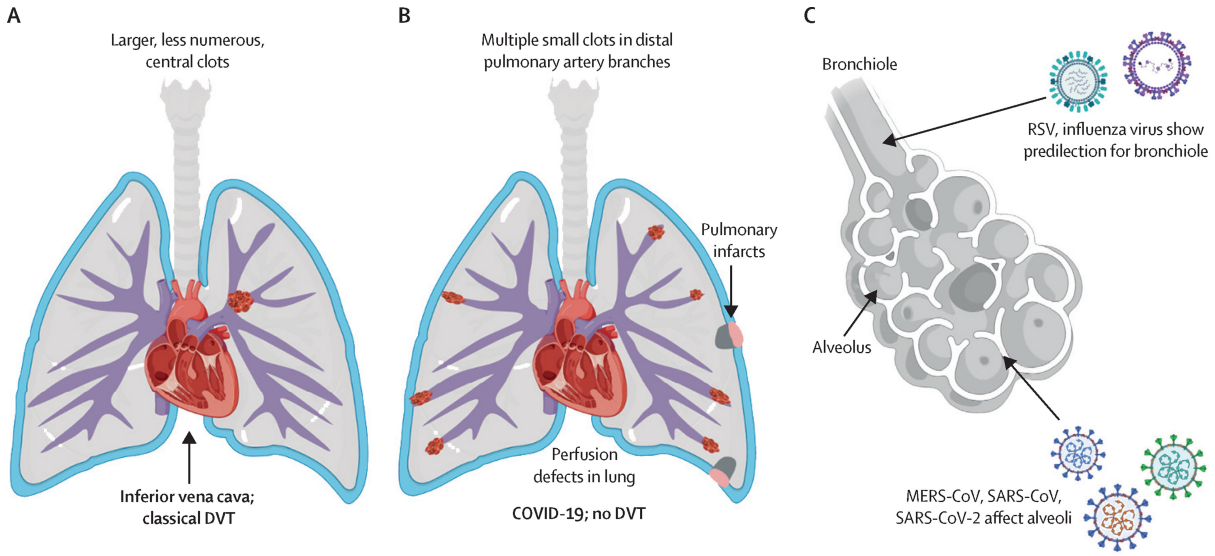

Figure 2: Classic pulmonary venous thromboembolism presents with a preponderance of a smaller number of proximal large emboli. McGonagle *et al.*[**41**] argues that the tendency of the SARS-CoV-2 virus to preferentially attack the alveoli, contrary to RSV and influenza viruses, triggers immunothrombosis, 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 [**42, 43**], blocks hemagglutination [**30–33, 44, 45**], and inhibits viral nuclear entry [**46**] and replication [**47–50**] 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 with permission from McGonagle *et al.*[**41**]

antiviral mechanism of action does not necessarily imply the prevention of hospitalizations and deaths, and the absence of an antiviral mechanism does not imply that reduction of hospitalizations and deaths will not be mediated by other mechanisms. Consequently, it is important to investigate whether this rapid normalization of room air SpO2 levels, observed in the patients treated with ivermectin-based multidrug protocols, results in the reduction of the probability for hospitalization and death in the treated patients.

To that end, Hazan *et al.*[**34**] attempted to show a hospitalization and mortality rate reduction benefit by comparison with an external group derived from a public CDC case surveillance database [**63**], but the methodology was criticized [**64, 65**] on the grounds that the particular external group used might not necessarily be representative of the risk profile of the patients in the case series. The reasons given were the use of the age > 50 constraint in building the external control group as well as filtering for patients with at least one comorbidity. Furthermore, we note that the mortality rate reduction was shown with p-value $p = 0.04$, which is only borderline statistically significant, and additional bias in the external control group could have been introduced by the details of the handling of missing data in the CDC database [**63**]. Stone *et al.*[**34**] did not investigate the existence of a hospitalization or mortality rate reduction benefit, although an attempt was made in the preprint of Stone *et al.*[**66**]. A comparison of the Babalola case series against the Thairu case series suggests statistically significant mortality rate reduction effect with the ivermectin-based protocol [**39**], 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.

The point of departure for our argument is the assumption that if one had followed standard guidelines, all patients with baseline room air SpO2 $\leq 90\%$ would have been hospitalized. Admittedly, hospitalization is a highly subjective endpoint, with possible regional variability in the criteria used to decide whether a patient should be admitted as inpatient [**67**], however this assumption is consistent with an early finding [**68**] that partial pressure of oxygen (PaO2) and SpO2 are both perceived as the most important factors for COVID-19 inpatient admission. It is also consistent with the NIH COVID-19 treatment guidelines [**69**] recommending that oxygen supplementation target an SpO2 level between 92% and 96%, as well as guidelines for several medical centers that recommended considering hospitalization when room air SpO2 falls below 94% [**70–74**] or 92% [**75**]. Studies from Serbia [**76**] and Peru [**77**] have shown a substantial increase in the mortality rate of hospitalized patients as the baseline room air SpO2, at the time of hospital admission, is decreased from 90% down to 80%. To be clear, baseline room air SpO2 $\leq 90\%$ is proposed

only as a *sufficient* condition for hospitalization, on the assumption that one follows widely accepted guidelines without attempting the Hazan and/or Stone/Gill multidrug treatment protocols [**34,35,38**]. It is not proposed as a *necessary* condition for hospitalization, since COVID-19 patients with baseline room air SpO2 above 90% could still be admitted to the hospital for other reasons. Indeed, Poskurica *et al.*[**76**] showed that from amongst the patients hospitalized in Serbia the average room air baseline oxygen level upon admission was 89% (IQR 7), indicating that some of the admitted patients came in with room air oxygen above 90%.

An immediate consequence of this assumption is that it enables us to use a simplified self-controlled case series methodology [**78**] to show the existence of the hospitalization rate reduction benefit, by lower-bounding the baseline hospitalization risk, without the multidrug treatment, with the ratio of the number of patients with baseline room air SpO2 $\leq$ 90% in the case series over the total number of patients in the case series. Equivalently, the number of counterfactual hospitalizations that would have occurred without the multidrug treatment for the patients in the case series is lower-bounded by the number of patients with baseline room air SpO2 $\leq$ 90%. Then, the counterfactual hospitalization rate without the multidrug treatment can be compared with the factual hospitalization rate that has been observed with treatment. This design is a simplification of the self-controlled case series method [**78**], since the space of possible outcomes of interest following the intervention (i.e. using the multidrug treatment) is strictly binary (hospitalization or no hospitalization) and does not involve a Poisson process of a multiplicity of events, distributed over a time period. This design is biased towards the null hypothesis, since it is likely that additional patients could have also been hospitalized under the conventional standard of care. It is further biased towards the null hypothesis, because low-risk patients have been included in the analysis, mainly from the Babalola case series [**36**].

The other consequence of this assumption is that, in order to assess the existence of a mortality rate reduction benefit, we can risk stratify the three case series under the constraint of baseline room air SpO2 $\leq$ 90%, and compare the observed mortality rate in the risk stratified case series, against the case fatality rate (CFR) of hospitalized patients in appropriate external control groups. This comparison is also biased towards the null hypothesis, because the CFR of hospitalized patients includes both patients with and without hypoxemia, and we expect it to be a lower bound of the true CFR for hypoxemic hospitalized patients admitted with baseline room air SpO2 $\leq$ 90%. The particular choice of risk-stratification can be employed because no deaths were observed amongst the patients that are excluded by the risk stratification. The risk stratification reduces the statistical power of the individual case series, however we are able to make up for it in our analysis by combining the statistical power of these case series together. We have conducted our own independent analysis of the CDC case surveillance public database [**63**], without using the comorbidities restriction, and calculated the hospitalized CFR with and without the age $\geq$ 50 constraint. However, we have not relied solely on the CDC database for our external control group; we have also taken into consideration several other additional external control groups [**79–85**].

For both endpoints of mortality and hospitalization rate reduction, we use the exact Fisher test to compare with controls. Then, we use a recently introduced statistical method for case series analysis [**27**] to confirm the statistical significance and calculate its resilience with respect to random and systemic selection bias. Because both of these comparisons are, by design, biased towards the null hypothesis, they are not intended to estimate an unbiased effect size for hospitalization or mortality rate reduction efficacy. However, given a positive finding that overcomes the expected bias towards the null, we can infer the existence of some positive efficacy, and consider this inference when developing a community standard of care. Overall, we have found the existence of statistically significant mortality rate reduction in the Stone case series, the combined Hazan + Stone case series, consisting of the patients collectively observed by Hazan *et al.*[**34**] and Stone *et al.*[**35**], and the combined Hazan + Stone + Babalola case series, consisting of the patients collectively observed by Hazan *et al.*[**34**], Stone *et al.*[**35**], and Babalola *et al.*[**36**]. It is more likely than not that these findings are not overturned by random selection bias. We have also found the existence of statistically significant hospitalization rate reduction in the Hazan and Stone case series, which is resilient both with respect to random and systemic selection bias (i.e. we can have more than 95% confidence that random selection bias does not overturn the finding and extensive systemic selection bias is needed to overturn it).

Previous research has already provided evidence in support of the Stone/Gill and Hazan multidrug protocols [**34,35,38**] in terms of biological plausibility, temporality, biological gradient, and consistency, as explained further in Section 4, all of which are important Bradford Hill criteria [**61,62**] for establishing causality. However, what is lacking is evidence in support of strength of association, which is one of the most important Bradford Hill criteria [**61,62**]. The importance of the present work is that our analysis closes this gap by determining the strength of the evidence in support of association between the multidrug treatment regimens used by Hazan *et al.*[**34**] and Stone *et al.*[**35**] and reduction of hospitalizations and deaths.

2. Methods

2.1. Description of case series

The Hazan case series consisted of 26 patients that were treated in the United States, via telemedicine, between August 2020 and February 2021 by Dr. Sabine Hazan and colleagues [**34**]. These patients were interested in participating in a clinical trial however, they did not satisfy the inclusion criteria because their presentation with baseline room air SpO2 $\leq$ 90% warranted in-hospital care, and they also declined hospitalization for a variety of reasons. We have excluded 2 patients that died because they did not consent to treatment (patients 10, 26 in Table 1 of Ref. [**34**]). One additional patient (patient 4 in Table 1 of Ref. [**34**]), who presented with shortness of breath and consented the treatment, did not present with hypoxemia (97% baseline room air SpO2); the patient survived and successfully avoided hospitalization. The remaining 23 patients presented with baseline room air SpO2 $\leq$ 90% and consented to treatment as outpatients. Out of the 23 patients, 20 patients had age $\geq$ 50, 11 patients had age $\geq$ 65, the youngest patients had age 43, 46, 47, and the oldest patients had age 87, 92, 94. Furthermore, 11 out of 24 patients had at least one COVID-19 vulnerable comorbidity (i.e. type-2 diabetes, heart or cardiovascular disease, COPD, obesity or severe obesity, chronic kidney disease, immunocompromised), 3 out of 24 patients had 2 distinct comorbidities, and 2 out of 24 patients had 3 comorbidities. Baseline SpO2 ranged from 73% to 90% and all 4 patients with age $<$ 50 also had baseline SpO2 below 90%. The treatment period overlaps with the first and second pre-delta periods, following the epidemic wave breakdown by Adjei *et al.*[**80**].

The Stone case series consisted of the 34 COVID-19 patients who presented with baseline room air SpO2 $\leq$ 93% and were treated in Harare, Zimbabwe between August 2020 and May 2021 in Dr. Jackie Stone's clinic by Dr. Stone and colleagues [**35**]. The patients were treated in an outpatient clinic setting or at home, via visiting nurses, due to limited access to hospital resources and very limited access to supplemental oxygen. Out of the 34 patients, 23 patients had age $\geq$ 50, 8 patients had age $\geq$ 65, the youngest patients had age 25, 32, 35, and the oldest patients had age 75, 80, $\geq$ 90. Baseline room air SpO2 ranged from 66% to 93%, with 28 out of 34 patients presenting with baseline room air SpO2 $\leq$ 90%. We also note that 9 out of 11 patients with age $<$ 50 also had baseline room air SpO2 $\leq$ 90%. During the treatment period the dominant strains in Zimbabwe were the B.1.351 (Beta variant), which peaked in January 2021, and the B.1.617.1 (Delta variant), which peaked in July 2021 [**86**]. Furthermore, the Beta variant accounted for 95% of the sequenced cases since March 2021 and during most of the treatment period; the Delta variant was detected in Zimbabwe during May 2021, at the tail end of the treatment period [**87**].

The Babalola case series consists of 61 patients that were treated in Nigeria with ivermectin-based multidrug protocols, of which 21 patients presented with hypoxemia, presenting with baseline room air SpO2 $\leq$ 93%, and 10 of the 21 patients presenting with baseline room air SpO2 $\leq$ 90% [**36, 88**]. Out of the 21 hypoxemic patients, 5 patients had age $\geq$ 50, 2 patients had age $\geq$ 65, the youngest patients had age 19, 21, 23, and the oldest patients had age 60, 68, 89 [**88**]. The patients were treated in the Abuja Federal Capital Territory between April 2021 and June 2021. As shown in Fig. 1 of Ref. [**39**], the treatment period corresponds to the interregnum between the second wave (Beta variant) and the third wave (Delta variant) in Nigeria.

In all three case series, all patients survived, however in the Babalola case series, 2 of the 61 hypoxemic patients had to use the ventilator and 3 additional patients needed supplemental oxygen, in spite of the provided treatment [**39**].

2.2. Treatment protocols

The multidrug treatment protocol used for the Hazan case series consisted of doxycycline (100 mg twice a day for 10 days), ivermectin (12 mg on day 1, day 4, and day 8), zinc (25 mg elemental zinc twice a day for 10 days), vitamin D3 (1,500 IU twice a day for 10 days), and vitamin C (1,500 mg twice a day for 10 days) [**34**]. The ivermectin dosage was spread out to allow an approximately constant level of the medication in the plasma. Two patients that presented with very low SpO2 at 72% and 73% received an increased dose of 36 mg of ivermectin on day 1. Hazan and colleagues used customized vitamins C, D, and zinc that were tested in her lab for consistency and quality [**89**]. All patients treated in this case series had pre-delta SARS-CoV-2 variants; Hazan later found it necessary to increase ivermectin dosage during the Delta variant [**89**]. Finally, 7 out of 24 patients received additional medications prior or during the 10-day treatment period: one patient received remdesivir, 3 patients received hydroxychloroquine, and 4 patients were enrolled in a clinical trial where they may have received placebo or a combination of hydroxychloroquine, azithromycin, vitamin D, and zinc. Hazan observed that for the highest-risk patients, although the combination of ivermectin, doxycycline, and Vitamin D was effective in restoring room air SpO2 levels in hypoxemic patients, it was not always sufficient for eradicating the virus, and in those cases it was necessary to also add hydroxychloroquine and azithromycin [**89**].

The baseline multidrug treatment protocol used in the Stone case series consisted of quadruple therapy combining nebulized silver, ivermectin, doxycycline and zinc [35, 38]. The use of nebulized nanosilver for COVID-19 treatment was a notable unique innovation that was introduced by Stone and adopted by CPCPZ physicians in Zimbabwe. The ivermectin dosage varied as follows: for the earliest patients a single 10mg stat dose was used; from September 11th 2020 the ivermectin dose was increased to 3 doses of 10-12 mg every 4 days in conjunction with Doxycycline (100 mg twice a day for 10 days) and zinc sulfate (60 mg per day for 10 days), with further escalation of the ivermectin dose to 12 mg on day 1, day 4, day 8 through December 2020. Afterwards, the ivermectin dosage was increased to 12 mg once a day for 5 days. The ivermectin dose was escalated to varying higher levels in very limited cases where the clinical response was inadequate in the first 24 hours, but no higher than a 48 mg single dose, based on the safety data from Guzzo *et al.*[90], when the clinical response was unsatisfactory within a few days. For certain severe cases, the Stone/Gill protocol [38] also calls for adding an individualized treatment with corticosteroids and anticoagulants on top of the baseline treatment. Although Stone and colleagues did not use hydroxychloroquine with this particular case series, her adoption of nebulized nanosilver was intended to also function as a fast-acting anti-viral that can eradicate viral multiplication in the lungs, analogously to Hazan's adjunct use of hydroxychloroquine and azithromycin in her highest-risk patients [89].

For the Babalola case series, the treatment protocol consisted of ivermectin 0.2mg/kg daily for 5 days in addition with zinc sulfate (50-100mg daily for 7 days) and vitamin C (1000mg daily for 7 days) [36, 39, 40]. However, 31 out of 61 patients also received hydroxychloroquine 200 mg per day for 3 days and azithromycin 500 mg per day for 3 days. Supplemental oxygen was only administered when the oxygen level dipped below a certain threshold, or when the patient was manifesting evidence of respiratory distress [88]. Due to the treatment provided, supplemental oxygen was not necessary for most of the patients. Babalola *et al.*[36] noted no statistically significant benefit with respect to viral clearance by the adjunct hydroxychloroquine and azithromycin therapies, which could be attributed to low dosage, relative to the dosage recommended in the original Zelenko protocol [5].

2.3. Endpoints

The relevant and decisive endpoints for evaluating any COVID-19 treatment protocols are the hard endpoints of mortality rate reduction and hospitalization rate reduction. Consequently, we investigate both endpoints.

2.4. Self-controlled case series method for establishing hospitalization rate reduction

We assume that, under the conventional standard of care, all patients with baseline SpO2 $\leq$ 90% will be hospitalized, given the immediate need for supplemental oxygen and the high likelihood of further deterioration, as the disease progresses. Consequently, we can use a simplified self-controlled case series method [78] to establish the existence of a hospitalization rate reduction benefit, as follows. For the Stone case series and the Hazan case series, all patients were treated on an outpatient setting and were able to recover without hospitalization [34, 35], so for the treatment group we count zero hospitalizations for all patients in the respective case series. For the Babalola case series, 2 patients were ventilated, and 3 other patients required the use of supplemental oxygen [36, 88], so for the treatment group we count 5 hospitalizations. For the self-control, we shall assume that all patients with baseline room air SpO2 $\leq$ 90%, from the same group of patients, would have been hospitalized if the conventional standard of care was followed. So, the number of patients with baseline room air SpO2 $\leq$ 90% are counted as counterfactual hospitalizations in the self-control.

It is worth noting that some of the patients with higher levels of SpO2 could have also been hospitalized, given the high likelihood that some of those patients could deteriorate under the conventional standard of care. Thus, this approach provides a lower bound for the control hospitalization rate, and it can be used to establish the existence of a hospitalization rate reduction benefit, however an odds ratio calculation can be expected to be biased towards the null hypothesis.

2.5. External controls for establishing mortality rate reduction

To establish the existence of a mortality rate reduction benefit we have extracted from the corresponding case series, the patients with room air baseline SpO2 $\leq$ 90%, allowing us to compare them against a conservative lower bound for the CFR of hospitalized patients, because we assume that under the conventional standard of care all such patients would have been hospitalized. We relied on several external control groups in the United States [63, 80], Zimbabwe [81, 82], Nigeria [83, 84], South Africa [79], and globally [85] to determine a reasonable lower bound estimate for the mortality rate of hypoxemic patients without use of any of the proposed ivermectin-based multidrug treatment protocols.

For the United States, one of the external controls is obtained from a CDC case surveillance public database [**63**], which was also used by Hazan *et al.*[**34**]. For each case, the available information that is potentially relevant to our analysis includes the case's month/year, age group (broken down categorically to the age brackets 0–17, 18– 49, 50-64, 65+), whether the case is symptomatic or asymptomatic, whether the case has been lab confirmed, whether there existed certain unspecified comorbidities, and whether the final outcome was hospitalization, ICU admission, or death. We filtered the database for all cases that are symptomatic, lab confirmed, resulting in hospitalization, and with known month/year. Contrary to the methods used in Hazan *et al.*[**34**], we did not filter for comorbidities, and we also did not filter from the outset for the age ≥ 50 restriction. After filtering, we counted the number of cases where it is known that the patient survived and the number of cases where it is known that the patient died.

We wish to highlight that the age ≥ 50 restriction is a reasonable proxy for baseline room air SpO2 $<$ 92%, noting that both are being scored equivalently in the 4C mortality score for in-hospital mortality of COVID-19 patients [**91**]. The 4C mortality score [**91**] was rated as one of the top two predictive models for in-hospital mortality probability in terms of accuracy and low risk of bias in a systematic review of several predictive models [**92**]. The baseline room air SpO2 $<$ 92% condition is satisfied by the entire Hazan case series [**34**]. Consequently, we do not agree with the criticism [**64**] against using an age ≥ 50 restriction in the external control group, as long as the corresponding treated case series is limited to severely hypoxemic patients with a conservative baseline room air SpO2 $\leq$ 90% risk-stratification threshold.

A problem with the CDC database [**63**] is that there is a substantial number of cases where the mortality endpoint is unknown or not available. Consequently, in order to conservatively estimate the hospitalized CFR, we have considered the consequences of two distinct assumptions about the cases in which the mortality endpoint data is unavailable: (a) to obtain a reliable CFR lower bound, we assumed that all cases with unknown mortality status have survived; (b) to obtain a conservative CFR upper bound, we assumed that for all cases with unknown mortality status the probability of death is the same as with the cases where the mortality status is known. Conservatively, we can assume that deaths are less likely to be unreported than survivals, therefore we can expect the true CFR to be located between the lower bound value and the conservative upper bound value. Using this approach, the inpatient CFR was calculated with and without the age ≥ 50 restriction over several relevant time intervals and without filtering for comorbidities. In particular, we have calculated the inpatient CFR over the epidemic waves in the United States between 2020 and 2022, and the treatment period corresponding to the Hazan case series. Following the Hazan *et al.*[**34**] methodology, we have also calculated the cumulative inpatient CFR on February 2021.

Because of the substantial amount of missing data on mortality outcomes in the CDC database [**63**], we have also used, as an alternate external control group, a CDC study [**80**] of the in-hospital CFR for patients hospitalized across the United States during the Delta variant (July 2021 to October 2021), early Omicron variant (January 2022 to March 2022), and late Omicron variant (April 2022 to June 2022), obtained from the Premier Healthcare Database Special COVID-19 release [**93**] (hereafter PHD-SR), in order to confirm consistency with the CFR intervals obtained from the CDC database [**63**]. The PHD-SR database reports data on several hundreds of hospitals across the United States. The CDC report [**63**] on the PHD-SR database allowed us to calculate the in-hospital CFR with or without the restriction age ≥ 50.

For Zimbabwe, the most relevant external control group is unpublished statistics of the in-hospital CFR in the Parirenyatwa group of hospitals, during the period between May 2020 and December 2020 [**81**]. This period intersects, but does not entirely overlap, with the treatment time interval corresponding to the Stone case series [**35**], so we also consider an alternative external control group from Masholand West Province, Zimbabwe [**82**], ranging between April 2020 and April 2022. Since the predominant variant in the Stone case series was the Beta variant [**35,87**], and because both external control groups have small sample size, we have also considered, as an additional external control group the in-hospital CFR in South Africa, which has been reported on a month-to-month basis between March 2020 and March 2021, with substantially larger sample sizes [**79**]. Particularly relevant is our calculation of the hospitalized CFR during the time period in which the Beta variant was dominant in South Africa.

For Nigeria, the availability of external control groups for estimating the hospitalized CFR is very limited, however we have identified the following two studies: The first study [**83**] consists of 226 hospitalized COVID-19 patients in Lagos Nigeria, who were treated between April 2020 and October 2020 in the Lagos University Teaching Hospital. The facility served both as an isolation center for COVID-19 patients, for contagion control purposes, and as an inpatient treatment center for patients that presented with moderate or severe COVID-19 disease. As a result, the study underestimates the true CFR of in-patients, noting that 30.5% of the treated patients were initially presenting as asymptomatic. The study also explicitly reported the CFR for hypoxemic patients, with hypoxemia defined by the authors as SpO2 $\leq$ 90% for adults and SpO2 $\leq$ 92% for children. We note that patients were treated with artermether-lumefantrine, ritonavir-boosted lopinavir, azithromycin, and vitamin C between April 2020 and June 2020, however the details of the treatment protocol were not given.

The second study [**84**] consists of 195 COVID-19 patients from Kano State, Nigeria, treated at the Kwanar Dawaki isolation center over a wider time period between April 2020 to March 2021. Similarly to the preceding study, the facility operated both as an isolation center and an inpatient treatment center, thus including patients whose initial COVID-19 presentation was asymptomatic, or mild to moderate, or severe to life-threatening. The authors reported the mortality outcomes for each of these three presentations, and for our statistical analysis we have calculated the CFR, both including and excluding the patients in the initially asymptomatic category. We note that patients with mild or moderate COVID-19 were treated with vitamin C, zinc sulfate, paracetamol, and loratadine. Between April 2020 and October 2020, patients with severe or life-threatening disease were also treated with azithromycin, hydroxychloroquine, oxygen, heparin, lopinavir, and corticosteroids. Between November 2020 and March 2021 hydroxychloroquine and lopinavir were replaced with calcium supplements and ivermectin. Again, the details of the respective treatment protocols were not given.

Last but not least, we have cited a World Heart Federation study [**85**] of 5,313 consecutive COVID-19 patients, prospectively recruited between June 2020 and September 2021 from 40 hospitals across 23 different countries, representing a geographically and economically diverse sampling of countries that includes countries classified by the World Bank as LIC, LMIC, MIC, and HIC. We reported the combined CFR for the entire sample of patients. Noting that both Zimbabwe and Nigeria are classified by the World Bank as LMIC [**94**], we have also calculated from the reported results the CFR specifically for the patients recruited from LMIC countries. In both calculations the CFR includes both in-hospital deaths as well as deaths within 30 days post discharge

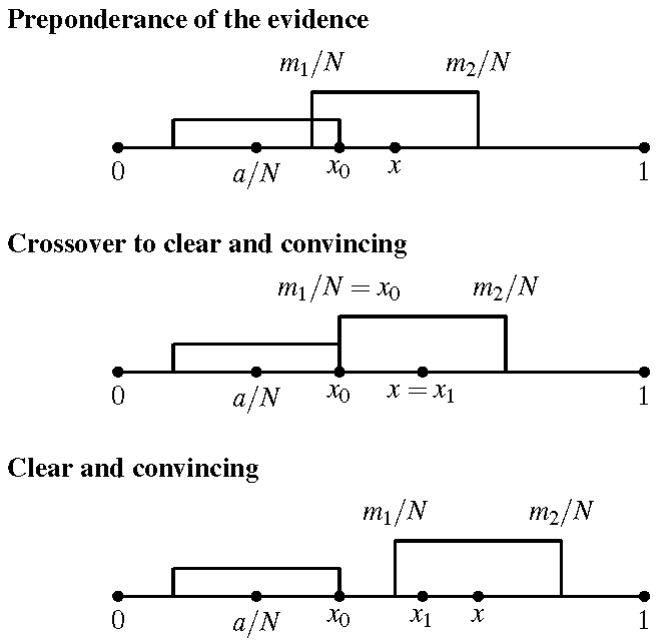

Figure 3: Comparison of a case series (N, a) of N treated patients, with a patients having an adverse outcome, against the population level probability x of an adverse outcome without treatment. The figure shows the relative position of the confidence interval for the probability of an adverse outcome with treatment and the confidence interval for the probability of an adverse outcome without treatment, which in turn determines whether the existence of some treatment efficacy has been shown by the *preponderance of evidence* and whether it is *clear and convincing*. Here, x_0 is the *efficacy threshold* for establishing existence of efficacy by the *preponderance of evidence* and x_1 is the *random selection bias threshold* for establishing existence of efficacy by the *clear and convincing* standard. This figure is adapted from the graphical abstract of Gkioulekas *et al.*[**27**] under the terms of the CC-BY-4.0 license.

2.6. Statistical analysis

External controls [**63, 80–85, 95**] are used to establish the existence of mortality rate reduction and a simplified self-controlled case series methodology [**78**] is used to establish the existence of hospitalization rate reduction. For the corresponding comparisons of the case series by Hazan [**34**], Stone [**35**], and Babalola [**36, 39, 40**] against the corresponding controls, as a preliminary step, we have used the two-sided exact Fisher test to calculate the p-value. We have also calculated the corresponding odd ratios and odd ratio confidence intervals, with 95% confidence. To increase statistical power, we have also analyzed the

combined Hazan + Stone and Hazan + Stone + Babalola case series. The first combination is well justified, given the similarity of the multidrug treatment protocols used, the high-risk status, in terms of age and baseline room air SpO2 of the majority of patients in both case series, and the similar rapid recovery of room air SpO2 levels shown in Fig. 1. The latter combination is presented on an exploratory basis as well as for sensitivity analysis, noting that Babalola's patients were younger, but the treatment protocol used was also less aggressive.

Because case series are susceptible to selection bias, establishing statistical significance via use of the exact Fisher test is necessary but not sufficient. In order to better ascertain the potential impact of selection bias, we have further analyzed the case series using a recently introduced case series threshold analysis statistical technique **[27]**, which is based on the Sterne interval solution **[96]** of the binomial proportion confidence interval problem and the Bayes factor **[97–101]**. Given a case series (N, a) of N treated patients with a adverse events (hospitalizations or deaths), and external controls that bound the population-level probability x of an adverse event without treatment into an interval $p_1 < x < p_2$, the method allows us to determine whether the contrast between the case series data (N, a) and the probability interval $[p_1, p_2]$ is sufficiently large to be statistically significant, and to quantify how much selection bias is required to overturn a positive finding. An assumption that underlies this method is that all adverse events counted in a can be attributed to the disease rather than the treatment, which limits the applicability of the method only to treatments that use repurposed medications with known acceptable safety. This assumption is satisfied by the respective multidrug protocols.

An intuitive conceptualization of the case series threshold analysis **[27]** statistical method is shown on Fig. 3, where we display schematically the *treatment interval*, appearing on the left, which is the confidence interval for the probability of an adverse outcome with treatment, and the *control interval*, appearing on the right, which is the confidence interval for the probability of an adverse outcome without treatment or under the current standard of care, for a patient group equivalent to the case series of treated patients. The treatment interval is the Sterne interval **[96]** corresponding to a binomial trial (N, a) of N events with a failures. The control interval quantifies the extent of potential selection bias by expanding any given point-wise population-level probability x of adverse outcomes without treatment into a confidence interval for the true value of that probability that is specific to our case series of N patients, if they have been selected randomly from the general population. For comparison purposes, we use conservative lower bounds for the population-level probability x.

The *efficacy threshold* $x_0(N, a, p_0)$ is the upper end point of the treatment interval using $1 - p_0$ confidence (we use $p_0 = 0.05$ for all calculations). The *random selection bias threshold* $x_1(N, x_0, p_0)$ is the minimum value of x for which the two intervals do not intersect. Before calculating the random selection bias threshold x_1, we use a Bayesian technique to adjust the efficacy threshold x_0 in the upwards direction to $x_0' \geq x_0$, if necessary. We say that the comparison shows the existence of efficacy by the *preponderance of evidence* when x is above the treatment interval, i.e. when $x \geq x_0'$. A preponderance of evidence finding means that it is more likely than not that random selection bias does not overturn the existence of some treatment effect, so there is compelling evidence for emergency adoption. We say that the comparison shows *clear and convincing* existence of efficacy when the two intervals do not intersect, i.e. when $x \geq x_1$. A clear and convincing finding means that we can have $1 - p_0$ confidence that random selection bias does not overturn the existence of some treatment effect.

The computer code needed to reproduce all the threshold calculations reported in this paper is given in a supplementary document **[102]**. All relevant mathematical details are given in the original paper on the case series threshold analysis method **[27]**. A concise description of the calculation of the unadjusted efficacy threshold x_0, the adjusted efficacy of threshold x_0', and the random selection bias threshold x_1 is as follows: Let $p(N, a, x)$ be the p-value for observing the case series (N, a) or a less probable case series under the null hypothesis that the probability of an adverse event in the case series is equal to the population-level probability x of an adverse event without treatment. We calculate the unadjusted efficacy threshold x_0 as the minimum value of x with $x > a/N$ that satisfies the statistical significance condition $p(N, a, x) < p_0$ with $p_0 = 0.05$. To adjust the efficacy threshold, we calculate a Bayesian factor $B(N, a, x_0, p_2)$ that compares the null hypothesis $H_0 : 0 \leq q \leq x_0$ against the alternate hypothesis $H_1 : x_0 < q \leq 1$, with q being the probability of an adverse event with treatment. For the prior of H_0, we use a uniform distribution of q over the interval $[0, t]$ choosing the value of t that maximizes the Bayesian factor. For the prior of H_1, we use a uniform distribution of q over the interval $[x_0, p_2]$, where p_2 is a free parameter that corresponds to the expected worst-case scenario without treatment, which we try to estimate as conservatively as possible in our calculations. If we find that $\log_{10} B(N, a, x_0, p_2) \geq 2$, then the efficacy threshold x_0 does not need to be adjusted and we just choose $x_0' = x_0$. Otherwise, we adjust the efficacy of threshold x_0 upwards to the adjusted efficacy threshold $x_0' \geq x_0$ to ensure that both $p(N, a, x_0') \leq p_0$ and $\log_{10} B(N, a, x_0', p_2) \geq 2$ are satisfied. Finally, the adjusted efficacy threshold x_0' is used to calculate the random selection bias threshold $x_1(N, x_0', p_0)$. Ref. **[27]** has shown that an upper bound to the random selection bias threshold

$x_1(N, x_0', p_0)$ can be obtained by calculating the unadjusted efficacy threshold with $1 - p_0$ confidence for a hypothetical case series $(N, \lceil x_0' N \rceil)$, with $\lceil x_0' N \rceil$ defined as the product $x_0' N$ rounded upwards towards the nearest integer. We have used this upper bound as a conservative proxy for the random selection bias threshold for the calculations reported in this paper. If we have additional information that the probability x of an adverse event without treatment satisfies a lower bound $x > p_1$ with $p_1 > x_1(N, x_0', p_0)$, then we can calculate the *selection bias tolerance*

$$F = \frac{p_1(1 - x_1(N, x_0', p_0))}{x_1(N, x_0', p_0)(1 - p_1)}, \tag{1}$$

which measures how much systemic selection bias is needed in order to overturn a clear and convincing finding of existence of efficacy. Systemic selection bias with magnitude f means that the patients in the case series have not been randomly selected from the population, and, instead, it is f times more likely to select the healthier patients (i.e. the ones that would have done well without treatment) than it would have been, if the selection was truly random. The interpretation of F, given by Eq. (1), is that systemic selection bias must have magnitude f with $f > F$ to overturn a clear and convincing finding.

In the calculations related to establishing the existence of mortality rate reduction, the parameter p_2 was chosen as follows. For the Hazan case series, we looked at the hospitalized CFR between August 2020 and February 2021 reported in the CDC database **[63]**, and chose the smallest number between: (a) the peak month by month CFR without age restriction; (b) the upper endpoint of the estimated CFR interval under the age ≥ 50 restriction averaged over the treatment period. For the Stone case series, we have set p_2 equal to the smallest number between: (a) the CFR reported in the Parirenyatwa hospitals in Harare, Zimbabwe **[81]**; (b) the CFR reported in the Masholand West Province **[82]**. For the combined case series Hazan + Stone and Hazan + Stone + Babalola, there is sufficient statistical power so that any value $p_2 \geq 10\%$ does not result in any non-negligible upward adjustment of the efficacy threshold x_0, so there is no need to justify a realistic estimate.

In the calculations related to establishing the existence of hospitalization rate reduction, for all case series, except for the Babalola case series **[36, 39, 40]**, using the most conservative choice possible of setting p_2 equal to the percentage of patients with baseline room air SpO2 $\leq 90\%$ does not result in any Bayesian adjustment of the corresponding efficacy thresholds. For the Babalola case series **[36, 39, 40]**, the counterfactual hospitalization rate fails to exceed the unadjusted efficacy threshold, consequently, for mathematical reasons, we have used the less conservative choice of setting p_2 equal to the percentage of patients that are hypoxemic with baseline SpO2 $\leq 93\%$.

2.7. Software

The calculation of the efficacy threshold and random selection bias threshold for the respective case series was calculated using the computer algebra program Maxima 5.46.0 **[103]**. Our independent analysis of the CDC database **[63]** as well as the preparation of the tables reporting on the external controls were conducted using R 4.1.3 **[104]**, in conjunction with the dplyr and magritt packages. The exact Fisher test calculations were also conducted using R 4.1.3 **[104]**, in conjunction with the stats package. The computer code used to generate Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8 is displayed in the supplementary document **[102]** associated with this paper. For our calculations we have used the January 20, 2023 snapshot of the CDC database, a copy of which can be made available by the corresponding author upon request. The details of the calculations of the efficacy threshold and the random selection bias thresholds, reported on Table 2, as well as our analysis of the I-Tech trial **[105]** treatment arm as a case series, and some additional supplementary material is also given in the supplementary document **[102]**.

3. Results

3.1. Description of the case series

Table 1 displays the following information about the Hazan, Stone, and Babalola case series, as well as the combined case series Hazan + Stone and Hazan + Stone + Babalola: total number of patients treated, number of patients treated with baseline room air SpO2 $\leq 93\%$, number of patients treated with baseline room air SpO2 $\leq 90\%$, number of deaths, number of patients that deteriorated (required supplemental oxygen or the ventilator), and the corresponding time period of treatment. We also display the percentage of patients with baseline room air SpO2 $\leq 90\%$ out of all treated patients. As explained in Section 2, we shall use a simplified self-controlled case series method to show the existence of hospitalization rate reduction efficacy, in which this percentage represents a lower bound of the expected counterfactual hospitalization rate that would have taken place under the conventional standard of care, specifically for the selected

patients in the respective case series. We note that there were no deaths in any of the case series [**34–36, 39**], except that 2 patients had to use the ventilator and 3 other patients required supplemental oxygen in the Babalola case series [**36, 88**].

Table 1: Case series of hypoxemic patients by Hazan *et al.*[**34**], Stone *et al.*[**35**], and Babalola *et al.*[**36**], and case series combinations. Second column lists the total number of all patients that comprise the case series. Third column lists the number of patients with baseline room air SpO2 $\leq$ 93%. Fourth column lists the number of patients with baseline room air SpO2 $\leq$ 90%, which is a sufficient threshold for hospitalization, with the corresponding percentage p_1, relative to the total number of patients in parentheses. These percentages are a lower bound of the expected number of hospitalizations that would have taken place, following the standard guidelines. Fifth column lists the number of deaths. Sixth column lists the number of patients that deteriorated, requiring supplemental oxygen or a ventilator. Seventh column lists the time period during which the patients were treated.

	Patients with baseline SpO2					
Case series	$\leq$ 100%	$\leq$ 93%	$\leq$ 90% (p_1)	**Deaths**	**Deterioration**	**Time Period**
Hazan	24	23	23 (95.8%)	0	0	2020-08 to 2021-02
Stone	34	34	28 (82.3%)	0	0	2020-08 to 2021-05
Babalola	61	21	10 (16.4%)	0	5	2021-04 to 2021-06
Hazan + Stone	58	57	51 (87.9%)	0	0	2020-08 to 2021-05
Hazan + Stone + Babalola	119	78	61 (51.3%)	0	5	2020-08 to 2021-06

Table 2: Efficacy thresholds x_0 and random selection bias thresholds x_1 for the case series given in Table 1. The second column gives the number N of patients in the case series and the number a of the corresponding adverse outcomes. The third column lists the preliminary efficacy threshold x_0 controlling only the p-value. The fourth column shows the corresponding log Bayes factor $\log_{10} B$ calculated using the p_2 value given in the fifth column. The sixth column lists the adjusted efficacy threshold x_0', which is increased, if needed, so that $\log_{10}(B) \geq 2$, thus controlling both the p-value and the log Bayes factor. The seventh column lists the random selection bias threshold x_1 obtained from the adjusted efficacy threshold x_0'.

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 90%)	(N, a)	x_0	$\log_{10} B$	p_2	**adj.** x_0'	x_1
Hazan	(23, 0)	14.6%	1.99	23.48%	14.7%	38.9%
Stone	(28, 0)	12.0%	2.13	23.3%	12.0%	32.0%
Hazan + Stone	(51, 0)	7.4%	1.97	10%	7.6%	18.5%
Hazan + Stone + Babalola	(61, 0)	6.2%	2.12	10%	6.2%	16.2%
Hospitalization rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 100%)	(N, a)	x_0	$\log_{10} B$	p_2	**adj.** x_0'	x_1
Hazan	(24, 0)	14.0%	2.94	95.8%	14.0%	37.3%
Stone	(34, 0)	9.9%	2.98	82.3%	9.9%	27.7%
Babalola	(61, 5)	17.9%	1.64	34.4%	20.0%	33.6%
Hazan + Stone	(58, 0)	6.5%	3.39	87.9%	6.5%	17.0%
Hazan + Stone + Babalola	(119, 5)	9.6%	2.36	51.3%	9.6%	17.2%

Table 2 shows the results of our calculation of the efficacy threshold and the random selection bias threshold for the case series listed in Table 1, both for showing the existence of mortality rate reduction efficacy and for showing the existence of hospitalization rate reduction efficacy. Shown on the table are the unadjusted efficacy threshold x_0 which controls the p-value, the corresponding Bayesian factor $\log_{10} B$ for the alternate hypothesis H_1 evaluated at the unadjusted efficacy threshold x_0, the adjusted efficacy threshold x_0' which controls both the p-value and the Bayesian factor, and the random selection bias threshold x_1 calculated from x_0'. The intuitive interpretation of the adjusted efficacy threshold x_0', for any of the given case series, is that the expected average rate of an adverse event (death or hospitalization) for equivalent patients with equivalent treatment is less or equal than x_0' with 95% confidence. The intuitive interpretation of the random selection bias threshold x_1, for any of the given case series, is that the expected average adverse event rate for patients at the population level with equivalent treatment and risk stratification will be less than x_1 with 95% confidence, under the assumption that only random selection bias exists in the case series.

Table 3: Self controlled exact Fisher test comparisons of factual hospitalization events in the Hazan, Stone, and Babalola case series, with multidrug treatment, against the counterfactual minimum number of hospitalizations that would occur without treatment, if at least all patients with baseline room air SpO2 $\leq$ 90% were hospitalized. Here, (N, a) is the treatment case series with N patients and a factual hospitalization events (use of ventilator or supplemental oxygen) and (N, b), is the counterfactual control case series with at least b counterfactual hospitalizations.

Case series	(N, a)	(N, b)	**OR (95% CI)**	p**-value**
Hazan	(24, 0)	(24, 23)	0 (0 – 0.02)	10^{-12}
Stone	(34, 0)	(34, 28)	0 (0 – 0.04)	10^{-13}
Babalola	(61, 5)	(61, 10)	0.46 (0.11 – 1.59)	0.27
Hazan + Stone	(58, 0)	(58, 51)	0 (0 – 0.01)	10^{-25}
Hazan + Stone + Babalola	(119, 5)	(119, 61)	0.04 (0.01 – 0.11)	10^{-17}

For mortality rate reduction, as explained in Section 2, we are going to use the CFR of hospitalized patients as the external control group, therefore, for the calculation of the corresponding thresholds on Table 2, we risk-stratify and use the subset of patients from the original case series with baseline room air SpO2 $\leq$ 90%, who would have certainly been hospitalized under the conventional standard of care. There are no reported deaths among the patients excluded by the risk stratification. For hospitalization rate reduction, we use the entire case series, since we shall be using the simplified self-controlled case series methodology. For the Babalola case series and the combined Hazan + Stone + Babalola case series, in order to calculate the corresponding hospitalization rate reduction thresholds, the 2 patients that used the ventilator and the additional 3 patients that received supplemental oxygen are counted as hospitalizations in the treatment group.

3.2. Existence of hospitalization rate reduction efficacy

To establish the existence of hospitalization rate reduction efficacy, we use a simplified self-controlled case series method **[78]** in which the case series (N, a) of N treated patients with a factual hospitalizations is compared against a counterfactual case series (N, b) with b the number of counterfactual hospitalizations that would have taken place if one followed standard guidelines. In the count for a, we count as hospitalization events all patients that needed to use a ventilator or supplemental oxygen. As a lower bound count for b, we use the number of patients with baseline room air SpO2 $\leq$ 90%. Table 3 shows the odds ratio, its 95% confidence interval, and the exact Fisher test p-value obtained from the comparison between (N, a) and (N, b). Statistically significant hospitalization rate reduction is inferred for the Hazan and Stone case series and for the combined Hazan + Stone and Hazan + Stone + Babalola case series. The Babalola case series fails to achieve statistically significant hospitalization rate reduction.

To assess the resilience of these results with respect to selection bias, we compare the adjusted efficacy threshold x_0' and the random selection bias threshold x_1, shown in Table 2, with the expected rate of hospitalizations that would have taken place under conventional treatment, which is lower-bounded by the percentage of patients with baseline room air SpO2 $\leq$ 90%, shown in Table 1. A direct comparison shows that the random selection bias threshold is exceeded by the expected hospitalization rate (see column 4 of Table 1), separately for the Hazan and Stone case series, as well as for the combined Hazan + Stone and Hazan + Stone + Babalola case series, given on the fourth column of Table 1. It follows that, based on this self-controlled case series argument, it is clear and convincing that in all of those case series there has been hospitalization rate reduction. This means that we can have 95% confidence that the existence of hospitalization rate reduction cannot be overturned by random selection bias, in spite of the small sample size in the case series involved. The Babalola case series fails to get beyond the threshold for a preponderance of evidence claim, given an 19.7% efficacy threshold and an expected 16.1% hospitalization rate under conventional treatment. Finally, we note that for the combined Hazan+Stone case series, using $p_1 = 87.9\%$ and $x_1 = 17.0\%$, gives selection bias tolerance $F = 35.5$. This means that in order to overturn the clear and convincing finding of existence of hospitalization rate reduction efficacy and downgrade it to a preponderance of evidence finding would require systemic selection bias that has magnitude $f > 35.5$ (see Section 2.6 for definitions). Including the Babalola case series, for the combined Hazan + Stone + Babalola case series, the selection bias tolerance decreases to $F = 5.1$ (using $p_1 = 51.3\%$ and $x_1 = 17.2\%$). In either case, the systemic selection bias tolerance is high enough for the clear and convincing finding for hospitalization rate reduction to have acceptable resilience.

3.3. Existence of mortality rate reduction efficacy

To investigate the existence of mortality rate reduction efficacy in the Hazan, Stone, and Babalola case series, as well as the combined Hazan + Stone and Hazan + Stone + Babalola case series, we consider risk-stratified case series with baseline room air SpO2 $\leq 90\%$ and compare them against external control groups [**63,79–85**] that provide the CFR or lower bounds of the CFR for hospitalized patients. The rationale is that, if they had followed the standard guidelines, then at least all patients in these risk-stratified case series would have been hospitalized, so, ultimately, they would have faced a mortality risk greater or equal than the average CFR of hospitalized patients. The external controls are in fact biased towards the null, i.e. they underestimate the mortality risk of the patients in the risk-stratified case series, if treated according to standard guidelines, because many patients with baseline room air oxygen saturation above 90% are also included in most of the external controls. Table 2 shows the calculation of the unadjusted and adjusted efficacy thresholds x_0 and x_0' and the random selection bias threshold x_1 for the risk-stratified case series. Table 4 summarizes the details of the United States external controls obtained from our own independent analysis of the CDC database [**63**], with a month by month breakdown given in Table 7 (without age restriction) and Table 8 (for age ≥ 50). Table 5 summarizes the details of several other external control groups relevant to our analysis [**79–85**]. Table 6 summarizes all of the exact Fisher test comparisons between the risk-stratified case series and the corresponding external control groups. We discuss in detail each case series and the combined case series in the following.

Table 4: Cumulative case fatality rate for symptomatic lab-confirmed COVID-19 patients that have been hospitalized in the United States, over specific time periods including the distinct SARS-CoV-2 variant waves and the case series treatment periods, calculated using a CDC database [**63**] (accessed January 20, 2023). The timing for the virus waves, used in the table, is consistent with Adjei *et al.*[**80**]. For the Hazan case series, the hospitalized CFR has been calculated both during the treatment period as well as cumulatively at the end of the treatment period. The CFR is given as an interval: the lower endpoint is calculated on the assumption that all patient cases with unknown outcome have survived; the higher endpoint is calculated on the assumption that for all patient cases with an unknown outcome the proportion of fatalities is equal to the proportion of fatalities in the cases where the outcome is known. The true CFR can be conservatively estimated to be between these two numbers.

Timing	Cases	Died	Lived	CFR
CFR for confirmed hospitalizations over all age groups				
First pre-delta period: 2020-01 to 2020-09	364543	40792	167139	11.19% to 19.62%
Second pre-delta period: 2020-10 to 2021-02	410826	41635	170400	10.13% to 19.64%
Third pre-delta period: 2021-03 to 2021-06	121261	2330	56980	1.92% to 3.93%
Delta: 2021-07 to 2021-12	328083	23064	141718	7.03% to 14%
Early Omicron: 2022-01 to 2022-03	120634	11690	45579	9.69% to 20.41%
Late Omicron: 2022-04 to 2022-12	152982	3104	68330	2.03% to 4.35%
Hazan (treatment interval): 2020-08 to 2021-02	491152	45868	204620	9.34% to 18.31%
Hazan (cumulative): 2020-01 to 2021-02	775369	82427	337539	10.63% to 19.63%
CFR for confirmed hospitalizations for age ≥ 50				
First pre-delta period: 2020-01 to 2020-09	252678	39547	102912	15.65% to 27.76%
Second pre-delta period: 2020-10 to 2021-02	315721	41039	125000	13% to 24.72%
Third pre-delta period: 2021-03 to 2021-06	76607	2291	33625	2.99% to 6.38%
Delta: 2021-07 to 2021-12	218513	22236	85640	10.18% to 20.61%
Early Omicron: 2022-01 to 2022-03	88570	11554	31503	13.05% to 26.83%
Late Omicron: 2022-04 to 2022-12	116502	3097	50746	2.66% to 5.75%
Hazan (treatment interval): 2020-08 to 2021-02	372828	45214	147387	12.13% to 23.48%
Hazan (cumulative): 2020-01 to 2021-02	568399	80586	227912	14.18% to 26.12%

3.3.1. Hazan case series

For the Hazan case series, the most extensive and available external control group is the CDC case surveillance database [**63**], where we have extracted all cases that are symptomatic, lab confirmed, resulting in hospitalization, and with known timing. We considered the time interval from August 2020 to February 2021, which is the time period during which Hazan's patients were treated [**34**], as well as the cumulative hospitalized CFR from the beginning of the pandemic on January 2020 to February 2021. For each case, the database reports whether the outcome was survival or death, however there was an extensive number of

Table 5: Case fatality rate for hospitalized patients, as reported in the United States [80, 95], South Africa [79], Zimbabwe [81, 82], and Nigeria [83, 84], as well as in a worldwide study [85]. PHD-SR corresponds to United States data from the Premier Healthcare Database Special COVID-19 Release [93].

Location	Timing	Cases	Died	CFR
CFR for confirmed hospitalizations over all age groups				
United States PHD-SR (Delta) [80]	2021-07 to 2021-10	163094	24658	15.12%
United States PHD-SR (Early Omicron) [80]	2022-01 to 2022-03	104395	13701	13.12%
United States PHD-SR (Late Omicron) [80]	2022-04 to 2022-06	20655	1004	4.86%
South Africa (first wave) [79]	2020-03 to 2020-08	83742	17042	20.35%
South Africa (beta) [79]	2020-09 to 2021-03	135472	33999	25.1%
South Africa (combined) [79]	2020-03 to 2021-03	219214	51041	23.28%
Zimbabwe (Parirenyatwa hospitals) [81]	2020-06 to 2020-12	336	119	35.42%
Zimbabwe (Masholand West Province) [82]	2020-04 to 2022-04	673	157	23.33%
Lagos, Nigeria (all patients) [83]	2020-04 to 2020-10	266	37	13.91%
Lagos, Nigeria (only hypoxemic patients) [83]	2020-04 to 2020-10	102	32	31.37%
Kano State, Nigeria (all patients) [84]	2020-04 to 2021-03	195	21	10.77%
Kano State, Nigeria (without asymptomatic) [84]	2020-04 to 2021-03	77	14	18.18%
World Heart Federation study (all patients) [85]	2020-06 to 2021-09	5313	801	15.08%
World Heart Federation study (LMIC) [85]	2020-06 to 2021-09	2526	492	19.48%
CFR for confirmed hospitalizations for age ≥ 50				
United States PHD-SR (Delta) [80]	2021-07 to 2021-10	114336	20943	18.32%
United States PHD-SR (Early Omicron) [80]	2022-01 to 2022-03	88639	12914	14.57%
United States PHD-SR (Late Omicron) [80]	2022-04 to 2022-06	17675	961	5.44%

cases in which the survival outcome was not reported, and excluding those cases would risk biasing the hospitalized CFR calculation. As explained in Section 2, we have calculated a lower bound for the CFR by assuming successful survival in all cases where the outcome is not reported. We have also calculated a conservative upper bound for the hospitalized CFR by assuming that the chances of survival for the cases with missing survival data are the same as for the cases where the data is available. Both of the lower and the conservative upper bound for the hospitalized CFR are displayed on Table 4. Furthermore, the hospitalized CFR calculation was done with and without the age ≥ 50 restriction.

On Table 4, we show that the resulting hospitalized CFR during the Hazan case series treatment period is between 9.34% and 18.31%, for all ages, and between 12.13% and 23.48% for age ≥ 50. If we use instead the cumulative time period from the beginning of the pandemic until February 2021, then the hospitalized CFR is between 10.63% and 19.63%, for all ages, and between 14.18% to 26.12% for age ≥ 50. We are assuming that survivals are proportionally more likely to be unreported than deaths.

To get a handle on the uncertainty involved in the hospitalized CFR calculation, we compare the CDC numbers with the reported hospitalized CFR calculated by Adjei *et al.*[80] using the Premier Healthcare Database Special COVID-19 Release (PHD-SR) [93] during the Delta, Early Omicron, and Late Omicron waves in the United States, displayed in Table 5. Table 4 shows the corresponding hospitalized CFR intervals, that we have calculated from the CDC case surveillance database [63], during the same waves, in addition to the pre-delta periods, as they have been defined by Adjei *et al.*[80]. For the Delta wave, over all ages, the CDC case surveillance database hospitalized CFR interval ranges from 7.03% to 14% and the PHD-SR database hospitalized CFR was reported as 15.12%, overshooting our conservative upper bound. With Early Omicron the CDC hospitalized CFR interval, under the age ≥ 50 restriction ranges from 13.05% to 26.83% and the corresponding hospitalized CFR from the PHD-SR database is 14.57%, which is closer to the lower bound rather than the upper bound CDC estimate. There is no consistent pattern from similar comparisons over the available waves about whether the real hospitalized CFR is more likely to be closer to the lower bound rather than the upper bound, other than that it tends to be confined within the neighborhood of those bounds.

An incidental finding of our analysis of the CDC case surveillance database [63] is that the hospitalized CFR remains mostly consistent between the first two pre-Delta periods, the Delta wave, and the Early Omicron wave, with and without the age ≥ 50 restriction. The first pre-Delta period through September 2020 appears to be the most lethal, and the second pre-Delta period is the one with the largest number of hospitalizations. The third pre-Delta period shows a dramatic temporary decrease in the hospitalized CFR, which coincided with the rollout of the COVID-19 vaccines to the high-risk demographic groups in

Table 6: Exact Fisher test comparisons between the Hazan, Stone, and Babalola case series and corresponding external control groups from Table 4 and Table 5, with respect to mortality rate reduction. The case series have been risk-stratified under the SpO2 $\leq 90\%$ constraint for the baseline room air oxygen saturation, to make them comparable with the CFR of hospitalized patients. Lower bounds are used for the CDC external control. Here, (N, a) is the treatment case series with N cases and a deaths; (M, b) is the external control with M cases and b deaths.

External control	(N, a)	(M, b)	**OR (95% CI)**	p**-value**
Hazan case series compared with				
CDC (treatment interval, any age)	(23, 0)	(491152, 45868)	0 (0 – 1.69)	0.267
CDC (treatment interval, age ≥ 50)	(23, 0)	(372828, 45214)	0 (0 – 1.26)	0.103
CDC (cumulative, any age)	(23, 0)	(775369, 82427)	0 (0 – 1.46)	0.165
CDC (cumulative, age ≥ 50)	(23, 0)	(568399, 80586)	0 (0 – 1.05)	0.065
World Heart Federation study (all patients)	(23, 0)	(5313, 801)	0 (0 – 0.98)	0.039
Stone case series compared with				
Zimbabwe (Parirenyatwa hospitals)	(28, 0)	(336, 119)	0 (0 – 0.26)	10^{-5}
Zimbabwe (Masholand West Province)	(28, 0)	(673, 157)	0 (0 – 0.47)	10^{-4}
South Africa (beta)	(28, 0)	(135472, 33999)	0 (0 – 0.42)	10^{-4}
South Africa (combined)	(28, 0)	(219214, 51041)	0 (0 – 0.46)	0.001
World Heart Federation study (LMIC)	(28, 0)	(2526, 492)	0 (0 – 0.58)	0.003
Babalola case series compared with				
Lagos, Nigeria (only hypoxemic patients)	(10, 0)	(102, 32)	0 (0 – 1.05)	0.06
Kano State, Nigeria (without asymptomatic)	(10, 0)	(77, 14)	0 (0 – 2.3)	0.355
World Heart Federation study (LMIC)	(10, 0)	(2526, 492)	0 (0 – 1.85)	0.225
Hazan + Stone case series compared with				
CDC (treatment interval, any age)	(51, 0)	(491152, 45868)	0 (0 – 0.73)	0.013
CDC (treatment interval, age ≥ 50)	(51, 0)	(372828, 45214)	0 (0 – 0.54)	0.002
World Heart Federation study (all patients)	(51, 0)	(5313, 801)	0 (0 – 0.42)	10^{-4}
Hazan + Stone + Babalola case series compared with				
CDC (treatment interval, any age)	(61, 0)	(491152, 45868)	0 (0 – 0.61)	0.006
CDC (treatment interval, age ≥ 50)	(61, 0)	(372828, 45214)	0 (0 – 0.45)	10^{-4}
World Heart Federation study (all patients)	(61, 0)	(5313, 801)	0 (0 – 0.35)	10^{-5}

the United States population. It is however unclear, to what extent the effect can also be attributed to the third pre-delta period being at the tail end of an epidemic wave of hospitalizations starting from 09/2020 and persisting until 06/2021 (see Table 7). For the purpose of our statistical analysis, we stress that the treatment time interval for the Hazan case-series does not intersect with the third pre-Delta period **[34]**, so we do not expect her results to be confounded by vaccination.

A close examination of the month by month hospitalized CFR during the treatment interval from August 2020 to February 2021, shown in Table 7 over all ages and in Table 8 over age ≥ 50, shows that the hospitalized CFR also has a dependence on the strain placed on the hospital system and varies from the interval 3.86% to 8.17% during September 2020 to the interval 13.3% to 25.89% during December 2020. This makes 25.89% a good candidate for the parameter p_2, however we have opted to use instead the more conservative choice $p_2 = 23.48\%$ on Table 2, which is the upper endpoint of the CFR during the treatment interval under the restriction age ≥ 50. This indicates the importance of averaging the hospitalized CFR over the entire treatment time period.

Exact Fisher test comparisons between the risk-stratified Hazan case series with $(N, a) = (23, 0)$ and the lower bounds of the CDC external controls is shown on Table 6. Regardless of whether the treatment interval CFR or the cumulative CFR is used, and regardless of whether the age ≥ 50 constraint is used for the definition of the external control group, all comparisons fail to demonstrate a statistically significant effect. Without the risk stratification, using instead $(N, a) = (24, 0)$, gives borderline statistical significance for mortality rate reduction, similarly with the analysis by Hazan *et al.***[34]**, only when compared against the CDC external control using the cumulative interval and the age ≥ 50 constraint. We have not included this result on Table 6, as we do not consider it to be a sufficiently conservative comparison. Borderline statistical significance is also obtained if one makes a comparison between the Hazan risk-stratified case

Table 7: Monthly case fatality rate for symptomatic lab-confirmed COVID-19 patients that have been hospitalized in the United States, during 2020 to 2022 over all age brackets, calculated using a CDC database [**63**] (accessed January 20, 2023). The CFR is given as an interval: the lower endpoint is calculated on the assumption that all patient cases with unknown outcome have survived; the higher endpoint is calculated on the assumption that for all patient cases with an unknown outcome the proportion of fatalities is equal to the proportion of fatalities in the cases where the outcome is known.

Timing	Cases	Died	Lived	CFR
2020-01	116	1	40	0.86% to 2.44%
2020-02	675	32	158	4.74% to 16.84%
2020-03	57703	8842	28437	15.32% to 23.72%
2020-04	72381	14518	34419	20.06% to 29.67%
2020-05	39618	4011	18999	10.12% to 17.43%
2020-06	44871	2890	20431	6.44% to 12.39%
2020-07	68853	6265	30435	9.1% to 17.07%
2020-08	45017	2871	18907	6.38% to 13.18%
2020-09	35309	1362	15313	3.86% to 8.17%
2020-10	57586	3322	26318	5.77% to 11.21%
2020-11	100089	10093	42949	10.08% to 19.03%
2020-12	114978	15288	43773	13.3% to 25.89%
2021-01	94337	10861	38448	11.51% to 22.03%
2021-02	43836	2071	18912	4.72% to 9.87%
2021-03	40133	947	19824	2.36% to 4.56%
2021-04	40967	934	20506	2.28% to 4.36%
2021-05	24688	279	11007	1.13% to 2.47%
2021-06	15473	170	5643	1.1% to 2.92%
2021-07	39648	2317	15427	5.84% to 13.06%
2021-08	73527	6515	29620	8.86% to 18.03%
2021-09	59634	4011	24769	6.73% to 13.94%
2021-10	43956	2146	18536	4.88% to 10.38%
2021-11	45134	2980	19892	6.6% to 13.03%
2021-12	66184	5095	33474	7.7% to 13.21%
2022-01	85570	10295	32695	12.03% to 23.95%
2022-02	26227	1292	9546	4.93% to 11.92%
2022-03	8837	103	3338	1.17% to 2.99%
2022-04	9862	92	4350	0.93% to 2.07%
2022-05	20395	384	8812	1.88% to 4.18%
2022-06	20881	527	9021	2.52% to 5.52%
2022-07	25504	748	11067	2.93% to 6.33%
2022-08	20540	467	9106	2.27% to 4.88%
2022-09	14671	254	6618	1.73% to 3.7%
2022-10	13704	182	6773	1.33% to 2.62%
2022-11	15120	345	7088	2.28% to 4.64%
2022-12	12305	105	5495	0.85% to 1.88%

series against the World Heart Federation study [**85**], which gives a 15.08% global CFR for hospitalized patients.

Similar results are obtained when the risk-stratified Hazan case series is analyzed using the case series threshold analysis method [**27**]. Comparing the hospitalized CFR from all CDC external controls, either using the treatment interval or the cumulative interval, and either using all ages or the age ≥ 50 constraint, against the adjusted efficacy threshold $x_0' = 14.7\%$, we see that all lower bound estimates of the CFR are below x_0 and all upper bound estimates of the hospitalized CFR are above x_0. It is therefore unclear whether the existence of mortality rate reduction has been established by the preponderance of evidence. With the age > 50 restriction, the corresponding hospitalized cumulative CFR lower bound is 14.18% which is very close to the adjusted efficacy threshold at 14.7%, however the hospitalized CFR lower bound over the treatment time period is reduced to 12.13%. Because the age ≥ 50 restriction is scored equivalently as hypoxemia, in the 4C model [**91**] for survival probability of hospitalized COVID-19 patients, it is a reasonable conservative proxy for obtaining a lower bound for the hospitalized CFR of hypoxemic patients. Therefore, we think that 12% hospitalized CFR is a reasonable lower bound for United States patients, for comparison with the corresponding case series thresholds.

We conclude that, although there is a very compelling signal of benefit, there is insufficient statistical

Table 8: Monthly case fatality rate for symptomatic lab-confirmed COVID-19 patients that have been hospitalized in the United States, during 2020 to 2022 for age ≥ 50, calculated using a CDC database [**63**] (accessed January 20, 2023). The CFR is given as an interval: the lower endpoint is calculated on the assumption that all patient cases with unknown outcome have survived; the higher endpoint is calculated on the assumption that for all patient cases with an unknown outcome the proportion of fatalities is equal to the proportion of fatalities in the cases where the outcome is known.

Timing	Cases	Died	Lived	CFR
2020-01	5	0	3	0% to 0%
2020-02	213	30	2	14.08% to 93.75%
2020-03	40115	8179	17344	20.39% to 32.05%
2020-04	53379	14299	21789	26.79% to 39.62%
2020-05	26388	3952	10862	14.98% to 26.68%
2020-06	28294	2816	11522	9.95% to 19.64%
2020-07	47177	6096	19003	12.92% to 24.29%
2020-08	31685	2823	12186	8.91% to 18.81%
2020-09	25422	1352	10201	5.32% to 11.7%
2020-10	43464	3305	18964	7.6% to 14.84%
2020-11	76327	10009	31164	13.11% to 24.31%
2020-12	89545	14966	32387	16.71% to 31.61%
2021-01	73653	10699	28894	14.53% to 27.02%
2021-02	32732	2060	13591	6.29% to 13.16%
2021-03	27244	947	12830	3.48% to 6.87%
2021-04	25778	907	12054	3.52% to 7%
2021-05	15043	268	6027	1.78% to 4.26%
2021-06	8542	169	2714	1.98% to 5.86%
2021-07	23885	2125	8457	8.9% to 20.08%
2021-08	47668	6147	17409	12.9% to 26.1%
2021-09	40547	3928	15395	9.69% to 20.33%
2021-10	31163	2112	12201	6.78% to 14.76%
2021-11	32053	2926	13034	9.13% to 18.33%
2021-12	43197	4998	19144	11.57% to 20.7%
2022-01	62477	10164	22269	16.27% to 31.34%
2022-02	19930	1287	7048	6.46% to 15.44%
2022-03	6163	103	2186	1.67% to 4.5%
2022-04	7160	91	3074	1.27% to 2.88%
2022-05	14497	384	6278	2.65% to 5.76%
2022-06	15797	527	6649	3.34% to 7.34%
2022-07	19396	742	8219	3.83% to 8.28%
2022-08	15703	467	6804	2.97% to 6.42%
2022-09	11250	254	4910	2.26% to 4.92%
2022-10	10988	182	5291	1.66% to 3.33%
2022-11	11987	345	5350	2.88% to 6.06%
2022-12	9724	105	4171	1.08% to 2.46%

power for a decisive finding of preponderance of evidence in support of mortality rate reduction, if we use the Hazan case series by itself.

3.3.2. Stone case series

For the Stone case series, the available external control groups include an unpublished report [**81**] by the Parirenyatwa group of hospitals in Harare Zimbabwe which reported 35.4% CFR for hospitalized COVID-19 patients admitted between May 2020 and December 2020, which overlaps with the treatment time interval of the Stone case series [**35**]. A reduced hospitalized CFR of 23.3% was reported [**82**] for COVID-19 patients in Masholand West Province, Zimbabwe between April 2020 and April 2022. Both reports are shown on Table 5. Combined, these two reports account for a total of 1009 patients with 27.3% averaged hospitalized CFR, and they are consistent with the 23.28% averaged hospitalized CFR reported in South Africa between March 2020 and March 2021 [**79**], with a substantially larger sample size of 219214 hospitalized patients. The predominant strain during the Stone case series treatment time interval was the Beta variant, with the Delta variant appearing at the tail end of the treatment time interval [**87**]. In South Africa, the Beta variant was dominant between September 2020 and March 2021 (the published month by month hospitalized CFR data do not go beyond March 2021), and an increased hospitalized CFR at 25.1% was observed during that time, up from a 20.35% hospitalized CFR during the preceding wave. A global study by the World Heart

Federation [**85**] has measured a 15.08% hospitalized CFR globally, with an increased 19.48% hospitalized CFR in nations, like Zimbabwe, that have been classified by the World Bank as LMIC. This data is displayed on Table 5.

Comparison of the risk-stratified Stone case series with $(N, a) = (28, 0)$ against all of these external controls using the exact Fisher test is shown on Table 6, and statistically significant mortality rate reduction is established from all of these comparisons with $p \leq 0.003$. For a more detailed analysis using the case series threshold analysis method [**27**], we use 20% hospitalized CFR as a reasonable lower bound for patients treated in the conventional way in Zimbabwe, noting, however, that had those patients have access to United States hospital facilities, the corresponding hospitalized CFR could have been lower but not below the 12% lower bound hospitalized CFR that we have assessed for the United States. For the calculation of the adjusted efficacy threshold and the random selection bias threshold of the Stone case series, we conservatively set p_2 equal to the smallest number between the CFR for hospitalized patients in the Parirenyatwa group of hospitals [**81**] and the CFR for hospitalized patients at Masholand West Province [**82**], which is $p_2 = 23.3\%$. Displayed on Table 2 is a 12.0% adjusted efficacy threshold and 32.0% random selection bias threshold for mortality rate reduction efficacy in the Stone case series. Using the 20% lower bound for hospitalized CFR, there is a comfortable margin separating it from the adjusted efficacy threshold, so we have a decisive preponderance of evidence finding that there is some mortality rate reduction effect by the treatment used in the Stone case series. However, with the exception of the hospitalized CFR obtained from the Parirenyatwa external control [**81**], the hospitalized CFR from all other external control groups does not exceed the random selection bias threshold, so we cannot claim a clear and convincing finding of mortality rate reduction, if the Stone case series is used by itself.

3.3.3. Babalola case series

The risk stratified Babalola case series of patients with baseline room air SpO2 $\leq$ 90% consists of only 10 patients with 0 deaths [**88**]. For an exact Fisher test comparison, we have considered external control groups in Nigeria, where the patients in the Babalola case series were treated. Table 5 shows a 13.91% hospitalized CFR for a small group of patients that were treated in Lagos, Nigeria [**83**]. The facility served both as an isolation center as well as an inpatient treatment facility and included COVID-19 positive asymptomatic patients. The authors also report a 31.37% hospitalized CFR, when selecting only for hypoxemic patients. Another study from Kano State, Nigeria [**84**] reports 10.77% hospitalized CFR, noting again that the treatment facility also served as an isolation center. After excluding the patients that initially presented as asymptomatic COVID-19 positive, the hospitalized CFR for the remaining patients is 18.18%, which is consistent with the hospitalized 19.48% CFR reported by the World Heart Federation study [**85**] for LMIC nations. The corresponding exact Fisher test comparisons of these external controls with $(N, a) = (10, 0)$ on Table 6 shows that all comparisons fail to reach statistical significance. Nevertheless, the comparison with hospitalized hypoxemic patients in Lagos, Nigeria does give $p = 0.06$ which is very close to the threshold for statistical significance. There is insufficient statistical power to draw any reliable conclusions.

3.3.4. Combined case series

For the combined Hazan + Stone case series, we have a total of 51 patients with baseline room air SpO2 $\leq$ 90% and 0 deaths. In both case series, very similar multidrug treatment protocols are being used, with the overlapping medications being ivermectin, zinc sulfate, and doxycycline, resulting in similar rapid recovery rates of room air SpO2 levels (see Fig. 1). Furthermore, the occasional use of adjunct hydroxychloroquine and azithromycin in some of the highest-risk patients in the Hazan case series is intended to have a similar antiviral effect as the use of nebulized nanosilver in the Stone case series [**89**]. Table 6 shows the exact Fisher test comparisons between the combined Hazan + Stone case series and the CDC database external controls over the treatment interval for the Hazan case series, both with and without the age $\geq$ 50 restriction, as well as with the World Heart Federation study [**85**] external control over all patients. All of these comparisons show statistically significant mortality rate reduction with $p \leq 0.013$. Furthermore, because the hospitalized CFR in the United States external controls is substantially lower than the hospitalized CFR in Zimbabwe and LMIC external controls, a positive finding using exclusively the United States external controls will be sustained if equivalent controls are used.

A comparison with an appropriate mixed external control is possible using the case series threshold analysis [**27**] method. For the combined Hazan + Stone case series, on Table 2, we show that the adjusted efficacy threshold is 7.6% and the random selection bias threshold is 18.5%, both for mortality rate reduction. For this calculation we have used the very conservative choice $p_2 = 10\%$, which is below the hospitalized CFR lower bound that we have adopted for United States patients, and results in negligible adjustment of the efficacy threshold. Increased choices for p_2 result in increased Bayes factors and a negligible decrease in the adjusted efficacy threshold and the random selection bias threshold. An estimated 12% lower bound for

the hospitalized CFR of the United States patients clearly exceeds the 7.6% adjusted efficacy threshold for the combined Hazan + Stone case series, so we can draw a decisive conclusion that mortality rate reduction can be claimed by the preponderance of evidence. If we use the 12% lower bound for the 23 patients in the Hazan case series and the 20% lower bound for the 28 patients in the Stone case series, all with baseline room air SpO2 $\leq$ 90%, the combined average hospitalized CFR lower bound is 16.4%, which does not exceed the random selection bias threshold of 18.5%, so we can rule out a decisive clear and convincing claim.

It is also interesting to consider the combined Hazan + Stone + Balalola case series, which adds up to 61 patients with baseline room air SpO2 $\leq$ 90% and 0 deaths. Table 6 shows the exact Fisher test comparisons between the combined Hazan + Stone + Babalola case series and the same external controls that were used in the previous comparison for the combined Hazan + Stone case series. All comparisons show statistically significant mortality rate reduction with $p \leq 0.006$. Furthermore, on Table 2, we display the adjusted efficacy threshold and the random selection bias threshold for the combined Hazan + Stone + Babalola case series, which are 6.2% and 16.2% correspondingly. For the calculation, we have used the conservative choice $p_2 = 10\%$, similarly to the previous calculation for the combined Hazan + Stone case series. If we use the very conservative lower bound of 12% for the hospitalized CFR under conventional treatment for all patients in the combined case series, then the 6.2% efficacy threshold is being exceeded by a wide margin, which establishes decisively the existence of a mortality rate reduction benefit by the preponderance of evidence, but fails to do so by the clear and convincing standard. On the other hand, if we use the 12% lower bound for the hospitalized CFR for the 23 patients in the United States, and use the 19.5% hospitalized CFR for LMIC nations from the World Heart Federation Study [**85**] for the 38 patients in Nigeria and Zimbabwe, then the average hospitalized CFR lower bound is 16.7%, which exceeds the random selection bias threshold of 16.2%, but with a very tight margin, making the claim susceptible to any systemic selection bias that might exist. Finally, if we adopt the most aggressive conservative lower bound for hospitalized CFR from the CDC case surveillance database [**63**], by disregarding the restriction age $\geq$ 50 and using smallest hospitalized CFR lower bound amongst the first two pre-Delta periods, the Delta wave, and the Early Omicron wave, which is 7.3%, noting that the Beta wave that was dominant in both Zimbabwe [**87**] and Nigeria [**39**] was generally more lethal than preceding waves [**79**], we are still showing a decisive finding of existence of mortality rate reduction by the preponderance of evidence.

4. Discussion

4.1. Summary of findings

We have analyzed the case series of hypoxemic patients reported by Hazan *et al.*[**34**], Stone *et al.*[**35**], and Babalola *et al.*[**36,39,40**] using a self-controlled case series methodology combined with the recently introduced case-series statistical analysis technique [**27**], to show clear and convincing evidence of the existence of hospitalization rate reduction. In this context, *"clear and convincing"* means that the result is statistically significant with at least 95% confidence, and we also have at least 95% confidence that the result cannot be overturned by any selection bias that could result, if the patient sample has been randomly selected from the general population. In a way, this is intuitively obvious, since the overwhelming majority of the treated patients would have been hospitalized under the conventional standard of care, but were all successfully treated in an outpatient setting and successfully recovered with no deaths or hospitalizations. More importantly, we have quantified the considerable resilience of this result with respect to systemic selection bias, that would threaten the validity of the result, if the selection of patients from the general population is not random. This resilience is particularly robust when combining the statistical power of the Hazan and Stone case series, where the more aggressive variations of the multidrug protocol were used on very high-risk patients.

The main focus has been on establishing the existence of mortality rate reduction by forming risk-stratified subseries of the highest risk patients presenting with severe hypoxemia (baseline room air SpO2 $\leq$ 90%) and comparing them against the CFR of hospitalized patients using a wide variety of external control groups. For the Hazan case series, there is insufficient statistical power to establish a mortality rate reduction benefit using our more conservative approach, and we note that the corresponding analysis by Hazan *et al.*[**34**] establishes mortality rate reduction, albeit with p-value $p = 0.044$, which is very near the 0.05 threshold for statistical significance. On the other hand, our conclusion is based on a comparison that is more biased against the establishment of mortality rate reduction, because in the external control group (the CDC case surveillance database [**63**]), for the considerable number of cases where the survival outcome is unknown, we have assumed that the patient survived. For the Stone case series alone, the existence of mortality rate reduction can be shown by the preponderance of evidence, when compared with the hospitalized CFR in Zimbabwe or more broadly with the average hospitalized CFR of LMIC nations. In this

context, "*preponderance of evidence*" means that the claim is statistically significant, if there is no selection bias, and, furthermore, that if the patients in the case series have been randomly selected from the general population, then it is more likely than not that the claim cannot be overturned by selection bias.

Combining the Hazan and Stone case series together decisively establishes the existence of mortality rate reduction by the preponderance of evidence, even when comparing against the most conservative estimate of hospitalized CFR in the United States, under the age > 50 restriction. Including the Babalola case series, to combine all three case series together, decisively shows mortality rate reduction by the preponderance of evidence against even the most conservative estimate of the hospitalization CFR using the CDC case surveillance database [**63**], even without the age > 50 restriction. Furthermore, the combined series takes us almost above the required threshold for establishing the existence of mortality rate reduction by the clear and convincing standard, if we use the external control groups that correspond to the respective locations where the patients were treated. However, if claimed, such a finding has almost no resilience with respect to systemic selection bias.

Although combining the Hazan and Stone case series makes for a very compelling argument, due to the similarity in the underlying multidrug treatment protocols and the similar recovery rates of SpO2 levels (see Fig. 1), the protocol used by the Babalola case series was less aggressive, using ivermectin monotherapy (with adjunct zinc sulfate and Vitamin C) or combined with low-dose hydroxychloroquine and azithromycin for some of the patients [**36**]. Furthermore, as shown in Fig. 1, the recovery rate of SpO2 levels in the Babalola case series is distinguishably slower than the rates observed in both of the Hazan and Stone case series. Thus, conclusions drawn from the Hazan+Stone combined case series are on more solid footing than conclusions drawn from the Hazan + Stone + Babalola combined case series.

Babalola *et al.*[**36**] found that adding hydroxychloroquine and azithromycin on top of ivermectin does not appear to contribute towards faster clearance of the virus. However, it is worth noting that the dosage of hydroxychloroquine was 200 mg per day for 3 days and the dosage for azithromycin was 500 mg per day for 3 days. In the original Zelenko protocol [**5**], hydroxychloroquine was given at 200 mg twice a day per day for 5 days and azithromycin was given at the same dosage for 5 days as opposed to 3 days. Thus, one cannot rule out the possibility that the lack of a positive effect could be attributed to underdosing, and the result does not necessarily extrapolate to the early treatment of COVID-19, initiated before the deterioration of SpO2 levels. Hazan communicated to us that in her clinical experience adding hydroxychloroquine and azithromycin on top of her baseline protocol of ivermectin, doxycycline, zinc, and vitamins C and D was necessary to eradicating the virus for some of her patients [**89**].

Noting that, for all three case series, patients were treated before the emergence of the omicron variants, natural immunity remained protective with respect to reinfections [**106**], so it is very likely that the results have not been confounded by prior immunity. Any impact of vaccination on mortality rate reduction is already baked into the hospitalized CFR calculations based on the CDC case surveillance database [**63**]. Furthermore, the treatment period for the Hazan case series does not intersect with the third pre-Delta period [**34**], which is when the COVID-19 vaccines were rolled out in the United States. Finally, we note that the vaccine uptake in Nigeria and Zimbabwe was substantially less than that of the United States [**107**], and Babalola *et al.*[**36**] explicitly reported that their 61 patients, who were treated with ivermectin-based protocols, were not vaccinated. It is unclear whether any patients in the Stone case series were vaccinated; some patients were treated before the rollout of the COVID-19 vaccines in Zimbabwe and some patients were treated afterwards [**35**]. However, given that all patients in the Stone case series presented with baseline room air SpO2 $\leq 93\%$, we can infer thar there was a catastrophically insufficient anti-viral immune response at the initial onset of the illness, specifically for the selected patients in the case series.

An incidental finding of our analysis of the CDC case surveillance database [**63**] is that the hospitalized CFR remained consistent between the first two pre-Delta periods, the Delta, and the Early Omicron waves. There was a temporary dramatic reduction of the hospitalized CFR during the third pre-Delta period, which could be plausibly attributed to the rollout of the COVID-19 vaccines to the high-risk segment of the United States population. Unfortunately, the hospitalized CFR resumed during the Delta variant at comparable levels with the first two pre-Delta periods. However, during Late Omicron, the hospitalized CFR decreased by an approximate factor of $1/5$, suggesting the beginning of a substantial decrease in the virulence of the SARS-CoV-2 virus.

4.2. Limitations

Our statistical analysis has several limitations. The reported results are applicable to the variants that were circulating at the time (pre-delta variants in the United States, Beta variant in Zimbabwe, Beta and possibly Delta variant in Nigeria) and to other variants of comparable lethality. More lethal variants could require more aggressive multidrug treatment protocols, and for far less lethal variants, treatment with prescription drugs may not be necessary. The small size of the case series, even when all three series are combined, is

preventing us from establishing a claim of clear and convincing existence of mortality rate reduction with at least some modest amount of systemic selection bias tolerance. Because this is not a large randomized controlled trial, we cannot provide an unbiased measurement of the *magnitude* of benefit; we can only investigate the strength of the evidence supporting the *existence* of benefit.

Although our simplified self-controlled case series methodology does establish a clear and convincing claim of hospitalization rate reduction with substantial systemic selection bias tolerance, hospitalization is a more subjective endpoint than mortality, and a limitation of this methodology is that using baseline room air SpO2 $\leq 90\%$ as a proxy for calculating a lower bound for the counterfactual hospitalization rate, under the conventional standard of care, is inevitably based on subjective hospitalization thresholds that have been recommended by the official standard of care guidelines promulgated by the NIH [**69**] and other government agencies from all around the world.

The CDC case surveillance database [**63**] external control group has a considerable amount of missing data, forcing us to use lower bound estimates of the hospitalized CFR that are likely to be underestimating its true magnitude, so neutral results should be interpreted with caution. Our analysis of the CDC case surveillance database [**63**] used the snapshot downloaded on January 20, 2023. Subsequent updates of the database result in negligible fluctuations in the hospitalized CFR. The available external control groups for Zimbabwe [**81,82**] and Nigeria [**84,84**] also have small sample sizes and could thus have some biases. The hospitalized CFR is dependent not only on the virulence of the particular COVID-19 strains but also on the hospital resources available and the extent to which those resources are strained by case load. We have tried to mitigate this by using conservative estimates, temporal averaging, and using several possible external control groups.

4.3. Applying the Bradford Hill criteria

Our statistical analysis examines the strength of association between the multidrug treatment protocols used and prevention of hospitalization and death, mediated by the restoration of SpO2 levels in hypoxemic patients. A well-known limitation of any observational study is that, in and of itself, it is not sufficient for establishing causality between the treatment and the observed reduction in hospitalizations and deaths. Consequently, to build the case towards making a claim of causality, it is necessary to work towards establishing at least some of the other Bradford Hill criteria [**61,62**].

In connection with that, we observe that: (a) *Temporality* has been shown by the immediate and statistically significant increase in SpO2 levels observed separately in the case series by Hazan *et al.*[**34**], Stone *et al.*[**35**], and Babalola *et al.*[**40**], shown in Fig. 1, shortly after the treatment is initiated; (b) *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 [**36,39,40**], but the Hazan and Stone/Gill multidrug protocols [**34,35,38**] added Vitamin D3 and doxycycline, and the Stone/Gill protocol also added nebulized nanosilver, corticosteroids, and blood thinners [**35,38**]. 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"* [**35**]. 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 did not fully recover after 10 days. (c) *Consistency* is satisfied because the rapid increase in SpO2 on hypoxemic patients in response to treatment has been observed in 3 distinct case series located in the United States, Zimbabwe, and Nigeria. (d) *Biological plausibility* is satisfied, given that there are many plausible biological mechanisms by which the baseline medicines and nutraceuticals used in the Hazan and Stone/Gill multidrug protocols can contribute to the treatment of COVID-19, with anti-viral, anti-inflammatory, and anticoagulant mechanisms of action, needed to effect a rapid increase of SpO2 levels, especially when used in combination. As noted in the introduction (see Fig. 2), viral invasion of the alveoli causes immunothrombosis, which leads to the formation of microemboli in the alveoli and in the pulmonary and bronchial distal arteries, which in turn interfere with the ability of the lungs to oxygenate, leading to oxygen desaturation. Antiviral action may eradicate the virus from the alveoli, immunomodulating/anti-inflammatory action may tend to decrease immunothrombosis and the rate of formation of further microemboli, and anticoagulation should increase the rate of elimination of the microemboli that have accumulated at the onset of treatment. 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 they are the baseline medications and nutraceuticals in the Stone/Gill multidrug protocol [**35,38**] that were used on all patients of the Stone case series.

Ivermectin may have several mechanisms of action [**53,108**] suggesting multiple targets and modes of action against COVID-19, including anti-viral, 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 the inflammation triggered by the viral particles [**32, 52**]. Ivermectin can inhibit viral attachment to human cells by binding onto several sites of the spike glycoprotein of the SARS-CoV-2 virus, which include a glycosylation binding site (site 10, N61) and other sites on the S1-NTD and S1-RBD regions [**32, 42**]. Spike protein-induced red blood cell and platelet aggregation can trigger events for blood clot formation and inflammation which causes serious pathologies, including the drop of SpO2 levels to severe hypoxemia. Ivermectin binds competitively to SARS-CoV-2 spike protein glycans, and reverses the bindings with red blood cells thus preventing clumping [**30–33**]. Finally, ivermectin may act as a zinc ionophore [**47**], 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 [**5, 109**]. 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 [**53**].

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 disease [**110**]. Doxycycline has now emerged as a compelling candidate for reducing lung damage and mitigating the cytokine storm in severe cases of COVID-19 [**54**]. Doxycycline has also demonstrated antiviral activity against various RNA viruses in laboratory settings, which is mediated by targeting host proteases utilized by coronaviruses, inhibiting viral fusion and replication [**48**]. By impeding viral replication, doxycycline holds the potential to alleviate the severity of the infection and limit lung damage. It has been shown to inhibit coreceptors DPP4/CD26 and CD147/EMMPRIN, crucial for viral entry into T lymphocytes [**48**]. Additionally, doxycycline may interfere with viral protein processing, including the cleavage of polyproteins and the maturation of essential viral proteins [**48**]. Furthermore, doxycycline acts as a zinc ionophore, enhancing the intracellular concentration of zinc, which has been associated with inhibiting SARS-CoV-2 replication [**48**]. 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 [**111**]. In doing so, it may help quell the excessive inflammatory response by mitigating the cytokine storm, preventing further lung damage. Its anti-inflammatory properties extend to inhibiting NF-κB activation, a transcription factor involved in producing proinflammatory cytokines [**54**].

Silver nanoparticles (AgNPs) have also shown potential in combating COVID-19 [**44**]. Dr. 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 [**38**]. While the exact mechanisms through which AgNPs impede the infectivity of the SARS-CoV-2 virus remains unknown, numerous studies have put forward compelling theories regarding their potential modes of action [**55**]. AgNPs reveal a multi-faceted approach to managing viral infections. As an immune booster, AgNPs can enhance the immune response [**112**]. Their anti-inflammatory and antimicrobial properties are effective in treating viruses like SARS-CoV-2. By reducing inflammation and combating microbial infections, AgNPs aid in managing the progression of viral diseases [**56**]. When used as an oral spray or mouthwash, they can alleviate the burden of pathogens residing in the nasal cavity and mouth [**57**]. 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 [**49**]. Additionally, AgNPs can generate reactive oxygen species (ROS), which exert an antiviral effect by directly impeding viral proteins and nucleic acids, exerting their antiviral effects [**50**]. 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 severe COVID-19 cases is blood clotting. Studies have shown that AgNPs possess the ability to impede platelet adhesion and disrupt integrin-mediated platelet responses [**44**]. AgNPs demonstrate antiplatelet and anticoagulant effects [**45**]. This property of AgNPs can potentially prevent blood clots formation, safeguarding patients from life-threatening complications, and contributing to the restoration of SpO2 levels.

Prior to the COVID-19 pandemic, an in-vitro study [**113**] had shown that using zinc ionophores to increase intracellular Zn^{2+} ions inhibits the ability of the SARS-CoV and the 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 at the early stages of the COVID-19 disease [**114**], thus motivating Zelenko's precursor of the McCullough protocol [**5**]. In the context of the Hazan and Stone/Gill multidrug protocols [**34, 35, 38**], the aforementioned combined zinc ionophore properties of both 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 that 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 [**58**].

Vitamin D supplementation can be beneficial by a wide range of mechanisms of action that 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 [**59**]. 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 [**59**]. Vitamin D may reduce the risk of respiratory failure by reducing matrix metalloproteinase-9 (MMP-9) concentration [**59**]. Finally, vitamin D may reduce the risk of RAS-mediated bradykin storm through 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 adverse effects to the brain and muscles [**59**].

Last but not least, 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 also down regulating pro-inflammatory cytokines [**60**].

This evidence in favor of biological plausibility, when considered in conjunction with the results of our statistical analysis and the observation that the Bradford Hill criteria of temporality, biological gradient, and consistency are also satisfied, add up towards a compelling argument in support of the Hazan [**34**] and Stone/Gill [**35,38**] multidrug treatment protocols.

4.4. Controversies and totality of evidence

The use of ivermectin in the treatment of COVID-19 has been the point of contentious controversy [**115,116**]. The World Health Organization (WHO) recommended against its use, and there have been calls to prohibit medical doctors from deviating from WHO's recommendations [**117**]. To disentangle the ongoing controversies surrounding the use of ivermectin in the treatment of COVID-19, 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 [**27,118**]. COVID-19, as explained in the introduction, is a multifaceted triphasic illness and it is very unlikely 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 [**119**]. This is why observational studies [**4,5,7,8,25–27**] of multidrug treatment protocols, that have been used by practicing doctors at the frontlines deserve special consideration.

In addition to our findings, other particularly interesting positive evidence include the Procter case series [**25,26**] of 869 high-risk patients, who were treated early according to the McCullough multidrug protocol [**11**], using hydroxychloroquine and ivermectin in combination with zinc, azithromycin, doxycycline, inhaled budesonide, dexamethasone, folate, thiamine, vitamin B12, and IV 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 [**27**], noting though that 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.*[**29**] has shown a signal of benefit with respect to mortality rate reduction, which is statistically significant for severe cases but not so for the non-severe ones, when adding low dose ivermectin to the standard of care. This finding is consistent with our finding of a statistically significant mortality rate reduction benefit, when using ivermectin at higher dosage 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 [**120,121**], and the ecological study on the state-level use of ivermectin in Peru [**122**] both provide additional compelling evidence in support of some efficacy of the pre-hospital early use of ivermectin for preventing hospitalizations and deaths in COVID-19 patients. A meta-analysis of ivermectin use in COVID-19 patients by Bryant *et al.*[**123**], which included both obserbational and randomized controlled trials, showed the association of ivermectin with statistically significant reduction of all cause mortality, and confirmed the robustness of their result with an exhaustive sensitivity analysis. Bryant *et al.*[**123**] combined outpatient with inpatient studies, and noted that there were very few outpatient trials using a mortality rate reduction endpoint. Thus, their results tend to support the inpatient use of ivermectin, but do not necessarily extrapolate to outpatient use. Several subsequent meta-analyses have confirmed the association of ivermectin with a mortality rate reduction benefit [**116**].

A randomized controlled trial from Bangladesh by Mahmud *et al.*[**124**] of a pre-hospital combination therapy (12mg single dose ivermectin and 100mg doxycycline twice daily for 5 days) that was a reduced

lower-dose variation of the Hazan and Stone/Gill multidrug protocol [**34, 35, 38**], 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 statistically significant mortality rate reduction with $p = 0.016$. Another small randomized controlled trial by Hashim *et al.*[**125**] 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 0.2mg/kg for 2 days and an optional third dose a week later, doxycycline for 200mg 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 an intense standard of care, which was initiated within 3 days from onset of symptoms, for both 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 treatment group against 6 deaths out of 22 patients in control group) which gives $p = 0.077$, via two-tailed exact Fisher test, not statistically significant but close to the 0.05 threshold.

Several randomized controlled trials, published in high-impact journals, tend to be cited as evidence against the use of ivermectin in the treatment of COVID-19 [**105, 126–130**]. Of these, the COVID-OUT trial [**126**] used a misleading 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. Because 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 the ivermectin treatment is too short compared to the 10-day treatment used by Hazan *et al.*[**34**], Stone *et al.*[**35**], and Borody *et al.*[**8**]. From the other five cited studies [**105, 127–130**], four of them tested ivermectin monotherapies against placebo [**127–130**], so their results do not necessarily extrapolate to multidrug protocols [**8, 11, 34, 35, 38**] using ivermectin in combination with other medications.

As noted in the introduction, 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 vantage point, the most compelling study is the I-Tech RCT [**105**], which recruited high-risk patients, with age $\geq$ 50 and at least one comorbidity, between May 2021 and October 2021 in Malaysia. The treatment group was treated with a 5-day high-dose course of ivermectin (0.4mg/kg), initiated within the first 7 days from symptom onset. Both arms of the trial were treated with corticosteroids, antibiotics, and anticoagulants, with each of these medications given to approximately 1/4 of the patients of both the treatment and control group, although it is not clearly articulated how many patients received ivermectin monotherapy. The paper reports 4.0% mortality rate in the control group and 1.2% mortality rate in the treatment group with $p = 0.09$, and although there is a signal of mortality rate reduction, it is deemed to be not statistically significant. On the other hand, from 241 patients with 3 deaths in the treatment group, we calculate [**102**] an efficacy threshold of 3.7%, which means that statistical significance can be achieved, if an equivalent control group with an asymptotically infinite size has mortality rate greater or equal than 3.7%. For untreated high-risk patients with comorbidities, we are expecting at least 5% mortality rate without any treatment [**27**]. Because some treatment was indeed offered to the control group, it did have 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, are very suggestive 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, in spite of the treatment being initiated within a 7-day window rather than the recommended 3-day window [**28**].

The ACTIV-6 trials [**127, 128**] were conducted between February 2022 and July 2022, catching the tail end of Early Omicron and overlapping for the most part with Late Omicron in the United States, and tested ivermectin monotherapy (0.4 mg/kg for 3 days [**127**] and 0.6 mg/kg for 6 days [**128**]) against placebo. No deaths were reported in the placebo arm of either trial, suggesting that the patients were low risk, possibly due to a combination of low age and low percentage of comorbidities, reduced virulence of the Omicron variants, and possibly prior partial natural immunity from previous COVID-19 infections. As such, these studies cannot prove the absence of a mortality rate reduction benefit. No statistically significant hospitalization rate reduction benefit was reported, and none should have been expected given that the treatment was monotherapy that, for a substantial proportion of the patients in the treatment group, was not given within the first 3 days from onset of symptoms.

The Lopez-Medina *et al.*[**129**] trial, which was conducted in Colombia between July 15 2020 and December 21 2020, testing ivermectin monotherapy (0.3mg/kg for 5 days) against placebo is not informative

with respect to mortality rate reduction, noting that one death is reported out of 198 patients in the control group and zero deaths are 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) [**107**], so the low mortality rate in the control group indicates that the patients were either very low risk or they accessed ivermectin over the counter as a result of failure of blinding [**131**]. In either case, the study prima facie enrolled very low-risk patients, given the atypically low mortality rate in the control group, so one cannot use it to justify a recommendation against the use of ivermectin for high-risk patients.

The TOGETHER ivermectin trial [**130**] tested ivermectin monotherapy (0.4mg/kg for 3 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: reduction in hospitalizations from 14% (treatment arm) to 11.6% (control arm); smaller reduction in deaths from 3.5% (treatment arm) to 3.1% (control arm), both not statistically significant. A curious characteristic of the trial is 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 have not conducted the corresponding per-protocol population analysis for hospitalization and death reduction. The data has not been made available to research groups interested in conducting the per-protocol reanalysis, even though it was requested for that purpose [**132**]. More than half of the patients initiated treatment during 4-7 days since onset of symptoms. During the study period, Brazil was confronted with the highly lethal Gamma variant. By the beginning of March 2021, the cumulative CFR was 2.4% but between March 23, 2021 and August 6, 2021 the average CFR was equal to 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) [**107**]. It is plausible that the ivermectin monotherapy was given too late, for too short a duration, and at insufficient dose to make a statistically significant difference with an unusually more lethal variant.

Last but not least, a Cochrane meta-analysis of ivermectin randomized controlled trials [**133**] 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.*[**124**] and Hashim *et al.*[**125**], both discussed previously), which reported positive results, solely due to using these drugs in combination. In total, the Cochrane meta-analysis [**133**] excluded 11 studies that used ivermectin-based multidrug therapies, with the sole justification that these were combined interventions, so the findings of the Cochrane meta-analysis [**133**] do not extrapolate to ivermectin-based multidrug treatments. Unlike the Bryant *et al.*[**123**] meta-analysis, the Cochrane meta-analysis [**133**] also excluded all observational controlled trials, in spite of known empirical evidence that observational and randomized controlled trials, on average, tend to provide similar effect size estimates [**134,135**]. 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 [**133**] and Bryant *et al.*[**123**].

The Cochrane meta-analysis selected 11 randomized controlled trials, of which 1 was later retracted, 3 were previously discussed (TOGETHER [**130**], Lopez-Medina *et al.*[**129**], and ITECH [**105**]), and 4 have no mortality reported in either the treatment or control group (Buanfrate *et al.*[**136**], Chaccour *et al.*[**137**], Krolewisky *et al.*[**138**], Mohan *et al.*[**139**]), due to all patients surviving. The remaining 3 studies are Vallejos *et al.*[**140**], Ravikirti *et al.*[**141**], and Gonzalez *et al.*[**142**]. Vallejos *et al.*[**140**] 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 0.15mg/kg to 0.2mg/kg) that found no hospitalization or mortality rate reduction efficacy. Ravikirti *et al.*[**141**] is an inpatient study of 112 patients with oxygen saturation above 90% using a similar ivermectin monotherapy (12mg per day, not adjusted by weight, for 2 days) reported no deaths in the treatment group and a compelling mortality rate reduction signal which is not statistically significant (we calculated $p = 0.11$ using two-tailed exact Fisher test, but the authors incorrectly report statistical significance). In both cases, the treatment group received clearly insufficient ivermectin monotherapy for 2 days.

The remaining study, Gonzalez *et al.*[**142**], 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 (0.15mg/kg to 0.22mg/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 approximately equal mortality rate for both treatment and control groups. Although the ivermectin dosage is approximately similar to what was used in the Babalola case series [**36**], it did not include zinc, vitamin C, and vitamin D, and although some antibiotics were used for some patients, those do not appear to have included doxycycline, and they were not used across the board on all patients. Our analysis has not been able to claim a hospitalization

or mortality rate reduction benefit for the patients in the Babalola case series either, where there were 5 deterioration events, albeit no deaths [**36,88**]. The Gonzalez [**142**] cohort included a large proportion of patients, approximately half of the entire cohort, with oxygen saturation below 80%, for which the Stone/Gill protocol [**38**] recommends a far more aggressive treatment of an initial 0.6mg/kg stat dose of ivermectin, followed by regular dosing, continuous nanosilver nebulization, doxycycline 100mg bd for an initial 5 days, aspirin 300 mg, and IV steroids for all such patients, to be then followed with the treatment used for less severe hypoxemic patients. 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 in Gonzalez *et al.*[**142**], is most likely to be attributed to the substantial difference in the risk profile between the two cohorts. Gonzalez *et al.*[**142**] does suggest that a minimal 5-day low-dose ivermectin-based protocol that excludes 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 [**105**], where 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 3.7% efficacy threshold that compares favorably against the expected mortality rate for such high-risk patients, when they are not offered any early treatment. The ACTIV-6 [**127,128**] and Lopez-Medina *et al.*[**129**] trials 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 high-risk patients. The TOGETHER trial [**130**] 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.*[**8**], Hazan *et al.*[**34**], and Stone *et al.*[**35**]. Gonzalez *et al.*[**142**] suggests that even a 5-day low-dose ivermectin monotherapy with adjunct anticoagulation is insufficient, by itself, in terms of effecting mortality rate reduction, 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 mainly by the inclusion of doxycycline in the Hazan and Stone case series [**34,35**]. Mahmud *et al.*[**124**] and Hashim *et al.*[**125**] are the only randomized controlled trials of the ivermectin + doxycycline combination (albeit at lower dosages) with a mortality endpoint that have been identified by the Cochrane meta-analysis [**133**]. Both studies have shown positive signals of efficacy with respect to mortality rate reduction (Mahmud *et al.*[**124**] for early outpatient treatment and Hashim *et al.*[**125**] for inpatients) in spite of 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 is the most plausible reason 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 [**34,35,38**] on hypoxemic COVID-19 patients.

5. Conclusion

Our statistical analysis has shown that the existence of hospitalization rate reduction is clear and convincing when the Stone/Gill or Hazan multidrug protocol is employed on severely hypoxemic patients, and it is very resilient to systemic selection bias as well. The existence of a mortality rate reduction effect is shown by the preponderance of evidence by combining the Hazan and Stone case series, and the threshold to clear and convincing can be crossed only when combining all three case series together. These findings support the strength of association with reduction of hospitalizations and deaths. Combined with previous results establishing the Bradford Hill criteria of temporality, biological gradient, consistency, and biological plausibility, they lend support to the adoption of these ivermectin-based multidrug treatment protocols by practicing physicians for the treatment of hypoxemic COVID-19 patients as a community standard of care. We cannot make any inferences, specifically from our analysis, about whether this multidrug regimen can replace any other well-established antiviral early treatments in the outpatient setting, nor can we make any inferences about using the constituent medications individually as monotherapies. The totality of evidence indicates that variable dosing of ivermectin, depending on severity of initial presentation, is essential and the inclusion of doxycycline, zinc, vitamin C, vitamin D, and either nanosilver nebulizations or adjunct use of hydroxychloroquine and azithromycin provide important synergistic effects that are necessary for the successful treatment of hypoxemic 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 oxygen desaturation, rather than wait for SpO2 levels to

drop first and only then attempt to normalize them again. For this reason, these results indicate signals of benefit that are coherent with the integration of the multidrug regimen of ivermectin, doxycycline, zinc sulfate, Vitamin C, and D3 in the McCullough protocol, although not as an antiviral treatment, but rather as a preemptive protective protocol to maintain SpO2 levels in inpatients and outpatients, to be combined with at least one additional separate antiviral agent for patients in the pre-hospital setting, as well as corticosteroids and anticoagulants for high-risk patients that still deteriorate.

There may be more opportunities to analyze additional retrospective data on hypoxemic patients treated with the Stone/Gill protocol during the 2020-2021 period, from other doctors in Zimbabwe and/or South Africa, using the external controls and statistical methodology presented in this paper, if increased collaboration between academic scientists and practicing medical doctors is encouraged. Further retrospective analysis of larger data sets of case series from other physicians, that were also confronted with the need to treat hypoxemic patients with limited resources, could increase the strength of the evidence in support of mortality rate reduction by increasing its resilience against possible selection bias, and should be explored, if such additional data becomes available. A retrospective study of treatment protocols used during the pandemic period are still relevant to policy makers and medical boards, and these protocols may become urgently needed again, if a highly lethal strain of COVID-19 reemerges. Beyond COVID-19, there is now probable cause to attempt using the Hazan and Stone/Gill protocols on future novel coronaviruses, if they present with a similar propensity to attack the alveoli and to cause sudden oxygen desaturation via the formation of microemboli in the lung capillaries and alveoli.

Abbreviations

α7nAChr, alpha-7 nicotinic acetylcholine receptor; AgNP, silver nanoparticles; CDC, Center for Disease Control and Prevention; CFR, Case Fatality Rate; CD147/EMMPRIN, Cluster of differentiation 147 / extracellular matrix metalloproteinase inducer; DPP4/CD26, Dipeptidyl peptidase 4 / cluster of differentiation 26; IL-6, Interleukin 6; LMIC, Low or middle income country; MMP-9, matrix metalloproteinase-9; NF-κB, Nuclear factor kappa B; RDRP, RNA Dependent RNA Polymerase; PaO2, Partial pressure of oxygen; S1-NTD, S1-N-Terminal Domain; S1-RBD, S1 Receptor Binding Domain; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO2, Peripheral oxygen saturation; TNF-α, tumor necrosis factor alpha; WHO, World Health Organization.

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Data availability statement

The computer code and the details of the calculations of the efficacy thresholds and random selection bias thresholds are available in a supplementary document **[102]**. The January 20, 2023 snapshot of the CDC database used for our calculations is available by the corresponding author upon request. The current version of the database can be downloaded from the CDC website **[63]**. The computer code used to generate Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8 is also available in the supplementary document **[102]**. The unpublished Parirenyatwa document **[81]** and an archive copy of the Stone/Gill protocol **[38]** are available in our supplementary data document **[102]**.

Author contributions

Conceptualization, E.G. and P.Mc.; methodology, E.G.; formal analysis, E.G.; software, E.G.; investigation, E.G., P.Mc. and C.A.; visualization, E.G, P.Mc.; writing – original draft, E.G. and C.A; writing – review and editing, E.G., P.Mc., and C.A. All authors have read and agreed to the published version of the manuscript.

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ORCID

Eleftherios Gkioulekas 0000-0002-5437-2534
Peter A. McCullough 0000-0002-0997-6355
Colleen Aldous 0000-0002-7199-9160

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