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Research Article

Rapid Recovery of Peripheral Oxygen Saturation in Hypoxic COVID-19 Patients With Ivermectin/Doxycycline/Zinc Multidrug Therapy

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Abstract: Several combination therapies for the early outpatient treatment of COVID-19 were proposed by independent research groups at the onset of the pandemic during 2020 and 2021. In this observational study, we report on the outcomes of an off-label triple combination therapy, consisting of ivermectin, doxycycline, and zinc, with adjunct vitamin C and D3 supplementation, which was used on high-risk COVID-19 patients. These patients refused an initial recommendation to seek inpatient care, despite a high-risk presentation compounded with one or more comorbidities and/or severe hypoxia. Telemedicine was used to administer personalized treatment to patients at home, who did not have access to supplemental oxygen. Descriptive statistics was used to describe patient characteristics and outcomes. Of 26 consecutive patients, 25 presented with baseline $SpO_2 \leq$ 90% on room air. All 24 of 26 patients accepting the 10-day treatment survived without hospitalization. Within 24 hours on combination therapy, a rapid response of SpO_2 levels on room air was observed with a statistically significant median +6% (IQR 5-7%) increase between baseline (day 1) and day 2, with 18 patients stabilized at $SpO_2 > 90\%$ by day 2, and with full recovery of SpO_2 levels on room air within 10 days for all 24 patients who completed the 10-day treatment. Faster recovery rates of room air SpO_2 levels were observed in patients receiving an additional 36 mg ivermectin stat dose. All other symptoms were resolved within less than 20 days for 23 of 24 patients accepting treatment. All 24 patients fully recovered within 33 days. The results are assessed in the context of previous case series with similar treatments, historical controls suggesting longer recovery time-scales with non-ivermectin treatments, and previous randomized controlled trials.

Keywords: Coronavirus, COVID-19, Doxycycline, Ivermectin, Sars-Cov-2, Zinc

Introduction

At the onset of Coronavirus Disease 2019 (COVID-19) and throughout years 2020 and 2021 there was minimal guidance from government authorities in the United States about the early outpatient treatment of COVID-19. Given the complexity of the disease, and the need to take decisive action to save lives in response to an emergency crisis (McCullough and Oskoui, 2020), several combination therapy protocols were proposed by independent research groups (Derwand et al., 2020; McCullough et al., 2020; Santin et al., 2021).

Combination therapies have a long history, which includes Borody's successful treatment of peptic ulcers with a triple-drug therapy targeting the Helicobacter pylori (George et al., 1990) and have previously demonstrated superior efficacy over monotherapies in treating several other diseases such as HIV, tuberculosis, Hepatitis B, C and the Herpes simplex virus (Dolai et al., 2024; Lange, 1995). Combination therapies offer several advantages, including mitigating the risk of antimicrobial resistance (Fischbach, 2011), allowing for reduced

dosages of individual agents to minimize adverse effects (Lehar et al., 2009), and leveraging multiple mechanisms of action to achieve enhanced efficacy.

This observational descriptive study presents the outcomes of a case series of 26 consecutive patients (hereafter Hazan case series) with severe COVID-19 who were offered a 10-day Ivermectin, Doxycycline, Zinc Combination Therapy (IDZCT), as initially proposed by Borody (Santin et al., 2021). Vitamins D3 and C were also included in this regimen to supplement common deficiencies in the elderly population. These patients, who had been referred to inpatient care, declined hospitalization, opting for outpatient treatment via telemedicine, and were managed at home without access to oxygen concentrators.

Ivermectin was chosen as the primary agent for IDZCT because of a wide range of multiple antiviral, anti-inflammatory, immunomodulatory, and antithrombotic mechanisms of action (Zaidi and Dehgani-Mobaraki, 2022), which may contribute towards an overall therapeutic benefit throughout all stages of the COVID-19 disease. Favorable characteristics of ivermectin include its excellent safety record, the wide range of well-tolerated dosage (Guzzo et al., 2002; Navarro et al., 2020), and lack of toxicity at higher doses beyond the therapeutic range (Chung et al., 1999; de Castro Jr et al., 2020), allowing for flexible dose adjustments.

Doxycycline was chosen to protect against opportunistic bacterial superinfections, because of no drug-drug interactions with ivermectin and zinc and no QT prolongation side effect (Malek and Granwehr, 2021). Doxycycline has additional anti-inflammatory mechanisms that mitigate the cytokine storm phase of COVID-19 (Chen et al., 2020; Wong et al., 2017) and antiviral mechanisms that inhibit both viral fusion and viral replication (Malek et al., 2020). Zinc was included in IDZCT because intracellular zinc is a known antiviral agent that inhibits viral replication by interfering with the RNA-dependent RNA polymerase (RdRp) protein driving the replication process of several RNA viruses, including SARS-CoV-2 (Derwand and Scholz, 2020). However, zinc requires a zinc ionophore to enter the cell. Both ivermectin and doxycycline may act as zinc ionophores, allowing intracellular zinc to exert an additional antiviral effect (Malek et al., 2020; Rizzo, 2020). Notably, zinc also has independent immunomodulatory mechanisms that are separate from its antiviral activity (Skalny et al., 2020).

The choice of a 10-day treatment period was empirically determined by Borody's research group in Australia, as this treatment appeared to be beneficial to patients with severe COVID-19 who did not initiate treatment within three to four days from the onset of symptoms. Previously, a shorter 5-day treatment period was recommended by the early Zelenko protocol (Derwand et al., 2020) for the early outpatient treatment of COVID-19 during the earliest viral replication phase of the illness and prior to the development of severe disease. Subsequently, treatment periods ranging from 5 to 30 days were recommended depending on patient response (McCullough et al., 2020, Figure 3). Standard dosages of zinc and doxycycline were used over the 10-day treatment period. In contrast, ivermectin dosing was tailored to individual patients, adjusted in 12 mg increments based on disease severity and treatment response, across the 10-day treatment period. This approach leveraged the medication's wide safety margin and the observed dose-response relationship with the oxygen saturation recovery rate, with patients receiving ivermectin in 12 mg pill formulations.

This study is of unique interest because rapid stabilization of oxygen saturation was observed on room air, within 24 hours, from a baseline $SpO_2 \leq 90\%$ (with one exception) for most patients accepting the IDZCT. Similar rapid stabilization of oxygen saturations was observed with ivermectin-based treatment in case series of hypoxic COVID-19 patients by Stone et al. (2022) (hereafter Stone case series) and Babalola et al. (2021) (hereafter Babalola case series). However, the Stone case series used more concomitant medications, used ivermectin synergistically with nebulized nanosilver to restore oxygen saturation, and treated patients in person by the physician or via traveling nurses visiting patients at home. Furthermore, the Babalola case series used a weaker incomplete protocol over a shorter 5-day period, with weaker effect, so it is not a replication of the Stone case series. The research gap addressed by this study is the replication of the observations of the Stone case series using a similar 10-day triple-drug protocol, without nebulized nanosilver, with fewer concomitant medications, and in a telemedicine setting.

For ethical reasons and because of lack of personal equipoise, this study did not use a control group and patients were treated with off-label therapy outside the scope of any clinical trial. As a result, this study cannot make inductive inferences about treatment efficacy and about disentangling treatment effects from natural recovery, regression to the mean, or selection bias. Nevertheless, we will conclude with a thorough assessment of the available evidence and suggest possibilities for future research.

Materials and Methods

Setting

This study is a retrospective observational case series reviewing and analyzing the medical records of consecutive COVID-19 patients who received individualized outpatient off-label medical care via telemedicine through an outpatient clinic (ProgenaBiome) in Ventura, CA. Most patients in this study were drawn during the time period between August 2020 and February

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2021 from a cohort initially considered for outpatient clinical trials, evaluating a hydroxychloroquine-based treatment protocol for COVID-19, which were administered by ProgenaBiome. These patients were excluded from those clinical trials due to either presenting with baseline room air $SpO_2 \leq 90\%$ or due to not satisfying the trials' inclusion criteria. Other patients in this study were initially enrolled in these outpatient clinical trials, but their participation was discontinued by the trial investigator because they were deemed treatment failures, when deteriorating to $SpO_2 \leq 90\%$ on room air or when being deemed too sick to qualify for continuing participation in a placebo-controlled outpatient clinical trial. Patients from both cohorts were advised to seek inpatient care, however all refused hospitalization for various personal reasons, including a preference to remain at home with family during a critical illness. Consequently, these patients were offered individualized outpatient medical care from their home by ProgenaBiome physicians via telemedicine using off-label medications outside the scope of any clinical trial. The case series in this study is comprised of all consecutive patients from both of these cohorts, who were initially diagnosed during the given time period (August 2020 to February 2021). Sabine Hazan, the lead author of this study, personally administered the off-label treatment to all patients. All patients received an informed consent form, via email, to read and sign if they agreed to participate in the study. The consent form informed patients about the potential risks of treatment and that they would be administered off-label treatment.

Patients

This is a consecutive case series of 26 patients who were offered IDZCT, either after exclusion from or after clinical failure of, a hydroxychloroquine/azithromycin outpatient trial for COVID-19. Of the 26 patients, 25 had baseline $SpO_2 \leq 90\%$, 24 of 26 declined hospitalization referral immediately, and 2 of 26 declined further hospitalization after receiving some inpatient care. All were offered IDZCT; 25 initiated treatment and 1 died before the first dose. Of the 25 patients, 24 patients fully complied with IDZCT, and 1 patient reconsidered his decision to refuse hospitalization after day 2, resulting in discontinuation of IDZCT. No eligible patient declined IDZCT in favor of an alternative outpatient management.

Inclusion criteria for this patient case series were:

(1) Informed consent
(2) Positive RT-qPCR COVID-19 test
(3) Age $\geq$ 18 years
(4) Agreement to practice two highly effective methods of birth control, if of childbearing potential

All screened patients were consecutive and met the inclusion criteria. Exclusion criteria were:

(1) Allergies or drug interactions with IDZCT components
(2) Contraindications to ivermectin and/or doxycycline, including seizure risk and pregnancy

No patients were excluded by the exclusion criteria.

Treatment

At home treatment was initiated as soon as was practical, within 72 hours of patients presenting to ProgenaBiome. IDZCT consisted of a protocol of 10 days of oral doxycycline (100 mg twice daily), ivermectin (12mg minimal dose on day 1, day 4, and day 8), zinc (25 mg twice daily), with adjunct use of vitamin D3 (1500 IU twice daily) and vitamin C (1500 mg twice daily). IDZCT was administered daily for 10 days only. Patients did not have access to oxygen concentrators at home and were treated on room air throughout the 10-day treatment period.

Because the rate of SpO_2 increase on room air appeared responsive to increased ivermectin dosage, ivermectin dose was escalated above the baseline in 12mg increments on a daily basis throughout the 10-day treatment period, whenever SpO_2 plateaued or exhibited a decreasing trend, aiming to sustain a continuous upward trend. Within the first 24 hours, ivermectin dose was further escalated to accelerate the rate of recovery with the goal of stabilizing patients on room air with $SpO_2 > 90\%$ by the end of day 2. Most patients showed an initial SpO_2 increase within 3-6 hours of ivermectin administration, informing subsequent dose escalations (also spaced ~ 3-6 hours apart, when needed) until SpO_2 exceeded 95%. An increased 36mg stat dose of ivermectin was given to some patients at the beginning of treatment, when the treating physician was concerned about patient prognosis within the next 24 hours. De facto, the stat dose was given to all patients with $SpO_2 \leq 75\%$. These ivermectin dose-escalations were not strictly protocolized but were determined empirically based on these general guidelines and individual patient's SpO_2 levels response. We stress that ivermectin dose escalation and frequent patient monitoring, required for its implementation, were not *ad hoc* modifications of IDZCT but an integral and mandatory component of IDZCT itself.

Some patients received concomitant medications before or during IDZCT as follows. Two patients received remdesivir from a prior hospitalization, one patient received monoclonal antibodies prior to initiating IDCZT treatment, patients who were deemed treatment failures in a preceding clinical trial may have received either hydroxychloroquine and azithromycin or placebo, and 4 patients received hydroxychloroquine concurrently with

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IDZCT. Detailed full disclosure of the use of concomitant medications is given in the Results section. These patients were not excluded from the case series because:

(1) The observed deterioration to baseline room air $SpO_2 \leq 90\%$ prior to IDZCT suggests failure of the known and/or conjectured antiviral mechanisms of remdesivir, monoclonal antibodies, hydroxychloroquine, and/or azithromycin for patients receiving these treatments prior to beginning IDZCT
(2) Concurrent administration of hydroxychloroquine for 3 patients was in response to more challenging prognosis, in the physician's judgment, and excluding these patients could result in selection bias towards more favorable observations
(3) In one patient, concurrent administration of hydroxychloroquine was due to treatment of a concurrent autoimmune condition that increased patient vulnerability to COVID-19 and excluding this patient would again result in similar selection bias as in item (2)

Drug Sourcing

Ivermectin and doxycycline were sourced from local pharmacies. Vitamin C, Vitamin D, and zinc used in this study were sourced from biomeboosters.com. These were customized and lab-tested for quality and consistency by ProgenaBiome. Testing included empirical observation that taking these supplements does not have an adverse effect on the gut microbiome that might result from the excipients used in the specific supplement formulation.

Oxygen Saturation Thresholds

Peripheral oxygen saturation on room air with $SpO_2 > 95\%$ was deemed to be *within curative range*, as it relates to resolution of hypoxia, although not implying full resolution of all symptoms. NIH guidelines defined $SpO_2 \leq 93\%$ as a sufficient condition for *severe COVID-19 disease* (National Institutes of Health, 2024). The lower threshold $SpO_2 \leq 90\%$ was deemed a sufficient (but not necessary) condition for recommending hospitalization to patients, for deeming them treatment failures in a previous outpatient clinical trial, or for excluding them from participation in an outpatient clinical trial. Because patients receiving IDZCT were being treated in an outpatient setting after refusing an initial hospitalization referral, they were deemed *stabilized* when $SpO_2 > 90\%$, meaning that continuing outpatient treatment was now better aligned with the physician's original inpatient referral criteria. Consequently, the treating physician strived to stabilize all patients receiving IDZCT within 24 hours.

Monitoring

Patients were required to self-record their symptoms for the first 10 days in their daily logs. Vital signs, including electrocardiograms (EKGs), blood pressure, and temperature (recorded in Fahrenheit), were measured at home using provided medical equipment. Additionally, patients self-collected SARS-CoV-2 testing swabs on days 1, 5, 10, and 30, which were then sent to a pathology lab for analysis. Pregnancy tests were conducted as necessary. Medication intake was monitored through daily communication between the treating physician and patients, ensuring compliance, and patients were instructed to report any adverse events during these daily interactions. There was no set time limit on patient monitoring for adverse events and/or symptoms resolution; patients were regularly monitored until the full resolution of all symptoms. FDA-approved oximeters were provided to patients to ensure the accuracy of room air SpO_2 measurements. Patients were instructed to self-monitor SpO_2 in a resting position, following standard guidelines provided to them. These guidelines included using a clear finger without nail polish, warming up the hands prior to measurement, making sure that the reading is stable for approximately half a minute, and averaging measurements in case of variability. Patients emailed pictures of the SpO_2 oximeter measurements to the treating physician to assert measurements.

Baseline SpO_2 on room air was measured before commencing treatment. Afterwards, room air SpO_2 was continuously monitored and reported to the treating physician during at least day 1 and day 2 to guide ivermectin dose adjustments, as needed. SpO_2 was continuously monitored until recovery of oxygen saturation with $SpO_2 > 95\%$. Continuous monitoring of SpO_2 beyond day 5 was generally unnecessary unless clinically indicated. All patients accepting treatment reported oxygen levels throughout their 10-day treatment period, except for 4 patients that missed data collection of room air SpO_2 on day 2.

Outcomes

This study reports on the following outcomes: Recovery of room air SpO_2 within 24 hours, patient survival, time from onset of treatment to resolution of all symptoms.

Data Analysis

Descriptive statistics were used to summarize the case series characteristics and outcomes. Intention-to-treat descriptive statistics included all 26 patients and per-protocol included the 24 of 26 patients that complied with the 10-day IDZCT protocol. Interquartile range (IQR) intervals were calculated using the 'quantile' function in R, which estimates the 25^{th} and 75^{th} percentiles using linear interpolation (Hyndman and Fan, 1996, definition 7).

The room air SpO_2 at baseline and after 24 hours were compared using the Wilcoxon Signed-Rank test. For the intention-to-treat comparison, the endpoint was the

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composite of "alive at 24 hours and SpO_2 increase of at least 3%" for the intention-to-treat comparison. Thus, paired SpO_2 analysis was applied on the 25 of 26 patients that were alive at 24 hours. For the per-protocol comparison, the corresponding endpoint was the composite of "complied with the 10-day IDZCT protocol and SpO_2 increase of at least 3%", with paired SpO_2 analysis applied on 24 of 26 patients that complied with IDZCT. Sensitivity analysis addressed the missing SpO_2 data after 24 hours by imputing the baseline SpO_2 value, both for intention-to-treat and per-protocol analysis. To mitigate survivorship bias in the intention-to-treat comparison, we conducted additional sensitivity analysis where the patient who died before initiating IDZCT was included with no-change imputation (day 2 SpO_2 imputed with baseline), worst-case imputation (day 2 SpO_2 imputed with 0%), and tipping point analysis (day 2 SpO_2 imputed with all values between baseline and 0% in 1% increments). Further sensitivity analysis addressed the use of concomitant medications by repeating this analysis for the subgroup of patients that did not receive any such medications.

A Kaplan-Meier plot was generated to visualize the probability of achieving full symptom recovery over time. Univariate Cox regression was used to identify predictors significantly associated with a shorter time to full recovery. These significant predictors were then included in the construction of an initial multivariate Cox regression model. This model was subsequently refined through stepwise selection, with predictors added or removed based on their impact on the Akaike Information Criterion (AIC), aiming to achieve a more parsimonious model. The Schoenfeld residuals test was used to check whether the proportional hazards assumption was satisfied by the refined model. Because of the small sample size, Kaplan-Meier survival and time-to-event analyses were exploratory and included the 24 patients with available follow-up; one patient who died before IDZCT initiation was excluded, and the date of death was unavailable for one additional patient.

All statistical calculations were performed using R version 4.1.3 (R Core Team, 2022). All tables presented in this study were automatically prepared via computer code. The underlying data and computer code used for all the data analysis and table preparation, is available in the supplementary document (Gkioulekas, 2026).

Results

Patients

Table 1 shows the details of the 26 patients who consented to treatment in the setting stated in the Methods section and comprise this case series. Included are patient demographic details (age, sex, and race), initial presentation (temperature, baseline SpO_2 on room air, symptoms other than hypoxia), date of positive RT-qPCR test, date of onset of treatment, and outcomes (day 2 SpO_2 on room air and date of symptom resolution). Because continuous monitoring of patients' SpO_2 levels on room air revealed a sustained upward trend throughout day 1 and day 2, Table 1 shows the baseline room air SpO_2 prior to IDZCT on day 1 and the peak value of room air SpO_2 by the end of day 2. Table 1 also shows the calculated number of days between positive RT-qPCR test and beginning of treatment and the number of days between the beginning of treatment and the resolution of symptoms.

Of the 26 patients, 21 were excluded from concurrent clinical trials. The remaining 5 patients were previously enrolled in an outpatient placebo-controlled clinical trial of a hydroxychloroquine, azithromycin, zinc triple-drug therapy for treating COVID-19; however, they were deemed treatment failures and their participation in that clinical trial was discontinued by the trial investigator (patients #4, #7, #8, #17, and #19). Prior to commencing IDZCT, these 5 patients received zinc, vitamin C, vitamin D, and they may have received either hydroxychloroquine and azithromycin or placebo. Two patients (patient #10 and patient #23) received on day 1 an initial stat dose of 36 mg ivermectin (instead of 12 mg) due to critically low baseline room air SpO_2 or expected clinical need. Three patients were prescribed hydroxychloroquine concurrently with IDZCT (patients #18, #20 for 10 days and patient #10 who discontinued IDZCT after day 1). One patient was on an ongoing hydroxychloroquine prescription for an autoimmune condition prior and during IDZCT (patient #6). Two patients were given remdesivir during hospitalization prior to consultation for IDZCT (patient #17 and #26). One patient was given monoclonal antibodies prior to initiating IDZCT (patient #21). All patients were unvaccinated against SARS-CoV-2.

For 25 out of 26 patients, the initial presentation was more severe than the 93% threshold for severe COVID-19, proposed by NIH guidelines (National Institutes of Health, 2024), with baseline room air $SpO_2 \leq 90\%$. Over all 26 patients, the median age was 66 years (IQR: 57.5 – 70.5 years), the median temperature upon first presentation was 38.6 ◦C (IQR: 38.3 − 38.9 ◦C), and the median baseline SpO_2 on room air was 88% (IQR: 87.25% – 89.75%), which increased after 24 hours to a median of 94% (IQR: 91% – 95%). The median time between positive RT-qPCR diagnosis and onset of treatment was 4 days (IQR: 1 – 11 days). The median time between the onset of treatment and the full resolution of all symptoms was 10 days (IQR: 6 – 14.5 days). Further analysis of the data presented in Table 1 is given in the context of the discussion of Tables 2, 4, and 5.

Table 1: Case series subjects, COVID-associated symptoms on presentation, and other characteristics

ID	Age	Race	Sex	Symptoms	Temp	SpO_2		RT-qPCR	Rx start		Resolved	
						base	+24hr		days	date	days	date
1	66	Caucasian	M	Runny nose, sore throat, dizzy, low energy	37.4	90	94	11/6/2020	38	12/14/2020	7	12/21/2020
2	62	Caucasian	M	SOB, chest congestion, productive cough, nausea, vomiting	40.6	77	87	11/30/2020	8	12/8/2020	10	12/18/2020
3	75	Caucasian	M	Low energy	38.3	88	96	10/15/2020	11	10/26/2020	6	11/1/2020
4	66	Caucasian	F	Loss of appetite, cough, chills, SOB	38.3	97	96	10/15/2020	11	10/26/2020	3	10/29/2020
5	66	Caucasian	F	Vomiting, weak, body aches, anosmia	38.3	89	95	12/18/2020	0	12/18/2020	4	12/22/2020
6	43	Caucasian	F	PE, headache, body ache, cough	38.3	88	94	1/26/2021	0	1/26/2021	17	2/12/2021
7	62	Caucasian	M	Productive cough, headache	38.9	86.5	91	11/13/2020	11	11/24/2020	14	12/8/2020
8	57	Caucasian	M	Cough, nasal congestion, SOB, body aches	38.9	88	96	10/26/2020	1	10/27/2020	14	11/10/2020
9	94	Hispanic	F	Low energy, SOB, confusion, loss of appetite, shaking	38.9	88	94	12/22/2020	19	1/10/2021	10	1/20/2021
10	66	Hispanic	M	Cough, SOB, respiratory failure	38.1	72	87	12/22/2020	NA	Declined	NA	Death
11	63	Hispanic	F	Cough, SOB	38.9	90	96	12/22/2020	19	1/10/2021	10	1/20/2021
12	47	Hispanic	M	SOB	40	84	91	12/16/2020	3	12/19/2020	6	12/25/2020
13	69	Caucasian	F	Cough, congestion, rash	38.9	88	91	11/13/2020	4	11/17/2020	16	12/3/2020
14	69	Caucasian	M	Post-nasal drip, cough, sinus pain	36.7	88	91	11/13/2020	4	11/17/2020	16	12/3/2020
15	71	Hispanic	M	Low energy, productive cough, anosmia	38.3	88	NA	12/13/2020	4	12/17/2020	19	1/5/2021
16	67	Hispanic	F	Dry cough, body aches, low energy, anosmia	37.8	88	NA	12/13/2020	4	12/17/2020	19	1/5/2021
17	46	Caucasian	F	Diarrhea, rash, renal pain	38.9	87	94	7/2/2020	37	8/8/2020	11	8/19/2020
18	86	Caucasian	M	Cough, fever, low energy	38.9	88	95	1/8/2021	1	1/9/2021	10	1/19/2021
19	59	Caucasian	F	Stomach pain, diarrhea, cough, rash	38.9	90	95	8/19/2020	28	9/16/2020	9	9/25/2020
20	54	Other	M	Cough, fever, loss of appetite, chills	38.4	88	NA	10/15/2020	1	10/16/2020	12	10/28/2020
21	92	Caucasian	M	Low energy	38.9	85	91	2/2/2021	3	2/5/2021	6	2/11/2021
22	63	Hispanic	M	Cough, low energy, loss of appetite	38.5	90	96	2/2/2021	0	2/2/2021	10	2/12/2021
23	57	Hispanic	M	Cough, SOB	36.7	73	90	12/30/2020	7	1/6/2021	33	2/8/2021
24	46	Hispanic	F	Chest pain, SOB	37	90	NA	2/17/2021	1	2/18/2021	6	2/24/2021
25	87	Hispanic	M	Severe SOB, low energy, trouble walking	38.7	90	95	2/17/2021	10	2/27/2021	6	3/5/2021
26	86	Caucasian	M	SOB	38.9	88	NA	10/6/2020	NA	Declined	NA	Death

NA: not available; SOB: shortness of breath; PE: pulmonary embolism; ID: identification number; Age: patient age in years; Symptoms: Patient symptoms upon presentation other than hypoxia; Temp: Patient temperature in Celsius upon first presentation; SpO_2: Room air peripheral oxygen saturation at baseline (base) and after 24 hours (+24 h); RT-qPCR: Date of first positive RT-qPCR test; Rx start: Onset of ivermectin-based multidrug treatment since positive RT-qPCR test (days) and date of beginning of IDZCT treatment administration (date); Resolved: Days to symptom resolution since initiating treatment (days) and date of symptom resolution (date)

Mortality Outcomes, Prior Hospitalization, and Patient Compliance With Treatment

Of the 26 patients, 24 patients (excluding patients #10 and #26) complied with the IDZCT and survived. Patient #26 consented to treatment and was prescribed medications, however he died before accessing the prescribed medications and/or initiating treatment. Patient #10 initially consented to treatment and his room air SpO_2 levels increased from a 72% baseline to 87% during the first 24 hours of treatment. Subsequently, the patient reconsidered his decision to refuse hospitalization, was denied access to previously prescribed ivermectin, doxycycline, and zinc in the hospital, and his condition deteriorated leading to his death. In the following, intention-to-treat analysis includes all 26 patients and per-protocol analysis includes the 24 patients that complied with IDZCT.

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Table 2: Demographic and clinical characteristics of patients upon presentation

Comorbidity	Intention-to-treat		Per-protocol	
	N	%	N	%
Sex				58.3
Male	16	61.5	14	41.7
Female	10	38.5	10	
Age				
41 to 50 years	4	15.4	4	16.7
51 to 60 years	4	15.4	4	16.7
61 to 70 years	11	42.3	10	41.7
71 to 80 years	2	7.7	2	8.3
81 to 90 years	3	11.5	2	8.3
91 years or older	2	7.7	2	8.3
Race				
Caucasian	15	57.7	14	58.3
Hispanic	10	38.5	9	37.5
Other	1	3.8	1	4.2
Baseline temperature (in Celsius)				
$T < 37$ (no fever)	2	7.7	2	8.3
$37 \leq T < 38$	3	11.5	3	12.5
$38 \leq T < 39$	19	73.1	17	70.8
$39 \leq T < 41$	2	7.7	2	8.3
Baseline SpO_2 on room air				
$90\% < SpO_2 \leq 95\%$	0	0.0	0	0.0
$85\% < SpO_2 \leq 90\%$	20	76.9	19	79.2
$80\% < SpO_2 \leq 85\%$	2	7.7	2	8.3
$75\% < SpO_2 \leq 80\%$	1	3.8	1	4.2
$70\% < SpO_2 \leq 75\%$	2	7.7	1	4.2

Intention-to-treat: Reports on all 26 patients
Per-protocol: Reports on 24 patients that adhered to 10-day ivermectin-based multidrug treatment
T = Temperature in Celsius prior to commencing ivermectin-based multidrug treatment
SpO_2: Baseline peripheral oxygen saturation on room air prior to commencing ivermectin-based multidrug treatment

There were no patients opting for hospitalization and remaining in the hospital for the entire course of their treatment, following the initial referral to inpatient care. Specifically, 24 of 26 patients immediately refused hospitalization and received IDZCT. Two patients accepted hospitalization but reconsidered their decision later (patient #17 and #26). These two patients had similar baseline SpO_2 on room air (87% and 88% correspondingly). Patient #17 differed from the cohort in terms of substantial delay in initiating IDZCT (37 days from positive RT-qPCR test), was relatively young (46 years), and recovered in 11 days. Patient #26 was much older (86 years) and consented to IDZCT but died before initiating IDZCT.

Patient Baseline Characteristics

Table 2 shows the demographic characteristics of the patients and their baseline temperature and room air SpO_2 upon presentation prior to treatment. Males are 61.5% of the entire cohort, thus more prevalent than females. The age distribution peaks at the 61 to 70 years interval with the majority of the patients being older than 50 years (22 patients for intention-to-treat and 20 patients for per-protocol). Some patients were older than 80 years (5 patients for intention-to-treat and 4 patients per-protocol). All patients but one (patient #4) had baseline room air $SpO_2 \leq 90\%$ with a majority at $85\% < SpO_2 \leq 90\%$. Of 26 intention-to-treat patients, 5 patients were at the 70% to 85% range with baseline SpO_2 as low as 72% (patient #10), 73% (patient #23), and 77% (patient #2). Fever temperature prior to treatment is also reported on Table 2 and categorized according to the thresholds of 37 °C, 38 °C, and 39 °C for low-grade, moderate-grade, and high-grade fever correspondingly. Most patients presented with moderate-grade fever. Two patients, who presented with no fever (patient #14 and patient #23), were both hypoxic with baseline SpO_2 on room air of 88% and 73% correspondingly.

Table 3 shows all known comorbidities of the patients and organizes them into two groups. One group consists of comorbidities associated with COVID-19 vulnerability (hereafter, *COVID-19 susceptible comorbidities*), according to recent CDC guidelines (Center for Disease Control and Prevention, 2025). The other group includes all other reported comorbidities.

Table 3 also shows the count of patients with a specific number of concurrent COVID-19 susceptible comorbidities and the count of patients with a specific number of any concurrent comorbidities. All patients had COVID-19 susceptible comorbidities. In the per-protocol subgroup, 18 of 24 patients had 2 to 4 concurrent COVID-19 susceptible comorbidities, and 20 of 24 patients had 2

to 6 concurrent comorbidities of any type. In the per-protocol group, the median number of all concurrent comorbidities was 4 (IQR: 4 – 6) and the median number of all concurrent COVID-19 susceptible comorbidities was 2 (IQR: 1.75 – 3).

Rapid Recovery of Oxygen Saturation on Room Air

An initial response of SpO_2 levels from the onset of IDZCT was observed within 3 to 6 hours for most patients. Figure 1 and Table 4 highlight the normalization of room air SpO_2 levels within 24 hours, for the 21 patients where day 2 data were available. Specifically, Table 4 displays the change Δ of room air SpO_2 between baseline (day 1), prior to commencing treatment for all patients, and its peak value at the end of day 2, the difference Δ_{90} between its day 2 peak value and the patient stabilization threshold of 90% SpO_2 on room air, and the difference Δ_{95} between its day 2 peak value and the curative threshold of 95% SpO_2 on room air. For all 20 of 21 patients, where data were available, SpO_2 on room air showed substantial increase by the end of day 2, without the use of oxygen concentrators, and 18 of these 21 patients were successfully stabilized with $SpO_2 > 90\%$ on room air (except for patients #2, #10, and #23, for whom $\Delta \geq +10\%$). By day 10, SpO_2 levels on room air were successfully restored above 95% for all 24 patients in the per-protocol subgroup and were maintained without further treatment.

Table 3: Prevalence of comorbidities in patients

Comorbidity	Intention-to-treat		Per-protocol	
	N	%	N	%
COVID-19 susceptible comorbidities				
Type 1 or type 2 diabetes	6	23.1	4	16.7
Heart or cardiovascular disease	7	26.9	6	25
Chronic obstructive pulmonary disease	3	11.5	3	12.5
Pulmonary embolism	1	3.8	1	4.2
Kidney disease	3	11.5	2	8.3
Liver disease (primary biliary cirrhosis)	1	3.8	1	4.2
Immunocompromised state (HIV/AIDS)	1	3.8	1	4.2
Overweight (BMI: 25.0–29.9 kg/m^2)	4	15.4	4	16.7
Obese (BMI: 30.0–39.9kg/m^2)	2	7.7	2	8.3
Morbidly obese (BMI: 40 kg/m^2 or more)	4	15.4	4	16.7
Hypertension	12	46.2	11	45.8
Sleep apnea	10	38.5	10	41.7
Asthma	2	7.7	2	8.3
Neurocognitive disorders (dementia or Alzheimer's)	3	11.5	3	12.5
Psychological disorders (anxiety or depression)	2	7.7	2	8.3
Other comorbidities				
Prediabetic	5	19.2	5	20.8
Hyperlipidemia	9	34.6	7	29.2
Thyroid	2	7.7	2	8.3
Rheumatic diseases (gout or Sjögren's)	2	7.7	1	4.2
Gastrointestinal disorders (GERD/gastritis)	3	11.5	2	8.3
Musculoskeletal disorders (osteoarthritis, osteopathy, or osteoporosis)	3	11.5	3	12.5
Other	2	7.7	2	8.3
Concurrent COVID-19 susceptible comorbidities in patients				
No concurrent comorbidities	0	0.0	0	0.0
One comorbidity	7	26.9	6	25
2 concurrent comorbidities	8	30.8	8	33.3
3 concurrent comorbidities	6	23.1	6	25
4 concurrent comorbidities	5	19.2	4	16.7
All concurrent comorbidities in patients				
No concurrent comorbidities	0	0.0	0	0.0
One comorbidity	4	15.4	4	16.7
2 concurrent comorbidities	5	19.2	5	20.8
3 concurrent comorbidities	3	11.5	2	8.3
4 concurrent comorbidities	8	30.8	8	33.3
5 concurrent comorbidities	4	15.4	4	16.7
6 concurrent comorbidities	2	7.7	1	4.2

Intention-to-treat: Reports on all 26 patients; Per-protocol: Reports on 24 patients that adhered to 10-day treatment; Other: includes glaucoma, prostate disease, and essential tremors; BMI: Body mass index; COVID-19: Coronavirus Disease 2019; GERD: Gastroesophageal reflux disease; HIV/AIDS: Human immunodeficiency virus, acquired immunodeficiency syndrome; kg/m^2: kilograms per meter squared

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Table 4: Baseline SpO_2 vs SpO_2 on day 2 at room air for all intention-to-treat patients

ID	SpO_2					ID	SpO_2				
	day 1	day 2	Δ	Δ_{90}	Δ_{95}		day 1	day 2	Δ	Δ_{90}	Δ_{95}
1	90	94	+4	+4	-1	14	88	91	+3	+1	-4
2	77	87	+10	-3	-8	15	88	NA	NA	NA	NA
3	88	96	+8	+6	+1	16	88	NA	NA	NA	NA
4	97	96	-1	+6	+1	17	87	94	+7	+4	-1
5	89	95	+6	+5	0	18	88	95	+7	+5	0
6	88	94	+6	+4	-1	19	90	95	+5	+5	0
7	86.5	91	+4.5	+1	-4	20	88	NA	NA	NA	NA
8	88	96	+8	+6	+1	21	85	91	+6	+1	-4
9	88	94	+6	+4	-1	22	90	96	+6	+6	+1
10	72	87	+15	-3	-8	23	73	90	+17	0	-5
11	90	96	+6	+6	+1	24	90	NA	NA	NA	NA
12	84	91	+7	+1	-4	25	90	95	+5	+5	0
13	88	91	+3	+1	-4	26	88	NA	NA	NA	NA

SpO_2: Peripheral oxygen saturation on room air
Day 1: Baseline SpO_2 on room air prior to commencing ivermectin-based treatment
Day 2: Peak SpO_2 on room air by the end of day 2
Δ = Change of SpO2 on room air from day 1 to day 2
Δ_{90} = Difference between peak SpO_2 on day 2 and the 90% SpO_2 stabilization threshold
Δ_{95} = Difference between peak SpO_2 on day 2 and the 95% SpO_2 curative threshold
NA: Not available; ID: identification number

The median Δ between day 1 and day 2 was +6% (IQR 5-7%). FDA-approved oximeters have an expected SpO_2 measurement error with 3% standard deviation (Silverston et al., 2022), which is half of the observed median Δ, and some of this error is mitigated when calculating measurement differences. The two outliers with the largest Δ were patient #10 (with Δ = +15%) and patient #23 (with Δ = +17%), both of who received the increased 36 mg ivermectin stat dose at the start of IDZCT. These two outliers are shown in Fig. 1 with red color, where an accelerated recovery rate was observed. The one other outlier with Δ = −1 was patient #4, for whom room air SpO_2 decreased from 97% to 96% over the initial 24-hour period. This patient was deemed high-risk because of shortness of breath upon presentation. Of note, both SpO_2 measurements were within the curative range (SpO_2 > 95%) for this patient and full resolution of all symptoms occurred within 72 hours from commencement of IDZCT treatment. For all other patients, the absolute minimum Δ is Δ ≥ +3%, with Δ = +3% observed for patients #13 and #14, both successfully stabilized at SpO_2 > 90% by the end of day 2. Peak SpO_2 data for day 2 is missing for 4 per-protocol patients, each of who had baseline room air SpO_2 ≥ 88%, close to the stabilization threshold.

Several comparisons of room air SpO_2 levels between baseline and day 2, using the Wilcoxon-Signed-Rank test revealed that the observed increase in SpO_2 levels was statistically significant. For per-protocol analysis, 18 of 24 patients met the composite endpoint "complied with the 10-day IDZCT protocol and SpO_2 increase of at least 3%", 1 of 24 patients did not meet the endpoint, and day 2 data was missing for 4 of 24 patients. Paired comparison gives effect size $r = 0.87$ with $N = 20$ and p-value $p = 1 \times 10^{-4}$. Sensitivity analysis where missing data is imputed with baseline. (no-change imputation) gives reduced effect size $r = 0.82$ with $N = 24$ and p-value $p = 1 \times 10^{-4}$. For intention-to-treat analysis, 19 of 25 patients met the composite endpoint "alive at 24 hours and SpO_2 increase of at least 3%", 1 of 25 patients did not meet the end point, and day 2 data was missing for 4 of 25 patients. Paired comparison gives effect size $r = 0.87$ with $N = 21$ and p-value $p = 7 \times 10^{-5}$. Sensitivity analysis with no-change imputation for missing data gives reduced effect size $r = 0.82$ with $N = 25$ and p-value $p = 7 \times 10^{-5}$. Note that the effect sizes were consistent with those obtained from the per-protocol analysis.

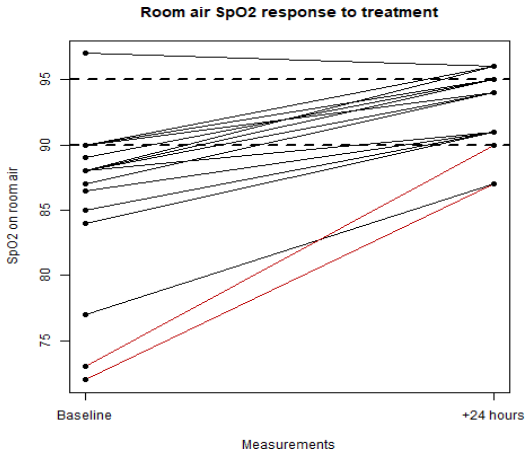

Fig. 1: Change in SpO_2 levels on room air are shown at baseline and after 24 hours (day 2) for the 21 intention-to-treat patients with available data for day 2. Red color shows the change in SpO_2 levels on room air for the two patients that received the 36 mg stat dose of ivermectin on day 1. Horizontal dotted lines demarcate the patient stabilization threshold of 90% and the curative threshold of 95% for room air SpO_2 levels

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To address survivorship bias in the intention-to-treat analysis, we considered the effect of including patient #26, with 88% baseline SpO_2 on room air, who died before starting IDZCT. For paired comparisons, day 2 SpO_2 for patient #26 was imputed with the entire range of values between baseline (no-change imputation) and 0% (worst-case imputation). Without further imputation on all other patients, the effect size ranged over the interval $0.72 \leq r \leq 0.86$ with $N = 22$ and p-value consistently statistically significant with $7 \times 10^{-5} \leq p \leq 8 \times 10^{-4}$. With no-change imputation on all other patients, the range for the effect size shifted to $0.7 \leq r \leq 0.81$ with $N = 26$ and p-value still statistically significant and ranging over the same interval.

Further sensitivity analysis considered the subgroup of patients who did not receive concomitant medications prior or concurrently with IDZCT, by removing patients #4, #6, #7, #8, #10, #17, #18, #20, #21, #26. From the remaining 16 patients, day 2 data was unavailable for 3 patients. Furthermore, all of these 16 patients complied with the 10-day IDZCT therapy, thus the per-protocol and intention-to-treat patients coincide over this subgroup. Comparison of the room air SpO_2 levels between baseline and day 2, including only the patients with available day 2 data resulted in effect size $r = 0.89$ with $N = 13$ and p-value $p = 0.0016$. Imputing SpO_2 levels on day 2 with baseline gave effect size $r = 0.85$ with $N = 16$ and p-value $p = 0.0016$. All comparisons revealed that the difference in median SpO_2 between baseline and day 2 remained consistently statistically significant with effect size ranging over $0.70 \leq r \leq 0.89$.

Full Symptom Resolution

Table 5 shows the distribution of the number of days between positive RT-qPCR test diagnosis and the onset of treatment and the number of days between the onset of treatment and resolution of all symptoms for the per-protocol subgroup of patients that completed the 10-day treatment.

Approximately half of the patients-initiated treatment within 5 days (13 of 24 patients), although there was an additional unknown delay between symptomatic infection and diagnosis with a RT-qPCR test that may have varied from patient to patient. Of 24 patients, 22 patients delayed treatment by no more than 20 days. However, 2 patients waited as long as 38 days (patient #1) and 37 days (patient #17).

SpO_2 levels on room air were fully resolved and sustained for all 24 per-protocol patients within 10 days. Table 5 shows that for 14 of these 24 patients all other symptoms were also fully resolved within 10 days, and for 23 of these 24 patients all other symptoms were fully resolved within 20 days. For patient #23, who presented with baseline SpO_2 of 73% on room air and no fever, symptoms resolved within 33 days. Fig. 2 shows a Kaplan-Meier plot that visualizes the probability of full recovery from all symptoms as a function of the number of days since the onset of IDZCT. The red dotted line demarcates full recovery prior to or at the conclusion of the 10-day IDZCT protocol. None of the per-protocol patients reached out to ProgenaBiome for treatment of long COVID symptoms after full symptom resolution.

Safety

An adverse drug event (dizziness) was reported by patient #1, who nonetheless successfully completed the IDZCT 10-day treatment. No adverse drug events were observed for the other patients during the course of their treatment.

Table 5: Number of days for onset of treatment and symptom resolution for per-protocol subgroup

Duration	Rx start		Resolved	
	N	%	N	%
0 days	3	12.5	0	0.0
1 to 5 days	10	41.7	2	8.3
6 to 10 days	3	12.5	12	50
11 to 20 days	5	20.8	9	37.5
21 to 30 days	1	4.2	0	0.0
31 to 40 days	2	8.3	1	4.2

Rx start: Number of days from date of positive RT-qPCR test to date of start of ivermectin-based treatment
Resolved: Number of days from date of start of ivermectin-based treatment to date of symptom resolution

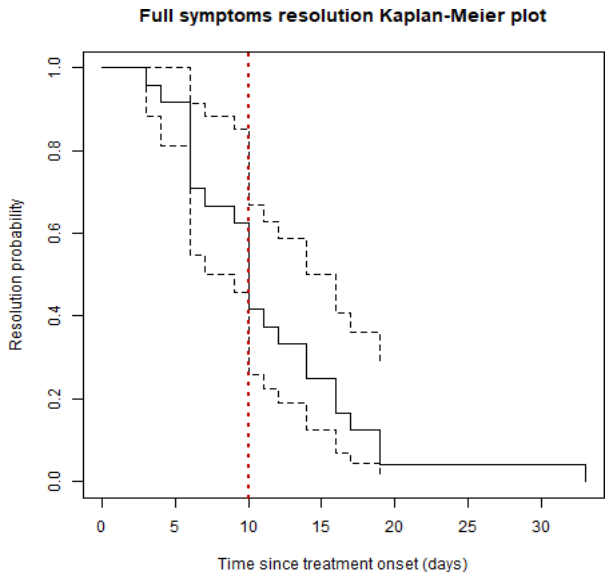

Fig. 2: Kaplan-Meier plot showing the observed probability of full recovery from all symptoms as a function of number of days since the onset of IDZCT treatment. The 95% confidence interval is plotted using dotted lines. A vertical red dotted line demarcates the observed probability for full recovery of symptoms within a period of 10 days, which is the duration of treatment

Time-to-Event Analysis of Time to Full Resolution of Symptoms

At the suggestion of an anonymous referee, we used univariate Cox regression to explore whether any of the available variables were associated with accelerated full resolution of all symptoms. We considered 41 distinct variables (details available in the supplementary document (Gkioulekas, 2026)), of which only the following had statistically significant association with time to full resolution of symptoms as follows:

(1) Baseline temperature ordinal scale stratified at the 37 ˚C, 38 ˚C, 39 ˚C thresholds with HR = 2.04 (95% CI: 1.03 – 4.01) and $p = 0.0396$
(2) Heart or cardiovascular disease comorbidity with HR = 3.85 (95% CI: 1.28 – 11.65) and $p = 0.0168$
(3) Sleep apnea comorbidity with HR = 0.31 (95% CI: 0.12 – 0.8) and $p = 0.015$
(4) Gastrointestinal disorder comorbidity with HR = 10.71 (95% CI: 1.97 – 58.31) and $p = 0.0061$

Of note, none of the corresponding p-values was sufficiently small to support statistical significance after applying a Bonferroni correction for multiple comparisons. On a strictly exploratory basis, applying stepwise reduction on a multivariate Cox regression model, incorporating all four variables, eliminates the baseline temperature scale as a predictor variable. Due to the small sample size of the case series and the small number of patients with gastrointestinal disorder comorbidity (n = 3), we considered retaining only the two variables of sleep apnea comorbidity (n = 10) and heart or cardiovascular disease comorbidity (n = 6). For this reduced model, the heart or cardiovascular disease comorbidity predictor has adjusted HR = 3.64 (95% CI: 1.2 – 11.02) and $p = 0.0223$ and the sleep apnea predictor comorbidity has adjusted HR = 0.32 (95% CI: 0.12 – 0.83) and $p = 0.0186$, both remaining consistent with the univariate estimates. Reintroduction of the gastrointestinal disorder comorbidity variable has a small effect on the hazard ratios of the other two variables relative to the size of their respective confidence intervals. For both models, the proportional hazards assumption, evaluated using the Schoenfeld residuals test, was satisfied by all predictors. Thus, sleep apnea is associated, for this sample of patients, with longer time to full resolution of all symptoms and cardiovascular or heart disease is associated with shorter time to full resolution of all symptoms.

Although these observations are interesting, there is no clear plausibility that these associations are causal or generalizable. Furthermore, we think that the sample size was too small to identify any variables that may have been correlated with reduced time to full resolution of all symptoms.

Further details of this statistical analysis are given in the supplementary document (Gkioulekas, 2026).

Discussion

Summary of Findings

The primary contribution of this study is the descriptive reporting of oxygen saturations trajectories in a high-risk outpatient cohort, who were treated with off-label IDZCT during an early pandemic period. Specifically, this study has contributed the following findings:

(a) At the onset of IDZCT, rapid increase of SpO_2 on room air was observed in the 21 hypoxic patients with available SpO_2 data on room air for day 2, of which 18 out of 21 were stabilized at $SpO_2 > 90\%$ within 24 hours
(b) This rapid increase in SpO_2 levels was statistically significant for these 21 patients, it remains statistically significant when missing day 2 data is imputed with the baseline SpO_2 levels on room air and/or when patients that took or may have taken concomitant medications are excluded
(c) The increase in SpO_2 levels was intensified on the severely hypoxic patients that received the 36 mg ivermectin stat dose in addition to the adaptive ivermectin dosage used on all other patients
(d) hospitalization was prevented for all 24 patients accepting IDZCT for a period of 10 days with complete and sustained recovery of oxygen levels on room air by day 10
(e) Of these 24 patients, complete resolution of all other symptoms was achieved within 20 days from the onset of treatment for 23 out of 24 patients
(f) All 24 patients accepting treatment survived

These results are noteworthy because these patients were treated via telemedicine at home on room air, without access to oxygen concentrators, and because all but one of the treated patients were hypoxic, with baseline $SpO_2 \leq 90\%$, for whom usual care would involve admission to the hospital. Nevertheless, the patients accepting treatment fully recovered without hospitalization. Because all patients were unvaccinated, these findings were not confounded by prior vaccination. Likewise, because all patients were treated before the emergence of the Omicron variant, natural immunity used to confer substantial protection against reinfections at that time (Murchu et al., 2022), therefore it is improbable that these patients had any prior natural immunity against SARS-CoV-2 that could have contributed to their recovery.

Results from Other Case Series With Similar Treatments

Rapid recovery of oxygen saturation levels was also observed in another study of 34 hypoxic patients, treated in Zimbabwe by Stone and colleagues on room air with a similar 10-day protocol from August 2020 through May

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2021 (Stone et al., 2022). Of note, unlike this study that systematically recorded SpO_2 recovery only at +24 hours, results were reported at +12 hours, +24 hours, and +48 hours, with most of the observed normalization of SpO_2 levels reported within a period of 12 hours from the onset of treatment and sustaining itself at the +24 hours and +48 hours time points (Stone et al., 2022, Table 2 and Figure 2). The 10-day protocol by Stone et al. (2022) used a multidrug combination that included ivermectin, nebulized nanosilver, doxycycline zinc, vitamin C, and vitamin D3 in which ivermectin dosage was adapted to patient severity (Gkioulekas et al., 2025a, Table 1). In the Stone case series, ivermectin dose adjustments were also determined based on empirical observations of patient response to treatment. However, more systematic criteria and processes were used for adjusting treatment, because patients were treated in person or via traveling nurses and it was possible to collect blood work and more detailed vitals. For the most severe COVID-19 patients (typically with baseline $SpO_2 \leq 80\%$ on room air), an ivermectin 0.6 mg/kg stat dose was administered, which was titrated to 1-2 mg/kg if the expected increase of SpO_2 levels was not observed. Subsequently, ivermectin dosage was maintained at 0.3-0.6 mg/kg daily until resolution of symptoms for 48 hours (usually within 10 days). For less severe presentations (typically with 80% to 90% baseline SpO_2 on room air), ivermectin was administered at 0.2-0.3 mg/kg daily for 5-7 days during the Beta variant and 0.4-0.6 mg/kg daily for 10 days during the Delta variant. The stopping criterion was again resolution of symptoms for 48 hours. Stone and colleagues combined ivermectin with nebulized nanosilver, the latter contributing fast but short-lasting increase in SpO_2 levels, which moderated the required ivermectin dosage. The full details of the treatment protocol used in the Stone case series are given in Gkioulekas et al. (2025a, Table 1). For the 34 hypoxic patients treated by Stone et al. (2022), of who 28 presented with baseline $SpO_2 \leq 90\%$, the outcomes were 0 deaths and 1 brief hospitalization event (Gkioulekas et al., 2025a, Table 3).

Babalola and colleagues also replicated these findings in a Nigerian cohort of 61 patients (April-June 2021) (Babalola et al., 2021), observing a sustained recovery of oxygen saturation levels. The protocol by Babalola et al. (2021) was limited to 5 days, used a fixed weight-adjusted dosage for ivermectin, included zinc and vitamin C, but did not include doxycycline or vitamin D3. Ivermectin was administered at 0.2 mg/kg daily for 5 days but it was not adjusted depending on patient severity or response to treatment. As a result, the rate of improvement was remarkably slower, requiring more than 5 days for a similar SpO_2 normalization effect (shown in Fig. 3). Although there were no reported deaths, of the 61 patients, 2 patients had to use a ventilator, and 3 patients were administered supplemental oxygen, counting a total of 5 deterioration events.

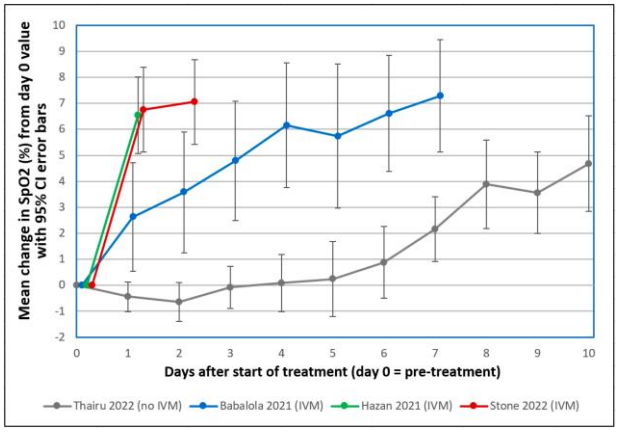

Fig. 3: Average change in room air SpO_2 levels from baseline (day zero) for patients with initial $SpO_2 \leq$ 93% in the Hazan, Stone, and Babalola case series, with 95% confidence intervals represented by error bars. These are compared against the Thairu case series where a non-ivermectin treatment protocol was used. The figure is reproduced from Stone et al. (2022) under the terms of the CC-BY-4.0 license

For cases of hypoxic COVID-19 patients treated under usual care hospital protocols that did not use ivermectin, there was a consistent trend of either decreasing or steady oxygen saturation levels, depending on the extent of pulmonary damage, which did not fully resolve within a 10-day period. This is displayed in Fig. 3, comparing the mean temporal change of room air SpO_2 levels observed for the Hazan, Stone, and Babalola case series against a case series of 26 hospitalized patients by Thairu and colleagues (hereafter Thairu case series), who were treated in Nigeria between September 2021 and November 2021 with a non-ivermectin protocol based on lopinavir, ritonavir, remdesivir, azithromycin, enoxaparin, and vitamin C (Thairu et al., 2022). Fig. 3, shows that in the Thairu case series, there is a decreasing trend in SpO_2 levels for the first two days, with slow recovery beginning only at the day 5 mark. By day 10, the Thairu case series still did not achieve the same level of recovery observed in the Hazan and Stone case series within the first 24 hours.

Furthermore, the difference in SpO_2 levels response between the ivermectin-treated case series and the Thairu case series was statistically significant, based on previously published statistical analysis (Scheim et al., 2024, Table 1).

Noting that the Thairu case series patients were treated during the Delta variant, it is important to highlight that similar decreasing trends in SpO_2 levels were also observed in patients with pre-delta variants:

(a) Annunziata and colleagues observed an 8-day decreasing trend, dipping below 90% oxygen saturation, which did not fully reverse itself within 15 days in 18 patients, treated at home from October

2020 to November 2020, despite a 6 day non-ivermectin treatment that included azithromycin, methylprednisolone, enoxaparin, and supplemental oxygen (Annunziata et al., 2021, Figure 4)

(b) Osman and colleagues observed a similar decreasing trend even in mildly ill COVID-19 patients over at least an 8-day period (Osman et al., 2020, Figure 5)

(c) Both Ding et al. (2020); Wang et al. (2020) observed that the extent of COVID-19 organized pneumonia in hospitalized patients, as measured with computerized tomography scans, which is known to be correlated with oxygen desaturation (Metwally et al., 2021), typically persists over a period of several weeks. Thus, for standard of care treatment of hospitalized patients, the typical expected time scale for a similar recovery effect is likely more than 8 days, if not several weeks, and, at best, no less than 5 days, under the less aggressive ivermectin-based treatment used in the Babalola case series

Hypothesis Generation from the Combined Available Evidence

This study did not use by design a contemporaneous control group because:

(a) It was not ethical to experiment in an outpatient setting on patients who were referred for hospitalized treatment but declined hospitalization

(b) We did not retain personal equipoise to ethically justify a control group because of the clinical observation that the rate of oxygen saturation recovery was responsive to increased dosage of ivermectin

(c) This was only a retrospective chart review of patients treated outside the context of any clinical trial.

Unfortunately, a consequence of this observational descriptive study design is that, in the absence of a contemporaneous control group from the same cohort, it is not possible to make any inductive inferences about treatment efficacy that can quantify an unbiased effect size. The clinically relevant questions concerning treatment efficacy are:

(1) Whether the IDZCT made some contribution towards the recovery of SpO_2 levels regardless of whether it can be quantified

(2) Whether the observed recovery of SpO_2 levels may have contributed towards patient survival

Question (2) is beyond the scope of this work, although we will summarize what is currently known concerning mortality rate reduction from the available Randomized Controlled Trials (RCTs). Our proposed treatment efficacy hypothesis is that IDZCT did indeed contribute towards the recovery of SpO_2 levels, separately from a potential regression to the mean effect and/or natural progression of the disease. Because IDZCT bundles the administration of ivermectin, doxycycline, zinc, and vitamins C and D3, with frequent 3–6-hour patient monitoring to implement SpO_2 -targetted ivermectin dose titration, the potential contribution of IDZCT may consist of a drug-only effect and an additional performance bias effect that may result from the frequent patient monitoring. Because monitoring and ivermectin titration are integral and mandatory for IDZCT, it is not clinically relevant to isolate the drug-only effect. Thus, a more precise statement of the efficacy hypothesis is that the full protocol, as delivered in practice, made some independent contribution to the recovery of SpO_2 levels, separately from any additional effects related to the natural progression of the disease and/or any regression to the mean. The alternative hypothesis is that the entire observed effect may be attributed solely to the natural progression of the disease. In addition, because IDZCT was initiated only for patients with baseline $SpO_2 \leq 90\%$, another variation of the alternative hypothesis is that the observed improvement may have been the combined effect of both regression to the mean and natural progression of the illness.

We propose, as an Inference to the Best Explanation (IBE) (Harman, 1965) that amongst these three hypotheses, the hypothesis of some treatment effect on the recovery of SpO_2 levels, if true, best explains the totality of all available evidence for the following reasons:

(a) Statistically significant SpO_2 improvement post-treatment (via Wilcoxon Signed-Rank test comparison) and sensitivity analysis excluding patients using concomitant medications and/or imputing missing data is inconsistent with the regression to the mean hypothesis

(b) The observed rapid recovery (3-6 hours for initial response and 24 hours for stabilization in most patients) compared with historical controls (5 days for lower-dose ivermectin-based treatment in the Babalola case series; at least 8 days to several weeks for non-ivermectin standard of care) is consistent with the treatment effect hypothesis and inconsistent with the natural progression of the disease hypothesis

(c) The observed dose-response relationship (specifically faster recovery of SpO_2 levels in the Stone case series vs the Babalola case series, where patients were treated against the same SARS-CoV-2 variants with ivermectin-based treatments of different intensity) is consistent with treatment effect and inconsistent with both alternate hypotheses

(d) Replicability of observed response of SpO_2 levels between the Hazan and Stone case series, where

similar protocols with dynamically adjusted ivermectin dosage were used to treat patients with different socioeconomic characteristics and exposed to different variants of SARS-CoV-2, is consistent with the treatment effect hypothesis

(e) Extensive research literature on the reversal of hemagglutination by ivermectin as the most plausible mechanistic explanation of the rapid recovery of SpO_2 levels (Scheim, 2022; Scheim et al., 2023; 2024) is consistent with the treatment effect hypothesis

(f) Experimental *in vitro* evidence confirming this mechanism for the Wuhan, Alpha, Delta, and Omicron B.1.1.529 SARS-CoV-2 variants (Boschi et al., 2022) is also consistent with the treatment effect hypothesis

It is widely agreed, as a middle ground position within a very vibrant philosophical debate, that IBE inference, which is distinct from deductive and inductive inferences, is a hypothesis-generating "logic of discovery" providing a logical argument for suggesting the most plausible hypothesis warranting further investigation (Ward, 2009). Although we acknowledge that each one of these considerations by itself may not be sufficient for a credible IBE argument, the combination of all of these considerations is quite compelling. It is also important to qualify that the available evidence is applicable only to the potential efficacy of the synergistic interaction of all medications and the vitamin supplementation used in the IDZCT protocol. It is not reasonable to expect that this IBE argument has any external validity concerning the potential efficacy of any of the individual medications, when used as monotherapies, and we do not advocate in favor of single-drug therapies for COVID-19. Specifically, any potential efficacy of IDZCT in terms of full resolution of all symptoms and mortality reduction should be attributed to the combined synergistic interaction of ivermectin, doxycycline, zinc, and vitamin supplementation.

Assessment of Mortality Rate Reduction Evidence from RCTs

Although the question of mortality rate reduction is beyond the scope of this study, there is a substantial body of RCT evidence that has investigated this endpoint, and this evidence needs to be reconciled specifically with the proposed IDZCT 10-day protocol. Several meta-analyses of Randomized Controlled Trials (RCTs) have shown an association of ivermectin with statistically significant mortality rate reduction, especially prior to the emergence of the less virulent Omicron variants (Bryant et al., 2021; Kory et al., 2021; Santin et al., 2021). Nevertheless, because of the heterogeneity of treatment protocols (monotherapy vs combination therapy, variability in dosage and duration of treatment), baseline characteristics of patients (low-risk vs high-risk patients), setting (outpatients vs inpatients), and viral variants in the underlying RCTs, the available ivermectin meta-analyses should be assessed with caution and recent calls highlighting the importance of accounting for the totality of the available evidence (Aldous et al., 2024a) deserve further consideration. For ivermectin-based treatments of COVID-19, the totality of the available evidence, showing both ivermectin effectiveness or lack thereof for the treatment of COVID-19, was initially reviewed by Santin et al. (2021) and further reviewed more extensively by Yagisawa et al. (2021; 2024); Aldous et al. (2024b). Of note, Yagisawa et al. (2024) identified 27 ivermectin meta-analyses published between November 2020 and March 2023, based on a total of 69 underlying studies, of which 15 suggested that ivermectin was effective in treating COVID-19 and 12 suggested lack of efficacy, and noted that the number of studies included in each meta-analysis ranged from 3 to 52.

As it remains unclear which of the above meta-analyses are reliable, it is more constructive to consider the underlying evidence. Following the more detailed critical review of the available evidence by Gkioulekas et al. (2025b), we use the 2022 Cochrane ivermectin meta-analysis (Popp et al., 2022) as a departure point and begin with their choice of 11 randomized controlled trials, which can be broken down as follows:

(a) 4 studies are not generalizable to the treatment of high-risk patients because they used low-risk cohorts, evidenced by the reporting of zero deaths on both the treatment and control arms of the trials (Buonfrate et al. (2022); Chaccour et al. (2021); Krolewiecki et al. (2021); Mohan et al. (2021)

(b) 3 studies used short-term ivermectin monotherapies for 2 or 3 consecutive days, therefore they are not generalizable to the 10-day IDZCT protocol used in this study (Reis et al., 2022; Vallejos et al., 2021; Ravikirti et al., 2021)

(c) 1 study was later retracted. The remaining studies are: Lopez-Medina et al. (2021), ITECH (Lim et al., 2022; Beltrán-González et al., 2020)

Lopez-Medina et al. (2021) tested a 5-day course of ivermectin monotherapy at 0.3 mg/kg and reported zero deaths out of 200 patients in the treatment arm and one death out of 198 patients in the control arm, suggesting that either a low-risk patient cohort was used or that patients in the control group might have accessed ivermectin over the counter (Scheim et al., 2021). In either case, the results do not generalize to the treatment of high-risk COVID-19 patients.

The ITECH study (Lim et al., 2022) is interesting because it used a 5-day protocol of ivermectin at the

higher dosage of 0.4 mg/kg on high-risk hospitalized patients (age ≥ 50 years with at least one comorbidity) with mild or moderate COVID-19, resulting in 1.2% mortality in the treatment group (3 deaths out of 241 patients) vs 4.0% mortality in the control group (10 deaths out of 249 patients). Although this result was not statistically significant, with $p = 0.09$, this was in part because the control group was underpowered; Gkioulekas et al. (2025b) noted that coupling the treatment arm of this trial with any asymptotically large control group with mortality rate ≥ 3.7% is sufficient for achieving statistical significance. On the other hand, the observed 1.2% mortality rate in the treatment arm of the trial highlights that further increase in ivermectin dosage was necessary for the survival of the 3 patients that died.

Beltrán-González et al. (2020) is also interesting because they tested a 5-day protocol of ivermectin at 0.15 to 0.22 mg/kg on hypoxic COVID-19 patients with 83% ± 8% average baseline oxygen saturation, between May 2020 and August 2020 in Mexico. The study reported minimal impact on the mortality rate (13.8% in the ivermectin group vs 16.2% in the control group). Considering that similar dosage and duration was used in the Babalola case series, this result is not generalizable to the treatment protocols used in this study and in Stone et al. (2022), where a faster recovery rate of room air SpO_2 was achieved than in the Babalola case series. Nevertheless, notwithstanding the temporal associations in the Babalola case series, the results by Beltrán-González et al. (2020) highlight the importance of effecting the fastest possible recovery of oxygen saturation as a necessary condition for reducing the mortality rate for hypoxic COVID-19 patients, which in turn requires adaptive dosage of ivermectin at the onset of treatment.

The 2022 Cochrane meta-analysis excluded all studies that investigated ivermectin-based combination therapies; however, they also published their list of all excluded studies. From that list, only two RCTs investigated ivermectin and doxycycline combination therapy:

(a) Mahmud et al. (2021) demonstrated statistically significant mortality rate reduction for a low dose combination therapy of ivermectin and doxycycline for moderately ill outpatients with baseline SpO_2 > 90% who started treatment within 3 days from the onset of symptoms
(b) Hashim et al. (2021) published a very small RCT, also testing a low-dose combination therapy of ivermectin and doxycycline; however, they used additional aggressive treatment on both arms of the trial, with no deaths on both arms of the trial for the outpatients, and some compelling but not statistically significant mortality rate reduction signal for inpatients in the severe category. Both studies were underdosed, but our interpretation is that they communicated signals of benefit

Following the publication of the 2022 Cochrane meta-analysis, we took note of some additional RCTs as follows:

(a) Three RCTs used 3-day ivermectin protocols at 0.3 mg/kg (Hayward et al., 2024) or 0.4 mg/kg (Bramante et al., 2022; Naggie et al., 2022) so they are not generalizable to the 10-day IDZCT protocol used in this study
(b) The ACTIV-6 600 study (Naggie et al., 2022) used an interesting 6-day ivermectin protocol at 0.6 mg/kg, however no mortality reduction effect was observed, because there were no deaths on either arm of the trial, so the study is not generalizable to high-risk patient cohorts, such as the cohort of COVID-19 patients reported in this study

In summary, several of the aforementioned ivermectin RCTs are not generalizable to the IDZCT and the patient cohort of this study because of at least one of the following reasons:

a. Short duration of treatment
b. Low dosage of ivermectin
c. Low-risk patients for whom there is insufficient statistical power to detect a mortality reduction benefit

The ITECH trial (Lim et al., 2022) is the only RCT for which none of these reasons is applicable. It is our interpretation that this study communicated a weak signal of mortality rate reduction efficacy, which was missed, in part, because of insufficient sample size for the control group and intense multidrug treatment (other than ivermectin) administered to both arms of the trial. Beltrán-González et al. (2020) is also relevant because it demonstrated that the weaker ivermectin dosage and duration used in the Babalola case series is insufficient for preventing mortality for patients with baseline $SpO_2 \leq 80\%$ on room air, despite the observed slower increase in oxygen saturations with the onset of treatment shown in Fig. 3.

Replication of IDZCT on Recent Variants

Although, shortly after the emergence of Omicron variants, inpatient mortality rates decreased substantially in the United States (Gkioulekas et al., 2025a, Table 4) there are several studies reporting on hypoxemic hospitalized COVID-19 patients, infected with the Omicron lineage and sublineages, requiring medical interventions including supplemental oxygen or other respiratory support (Relan et al., 2026; Wajdowicz et al., 2026; Wang et al., 2023; 2024). To replicate the IDZCT in hypoxic patients infected with Omicron variants, it is important to adjust dosing to ensure patient stabilization within 24 hours and a consistently increasing trend of SpO_2

levels, starting from an appropriate minimum 10-day dosing schedule, which could be either the minimum dosing schedule used in this study or the weight-adjusted schedule used in the Babalola case series extended to 10 days.

For the initial ivermectin stat dose, one could adopt the more systematic approach suggested by Stone (Gkioulekas et al., 2025a, Table 1). Duration of treatment can be set at 10 days or it can be empirically extended by continuing treatment until full resolution of symptoms for 48 hours. Doxycycline, Vitamin C and D3, and zinc can be administered at the daily dosage used in this study for all patients, with doxycycline limited to a 10-day period.

Implications for Future Research

Early in the pandemic, it was proposed, because of pharmacokinetic considerations, to investigate nebulized ivermectin (Pena-Silva et al., 2021). Oral formulations of ivermectin (tablet, capsule, or liquid) take on average 3.5 hours (ranging from 1 hour to 6 hours for individual patients) to reach peak concentration in the plasma (Edwards et al., 1988, Table 1), however the in vitro observation of reversal of red blood cell hemagglutination by ivermectin was observed over a time scale of 30 minutes (Boschi et al., 2022, Methods).

Consequently, a testable prediction of the combined treatment effect hypothesis and the hemagglutination-reversal mechanistic hypothesis is that use of nebulized ivermectin may compress the observed SpO_2 recovery temporal association to approximately a 30 min to 1 hour interval. A controlled study comparing IDZCT against IDZCT plus nebulized ivermectin stat dose with continuous SpO_2 monitoring and temporal tracking of ivermectin administration can test this prediction, while being ethically acceptable to clinical investigators that do not retain personal equipoise about treatment efficacy. This study design would allow an inductive inference for a causal relation between IDZCT and SpO_2 recovery, and would be able to disentangle the treatment effect from natural recovery and regression to the mean. Furthermore, replicating the temporal association over a much shorter time scale would strengthen the credibility of a treatment effect.

Because we recognize that community-level clinical equipoise concerning ivermectin-based treatments may remain, clinical investigators who retain personal equipoise about treatment efficacy may best investigate IDZCT with controlled studies on hospitalized patients comparing IDZCT plus standard of care against standard of care, using oxygen-free days and mortality as endpoints. There are some obvious challenges in properly implementing dynamic ivermectin dosage adjustment in a blinded design, therefore we also recommend continuous tracking of SpO_2 and timing of ivermectin administration to compare the continuous temporal SpO_2 response between the two arms of the trial. As a practical matter, SpO_2 response comparisons between the two arms of the trial would be more convenient if all patients were administered the 36mg stat dose at the onset of treatment in the treatment arm of the trial. This study design would also allow inductive inferences regarding treatment efficacy.

A previously published detailed critical appraisal of this treatment (Gkioulekas et al., 2025a-b) was primarily constrained by the small sample size of the available case series. Given the adoption of IDZCT protocols by several physicians in Zimbabwe and South Africa (Stone and Aldous, 2024), the publication of further contemporaneous case series may further strengthen comparisons of the available case series against the available historical controls from that time period. This would strengthen existing IBE arguments; however, it would fall short of allowing an inductive inference regarding treatment efficacy.

Limitations

Limitations of this study include the small sample size of the patient case series, lack of statistical power for time-to-event analysis, missing data for SpO_2 on day 2 for 4 patients, the lack of systematic recording of SpO_2 levels over the full 10-day period, lack of standardized timing for SpO_2 measurements between baseline and day 2, and the retrospective patient chart review study design. This study did not evaluate the impact on mortality rate reduction.

Traditional self-selection bias into treatment vs no-treatment does not apply, because of 26 consecutive patients, identified as per the Methods section, all were offered IDZCT, 25 initiated IDZCT and 1 died before initiating IDZCT, but no eligible patient entirely declined IDZCT in favor of an alternative outpatient management. However, the cohort is defined by refusal of hospitalization, which may correlate with favorable prognosis, health literacy, or favorable disease trajectory, resulting in selection bias at the patient recruitment stage. Furthermore, compared with general hospitalized COVID-19 cohorts, this case series represents a subgroup with greater baseline hypoxemia and/or prior clinical trial exclusion or treatment failure. While lower baseline SpO_2 predicts worse overall prognosis in terms of patient survival, it also provides greater range for absolute SpO_2 improvement, raising potential for regression to the mean. Although historical controls are inconsistent with attributing the entire effect to regression to the mean, a controlled study may provide a more definitive inductive inference.

While the study found an association between IDZCT and a rapid recovery of SpO_2 levels on room air within 24 hours from the onset of treatment, the lack of a contemporaneous control group from the same cohort precludes inductive inferences regarding treatment efficacy (i.e. quantifying how much of the observed

response can be attributed to the treatment as opposed to spontaneous recovery). To minimize survivorship bias in pre-post SpO_2 comparisons, we conducted sensitivity analysis including the patient that died before initiating treatment. Tipping point analysis showed that results are robust for any imputation ranging from no-change to worst-case. The analysis of predictors of time to recovery using time-to-event analysis is constrained by the limited sample size of the case series and should be considered exploratory in nature.

This study did not provide protocolized thresholds for ivermectin dose escalation. However, we proposed guidelines for empirically deciding these thresholds for the treatment of current or future COVID-19 variants. Furthermore, had we provided protocolized thresholds, they would have been specific to the COVID-19 variants that were prevalent in the United States during the treatment period and not generalizable to other variants. In addition, because of the frequent patient monitoring, required to implement ivermectin dose escalation, a theoretical performance bias effect is possible in addition to the IDZCT drug-only effect. This study cannot disentangle the independent drug-only effect of IDZCT from any potential performance bias. However, because ivermectin dose escalation is an integral and mandatory component of IDZCT, treatment efficacy concerns the combined effect of the full IDZCT protocol, as delivered to patients, and it is not clinically relevant to disentangle the two effects from each other.

Although patients were provided standardized, FDA-approved pulse oximeters with written instructions on proper measurement technique to reduce artifact and SpO_2 measurements were documented by photograph and transmitted to the physician, unsupervised home self-measurement cannot exclude residual technique-related artifact, and some physiological SpO_2 variability over 3-6-hour intervals cannot be ruled out. As assessments were non-blinded, expectation bias in measurement or selective reporting is possible. While within-patient pre-post comparisons mitigate systematic device-specific or patient-specific bias, random measurement and physiological variation may still influence observed differences. As a telemedicine study of at-home patients, we could not standardize or track oral hydration, which could contribute to some improvement of SpO_2 levels on room air. Fever resolution is another potential contributor, though two patients were afebrile with severe hypoxia prior to treatment and still improved (patient #14 with baseline SpO_2 = 88%, patient #23 with baseline SpO_2 = 73%).

Because the patient cohort was unvaccinated and treated before the emergence of the Omicron lineage and sublineages, this study was not confounded by vaccine induced immunity and it is improbable that it was confounded by natural immunity, as previously explained. However, this may also raise concerns about the generalizability of the IDZCT to vaccinated patients and to Omicron variants, which should be further investigated. Indeed, prior experimental research has already shown that higher dosages of ivermectin are required *in vitro* to reverse hemagglutination induced by the Omicron B.1.1.529 variant relative to pre-omicron variants (Boschi et al., 2022), although we are not aware of any further experimental replication on subsequent Omicron sublineages. On the other hand, because this variant is less invasive in the respiratory system (Hui et al., 2022), SpO_2 tracking, by itself, may not even be a sufficient proxy of patient deterioration for properly guiding ivermectin dose adjustments, and the combination of multiple measures may be necessary. These are all particularly important questions that require careful investigation.

Conclusion

This study observed rapid recovery of hypoxic COVID-19 patients in response to ivermectin, doxycycline, zinc combination therapy, with adjunct vitamin C and D3 supplementation, within 24 hours and without reliance on oxygen concentrators. A treatment period of 10 days was sufficient for the complete and sustained recovery in all patients accepting the 10-day treatment, who avoided hospitalization and survived. With room air SpO_2 being an important indicator of the overall status of COVID-19 patients and closely correlated with mortality risk, these findings provided evidence in favor of the IDZCT. This small study also suggests that the benefits of IDZCT include the alleviation of suffering for hypoxic COVID-19 patients by restoring oxygen saturation levels. Future research studies of ambulatory combination therapy should be targeted to acute patients at continued high risk for hospitalization and death.

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Author's Contributions

Sabine Hazan: Conceptualization, investigation, resources, data curation, writing-review and edited, supervision, project administration, funding acquisition.

Adriana Vidal: Data curation, writing-review and edited, project administration.

Eleftherios Gkioulekas: Methodology, software, formal analysis, data curation, writing-original draft, writing-review and edited, visualization.

Anoja W. Gunaratne and Sibasish Dolai: Conceptualization, writing-review and edited.

Robert L. Clancy and Thomas J. Borody: Conceptualization, supervision, writing-review and edited.

Peter A. McCullough: Conceptualization, writing-original draft, writing-review and edited.

Ethics

Patients receiving IDZCT were provided individualized clinical care, outside the context of any clinical trial, in accordance with the best clinical judgment of the treating physician. This study involved retrospective analysis of de-identified patient data. This study was reviewed by the Institutional Review Board of Ethical & Independent Review Services, https://www.eandireview.com, (IRB #21006) and determined to be exempt from further IRB supervision due to minimal risk associated with its retrospective patient chart review design.

Ethical and Independent Review Services (E&I) was an independent Institutional Review Board (IRB) based in Missouri, United States, accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Ethical and Independent Review Services was subsequently acquired by Versiti Clinical Trial Services (Salus IRB), https://versiticlinicaltrials.org/, also an AAHRPP accredited independent IRB based in Texas, United States. This study complied with the Declaration of Helsinki and with all relevant local regulatory standards. All ethical guidelines for patient privacy and data confidentiality were followed.

Competing Interests

Peter McCullough is the Founder and President of the McCullough Foundation. He is also the Chief Scientific Officer of the Wellness Company, which had no role in conducting this study. The Wellness Company, which currently prescribes ivermectin and doxycycline in some of its emergency medicine kits, did not exist during the time period when the patients in this case series were treated. Sabine Hazan is the Chief Executive Officer of Progena Biome, LLC and Ventura Clinical Trials and she is the Founder of the Microbiome Research Foundation. She owns patents for the treatment and prophylaxis of COVID-19 and patents in the microbiome. She has a pecuniary interest in Topelia Aust Ltd in Australia and Topelia Therapeutics, Inc. in the USA where the development of treatment and prophylaxis options for COVID-19 are being pursued, including the combination therapy reported in this study. Thomas Borody has pecuniary interest in Topelia Aust Ltd in Australia and Topelia Therapeutics, Inc. in the USA. He has filed patents in the field of COVID-19 research and donated them to Topelia Aust Ltd in Australia for no compensation. Funds for this study were obtained from donations to the Microbiome Research Foundation. Donated funds were used to cover study expenses, including medications, supplies, equipment, testing, and operational costs. The donors had no role in conducting this study. Topelia Aust Ltd did not provide funding for this study.

List of Abbreviations

ACE2, Angiotensin-Converting Enzyme 2; COVID-19, Coronavirus Disease 2019; IDZCT, ivermectin, doxycycline, zinc combination therapy; IBE, inference to the best explanation; IQR, interquartile range; RCT, randomized controlled trial; RdRp, RNA Dependent RNA Polymerase; RT-qPCR, Reverse Transcription quantitative Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO_2 Peripheral oxygen saturation.

Dedication

We dedicate this paper to the blessed memory of our senior author, Professor Tom Borody, who passed away on October 6, 2025.

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