

Ivermectin is Associated with Increase in SPO₂ in Hypoxemic SARS-CoV-2 Patients: Pharmacodynamic Profile and Correlates

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ABSTRACT

Background and objectives: Hypoxemic respiratory failure is a common mode of demise in COVID-19 disease. We aimed to describe the time course of SPO₂ changes in COVID-19 patients treated with and without ivermectin.

Methods: This was a parallel group, prospective comparative study of propensity matched COVID-19 patients (Cycle threshold Ct<25, SPO₂<94%). 21 of the patients received Ivermectin (IVM) inclusive regime at 12 mg daily for 5 days, while 26 others received Non-ivermectin Inclusive Regime (NIVM).

Results: The IVM group demonstrated earlier and greater increase in SPO₂ (p=0.000) which paralleled greater and faster virological clearance (p=0.000) on Repeat measures Analysis of Variance RMANOVA. There was a significant correlation between absolute SPO₂ and absolute Ct on day 5 (r=0.77) and day 7 (r=0.77) both p=0.000. Incremental SPO₂ also correlated with incremental Ct. by day 5 (r=0.397, p=0.003) and day 7 (r=0.315, p=0.0002) relative to baseline. Increase in platelet count correlated with increased SPO₂ (r=0.252, p=0.029) on IVM, but negatively with NIVM (r=-0.28, p=0.17). Inflammatory markers such as ESR, CRP or D-dimer showed no significant correlation with SPO₂. Increase in SPO₂ on IVM was magnified in males.

Conclusion: IVM regime appears to be associated with faster and greater increase in SPO₂ paralleling faster viral clearance in COVID-19 patients.

Keywords: Ivermectin; Arterial oxygen saturation; COVID-19; Viral load

INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 has caused global disruptions in all spheres of life, as well as morbidity and mortality in excess of 6 million as of April 2022 [1].

A central feature of this disease, which is commonly the mode of demise, is the variable degree of hypoxemia/respiratory failure (Acute Respiratory Disease Syndrome) [2,3]. This is thought to arise from Immunothrombosis of small pulmonary micro vessels, caused by inflammation, hypercytokinemia (raised IL-1 beta, IL-6, TNF-alpha) [4,5] and coagulation/microthrombosis, with platelet consumption and fibrinolysis [6,7].

There is also Ventilation/Perfusion (V/Q) mismatch, with perfusion of non-ventilated alveolar spaces in severe COVID-19, and this may contribute to the arterial hypoxemia and consequent reduction in blood oxygen saturation [8]. The SPO₂% (arterial

oxygen saturation) measured by digital arterial pulse oximeter, is further employed in the classification of the severity of COVID-19 patients into mild outpatient, mild in patient, moderate, severe or critical status [9]. Thus, the SPO₂% is both a diagnostic and prognostic parameter in COVID-19 disease and is adopted by the World Health Organization [10] to classify COVID-19 severity.

In addition to vaccines, several novel and repurposed medications have been used to treat or prevent COVID-19 disease [11,12]. Ivermectin has been used both in chemo-prophylaxis, and as a repurposed active treatment of COVID-19, especially in Low and Middle Income Countries [13]. A critical goal of anti COVID-19 therapeutic regime is the reversal of pathophysiological basis of the disease, especially the systemic and pulmonary microthrombosis and cytokine-induced-inflammation, as adumbrated above [11-14].

In this regard, we have previously reported the beneficial effect of Ivermectin on SPO₂% in a placebo-controlled double blind

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study [15], as well as in a single blind study comparing ivermectin alone with ivermectin combined with hydroxychloroquine and Azithromycin [16]. These observations have been confirmed by Stone, et al. [17], who reported a rapid onset of increase in SPO₂% within 24 hours, in Zimbabwean and American patients with severe COVID-19, in a retrospective study.

A pharmacodynamic effect of ivermectin to increase arterial oxygen saturation (SPO₂%) in an inflammatory disease, such as COVID-19, may also suggest possible utility in chronic non-infectious pulmonary diseases such as acute severe asthma or exacerbation of chronic obstructive Lung Disease which are also mediated by inflammatory cytokines [18,19]. It is therefore of great clinical importance to further evaluate the correlates and determinants of this salutary clinical effect. The aims of our present study were: (1) to examine the time course of SPO₂% and change in SPO₂% in patients treated with Ivermectin (IVM) and those not treated with Ivermectin (NIVM); (2) to examine the correlation of virological load of SARS-CoV2 (measured as Cycle threshold (Ct) which is inversely proportional to the viral load) on SPO₂%; (3) to determine the impact of age, gender, platelet count, Hemoglobin, D-dimer, and inflammatory parameters (C-Reactive Protein (CRP) and Neutrophil Lymphocyte Ratio) on the efficacy of Ivermectin to increase SPO₂%.

METHODOLOGY

This is a sister publication to Thairu, et al. [20] in which other parameters are compared between the IVM and NIVM group. This study focuses on changes in SPO₂ and associated correlates. Thus, some of the tables and graphs are duplicated for ease of reference of the reader. The study was undertaken at COVID-9 Control Center, Gwagwalada, Federal Capital Territory, Abuja, Nigeria. The study received ethical review and approval from the University of Abuja Research and Ethics committee. The design of the study was a parallel group, non-randomized type. The studies were undertaken between April and November 2021. Group 1 (Ivermectin, IVM group) received a regimen inclusive of ivermectin 200 ug/kg/day for 5 consecutive days. This usually came to approximately 12 mg daily for 5 days. The patients in this group also received some concurrent medications: Out of a total of 61 IVM patients, 30 received only ivermectin 12 mg daily for 5 days while 31 received IVM 12 mg daily for 5 days together with Hydroxychloroquine HCQ 200 mg daily for 3 days and Azithromycin AZM 500 mg daily for 3 days. Additional medications received in this group were Zinc sulphate 50-100 mg for 7 days and Vitamim C 1000 mg daily for 7 days. In addition, 2 patients received lopinavir/ritonavir and 3 patients received Remdesivir. Group 2 patients did not receive Ivermectin in their regimen (Non-Ivermectin group, NIVM. n=26). They all received Zinc sulphate 50-100 mg daily for 7 days and Vitamin C 1000 mg daily for 7 days. 5 patients in this group received lopinavir/ritonavir combination (Alluvia) 200 mg twice daily for 5 days. Another 5 received Remdesivir, 200 mg stat and then 100 mg daily for 6-11 days, dependent on clinical response. All 26 patients in the group received Clexane (Enoxapramine). Inclusion criteria to study: Quantitative real time RT-PCR positivity for SARS-CoV-19 and clinical symptoms including cough or dyspnea. The N-gene (Nucleocapsid gene) and the E-gene (Envelope gene) Cycle threshold (Ct) of the virus were measured. To make the two groups comparable, the Ct was restricted to 25 and below at baseline (Propensity matching) [21]. Patients were also propensity matched to baseline SPO₂ less than 94% for the purposes of the

Repeat Measures Analysis of Variance assessment (RMANOVA). All patients included gave informed consent to participate in the study. Patients were excluded from the study, if they did not give consent, or were pregnant, had cardiovascular or pre-existing respiratory disorder, which might affect the digital pulse oximeter measurements.

Transmissive digital pulse oximetry

The partial pressure of pulsatile digital arterial oxygen saturation (SPO₂%) was measured using medical/clinical pulse oximeters as we have described prior. The transmissive pulse oximeter was placed on the finger tip of a digit in the non-dominant hand [22].

The patients digits were alcohol cleaned before each measurement, which was daily and at about the same time of each day throughout the study. Fingers with nail polish or tight rings were avoided. No patient had hypotension, cold extremities or severe obesity which may affect pulsatile blood flow and hence the pulse oximeter reading. Pulse oximeter reading correlates well with arterial blood gases and has accuracy of within 2% [23].

Inflammatory and thrombotic/ hematologic parameters

Inflammatory markers such as the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP), lymphocyte count and Neutrophil Lymphocyte Ratio (NLR) and thrombotic/hematologic parameters such as platelet count and the D-dimer in the 2 groups were also measured.

Statistical analysis

Data were stated as mean +/-SD or SEM, or with 95% Confidence Intervals. Statistical analyses included Repeated Measures Analysis of Variance (RMANOVA) for time effect, treatment effect and time-treatment interactions. One way ANOVA, unpaired t tests, with 95% Confidence interval for the difference were quoted as appropriate. Using both absolute and change in SPO₂% over time as dependent variable, the Linear regression analyses was computed against various parameters to assess possible significant Pearson's correlations and P values. Appropriate graphs with line of best fit were displayed in certain instances. Box and whisker plots were employed where appropriate. The null hypothesis of no difference was rejected if p<0.05. This trial was registered with Pan African Clinical Trials Registry PACTR 202108891693522.

RESULTS

The baseline clinical and demographic parameters of the patients in the two groups are summarized in Table 1, after propensity matching as above. The two groups were statistically comparable. However, Lymphocyte count and D dimer were lower for the NIVM group, while number with cough, myalgia and headache were higher for the IVM group.

The comparative time course (IVM vs. NIVM) of the Cycle threshold (Inverse of SARS-CoV-2 viral load) for E-and N-gene are shown in Figures 1 and 2. Note that increase in Ct (and hence viral clearance) is statistically faster in the IVM group (P=0.0000) after allowing for time treatment interaction. Note that by day 5, most in the IVM group are already in the 35-40 Ct range, as opposed to NIVM group where the Ct counts are still hovering around the 30 or less mark. A Ct count of above 35 is regarded as 'negative' by most laboratories.

Table 1: Propensity matched baseline variables in the IVM and NIVM groups (SPO₂% <94).

Variable	IVM only	Non-IVM	Overall	P-value (test)
Total numbers	21	26	47	
Mean age (SD) years	39.8	44.8	42.6	0.219 (test)
Sex (Male %)	13(61.9)	17(65.4)	30(63.8)	0.805 (chi ²)
Oxygen use	2(9.5)	7(29.2)	9(20)	0.100(chi ²)
Ventilator	2(9.5)	1(5.0)	3(7.3)	0.578 (chi ²)
Vaccination	0(0.0)	7(53.9)	7(31.8)	0.008(chi ²)
Hematology				
Hemoglobin g/dl	12.03	12.49	12.3	0.49
WBC × 10 ⁹ cells/liter	9.82	8.9	9.31	0.175
Lymphocyte × 10 ⁹ cells/liter	32.67	45.65	39.85	0.001
Neutrophils × 10 ⁹ cells/liter	61.14	57.84	59.32	0.422
Neutrophil to lymphocyte ratio (NLR)	2.9	1.21	2.01	0.0046
Platelet count × 10 ⁹ cells/liter	193.7	183.2	187.9	0.534
Viral load cycle threshold Ct.				
N-gene CT	27.33	18.25	22.31	0
E-gene CT	21.18	15.5	18.03	0
Inflammatory markers				
ESR ml/h Westergren	12.62	12.15	12.36	0.442
C-reactive protein mg/l	15.13	11.51	13.13	0.01
D-dimer ng/ml FEU (Fibrinogen equivalent Unit)	218.9	207.5	212.6	0.067
SpO ₂ ,%	89.1	87.1	88	0.961
Symptoms at baseline (%)				
Diarrhea	3(15.8)	2(8.0)	5(11.3)	0.42
Anosmia	7(35.0)	15(57.7)	22(47.8)	0.127
Ageusia	5(23.8)	8(30.8)	13(27.7)	0.596
Dyspnea	3(15.0)	4(15.4)	7(15.2)	0.971
Headache	12(60.0)	6(23.1)	18(39.1)	0.011
Cough	17(80.9)	7(26.9)	24(51.1)	0
Myalgia scores	1.57	2	1.8	0.0062
deficiency	deficiency	deficiency	deficiency	deficiency

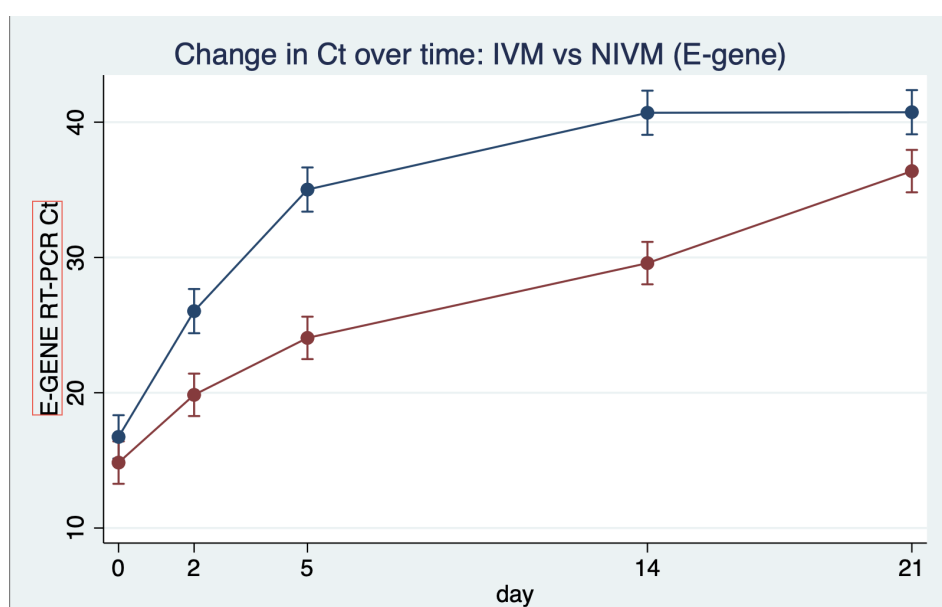


Figure 1: Change in E-gene Rt-PCR Cycle threshold (Ct) over time (baseline restricted to between 12-16 for propensity matching). Error bars are 95% CI for all graphs. Note that by day 5, most patients on IVM are already in the 35-40 brackets as opposed to the non-IVM group. P=0.000. **Note:** (—●—) IVM, (—●—) NON-IVM.

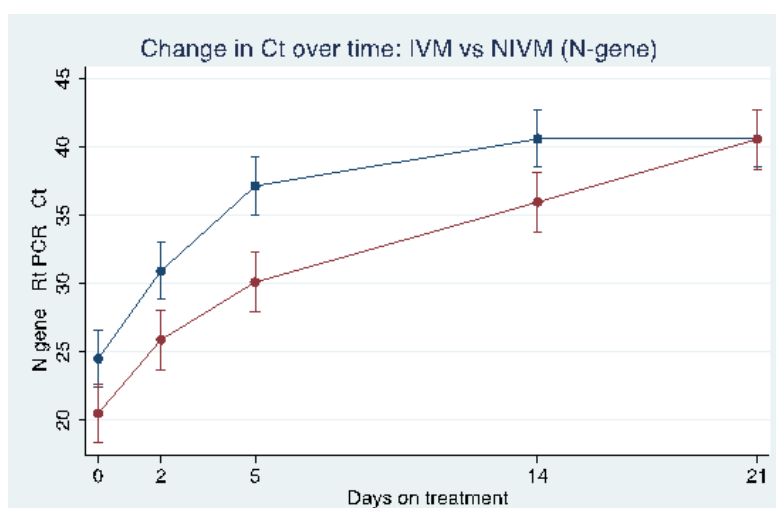


Figure 2: Change in N-Gene Rt-PCR Cycle threshold over time, Propensity matched (Baseline between 20-25). Note that by day 5, most patients on IVM are already in the 35-40 bracket as opposed to the non-IVM group, $P=0.000$. Note: (—●—) IVM, (—●—) NON-IVM.

Change in $SPO_2\%$: The comparative time course (IVM vs. NIVM) of the $SPO_2\%$ (arterial oxygen saturation) is shown in Figure 3. Excluded are patients who received oxygen, so this was 'room air only' assessment. There was a statistically significant treatment difference between IVM and NIVM by repeated measures analysis of variance RMANOVA ($p=0.000$) By day 5, in the IVM group, the $SPO_2\%$ increased to 97% (+7.9%) compared to only 89.3% (+2.2%) in the NIVM group. There was also a temporal correspondence with the changes in Ct mirroring the change in $SPO_2\%$.

Correlations with absolute $SPO_2\%$ and change in $SPO_2\%$ (Delta SPO_2)

Table 2 explores linear correlations between absolute $SPO_2\%$ on days 2, 5 and 7 and change in $SPO_2\%$ (Delta $SPO_2\%$) on the one hand with selected variables. Pairwise correlation (r) between Day 5 SPO_2 , Day 7 SPO_2 , Delta SPO_2 -Day 5 (Day 5 SPO_2 minus baseline SPO_2) and Delta SPO_2 -Day 7 (Day 7 SPO_2 minus baseline SPO_2) as well as other parameters (P values displayed). There were significant correlations between day 5 N_Ct, day 5 E_Ct, against Day 5 SPO_2 , Day 7 SPO_2 , Delta day 7 SPO_2 and Delta day 5 SPO_2 . There was also a strong trend in association between change in Ct and change in SPO_2 . Strong associations are also seen between hemoglobin levels

and ESR against $SPO_2\%$. Lymphocyte count correlated negatively with $SPO_2\%$. (The lower the lymphocyte counts the higher the $SPO_2\%$). There is also a weak and insignificant negative correlation between change in NLR and change in SPO_2 , suggesting that as NLR decreases, SPO_2 increases.

Figure 4 is a scatterplot showing a strong relationship between Nucleocapsid Gene Cycle threshold (Inversely proportional to viral load) and $SPO_2\%$ on day 5. $r=0.7689$, $P=0.0000$. The results for Envelope gene are similar $r=0.646$, $P=0.0000$. The relationship is still strong by day 7.

Figure 5 is a scatterplot depicting the significant relationship between change in E_Ct and change in SPO_2 by day 5 ($r=0.225$, $P=0.0396$).

Figures here explore the relationship between change in platelet count and change in $SPO_2\%$. A significant association was seen between increase in platelet count and increase in SPO_2 . ($r=0.252$ $P=0.029$). This trend is strengthened when restricted to patients who received IVM $r=0.389$ $p=0.0056$ and reversed when limited to patients who did not receive Ivermectin NIVM. $r=-0.277$ $P=0.170$ (Figures 6-8).

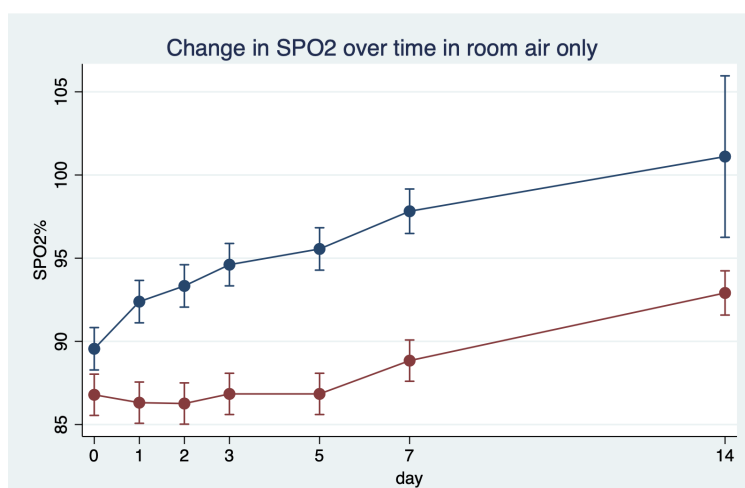


Figure 3: Change in SPO_2 over time in room air for Ivermectin IVM and Non-Ivermectin NIVM based treatment after propensity matching of baseline to SPO_2 less than 94%, (95% CI Bars shown). RMANOVA allowing for time*treatment interaction $LR=40.12$, $P<0.0001$. Note: (—●—) IVM, (—●—) NON-IVM.

Table 2: Linear regression table showing pairwise correlation (r) between Day 5-SPO₂, Day 7-SPO₂, Delta SPO₂_Day 5 and Delta SPO₂_Day 7 and other parameters (P values).

Parameter	Day 5 SPO ₂	Day 7 SPO ₂	Delta SPO ₂ (7) (Day 7-baseline)	Delta SPO ₂ (5) (Day 5-baseline)
Day 5 N-Ct	0.769(0.0000)*	0.772(0.0000)*	0.337(0.0031)**	0.397(0.0002)**
Day 5 E-Ct	0.646(0.0000)*	0.620(0.0000)*	0.315(0.0059)**	0.401(0.0002)**
Delta N-Ct (Day 5-baseline)			0.206(0.0758)#	0.076(0.492)
Delta E-Ct (Day 5-baseline)			0.207(0.0743)#	0.225 (0.0396)**
Delta-CRP (Day 7-baseline)			-0.082(0.485)	
Delta-ESR (Day 7-Baseline)			0.0071(0.952)	
Delta-DDimer (Day 7-Baseline)			0.129(0.269)	
Day 7 CRP		-0.034(0.773)		
Day 7 D_Dimer		0.0111(0.925)		
Day 7 ESR		0.388(0.0006)*		
Day 7 Platelet		0.076(0.5151)		
Day 7 Hb		0.0194(0.096)*		
Day 7 Lymphocyte		-0.387 (0.0006)*		
Delta platelet (Day 7-baseline)			0.252(0.029)**	
Delta Hb (Day 7-baseline)			0.169(0.147)	
Delta lymphocyte (Day 7-baseline)			0.659(0.615)	
Delta Neutrophil (Day 7-baseline)			0.125(0.287)	
Day 7 NLR		0.208 (0.073)#		
Delta NLR			-0.098 -0.399	

Note: *Significant association against SPO₂ absolute values; **Significant association against change in SPO₂ values; # Strong trend towards significant association.

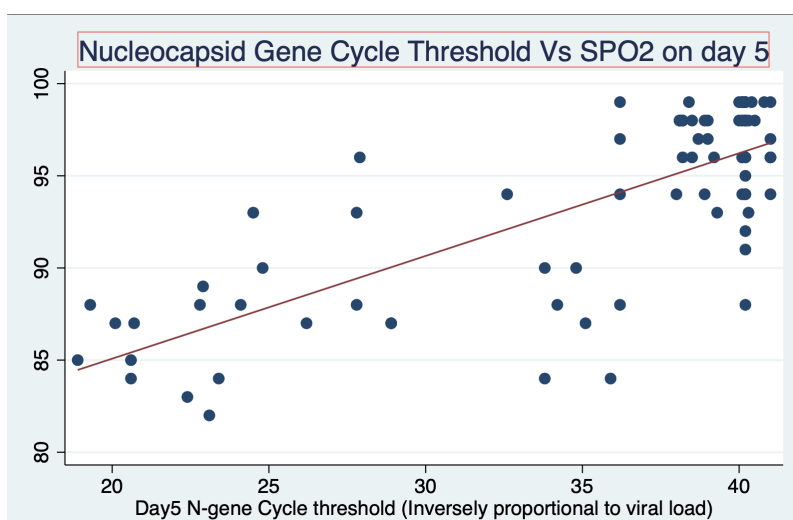


Figure 4: Strong relationship between Nucleocapsid Gene Cycle threshold (Inversely proportional to viral load) and SPO₂% on day 5. $r=0.7689$, $P=0.0000$. Note: (●) Day 5 SPO₂, (—) Fitted values.

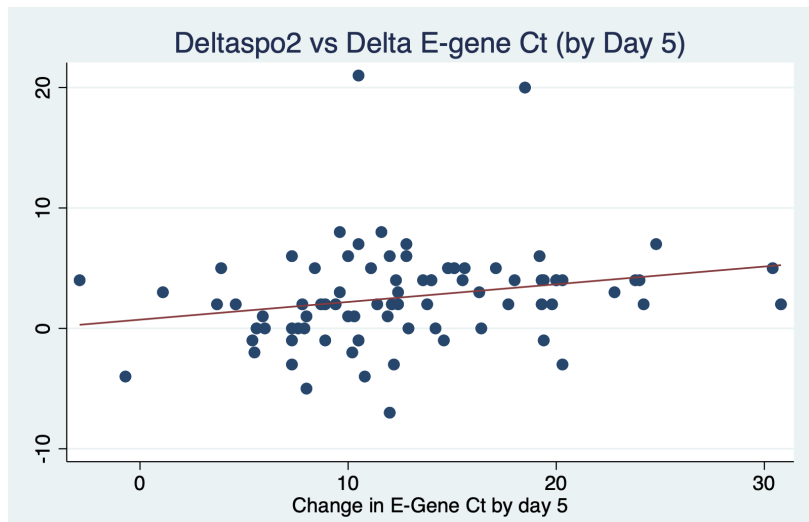


Figure 5: Change in SPO₂ from baseline versus change in Envelope Gene Cycle Threshold by day 5. $r=0.225$, $P=0.0396$. Note: (●) Change in SPO₂%, (—) Fitted values.

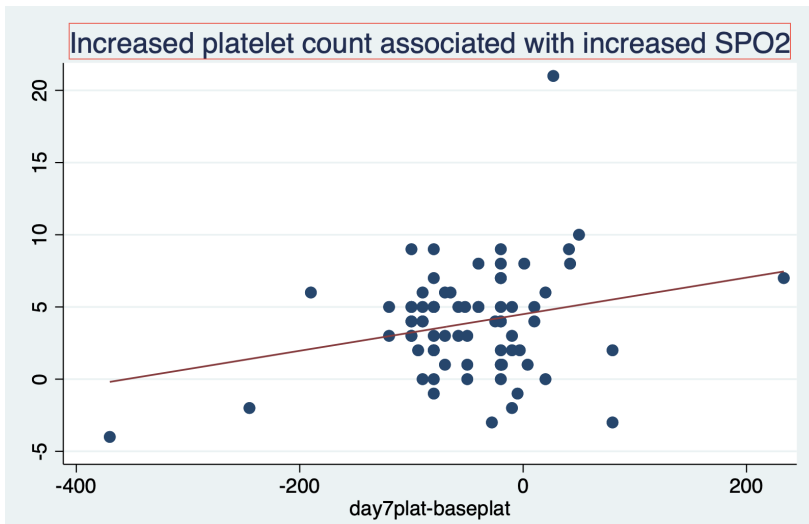


Figure 6: Change in SPO₂ from baseline versus change in Envelope Gene Cycle Threshold by day 5. $r=0.225$, $P=0.0396$. Note: (●) Day 7 SPO₂-basespo₂, (—) Fitted values.

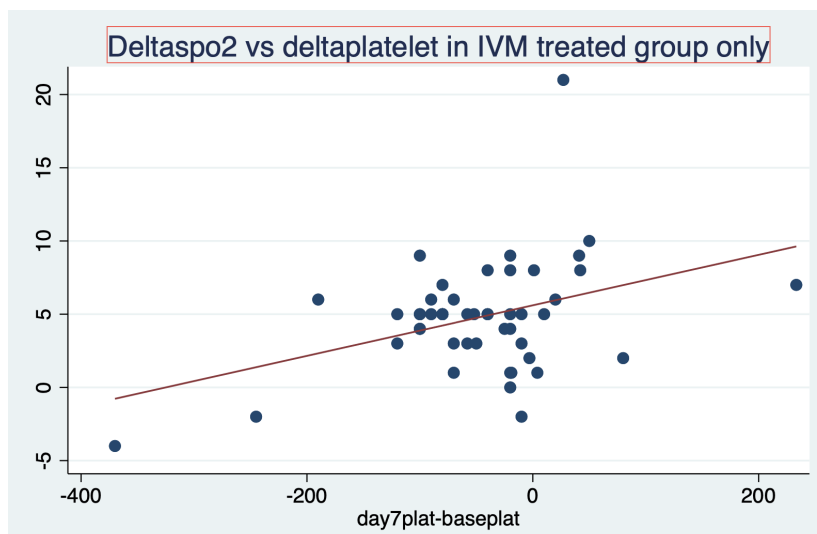


Figure 7: The association between increasing platelet count and increasing SPO₂ is strengthened when restricted to patients who received IVM. $r=0.389$ $p=0.0056$. Note: (●) Day 7 SPO₂-basespo₂, (—) Fitted values.

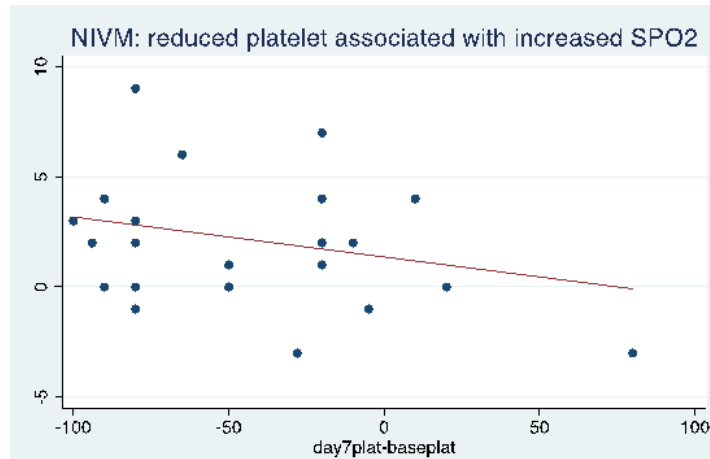


Figure 8: For Non-Ivermectin treated patients, the above trend is reversed, and reduced platelet count is associated with increased SPO₂. $r=-0.277$ $P=0.170$. **Note:** (●) Change in SPO₂%, (—) Fitted values.

Figures here explore the effect of sex on the increase in SPO₂% with IVM (Day 2 and 7 respectively). Day 2 mean increase in SPO₂=1.9% On IVM vs. -0.3% on NIVM where sex is female. (P=0.173). But Day 2 mean increase in SPO₂=1.3% on IVM vs.

-0.8% on NIVM where sex is Male. (P=0.010). It suggests that the increase is amplified where sex is male. From the graph, it can be seen that there are instances with dramatic increase in SPO₂ on the IVM arm (Figures 9 and 10).

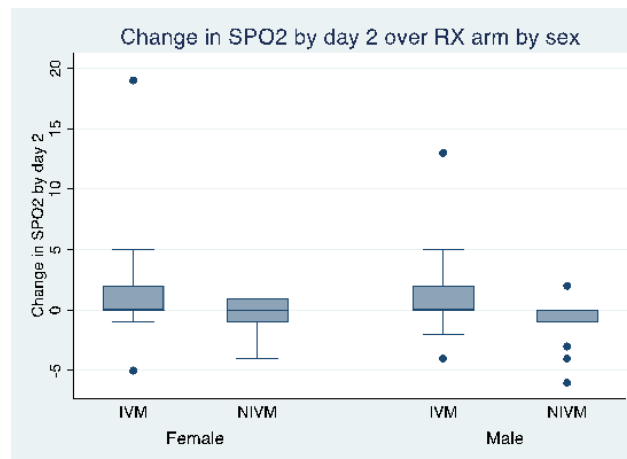


Figure 9: Change in SPO₂% by day 2 over treatment arm by sex. Note the dramatic increase in certain instances on day 2 in the Ivermectin arm. The difference in the treatment arms appears amplified by male sex. **Note:** Day 2 mean increase in SPO₂=1.9% On IVM vs. -0.3% on NIVM where sex is female. (P=0.173) but Day 2 mean increase in SPO₂=1.3% on IVM vs. -0.8% on NIVM where sex is Male. (P=0.010).

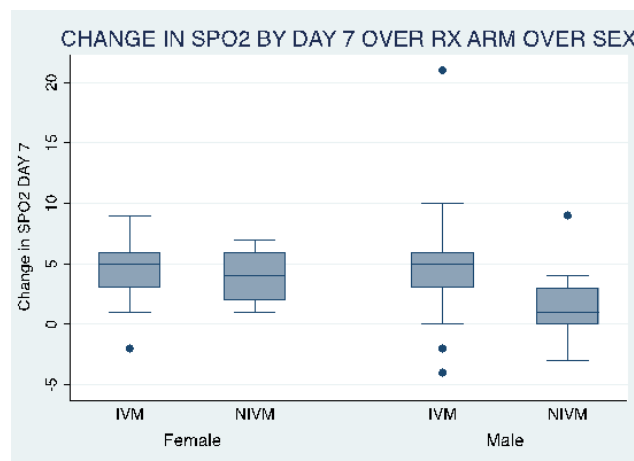


Figure 10: Change in SPO₂% by day 7 over treatment arm by sex. Note the dramatic increase in certain instances on day 7 in the Ivermectin arm. As in figure 5, the difference in the treatment arms appears amplified by male sex. **Note:** Day 7 mean increase in SPO₂=4.6% On IVM vs. 3.8% on NIVM where sex is female. (P=0.553), but Day 7 mean increase in SPO₂=4.6% on IVM vs. 1.4% on NIVM where sex is Male. (P=0.0023).

DISCUSSION

The goal of this study was to investigate the time profile of arterial oxygen saturation in COVID-19 in IVM treated versus NIVM treated individuals. Secondly, we set out to explore correlates and determinants of change in digital arterial oxygen saturation measured by pulse oximeter in COVID-19 patients. In this propensity-matched study utilizing patients on room air with $\text{SPO}_2\% < 94$, our results demonstrate a significantly greater increase in $\text{SPO}_2\%$ in the IVM containing regime than the NIVM group. ($P=0.000$ RMANOVA). $\text{SPO}_2\%$ increased from baseline by +7.9% on IVM but by only +2.2% on NIVM regimen by day 5. There was also a temporal correspondence between the $\text{SPO}_2\%$ time profile, with the fall in viral load (increase in Cycle threshold Ct of genes E and N). These findings confirm our previous reports on ivermectin virucidal pharmacodynamics against SARS-CoV-2 and the concomitant increase in arterial oxygen saturation in COVID-19 disease. [15,16]. Other workers have also reported a rapid rise in $\text{SPO}_2\%$ within 24 hours in severe COVID-19 patients, when treated with ivermectin in the US and Zimbabwe [17,24].

With the data at our disposal, we investigated statistically which factors may be associated with this increase in $\text{SPO}_2\%$. As above, absolute Cycle threshold Figures correlated strongly with absolute SPO_2 Figures, and trends in both parameters also correlated, although less strongly. This suggests a quantitative relationship between the drug regimens induced virucidal effect and the increased arterial oxygen saturation in individual patients. To our knowledge, this is a novel report. Change in inflammatory indices such as C reactive protein; ESR, Neutrophil count and Neutrophil/lymphocyte ratio were poorly correlated with change in $\text{SPO}_2\%$. By contrast, there was a significant correlation between increased platelet count and increase in $\text{SPO}_2\%$. This change is accentuated when the analysis is limited to IVM using patients but reversed with NIVM patients. Change in D dimer levels did not significantly correlate with change in SPO_2 . Absolute day 7 hemoglobin correlates very weakly with day 7 SPO_2 , although delta hemoglobin did not correlate with delta SPO_2 . These results suggest that changes in hematological/thrombotic variables may play a role in the increase in oxygen saturation reported in this study. Gender may also contribute to the magnitude of the increase in $\text{SPO}_2\%$. Our findings suggest that the noticeable increase in SPO_2 in the IVM arm is accentuated by male sex. It is established that female gender by innate immunological and or ACE2 or Transmembrane Serine Protease 2 (TMPRSS2) viral entry receptors, which are under androgenic regulation, are less prone to severe COVID-19 than men [25]. There was a significantly greater increase in $\text{SPO}_2\%$ on NIVM in female than in Male patients, whilst this gender difference was not seen in the IVM group. Speculatively, this may indicate an interaction between IVM to mitigate the androgen mediated platelet hypercoagulability in men [26] and thus cause similar $\text{SPO}_2\%$ increase. Collectively, our findings strongly suggest that diminution in SARS-CoV-2 viral load (inverse of Ct), platelet count changes and gender are significant contributors to the increased $\text{SPO}_2\%$ in these patients. The molecular mechanisms of these findings, however, remain unexplained by this study. The hypoxemia and reduced $\text{SPO}_2\%$ in COVID-19 patients follows SARS-CoV-2 viral invasion of alveolar macrophages, which cause elaboration of the NF kappa B transcription and production of the pro inflammatory cytokines (IL-1B and NLRP3 inflammasome) [27]. This is succeeded by a feed forward release of IL-6, Tumor Necrosis Factor TNF alpha, massive release of neutrophils and

Neutrophil Extracellular Traps (NETs). The neutrophils cause activation of coagulation, platelet sequestration and thrombin activation, clot and fibrin formation, with virucidal activity [28]. The resultant cytokine induced "immunothrombosis" cause a bidirectional mutual activation of alveolar microvascular thrombosis and inflammation with inflammatory cell infiltrates, necrosis and perfusion of unventilated alveoli, V/Q mismatch and fall in arterial oxygenation [29]. A contribution from bronchial nicotinic cholinergic mediated inflammation has also been suggested [29].

The greater beneficial effect of Ivermectin Containing Regimen (IVM) than IVM on $\text{SPO}_2\%$ in COVID-19 may conceivably be attributed to the inhibition by ivermectin of pro-inhibitors cytokines by its suppression of the JAK-STAT pathway [30], competitive interaction with SARS-CoV-2 spike protein S reducing viral binding and entry [31] and direct activation of neuronal acetylcholine receptor and the vagus nerve [32] causing reduced bronchial inflammation and dilation. A limitation of our study was the unavailability of inflammatory cytokine measurements. Although viral load (Ct) may serve as a surrogate for cytokines, the actual blood or breath levels of IL-1B, IL-6, TNF would have provided a direct assessment of their kinetics and oxygenation impact. Owing to the fact that ivermectin increases $\text{SPO}_2\%$ at least in part by cytokine suppression, it is attractive to speculate that it might also enhance arterial oxygenation in non-infectious chronic respiratory disorders such as bronchial asthma or chronic obstructive pulmonary disease (COPD) where inflammation and cytokines also play a role [18,32]. This should be a subject of future inquiry.

CONCLUSION

Ivermectin regime (IVM) caused a more rapid onset and greater increase in $\text{SPO}_2\%$, than the NIVM arm, in hypoxemic COVID-19 patients breathing room air. The rise in $\text{SPO}_2\%$ was concomitant with a fall in SARS-CoV-2 viral load (increased Ct) with a temporal correspondence and correlation. The $\text{SPO}_2\%$ correlated significantly with changes in platelet count. Males not receiving ivermectin (NIVM) had a blunted increase in $\text{SPO}_2\%$ compared to the females in the same group. By contrast, ivermectin (IVM) conferred similar increase in $\text{SPO}_2\%$ in Males and females. Ivermectin may increase arterial oxygenation mainly through its virucidal action.

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