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

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**Abstract: Aim:** This critical appraisal is focused on three published case series of 119 COVID-19 patients with hypoxemia who were successfully treated in the United States, Zimbabwe, and Nigeria with similar off-label ivermectin-based multidrug treatments that may include ivermectin, nebulized nanosilver, doxycycline, zinc, and vitamins C and D, resulting in rapid recovery of oxygen levels. **Methods:** We used a simplified self-controlled case series method to investigate the association between treatment and the existence of hospitalization rate reduction. External controls of hospitalized patients were compared against the subgroup of patients with baseline room air SpO2 $\leq$ 90% to investigate the association between treatment and the existence of mortality rate reduction. A narrative review was conducted to assess the Bradford Hill criteria for a causal association. **Results:** No deaths were reported in any of the three case series. One case series reported 5 hospitalization equivalent events (2 ventilations and 3 uses of supplemental oxygen). Combined, the three case series comprised 119 patients of which 61 patients presented with baseline room air SpO2 $\leq$ 90%. All appropriate external controls were lower-bounded by 12% case fatality rate for hospitalized patients. The existence of hospitalization rate reduction was statistically significant and resilient against both random and systemic selection bias for two out of three case series with the most aggressive treatments. The existence of mortality rate reduction was statistically significant when at least the two case series with the most aggressive treatments were combined. It is more likely than not that random selection bias alone cannot explain this reduction in mortality. **Conclusion:** The efficacy of the two most aggressive ivermectin-based multidrug treatment protocols is supported by the Bradford Hill criteria for 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, Coronavirus Disease 2019 (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, 768,187,096 confirmed cases of COVID-19 and 6,945,714 deaths have been reported to the WHO as of June 21 2023, amounting to an average Case Fatality Rate (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 innovated and discovered early outpatient multidrug treatments using several repurposed medications in combination [**3–15**].

In the United States, several independent efforts coalesced into the formulation of a sequenced multidrug protocol [**10, Fig. 3**] (hereafter, *McCullough protocol*), which is based on the pathophysiological understanding of COVID-19 as a triphasic illness with three overlapping phases: (1) viral proliferation; (2) hyperinflammatory cytokine storm (COVID-19 pneumonia); and (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 how the disease presents in 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. A recently published update of the McCullough protocol [**16, Fig. 3**] introduced some adjustments including virucidal nasal washes and oral gargles [**17–24**]. A large case series of 869 high-risk patients [**25, 26**], who 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 the reduction of mortality and hospitalizations, which 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 to prevent hospitalization is approximately within the first 3 days.

The present study is focused on previously proposed ivermectin-based multidrug protocols that can rescue patients with hypoxemia and result in the rapid recovery of peripheral oxygen saturation levels (SpO2), upon initiation of treatment [**29–33**]. Thus, the focus is on COVID-19 patients whose condition has deteriorated, due to lack of early treatment or due to insufficient response to some initial attempt at an early treatment. The available empirical evidence consists of case series that were reported by Hazan and colleagues [**30**], Stone and colleagues [**29**], and Babalola and colleagues [**31**]. Hazan's baseline protocol, used on United States COVID-19 patients, was a 10-day treatment with ivermectin, doxycycline, zinc, vitamin C, vitamin D [**30**], which was administered via telemedicine. The Stone/Gill multidrug protocol [**34, 35**], which was used in Zimbabwe patients reported on by Stone *et al.*[**29**], is a more aggressive 10-day multidrug protocol that consisted of nebulized nanosilver, ivermectin, doxycycline, zinc, vitamin C and D, with additional corticosteroids and anticoagulants added based on the bloodwork results. The Stone/Gill multidrug protocol [**34, 35**] 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 in 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. Babalola's protocol was less aggressive, with a baseline protocol consisting of a 5-day treatment of ivermectin, zinc, and Vitamin C, with some adjunct use of low-dose hydroxychloroquine and azithromycin on some patients.

Thairu *et al.*[**32**] compared the 61 patients from the Babalola case series with 26 additional patients who were treated with a non-ivermectin standard-of-care protocol (hereafter *Thairu case series*), of which 4 patients died. Babalola *et al.*[**33**] highlighted that SpO2 levels in the 61 patients in the Babalola case series recovered more rapidly than the 26 patients in the Thairu case series. Furthermore, according to Stone *et al.*[**29**], for the Hazan and Stone case series, where the most aggressive multidrug treatment protocols were used, a statistically significant normalization trend of SpO2 was observed within 24 hours, followed by a slower rate of recovery in 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.*[**36**], 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). Thus, a multidrug treatment regimen with both immunomodulating and anticoagulant mechanisms of action could rapidly restore the ability of the lungs to oxygenate, by addressing the pulmonary microemboli and restoring the oxygenation supply from both the distal bronchial and pulmonary arteries and from the alveoli [**40**]. 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.*[**49**], showing chest computed tomography with *"multiple, focal, possibly overperfused ground glass opacities"* [**49**], before further deterioration takes hold.

Scheim [**39**] recently explained that the formation of the pulmonary microemboli responsible for this presentation is caused by red blood cell clumping mediated by glycan bindings between the glycans on the SARS-CoV-2 viral spike protein and sialoglycoproteins on the surface of red blood cells. He also noted that the reason why common cold viruses do not cause a similar formation of microemboli is because, unlike the more virulent SARS, SARS-CoV-2, and MERS viruses, common cold viruses express hemagglutinin esterase, which releases these glycan bindings. This hypothesis is supported by an in vitro experiment by Boschi and colleagues [**38**], where they observed that adding viral spike protein from the Wuhan, Alpha, Delta, and Omicron variants to human blood induced red blood cell clumping. The experiment also showed in vitro that ivermectin blocks hemagglutination, if it is added before the spike protein, and reverses hemagglutination when it is added afterwards. Further indirect support for this hypothesis follows from the association between increased propensity for red blood cell aggregation and the risk factors for severe COVID-19 presentation in humans as well as the clinical susceptibility of mammalian species to COVID-19 [**40**]. Furthermore, in vivo animal studies showed that experimentally induced red blood cell clamping causes the same symptomatic presentation that was observed in humans with severe COVID-19 [**40**]. Hydroxychloroquine, ivermectin, fluvoxamine, and resveratrol have been identified as agents that may inhibit the aggregation of red blood

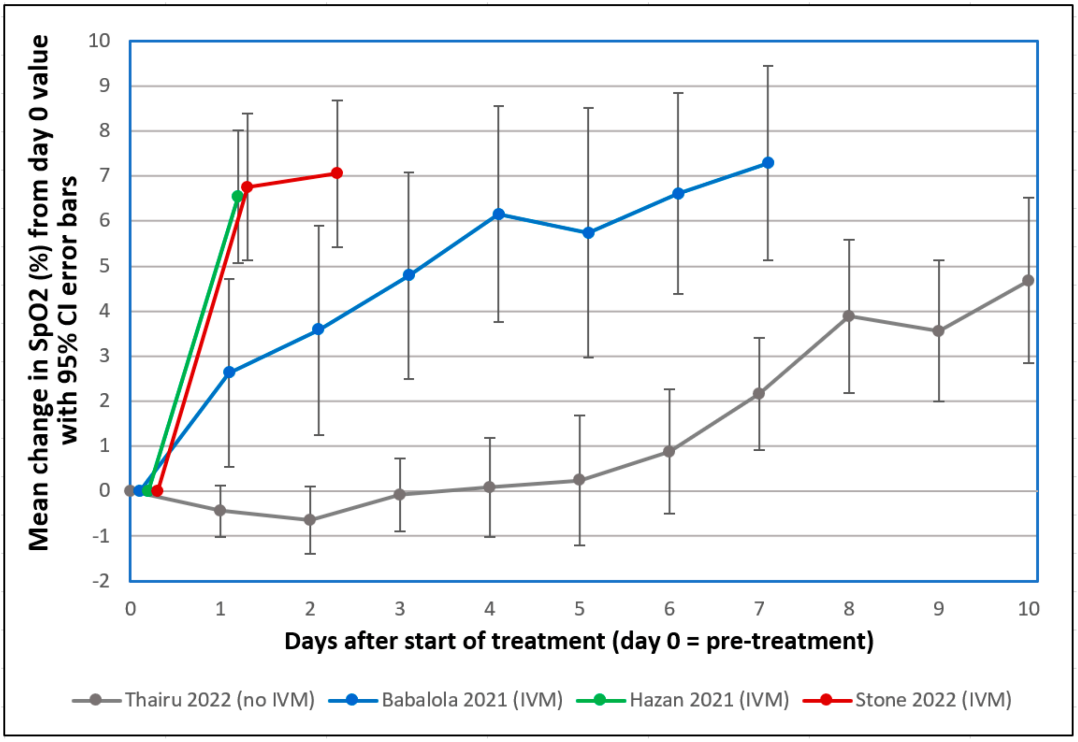


Figure 1: Mean change to room air SpO2 levels from initial value at Day 0 for the patients in the Hazan case series [**30**], the Stone case series [**29**], and the Babalola case series [**31**] with baseline room air SpO2 $\leq$ 93%, with error bars showing 95% confidence intervals. The most rapid increase is observed for the Hazan and Stone case series [**29, 30**]. Slower increase is observed in the Babalola case series [**31**]. 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.*[**32**]. Stone *et al.*[**29**] 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 [**31**] and the Thairu *et al.*[**32**] case series. The figure is reproduced from Stone *et al.*[**29, Fig. 6**] under the terms of the CC-BY-4.0 license.

cells [**40, 50**]. Conversely, red blood cell disaggregation is the most likely mechanism of action driving the rapid recovery of SpO2 in the patients treated with the Hazan and Stone/Gill Stone/Gill ivermectin-based multidrug protocols [**29, 30, 50**].

Stone observed that nanosilver nebulizations, which were pioneered in treating COVID-19 patients in her clinic, appeared to act synergistically with ivermectin towards rapidly restoring room air SpO2 in hypoxemic patients [**51**]. Zachar has proposed that, because of their negative zeta potential, silver nanoparticles, with size less than 10nm, are electrostatically attracted to the positively charged spike glycoproteins on SARS-COV-2 viral particles, which are separated from each other with distances ranging from 10 nm to 20 nm [**52**]. The spikes of free viral particles are disabled when being coated all around with silver nanoparticles. As ivermectin tends to release glycan bindings between viral particles and red blood cells, nanosilver particles may disable the freed viral particles and prevent them from reattaching themselves to red blood cells. Consequently, combining both mechanisms should further accelerate the red blood cell disaggregation. A small randomized case study showed that intravenous injections of nanosilver particles given to COVID-19 pneumonia patients did result in statistically significant mortality rate reduction [**53**], with no observed adverse events. Although the antiviral properties of nanosilver against a very broad range of viruses is well-known [**54**], it has not been widely adopted in proposed COVID-19 treatment protocols.

From an epidemiological perspective, a fundamental question that still has to be addressed is whether the Hazan and Stone/Gill protocols were successful in preventing hospitalizations and deaths. To that end, Hazan and colleagues [**30**] attempted to show a hospitalization and mortality rate reduction benefit by comparison with an external group derived from a public CDC case surveillance database [**55**]. However, their mortality

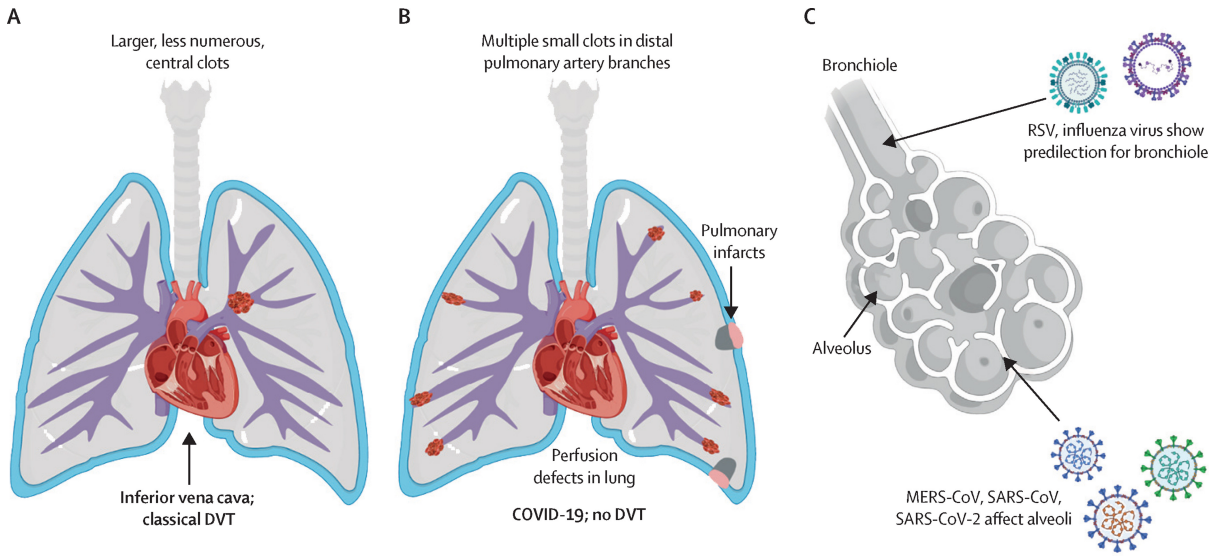


Figure 2: Classic pulmonary venous thromboembolism presents with a preponderance of a smaller number of proximal large emboli. McGonagle *et al.*[**36**] argues that the tendency of the SARS-CoV-2 virus to preferentially attack the alveoli, contrary to RSV and influenza viruses, triggers immunothrombosis, 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 [**37**], blocks hemagglutination [**38–43**], and inhibits viral nuclear entry [**44**] and replication [**45–48**] in the alveoli. Aspirin and anticoagulation can address the accumulated pulmonary microemboli. By resolving the congestion of the alveoli with SARS-CoV-2 viral particles, immunothrombotic production of new microemboli stops, supplemental home oxygen becomes effective and the patient can be kept out of the hospital, provided the work of breathing is tolerable and good support measures are in place. This figure has been reproduced from McGonagle *et al.*[**36, Fig. 1**] with permission from Elsevier.

rate reduction finding was borderline statistically significant with $p = 0.04$ and bias in the external control group could have been introduced by the handling of missing data in the CDC database [**55**]. Stone *et al.*[**30**] 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.*[**56**]. A comparison of the Babalola case series against the Thairu case series suggests a statistically significant reduction in mortality rate with the ivermectin-based protocol [**32**]; 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 primary objective of this study is to identify appropriate historical/external control groups for the case fatality rate (CFR) of hospitalized patients in the United States, Zimbabwe, and Nigeria and compare them against the Hazan, Stone, and Babalola case series in order to establish the existence of some mortality rate reduction benefit. We used a risk-stratification scheme to make the case series comparable to the CFR of hospitalized patients and we also considered comparisons between the combined case series and the external controls in order to increase the statistical power. The external controls were sourced from the research literature [**57–63**], however, we also conducted a detailed independent analysis of the CDC database [**55**] to construct an appropriate external control for the United States patients. To investigate the existence of some hospitalization rate reduction efficacy, we used a self-controlled approach, which we think is self-evident, but was not explicitly attempted previously [**29–33**]. Both comparisons are susceptible to bias towards the null hypothesis, so they cannot be used to obtain unbiased effect sizes. On the other hand, the decision on whether these protocols should be used is binary, and a positive finding that can overcome the expected bias towards the null hypothesis is positive evidence in favor of these protocols.

A secondary objective of this study is to embed the quantitative argument of our primary objective within a broader causality inference argument, based on the Bradford Hill criteria [**64**]. Our quantitative argument establishes the strength of association criterion between the Hazan and Stone/Gill multidrug protocols and reduction in hospitalization rate and mortality rate amongst the treated patients, which was not previously

done in a uniform or convincing way. We will argue, via a narrative review, that prior research establishes the additional Bradford Hill criteria of temporality, consistency, biological plausibility, and coherence. In doing so, we have taken heed of the proposed refinements of the Bradford Hill criteria by Howick and colleagues [**65**]. Combined with showing that the strength of association criterion is satisfied, there are sufficient grounds for a causality inference, with the caveat that, as noted by Ward [**66**], the inference is not a deductive or inductive inference, but an *"inference to the best explanation"* [**67**].

## 2. Materials and Methods

### 2.1. Description of case series

The Hazan case series consisted of 26 patients who were treated in the United States, via telemedicine, between August 2020 and February 2021 by Hazan and colleagues [**30**]. 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 excluded 2 patients that died because they did not consent to treatment (patients 10 and 26 in Ref. [**30, Table 1**]). One of the two excluded patients received only an initial dose of 36mg ivermectin, with reported room air SpO2 increase from baseline 73% to 87% within 24 hours, but declined further treatment (patient 10 in Ref. [**30, Table 1**]). The remaining 24 patients consented to treatment, of which 23 patients presented with baseline room air SpO2 $\leq$ 90%. Of the 23 patients, 20 patients had age $\geq$ 50 years, 11 patients had age $\geq$ 65 years, the youngest patients had age 43, 46, and 47, and the oldest patients had age 87, 92, and 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, or 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 years also had baseline SpO2 below 90%. The treatment period overlapped with the first and second pre-delta periods, following the epidemic wave breakdown by Adjei *et al.*[**58**].

The Stone case series consisted of 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 [**29**]. 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. Of the 34 patients, 23 patients had age $\geq$ 50 years, 8 patients had age $\geq$ 65 years, the youngest patients had age 25, 32, and 35, and the oldest patients had age 75, 80, and $\geq$ 90. Baseline room air SpO2 ranged from 66% to 93%, with 28 of 34 patients presenting with baseline room air SpO2 $\leq$ 90%. We also note that 9 out of 11 patients with age $<$ 50 years 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 [**68**]. 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 [**69**].

The Babalola case series consisted of 61 patients who were treated in Nigeria with ivermectin-based multidrug protocols, of which 21 patients presented with hypoxemia and baseline room air SpO2 $\leq$ 93%, and 10 of the 21 patients presented with baseline room air SpO2 $\leq$ 90% [**31,70**]. Of the 21 hypoxemic patients, 5 patients had age $\geq$ 50 years, 2 patients had age $\geq$ 65 years, the youngest patients had age 19, 21, and 23, and the oldest patients had age 60, 68, and 89 [**70**]. Patients were treated in the Abuja Federal Capital Territory between April 2021 and June 2021. As shown in Ref. [**32, Fig. 1**], the treatment period corresponds to the interregnum between the second wave (Beta variant) and the third wave (Delta variant) in Nigeria.

### 2.2. Treatment protocols

Table 1 summarizes the details of the treatment protocols used in the Hazan, Stone, and Babalola case series. The details of the treatment protocols used in the Hazan and Babalola case series are given in the respective publications [**30,31**]. The details of the Stone/Gill protocol were reported in detail in an online document [**34**], and briefly summarized by Stone *et al.*[**29**]. An updated version of the online document was provided to us by Stone and archived on Figshare [**35**].

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) [**30**]. The ivermectin dosage was spread out to allow an approximately constant level of the medication in the plasma. Two patients who presented with very low baseline room air 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 which were tested in her laboratory for consistency and quality [**71**]. 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 [**71**]. Finally, 7 out of 24 patients received additional medications prior to 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 to eradicate the virus, and in those cases it was also necessary to add hydroxychloroquine and azithromycin [**71**].

The baseline multidrug treatment protocol used in the Stone case series combined nebulized nanosilver, ivermectin, doxycycline, zinc, vitamin C, and vitamin D. Stone treated her patients in an urgent care setting, which allowed the treatment to be customized to the needs of the individual patient. As shown on Table 1, patients were initially treated and assessed by trained nurses. Most patients were then treated using either a baseline protocol for mild disease or the more aggressive baseline protocol for severe disease, based on symptomatic presentation and results from bloodwork. The baseline protocol for severe disease mirrored the one for mild disease but intensified the use of ivermectin, based on the safety data from Guzzo *et al.*[**72**], and increased nanosilver nebulizations when oxygen saturation fell below 90%. Although doxycycline, zinc, vitamins C and D were consistently given for 10 days in the baseline protocols for both mild and severe disease, ivermectin and nanosilver nebulizations were generally continued up to 48 hours after the resolution of symptoms. Depending on bloodwork results, prednisone, enoxaparin, xarelto, ceftriaxone were added to the respective baseline protocols when needed for some patients. For patients with very poor prognosis (typically with baseline room air SpO2 $\leq$ 80%), a salvage protocol was attempted to prevent hospitalization, as shown on Table 1. Although Stone and colleagues did not use hydroxychloroquine in this particular case series, the adoption of nebulized nanosilver was intended to also function as a fast-acting antiviral that could eradicate viral multiplication in the lungs, analogously to Hazan's adjunct use of hydroxychloroquine and azithromycin in her highest-risk patients [**71**].

For the Babalola case series, the treatment protocol consisted of ivermectin 0.2 mg/kg daily for 5 days in addition to zinc sulfate (50-100 mg daily for 7 days) and vitamin C (1000 mg daily for 7 days) [**31–33**]. However, 31 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 manifested evidence of respiratory distress [**70**]. Due to the treatment provided, supplemental oxygen was not necessary for most patients.

In all three case series, all patients survived, however, in the Babalola case series, 2 of the 61 hypoxemic patients had to use a ventilator and 3 additional patients needed supplemental oxygen, despite the provided treatment [**32**].

### 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 [**73**] to establish the existence of a hospitalization rate reduction benefit, as follows: Each case series can be defined as a treatment group in which the factual use of supplemental oxygen or ventilator, in spite of the attempted treatment, are counted as hospitalization events. Each case series can also be viewed as a control in which the number of patients with baseline room air SpO2 $\leq$ 90% are counted as counterfactual hospitalizations that would have taken place if standard guidelines had been followed instead. This enables a comparison between the multidrug treatment interventions and the standard protocols. This

Table 1: Treatment protocols used for the patients in the Hazan case series [**30**], Stone case series [**29**], and Babalola case series [**31**]

| **Protocol** | **Treatment** |
|---|---|
| Hazan *et al.*[**30**] | ► *Baseline protocol:* 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).<br>► *Additional medications:* Two patients who presented with baseline room air SpO2 at 72% and 73% received 36 mg of ivermectin on day 1. |
| Stone *et al.*[**29**] [a] | ► *Initial treatment by trained nurses:* Administered, if baseline room air SpO2 $>$ 80%, not tachypneic, tachycardic, or confused (otherwise the *salvage protocol* is used). Initial administration of nanosilver nebulization 5-8 ml. Patient was then canulated. During canulation: **(a)** Draw blood for bloodwork; **(b)** administer ivermectin at minimum dose 0.2mg/kg (increased to 0.6mg/kg during Delta); **(c)** If patient is hypoxic, febrile, or systemically unwell: IV ceftriaxone 1g and either dexamethasone 8 mg stat or hydrocortisone 100-200 mg stat, as clinically indicated; **(d)** diabetes management, if needed.<br>► *Doctor administered individualized treatment:* If patient presented with mild disease and was covid positive on PCR or antigen test, then *baseline protocol for mild disease* was used. Clinical diagnosis based on symptoms: hypoxia, raised LDH, low lymphocytes, raised monocytes, raised D dimer, suggestive radiology. *Baseline protocol for severe disease* or *salvage protocol* are used, if needed.<br>► *Baseline protocol for mild disease:* ivermectin at 0.1-0.2 mg/kg on day 1, day 4, day 8; nanosilver nebulizations 5-8ml three times daily for 5-7 days; doxycycline 100 mg twice a day for 10 days, zinc 60mg per day for 10 days; vitamin C 1g three times daily and vitamin D 5000-10000 IU daily for 10 days. Ivermectin dose increased to 12 mg once a day for 5-7 days in December 2020 and later to 0.4-0.6 mg/kg for 5-7 days by July 2021, and was given for up to 48 hours after resolution of symptoms.<br>► *Baseline protocol for severe disease:* ivermectin 0.2mg to 0.3mg/kg daily for 5 days, during the Beta wave and 0.4-0.6 mg/kg during the delta wave for 10 days; silver nebulizations 5-8ml at least three times per day and continuously as needed when room air SpO2 $\leq$ 90%; Doxycycline 100mg twice daily for 10 days; zinc 20mg twice daily for 10 days; vitamin C 1g three times daily and vitamin D 5000-10000 IU daily for 10 days.<br>► *Criteria for baseline protocol for severe disease*: If any of the following were present: **(a)** the Lymphocyte to LDH ratio was over 210; **(b)** the D-Dimer was raised; **(c)** the CRP was raised; **(d)** the patient was in stage 3 (thrombosis) of the disease as per McCullough's definitions [**10**].<br>► *Additional medications:* **(a)** If patient is hypoxic and CRP$>$ 20, then prednisone 40mg-60mg daily is added. **(b)** If D-Dimer is raised, subcutaneous Enoxaparin at 80mg-100mg is administered followed by Rivaroxaban/Xarelto at 20mg daily for 30 days. **(c)** If neutrophils are raised and the patient is canulated, ceftriaxone at 1g daily is given until oral treatment is considered adequate. Oral treatment replaces ceftriaxone with either doxycycline 100 mg twice a day for 10 days or azithromycin 500 mg twice a day and then 500 mg once a day for 5 days. Both are used, when coinfection with mycoplasma cannot be excluded.<br>► *Salvage protocol:* If initial assessment indicates poor prognosis and likely need for hospital referral, the following protocol is attempted: **(a)** ivermectin 0.6mg/kg stat dose, may titrate to effect up to 1-2mg/kg if SpO2 does not increase, maintain at 0.3-0.6 mg/kg for up to 10 days until symptom free for 48 hours. **(b)** continuous nanosilver nebulizations, until room air SpO2 $\geq$ 90%, then reduce to three nebulizations per day. **(c)** doxycycline 200 mg stat, then 100 mg for a minimum of 5 days (increased to 10 days during Delta) OR IV ceftriaxone 1-2 gr daily if unable to take oral meds. **(d)** zinc sulfate 20-40 mg three times daily orally. **(e)** aspirin 300 mg daily. **(f)** prednisone 1mg/kg or dexamethasone 8mg IV stat, followed by prednisolone 40-80mg once daily, if CRP $>$ 20 or room air SpO2 $\leq$ 80%. **(g)** enoxaparin 80mg subcutaneously once daily transitioning to rivaroxaban 20 mg once daily if the D Dimer is raised for at least 30 days or longer if D Dimer has not come down. **(h)** Midazolam (only if confused and pulling out lines or pulling off oxygen). If the patient responds to treatment, regular protocol follows. If the patient does not respond to treatment, referral to hospital is arranged, or palliative support is provided at home, if hospital beds not available, as a last resort.<br>► *Criteria for using the salvage protocol:* At least one of the following: **(a)** Patient is not ambulant; **(b)** Tachypneic with rate over 22 per minute or slow respiratory rate from exhaustion; **(c)** Confusion or decreased/loss of consciousness; **(d)** Symptomatic for longer than 10 days and elevated pulse rate and/or above-mentioned symptoms. Patients that satisfied the above criteria were often significantly hypoxic with baseline room air SpO2 $\leq$ 80%. |
| Babalola *et al.*[**31**] | ► *Baseline protocol:* ivermectin 0.2 mg/kg daily for 5 days, zinc sulfate (50-100 mg daily for 7 days), vitamin C (1000 mg daily for 7 days)<br>► *Additional medications:* hydroxychloroquine 200 mg per day for 3 days and azithromycin 500 mg per day for 3 days (given to 31 of 61 patients). |

[a] Some of the phrasing has been either copied to or summarized from an updated treatment protocol document provided to us by Stone [**35, 51**].

design is a simplification of the self-controlled case series method because 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 multiplicity of events distributed over a time period.

Although hospitalization is a highly subjective endpoint, with possible regional variability in the criteria used to decide whether a patient should be admitted as an inpatient [**74**], using the baseline room air threshold SpO2 $\leq$ 90% as a sufficient condition for counterfactual hospitalization events is nevertheless consistent with an early finding [**75**] that the 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 National Institute of Health (NIH) COVID-19 treatment guidelines [**76**] recommending that oxygen supplementation target an SpO2 level between 92% and 96%, as well as guidelines from medical centers recommending that hospitalization should be considered when room air SpO2 falls below 94% [**77**] or 92% [**78**]. Furthermore, studies from Serbia [**79**] and Peru [**80**] showed a substantial increase in the mortality rate of hospitalized patients as the baseline room air SpO2, at the time of hospital admission, decreased from 90% to 80%. This provides an objective rationale for using the baseline room air SpO2 $\leq$ 90% threshold as a sufficient condition for hospitalization, in the context of standard guidelines that preclude a pre-hospital intervention.

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's counterfactual 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. Nevertheless, a positive finding that overcomes this bias is sufficient for establishing the existence of some hospitalization rate reduction efficacy.

### 2.5. External controls for establishing mortality rate reduction

To establish the existence of a mortality rate reduction benefit, we risk-stratified the three case series under the constraint of baseline room air SpO2 $\leq$ 90% and compared the observed mortality rate in the risk stratified case series against the CFR of hospitalized patients in appropriate external control groups. We relied on several external control groups in the United States [**55,58**], Zimbabwe [**59,60**], Nigeria [**61,62**], South Africa [**57**], and globally [**63**] to determine a reasonable lower-bound estimate for the mortality rate of hypoxemic patients without the use of any of the proposed ivermectin-based multidrug treatment protocols. The rationale for this comparison is a consequence of the underlying premise that if standard guidelines had been followed instead, then all patients with baseline room air SpO2 $\leq$ 90% would have been referred to the hospital, where they would have been confronted with an averaged CFR greater than or equal to the average CFR of hospitalized patients.

This comparison has a bias towards the null hypothesis, because in the external controls, the CFR for hospitalized patients includes both patients with and without hypoxemia. Indeed, Poskurica *et al.*[**79**] showed that among the patients hospitalized in Serbia the average room air baseline oxygen level upon admission was 89% (with 7% IQR), indicating that some of the admitted patients came in with room or oxygen above 90%. Consequently, a negative result obtained by this comparison will be inconclusive, however, a positive result will establish the existence of some benefit. The particular choice of risk stratification can be employed because no deaths were observed among the patients excluded by the risk stratification.

For all external controls, except for the CDC case surveillance public database [**55**], we simply gathered and organized the CFRs for hospitalized patients, as reported in the respective publications. We independently analyzed the CDC case surveillance public database [**55**] in this study, using different methodology than that of Hazan *et al.*[**30**], as follows: 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 laboratory-confirmed, whether certain unspecified comorbidities exist, and whether the final outcome was hospitalization, ICU admission, or death. We filtered the database for all cases that were symptomatic, lab confirmed, resulting in hospitalization, and with known month/year. Contrary to Hazan *et al.*[**30**], we did not filter for comorbidities. However, we did calculate the hospitalized CFR of hospitalized patients both with and without the age $\geq$ 50 years restriction because it 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 [**81**]. The 4C mortality score was rated as one of the top two predictive models for in-hospital mortality probability in terms of accuracy and a low risk of bias in a systematic review of several predictive models [**82**]. After filtering, we

counted the number of cases in which it was known that the patient survived and the number of cases in which it was known that the patient died. Because of the substantial number of cases in which the mortality endpoint is unknown or unavailable, we conservatively estimated a range for the CFR of hospitalized patients as follows: (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 within cases where the mortality status is known. This approach assumes that deaths are less likely to be unreported than survivals.

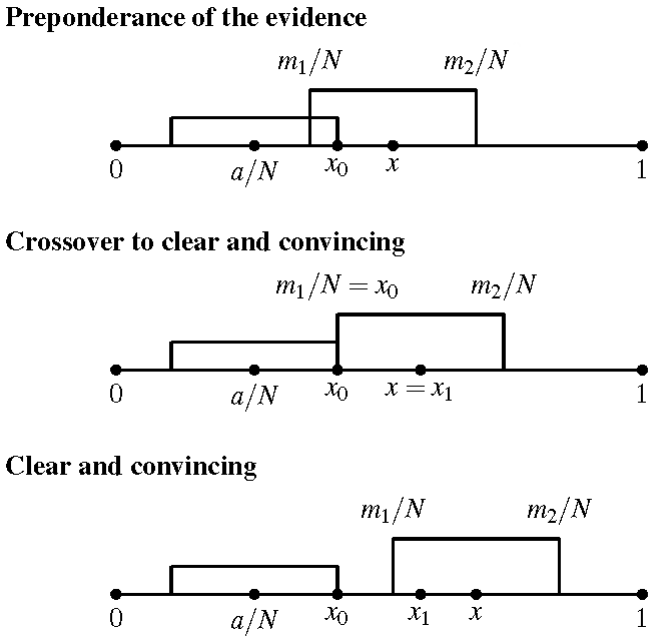


Figure 3: Comparison of a case series $(N, a)$ of $N$ treated patients, with $a$ patients having an adverse outcome, against the population level probability $x$ of an adverse outcome without treatment. The figure shows the relative position of the confidence interval for the probability of an adverse outcome with treatment (with upper endpoint $x_0$) and the confidence interval $[m_1/N, m_2/N]$ 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 [**55,58–63,83**] were used to establish the existence of mortality rate reduction and a simplified self-controlled case series methodology [**73**] was used to establish the existence of hospitalization rate reduction. For the corresponding comparisons of the case series by Hazan [**30**], Stone [**29**], and Babalola [**31–33**] against the corresponding controls, as a preliminary step, we used the two-sided exact Fisher test to calculate the $p$-value. The threshold $p < 0.05$ was used for statistical significance. We calculated the corresponding odd ratios and odd ratio confidence intervals, with 95% confidence. To increase the statistical power, we 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. For the purpose of sensitivity analysis, we also analyzed the combined Hazan + Babalola and Stone + Babalola case series.

Because case series are susceptible to selection bias, establishing statistical significance using the exact

Fisher test is necessary but not sufficient. To better ascertain the potential impact of selection bias, we further analyzed the case series using a recently introduced case series threshold analysis statistical technique [**27**], which is based on the Sterne interval solution [**84**] of the binomial proportion confidence interval problem and the Bayes factor [**85–89**]. 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 was 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 schematically display 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 [**84**] 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 $p_0 = 0.05$ as the threshold for statistical significance for all calculations). The *random selection bias threshold* $x_1(N, x_0, p_0)$ is the minimum value of $x$ at which the two intervals do not intersect. Before calculating the random selection bias threshold $x_1$, we used a Bayesian technique to adjust the efficacy threshold $x_0$ in the upwards direction to $y_o \geq x_0$, if necessary. We say that the comparison shows the existence of efficacy by the *preponderance of evidence* when $x$ is above the treatment interval, that is when $x \geq y_0$. 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, that is 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 required to reproduce the threshold calculations reported in this paper is available on Figshare [**35**]. All relevant mathematical details on the case series threshold analysis method are provided in the original paper [**27**]. A concise description of the calculation of the unadjusted efficacy threshold $x_0$, the adjusted efficacy threshold $y_0$, 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 $H_1 : x_0 < q \leq 1$, where $q$ is 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 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 simply choose $y_0 = x_0$. Otherwise, we adjust the efficacy of threshold $x_0$ upwards to the adjusted efficacy threshold $y_0 \geq x_0$ to ensure that both $p(N, a, y_0) \leq p_0$ and $\log_{10} B(N, a, y_0, p_2) \geq 2$ are satisfied. Finally, the adjusted efficacy threshold $y_0$ is used to calculate the random selection bias threshold $x_1(N, y_0, p_0)$. Ref. [**27**] showed that an upper bound to the random selection bias threshold $x_1(N, y_0, p_0)$ can be obtained by calculating the unadjusted efficacy threshold with $1 - p_0$ confidence for a hypothetical case series $(N, \lceil y_0 N \rceil)$, where $\lceil y_0 N \rceil$ is defined as the product $y_0 N$ rounded upwards towards the nearest integer. We used this upper bound as a conservative proxy for the random selection bias threshold in the calculations reported in this study. If additional information is available that the probability $x$ of an adverse event without treatment satisfies a lower bound $x > p_1$ with $p_1 > x_1(N, y_0, p_0)$,

then we can calculate the *selection bias tolerance* $F = [p_1(1-x_1)]/[x_1(1-p_1)]$ which measures the magnitude of systemic selection bias needed to overturn a clear and convincing finding 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. those that would have done well without treatment) than it would have been, if the selection was truly random. The interpretation of $F$, is that any systemic selection bias must have magnitude $f$ with $f > F$ to downgrade a clear and convincing finding into a preponderance of evidence finding.

### 2.7. Software

The efficacy threshold and random selection bias threshold for the respective case series were calculated using the computer algebra program Maxima 5.46.0 [**90**]. Our independent analysis of the CDC database [**55**] as well as the preparation of the tables reporting on the external controls were conducted using R 4.1.3 [**91**], in conjunction with the dplyr and magritt packages. For our calculations, we used the January 20, 2023 snapshot of the CDC database [**55**]. The exact Fisher test calculations were also conducted using R 4.1.3 [**91**], in conjunction with the stats package. The computer code used for all calculations is available on Figshare [**35**].

Table 2: Demographic characteristics of the Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31**] case series

| | **Hazan** | | **Stone** | | **Babalola** | | **H+B** | | **S+B** | | **H+S** | | **H+S+B** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Sex** | | | | | | | | | | | | | | |
| Male | 14 | 58.3 | 20 | 58.8 | 39 | 63.9 | 53 | 62.4 | 59 | 62.1 | 34 | 58.6 | 73 | 61.3 |
| Female | 10 | 41.7 | 14 | 41.2 | 22 | 36.1 | 32 | 37.6 | 36 | 37.9 | 24 | 41.4 | 46 | 38.7 |
| **Age brackets** | | | | | | | | | | | | | | |
| 21 to 30 years | 0 | 0.0 | 1 | 2.9 | 12 | 19.7 | 12 | 14.1 | 13 | 13.7 | 1 | 1.7 | 13 | 10.9 |
| 31 to 40 years | 0 | 0.0 | 5 | 14.7 | 19 | 31.1 | 19 | 22.4 | 24 | 25.3 | 5 | 8.6 | 24 | 20.2 |
| 41 to 50 years | 4 | 16.7 | 7 | 20.6 | 10 | 16.4 | 14 | 16.5 | 17 | 17.9 | 11 | 19 | 21 | 17.6 |
| 51 to 60 years | 4 | 16.7 | 9 | 26.5 | 7 | 11.5 | 11 | 12.9 | 16 | 16.8 | 13 | 22.4 | 20 | 16.8 |
| 61 to 70 years | 10 | 41.7 | 8 | 23.5 | 8 | 13.1 | 18 | 21.2 | 16 | 16.8 | 18 | 31 | 26 | 21.8 |
| 71 to 80 years | 2 | 8.3 | 3 | 8.8 | 0 | 0.0 | 2 | 2.4 | 3 | 3.2 | 5 | 8.6 | 5 | 4.2 |
| 81 to 90 years | 2 | 8.3 | 1 | 2.9 | 1 | 1.6 | 3 | 3.5 | 2 | 2.1 | 3 | 5.2 | 4 | 3.4 |
| 91 years or older | 2 | 8.3 | 0 | 0.0 | 0 | 0.0 | 2 | 2.4 | 0 | 0.0 | 2 | 3.4 | 2 | 1.7 |
| **Baseline SpO2 at room air** | | | | | | | | | | | | | | |
| $93\% < \text{SpO2} \leq 100\%$ | 1 | 4.2 | 0 | 0.0 | 39 | 63.9 | 40 | 47.1 | 39 | 41.1 | 1 | 1.7 | 40 | 33.6 |
| $90\% < \text{SpO2} \leq 93\%$ | 0 | 0.0 | 6 | 17.6 | 11 | 18 | 11 | 12.9 | 17 | 17.9 | 6 | 10.3 | 17 | 14.3 |
| $85\% < \text{SpO2} \leq 90\%$ | 19 | 79.2 | 16 | 47.1 | 7 | 11.5 | 26 | 30.6 | 23 | 24.2 | 35 | 60.3 | 42 | 35.3 |
| $80\% < \text{SpO2} \leq 85\%$ | 2 | 8.3 | 7 | 20.6 | 0 | 0.0 | 2 | 2.4 | 7 | 7.4 | 9 | 15.5 | 9 | 7.6 |
| $75\% < \text{SpO2} \leq 80\%$ | 1 | 4.2 | 4 | 11.8 | 3 | 4.9 | 4 | 4.7 | 7 | 7.4 | 5 | 8.6 | 8 | 6.7 |
| $70\% < \text{SpO2} \leq 75\%$ | 1 | 4.2 | 0 | 0.0 | 0 | 0.0 | 1 | 1.2 | 0 | 0.0 | 1 | 1.7 | 1 | 0.8 |
| $65\% < \text{SpO2} \leq 70\%$ | 0 | 0.0 | 1 | 2.9 | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 1 | 1.7 | 1 | 0.8 |
| Missing SpO2 | 0 | 0.0 | 0 | 0.0 | 1 | 1.6 | 1 | 1.2 | 1 | 1.1 | 0 | 0.0 | 1 | 0.8 |

**Hazan** = the Hazan case series by Hazan *et al.*[**30**]; **Stone** = the Stone case series by Stone *et al.*[**29**]; **Babalola** = the Babalola case series by Babalola *et al.*[**31**]; **H+B** = the combined Hazan + Babalola case series; **S+B** = the combined Stone + Babalola case series; **H+S** = the combined Hazan + Stone case series; **H+S+B** = the combined Hazan + Stone + Babalola case series.

## 3. Results

### 3.1. Description of the case series

Table 2 shows the distribution of the demographic characteristics of the Hazan, Stone, and Babalola case series in terms of gender, age brackets and baseline SpO2 at room air. The demographic characteristics for

Table 3: Demographic characteristics of the Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31**] case series, after risk stratification for baseline room air SpO2 $\leq$ 90%

| | **Hazan** | | **Stone** | | **Babalola** | | **H+B** | | **S+B** | | **H+S** | | **H+S+B** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Sex** | | | | | | | | | | | | | | |
| Male | 14 | 60.9 | 16 | 57.1 | 6 | 60 | 20 | 60.6 | 22 | 57.9 | 30 | 58.8 | 36 | 59 |
| Female | 9 | 39.1 | 12 | 42.9 | 4 | 40 | 13 | 39.4 | 16 | 42.1 | 21 | 41.2 | 25 | 41 |
| **Age brackets** | | | | | | | | | | | | | | |
| 21 to 30 years | 0 | 0.0 | 1 | 3.6 | 2 | 20 | 2 | 6.1 | 3 | 7.9 | 1 | 2 | 3 | 4.9 |
| 31 to 40 years | 0 | 0.0 | 3 | 10.7 | 4 | 40 | 4 | 12.1 | 7 | 18.4 | 3 | 5.9 | 7 | 11.5 |
| 41 to 50 years | 4 | 17.4 | 6 | 21.4 | 1 | 10 | 5 | 15.2 | 7 | 18.4 | 10 | 19.6 | 11 | 18 |
| 51 to 60 years | 4 | 17.4 | 8 | 28.6 | 1 | 10 | 5 | 15.2 | 9 | 23.7 | 12 | 23.5 | 13 | 21.3 |
| 61 to 70 years | 9 | 39.1 | 6 | 21.4 | 1 | 10 | 10 | 30.3 | 7 | 18.4 | 15 | 29.4 | 16 | 26.2 |
| 71 to 80 years | 2 | 8.7 | 3 | 10.7 | 0 | 0.0 | 2 | 6.1 | 3 | 7.9 | 5 | 9.8 | 5 | 8.2 |
| 81 to 90 years | 2 | 8.7 | 1 | 3.6 | 0 | 0.0 | 2 | 6.1 | 1 | 2.6 | 3 | 5.9 | 3 | 4.9 |
| 91 years or older | 2 | 8.7 | 0 | 0.0 | 0 | 0.0 | 2 | 6.1 | 0 | 0.0 | 2 | 3.9 | 2 | 3.3 |
| **Baseline SpO2 at room air** | | | | | | | | | | | | | | |
| 85% $<$ SpO2 $\leq$ 90% | 19 | 82.6 | 16 | 57.1 | 7 | 70 | 26 | 78.8 | 23 | 60.5 | 35 | 68.6 | 42 | 68.9 |
| 80% $<$ SpO2 $\leq$ 85% | 2 | 8.7 | 7 | 25 | 0 | 0.0 | 2 | 6.1 | 7 | 18.4 | 9 | 17.6 | 9 | 14.8 |
| 75% $<$ SpO2 $\leq$ 80% | 1 | 4.3 | 4 | 14.3 | 3 | 30 | 4 | 12.1 | 7 | 18.4 | 5 | 9.8 | 8 | 13.1 |
| 70% $<$ SpO2 $\leq$ 75% | 1 | 4.3 | 0 | 0.0 | 0 | 0.0 | 1 | 3 | 0 | 0.0 | 1 | 2 | 1 | 1.6 |
| 65% $<$ SpO2 $\leq$ 70% | 0 | 0.0 | 1 | 3.6 | 0 | 0.0 | 0 | 0.0 | 1 | 2.6 | 1 | 2 | 1 | 1.6 |

**Hazan** = the Hazan case series by Hazan *et al.*[**30**]; **Stone** = the Stone case series by Stone *et al.*[**29**]; **Babalola** = the Babalola case series by Babalola *et al.*[**31**]; **H+B** = the combined Hazan + Babalola case series; **S+B** = the combined Stone + Babalola case series; **H+S** = the combined Hazan + Stone case series; **H+S+B** = the combined Hazan + Stone + Babalola case series.

the combined case series Hazan + Stone, Hazan + Babalola, Stone + Babalola, and Hazan + Stone + Babalola are also shown. Table 3 shows the same demographic characteristics for the risk stratified case series under the restriction of baseline room air SpO2 $\leq$ 90%. To apply this restriction, we excluded one patient from the Babalola case series for whom the baseline room air SpO2 was not available.

Males appear to be more prevalent than females in all three case series by factors of 1.41 (Hazan case series), 1.42 (Stone case series), and 1.77 (Babalola case series), as shown on Table 2. After introducing risk stratification with baseline room air SpO2 $\leq$ 90% we observed on Table 3 a minimal perturbation of these factors to 1.55 (Hazan case series), 1.33 (Stone case series), 1.5 (Babalola case series).

The Hazan and Stone case series showed similar patient distributions by age brackets. With the high-risk age brackets corresponding to patients older than 40 years, we observed that with both the Hazan and Stone case series, under risk stratification with the constraint of baseline room air SpO2 $\leq$ 90%, the corresponding age bracket percentages were perturbed by no more than 2%. For the lower risk age brackets of patients younger than 40 years, we observed that the Hazan case series had no patients with baseline room air SpO2 $\leq$ 90%, however, the Stone case series had 4 patients (14.3%) with baseline room air SpO2 $\leq$ 90%. The Babalola case series had a higher prevalence of younger patients compared to the Hazan and Stone case series. After risk stratification with baseline room air SpO2 $\leq$ 90%, there was still a higher prevalence of younger patients in the Babalola case series (6 patients younger than 40 years and 4 patients older than 40 years). The increased prevalence of younger patients in the risk-stratified Stone and Babalola case series could be attributed to lower socioeconomic status of the African patients, relative to the United States patients treated in the Hazan case series. Qualitatively, we observed that risk stratification did not change the shape of the patient distribution across age brackets.

In terms of baseline room air SpO2, the majority of patients in both the Hazan and Stone case series were concentrated in the 85% to 90% bracket. The majority of patients in the Babalola case series were in the 93% to 100% bracket, but they are also concentrated in the 85% to 90% bracket after risk-stratification. A comparison of the Hazan case series against the Stone and Babalola case series shows that in both the Stone and Babalola case

series there was a higher prevalence of patients in the 80% to 85% bracket and the 75% to 80% bracket. This can be quantified by observing that in the risk stratified case series, shown on Table 3, 82.6% of the patients in the Hazan case series were in the 85% to 90% bracket, whereas 60.5% of the patients in the combined Stone + Babalola case series were in the same bracket. This indicates that a qualitative comparison of the subgroup of patients with severe hypoxemia across the three case series shows that the African patients, on average, presented with more severe illness than the American patients.

Table 4: Case series of hypoxemic patients by Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31**], and case series combinations.

| | **Patients with baseline SpO2** | | | | | |
|---|---|---|---|---|---|---|
| **Case series** | $\leq 100\%$ | $\leq 93\%$ | $\leq 90\%$ ($p_1$) | **Deaths** | **Deterioration** | **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 + Babalola | 85 | 44 | 33 (38.8%) | 0 | 5 | 2020-08 to 2021-06 |
| Stone + Babalola | 95 | 55 | 38 (40.0%) | 0 | 5 | 2020-08 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 |

SpO2 = baseline room air peripheral oxygen saturation; deterioration = number of events where use of supplemental oxygen or use of the ventilator was required; $p_1$ = percentage of patients with baseline room air SpO2 $\leq 90\%$, which is also a lower bound of the expected number of hospitalizations that would have taken place, if standard guidelines had been followed.

Table 4 displays the following information about the Hazan, Stone, and Babalola case series, as well as the combined case series: 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 ventilator), and the corresponding time period of treatment. We also display the percentage $p_1$ of patients with baseline room air SpO2 $\leq 90\%$ among all treated patients. As explained in Section 2, we used a simplified self-controlled case series method to demonstrate 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 [**29–32**], except that 2 patients had to use a ventilator and 3 other patients required supplemental oxygen in the Babalola case series [**31,70**].

### 3.2. Description of external controls for the United States

The following external controls were used to investigate the mortality rate reduction endpoint. Table 5 shows the United States CFR of hospitalized patients at the national level throughout the years of 2020, 2021, and 2022, calculated via the CDC's COVID-19 case surveillance public database [**55**]. The selection criteria for constructing the subgroup of hospitalized cases is described in the methods section. Table 5 shows the CFR of hospitalized patients both over all age brackets as well as for the age $\geq 50$ years age brackets. The CFR of hospitalized patients is reported as an interval: the calculation of the lower bound assumes survival for all cases with missing mortality data; the calculation of the upper bound assumes that for all cases with missing mortality data the likelihood of death is the same as in the cases with known data. A close examination of the monthly CFR of hospitalized patients shows that it had a dependence on the strain placed on the hospital system, as indicated by the total number of cases per month. A similar finding was observed by Jassat *et al.*[**57**] with the month-to-month CFR of hospitalized patients reported in South Africa hospitals. Therefore, for external control purposes, it is important to consider the averaged CFR of hospitalized patients over the entire treatment time period.

Table 6 shows the average CFR of hospitalized patients for the time period during which patients were treated for the Hazan case series, between August 2020 and February 2021, and the cumulative CFR of hospitalized patients through the end of the Hazan case series treatment time period (January 2020 to February 2021). The CFR of hospitalized patients is reported over all age brackets and over the age $\geq 50$ years age

Table 5: Monthly case fatality rate for symptomatic lab-confirmed COVID-19 patients that have been hospitalized in the United States, during 2020, 2021, and 2022.

| Period | all ages | | | | age $\geq$ 50 years | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | Died | Lived | CFR | Cases | Died | Lived | CFR |
| 2020-01 | 116 | 1 | 40 | 0.86% to 2.44% | 5 | 0 | 3 | 0% to 0% |
| 2020-02 | 675 | 32 | 158 | 4.74% to 16.84% | 213 | 30 | 2 | 14.08% to 93.75% |
| 2020-03 | 57703 | 8842 | 28437 | 15.32% to 23.72% | 40115 | 8179 | 17344 | 20.39% to 32.05% |
| 2020-04 | 72381 | 14518 | 34419 | 20.06% to 29.67% | 53379 | 14299 | 21789 | 26.79% to 39.62% |
| 2020-05 | 39618 | 4011 | 18999 | 10.12% to 17.43% | 26388 | 3952 | 10862 | 14.98% to 26.68% |
| 2020-06 | 44871 | 2890 | 20431 | 6.44% to 12.39% | 28294 | 2816 | 11522 | 9.95% to 19.64% |
| 2020-07 | 68853 | 6265 | 30435 | 9.1% to 17.07% | 47177 | 6096 | 19003 | 12.92% to 24.29% |
| 2020-08 | 45017 | 2871 | 18907 | 6.38% to 13.18% | 31685 | 2823 | 12186 | 8.91% to 18.81% |
| 2020-09 | 35309 | 1362 | 15313 | 3.86% to 8.17% | 25422 | 1352 | 10201 | 5.32% to 11.7% |
| 2020-10 | 57586 | 3322 | 26318 | 5.77% to 11.21% | 43464 | 3305 | 18964 | 7.6% to 14.84% |
| 2020-11 | 100089 | 10093 | 42949 | 10.08% to 19.03% | 76327 | 10009 | 31164 | 13.11% to 24.31% |
| 2020-12 | 114978 | 15288 | 43773 | 13.3% to 25.89% | 89545 | 14966 | 32387 | 16.71% to 31.61% |
| 2021-01 | 94337 | 10861 | 38448 | 11.51% to 22.03% | 73653 | 10699 | 28894 | 14.53% to 27.02% |
| 2021-02 | 43836 | 2071 | 18912 | 4.72% to 9.87% | 32732 | 2060 | 13591 | 6.29% to 13.16% |
| 2021-03 | 40133 | 947 | 19824 | 2.36% to 4.56% | 27244 | 947 | 12830 | 3.48% to 6.87% |
| 2021-04 | 40967 | 934 | 20506 | 2.28% to 4.36% | 25778 | 907 | 12054 | 3.52% to 7% |
| 2021-05 | 24688 | 279 | 11007 | 1.13% to 2.47% | 15043 | 268 | 6027 | 1.78% to 4.26% |
| 2021-06 | 15473 | 170 | 5643 | 1.1% to 2.92% | 8542 | 169 | 2714 | 1.98% to 5.86% |
| 2021-07 | 39648 | 2317 | 15427 | 5.84% to 13.06% | 23885 | 2125 | 8457 | 8.9% to 20.08% |
| 2021-08 | 73527 | 6515 | 29620 | 8.86% to 18.03% | 47668 | 6147 | 17409 | 12.9% to 26.1% |
| 2021-09 | 59634 | 4011 | 24769 | 6.73% to 13.94% | 40547 | 3928 | 15395 | 9.69% to 20.33% |
| 2021-10 | 43956 | 2146 | 18536 | 4.88% to 10.38% | 31163 | 2112 | 12201 | 6.78% to 14.76% |
| 2021-11 | 45134 | 2980 | 19892 | 6.6% to 13.03% | 32053 | 2926 | 13034 | 9.13% to 18.33% |
| 2021-12 | 66184 | 5095 | 33474 | 7.7% to 13.21% | 43197 | 4998 | 19144 | 11.57% to 20.7% |
| 2022-01 | 85570 | 10295 | 32695 | 12.03% to 23.95% | 62477 | 10164 | 22269 | 16.27% to 31.34% |
| 2022-02 | 26227 | 1292 | 9546 | 4.93% to 11.92% | 19930 | 1287 | 7048 | 6.46% to 15.44% |
| 2022-03 | 8837 | 103 | 3338 | 1.17% to 2.99% | 6163 | 103 | 2186 | 1.67% to 4.5% |
| 2022-04 | 9862 | 92 | 4350 | 0.93% to 2.07% | 7160 | 91 | 3074 | 1.27% to 2.88% |
| 2022-05 | 20395 | 384 | 8812 | 1.88% to 4.18% | 14497 | 384 | 6278 | 2.65% to 5.76% |
| 2022-06 | 20881 | 527 | 9021 | 2.52% to 5.52% | 15797 | 527 | 6649 | 3.34% to 7.34% |
| 2022-07 | 25504 | 748 | 11067 | 2.93% to 6.33% | 19396 | 742 | 8219 | 3.83% to 8.28% |
| 2022-08 | 20540 | 467 | 9106 | 2.27% to 4.88% | 15703 | 467 | 6804 | 2.97% to 6.42% |
| 2022-09 | 14671 | 254 | 6618 | 1.73% to 3.7% | 11250 | 254 | 4910 | 2.26% to 4.92% |
| 2022-10 | 13704 | 182 | 6773 | 1.33% to 2.62% | 10988 | 182 | 5291 | 1.66% to 3.33% |
| 2022-11 | 15120 | 345 | 7088 | 2.28% to 4.64% | 11987 | 345 | 5350 | 2.88% to 6.06% |
| 2022-12 | 12305 | 105 | 5495 | 0.85% to 1.88% | 9724 | 105 | 4171 | 1.08% to 2.46% |

Calculations used a CDC database [**55**], accessed January 20, 2023.
CFR = Case Fatality Rate; lower bound is (Died)/(Cases) and assumes survival for all cases with unknown outcome; upper bound is (Died)/(Lived+Died), and assumes 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.

brackets. Using the age $\geq$ 50 restriction as a proxy for hypoxemia, we obtained a conservative 12.13% lower-bound for the CFR of hospitalized patients over the treatment time period that the risk-stratified Hazan case series should be compared against. The cumulative CFR of hospitalized patients through February 2021 had a 14.18% lower bound, which is consistent with the external control used by Hazan *et al.*[**30**]. However, we believe that 12% is the most reliable lower bound for the CFR of hospitalized patients for United States patients during the treatment period of the Hazan case series. Incidentally, we will see that 12% was also a lower bound for all other external controls in Africa, considered in this paper, therefore it can be used when analyzing combined case series with respect to the mortality rate reduction endpoint, for very conservative

comparisons.

Table 6: Cumulative case fatality rate for symptomatic lab confirmed COVID-19 patients that have been hospitalized in the United States over specific time periods.

| Period | 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 $\geq 50$** | | | | |
| 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% |

Calculations used a CDC database [**55**], accessed January 20, 2023. The timing for the virus waves who reported in the table is consistent with Adjei *et al.*[**58**].
CFR = Case Fatality Rate; lower bound is (Died)/(Cases) and assumes survival for all cases with unknown outcome; upper bound is (Died)/(Lived+Died), and assumes 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.

Because of the substantial amount of missing data on mortality outcomes in the CDC database [**55**], we also considered, as an alternate external control group, a CDC study [**58**] of the in-hospital CFR for patients hospitalized across the United States obtained from the Premier Healthcare Database Special COVID-19 release [**92**] (hereafter PHD-SR), in order to confirm consistency with the CFR intervals obtained from the CDC database [**55**]. The PHD-SR database reported data from several hundreds of hospitals across the United States. Table 7 shows the in-hospital CFR with or without the restriction age $\geq 50$ years during the Delta wave (July 2021 to October 2021), early Omicron wave (January 2022 to March 2022), and late Omicron wave (April 2022 to June 2022), calculated from the data reported by the CDC report [**55**] on the PHD-SR database. Table 7 also summarizes the estimates for the CFR of hospitalized patients from all other external control groups [**57, 59–63**].

To determine the uncertainty involved in the calculations of the CFR for hospitalized patients from the CDC case surveillance database [**55**], Table 6 also shows the intervals for the CFR of hospitalized patients during the same waves, in addition to the pre-delta periods, as defined by Adjei *et al.*[**58**], to compare them against the numbers reported from the PHD-SR database on Table 7. For the Delta wave, over all ages, the CDC case surveillance database interval for the corresponding CFR of hospitalized patients ranged from 7.03% to 14% and the PHD-SR database CFR of hospitalized patients was reported as 15.12%, overshooting our conservative upper bound. With Early Omicron the CDC interval for the CFR of hospitalized patients, under the age $\geq 50$ restriction ranged from 13.05% to 26.83% and the corresponding CFR of hospitalized patients from the PHD-SR database was 14.57%, which is closer to the lower bound rather than the upper bound of the CDC estimate. There was no consistent pattern from similar comparisons over the available waves regarding whether the actual CFR of hospitalized patients was more likely to be closer to the lower bound rather than the upper bound, except that it tended to be confined within the neighborhood of those bounds.

An incidental finding of our analysis of the CDC case surveillance database [**55**] is that the CFR of hospitalized patients remained mostly consistent between the first two pre-Delta periods, the Delta wave,

Table 7: Case fatality rate for hospitalized patients, as reported in the United States, South Africa, Zimbabwe, Nigeria, and worldwide.

| Location | Period | Cases | Died | CFR |
|---|---|---|---|---|
| **CFR for confirmed hospitalizations over all age groups** | | | | |
| United States PHD-SR (Delta) [**58**] | 2021-07 to 2021-10 | 163094 | 24658 | 15.12% |
| United States PHD-SR (Early Omicron) [**58**] | 2022-01 to 2022-03 | 104395 | 13701 | 13.12% |
| United States PHD-SR (Late Omicron) [**58**] | 2022-04 to 2022-06 | 20655 | 1004 | 4.86% |
| South Africa (first wave) [**57**] | 2020-03 to 2020-08 | 83742 | 17042 | 20.35% |
| South Africa (beta) [**57**] | 2020-09 to 2021-03 | 135472 | 33999 | 25.1% |
| South Africa (combined) [**57**] | 2020-03 to 2021-03 | 219214 | 51041 | 23.28% |
| Zimbabwe (Parirenyatwa hospitals) [**59**] | 2020-06 to 2020-12 | 336 | 119 | 35.42% |
| Zimbabwe (Mashonaland West Province) [**60**] | 2020-04 to 2022-04 | 673 | 157 | 23.33% |
| Lagos, Nigeria (all patients) [**61**] | 2020-04 to 2020-10 | 266 | 37 | 13.91% |
| Lagos, Nigeria (only hypoxemic patients) [**61**] | 2020-04 to 2020-10 | 102 | 32 | 31.37% |
| Kano State, Nigeria (all patients) [**62**] | 2020-04 to 2021-03 | 195 | 21 | 10.77% |
| Kano State, Nigeria (without asymptomatic) [**62**] | 2020-04 to 2021-03 | 77 | 14 | 18.18% |
| World Heart Federation study (all patients) [**63**] | 2020-06 to 2021-09 | 5313 | 801 | 15.08% |
| World Heart Federation study (LMIC) [**63**] | 2020-06 to 2021-09 | 2526 | 492 | 19.48% |
| **CFR for confirmed hospitalizations for age** $\geq 50$ | | | | |
| United States PHD-SR (Delta) [**58**] | 2021-07 to 2021-10 | 114336 | 20943 | 18.32% |
| United States PHD-SR (Early Omicron) [**58**] | 2022-01 to 2022-03 | 88639 | 12914 | 14.57% |
| United States PHD-SR (Late Omicron) [**58**] | 2022-04 to 2022-06 | 17675 | 961 | 5.44% |

CFR = Case Fatality Rate; PHD-SR = Premier Healthcare Database Special COVID-19 Release [**92**]

and the Early Omicron wave, with and without the age $\geq 50$ years restriction. The first pre-Delta period through September 2020 was the most lethal, and the second pre-Delta period had the largest number of hospitalizations. The third pre-Delta period showed a dramatic temporary decrease in the CFR of hospitalized patients, which coincided with the rollout of the COVID-19 vaccines to the high-risk demographic groups in the United States population. However, the extent to which 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 5) remains unclear.

### 3.3. Description of external controls for Africa

Table 7 shows the estimated CFR for hospitalized patients from the African external control groups [**57, 59–63**], and the corresponding total number of cases and the time period for each of the external controls.

For Zimbabwe, the most relevant external control group is the unpublished statistics of the in-hospital CFR in the Parirenyatwa group of hospitals, between May 2020 and December 2020 [**59**], reporting a 35.42% CFR for hospitalized patients. Because this period intersects, but does not entirely overlap, with the treatment time interval corresponding to the Stone case series [**29**], we also considered an alternative external control group from Mashonaland West Province, Zimbabwe [**60**], ranging between April 2020 and April 2022, reporting a 23.33% CFR for hospitalized patients. Since the predominant variant in the Stone case series was the Beta variant [**29, 69**], and because both external control groups had small sample size, we also considered, as an additional external control group the in-hospital CFR in South Africa, which was reported on a month-to-month basis between March 2020 and March 2021, with substantially larger sample sizes [**57**]. The average CFR for hospitalized patients in South Africa over the entire reported time period was 23.28%. During the time period between September 2020 and March 2021, during which the beta variant was dominant in South Africa, the reported hospitalized CFR for hospitalized patients was 25.1%, and in the pre-beta time period it was 20.35%

For Nigeria, the availability of external control groups for estimating the CFR for hospitalized patients is very limited, however, we identified the following two studies: The first study [**61**] consisted of 226 hospitalized COVID-19 patients in Lagos, Nigeria, who were treated between April 2020 and October 2020 in the Lagos

University Teaching Hospital, and reported an overall 13.91% CFR. The facility served both as an isolation center for COVID-19 patients, for contagion control purposes, and as an inpatient treatment center for patients with moderate or severe COVID-19. As a result, the study underestimated the true CFR of in-patients, noting that 30.5% of the treated patients were initially asymptomatic. The study also explicitly reported 31.37% CFR for hypoxemic hospitalized patients, with hypoxemia defined by the authors as SpO2 $\leq$ 90% for adults and SpO2 $\leq$ 92% in children. Patients were treated with artemether-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 [**62**] consisted of 195 COVID-19 patients from Kano State, Nigeria, treated at the Kwanar Dawaki isolation center over a wider period between April 2020 and 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, 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 calculated the CFR, both including and excluding the patients in the initially asymptomatic category: over all patients, the average CFR was 10.77%, and excluding the asymptomatic patients the average CFR increased to 18.18%. 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. The details of the respective treatment protocols were not provided.

Last but not least, we cited a World Heart Federation study [**63**] 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 included countries classified by the World Bank as LIC, LMIC, MIC, and HIC. The combined CFR for the entire sample of patients was 15.08%. Noting that both Zimbabwe and Nigeria are classified by the World Bank as LMIC [**93**], the CFR obtained from the subgroup of patients recruited from LMIC counties was 19.48%. In both calculations the CFR included both in-hospital deaths and deaths within 30 days after discharge

### 3.4. Case series threshold analysis

Table 8 shows the results of our calculation of the efficacy threshold and random selection bias threshold for the case series listed in Table 4, both with respect to the mortality rate reduction endpoint and the hospitalization rate reduction endpoint. Shown on the table are: the unadjusted efficacy threshold $x_0$ that 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 $y_0$ which controls both the $p$-value and the Bayesian factor; the random selection bias threshold $x_1$ calculated from $y_0$. The intuitive interpretation of the adjusted efficacy threshold $y_0$, 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 than or equal to than $y_0$ with 95% confidence. The intuitive interpretation of the random selection bias threshold $x_1$, for any 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.

For the mortality rate reduction endpoint, we used the CFR of hospitalized patients as the external control group, therefore, for the calculation of the corresponding thresholds on Table 8, we risk-stratified and used 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 were no reported deaths among the patients excluded by risk stratification. For the hospitalization rate reduction endpoint, we used the entire case series, since we used the simplified self-controlled case series methodology. Because the entire case series includes some lower-risk patients, predominantly from the Babalola case series, using any kind of risk stratification, when analyzing the hospitalization rate reduction endpoint, would increase the counterfactual hospitalization rate for the self control and would result in a less conservative argument. Therefore, we opted not to use any risk stratification in the threshold calculations for the hospitalization rate reduction endpoint.

As explained in the methods section, the adjusted efficacy threshold $y_0$ is adjusted upwards from the efficacy threshold $x_0$ when $\log_{10} B < 2$, to control both the $p$-value and the Bayesian factor. These adjustments are more likely to be needed for very small case series or when the efficacy signal is very weak [**27**]. Except

Table 8: Efficacy thresholds and random selection bias thresholds for the mortality endpoint and the hospitalization endpoint for the case series by Hazan *et al.*[**30**], Stone *et al.*[**29**], Babalola *et al.*[**31**], and the combined case series.

| **Mortality rate reduction thresholds using 95% confidence intervals** | | | | | | |
|---|---|---|---|---|---|---|
| **Case series** (SpO2 $\leq$ 90%) | $(N, a)$ | $x_0$ | $\log_{10} B$ | $p_2$ | $y_0$ | $x_1$ |
| 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 + Babalola | (33, 0) | 10.2% | 2.03 | 18.18% | 10.2% | 28.5% |
| Stone + Babalola | (38, 0) | 8.9% | 2.14 | 18.18% | 8.9% | 24.8% |
| 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%) | $(N, a)$ | $x_0$ | $\log_{10} B$ | $p_2$ | $y_0$ | $x_1$ |
| 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 + Babalola | (85, 5) | 13.4% | 2.05 | 38.8% | 13.4% | 23.5% |
| Stone + Babalola | (95, 5) | 12.0% | 2.12 | 40% | 12.0% | 21.0% |
| 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% |

$N$ = number of patients in the case series; $a$ = number of adverse outcomes with treatment (hospitalizations or deaths respectively); $x_0$ = efficacy threshold controlling only the $p$-value requirement $p(N, a, x) < 0.05$ for all $x > x_0$; $\log_{10} B$ = decimal logarithm of Bayesian factor $B(N, a, x_0, p_2)$ evaluated at the efficacy threshold $x_0$, comparing the null hypothesis $H_0 : 0 \leq q \leq x_0$ against the alternate hypothesis $H_1 : x_0 \leq q \leq 1$, with $q$ the expected probability of an adverse event with treatment; $p_2$ = expected worst-case probability of an adverse event without treatment; $y_0$ = adjusted efficacy threshold controlling both the $p$-value and the requirement $\log_{10} B(N, a, x, p_2) \geq 2$ for all $x > y_0$; $x_1$ = random selection bias threshold.

for the Babalola case series threshold for the hospitalization rate reduction endpoint, which was increased by 2.1%, all other adjustments to the efficacy threshold were less than 0.2%.

The parameter $p_2$, shown on Table 8, is the expected worst-case probability of an adverse outcome in the control, and it is used to define the priors used in the calculation of the Bayesian Factor $\log_{10} B$. Decreasing $p_2$ tends to decrease the contrast between the null hypothesis $H_0$ and the alternate hypothesis $H_1$ in the calculation of $\log_{10} B$, so the conservative approach is to use lower bounds for $p_2$.

For the mortality rate reduction endpoint, the $p_2$ parameter was chosen as follows. For the Hazan case series, we considered measures of the United States CFR for hospitalized patients over the treatment period between August 2020 and February 2021 as shown on Table 5. The peak month by month CFR for hospitalized patients without any age restriction occurred on December 2020, ranging from 13.3% to 25.89%, suggesting 25.89% as a possible choice for $p_2$; however, the CFR for hospitalized patients averaged over the entire treatment period with the age $\geq$ 50 years restriction is reported on Table 6 as ranging from 12.13% to 23.48%. Thus, we chose the smallest of the two upper bounds and set $p_2 = 23.48\%$. For the Stone case series we chose $p_2 = 23.3\%$, which was the smallest number between: (a) the 35.42% CFR for hospitalized patients reported in the Parirenyatwa hospitals in Harare, Zimbabwe; (b) the 23.33% CFR for hospitalized patients reported in the Mashonaland West Province, Zimbabwe (see Table 7). For the combined case series Hazan + Babalola and Stone + Babalola, we used $p_2 = 18.18\%$, which was the CFR for patients hospitalized in Kano State, Nigeria, excluding the asymptomatic patients, as shown on Table 7, noting that it is the more conservative choice given that higher values for $p_2$ were chosen for the Hazan and Stone case series. For the combined case series Hazan + Stone and Hazan + Stone + Babalola, there was sufficient statistical power to ensure that any value $p_2 \geq 10\%$ does not result in any non-negligible upward adjustment of the efficacy threshold $x_0$, so we chose $p_2 = 10\%$.

For the hospitalization reduction rate endpoint, we set $p_2$ equal to the counterfactual hospitalization rate for the self-control, which was lower-bounded by the percentage of patients with baseline room air SpO2 $\leq$ 90% shown on Table 4, for all case series except for the Babalola case series. This was the most conservative

choice possible, and it did not result in any upwards adjustments of the efficacy thresholds. For the Babalola case series, this choice was mathematically inconsistent because the counterfactual hospitalization rate fails to exceed the unadjusted efficacy threshold, consequently we used the less conservative choice of setting $p_2 = 34.4\%$ equal to the percentage of patients that were hypoxemic with room air baseline SpO2 $\geq 93\%$ (21 patients out of 61, as shown on Table 4).

Table 9: Self-controlled exact Fisher test comparisons of factual vs counterfactual hospitalization events in the Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31**] case series and in the combined case series.

| **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 + Babalola | (85, 5) | (85, 33) | 0.1 (0.03 – 0.28) | $10^{-7}$ |
| Stone + Babalola | (95, 5) | (95, 38) | 0.08 (0.02 – 0.23) | $10^{-9}$ |
| 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) | $10^{-17}$ |

$(N, a)$ = treatment case series with $N$ patients and $a$ factual hospitalization events (use of supplemental oxygen or ventilator); $(N, b)$ = counterfactual control case series with $N$ patients and at least $b$ counterfactual hospitalizations, lower-bounded by the number of patients with baseline room air SpO2 $\leq 90\%$; OR = odds ratio; CI = confidence interval.

### 3.5. Existence of hospitalization rate reduction efficacy

Table 9 shows the odds ratio, 95% confidence interval, and the exact Fisher test $p$-value obtained from the comparison between the complete case series $(N, a)$ and the corresponding self control series $(N, b)$. Here, $N$ is the total number of patients, $a$ is the factual number of hospitalization events that include the reported use of supplemental oxygen and the use of ventilators, and $b$ is a lower bound of the counterfactual number of hospitalizations that would have occurred if one had followed standard protocols, obtained by counting the number of patients with baseline room air SpO2 $\leq$ 90%. A statistically significant reduction in the hospitalization rate was inferred for the Hazan and Stone case series and for the combined Hazan + Stone, Hazan + Babalola, Stone + Babalola, and Hazan + Stone + Babalola case series. The Babalola case series, by itself, failed to achieve statistically significant hospitalization rate reduction. These comparisons are biased towards the null hypothesis of no efficacy because $b$ underestimates the total number of counterfactual hospitalizations that would have occurred under the standard guidelines.

Because of the self-controlled design, these comparisons are not susceptible to selection bias, however, hospitalization is not an entirely objective endpoint, therefore there is the possibility of some bias in the estimation of the counterfactual hospitalization rate lower bounds, which can mathematically be redefined as an equivalent selection bias in the treatment arm. Nevertheless, a direct comparison between the random selection bias thresholds $x_1$ for the hospitalization rate reduction endpoint, shown on Table 8, and the lower bounds for the counterfactual hospitalization rates (see column 4 of Table 4), shows that they are separated by large gaps for the Hazan case series, the Stone case series, and all possible combinations of the three case series. This means that we can have 95% confidence that the existence of hospitalization rate reduction cannot be overturned by equivalent random selection bias, resulting from any theoretical inaccuracies in the estimation of the counterfactual hospitalization rate.

The selection bias tolerance $F$ can be used to quantify the magnitude of the gap between the random selection bias threshold and the counterfactual hospitalization rate. For the combined Hazan + Stone case series, using $p_1 = 87.9\%$ and $x_1 = 17.0\%$, gives a selection bias tolerance $F = 35.5$. Including the Babalola case series, for the combined Hazan + Stone + Babalola case series, this selection bias tolerance decreases to $F = 5.1$ (using $p_1 = 51.3\%$ and $x_1 = 17.2\%$). In both cases the systemic selection bias tolerance is high enough for a clear and convincing finding for hospitalization rate reduction with excellent resilience. The combinations Hazan + Babalola and Stone + Babalola are relevant only for sensitivity analysis, and the corresponding selection bias tolerance is $F = 1.59$ (Hazan + Babalola) and $F = 2.02$ (Stone + Babalola). Both

results give acceptable resilience. We stress that, in this context, $F$ quantifies the maximum selection bias that is mathematically equivalent to any expected bias in the lower bound for the counterfactual hospitalization rate estimate, for which a clear and convincing finding can be supported.

Table 10: Exact Fisher test comparisons between the Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31**] case series and corresponding external control groups from Table 6 and Table 7, with respect to mortality rate reduction.

| **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 $\geq$ 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 $\geq$ 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 (Mashonaland 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 + Babalola case series compared with** | | | | |
| CDC (treatment interval, any age) | (33, 0) | (491152, 45868) | 0 (0 – 1.15) | 0.07 |
| CDC (treatment interval, age $\geq$ 50) | (33, 0) | (372828, 45214) | 0 (0 – 0.86) | 0.028 |
| World Heart Federation study (all patients) | (33, 0) | (5313, 801) | 0 (0 – 0.67) | 0.011 |
| **Stone + Babalola case series compared with** | | | | |
| CDC (treatment interval, any age) | (38, 0) | (491152, 45868) | 0 (0 – 0.99) | 0.046 |
| CDC (treatment interval, age $\geq$ 50) | (38, 0) | (372828, 45214) | 0 (0 – 0.74) | 0.012 |
| World Heart Federation study (all patients) | (38, 0) | (5313, 801) | 0 (0 – 0.58) | 0.005 |
| **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 $\geq$ 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 $\geq$ 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) | $10^{-5}$ |

$(N, a)$ = treatment case series with $N$ cases and $a$ deaths; $(M, b)$ = external control with $M$ cases and $b$ deaths with data shown on Table 6 and Table 7; OR = Odds Ratio; CI = Confidence Interval;
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.

### 3.6. Exact Fisher test comparisons for the mortality rate reduction endpoint

Table 10 shows exact Fisher test comparisons between the appropriate external control groups and the Hazan, Stone, Babalola case series, as well as the four combined case series. For the Hazan case series, we used as an external control the United States hospitalized patients obtained from the CDC database [**55**], with and without the age $\geq 50$ years restriction, over both the treatment time period and the cumulative time period from the beginning of the pandemic. In constructing these external controls, we assumed survival for all cases with unknown mortality outcome, to ensure a conservative comparison in which any bias will tend towards the null hypothesis. We also used the mortality outcomes of the 5313 hospitalized patients reported by the World Heart Federation study [**63**] with no restrictions as a global control group over all patients. For the Stone case series, we used the external control groups from Zimbabwe [**59,60**] and South Africa [**57**], shown on Table 7, and the subgroup of 2526 hospitalized patients from LMIC countries reported by the World Heart Federation study [**63**]. For the Babalola case series, we used the external control from Lagos, Nigeria [**61**], limited to hypoxemic patients, the external control from Kano State, Nigeria [**62**], in which we have excluded asymptomatic patients that were merely isolated in the hospital facility, and on the subgroup of hospitalized patients reported in the World Heart Federation study from LMIC countries [**63**]. For all four of the combined case series we have used as external controls the United States hospitalized patients from the CDC database over the treatment time period corresponding to the Hazan case series, with and without the age $\geq 50$ years restriction, assuming survival for all cases with an unknown mortality outcome. This comparison is obviously biased, however, it is biased towards the null hypothesis, because all external controls from Africa found higher CFR for hospitalized patients compared to the lower bound for the United States CFR of hospitalized patients. We also used the entire group of hospitalized patients reported in the World Heart Federation study [**63**], which gives a more conservative estimate for the CFR for hospitalized patients compared to the subgroup limited to patients from LMIC countries.

### 3.7. Mortality rate reduction efficacy for the Hazan, Stone, and Babalola case series

For the Hazan case series, Table 10 shows comparisons between the risk-stratified Hazan case series with $(N, a) = (23, 0)$ and the lower bounds of the CDC external controls and the CFR of hospitalized patients from the World Heart Federation study [**63**]. Regardless of whether the treatment interval CFR or the cumulative CFR is used, and whether the age $\geq 50$ years constraint is used for the definition of the external control group, all comparisons fail to demonstrate a statistically significant effect. Borderline statistical significance is obtained only when one compares the Hazan risk-stratified case series against the World Heart Federation study [**63**], which provided 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 CFR for hospitalized patients from all CDC external controls, using either the treatment interval or the cumulative interval, and using either all ages or the age $\geq 50$ years constraint, against the adjusted efficacy threshold $y_0 = 14.7\%$, we see that all lower bound estimates of the CFR are below $y_0$ and all upper bound estimates of the CFR for hospitalized patients are above $y_0$. It is therefore unclear whether the existence of mortality rate reduction has been established by the preponderance of evidence. With the age $> 50$ years restriction, the corresponding cumulative CFR lower bound for hospitalized patients is 14.18% which is very close to the adjusted efficacy threshold of $y_0 = 14.7\%$; however, the CFR lower bound for hospitalized patients over the treatment time period is reduced to 12.13%. We conclude that, although there is a very compelling signal of benefit, there is insufficient statistical power for a decisive finding of preponderance of evidence in support of mortality rate reduction, if we use the Hazan case series by itself.

For the Stone case series, all comparisons shown on Table 10 give a statistically significant mortality rate reduction finding with $p \leq 0.003$. The Parirenyatwa group of hospitals in Harare, Zimbabwe reported 35.4% CFR for hospitalized COVID-19 patients admitted between May 2020 and December 2020, which overlaps but does not encompass the treatment time period of the Stone case series[**59**]. A reduced CFR for hospitalized patients of 23.3% was reported [**60**] for COVID-19 patients in Mashonaland West Province, Zimbabwe between April 2020 and April 2022. Both reports are presented in Table 7. Combined, these two reports account for a total of 1009 patients with 27.3% averaged CFR for hospitalized patients, and they are consistent with the 23.28% averaged CFR for hospitalized patients reported in South Africa between March 2020 and March 2021 [**57**], 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 [**69**]. In South Africa, the Beta variant was dominant between September 2020

and March 2021 (the published monthly CFR data for hospitalized patients did not go beyond March 2021), and an increased CFR of 25.1% for hospitalized patients was observed during that time, up from a 20.35% CFR for hospitalized patients during the preceding wave. The World Heart Federation measured 19.48% CFR for hospitalized patients in LMIC countries, such as Zimbabwe **[63]**. These numbers can be compared against the mortality rate reduction endpoint thresholds calculated on Table 8, where we reported for the Stone case series $y_0 = 12.0\%$ adjusted efficacy threshold and $x_1 = 32.0\%$ random selection bias threshold. The adjusted efficacy threshold $y_0 = 12.0\%$ is exceeded by the reported CFR for hospitalized patients from all of the above external controls, therefore we can reliably claim a mortality rate reduction finding by the preponderance of evidence. Although, the 35.4% CFR for hospitalized patients reported for the Parirenyatwa hospitals in Harare, Zimbabwe **[59]** exceeds the random selection bias threshold $x_1 = 32.0\%$, we hesitate to claim a clear and convincing finding, since this result is not sustained across the majority of the other external control groups.

For the Babalola case series, all comparisons shown on Table 10 between the risk-stratified case series $(N, a) = (10, 0)$ and the external controls from Nigeria **[61, 62]** and the World Heart Federation study **[63]** failed to reach statistical significance. Nevertheless, the comparison with hospitalized hypoxemic patients in Lagos, Nigeria gives $p = 0.06$ which is close to the threshold for statistical significance. There is insufficient statistical power to draw any reliable conclusions, consequently we did not calculate the adjusted efficacy threshold $y_0$ or the random selection bias threshold $x_1$.

### 3.8. Mortality rate reduction efficacy for the combined case series

The combined Hazan + Stone case series includes 51 patients with baseline room air SpO2 $\leq 90\%$ and 0 deaths. In both case series, similar multidrug treatment protocols were used, with the overlapping medications being ivermectin, zinc sulfate, doxycycline, vitamin C, and vitamin D, resulting in similar rapid recovery rates of room air SpO2 levels (see Fig. 1). The exact Fisher test comparisons, shown on Table 10, 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 $\geq 50$ years restriction, as well as with the World Heart Federation study **[63]** external control over all patients, consistently show a statistically significant reduction in mortality rate with $p \leq 0.013$. Furthermore, because the CFR lower bound for hospitalized patients in the United States external controls is substantially lower than the CFR for hospitalized patients 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, as shown in Table 8, the adjusted efficacy threshold was $y_0 = 7.6\%$ and the random selection bias threshold was $x_1 = 18.5\%$, both for mortality rate reduction. An estimated 12% lower bound for the CFR for hospitalized patients in the United States 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 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 CFR lower bound for hospitalized patients 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 + Babalola case series, which includes 61 patients with baseline room air SpO2 $\leq 90\%$ and 0 deaths. The exact Fisher test comparisons, reported on Table 10, between the combined Hazan + Stone + Babalola case series and the same external controls used in the previous comparison for the combined Hazan + Stone case series show statistically significant reduction in the mortality rate with $p \leq 0.006$. Furthermore, Table 8 shows the adjusted efficacy threshold and the random selection bias threshold for the combined Hazan + Stone + Babalola case series, which were $y_0 = 6.2\%$ and $x_1 = 16.2\%$ respectively for the mortality rate reduction endpoint. If we use the very conservative lower bound of 12% for the CFR of hospitalized patients under conventional treatment for all patients in the combined case series, then the 6.2% efficacy threshold is exceeded by a wide margin, which decisively establishes 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 CFR of hospitalized patients for the 23 patients in the United States, and use the 19.5% CFR for hospitalized patients in LMIC nations from the World Heart Federation Study **[63]** for the 38 patients in Nigeria and Zimbabwe, then the average CFR lower bound is 16.7%, which exceeds the random selection bias threshold of $x_1 = 16.2\%$, 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 [**55**], by disregarding the restriction age $\geq 50$ years and using the smallest CFR lower bound for hospitalized patients 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 [**69**] and Nigeria [**32**] was generally more lethal than preceding waves [**57**], we are still showing a decisive finding of the existence of mortality rate reduction by the preponderance of evidence.

Lastly, we considered, strictly for the purpose of sensitivity analysis, the combined Hazan + Babalola and Stone + Babalola case series. Table 10 shows that all of the exact Fisher test comparisons between the combined Stone + Babalola case series and the external controls show statistically significant mortality rate reduction with $p < 0.046$. For the combined Hazan + Babalola case series, comparison with the United States external control group of hospitalized patients from the CDC database [**55**] with no age restrictions fails to reach statistical significance with $p = 0.07$. The other two comparisons are statistically significant with $p < 0.028$. As noted earlier, the age $\geq 50$ years is an appropriate proxy for the additional risk factor of hypoxemia upon hospital admission for hospitalized patients, so the statistically significant comparison with the United States external control group of hospitalized patients from the CDC database with the age $\geq 50$ years restriction is more appropriate. Table 8 reports $y_0 = 10.2\%$ for the adjusted efficacy threshold of the combined Hazan + Babalola case series and $y_0 = 8.9\%$ for the adjusted efficacy threshold of the combined Stone + Babalola case series. Both thresholds are exceeded by the 12% lower bound for the hospitalized CFR of hospitalized patients of both United States and African external controls, thereby establishing a mortality rate reduction finding by the preponderance of evidence.

### 3.9. Applying the Bradford Hill criteria

Our statistical analysis examined the strength of the association between the multidrug treatment protocols used at prevention of hospitalization and death mediated by the restoration of SpO2 levels in hypoxemic patients. We will now argue that previous research has already established the Bradford-Hill criteria of temporality, biological gradient, consistency, biological plausibility, and coherence. From the standpoint of the Bradford Hill criteria generalizations proposed by Howick *et al.*[**65**], strength of association combined with biological gradient and temporality provide *direct evidence*, biological plausibility provides *mechanistic evidence*, and the combination of consistency and coherence provides *parallel evidence*. We retained the original terminology by Bradford Hill [**64**] as it is likely to be more familiar to the readers.

#### 3.9.1. Temporality

In the context of the ivermectin-based multidrug protocols, temporality is clearly satisfied because of the immediate increase in SpO2 levels within 24 to 48 hours observed separately in the case series by Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31**], shortly after initiating treatment. This rapid response was first noted by Thairu *et al.*[**32**] and Babalola and colleagues [**33**]. Stone and colleagues [**29**] first presented the visualization shown in Fig. 1, contrasting the difference in SpO2 recovery rates between the Hazan, Stone, and Babalola case series vs the Thairu case series, all risk-stratified, using baseline room air SpO2 $\leq 93\%$ risk stratification.

Scheim *et al.*[**50**] compared the SpO2 recovery rates of the Hazan, Stone, and Babalola series against the Thairu case series using the Mann-Whitney U-test and showed that the observed SpO2 recovery rates are statistically significant from Day 1 ($p < 10^{-8}$ for the Hazan and Stone case series and $p = 0.00149$ for the Babalola case series, with baseline room air SpO2 $\leq 93\%$ risk stratification). From a qualitative viewpoint, for the patients in the Thairu case series, Fig. 1 shows a decreasing trend in room air SpO2 during the first 3 days, contrasted by the rapidly increasing trend in the Hazan, Stone, and Babalola case series over the same period. Although the patients in the Thairu case series were treated during the delta variant, similar decreasing trends in SpO2 were observed with pre-delta variants over a period of at least 8 days by Annunziata and colleagues [**94, Fig. 4**] (October 2020 to November 2020, despite a 6 day protocol that included azithromycin, methylprednisolone, enoxaparin) and even in less severe presentations reported by Osman and colleagues [**95, Fig. 5**] (March 2020 to August 2020; no information provided concerning medications).

The short temporal distance between the onset of treatment and the response, further strengthens the temporality evidence. As was noted by Howick *et al.*[**65**] a short time interval between the onset of treatment and response allows for *"less room for confounders (especially spontaneous remission) to interfere"*[**65**]. Furthermore,

the rapid response is consistent with the confluence of possibly multiple mechanisms of action that are responsible for a quick resolution of the microemboli of red blood cells that mediate the decrease of SpO2.

#### 3.9.2. Biological gradient

Biological gradient has been shown by the observation (see Fig. 1) that SpO2 recovery is more rapid in the Hazan case series and the Stone case series, compared to the Babalola case series, noting that Babalola's protocol used mainly ivermectin, zinc sulfate, and vitamin C [**31–33**], but the Hazan and Stone/Gill multidrug protocols [**29, 30, 34, 35**] added Vitamin D3 and doxycycline, and the Stone/Gill protocol also added nebulized nanosilver, corticosteroids, and blood thinners [**29, 34, 35**]. 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"* [**29**]. Fig. 1 also shows that the recovery rate of SpO2 in the patients treated with ivermectin-based multidrug protocols is substantially faster than that of 26 patients treated with a non-ivermectin protocol of lopinavir/ritonavir, remdesivir, azithromycin, enoxaparin, and vitamin C; in fact for those patients SpO2 levels were initially declining over a period of several days and did not fully recover after 10 days, a pattern that has also been replicated by other studies conducted during pre-delta variants [**94, 95**].

#### 3.9.3. Consistency

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

#### 3.9.4. Biological plausibility

Biological plausibility requires arguing that there are known mechanisms of action they can explain a causal association between the treatment intervention and the rapid recovery of room air SpO2 levels in hypoxemic patients. The prevention of deaths and hospitalizations can then be attributed, in part, to the speed with which room air SpO2 levels are normalized. 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 [**36**]. Glycan bindings between the spike protein on the viral particles and the red blood cells tend to sustain these microemboli and ivermectin has been shown to play an important role in releasing these glycan bindings [**38–40, 50**]. However, this is only one of many mechanisms by which severe COVID-19 pneumonia injures patients, and it is just as important to eradicate the virus, calm the cytokine storm, and accelerate the disaggregation of previously accumulated microemboli [**10**]. 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 used in various combinations in the Hazan, Stone, and Babalola case series.

Ivermectin may have several mechanisms of action [**96, 97**] suggesting multiple targets and modes of action against COVID-19, including antiviral, anti-inflammatory, and anticoagulant effects. Ivermectin has anti-inflammatory and immunomodulatory properties because it acts as a positive allosteric modulator of the alpha-7 nicotinic acetylcholine receptor ($\alpha$7nAChr), which enhances the cholinergic anti-inflammatory pathway, resulting in a balanced response to inflammation triggered by viral particles [**41, 98**]. Ivermectin can inhibit viral attachment to human cells by binding to several sites of the spike glycoprotein of the SARS-CoV-2 virus, including a glycosylation binding site (site 10, N61) and other sites on the S1-NTD and S1-RBD regions [**41**]. Spike protein-induced red blood cell and platelet aggregation can trigger blood clot formation and inflammation which causes serious pathologies, including a drop in SpO2 levels to severe hypoxemia [**39**]. Ivermectin binds competitively to SARS-CoV-2 spike protein glycans, and reverses the bindings with red blood cells thus preventing clumping [**38–41, 50**]. This mechanism may explain, in part, the rapid recovery of SpO2 levels in hypoxemic COVID-19 patients in response to the ivermectin-based multidrug protocols proposed by

Hazan [30] and Stone [29]. Finally, ivermectin may act as a zinc ionophore [45], 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 [5,99]. 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 [96].

Prior to the COVID-19 pandemic, doxycycline's antiviral and anti-inflammatory properties were found to be an option for reducing lung damage and dampening the cytokine storm associated with severe diseases [100]. Doxycycline has emerged as a compelling candidate for reducing lung damage and mitigating the cytokine storm in severe COVID-19 [101]. Doxycycline has also demonstrated antiviral activity against various RNA viruses in laboratory settings, which is mediated by targeting host proteases utilized by coronaviruses and inhibiting viral fusion and replication [46]. By impeding viral replication, doxycycline has the potential to alleviate the severity of infection and limit lung damage. It has been shown to inhibit the coreceptors DPP4/CD26 and CD147/EMMPRIN, which are crucial for viral entry into T lymphocytes [46]. Additionally, doxycycline may interfere with viral protein processing, including cleavage of polyproteins and maturation of essential viral proteins [46]. Furthermore, doxycycline acts as a zinc ionophore, enhancing the intracellular concentration of zinc, which has been associated with inhibition of SARS-CoV-2 replication [46]. 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-$\alpha$), and doxycycline has been found to reduce these proinflammatory cytokines [102]. In doing so, it may help to quell the excessive inflammatory response by mitigating the cytokine storm, thereby preventing further lung damage. Its anti-inflammatory properties extend to inhibiting NF-$\kappa$B activation, a transcription factor involved in producing proinflammatory cytokines [101].

Silver nanoparticles (AgNPs) have also shown potential for combating COVID-19 [42]. 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 [34,35]. Although the exact mechanisms through which AgNPs impede the infectivity of SARS-CoV-2 remain unknown, numerous studies have proposed compelling theories regarding their potential modes of action [103]. AgNPs reveal a multifaceted approach for managing viral infections. As an immune booster, AgNPs can enhance the immune response [104]. Their anti-inflammatory and antimicrobial properties are effective in treating viruses such as SARS-CoV-2. By reducing inflammation and combating microbial infections, AgNPs aid in managing the progression of viral diseases [105]. 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 [47]. Additionally, AgNPs can generate reactive oxygen species (ROS), which exert an antiviral effect by directly impeding viral proteins and nucleic acids [48]. However, it is important to note that these mechanisms can be sensitive to the size, shape, surface charge, and concentration of the AgNPs employed. One of the serious complications observed in patients with severe COVID-19 is blood clotting. Studies have shown that AgNPs can impede platelet adhesion and disrupt integrin-mediated platelet responses [42]. AgNPs have antiplatelet and anticoagulant effects [43]. Furthermore, AgNPs are electrostatically attracted to the positively charged spike protein of the SARS-CoV-2 virus, and silver nanoparticles with size less than 10 nm can coat free viral particles and prevent their attachment to red blood cells via glycan bindings [39,52]. This property of AgNPs can potentially prevent the formation of microclots, safeguarding patients from life-threatening complications and contributing to the rapid restoration of SpO2 levels.

Prior to the COVID-19 pandemic, an in vitro study [106] showed that using zinc ionophores to increase intracellular $Zn^{2+}$ ions inhibits the ability of SARS-CoV and equine arteritis virus to replicate by interfering with the function of the RDRP enzyme. It was thus conjectured that a similar mechanism could inhibit the replication of SARS-CoV-2 in the early stages of COVID-19 [107], thus motivating Zelenko's precursor of the McCullough protocol [5]. In the context of the Hazan and Stone/Gill multidrug protocols [29,30,34,35], the aforementioned combined zinc ionophore properties of ivermectin and doxycycline may act synergistically with zinc supplementation to limit viral replication via the same mechanism. Furthermore, zinc by itself may have additional mechanisms of action which include improving the clearance of viruses and bacteria by mucosal immunity, increasing the immune antiviral response by interferon-$\alpha$ upregulation, and limiting cytokine injury by downregulating the production of proinflammatory cytokines [108].

Vitamin D supplementation can be beneficial by a wide range of mechanisms of action which include stimulating the production of antimicrobial peptides by immune cells, protecting the lungs by reducing the production of proinflammatory cytokines, increasing surfactant concentration in the alveoli, and limiting

pulmonary vasoconstriction [**109**]. Furthermore, Vitamin D may protect against endothelial dysfunction by reducing oxidative stress, by reducing the proinflammatory cytokines TNF-$\alpha$ and IL-6, and by inhibiting NF-$\kappa$B activation [**109**]. Vitamin D may reduce the risk of respiratory failure by reducing matrix metalloproteinase-9 (MMP-9) concentration [**109**]. Finally, vitamin D may reduce the risk of RAS-mediated bradykinin storm by modulating the RAS and downregulating renin expression and generation, thus reducing the risk of cardiovascular and pulmonary adverse effects from COVID-19, as well as adversely affecting the brain and muscles [**109**].

Finally, high-dose vitamin C supplementation may be beneficial to COVID-19 patients in two ways: (a) it can prevent the depletion of vitamin C levels in patients presenting with severe COVID-19, which may be caused by the metabolic response to the illness; (b) it may also modulate the immune system by increasing $\alpha/\beta$ interferons, thereby escalating the antiviral immune response, while downregulating proinflammatory cytokines [**110**].

#### 3.9.5. Coherence

Coherence requires that a causality claim should be consistent with and not contradict what is currently known from previous research. This is particularly important, in the context of the ivermectin-based multidrug protocols used in the Hazan, Stone, and Babalola case series, due to conflicting results and controversies concerning the use of ivermectin in treating COVID-19 [**111–114**]. To disentangle these controversies, it is important to remember that evidence of efficacy or of lack of efficacy of single drug monotherapies do not necessarily extrapolate to multidrug protocols that use several medications in combination and studies of inpatients do not extrapolate to studies of outpatients and vice versa [**27,115**]. 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 [**116**]. For this reason, observational studies [**4–7,25–27**] of multidrug treatment protocols, that have been used by practicing doctors at the frontlines deserve special attention.

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 [**10**], using hydroxychloroquine and ivermectin in combination with zinc, azithromycin, doxycycline, inhaled budesonide, dexamethasone, folate, thiamine, vitamin B12, and intravenous fluids for a minimum of 5 days. Comparison of outcomes against historical controls, using the case series threshold analysis technique, has shown that the existence of both hospitalization and mortality rate reduction benefits is clear and convincing [**27**], although the patients, for the most part, were treated early as outpatients before the onset of oxygen desaturation. A study on 280 high-risk hospitalized patients by Rajter *et al.*[**117**] showed a signal of benefit with respect to mortality rate reduction, which is statistically significant for severe cases but not for non-severe cases, when adding low-dose ivermectin to the standard of care. This finding is consistent with our finding of a statistically significant reduction in the mortality rate, when using ivermectin at higher dosages and as part of a synergistic multidrug treatment protocol on patients with hypoxemia.

The prospective observational study of prophylactic use of ivermectin conducted in Itaji, Brazil [**118,119**], and an ecological study on the state-level use of ivermectin in Peru [**120**] both provide additional compelling evidence in support of the efficacy of the prophylactic and pre-hospital early use of ivermectin for reducing the risk of COVID-19 infections and for preventing hospitalizations and deaths in COVID-19 patients. The Itaji studies [**118,119**] are compelling because they involved more than half of the city population, ensuring negligible risk of confounding by selection bias, and because a dose-response effect was observed with respect to statistically significant hospitalization and mortality rate reduction. The Peru study [**120**] is a natural experiment that provides evidence of causality between ivermectin use and reduction of excess deaths, since it tracks the variability of excess deaths before the introduction of state-level use of ivermectin, during its use, resulting in 14-fold reduction in excess deaths, and after its use was prohibited, resulting in 13-fold increase in excess deaths. Both studies have been discussed in further detail elsewhere [**114**]. Yagisawa and colleagues [**112,113**] have conducted extensive reviews of additional evidence in support of using ivermectin in the treatment of COVID-19.

A meta-analysis of ivermectin use in COVID-19 patients by Bryant *et al.*[**121**], which included both observational and randomized controlled trials, showed the association of ivermectin with a statistically significant reduction in all-cause mortality, and confirmed the robustness of their result with an exhaustive

sensitivity analysis. Bryant *et al.*[**121**] combined outpatient and inpatient studies and noted that there were very few outpatient trials that used a mortality rate reduction endpoint. Thus, their results tend to support the inpatient use of ivermectin, but do not necessarily extrapolate to outpatient use. A thorough discussion of other ivermectin meta-analysis studies was given by Yagisawa *et al.*[**112,113**]. Although meta-analysis studies are at the top of the evidence-based medicine pyramid, in terms of design quality, because of heterogeneity in the treatment protocols used in the treatment and control arms of the included studies, variations in dosage and timing, the evolution of the virus into diverging variants with different multiplication rates and lethality throughout the course of the pandemic, and variability in the prevalence of low-risk vs high-risk patients, a very careful qualitative evaluation of the available underlying evidence is necessary to draw conclusions supported with a sufficient level of certainty.

A randomized controlled trial from Bangladesh by Mahmud *et al.*[**122**] of a pre-hospital combination therapy (12 mg single dose ivermectin and 100 mg doxycycline twice daily for 5 days) that was a reduced lower-dose variation of the Hazan and Stone/Gill multidrug protocol [**29,30,34,35**], given within the first 3 days from the onset of illness, to a combination of 363 low-risk and high-risk patients that excluded patients with hypoxemia (i.e. SpO2 $\leq$ 90%), showed a statistically significant reduction in mortality rate with $p = 0.016$. Another small randomized controlled trial by Hashim *et al.*[**123**] with a cohort of 84 outpatients (classified as mild or moderate) and 33 inpatients (classified as severe or critical), treated between July 1, 2020 and September 30, 2020, used a similar protocol for the treatment group (ivermectin 0.2 mg/kg for 2 days and an optional third dose a week later, doxycycline for 200 mg per day for 5-10 days; standard of care) and only standard of care for the control group, with the standard of care including daily zinc, Vitamin C, D3, azithromycin (250mg/day for 5 days), and dexamethasone or methylprednisolone as needed. No deaths were reported in either group, for the outpatient cohort, due to an intense standard of care, which was initiated within 3 days from the onset of symptoms, for both the treatment and control groups. However, for inpatients in the severe category, there was some mortality rate reduction benefit (0 deaths out of 11 patients in the treatment group against 6 deaths out of 22 patients in the control group) which gives $p = 0.077$, via two-tailed exact Fisher test, not statistically significant but close to the threshold of 0.05.

Several randomized controlled trials, published in high-impact journals, tend to be cited as evidence against the use of ivermectin in treating COVID-19 [**124–130**]. Among these, the COVID-OUT trial [**124**] used a factorial design that compared a treatment group of patients, that received either a 3-day course of ivermectin (approximately 0.4mg/kg) or a 3-day course of ivermectin combined with a 14-day course of metformin, against a control group, that received placebo or placebo combined with a 14-day course of metformin. Since the study did show a statistically significant signal of efficacy for metformin, including it in both the treatment and control arms of the ivermectin trial strongly biases the results towards the null hypothesis, with respect to establishing any efficacy for ivermectin; therefore, neutral results from this study cannot be used to support a recommendation against the use of ivermectin. Furthermore, the duration of ivermectin treatment was too short compared to the 10-day multidrug treatment used by Hazan *et al.*[**30**], Stone *et al.*[**29**], and Borody *et al.*[**7**]. From the other six cited studies [**125–130**], five tested ivermectin monotherapies against placebo [**126–130**]; therefore their results do not necessarily extrapolate to multidrug protocols [**7,10,29,30**] using ivermectin in combination with other medications.

The most decisive endpoints for recommending or not recommending a treatment regimen for a potentially lethal disease are reduction in hospitalizations and deaths, as opposed to soft endpoints such as duration of illness or time to viral clearance. From this perspective, the most compelling study is the I-Tech RCT [**125**], which recruited high-risk patients, with age $\geq$ 50 years and at least one comorbidity between May 31, 2021 and October 25, 2021 in Malaysia. The treatment group was administered with a 5-day high-dose course of ivermectin (0.4 mg/kg), initiated within the first 7 days from symptom onset. Both arms of the trial were treated with corticosteroids, antibiotics, and anticoagulants, with each one of these medications given to approximately 1/4 of the patients of both the treatment and control group, although the number of patients receiving ivermectin monotherapy was not clearly articulated. The paper reported a 4.0% mortality rate in the control group and 1.2% mortality rate in the treatment group with $p = 0.09$, and although there was a signal of mortality rate reduction, it was deemed to be not statistically significant. On the other hand, from 241 patients with 3 deaths in the treatment group, we calculated [**35**] an adjusted efficacy threshold of $y_0 = 3.7\%$, which means that statistical significance can be achieved, if an equivalent control group with an asymptotically infinite size has mortality rate greater than or equal to 3.7%. For untreated high-risk patients with comorbidities, we expect a mortality rate of at least 5% without any treatment for pre-omicron variants [**27**]. Because some treatment was offered to the control group, it had a modest effect in reducing the mortality

rate to 4.1%. However, comparison of the treatment arm of the trial against historical controls of high-risk patients with comorbidities, receiving no treatment, suggest that the multidrug treatment that was actually administered to the treatment arm of the trial was more likely than not effective in reducing mortality rate, despite the treatment being initiated within a 7-day window.

The first ACTIV-6 trial [**126**] enrolled patients between June 23, 2021 and February 4, 2022, overlapping with the Delta variant and the Early Omicron variants, and tested ivermectin monotherapy (0.4 mg/kg for 3 consecutive days) against placebo. Subsequently, the second ACTIV-6 trial [**127**] enrolled patients between February 16, 2022 and July 22, 2022, catching the tail end of Early Omicron and overlapping for the most part with Late Omicron in the United States, and tested an ivermectin monotherapy at higher dosage (0.6 mg/kg for 6 consecutive days) against placebo. No deaths were reported in the placebo arm of either trial, suggesting that the patients were low-risk, possibly owing to some combination of low age and low percentage of comorbidities, reduced virulence of the Omicron variants, prior partial natural immunity from previous COVID-19 infections, and prior vaccine-induced immunity. As such, these studies did not prove the absence of a mortality rate reduction benefit for high-risk patients. No statistically significant reduction in hospitalization rates was reported, and none should have been expected because the treatment was monotherapy that, for a substantial proportion of the patients in the treatment group, was not administered within the first 3 days from the onset of symptoms, which is the ideal window of opportunity for preventing hospitalizations [**28**].

The Lopez-Medina *et al.*[**128**] trial was conducted in Colombia between July 15 2020 and December 21 2020, testing ivermectin monotherapy (0.3 mg/kg for 5 consecutive days) against placebo, was not informative with respect to mortality rate reduction, noting that one death was reported out of 198 patients in the control group and zero deaths were reported out of 200 patients in the treatment group. During the study period, the average CFR in Columbia was 2.58% (number of cases increased from 154277 to 1.5 million and number of deaths increased from 5455 to 40268 between July 15 2020 and December 21 2020) [**131**], so the low mortality rate in the control group indicates that the patients were either at very low risk or they accessed ivermectin over the counter as a result of failure of blinding [**132**]. In either case, the study prima facie enrolled low-risk patients, given the atypically low mortality rate in the control group; therefore it cannot be used to justify a recommendation against the use of ivermectin in treating high-risk patients.

The TOGETHER ivermectin trial [**129**] tested ivermectin monotherapy (0.4 mg/kg for 3 consecutive days) in Brazil between March 23, 2021 and August 6, 2021 against placebo. The results in the intention-to-treat population from both arms of the trial were as follows: reduction in hospitalizations from 14% (control arm) to 11.6% (treatment arm) and smaller reduction in deaths from 3.5% (control arm) to 3.1% (treatment arm), both not statistically significant. A curious characteristic of the trial was that in the treatment arm, the intention-to-treat population decreased from 679 to a per-protocol population of 624, however, in the control arm, there was a massive decrease from a 679 intention-to-treat population to a 288 per-protocol population, signaling a possible loss of blinding. The authors did not conduct the corresponding per-protocol population analysis for either hospitalization or death reduction. The data have not been made available to research groups interested in conducting the per-protocol reanalysis, even though it was requested for that purpose [**133**]. More than half of the patients initiated treatment 4-7 days after the onset of symptoms. During the study period, Brazil was exposed to the highly lethal Gamma variant. By the beginning of March 2021, the cumulative CFR was 2.4%; however, between March 23, 2021 and August 6, 2021 the average CFR was 3.29% (the number of cases increased from 12.00 million to 20.07 million and the number of deaths increased from 295,042 to 559,607) [**131**]. It is plausible that the ivermectin monotherapy, used in the treatment group, was administered too late, for too short a duration, and at an insufficient dose to make a statistically significant difference with an unusually more lethal variant.

The PRINCIPLE ivermectin trial [**130**] was conducted in the United Kingdom between June 23, 2021 and July 1, 2022 testing ivermectin (0.3 mg/kg for 3 consecutive days) plus "usual care" against "usual care". According to the authors, "usual care" included the use of monoclonal antibodies and other antiviral medications for *"a minority of extremely clinically vulnerable patients"* [**130**], which may have biased the trial towards the null hypothesis. Otherwise, the study protocol indicates that prior to hospitalization, "usual care" was only supportive care, so for most patients the comparison was between ivermectin monotherapy against placebo. For the first month, the trial recruited high-risk patients (age $\geq$ 65 years or age $\geq$ 18 years with comorbidity or breathlessness) but after July 29, 2021, the trial recruited both low-risk and high-risk patients with positive COVID-19 test and symptomatic infection with up to 14 days since the onset of symptoms. Although the authors reported randomization at 5 days median (IQR 3-7 days) since onset of symptoms, the initiation of treatment was further delayed because the medications were shipped to the patients. The

authors reported no statistically significant reduction on the composite hospitalization + mortality endpoint. Considering the late onset of treatment and the short treatment duration of only 3 days, it is not surprising that hospitalizations were not reduced, which is why it is important to also consider the mortality endpoint. The authors did report that the ivermectin group included 2,157 patients with 3 deaths but did not report the number of deaths in the control group and did not compare the treatment arm against the control arm in terms of a mortality endpoint. However, because the trial recruited patients without any risk stratification, except for the first month, we may compare the ivermectin group against the concurrent mortality rate of the entire population in the United Kingdom (685 deaths out of 265,355 cases between June 23, 2021 and July 1, 2022) [**131**]. There is a two-fold mortality rate decrease (0.13% CFR for ivermectin group vs 0.25% CFR for the entire United Kingdom population), however, a two-tailed exact Fisher test shows that it is not statistically significant (OR 0.54; 95% CI 0.11–1.58; $p = 0.39$), because the sample size of the ivermectin group is underpowered. A simple calculation shows that to capture a two-fold mortality rate reduction would have required increasing the ivermectin group sample size by a factor of 4. However, the authors terminated the ivermectin treatment arm based on futility criteria using the composite hospitalization + death endpoint. It is worth noting that despite the late administration and short duration of ivermectin treatment, the PRINCIPLE trial showed statistically significant reduction of time to sustained alleviation of symptoms [**130, Figure S6**] and statistically significant reduction of the following long-COVID symptoms at 3 months in the ivermectin group: shortness of breath [**130, Table S7**], inability to concentrate/brain fog [**130, Table S24**], pins and needles or numbness [**130, Table S29**], generalized body pains [**130, Table S31**], joint pains [**130, Table S33**], and fatigue [**130, Table S34**].

Finally, a Cochrane meta-analysis of ivermectin randomized controlled trials [**134**] 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.*[**122**] and Hashim *et al.*[**123**], both discussed previously), which reported positive results, solely due to the use of these drugs in combination. In total, the Cochrane meta-analysis [**134**] excluded 11 studies that used ivermectin-based multidrug therapies, with the sole justification that these were combined interventions; therefore the findings of the Cochrane meta-analysis [**134**] do not extrapolate to ivermectin-based multidrug treatments. Unlike the Bryant *et al.*[**121**] meta-analysis, the Cochrane meta-analysis [**134**] also excluded all observational controlled trials, despite known empirical evidence that observational and randomized controlled trials, on average, tend to provide similar effect size estimates [**135, 136**]. 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 [**134**] and Bryant *et al.*[**121**].

The Cochrane meta-analysis selected 11 randomized controlled trials, of which 1 was later retracted, 3 were previously discussed (TOGETHER [**129**], Lopez-Medina *et al.*[**128**], and ITECH [**125**]), and 4 have no mortality reported in either the treatment or control group (Buanfrate *et al.*[**137**], Chaccour *et al.*[**138**], Krolewisky *et al.*[**139**], Mohan *et al.*[**140**]), due to all patients surviving. The remaining 3 studies were Vallejos *et al.*[**141**], Ravikirti *et al.*[**142**], and Gonzalez *et al.*[**143**]. Vallejos *et al.*[**141**] is an outpatient study involving 500 patients that used an ivermectin monotherapy in the treatment group for 2 days (dose staggered by weight, ranging from 0.15 mg/kg to 0.2 mg/kg) that found no hospitalization or mortality rate reduction efficacy. Ravikirti *et al.*[**142**] is an inpatient study of 112 patients with oxygen saturation above 90% using a similar ivermectin monotherapy (12 mg per day, not adjusted by weight, for 2 days) and reported no deaths in the treatment group and a compelling mortality rate reduction signal that is not statistically significant (we calculated $p = 0.11$ using two-tailed exact Fisher test, but the authors incorrectly report statistical significance). In both cases, the treatment group received insufficient ivermectin monotherapy for only 2 days.

The remaining study, Gonzalez *et al.*[**143**], is an interesting inpatient randomized controlled trial of 106 patients with very severe hypoxemia (average oxygen saturation reported as $83\% \pm 8\%$ who were seen between May and August 2020 in Mexico. The patients in the treatment group received standard of care and ivermectin (0.15 mg/kg to 0.22 mg/kg dose staggered by weight for 5 days), with the standard of care including thromboprophylaxis for 90% of patients, steroids for approximately half of the patients, and macrolides for approximately 1/5 of patients. The study reported an approximately equal mortality rate in both the treatment and control groups. Although the ivermectin dosage was approximately similar to that used in the Babalola case series [**31**], it did not include zinc, vitamin C, and vitamin D, and although some antibiotics were used for some patients, they did not appear to have included doxycycline, and they were not used across the board in all patients. Our more conservative analysis has not been able to claim a hospitalization or mortality rate reduction benefit for patients in the Babalola case series either, where there were 5 deterioration events, albeit no deaths [**31, 70**]. The Gonzalez [**143**] cohort included a large proportion of patients, approximately half of the

entire cohort, with oxygen saturation below 80%, for which the Stone/Gill protocol [**34,35**] recommends a far more aggressive salvage protocol with an initial 0.6 mg/kg stat dose of ivermectin, titrated up to 1-2mg/kg, if SpO2 does not increase, then maintained at 0.3-0.6 mg/kg for up to 10 days or until symptom free for 48 hours, in conjunction with continuous nanosilver nebulizations, while room air SpO2 $\leq$ 90%, doxycycline, corticosteroids, and anticoagulants (see Table 1). In the Babalola case series, only 10 out of 61 patients had room air oxygen saturation below or equal to 90%, so the absence of deaths in the Babalola case series, which has not been sustained by Gonzalez *et al.*[**143**], is most likely to be attributed to the substantial difference in the risk profile between the two cohorts. From Gonzalez *et al.*[**143**] we infer that a minimal 5-day low-dose ivermectin-based protocol that excludes nanosilver nebulizations, doxycycline, zinc, and vitamins C and D appears to be insufficient for the treatment of the most severe hypoxemic patients.

In summary, from amongst the cited randomized controlled trials on outpatients, the I-Tech trial [**125**], in which a high-dose ivermectin-based multidrug treatment protocol was used relatively early on high-risk outpatients, over a 5-day period in the treatment arm, presents a compelling signal of benefit with respect to mortality rate reduction, with a 3.7% efficacy threshold that compares favorably with the expected mortality rate for such high-risk patients, when they are not offered any early treatment. ACTIV-6 [**126,127**] and Lopez-Medina *et al.*[**128**] used ivermectin monotherapies on prima facie low-risk patients, and therefore cannot be used to justify a negative recommendation against the use of ivermectin for treating high-risk patients. The TOGETHER trial [**129**] 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.*[**7**], Hazan *et al.*[**30**], and Stone *et al.*[**29**]. The PRINCIPLE trial [**130**] showed that ivermectin use, despite short duration and late administration, resulted in statistically significant reduction of time to sustained recovery of symptoms and prevalence of certain long covid symptoms within a 3-month window; a two-fold mortality rate reduction was also observed relative to the population-level concurrent CFR, but the study was interrupted before reaching statistical significance. Gonzalez *et al.*[**143**] shows that even a 5-day low-dose ivermectin monotherapy with adjunct anticoagulation is insufficient, by itself, in terms of reducing the mortality rate, when treating the most severe hypoxemic COVID-19 patients in a hospital setting. However, the oxygen saturation recovery trend in the Babalola case series (see Fig. 1) shows that even alone, ivermectin does have an active role in driving the normalization of oxygen saturation, which appears to be further intensified mainly by the inclusion of doxycycline in the Hazan and Stone case series [**29,30**]. Mahmud *et al.*[**122**] and Hashim *et al.*[**123**] are the only randomized controlled trials of ivermectin + doxycycline combination (albeit at lower dosages) with a mortality endpoint that have been identified by the Cochrane meta-analysis [**134**]. Both studies showed positive signals of efficacy with respect to mortality rate reduction (Mahmud *et al.*[**122**] for early outpatient treatment and Hashim *et al.*[**123**] for inpatients) despite the low ivermectin dosage, thus corroborating the possible existence of a very important synergistic effect between ivermectin and doxycycline. This synergistic interaction of ivermectin and doxycycline and the variable dosage of ivermectin based on the severity of disease are the most plausible reasons for the rapid normalization of SpO2 levels in hypoxemic patients and for our finding of some hospitalization and mortality rate reduction benefit from the use of the Hazan and Stone/Gill protocols [**29,30,34,35**] on hypoxemic COVID-19 patients.

## 4. Discussion

### 4.1. Summary of findings on strength of association

We analyzed the case series of hypoxemic patients reported by Hazan *et al.*[**30**], Stone *et al.*[**29**], and Babalola *et al.*[**31–33**] using a self-controlled case series methodology combined with the recently introduced case series statistical analysis technique [**27**], and showed clear and convincing evidence of the existence of some 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 can result, if the patient sample is randomly selected from the general population. 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 quantified the considerable resilience of this result with respect to systemic selection bias, which can 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 most aggressive variations of the multidrug protocol were used in very high-risk patients.

The main focus has been on establishing the existence of some mortality rate reduction by forming a 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.*[**30**] establishes mortality rate reduction, albeit with $p$-value $p = 0.044$, which is very close to 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 [**55**]), for a 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 it is more likely than not that the claim cannot be overturned by selection bias, if the patients in the case series have been randomly selected from the general population.

Combining the Hazan and Stone case series decisively establishes the existence of mortality rate reduction by the preponderance of evidence, even when compared against the most conservative estimate of CFR for hospitalized patients in the United States, under the age $>$ 50 years restriction. Including the Babalola case series, to combine all three case series, decisively shows mortality rate reduction by the preponderance of evidence against even the most conservative estimate of the CFR for hospitalized patients using the CDC case surveillance database [**55**], even without the age $>$ 50 years 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, owing 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 [**31**]. Furthermore, as shown in Fig. 1, the recovery rate of SpO2 levels in the Babalola case series was distinctly slower than the recovery rates observed in both the Hazan and Stone case series. Thus, conclusions drawn from the Hazan + Stone combined case series are more reliable than conclusions drawn from the Hazan + Stone + Babalola case series or from the combined Hazan + Babalola or Stone + Babalola case series. Nevertheless, in terms of sensitivity analysis, all of these combinations have also yielded positive results for strength of association between the multidrug protocols and reduced hospitalization and mortality rate.

Babalola *et al.*[**31**] found that adding hydroxychloroquine and azithromycin to ivermectin did not appear to contribute to faster clearance of the virus. However, it is worth noting that the dosage of hydroxychloroquine was 200 mg/day for 3 days and the dosage for azithromycin was 500 mg/day for 3 days. In the original Zelenko protocol [**5**], hydroxychloroquine was administered at 200 mg twice a 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 to her baseline protocol of ivermectin, doxycycline, zinc, and vitamins C and D was necessary to eradicate the virus for some of her patients [**71**].

Because for all three case series, patients were treated before the emergence of the omicron variants, natural immunity remained protective with respect to reinfections [**144**], so it is very likely that the results have not been confounded by prior immunity. Babalola and colleagues [**31**] reported that their 61 patients, who were treated with the ivermectin-based multidrug protocols were not vaccinated. In the United States, the vaccine roll out started in mid-December 2020 [**145**], and given the two-dose schedule we expect that patients in the Hazan case series were not fully vaccinated until the beginning of February 2021, which was the final month for the treatment time period of the Hazan case series [**30**]. Furthermore, the treatment time period for the

Hazan case series does not intersect with the third pre-delta period [**30, 58**] during which a substantial decline in the hospitalized CFR was observed in the CDC database [**55**]. In Zimbabwe, vaccines were rolled out on February 2021 [**146**], so they were available for 4 out of 10 months of the treatment time period for the Stone case series [**29**]. Nevertheless, given that all patients in the Stone case series presented with baseline room air SpO2 $\leq$ 93% and all but one of the patients in the Hazan case series presented with SpO2 $\leq$ 90%, we can infer that there was insufficient antiviral immune response at the initial onset of the illness, specifically for any of the selected patients in these case series that may had been fully vaccinated.

An incidental finding from our analysis of the CDC case surveillance database [**55**] 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 in the hospitalized CFR during the third pre-Delta period, which coincided with the initial 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 levels comparable to the first two pre-Delta periods, and persisted through the Early Omicron period. However, during the Late Omicron period, the hospitalized CFR decreased by an approximate factor of 1/5, suggesting the beginning of a substantial decrease in the virulence of SARS-CoV-2.

With the emergence of the Omicron variants during 2022, the overall CFR in the United States decreased and the earlier Delta variants were displaced because natural immunity against Omicron variants also prevented infections with the Delta variant [**147**]. The decreased lethality of the Omicron variants can be explained by their reduced efficiency in invading the lung parenchyma and, from there, the bloodstream [**148**]. However, the in vitro study by Boschi *et al.*[**38**] showed that the Omicron spike proteins induce red blood cell clumping even at approximately 10 times less minimum concentration than the spike proteins of the Wuhan, Alpha, and Delta variants, which can be explained, in part, by the increased electrostatic surface potential of the Omicron spike proteins [**38**]. Boschi *et al.*[**38**] also showed that the minimum ivermectin concentration needed to inhibit or release hemagglutination induced by the Omicron spike protein is equal to the minimum ivermectin concentration needed to result in the same effect against the Delta spike protein. Furthermore, Table 5 shows that, although COVID-19 hospitalizations decreased during the Late Omicron period in the United States, some patients still presented with severe life-threatening COVID-19 disease. Ivermectin-based multidrug protocols remain relevant for handling these severe cases.

### 4.2. Limitations

Our statistical analysis has several limitations. The main weakness of our analysis is the small sample size of the case series, even when combining all three series, that prevents us from establishing a claim of clear and convincing mortality rate reduction with some modest amount of systemic selection bias tolerance. 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 other variants of comparable lethality. More lethal variants may require more aggressive multidrug treatment protocols, and for far less lethal variants, treatment with prescription drugs may not be necessary. As 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 establishes a clear and convincing claim of hospitalization rate reduction with substantial systemic selection bias tolerance, hospitalization is a more subjective endpoint than mortality. 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 recommended by the official standard of care guidelines promulgated by the NIH [**76**] and other government agencies worldwide.

The CDC case surveillance database [**55**] 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 underestimate its true magnitude, so neutral results should be interpreted with caution. Our analysis of the CDC case surveillance database [**55**] used the snapshot downloaded on January 20, 2023. Subsequent updates of the database resulted in negligible fluctuations in the hospitalized CFR over the same periods. The available external control groups for Zimbabwe [**59, 60**] and Nigeria [**62, 62**] also have small sample sizes and could thus have some biases. 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 tried to mitigate this by using conservative estimates, temporal averaging, and several possible external control groups.

### 4.3. Epistemology of the Bradford Hill criteria

Our statistical analysis has shown the strength of association between the ivermectin-based multidrug protocols and the reduction in hospitalization and mortality rates. We have also argued that the Bradford Hill criteria [**64**] of temporality, biological gradient, consistency, biological plausibility, and coherence are satisfied. Using the Bradford Hill criteria to infer causality has been controversial [**149**], because one may argue that neither one of the criteria is necessary nor sufficient for establishing causality, with the underlying concern being the strength of the inference that follows once the Bradford Hill criteria have been established.

Howick and colleagues [**65**] have proposed revised Bradford Hill "guidelines for causation" and several clear counterexamples of convincing inferences that can be supported via their revised Bradford Hill "guidelines" without support from a randomized controlled trial. In their reorganization, Howick *et al.*[**65**] separated the available evidence in three categories: direct evidence, mechanistic evidence, and parallel evidence. Direct evidence includes: *size of effect* (superseding "strength of association"), *temporal and spatial proximity* (extending "temporality"), *dose responsiveness* (superseding "biological gradient"). Mechanistic evidence includes *plausible mechanism* (extending "biological plausibility") and *coherence*. Parallel evidence includes *replicability* (superseding "consistency") and *similarity* (extending "analogy"). Howick *et al.*[**65**] excluded Bradford Hill's "specificity" and "experiment". The salient differences resulting from the proposed revision by Howick *et al.*[**65**] were the following: (a) Direct evidence play the decisive role whereas mechanistic and parallel evidence play only supporting roles; (b) For "size of effect" the key consideration is to show that the magnitude of the association exceeds the magnitude of any plausible confounders; (c) temporal/special proximity highlights that the strength of Bradford Hill's concept of temporality is stronger when the proximal distance between intervention and response is decreased and when it is consistent with the underlying mechanism of action, and the guideline is extended to encompass spatial proximity; (d) plausible mechanism extends Bradford Hill's "biological plausibility" to non-biological mechanisms.

In connection with these revised criteria we note that: (a) the observed SpO2 recovery from the onset of treatment is indeed remarkably immediate for both the Hazan and Stone case series, occurring within 24 hours; (b) using the case series threshold analysis technique [**27**], we found that a claim of the effect size exceeding plausible confounders is clear and convincing with respect to the hospitalization rate reduction endpoint and supported by the preponderance of evidence with respect to the mortality rate reduction endpoint; (c) in addition to good direct evidence, both mechanistic and parallel evidence have been established.

Ward [**66**] has highlighted and responded to another angle of attack against the Bradford Hill criteria, which is also applicable to the revised "guidelines" by Howick *et al.*[**65**]. One may argue that, whereas a causal inference from a randomized controlled trial is an inductive inference, any inference justified via the Bradford Hill criteria is neither a deductive nor inductive argument, because of its qualitative nature, and therefore not legitimate. Ward [**66**] resolved this potential criticism by observing that an inference based on the Bradford Hill criteria is in fact what philosophers identified as *inference to the best explanation*.

The concept of "inference to best explanation" was crystallized by Harman [**67**], who defined it as a logical inference that begins with an array of factual evidence and infers the truth of a specific hypothesis by arguing that this specific hypothesis, if true, provides the best explanation for the available evidence relative to any other alternative hypothesis. This method of non-deductive reasoning is distinct from enumerative induction (i.e. if all observed A's are B's then we conclude that all A's are B's, as per Harman [**67**]). It is also distinct from the broader definition of inductive reasoning highlighted by Ward [**66**], according to which *"an inductive inference is any logical inference that is not [a] deductively valid inference where . . . it is improbable, given that the premises are true, that the conclusion is false"* [**66**]. With an inductive inference, the strength of the inference can be quantified probabilistically, whereas an inference to the best explanation argument has either a qualitative nature or a hybrid combination of both quantitative and qualitative considerations. In the context of the Bradford Hill criteria, Ward [**66**] argued that given a strong association, an argument showing several of the other Bradford Hill criteria constitutes an inference to the best explanation argument in favor of the hypothesis that the association is causal. A properly conducted randomized controlled trial, on the other hand, can establish the internal validity of causality, specifically for the trial sample, by providing an inductive argument, in the broader sense, in support of rejecting the null hypothesis.

Although Ward [**66**] argued that inductive inference arguments are generally stronger than inference to the best explanation arguments, Harman [**67**] did argue, in our view convincingly, that the narrower concept of enumerated inductive arguments should be understood as a special case in the broader class of inference to the best explanation arguments. We believe that Harman's argument can be expanded to the epistemology of randomized controlled trials, by noting that it is necessary to be able to argue in favor of the external

validity of the trial results, as was highlighted in detail by Deaton and Cartwright [**150**]. Thus, although the internal validity of a causality finding by a randomized controlled trial is supported by inductive reasoning, the additional argumentation that is needed to support the external validity of the trial itself is an inference to the best explanation type argument that may require consideration of qualitative background knowledge that cannot be captured in a strictly inductive reasoning framework. The other side of the argument is that, although Ward acknowledged [**66**] the ongoing debate about whether or not an inference to the best explanation argument can be used to establish the truth of a hypothesis, Howick and colleagues [**65**] proposed several counterexamples where their revised Bradford Hill criteria give strong arguments in favor of causality, that are inference to the best explanation arguments, even in the absence of randomized controlled trials. These considerations lend support to the argument by Aldous and colleagues [**151**] that quality of study design (in the sense of the evidence-based medicine pyramid) does not necessarily imply higher certainty concerning the validity of the study's results, and conversely higher certainty does not necessarily require a study design of higher quality, which is why Aldous *et al.*[**151**] highlighted the need for a paradigm shift towards considering the totality of the available evidence.

We conclude with an important observation by Phillips and Goodman [**149**] who focused on some additional oftentimes overlooked insights by Bradford Hill [**64**]. One of them is that, aside from making causality inferences, policy actions should be informed not only by the strength of the available evidence but also by the *"absolute costs and benefits of potential actions"* [**149**]. With the proposed ivermectin-based multidrug protocols, based on repurposed medicines, the potential absolute costs of using them are negligible but the potential benefits are life-saving. This consideration was just as salient as the strength of the evidence in support of causality when deciding whether these protocols should have been more widely encouraged at the time when they could have saved more lives.

## 5. Conclusion

Our statistical analysis has shown that the existence of some hospitalization rate reduction is clear and convincing when the Stone/Gill or Hazan multidrug protocol is employed in severely hypoxemic patients, and it is also very resilient to systemic selection bias. 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. These findings support the strength of association between the Hazan and Stone/Gill multidrug protocols and reduction in hospitalizations and deaths. Combined with previous results establishing the Bradford Hill criteria of temporality, biological gradient, consistency, biological plausibility, and coherence 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 the reviewed evidence indicates that variable dosing of ivermectin, depending on the severity of initial presentation, is essential and the inclusion of doxycycline, zinc, vitamin C, vitamin D, and nanosilver nebulizations provide important synergistic effects that are necessary for the successful treatment of hypoxemic patients.

Given the capability of this combination of medications to rapidly normalize the SpO2 levels of hypoxemic patients, it is a compelling extrapolation to also use these protocols in the treatment of high-risk symptomatic COVID-19 outpatients to prevent red blood cell clumping and/or oxygen desaturation, rather than wait for complications to arise and only then attempt to address them. 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, who 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.

**Abbreviations**

$\alpha$7nAChr, alpha-7 nicotinic acetylcholine receptor; AgNP, silver nanoparticles; CDC, Center for Disease Control and Prevention; CFR, Case Fatality Rate; CD147/EMMPRIN, Cluster of differentiation 147 / extracellular matrix metalloproteinase inducer; COVID-19, Coronavirus Disease 2019; DPP4/CD26, Dipeptidyl peptidase 4 / cluster of differentiation 26; IL-6, Interleukin 6; LMIC, Low or middle income country; MMP-9, matrix metalloproteinase-9; NF-$\kappa$B, Nuclear factor kappa B; NIH, National Institute of Health; RDRP, RNA Dependent RNA Polymerase; PaO2, Partial pressure of oxygen; S1-NTD, S1-N-Terminal Domain; S1-RBD, S1 Receptor Binding Domain; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO2, Peripheral oxygen saturation; TNF-$\alpha$, tumor necrosis factor alpha; WHO, World Health Organization.

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**Availability of data and materials**

The January 20, 2023 snapshot of the CDC database used for our calculations is available from the corresponding author upon request, because of the large size of the data file (0.9GB with compression). The current version of the database can be downloaded from the CDC website [**55**]. The baseline room air SpO2 data for the Hazan and Stone case series are available from the respective publications [**29,30**]. We have made the following data and materials available on Figshare [**35**]: (1) the computer code and the details of the calculations of the efficacy thresholds and random selection bias thresholds for all case series discussed in this paper; (2) the computer code used to generate the LaTeX code for typesetting Table 2, Table 3, Table 5, Table 6, Table 7, Table 9, and Table 10 directly from the data; (3) the baseline room air SpO2, age, and sex data for the Babalola case series, with permission from Olufemi Babalola; (4) the unpublished Parirenyatwa hospitals redzone statistics document [**59**] and an updated version of the Stone/Gill protocol document [**34**], provided to us by Jackie Stone.

**Author contributions**

EG and PMc conceptualized the formulation and goals of the study. EG conducted the statistical analysis, developed the corresponding computer software, and curated the research data. EG and CA wrote the initial draft of the paper. EG, PMc, and CA contributed revisions to the initial draft of the paper. All authors have read and approved the final manuscript. EG and CA confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

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

**Patient consent for publication**

Not applicable.

**Conflict of interest**

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

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