Rapid increase of SpO2 on room air for 34 severe COVID-19 patients after ivermectin-based combination treatment: 55-62% normalization within 12-24 hours

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Abstract

Background. The emergence of COVID-19 in March 2020 challenged Zimbabwe to mount a response with limited medical facilities and therapeutic options. Ivermectin (IVM) had by then been safely used to treat a variety of human diseases affecting millions, as noted by the Nobel Committee in awarding its 2015 prize for medicine. Based upon early clinical indications of efficacy against COVID-19, IVM-based combination treatments were deployed to treat this infection in Zimbabwe.

Methods. Data were retrospectively analyzed for 34 severe COVID-19 patients treated with IVM-based combination therapy between August 2020 and May 2021, for whom pre- and post-treatment SpO2 values were all recorded on room air. Mortality and deterioration outcomes were also analyzed for a larger set of 92 severe COVID-19 patients receiving IVM-based treatment.

Results: For the 34-patient SpO2 tracking series, all but two patients had significantly increased SpO2 values after the first IVM dose, and all patients recovered. Mean increases in SpO2 as percentages of full normalization to SpO2=97 were 55.1% at +12 hours and 62.3% at +24 hours post-treatment. These results paralleled similar sharp increases in SpO2, all on room air, for a series of 24 RT-qPCR confirmed, mostly severe COVID-19 patients in the USA (California) who were given IVM combination treatment, all of whom recovered. For 19 of those patients having SpO2 $\leq$ 90 prior to IVM, the mean SpO2 normalization at +24 hours post-treatment was 65.2% as calculated from the SpO2 values reported. For our larger series of 92 severe COVID-19 patients in Zimbabwe, median age 53, only two died and two more deteriorated prior to recovery, far less than a predicted 7 deaths and 17 deteriorations for the demographics and risk factors of these patients.

Conclusions. The rapid, marked increases in SpO2 for both the Zimbabwe and California patients stand in sharp contrast to the decline in SpO2 and associated pulmonary function following onset of moderate or severe COVID-19 symptoms under standard care. These rapid SpO2 increases and low mortality rates support extended deployment of IVM treatment for COVID-19, complementary to immunizations for prevention.

Background

Evaluations of efficacy for COVID-19 therapeutics are challenging since most patients with this disease typically recover; the worldwide cumulative case fatality rate is 2% as of September 2021.[1]. Thus, randomized clinical trial (RCT) results are important, yet interpretations, for example, of the more than 20 mostly positive RCT results for COVID-19 treatment with the drug ivermectin (IVM), a macrocyclic lactone used widely worldwide since 1987, as summarized below, are controversial. Even for a drug such as remdesivir that was tested with several RCTs having large patient cohorts, opposite conclusions were drawn by the US FDA[2] and the World Health Organization[3] as to efficacy against COVID-19.

As a complement to positive RCT results for a COVID-19 therapeutic, a quantifiable determination of rapid, major improvement in pulmonary function, especially for severe COVID-19 patients, would further indicate efficacy and provide insights into that drug's underlying biological mechanism. The simplest indicator of lung function is blood oxygen saturation level, SpO2, as detectable using a pulse oximeter. However, the immediate administration of supplemental oxygen to any severe COVID-19 patient would typically preclude meaningful

pre-and post-treatment comparisons of SpO2 values. For this retrospective study conducted in Zimbabwe, ironically, challenges that constrained treatment capabilities also provided the opportunity to track changes in SpO2, all on room air, for 34 severe COVID-19 patients within 12 to 48 hours after beginning IVM treatment (see Figure 1). At the same time, these challenges tested whether severe COVID-19 patients with limited opportunities for hospitalization could be successfully treated at home or in clinics with rudimentary facilities.

Zimbabwe, a landlocked country in Southern Africa that shares a border with South Africa, had its first reported case of COVID-19 in March 2020.[4] Eight cases and one death from COVID-19 followed in the same month.[5] The first death occurred in the Wilkins hospital, Zimbabwe's main COVID-19 treatment center in the capital city of Harare. Facilities were limited at this hospital at the time; no capacity for ventilation was available. Given the rapid increase in COVID-19 patients in Harare after March 2020,[6] additional medical facilities began treating them.

COVID-19 wards were created at a general practice clinic by converting two staff rooms into a 4-bed ward and a storeroom into a 2-bed ward. Available equipment included several oxygen cylinders, an oxygen concentrator, six beds, and three monitors for SpO2 and blood flow parameters. The staff consisted of the lead author and another primary care physician who was off duty for several weeks after being injured in a vehicle accident on July 27, 2020, and either one or two nurses at different times, each on 12-hours shifts. During the initial months of the pandemic, in the absence of proven therapies and protocols, the standard of care evolved through early August 2020 to include corticosteroids, clopidogrel, aspirin, enoxaparin, rivaroxaban, a nebulized nano-silver preparation, zinc sulfate, hydroxychloroquine, azithromycin, doxycycline and in some cases an IV antibiotic.

However, the efficacy of these treatments was found to be limited, and by the end of July 2020, several COVID-19 deaths were recorded in the country. Based upon reports of initial success using IVM for COVID-19 treatment from colleagues in Johannesburg, South Africa, the College of Primary Care Physicians of Zimbabwe (CPCPZ) adopted and included IVM in their COVID-19 treatment protocol from August 8, 2020, starting initially with a 10-12 mg stat dose. Treatment of COVID-19 with IVM continued after the first patients showed improved outcomes, with more rapid recoveries achieved at doses higher than the standard of 200 ug/kg as initially used.

In August 2020, after it became apparent that IVM added to standard of care was significantly reducing the death rate, together with the hospital system being overwhelmed, CPCPZ physicians decided to treat COVID-19 patients where an IVM-based protocol could be administered, including at local general practice clinics which had nursing care and oxygen, and at some patients' homes with nursing support and oxygen supplementation as available. As knowledge of this successful treatment regimen spread in Zimbabwe, other physicians began offering the same treatment, with improved outcomes, which led to the formation of the Zimbabwe COVID Front Line Clinicians Society.

IVM for COVID-19 treatment

The decision to include IVM in COVID-19 treatment protocols in Zimbabwe was made as the pandemic swept through that nation, overwhelming limited clinical care facilities, with no drug developed to treat COVID-19

being generally accepted as effective. A published case-controlled study of IVM treatment for COVID-19 conducted at four US hospitals[7] that had been initially released in a preprint in June 2020 found a 40% reduction in mortality among 173 patients treated with low dose IVM vs 107 case-matched controls (15% vs 25.2% deaths). Interest in IVM was supported by its Nobel prize-honored pedigree and its extensive use to treat a variety of human diseases in over 3.7 billion doses worldwide since 1987.[8–10] Another favorable characteristic of this drug is its extraordinary record of safety, well tolerated at high doses,[11,12] including in studies for COVID-19 treatment.[13,14] It is generally non-toxic even at doses far exceeding the therapeutic range.[15,16] Since August 2020, inpatient and outpatient treatments of COVID-19 with IVM have been applied across 25 countries,[10] with more than 20 RCTs conducted for IVM treatment regimens.[10,17,18]

Seven of nine meta-analyses of these RCTs for IVM treatment reporting in 2021, all conducted using Cochrane analysis methodology, found significant[18–22] or possible[23,24] indications of IVM efficacy, with a mean 0.33 relative risk (RR) of mortality vs controls. Most of these 20 RCTs for IVM treatment of COVID-19 showed statistically significant mortality reductions or other clinical benefits. Among the most recent and detailed of the nine meta-analyses noted above reported a pooled total 67% reduction in mortality for IVM vs controls, with a statistical significance for an overall effect of p=0.005.[20] A comprehensive review of the entire body of clinical studies for IVM treatment of COVID-19 by the Nobel co-laureate for IVM, Dr Satoshi Omura and colleagues, concluded that IVM yielded major reductions in mortality.[10] Two animal studies of IVM treatment at low human-equivalent doses, one for the SARS-CoV-2 virus in golden hamsters[25] and another for a related betacoronavirus (MHV-A59) in mice,[26] found statistically significant treatment benefits, consistent with those found in the RCTs noted above. The indicated biological mechanism of IVM, competitive binding with SARS-CoV-2 spike protein,[27] is likely non-epitope specific, possibly yielding full efficacy against emerging viral mutant strains.

The demonstrated safety of IVM at much higher than standard doses[11–14] allowed the latitude for dose escalation for IVM treatment of COVID-19 over time. On September 19, 2020, the CPCPZ held a seminar at which the use of a combination of IVM, doxycycline and zinc was presented, along with aggressive diabetes control, steroid use and anticoagulation, and this was suggested as the most effective and affordable care available at the time. Afterwards, combination therapy centered around IVM plus doxycycline and zinc became the standard COVID-19 treatment protocol used by the CPCPZ. The potential efficacy of these adjuncts was later supported by successful clinical trials results with treatments using IVM in combination with doxycycline[28] or with doxycycline and zinc.[29] This combination therapy for COVID-19 has been researched and advanced by Thomas Borody,[30] who in 1990 published the first clinical trial of using a triple therapy of three inexpensive repurposed drugs for *H. pylori*,[31] the underlying bacterial cause of peptic ulcers. This triple therapy of repurposed drugs became the worldwide standard of care for peptic ulcers a decade later, after the patents for the palliative drugs Tagamet and Zantac expired, and the discovery of *H. pylori* as the cause of peptic ulcers was honored with the Nobel Prize for Medicine in 2005.[30]

Methods

This study is a retrospective review of clinical data collected during the course of treatment of COVID-19 patients with therapeutic agents selected by their physicians to offer the greatest chances for clinical benefits and recovery.

Outcomes

Outcomes tracked were 1) changes in SpO2 values from within one hour before treatment to 12, 24 and 48 hours after treatment, for a set of 34 COVID-19 patients for whom a pre-treatment SpO2 value and at least one SpO2 value up to +48 hours after start of treatment (first IVM dose) were available, all obtained on room air; and 2) mortality/deterioration: recovery, deterioration to critical status, or death for a larger set of 92 COVID-19 patients. For most of these patients, blood values for lymphocyte count, LDH, D-Dimer and CRP were also recorded, but complete blood test results were not obtained for every patient and therefore were not analyzed.

Participants

Sixty of the patients analyzed in this study, including all 34 in the SpO2 tracking series, were from Harare, treated by CPCPZ physicians either at local clinics or at patients' homes. Additional data for the mortality/deterioration series were obtained through inquiries sent on March 10, 2021, to all in a WhatsApp group of CPCPZ physicians treating COVID-19 with IVM asking for records of any of their patients so treated. Six physicians responded by furnishing records of 32 such patients, grouped with the 60 patients treated by CPCPZ physicians to comprise the mortality/deterioration series. For most of these six physicians, not every patient treated to recovery without incident was included, but it was confirmed that no other patient treated by them with IVM had died. Under pressures of patient care during the pandemic, record-keeping tended to be most comprehensive for the sickest patients, who thus are represented disproportionately in this study.

Table 1
Age group, sex, and pre-treatment SpO2 (%) value range of the 92-patient mortality/ deterioration series (mean age=54; median age=53).

Age		Initial SpO2 (%)			
Group	**Sex**	**66-84**	**85-89**	**90**	**Total**
25-49					
	Female	5	9	1	15
	Male	6	11	0	17
	Total	**11**	**20**	**1**	**32**
50-59					
	Female	2	6	0	8
	Male	8	8	2	18
	Total	**10**	**14**	**2**	**26**
60-69					
	Female	4	6	0	10
	Male	6	7	0	13
	Total	**10**	**13**	**0**	**23**
70-79					
	Female	1	1	1	3
	Male	1	0	2	3
	Total	**2**	**1**	**3**	**6**
80+					
	Female	0	2	0	2
	Male	1	2	0	3
	Total	**1**	**4**	**0**	**5**
TOTAL		**34**	**52**	**6**	**92**

Inclusion and Exclusion criteria

In both the SpO2 tracking and mortality/deterioration series, patients selected for analysis were of age 18 or older and had treatment start dates between August 8, 2020, and May 31, 2021. Patients selected had an SpO2 value on intake of 51% or above and were administered a treatment protocol including IVM. Furthermore, patients selected were required to have been found COVID-19 positive either by a PCR test or a clinical diagnosis made by criteria including exposure to a COVID-19 patient, hypoxia, lymphopenia,

monocytosis, elevated LDH, elevated dimer, and/or radiology consistent with pulmonary abnormalities caused by the virus.

For the mortality/deterioration analysis, the set of patients was further restricted to those with pre-treatment SpO2 of 90% or below (and a minimum SpO2 for all patients of 51%, as noted above). Table 1 shows the distribution of age, sex and pre-treatment SpO2 value of the 92 patients in this series. For the SpO2 tracking series, the subset of patients was restricted to those patients with pre-treatment SpO2 values of 51% through 93%. That series was further restricted to those for whom these SpO2 values were recorded and positively documented to have all been obtained on room air (in almost every case because oxygen was not available), and at least one SpO2 value obtained within 48 hours after IVM administration, with 34 patients fitting those criteria. Six of those patients had pre-treatment SpO2 values of 91-93% and were thus not included in the 92-patient mortality/deterioration series. All patients in both the mortality/deterioration and SpO2 tracking series thus fit the US National Institutes of Health's definition of severe COVID-19, a sufficient condition of which is SpO2 of 93% or below.[32]

Treatment

In the 92-patient mortality/deterioration series and in the overlapping 34-patient SpO2 tracking series, every patient received IVM at dosages described below in addition to selected other agents from the standard of care before August 2020. These other agents included corticosteroids, clopidogrel, aspirin, enoxaparin, a nebulized nano-silver preparation, rivaroxaban, zinc sulfate, azithromycin, doxycycline, and in some cases, an IV antibiotic. Patients treated in a clinic were assessed by a nurse upon admittance, with blood drawn and PCR tests conducted as feasible given the patient's condition and with severe symptoms necessitating immediate treatment. For those patients who contacted a CPCPZ physician from home requesting treatment, an online questionnaire was first completed by the patient, after which, if COVID-19 was still a suspected diagnosis, a nurse visit to the home was conducted, with associated follow up per the procedures described for in-clinic patients.

As evidence of IVM safety and tolerability accrued following its use beginning in August 2020, its stat dose of 10 mg as used for the earliest patients was increased on September 11, 2020, to 10-12 mg every four days for three doses. Subsequently, the dosage was further increased to 12 mg IVM on the day of admission and then on days 4 and 8 plus doxycycline (100mg b.i.d.) and zinc sulfate (60mg/day). The latter regimen was used up through December 2020, when the second pandemic wave emerged in Zimbabwe. At that time, additional evidence of safety and tolerability of this regimen supported further dose escalation to a standard IVM dose regimen of 12 mg daily for five consecutive days, with adjunct use of doxycycline and zinc sulfate continued at the doses noted. In some cases, for which this standard treatment regimen did not yield significant clinical gains within a few days, even higher doses of IVM were used, in some cases as high as 100 mg for a single dose. Transient adverse effects (AEs) such as blurred vision characteristic of high dose IVM often occurred at those dose levels, but no serious AEs associated with IVM were manifested in any patient. Each of the 34 patients in the SpO2 tracking series was treated with IVM, doxycycline and zinc.

Data collection

For patients in the SpO2 tracking series that were treated in clinics, values were tracked using monitors that continually displayed SpO2 values and readings for pulse rate and blood pressure and waveform images of blood pulses. For those treated at home, the intake nurse provided a pulse oximeter to the patient, unless the patient had one which the nurse deemed of reliable quality. The patient or a family member took SpO2 readings regularly, using the same oximeter as used for the pre-treatment reading. In most cases, these readings were taken daily, with much lower frequency after SpO2 values had risen significantly and the patient's clinical condition had correspondingly improved. Patients were instructed to message the nurse immediately if SpO2 ever decreased from a higher value to 93% or below or if any new clinical symptoms of concern developed.

Patient outcomes were categorized as recovered, died, or deteriorated before recovery, as follows. Recovered: patients who recovered following IVM treatment and were still alive on September 1, 2021, three months or more after intake. Died: those who died following IVM treatment, whether or not the cause could have been unrelated to COVID-19. Deteriorated (before recovery): if at any time following the first dose of IVM, any incident or condition, whether of indicated connection to COVID-19 or not, either caused them to be hospitalized or made that a reasonable course of action had that been an available and viable option.

Analytical methods

For the 34-patient SpO2 tracking series, a measure of percent normalization toward a fully optimal SpO2 value of 97 was applied, which for pre-and post-treatment SpO2 values S_0 and S_1, is: $100*(S_1-S_0)/(97-S_0)$, capped at 100%. Pre- and post-treatment SpO2 values were plotted for all 34 patients using this percent normalization measure in Figure 1 and were also presented directly in Figure 2, Figure 3, and Table S2. Regarding the 92-patient mortality/deterioration series, precise statistical comparisons of results from treatment vs control groups cannot be made other than in the context of an RCT. It is nevertheless of interest to compare the mortality results for this Zimbabwe mortality/deterioration patient series to the expected mortality of COVID-19 patients with similar characteristics. A review conducted in 2021 considered 46 prediction models for COVID-19 mortality,[33] two of which[34,35] were rated as having a low risk of bias; the same two were identified as being of the highest quality in another overview of COVID-19 mortality risk assessment models.[36]

The risk assessment model used here is the one of these two that used pre-treatment SpO2 as one of its prediction variables.[35] This model, designated as the 4C mortality risk predictor, was developed by 35 investigators on behalf of a consortium of 260 hospitals in the UK. It was derived from 57,824 hospitalized patients, a comparable group to this study's mortality/deterioration series of patients, who, as noted, all had pre-treatment SpO2 values ≤ 90% and would have been hospitalized had that been an available, viable option. The overall mortality rate of 4C model patients, using data collected February through June 2020, was 31%. In Harare's main hospital system, the Parirenyatwa Group, in its red zone, where COVID-19 patients are admitted and treated, per statistics available for June through December 2020, the COVID-19 case fatality rate (CFR) was 35.4% (119 deaths of 336 total patients).[37] This exceeds the overall CFR for the patient set of the 4C mortality risk predictor and indicates that using the 4C mortality risk predictor for the patient set in this study would not overestimate the risk factor.

The same UK consortium that developed the 4C mortality predictor also developed a model to assess the risk of clinical deterioration among inpatients with confirmed or highly suspected cases of COVID-19.[38] This deterioration model was developed using 73,948 patients recruited between February and August 2020, with clinical deterioration defined as any requirement of ventilatory support or critical care, or death. This model was also applied to the Zimbabwe mortality/deterioration series, and predicted deterioration outcomes were compared with the number of patients who could be considered to have deteriorated, per the criteria specified above.

To calculate both mortality and deterioration probability estimates for the Zimbabwe mortality/deterioration series, three base variables were used: age, sex and pre-treatment SpO2 value on room air, while for mortality, the 4C model used the count of comorbidities as another variable, as was also recorded for the study patients. Abnormal values for respiratory rate, urea, CRP, lymphocyte count, and presence of radiographic chest infiltrates would have added extra points and would have increased associated probabilities to these risks calculated for mortality and/or deterioration. However, since only these four base variables were available for every patient, only these were used to calculate the 4C-predicted risks.

The comorbidities used in the 4C mortality predictor were the following: chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic renal disease, mild to severe liver disease, dementia, chronic neurological disease, connective tissue disease, diabetes, HIV or AIDS, malignancy, and clinician-defined obesity.[38] For applying this risk predictor to the Zimbabwe mortality/deterioration patient series, these were the comorbidities used for the counts shown in Table S1. For some of these patients, certain variables used for the deterioration but not the mortality risk calculation would likely have significantly increased the deterioration probability values, and the calculated deterioration risk estimate is lower than that for mortality.

The 4C mortality and deterioration risk predictors were used to calculate probabilities for each of the 92 patients for mortality and deterioration, respectively. Although the Poisson distribution function can roughly approximate the probability of having a given number n or less total events from such a series having different probabilities, Monte Carlo simulation gives a much more precise probability estimate.[39] Monte Carlo simulations were executed, with 10,000,000 simulations performed ten times each for the mortality and deterioration estimations. These were performed using visual basic source code as listed in Supplementary File S3.

Ethics Approval

The Medical Research Council of Zimbabwe granted IRB approval (#E293) for this retrospective study. Patients consented for their medical treatment and to having their de-identified data used in this study.

Results

For COVID-19 patients treated with IVM in Zimbabwe between August 8, 2020, and May 31, 2021, results are presented for the following: A) Pre- and post-treatment SpO2 values for 34 patients for whom these values were recorded all on room air, each patient having a pre-treatment SpO2 value of 51-93% and at least one

post-treatment value obtained within 48 hours after first dose of IVM; and B) analysis of mortality and deterioration outcomes for 92 patients having pre-treatment SpO2 values of 51-90%.

Results for pre-and post-treatment SpO2 values

Figures 1 and 2 and Table S2 show the progression of pre-treatment and post-treatment SpO2 values within 48 hours after first dose of IVM for the 34 patients described above, all of whom were treated with IVM, doxycycline and zinc. All of these patients recovered. SpO2 values are shown at pre-treatment, all recorded within one hour before the start of treatment and at 12, 24 and 48 hours after treatment. The SpO2 value shown for a given patient at time x is that for the latest post-treatment time ≤ x. (Thus, for some patients, for example, having a post-treatment value within 12 hours before +24 hours but none in the next 24-hour period, the latest value at +48 hours is the same as that at +24 hours.)

Figure 1 shows, for all 34 patients, SpO2 value changes from before IVM administration to post-treatment as percentages of full normalization to an optimal SpO2 value of 97 (95 is considered the minimum normal SpO2 value for a healthy child or adult by the US CDC[41]). Red, orange and blue lines show, respectively, SpO2 values at +12, +24 and +48 hours post-treatment. The mean (±SD) SpO2 changes as this specified percent of optimal normalization were 55.1% ± 28.0% at +12 hours, 62.3% ± 26.3% at +24 hours and 64.3% ± 24.5% at +48 hours. As shown in Figure 1, these percentages of full normalization to SpO2=97 have a roughly uniform distribution across the full range of pre-treatment SpO2 values, from 66 to 93.

Figure 2 shows all pre-and post-treatment SpO2 values grouped into nine graphs (A-I) by the range of pre-treatment SpO2 values and post-treatment times (after first IVM dose) of +12, +24 and +48 hours. As shown in Figure 2 and identically in Table 2, those patients with lowest, mid-range and highest pre-treatment SpO2 values had mean SpO2 increases at +12 hours of 12.8, 5.4 and 2.8, respectively (all SpO2 values in percentage units). Figure 3 shows pre-and post-treatment SpO2 values throughout the entire observation period for each of the 34 patients. Note that these values were recorded less frequently after SpO2 had normalized.

Table 2
Mean ± SD of changes in SpO2 from pre- to post-treatment (after first IVM dose) for 34 severe COVID-19 patients treated with IVM, doxycycline and zinc.

SpO2 (%)			
Pre-treatment	at +12 hours	at +24 hours	at +48 hours
66 - 84%	+12.8 ± 6.7	+11.4 ± 6.1	+11.7 ± 5.8
85 - 89%	+5.4 ± 2.6	+6.2 ± 2.8	+6.3 ± 3.0
90 - 93%	+2.8 ± 2.7	+3.7 ± 2.3	+3.9 ± 1.8

Figure 4 shows successive SpO2 values for one patient who had a particularly rapid increase in these values after his first dose of IVM. This patient was a 25-year-old male, treated by a CPCPZ physician at a GP clinic without a supplemental oxygen capability. He received his first 12 mg IVM dose (repeated over the next four

days) immediately after entering the clinic with respiratory distress and bilateral pneumonia indicated by stethoscopic examination. His COVID-19 diagnosis was confirmed by a positive result from a rapid antigen test. As shown, his SpO2 values increased from that recorded immediately before treatment (79%) to values at 45 minutes (87%), 90 minutes (92%) and 3 hours (95%) post-treatment. He was discharged later that same day, and his home SpO2 readings then fluctuated between 92% and 95% over the next three days. By the fourth day after discharge, his SpO2 stabilized at 97%, his pulse dropped to 77 from prior values over 100, and he resumed working from home.

For the 34 patients in the SpO2 tracking series, as shown in Figure 2, all but two had increases in SpO2 within the first 48 hours after first dose of IVM. As shown in Figure 3, this overall increase in SpO2 continued throughout the entire observation period. However, several studies of moderate and severe COVID-19 patients under standard care that track SpO2, pulmonary abnormalities, or both establish that for most patients, SpO2 decreases in tandem with an increase in the extent of pulmonary CT abnormalities from the day of onset of disease symptoms through the second week following.[42–48] Thus, the expected change in SpO2 within 48 hours after first IVM dose would be < 0, and one-tailed paired t-test calculations can assess whether SpO2 values increased significantly > 0 at each time period tracked.

Taking into account some missing post-treatment values (see Table S2), there are 25, 33 and 34 pairs of pre- and post-treatment SpO2 values at +12 hours, +24 and +48 hours, respectively. Applying these paired t-test calculations, the SpO2 increases were highly significant for each time period: t=6.28, p=8.5E-07 at +12 hours; t=8.42, p=6.36E-10 at +24 hours, and t=8.81, p=3.47E-10 at +48 hours.

Results for mortality and deterioration

The mortality/deterioration series, as noted above, consisted of 92 COVID-19 patients with pre-treatment SpO2 values between 51% and 90%. Table S1 shows individual values for these patients for age, sex, pre-treatment SpO2 value, number of comorbidities, treatment outcome (recovered, deteriorated or died), and the respective probabilities from the 4C mortality and deterioration risk predictors.

Of these 92 patients, 90 recovered, and two died. (The latter two patients did not have recorded SpO2 values on room air and were not included in the 34-patient SpO2 tracking series.) To compare this result with the mortality outcome expected for a series of 92 COVID-19 patients with matching values of age, sex, pre-treatment SpO2 and the number of comorbidities, 4C mortality probabilities were calculated for each patient. Monte Carlo simulations were then executed, with 10,000,000 simulations run ten times. The number of simulated deaths in each run ranged from 7.079 to 7.081, with a mean of 7.080, and the mean of the associated individual standard deviations = 2.494. The probability of having zero to two simulated deaths in this series ranged in these ten runs was 0.0214 (identically for mean, minimum and maximum values).

Two patients other than the two who died fit the deterioration criteria noted above. One was transferred to a hospital for three days because he became weak from not eating, and another was hospitalized for six days due to a drop in oxygen saturation. Both resumed IVM treatment after returning home and subsequently recovered. These two plus the two patient deaths yield a total of four deteriorations according to the 4C risk model for deterioration. 4C deterioration probabilities were calculated for each of the 92 patients, and Monte Carlo simulations were then executed for deterioration risk estimation, with 10,000,000 simulations run ten

times. The number of simulated deteriorations in each run was 17.23 (identically for the mean, minimum and maximum of these values), with the mean of the associated individual standard deviations = 3.54. The probability of having zero to four simulated deteriorations in this series ranged in these ten runs from 0.0000196 to 0.0000216, with a mean of 0.0000207.

With the caveat above as to the limits of statistical analyses outside the context of an RCT, this calculation nevertheless suggests that the occurrence of four or fewer deteriorations among these 92 severe COVID-19 patients would be highly improbable under standard care. For comparison, note that in this series of 92 patients, 21 had pre-treatment SpO2 values ≤ 78%, and among these 21 patients, only two deteriorated (the patients who died). In sharp contrast were deterioration outcomes reported by Mukhtar et al. in a study of 72 critically ill COVID-19 patients.[49] Thirty-four of those 72 patients had hospital admission SpO2 values ≤ 78% on room air, and all of those subsequently required mechanical ventilation, whereas only 16 of 38 (42%) of patients having intake SpO2 value > 78% required ventilation (Mohamed Hasanin, corresponding author of this study, personal communication, August 15, 2021).

Discussion

This study is a retrospective review of clinical data collected amid the challenges of providing treatment with limited facilities and resources to COVID-19 patients with severe disease. Under such conditions, it was not possible to obtain blood test values for all patients, including values for lymphocyte count, LDH, D-Dimer and CRP, which were thus not analyzed. On the other hand, the lack of availability of oxygen supplementation for many of the patients treated resulted in the rare opportunity to track changes in SpO2 values all recorded on room air before and after administration of IVM to 34 patients, with several of these patients having presented with SpO2 values well below 90%.

The increase in SpO2 for these 34 patients as the percentage of fully optimal normalization to SpO2=97, as reported above, was (mean ±SD) 55.1% ± 28.0% at +12 hours, which rose to 62.3% ± 26.3% at +24 hours and then to 64.3% ± 24.5% at +48 hours after first IVM dose. All but two of these 34 patients had SpO2 values that increased at all post-treatment times for which values were obtained. Paired t-test calculations yield $p<0.0000001$ for the SpO2 increases at +12, +24 or +48 hours having occurred by chance had the IVM-based combination therapy applied had no clinical activity against COVID-19. Because the dearth of significant spontaneous improvements in SpO2 levels and respiratory function one day after a severe COVID-19 patient's presentation for medical care is a well-established norm for this disease per the studies cited above, these probability values are significant and noteworthy.

The results for this SpO2 tracking series, with recoveries for all 34 patients, parallel those recently reported by Hazan et al., for which SpO2 values all on room air for 24 RT-qPCR confirmed COVID-19 patients were tracked before and +24 hours after combination treatment with IVM, doxycycline and zinc.[40] For the 19 severe COVID-19 patients in that series who had pre-treatment SpO2 values of 90% and below (minimum=77%) and had +24 hour post-treatment SpO2 values (see Table S3), the mean (±SD) SpO2 values were 86.7 ± 4.5 pre-treatment and 93.3 ± 2.6 at +24 hours after first IVM dose. As the percentage of normalization to SpO2=97, the mean (±SD) relative SpO2 increase for these 19 patients was 65.2% ± 17.5%, which is close to the +24 hour relative increase of 62.3% for the 34-patient Zimbabwe SpO2 tracking series. The one-tailed paired t-test for these

increased SpO2 values in these 19 patients yields t=9.34, p=1.27E-08, which as for the Zimbabwe SpO2 series is highly significant.

The similar results for the SpO2 patients in the Zimbabwe SpO2 series and the 24 patients of Hazan et al. suggest that the triple therapy of IVM, doxycycline and zinc provides efficacy regardless of which other adjunct agents were used, or may indicate that each study used different sets of adjuncts that further boosted the activity of this regimen to the degree of efficacy manifested in the clinical outcomes for each. One limitation of this study is that except for nebulized nano-silver, used for all patients at the start of the treatment regimen, other adjuncts were deployed on a case-by-case basis, per the patient's condition. Also, IVM dosages were increased during the study period based on the observations that no serious AEs were observed at higher doses, and higher doses appeared to be most effective for the patients with the most severe symptoms. A follow-up clinical study of IVM-based combination treatment of COVID-19 would benefit from a more structured specification and tracking of dosages and adjuncts used.

The distinct improvements in respiratory function for this study's 34-patient SpO2 tracking series, paralleling similar results reported by Hazan et al., provide a quantifiable demonstration of rapid clinical improvement in severe COVID-19 patients after IVM treatment. Such rapid improvements had been observed since the first major clinical trial of IVM treatment of COVID-19.[7] The lead investigator of that clinical trial had observed that stabilization and then improvement in breathing function frequently occurred in 12-48 hours after IVM treatment, even for patients who had been deteriorating rapidly and had required supplemental oxygen at up to a 50% mixture.[50]

The SpO2 increases within a day after IVM treatment observed in this study and by Hazan et al. provide a distinct indication that IVM not only yields statistically significant clinical benefits in groups of patients as reported in most of the 20 RCTs for IVM treatment but provides rapid, directly observable resolution of pulmonary dysfunction as tracked by SpO2 values for COVID-19 patients. This finding offers clues as to the potential biological mechanism of IVM activity against SARS-CoV-2 since, for example, even an effective freeze on viral replication or rapid repair of damaged pulmonary alveoli would be unlikely to cause such rapid clinical improvements. One indicated biological mechanism of IVM activity, competitive binding with SARS-CoV-2 spike protein, as reviewed,[27] may, through a reversal of viral hemagglutination, act quickly to increase pulmonary capillary flow and in turn account for normalization of blood oxygenation. An additional plausible mechanism of IVM activity is the activation of the cholinergic anti-inflammatory pathway under the control of the vagus nerve,[51] which is regulated by acetylcholine and potentiated by the high-affinity binding of IVM (a positive allosteric modulator) to the alpha 7 cholinergic receptor a7nAChr[52] expressed on bronchial, vascular as well as to cytokine-producing cells (i.e., TNF, IL1 and IL6 secreting macrophages, lymphocytes and mast cells).[53]

For the SpO2 tracking series, the pattern of rapid increases in SpO2 after start of IVM treatment as occurred for all but two of these 34 patients resulted in recoveries for all of them. This same pattern of highly successful outcomes extended to the 92-patient mortality/deterioration series, with recoveries of all but two patients. As noted above, although statistical significance cannot be determined through the 4C mortality and deterioration calculations, these odds calculations suggest that the probabilities for achieving the mortality and deterioration results obtained in this study were, respectively, low and extremely low under standard care.

No serious adverse effects (AEs) from IVM treatment were observed in any patient, although transient AEs such as blurred vision characteristic of higher-dose IVM administration were observed in some patients given doses as high as 100 mg. While comparative results using higher vs lower doses were not systematically tracked, the practice of increasing IVM doses for patients not initially responding to treatment worked out well and supports the indication that higher doses provide greater efficacy.

Conclusions

Pre-and post-treatment SpO2 values were recorded all on room air for 34 severe COVID-19 patients who were treated with the combination therapy of IVM, doxycycline and zinc plus other adjuncts. This application of multiple drugs against COVID-19 was based on Zimbabwe's experience with prior infectious diseases, for which early, aggressive use of multiple drugs has been a core treatment principle. For these 34 patients, all but two had increases in SpO2 from pre- to post-treatment, at every time interval of +12, +24 and +48 hours after first IVM dose for which values were recorded. The mean increase in SpO2 value as a percentage of full normalization to SpO2=97 was 55.1% at +12 hours and 62.3% at +24 hours after first IVM dose. These results closely parallel the mean SpO2 normalization of 65.2% as calculated from SpO2 values reported by Hazan et al. for 19 RT-qPCR confirmed COVID-19 patients having pre-treatment SpO2 $\leq$ 90, with all SpO2 values on room air.

The marked, rapid normalizations of blood oxygenation, $p<0.0000001$ for the 34-patient SpO2 tracking series in each time period analyzed (paired t-test), stand in sharp contrast to the well-established typical decline in SpO2 during at least the first week after onset of moderate or severe COVID-19 symptoms and establish a cause-and-effect clinical benefit for IVM-based combination treatment of this disease. Furthermore, for the larger set of 92 severe COVID-19 patients treated with IVM and other adjunct agents, all having pre-treatment SpO2 values of 90 and below, all but two recovered, and only two of those recovering patients experienced deterioration before recovery. These two deaths and four deteriorations (including the two deaths) are much less than the expected seven deaths and 17 deteriorations predicted using the well-regarded 4C COVID-19 risk assessment model.

For the patients of this Zimbabwe study and the Hazan critical series, treatment at home or in clinics with basic facilities freed up hospital resources for other patients, and the treatment approach modeled in these studies could significantly relieve the pressure on overwhelmed health facilities. IVM is widely available worldwide, inexpensive, and one of the safest drugs in modern medicine, with its safety in "improving the health and wellbeing of millions" noted explicitly by the Nobel Committee in awarding its 2015 prize for the discovery of IVM.[54] These study results, therefore, support the extended deployment of IVM for COVID-19 treatment, complementary to immunizations for prevention.

Declarations

Funding

No funding was received for this study.

Conflict of Interests

All authors report no conflicts of interest.

Data availability statement

Data underlying the study cannot be made publicly available due to ethical concerns about patient confidentiality. Data will be made available to qualified researchers on request to the corresponding author.

References

1. Worldometer coronovirus statistics. https://www.worldometers.info/coronavirus/#countries. Accessed September 22, 2021.
2. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: Therapeutic Management of Patients With COVID-19.* Bethesda, MD: US National Institutes of Health; May 24, 2021: https://www.covid19treatmentguidelines.nih.gov/.
3. *WHO recommends against the use of remdesivir in COVID-19 patients*. World Health Organization; November 20, 2020: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients.
4. Chirisa S. Zimbabwe Confirms Its First Case Of Coronavirus. *Harare.com.* March 20, 2020. https://iharare.com/zimbabwe-confirms-first-case-of-coronavirus-2/.
5. *Coronavirus disease 2019 (COVID-19), Situation Report – 72.* World Health Organization; April 1, 2020: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2.
6. *Coronavirus disease 2019 (COVID-19), Situation Report – 193.* World Health Organization; July 31, 2020: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200731-covid-19-sitrep-193.pdf?sfvrsn=42a0221d_4.
7. Rajter JC, Sherman MS, Fatteh N, et al. Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID-19 (ICON study). *CHEST.* 2020; doi:10.1016/j.chest.2020.10.009.
8. Campbell WC. History of avermectin and ivermectin, with notes on the history of other macrocyclic lactone antiparasitic agents. *Curr Pharm Biotechnol.* 2012;13(6):853–865.
9. Crump A, Ōmura S. Ivermectin, 'wonder drug' from Japan: the human use perspective. *Proc Jpn Acad Ser B Phys Biol Sci.* 2011;87(2):13–28.
10. Yagisawa M, Foster PJ, Hanaki H, et al. Global Trends in Clinical Studies of Ivermectin in COVID-19. *The Japanese Journal of Antibiotics.* 2021;74(1).
11. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol.* 2002;42(10):1122–1133.
12. Navarro M, Camprubí D, Requena-Méndez A, et al. Safety of high-dose ivermectin: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy.* 2020;75(4):827–834.
13. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. *EClinicalMedicine.* 2021;37.

14. López-Medina E, López P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;10.1001/jama.2021.3071.
15. de Castro CG, Jr., Gregianin LJ, Burger JA. Continuous high-dose ivermectin appears to be safe in patients with acute myelogenous leukemia and could inform clinical repurposing for COVID-19 infection. *Leuk Lymphoma.* 2020;61(10):2536–2537.
16. Chung K, Yang CC, Wu ML, et al. Agricultural avermectins: an uncommon but potentially fatal cause of pesticide poisoning. *Ann Emerg Med.* 1999;34(1):51–57.
17. Kory P, Meduri GU, Varon J, et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. *American Journal of Therapeutics.* 2021;28(3):e299-e318.
18. Hill A, Garratt A, Levi J, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. *Open Forum Infectious Diseases.* 2021;10.1093/ofid/ofab358.
19. Hariyanto TI, Halim DA, Rosalind J, et al. Ivermectin and outcomes from Covid-19 pneumonia: A systematic review and meta-analysis of randomized clinical trial studies. *Reviews in Medical Virology.* 2021;https://doi.org/10.1002/rmv.2265:e2265.
20. Karale S, Bansal V, Makadia J, et al. A Meta-analysis of Mortality, Need for ICU admission, Use of Mechanical Ventilation and Adverse Effects with Ivermectin Use in COVID-19 Patients. *medRxiv.* 2021;doi:10.1101/2021.04.30.21256415.
21. Bryant A, Lawrie TA, Dowswell T, et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. *American Journal of Therapeutics.* 2021;doi:10.1097/MJT.0000000000001402.
22. Zein AFMZ, Sulistiyana CS, Raffaelo WM, et al. Ivermectin and mortality in patients with COVID-19: A systematic review, meta-analysis, and meta-regression of randomized controlled trials. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews.* 2021;https://doi.org/10.1016/j.dsx.2021.102186:102186.
23. Kow CS, Merchant HA, Mustafa ZU, et al. The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis. *Pharmacological Reports.* 2021;10.1007/s43440-021-00245-z.
24. Rodríguez-Gutiérrez R, Raygoza-Cortez K, Garcia-Leal M, et al. Ivermectin in the Prophylaxis and Treatment of Patients with SARS-CoV-2: A Living Systematic Review and Meta-Analysis. http://ssrn.com/abstract=3802499. Published 2021. Accessed June 13, 2021.
25. Melo GD, Lazarini F, Larrous F, et al. Anti-COVID-19 efficacy of ivermectin in the golden hamster. *bioRxiv.* 2020;doi:10.1101/2020.11.21.392639.
26. Arévalo AP, Pagotto R, Pórfido JL, et al. Ivermectin reduces *in vivo* coronavirus infection in a mouse experimental model. *Scientific Reports.* 2021;11(1):7132.
27. Scheim DE. From cold to killer: How SARS-CoV-2 evolved without hemagglutinin esterase to agglutinate, then clot blood cells in pulmonary and systemic microvasculature. http://ssrn.com/abstract=3706347. Published 2020. Accessed March 30, 2021.
28. Mahmud R, Rahman MM, Alam I, et al. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. *Journal of International Medical Research.*

2021;49(5):03000605211013550.

29. Hashim HA, Maulood MF, Rasheed AM, et al. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv.* 2020;doi:10.1101/2020.10.26.20219345.
30. Santin AD, Scheim DE, McCullough PA, et al. Ivermectin: a multifaceted drug of Nobel prize-honored distinction with indicated efficacy against a new global scourge, COVID-19. *New Microbes and New Infections.* 2021;https://doi.org/10.1016/j.nmni.2021.100924.
31. George LL, Borody TJ, Andrews P, et al. Cure of duodenal ulcer after eradication of *Helicobacter pylori*. *Med J Aust.* 1990;153(3):145–149.
32. US National Institutes of Health (NIH). Clinical Spectrum of SARS-CoV-2 Infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Updated April 21, 2021. Accessed June 2, 2021.
33. Miller JL, Tada M, Goto M, et al. Prediction Models for Severe Manifestations and Mortality due to COVID-19: A Rapid Systematic Review. *medRxiv.* 2021;doi:10.1101/2021.01.28.21250718.
34. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ.* 2020;371:m3731.
35. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ.* 2020;370:m3339.
36. Sperrin M, McMillan B. Prediction models for covid-19 outcomes. *BMJ.* 2020;371:m3777.
37. *Parirenyatwa group of hospitals redzone statistics for the period 5 May 2020 to 31 December* 2020 *(report, no public URL available).* Harare, Zimbabwe: Parirenyatwa group of hospitals, Infection Prevention and Control Department;2021: https://drive.google.com/file/d/1ZLe45XMqJUW1zXyLQjMXpKRXfsXvqBm-/view?usp=sharing.
38. Gupta RK, Harrison EM, Ho A, et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. *The Lancet Respiratory Medicine.* 2021;9(4):349–359.
39. Holmes S, Huber W. *Modern Statistics for Modern Biology.* 1st edition ed. Cambridge, United Kingdom: Cambridge University Press; 2019:1-15.
40. Hazan S, Dave S, Gunaratne AW, et al. Effectiveness of Ivermectin-Based Multidrug Therapy in Severe Hypoxic Ambulatory COVID-19 Patients. *medRxiv.* 2021;doi:10.1101/2021.07.06.21259924.
41. U.S. Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). The Basics of Oxygen Monitoring and Oxygen Therapy during the COVID-19 Pandemic. https://www.cdc.gov/coronavirus/2019-ncov/videos/oxygen-therapy/Basics_of_Oxygen_Monitoring_and_Oxygen_Therapy_Transcript.pdf. Accessed September 23, 2021.
42. Osman AM, Farouk S, Osman NM, et al. Longitudinal assessment of chest computerized tomography and oxygen saturation for patients with COVID-19. *Egyptian Journal of Radiology and Nuclear Medicine.*

2020;51(1):255.
43. Metwally MI, Basha MAA, Zaitoun MMA, et al. Clinical and radiological imaging as prognostic predictors in COVID-19 patients. *Egyptian Journal of Radiology and Nuclear Medicine.* 2021;52(1):100.
44. Aoki R, Iwasawa T, Hagiwara E, et al. Pulmonary vascular enlargement and lesion extent on computed tomography are correlated with COVID-19 disease severity. *Japanese Journal of Radiology.* 2021;39(5):451–458.
45. Ding X, Xu J, Zhou J, et al. Chest CT findings of COVID-19 pneumonia by duration of symptoms. *European Journal of Radiology.* 2020;127.
46. Wang Y, Dong C, Hu Y, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology.* 2020;296(2):E55-e64.
47. Quispe-Cholan A, Anticona-De-La-Cruz Y, Cornejo-Cruz M, et al. Tomographic findings in patients with COVID-19 according to evolution of the disease. *Egyptian Journal of Radiology and Nuclear Medicine.* 2020;51(1):215.
48. Annunziata A, Coppola A, Carannante N, et al. Home Management of Patients with Moderate or Severe Respiratory Failure Secondary to COVID-19, Using Remote Monitoring and Oxygen with or without HFNC. *Pathogens.* 2021;10(4).
49. Mukhtar A, Rady A, Hasanin A, et al. Admission SpO(2) and ROX index predict outcome in patients with COVID-19. *Am J Emerg Med.* 2021;50:106–110.
50. J.J. Rajter, personal communications (emails) of May 28, 2020.
51. Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor α7 subunit is an essential regulator of inflammation. *Nature.* 2003;421(6921):384–388.
52. Krause RM, Buisson B, Bertrand S, et al. Ivermectin: a positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor. *Mol Pharmacol.* 1998;53(2):283–294.
53. Ren C, Tong YL, Li JC, et al. The Protective Effect of Alpha 7 Nicotinic Acetylcholine Receptor Activation on Critical Illness and Its Mechanism. *Int J Biol Sci.* 2017;13(1):46–56.
54. *The 2015 Nobel Prize in Physiology or Medicine - Press release.* The Nobel Assembly at Karolinska Institutet; October 5, 2015: https://www.nobelprize.org/prizes/medicine/2015/press-release/.

Figures

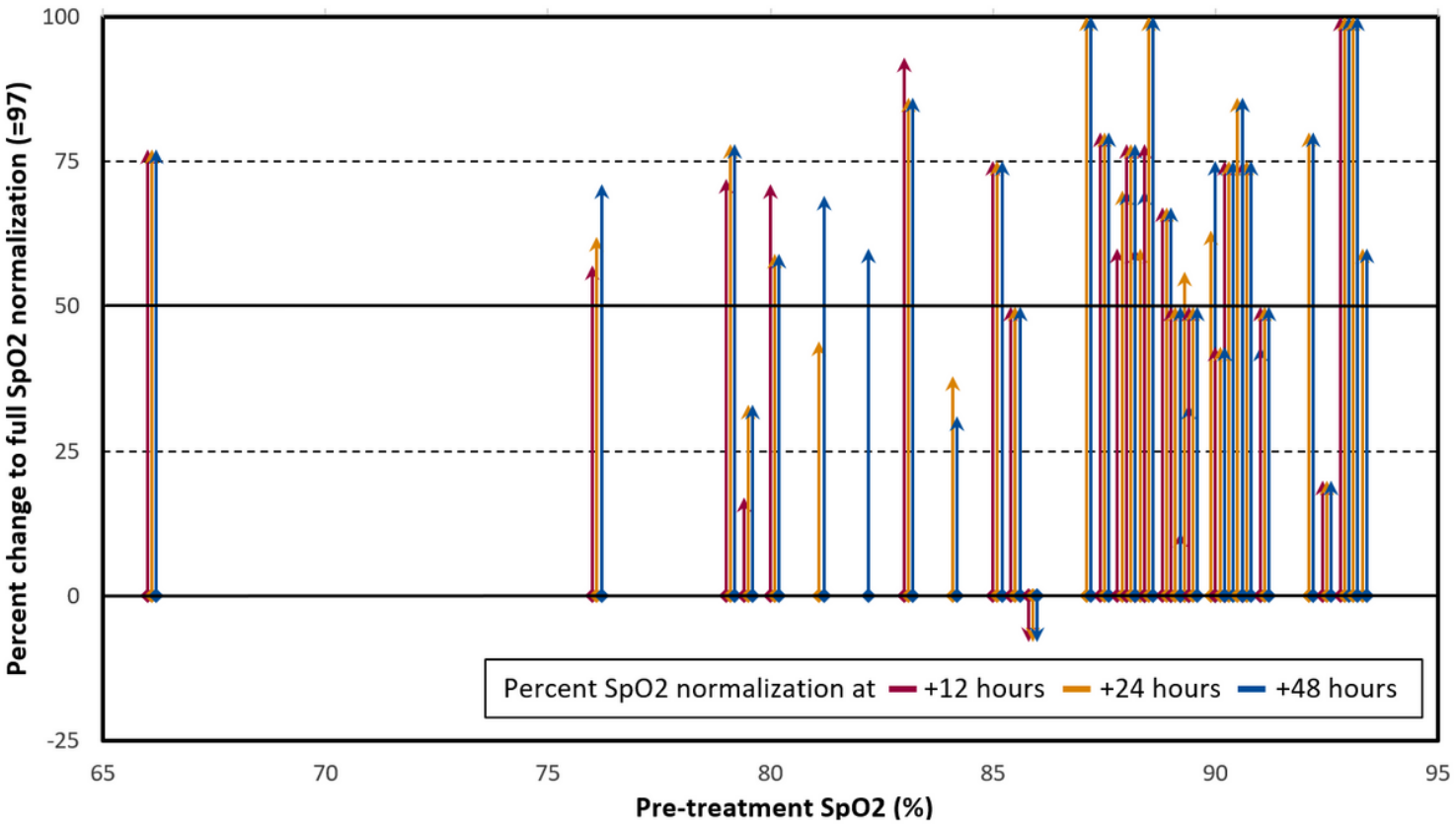

Figure 1

Changes in pre- to post-treatment SpO2 values, all on room air, for 34 severe COVID-19 patients treated with ivermectin (IVM), doxycycline and zinc, as percentages of optimal normalization to SpO2=97. Red, orange and blue lines represent, respectively, changes in SpO2 values at +12, +24 and +48 hours after first dose of IVM. X values were increased slightly (<1.5) as needed to accommodate clusters of values. For pre-and post-treatment SpO2 values S0 and S1, the y axis is the percent of optimal normalization to SpO2=97, that is: 100* (S1-S0)/(97-S0), capped at 100%. Mean (±SD) SpO2 changes (y values) were 55.1% ± 28.0% at +12 hours, 62.3% ± 26.3% at +24 hours and 64.3% ± 24.5% at +48 hours. These results closely parallel changes in SpO2, all on room air, reported by Hazan et al. for 19 RT-qPCR confirmed COVID-19 patients having pre-treatment SpO2 ≤ 90.40 At 24 hours after treatment with IVM, doxycycline and zinc, the mean SpO2 increase as a percentage of normalization to SpO2=97 was 65.2%, as calculated from the SpO2 values reported, close to the 62.3% at +24 hours for this 34-patient series. All patients in both of these IVM-treated cohorts recovered.

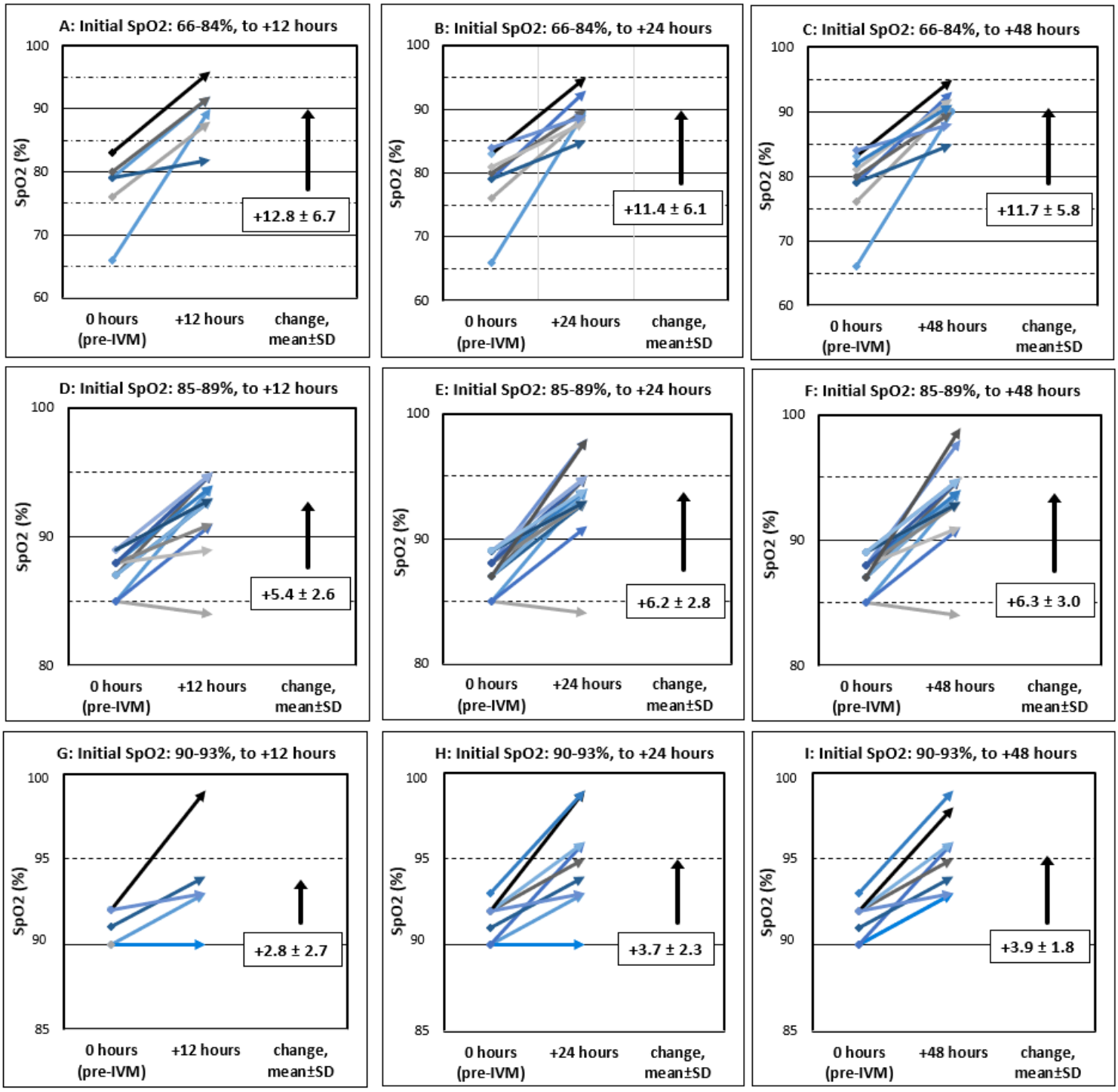

Figure 2

Pre- and post-treatment SpO2 values, all on room air, for 34 severe COVID-19 patients treated with IVM, doxycycline and zinc. Graphs A-I are in horizontal groupings by the range of pre-treatment SpO2 value and in vertical groupings by elapsed time after first dose of IVM. (The lowest SpO2 value in the stipulated range of 51-93% was 66%.) For these elapsed times of x=12, 24, and 48 hours, the SpO2 value shown for a given patient is at the latest post-treatment time ≤ x. All pre-treatment SpO2 values are from within one hour before the start of treatment.

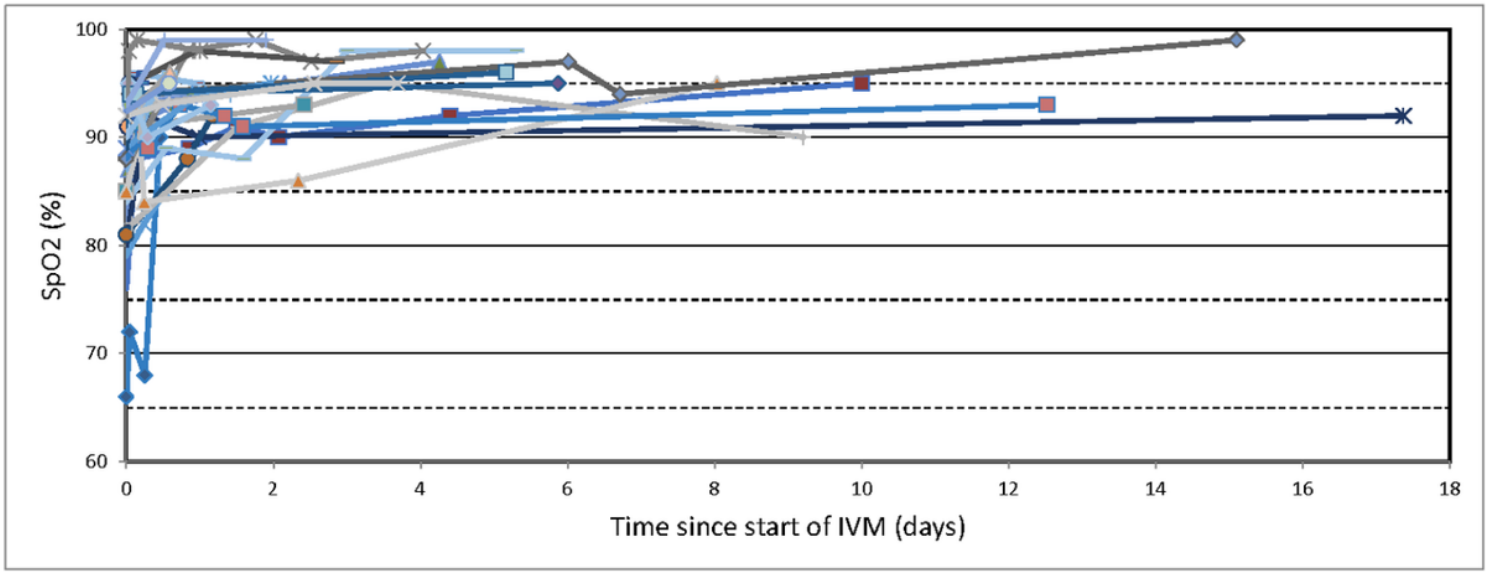

Figure 3

SpO2 values, all on room air, tracked for 34 severe COVID-19 patients treated with IVM, doxycycline and zinc.

Figure 4

Changes in SpO2 over 3 hours for a COVID-19 patient after administration of IVM. SpO2 values are shown (all on room air), with pulse rates (bpm) below those, at pre-treatment (A) and for 45 minutes (B), 90 minutes (C), and 3 hours (D) after first dose of IVM. This patient was diagnosed with COVID-19 by a positive result from a rapid antigen test and treated with combination therapy including IVM, doxycycline and zinc plus other oral and nebulized adjunct agents from among those itemized above.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- JCStoneetal.2021.RapidincreaseofSpO2onroomairfor34severeCOVID19patients.Supplementarytables.pdf