

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 $\text{SpO}_2 \leq 90\%$ 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 $\text{SpO}_2 > 90\%$ 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. In the context of previous work, the rapid recovery of SpO_2 levels on room air, observed in this study, provides further evidence supporting the Bradford Hill criteria of temporality, consistency, and biological gradient in favor of the combination therapy.

Keywords: coronavirus; COVID-19; doxycycline; ivermectin; SARS-CoV-2; zinc

1. 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, Scholz, and Zelenko, 2020; McCullough et al., 2020; Santin, Scheim, McCullough, Yagisawa, and Borody, 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 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 combination therapy consisting of ivermectin, doxycycline, and zinc, 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 this combination therapy because of multiple direct antiviral mechanisms which include: (a) competitive binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptor which inhibits viral entry to cells (Lehrer and Rheinstein, 2020); (b) inhibiting intracellular viral replication by preventing the importation of viral proteins into the cell nucleus (Caly, Druce, Catton, Jans, and Wagstaff, 2020); (c) acting as a zinc ionophore, facilitating the entry of Zn^{+2} ions through the cellular membrane, which inhibit viral replication (Rizzo, 2020). 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, Yang, Wu, Deng, and Tsai, 1999; de Castro Jr., Gregianin, and Burger, 2020), allowing for flexible dose adjustments. Further therapeutic benefits of ivermectin follow from its anti-inflammatory and immunomodulatory properties that mitigate the cytokine storm triggered by SARS-CoV-2 viral particles (Aminpour et al., 2022) subsequent to the viral phase of the illness. In total, ivermectin has 20 distinct mechanisms of action that may contribute towards an overall therapeutic benefit (Zaidi and Dehgani-Mobaraki, 2022). However, in hindsight, the primary driver of the success of this combination therapy is the competitive binding of ivermectin to several other sites of the viral spike protein (Aminpour et al., 2022). These sites are used by the SARS-CoV-2 viral particles to attach themselves to red blood cells via glycan bindings and induce the microclots that are primarily responsible for oxygen desaturation in severely ill COVID-19 patients (Schein, 2022). It has been experimentally confirmed, *in vitro*, that the viral spike protein causes this red blood cell aggregation, and that ivermectin can both reverse this aggregation when added to a blood sample after clumping has occurred and prevent it when added beforehand (Boschi et al., 2022). This study provides further corroboration of this mechanism *in vivo*.

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, Granwehr, and Kontoyiannis, 2020). Of note, doxycycline is also a zinc ionophore, allowing zinc ions to enter cells and inhibit viral replication (Malek et al., 2020).

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; te Velthuis et al., 2010). However, zinc requires a zinc ionophore to enter the cell. As previously noted, both ivermectin and doxycycline can act as zinc ionophores, allowing intracellular zinc to exert an additional antiviral effect. 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 it became apparent that this treatment was beneficial to patients with severe COVID-19 who did not initiate treatment within three to four days from the onset of symptoms. Previously, a 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. A small subset of patients required a customized treatment approach, incorporating hydroxychloroquine, to intensify the antiviral mechanisms of the baseline protocol and clear the virus, similar to how certain *Helicobacter pylori* infections may necessitate quadruple therapy when triple therapy is insufficient.

This study is of unique interest for the following reasons: (1) Almost all patients were hypoxic, with $\text{SpO}_2 \leq 90\%$ on room air and all had COVID susceptible comorbidities. (2) Circumstances necessitated treating the patients on room air, as they did not have access to oxygen concentrators at home. (3) Rapid stabilization of oxygen saturation above 90% was observed in response to the combination therapy for almost all patients accepting treatment within 24 hours, followed with full recovery of oxygen saturation levels within 10 days. Thus, within the framework of the Bradford Hill criteria (Hill, 1965; Howick, Glasziou, and Aronson, 2009), these results provide evidence supporting the Bradford Hill criterion of *temporality* in favor of using the combination therapy to treat COVID-19 patients at home, ideally at the early onset of symptoms.

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, in the Stone case series, ivermectin was used synergistically with nebulized nanosilver to restore oxygen saturation and patients were treated in person by the physician or via travelling nurses visiting patients at home. The combined data of the Babalola and Stone case series does not support the Bradford Hill criterion of consistency, because of substantial differences in the treatment protocols and the recovery rates. An important contribution of this study is the confirmation of the results by Stone et al. (2022), thus supporting the Bradford Hill criterion of consistency. Furthermore, this study demonstrated that a similar recovery rate of oxygen saturation can be achieved in a telemedicine context and without the use of nebulized nanosilver, provided that ivermectin dosage is dynamically adjusted based on patient response to treatment.

2. Material and Methods

2.1. 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 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 $\text{SpO}_2 \leq 90\%$ 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 $\text{SpO}_2 \leq 90\%$ 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). 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.

2.2. Patients

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 the combination therapy components; (2) contraindications to ivermectin and/or doxycycline, including seizure risk and pregnancy.

2.3. Treatment

At home treatment was initiated as soon as was practical, within 72 hours of patients presenting to ProgenaBiome. Treatment, defined as “*ivermectin, doxycycline, zinc combination therapy*” (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 SpO₂ increase on room air was 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 SpO₂ 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 SpO₂ > 90% by the end of day 2. 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 SpO₂ \leq 75%.

2.4. 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 confirmation 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.

2.5. 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 SpO₂ measurements. Patients were instructed to self-monitor SpO₂ 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, confirming that the reading is stable for approximately half a minute, and averaging measurements in case of variability. Patients emailed pictures of the SpO₂ oximeter measurements to the treating physician to confirm measurements. Baseline SpO₂ on room air was measured before commencing treatment. Afterwards, room air SpO₂ was continuously monitored and reported to the treating physician during at least day 1 and day 2 to guide ivermectin dose adjustments, as needed. SpO₂ was continuously

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

ID	Age	Race	Sex	Symptoms	Temp		SpO ₂ base	RT-qPCR		Rx start		Resolved
					base	+24 hr		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	11/11/2020
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; SpO₂: 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).

monitored until recovery of oxygen saturation with $\text{SpO}_2 > 95\%$. 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.

2.6. Outcomes

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

2.7. Data analysis

Descriptive statistics were used to summarize the case series characteristics and outcomes. Interquartile range (IQR) intervals were calculated using the 'quantile' function in R, which estimates the 25th and 75th 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. Sensitivity analysis addressed the missing SpO_2 data after 24 hours by imputing the baseline SpO_2 value. 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 confirm that the proportional hazards assumption was satisfied by the refined model. 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, 2025)

3. Results

3.1. 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 treatment 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, 24 patients adhered to the prescribed 10-day treatment (all except patient #10 and patient #26). Patients #10 and #26 both consented to treatment; however, patient #10 discontinued IDZCT treatment on day 2 and his condition deteriorated leading to his death. Patient #26 died before starting IDZCT treatment. Thus, for intention-to-treat calculations, data from all 26 patients was utilized, whereas for per-protocol analysis the subgroup of 24 patients that adhered to the 10-day treatment protocol was utilized.

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.

Table 2: Demographic and clinical characteristics of patients upon presentation

Characteristic	Intention-to-treat		Per-protocol	
	N	%	N	%
Sex				
Male	16	61.5	14	58.3
Female	10	38.5	10	41.7
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 SpO₂ on room air				
$90\% < \text{SpO}_2 \leq 95\%$	0	0.0	0	0.0
$85\% < \text{SpO}_2 \leq 90\%$	20	76.9	19	79.2
$80\% < \text{SpO}_2 \leq 85\%$	2	7.7	2	8.3
$75\% < \text{SpO}_2 \leq 80\%$	1	3.8	1	4.2
$70\% < \text{SpO}_2 \leq 75\%$	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;

SpO₂: Baseline peripheral oxygen saturation on room air prior to commencing ivermectin-based multidrug treatment.

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 SpO₂ or expected clinical need. Three patients were prescribed hydroxychloroquine concurrently with IDZCT treatment (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 treatment (patient #6). Two patients were given remdesivir during hospitalization prior to consultation for IDZCT treatment (patient #17 and #26). One patient was given monoclonal antibodies prior to initiating IDZCT treatment (patient #21). All patients were unvaccinated against SARS-CoV-2.

For 25 out of 26 patients, the initial presentation was severe with baseline room air SpO₂ ≤ 90%, all below the 93% threshold for severe COVID-19, proposed by NIH guidelines (National Institutes of Health, 2024). For the intention-to-treat group, 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 SpO₂ on

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: 30.0–39.9 kg/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/m²:** kilograms per meter squared.

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 Table 2, Table 4, and Table 5.

3.2. Patient baseline characteristics

Table 2 shows the demographic characteristics of the patients and their baseline temperature and room air SpO₂ 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 SpO₂ ≤ 90% with a majority at 85% < SpO₂ ≤ 90%. Of 26 intention-to-treat patients, 5 patients were at the 70% to 85% range with baseline SpO₂ 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 SpO₂ 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, according to current 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).

3.3. Rapid recovery of oxygen saturation on room air

The most important result of this study is the rapid response of room air SpO₂ levels to treatment, without the use of oxygen concentrators. Figure 1 and Table 4 highlight this rapid normalization of room air SpO₂ levels within 24 hours, for the 21 patients where day 2 data were available. Specifically, Table 4 displays the change Δ of room air SpO₂ 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% SpO₂ on room air, and the difference Δ_{95} between its day 2 peak value and the curative threshold of 95% SpO₂ on room air. For all 20 of 21 patients, where data were available, SpO₂ 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 SpO₂ > 90% on room air (except for patients #2, #10, and #23, for whom $\Delta \geq +10\%$). By day 10, SpO₂ levels on room air were successfully restored above 95% for all 24 patients in the per-protocol subgroup and were maintained without further treatment.

The median Δ between day 1 and day 2 was +6% (IQR 5% – 7%), which provides evidence supporting the Bradford Hill criterion of temporality in favor of this combination therapy (further addressed in the Discussion section). FDA-approved oximeters have an expected SpO₂ measurement error with 3% standard deviation (Silverston, Ferrari, and Quaresima, 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 $\Delta = +15\%$) and patient #23 (with $\Delta = +17\%$), both of who received the increased 36 mg ivermectin stat dose at the start of IDZCT treatment. These two outliers are shown in Fig. 1 with red color and the observed accelerated recovery rate provides some partial supporting evidence towards the Bradford Hill criterion of biological gradient. The one other outlier with $\Delta = -1$ was patient #4, for whom room air SpO₂ decreased from 97% to 96% over the initial 24-hour period. This patient was deemed

Table 4: Baseline SpO₂ vs SpO₂ 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

SpO₂: Peripheral oxygen saturation on room air.

day 1: Baseline SpO₂ on room air prior to commencing ivermectin-based treatment.

day 2: Peak SpO₂ on room air by the end of day 2.

Δ = Change of SpO₂ on room air from day 1 to day 2.

Δ₉₀ = Difference between peak SpO₂ on day 2 and the 90% SpO₂ stabilization threshold.

Δ₉₅ = Difference between peak SpO₂ on day 2 and the 95% SpO₂ curative threshold.

NA: Not available; **ID**: identification number.

high-risk because of shortness of breath upon presentation. Of note, both SpO₂ measurements were within the curative range (SpO₂ > 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 SpO₂ > 90% by the end of day 2. Peak SpO₂ data for day 2 is missing for 4 per-protocol patients, each of who had baseline room air SpO₂ ≥ 88%, close to the stabilization threshold.

Comparison of the room air SpO₂ levels between baseline and day 2, using the Wilcoxon signed-rank test on the subgroup of patients with available data on day 2, revealed that the observed increase in SpO₂ levels was statistically significant. The effect size was $r = 0.87$ both for intention-to-treat and per-protocol analysis with $N = 21$ and p -value $p = 7 \times 10^{-5}$ for the intention-to-treat patients and $N = 20$ and p -value $p = 10^{-4}$ for the per-protocol patients. Sensitivity analysis revealed that these results were resilient when SpO₂ levels on day 2 were imputed with baseline SpO₂ levels, resulting in effect size $r = 0.81$ with $N = 26$ and p -value $p = 7 \times 10^{-5}$ for the intention-to-treat patients and effect size $r = 0.82$ with $N = 24$ and p -value $p = 10^{-4}$ for the per-protocol patients.

3.4. Mortality and hospitalization outcomes

The per-protocol outcome was 24 patients adhering to treatment for the full 10-day protocol with 0 deaths and 0 hospitalizations. The intention-to-treat outcome was 2 deaths (patients #10 and #26) out of 26 patients.

3.5. 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

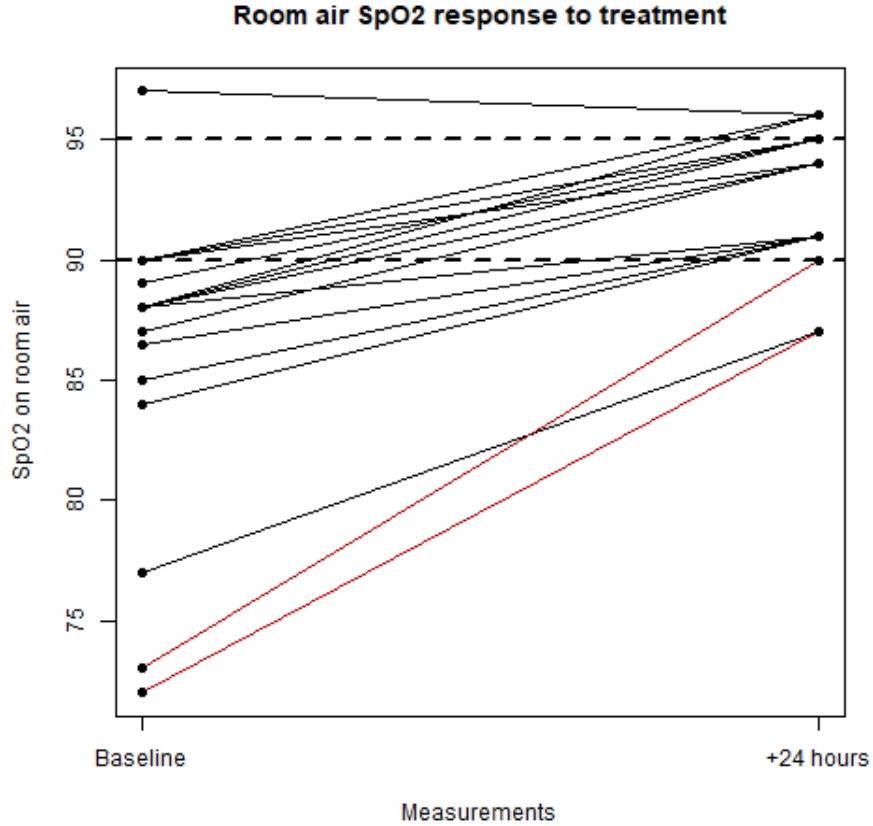


Figure 1: Change in SpO₂ levels on room air are shown at baseline and after 24 hours (day 2) for the 21 intention-to-treat patients with available data for day 2. Red color shows the change in SpO₂ levels on room air for the two patients that received the 36 mg stat dose of ivermectin on day 1. Horizontal dotted lines demarcate the patient stabilization threshold of 90% and the curative threshold of 95% for room air SpO₂ levels.

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

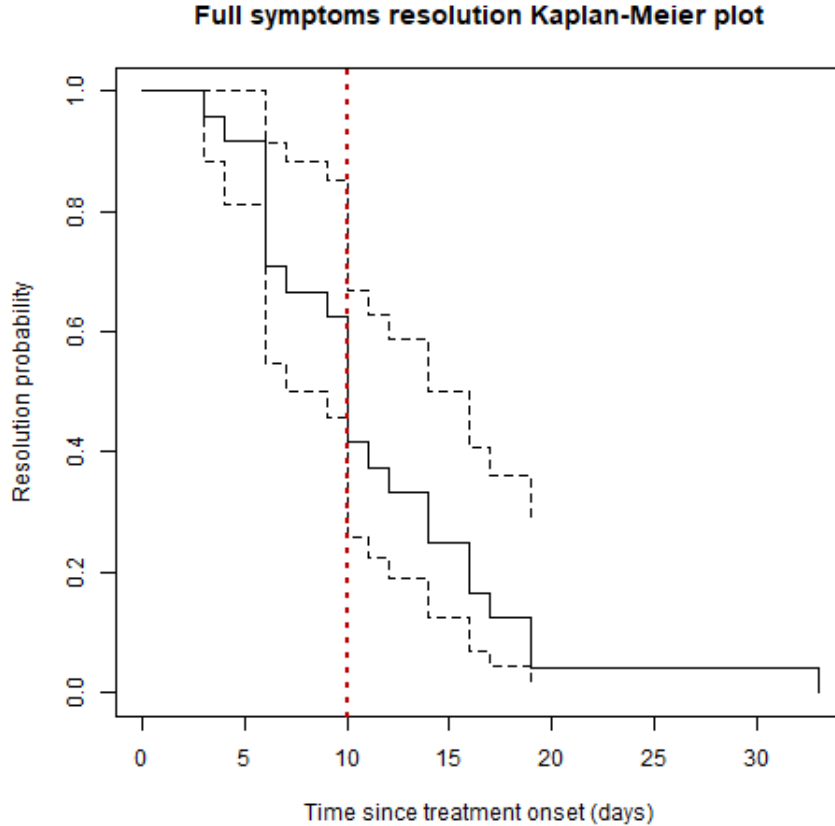


Figure 2: Kaplan-Meier plot showing the observed probability of full recovery from all symptoms as a function of number of days since the onset of IDZCT treatment. The 95% confidence interval is plotted using dotted lines. A vertical red dotted line demarcates the observed probability for full recovery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

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).

SpO₂ 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 SpO₂ 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 treatment. 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.

3.6. 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 are associated with accelerated full resolution of all symptoms. We considered 41 distinct variables (details available in the supplementary document (Gkioulekas, 2025)), 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 is 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. Further details of this statistical analysis are given in the supplementary document (Gkioulekas, 2025).

3.7. 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.

4. Discussion

This study has contributed the following findings: (a) At the onset of IDZCT treatment, rapid increase of SpO₂ on room air was observed in the 21 hypoxic patients with available SpO₂ data on room air for day 2, of which 18 out of 21 were successfully stabilized at SpO₂ > 90% within 24 hours; (b) this rapid increase in SpO₂ levels was statistically significant for these 21 patients, it remains statistically significant when missing day 2 data is imputed with the baseline SpO₂ levels on room air, and it 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; (c) hospitalization was successfully prevented for all 24 patients accepting IDZCT treatment for a period of 10 days with complete and sustained recovery of oxygen levels on room air by day 10; (d) 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; (e) All 24 patients accepting treatment survived.

These results are noteworthy because the successful treatment of these patients was achieved via telemedicine and the patients were treated at home on room air without access to oxygen concentrators. They are also noteworthy because all but one of the treated patients were hypoxic, with baseline SpO₂ ≤ 90%, for whom usual care would involve admission to the hospital. Nevertheless, the patients accepting treatment were successfully treated as outpatients. 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.

Noting that the presence of red blood cell microclots in the lungs and throughout the vascular system is the best explanation for oxygen desaturation in severe COVID-19 patients (McGonagle, Bridgewood, and Meaney, 2021), the rapid recovery of oxygen saturation levels within 24 hours, observed in this study, is consistent with mechanistic evidence from an *in-vitro* experiment showing that the addition of spike protein from SARS-CoV-2 to human blood causes red blood cell clumping, which is rapidly reversed with the addition of ivermectin (Boschi et al., 2022). Further mechanistic and parallel evidence has elucidated this observed rapid reversal of red blood cell clumping in response to ivermectin exposure and explains why other coronaviruses, like the common cold, do not cause a similar clumping effect (Aminpour et al., 2022; Scheim, 2022; Scheim et al., 2024; Scheim, Vottero, Santin, and Hirsh, 2023).

In addition, 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 2021 (Stone et al., 2022). 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, McCullough, and Aldous, 2025a, Table 1). Stone also relied on empirical observations of patient response to treatment to determine ivermectin dose adjustments. However, Stone developed more systematic criteria and processes for adjusting her protocol, because she was able to treat patients in person or via travelling nurses and could collect bloodwork and more detailed vitals. For the most severe COVID-19 patients (typically with baseline SpO₂ ≤ 80% on room air), Stone administered an ivermectin 0.6 mg/kg stat dose, which was titrated to 1-2 mg/kg if the expected increase of SpO₂ 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 SpO₂ on room air), Stone used ivermectin 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 combined ivermectin with nebulized nanosilver, the latter contributing fast but short-lasting increase in SpO₂ levels, which moderated the required ivermectin dosage. The full details of Stone's protocol 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 SpO₂ ≤ 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 SpO₂ 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.

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 demonstrated in Fig. 3, comparing the mean temporal change of room air SpO₂ 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 SpO₂ 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, statistical analysis previously confirmed that the difference in SpO₂ levels response between the ivermectin-treated case series and the Thairu case series is statistically significant (Scheim et al., 2024).

Noting that the Thairu case series patients were treated during the Delta variant, it is important to highlight that similar decreasing trends in SpO₂ levels were also observed in patients with pre-delta variants: (a)

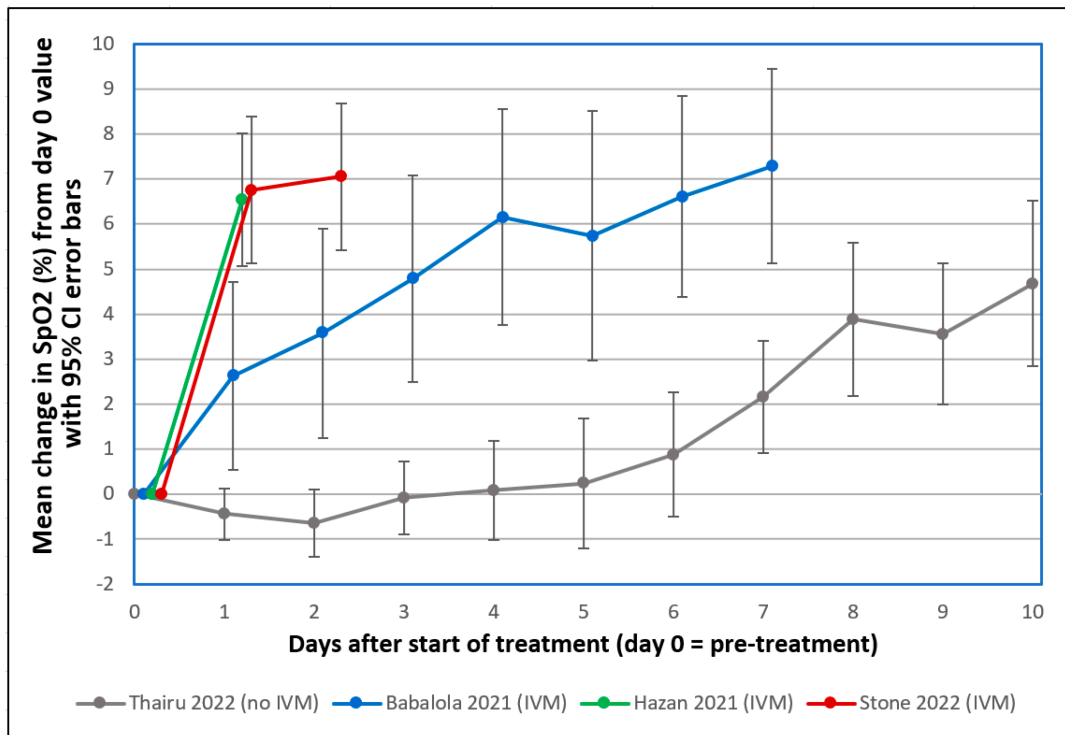


Figure 3: Average change in room air SpO₂ levels from baseline (day zero) for patients with initial SpO₂ ≤ 93% in the Hazan, Stone, and Babalola case series, with 95% confidence intervals represented by error bars. These are compared against the Thairu case series where a non-ivermectin treatment protocol was used. The figure is reproduced from Stone et al. (2022, Fig. 6) under the terms of the CC-BY-4.0 license.

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, Farouk, Osman, and Abdrabou, 2020, Figure 5); (c) Both Ding, Xu, Zhou, and Long (2020) and 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, it is not plausible to explain the observed rapid recovery of oxygen saturation levels within one day as the coincidental natural course of the disease for all 24 patients treated with the IDZCT protocol.

In addition, the observed recovery cannot be explained by concurrent care with hydroxychloroquine or monoclonal antibiotics, given that this effect was not observed in any studies of these medications in hospitalized patients to our knowledge and given that not all of the 24 patients received such concurrent care. Likewise, attributing the recovery to placebo effect is not plausible, in light of the dose-response relationship between ivermectin dosage and rate of recovery, as suggested by Fig. 1 and Fig. 3. Finally, our self-controlled statistical analysis comparing baseline and day 2 SpO₂ levels suggests that it is improbable that the observed recovery is a random result (i.e. regression to the mean) for all patients.

These observations provide evidence supporting the Bradford Hill criterion of temporality in favor of IDZCT combination therapy. The strength of the temporality evidence is amplified by the short response time interval and by the strong magnitude of the response compared with non-ivermectin care. Furthermore, the observed consistency in SpO₂ response between the Hazan and Stone case series, shown in Fig. 3,

both of which adjusted ivermectin dosage to patient severity and patient response to treatment, despite the demographic differences in the underlying populations, support the Bradford Hill criterion of consistency. Finally, there is an observable slower rate of recovery in the Babalola case series, where doxycycline and vitamin D were not used and ivermectin dosage was adjusted only by weight and not by patient severity and response to treatment. That provides evidence in support of the Bradford Hill criterion of biological gradient. Our Fig. 1, showing a visibly faster rate of recovery of SpO₂ levels in the 2 patients that received an additional 36 mg ivermectin stat dose at the onset of treatment provides further support for the Bradford Hill criterion of biological gradient. These are just a few of the highlights of a more extensive epidemiological analysis based on the Bradford Hill criteria (Gkioulekas et al., 2025a; Gkioulekas, McCullough, and Aldous, 2025b), interpreting the available direct evidence from all three case series, within the context of all other available mechanistic and parallel 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) there was no 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. The 2 patients who did not comply with the 10-day protocol are a natural contemporaneous control group; however, it is hardly sufficient for any meaningful case-control statistical analysis. Of note, Gkioulekas et al. (2025a) identified appropriate population-level contemporaneous historical controls from the respective locations and provided further statistical interpretation of the available data from the three case series.

Several meta-analyses of randomized controlled trials (RCTs) have confirmed the 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, Dancis, Dancis, and Oldfield, 2024) 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, Foster, Hanaki, and Omura (2021, 2024). 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 combination therapy 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), and Gonzalez et al. (2022).

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 (Schein, Hibberd, and Chamie-Quintero, 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 $\geq 3.7\%$ 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.

Gonzalez et al. (2022) 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 $83\% \pm 8\%$ 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 SpO₂ was achieved than in the Babalola case series. Nevertheless, notwithstanding the temporal associations in the Babalola case series, the results by Gonzalez et al. (2022) 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 SpO₂ $> 90\%$ 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) and Naggie et al. (2022)) so they are not generalizable to the 10-day combination therapy protocol used in this study; (b) the ACTIV-6 600 study (Naggie et al., 2023) 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 treatment protocol and 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. Gonzalez et al. (2022) 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 SpO₂ $\leq 80\%$ on room air, despite the observed slower increase in oxygen saturations with the onset of treatment shown in Fig. 3. Future work should study whether the more aggressive adaptive ivermectin dosage, used in this study, targeting patient stabilization with at least 90% SpO₂ within the first 24 hours, is sufficient for achieving a mortality reduction benefit, or whether the adaptive dosage should be further intensified for the first 24 hours.

To replicate this protocol on future hypoxic patients with an aggressive COVID-19 infection, rather than following a predefined ivermectin dosing schedule, it is more important to adjust dosing to ensure patient stabilization within 24 hours and a consistently increasing trend of SpO₂ 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.

Limitations of this study include the small sample size of the patient case series, missing data for SpO₂ on day 2 for 4 patients, and the lack of systematic recording of SpO₂ levels over the full 10-day period. While this study demonstrated the rapid recovery of SpO₂ levels on room air in response to treatment, no control group was used in this study. Thus, establishing a causal temporal association, as an inference to the best explanation, requires the qualitative assessment of the results reported in this study in the context of other studies indicating the natural progression of the disease under more conventional hospital protocols or similar but less aggressive protocols, as previously discussed. This study did not evaluate the impact on mortality rates. Because for 25 out of 26 patients the baseline SpO₂ on room air was SpO₂ ≤ 90%, one may infer some selection bias for this cohort towards selecting for patients that were more difficult to treat than the average hospitalized COVID-19 patient. 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. The ivermectin dosing schedule was specific to COVID-19 variants during the treatment period, and should be empirically adjusted depending on patient response, to successfully treat more lethal variants, should they reemerge again, or more severe cases of high-risk COVID-19 reinfections.

5. Conclusion

This study demonstrated 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 SpO₂ 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 combination therapy. This small study also suggests that the benefits of this combination therapy 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.

List of abbreviations

ACE2, Angiotensin-Converting Enzyme 2; COVID-19, Coronavirus Disease 2019; IDZCT, ivermectin, doxycycline, zinc combination therapy; 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; SpO₂ , 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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Author's contributions

Sabine Hazan: Conceptualization, Investigation, Resources, Data Curation, Writing Review & Editing, Supervision, Project Administration, Funding Acquisition. **Adriana Vidal:** Data Curation, Writing Review & Editing, Project Administration. **Eleftherios Gkioulekas:** Methodology, Software, Formal Analysis, Data Curation, Writing–Original Draft, Writing Review & Editing, Visualization. **Anoja W. Gunaratne:** Conceptualization, Writing Review & Editing. **Sibasish Dolai:** Conceptualization, Writing Review & Editing. **Robert L. Clancy:** Conceptualization, Supervision, Writing Review & Editing. **Peter A. McCullough:** Conceptualization, Writing–Original Draft, Writing Review & Editing. **Thomas J. Borody:** Conceptualization, Supervision, Writing Review & Editing.

Ethics

This study was approved by the Institutional Review Board of Ethical & Independent Review Services (<https://www.eandireview.com/>) with IRB #21006. This study complied with the 2013 Declaration of Helsinki (World Medical Association, 2013) and applicable 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 ProgenaBiome, 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.

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