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# High-Dose Dexamethasone Versus Tocilizumab in Moderate to Severe COVID-19 Pneumonia: A Randomized Controlled Trial

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## Abstract

### Background and objectives

Recent randomized controlled trials (RCTs) have indicated potential therapeutic benefits with high-dose dexamethasone (HDD) or tocilizumab (TCZ) plus standard care in moderate to severe coronavirus disease 2019 (COVID-19) with acute respiratory distress syndrome (ARDS). No study has compared these two against each other. We aimed to compare the efficacy and safety of HDD against TCZ in moderate to severe COVID-ARDS.

### Methods

Patients admitted with moderate to severe COVID-19 ARDS with clinical worsening within 48 hours of standard care were randomly assigned to receive either HDD or TCZ plus standard care. The primary outcome was ventilator-free days (VFDs) at 28 days. The main secondary outcomes were 28-day all-cause mortality and the incidence of adverse events. Our initial plan was to perform an interim analysis of the first 42 patients.

### Results

VFDs were significantly lower in the HDD arm (median difference: 28 days; 95% confidence interval (CI): 19.35-36.65; Cohen's d = 1.14; $p < 0.001$). We stopped the trial at the first interim analysis due to high 28-day mortality in the HDD arm (relative risk (RR) of death: 6.5; $p = 0.007$; NNT (harm) = 1.91). The incidence of secondary infections was also significantly high in the HDD arm (RR: 5.5; $p = 0.015$; NNT (harm) = 2.33).

### Conclusions

In our study population, HDD was associated with a very high rate of mortality and adverse events. We would not recommend HDD to mitigate the cytokine storm in moderate to severe COVID-19 ARDS. TCZ appears to be a much better and safer alternative.

**Categories:** Emergency Medicine, Internal Medicine, Infectious Disease
**Keywords:** covid-19, acute respiratory distress syndrome (ards), high-dose dexamethasone, fungal infection, secondary infection, pulse dose steroids, tocilizumab, cytokine storms

## Introduction

Coronavirus disease 2019 (COVID-19) has been associated with high mortality in moderate and severe acute respiratory distress syndrome (ARDS). The hyper-inflammatory response triggered by SARS-CoV-2 is characterized by the overproduction of pro-inflammatory cytokines, leading to organ dysfunction [1,2]. Intervening timely with immunomodulatory therapies might mitigate the severity. Based on this assumption, researchers have been focusing on several interventions, including IL-6 inhibitors and corticosteroids [3-10]. The largest trial of tocilizumab (TCZ) to date has shown significant survival benefits with TCZ plus standard care [11]. However, the dose of corticosteroids in COVID-19 has remained controversial. Although the results of two recent randomized controlled trials (RCTs) have shown potential therapeutic benefits with dexamethasone, the practice remains variable [12,13].

The COVID-19 pandemic has exhausted the resources of low- and middle-income countries. The scenario was remarkably grim in India, amidst the second wave, with insufficient TCZ supply [14]. Affordable and widely available effective alternate immunomodulatory therapies besides TCZ were urgently needed. We

hypothesized that timely treatment with high-dose dexamethasone (HDD) may downregulate the integrated pathways of inflammation-coagulation-fibroproliferation and potentially improve patient outcomes. To the best of our understanding, this is the first RCT to compare the efficacy of HDD against TCZ in patients with moderate to severe COVID-19 ARDS.

# Materials And Methods

## Study design

This study was conducted between May 6 and June 28, 2021, at a tertiary care hospital in India. Our objective was to investigate the efficacy and safety of early rescue therapy with HDD versus TCZ in COVID-19 unresponsive to standard care. The study protocol, statistical analysis proposal, and criteria for premature study termination were planned a priori (Figure *4* and Figure *5* in the Appendices). The trial was approved by the Institutional Ethics Committee (reference number: NK/7349/Study/939) and registered in the clinical trial registry of India (CTRI/2021/04/033263 (April 30, 2021)). Prior to enrolment and randomization, written informed consent was taken from the participants or their legal representatives.

## Participants

Participants aged 18 years and older, with confirmed SARS-CoV-2 infection by reverse-transcriptase polymerase chain reaction (RT-PCR) assay, were recruited. Patients with a partial pressure of arterial oxygen to fraction of inspired oxygen ($PaO_2/FiO_2$) ratio of less than 200 on admission and receiving standard care were screened for eligibility. Among these patients, those with clinical worsening in less than 48 hours of the initiation of standard care were randomized. Clinical worsening was defined as follows: (1) decrease in $PaO_2/FiO_2$ by more than 50 of the baseline admission value, (2) oxygenation/ventilation device is upgraded, and (3) static or rising levels of C-reactive protein (CRP > 50 mg/L).

The exclusion criteria included patients with prior history of immunosuppression and use of immunosuppressive drugs, raised septic biomarkers suggestive of invasive bacterial or fungal infection, AST/ALT ⩾ five times the upper limit of normal, leukocytes < $2 \times 10^3$/µL, thrombocytes < $50 \times 10^3$/µL, and acute or chronic diverticulitis.

## Randomization

Block randomization was done using an online random number generator with varying block sizes with the unique subject or patient code generated against the block sequence number [15]. This is an open-label study, and after randomization, there was no masking. The investigators, treating clinical teams, and participants were not blinded, whereas the research personnel compiling and analyzing the outcome data were blinded to the group allotment.

## Procedure

Patients with COVID-19 who were admitted to our hospital with $PaO_2/FiO_2$ < 200 received standard care as per the hospital treatment protocol. Standard care included (a) oxygen supplementation; (b) intravenous (i.v.) remdesivir loading dose of 200 mg on day 1, followed by 100 mg for the next four days; (c) i.v. dexamethasone 6 mg for 10 days; (d) therapeutic low-molecular-weight heparin 1.5 mg/kg/day; and (e) proning.

Within 48 hours of the initiation of standard care, if a patient showed clinical worsening, they were randomized to one of the intervention arms, HDD or TCZ. Patients in the HDD arm received i.v. dexamethasone 20 mg once daily for three days plus standard care until day 10. HDD dose of 20 mg was selected on the basis of a recent RCT [13]. Patients in the TCZ arm received a single i.v. infusion of TCZ 6 mg/kg plus standard care of 6 mg dexamethasone for 10 days. An additional dose of TCZ (6 mg/kg) will be administered if the patient shows no clinical improvement within 24 hours. The low dosing of TCZ was based on a previous study and due to supply considerations [14,16].

## Outcomes

The primary outcome was ventilator-free days (VFDs) within 28 days since randomization. The secondary endpoints were all-cause mortality, the incidence of adverse events (i.e., secondary infections, insulin requirement for hyperglycemia, and vasopressor requirement), variation in the Sequential Organ Failure Assessment (SOFA) score and WHO Clinical Progression Scale (WHO-CPS), duration of ICU stay, CRP variation, time to negative result on RT-PCR, and time to discharge.

## Statistical analysis

The study was designed to compare the means of VFDs across the two groups to demonstrate an effect size of 0.8 (Cohen's d) with a power of 80% and α at 0.05. A sample size of 42 across two groups (21 per group) was estimated using G power 3.1.9.4. A priori, when this sample size had been reached, we planned for an

interim analysis to decide whether to proceed with recruitment to our secondary sample size or to stop the trial based on preset criteria (Figure *5* in the Appendices). Normality was assessed using skewness indicators and/or Q-Q plots. Categorical data have been expressed as count (%) and were analyzed using the Chi-squared/Fisher's exact test. Time to event analysis has been done using the Kaplan-Meier (K-M) survival estimates, competing risks regression, and Cox proportional hazards, where assumptions have been met and the model fit was significantly better than the null. Missing data was less than 5%, so no imputation methods were used. The analysis has been done using SPSS version 25.0 for Windows (SPSS Inc., Chicago, IL, USA), Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC), and R studio 1.4.1130.0.

## Results

A total of 87 patients with COVID-19 ARDS on admission were screened for inclusion, of whom 42 were randomized (Figure *1*). The demography, clinical characteristics, and biomarkers of the patients at baseline and intervention are presented in Table *1*.

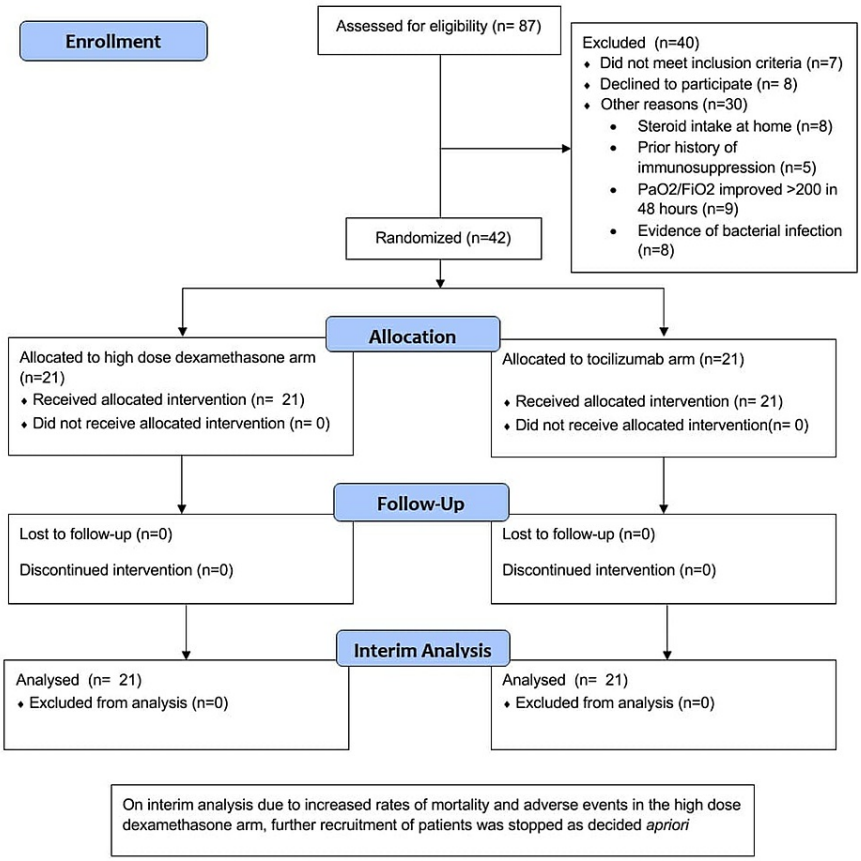



**FIGURE 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study.**

| | High-dose dexamethasone arm (n = 21) | Tocilizumab arm (n = 21) | p-value |
|---|---|---|---|
| Age, median (IQR), years | 51 (45–58) | 50 (44–65) | 0.920[a] |
| BMI, median (IQR), kg/m$^2$ | 30.20 (26.4–35.6) | 27.45 (25.90–30.61) | 0.232[a] |

| | | | | |
|---|---|---|---|---|
| Sex, number (%) | Male | 12 (57.14%) | 12 (57.14%) | 1.000[b] |
| | Female | 9 (42.86%) | 9 (42.86%) | |
| Coexisting conditions, number (%) | Diabetes mellitus | 7 (33.33%) | 8 (38.10%) | 0.747[b] |
| | Hypertension | 11 (52.38%) | 13 (61.90%) | 0.533[b] |
| | Chronic kidney disease | 0 (0%) | 0 (0%) | - |
| | Coronary artery disease | 0 (0%) | 1 (4.76%) | 1.000[b] |
| | Chronic liver disease | 0 (0%) | 0 (0%) | - |
| | Chronic obstructive pulmonary disease | 0 (0%) | 2 (9.52%) | 1.000[b] |
| | Asthma | 0 (0%) | 1 (4.76%) | 1.000[b] |
| | Hypothyroid | 2 (9.52%) | 1 (4.76%) | 1.000[b] |
| | Pregnancy | 1 (4.76%) | 2 (9.52%) | 0.698[b] |
| Days from symptom onset, median (IQR), days | On admission | 6 (6–7) | 7 (6–7) | 0.039[a] |
| | On the first dose of intervention (high-dose dexamethasone or tocilizumab) | 7 (7–8) | 8 (7–9) | 0.011*[a] |
| $PaO_2/FiO_2$, median (IQR), mmHg | On admission | 125.14 (110.29–138.67) | 134.5 (117–181) | 0.07[a] |
| | On the first dose of intervention (high-dose dexamethasone or tocilizumab) | 81.07 (68.22–91.60) | 80.93 (62.20–113) | 0.920[a] |
| Respiratory support at admission, number (%) | Invasive mechanical ventilation | 0 (0%) | 0 (0%) | 0.617[b] |
| | Noninvasive ventilation | 2 (9.52%) | 1 (4.76%) | |
| | High-flow nasal cannula | 1 (4.76%) | 2 (9.52%) | |
| | Non-rebreather mask | 15 (71.43%) | 12 (57.14%) | |
| | Face mask/nasal prongs | 3 (14.29%) | 6 (28.57%) | |
| Respiratory support at intervention, number (%) | Invasive mechanical ventilation | 1 (4.76%) | 1 (4.76%) | 0.597[b] |
| | Noninvasive ventilation | 8 (38.10%) | 5 (23.81%) | |
| | High-flow nasal cannula | 12 (57.14%) | 15 (71.43%) | |
| | Non-rebreather mask | 0 (0%) | 0 (0%) | |
| | Face mask/nasal prongs | 0 (0%) | 0 (0%) | |
| Hours in prone position during hospital stay, median (IQR) | | 96 (0–128) | 48 (0–80) | 0.063[a] |
| Laboratory variables at admission, median (IQR) | C-Reactive protein, median (IQR), mg/dL | 54.2 (33.4–75.1) | 75 (47–90) | 0.218[a] |
| | White blood cell count, median (IQR), × $10^3$/μL | 8.4 (7.6–10.7) | 8.1 (7.30–9.70) | 0.413[a] |
| | Neutrophil/lymphocyte ratio | 15.62 (12.21–20.75) | 16.40 (10.33–21.40) | 0.811[a] |
| | Platelet count, × $10^3$/μL | 246 (189–316.5) | 221 (168–276 ) | 0.083[a] |
| | Ferritin, ng/mL | 702.5 (503.2–989) | 522 (321.8–969) | 0.252[a] |
| | D-Dimer, ng/mL | 1568 (694–3455) | 853 (512–2388) | 0.204[a] |
| Laboratory variables at | C-Reactive protein, median (IQR), mg/dL | 89.2 (72–135.70) | 111 (74.30–151.40) | 0.443[a] |
| | White blood cell count, median (IQR), × $10^3$/μL | 11.2 (9.3–13.20) | 10.6 (9.1–11.70) | 0.227[a] |
| | Neutrophil/lymphocyte ratio | 17 (10.94–21.78) | 13 (9.73–19.10) | 0.489[a] |

| | | | | |
|---|---|---|---|---|
| intervention, median (IQR) | Platelet count, median (IQR), × $10^3$/μL | 233 (196–347.5) | 258 (172–357) | 0.597[a] |
| | Ferritin, median (IQR), ng/mL | 607 (428.45–1410) | 631.9 (256.65–992.77) | 0.170[a] |
| | D-Dimer, median (IQR), ng/mL | 1118 (541.65–3513.1) | 649 (389.38–1734.75) | 0.930[a] |

**TABLE 1: Demography, clinical characteristics, and biomarkers of patients at baseline and intervention.**

*p-value < 0.05 was considered significant; a: Mann–Whitney U-test; b: Chi-squared/Fisher's exact test.

IQR: interquartile range; PaO2/FiO2: partial pressure of arterial oxygen to fraction of inspired oxygen.

## Univariate analysis

*Primary Outcome*

VFDs were significantly lower in the HDD group (9.76 ± 12.94 (95% CI: 3.87-25.65) versus 22.86 ± 9.75 (95% CI: 18.42-27.30); Cohen's d = 1.14; p < 0.001) at a calculated power of 99.99% (Figure *2a*). The median difference was 28 days (95% CI: 19.35-36.65) (Table *2*).

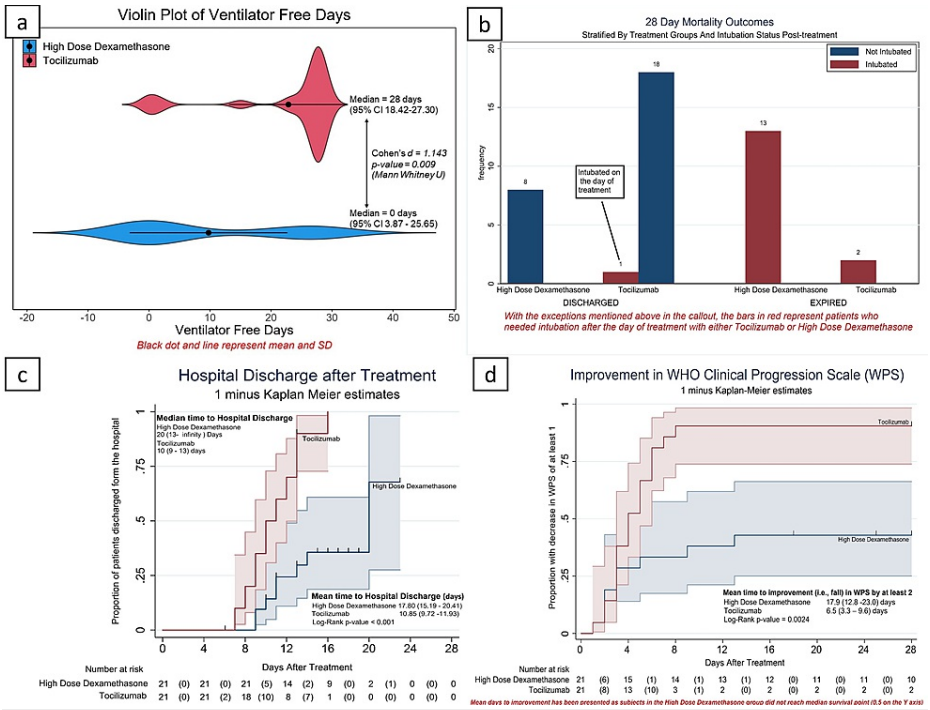



**FIGURE 2: Outcomes. (a) Violin plot of ventilator-free days. (b) Bar diagram showing mortality distributed among the treatment group and posttreatment intubation status. One patient was intubated on the day of therapy in the tocilizumab arm and was successfully extubated as well. (c) Kaplan–Meier estimates of cumulative hospital discharge rates and (d) improvement in WHO Clinical Progression Scale.**

| Outcomes | | HDD arm (n = 21) | TCZ arm (n = 21) | p-value |
|---|---|---|---|---|
| Primary outcome | | | | |
| Ventilator-free days | Mean ± SD (95% CI) | 9.76 ± 12.94 (3.87–25.65) | 22.86 ± 9.75 (18.42–27.30) | |
| | Median (IQR) | 0 (0–25) | 28 (24–28) | 0.001*[a] |
| Secondary outcome | | | | |
| 28-Day results | All-cause mortality, number (%) | 13 (61.90%) | 2 (9.52%) | <0.001*[b] |
| | Intubation rates posttreatment, number (%) | 13 (61.90%) | 2 (9.52%) | <0.001*[b] |
| | ICU free, median (IQR), days | 1 (1–5) | 4 (3.5–5.5) | 0.017*[a] |
| | MV duration, median (IQR), days | 12 (2.5–15.5) | 0 (0–3) | <0.001*[a] |
| Discharged from the hospital within 28 days, number (%) | | 8 (38.10%) | 19 (90.48%) | 0.030*[b] |
| SOFA score, median, (IQR) | On treatment day | 5 (4–8) | 5 (4–6) | 0.353[a] |
| | 48 hours later | 4 (4–8) | 4 (4–5) | 0.303[a] |
| | 7 days after intervention | 5 (2–7) | 2 (2–2) | 0.002*[a] |
| WHO-CPS score, median, (IQR) | On treatment day | 6 (6–6) | 6 (6–6) | 0.573[a] |
| | 7 days after intervention | 6 (5–8) | 5 (3–5) | <0.001*[a] |
| Mean time (days) to improvement in WHO-CPS score by 1 (i.e., a decrease by 1) | | 17.90 (underestimated) | 6.48 (underestimated) | 0.002*[c] |
| Renal replacement therapy, number (%) | | 2 (9.52%) | 0 (0%) | 0.488[b] |
| Vasopressor use, number (%) | | 13 (61.90%) | 3 (14.29%) | 0.001*[b] |
| Time to RT-PCR negative status (days), median (IQR) | | 19 (17–19) | 17 (16–17) | 0.026*[a] |
| Hospital stay, median (IQR), days | | 17 (13–17) | 12 (11–12) | 0.003*[a] |

**TABLE 2: Outcomes.**

*p-value < 0.05 was considered significant; a: Mann–Whitney U-test; b: Chi-squared/Fisher's exact test; c: log-rank test from Kaplan–Meier survival estimates (see text and Appendices for further details).

HDD: high-dose dexamethasone; TCZ: tocilizumab; CI: confidence interval; IQR: interquartile range; MV: mechanical ventilation; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment score; WHO-CPS: World Health Organization Clinical Progression Scale; RT-PCR: reverse-transcriptase polymerase chain reaction.

*Secondary Outcomes*

All-cause mortality at 28 days was significantly higher at 61.9% (95% CI: 39.06%-80.46%) in the HDD group, compared with 9.52% (95% CI: 2.21%-32.89%) in the TCZ group, with a $p < 0.001$, a large effect size of $w = 0.72$, and calculated power > 97% (Figure *2b*). The relative risk (RR) of death in the HDD group was 6.5 (95% CI: 1.67-25.33; $p = 0.007$; NNT (harm) = 1.91). The preventable fraction for mortality in the TCZ group was computed as 0.79 (95% CI: 0.064-0.98) with a preventable fraction in the population of 0.333. The proportion of patients discharged at day 28 was significantly higher in the TCZ group at 90.48% (95% CI: 67.1%-97.79%) versus 38.10% (95% CI: 19.54%-60.93%) in the HDD group (Table *2*).

The SOFA and WHO-CPS scores were significantly better in the TCZ group on day 7 after the intervention, paralleling an improvement in the $PaO_2/FiO_2$ ratio on day 7 in the TCZ group (median difference: 132.96 (95% CI: 55.15-210.77; $p < 0.001$)) (Figure *6* in the Appendices). The proportion of patients requiring vasopressors was 61.90% in the HDD group against 14.29% in the TCZ group ($p = 0.001$). The median number

of days a patient remained RT-PCR positive for SARS-CoV-2 was higher in the HDD group. The duration of hospital stay was also high in the HDD group (Table 2).

The distributions of $PaO_2/FiO_2$, total leucocyte count (TLC), neutrophil/lymphocyte (N/L) ratio, CRP, ferritin, and D-dimer in both groups at various time points are presented in Figure 3 (also see Table 4, Figure 6, and Figure 7 in the Appendices). CRP had the best negative correlation with $PaO_2/FiO_2$ (Figure 8 in the Appendices).

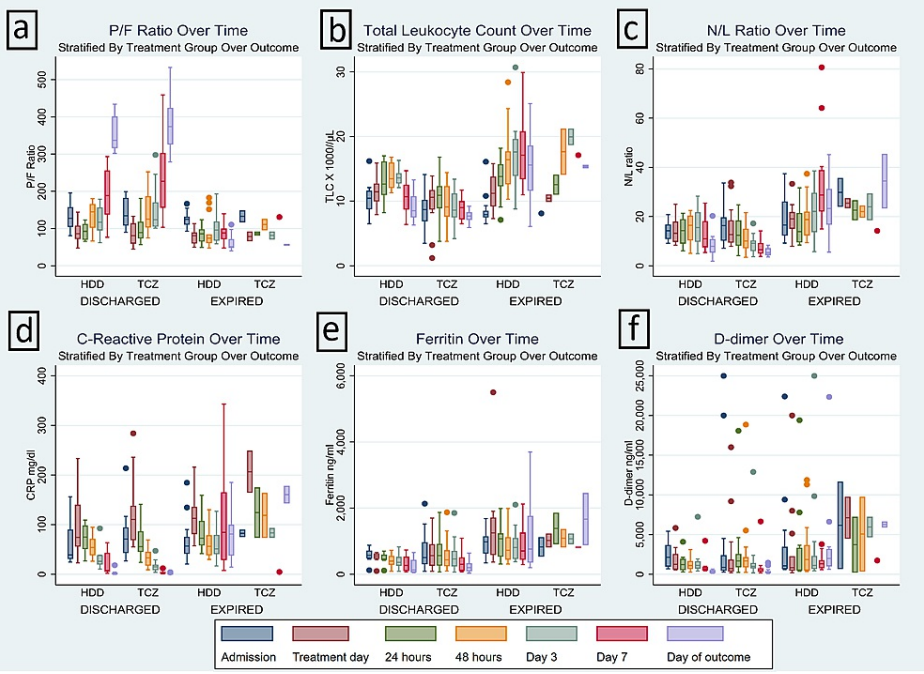



**FIGURE 3: Boxplots of biomarkers stratified by treatment groups and outcome (discharged/expired) at various time points: (a) PaO2/FiO2 ratio (PFR), (b) total leukocyte count (TLC), (c) neutrophil/lymphocyte ratio (N/L ratio or NLR), (d) C-reactive protein (CRP), (e) D-dimer, and (f) ferritin.**

## Multivariate and survival analysis

The median time to discharge was 20 days (95% CI: 13 to infinity) in the HDD group against 10 days (95% CI: 9-13) with a log-rank test p-value < 0.001 (Figure 2c). The median time to RT-PCR negative status was 12 days (95% CI: 11-14) in the HDD group and 10 days (95% CI: 9-10) in the TCZ group (log-rank test p = 0.006). A K-M analysis with a similarly censored time variable and WHO-CPS improvement as the dependent variable gave a mean time to the improvement of 17.9 (95% CI: 12.80-23.00) in the HDD group against 6.48 (95% CI: 3.40-9.55) in the TCZ group (Figure 2d and Table 5 in the Appendices).

After assessing for proportionality, the Cox proportional hazards model was fit on the above and adjusted for the variables $PaO_2/FiO_2$ ratio at baseline, days from symptom onset at intervention, CRP, TLC, and N/L ratio at intervention. This gave a hazard ratio of 3.69 (95% CI: 1.34-10.15; p = 0.024) for WHO-CPS improvement in the TCZ group (Figure 2d and Table 6 in the Appendices).

A competing risks regression with days posttreatment as the time variable and death as competing interest gave an adjusted sub-hazard ratio (SHR) for discharge of 5.86 (95% CI: 1.49-23.04; p = 0.011) in the TCZ group. Similarly, with discharge as a competing interest, the TCZ group had an adjusted SHR for death of 0.085 (95% CI: 0.016-0.44; p = 0.003) (Table 7, Figure 9, and Figure 10 in the Appendices).

## Adverse event outcomes

The main reason the trial was stopped at the interim analysis stage was the increased mortality and adverse event rate observed in the HDD arm. This was chiefly due to new infections in HDD (relative risk: 5.5; 95% CI: 1.38-21.86; p = 0.015; NNT (harm) = 2.33; 95% CI: 5.53-1.48). Table 3 summarizes the adverse events per Common Terminology Criteria for Adverse Events (CTCAE) version 5 [17]. The overall adverse event rate per

100 patient days was 61.43 in the HDD group versus 27.72 in the TCZ group.

| | | Adverse events, number of patients (%) | | | Number of events | | Event rate ratio HDD/TCZ | p-value (exact rate ratio test) |
|---|---|---|---|---|---|---|---|---|
| | | Total (n = 42) | HDD (n = 21) | TCZ (n = 21) | HDD (number in 306 patient days) | TCZ (number in 220 patient days) | | |
| Deaths | | 15 (36.06%) | 13 (61.9%) | 2 (9.52%) | 13 | 2 | 4.67 (1.06–42.65) | 0.023* |
| Infections | | 13 (30.95%) | 11 (52.38%) | 2 (9.52%) | 25 | 2 | 8.9 (2.24–78.28) | <0.001* |
| Grade 3 or worse adverse events by CTCAE version 5, MedDRA system organ class preferred terms | | | | | | | | |
| Cardiac disorders | Supraventricular tachycardia | 1 (2.38%) | 0 (0%) | 1 (4.76%) | 0 | 1 | 0 (0–28.04) | 0.41 |
| | Sinus bradycardia | 1 (2.38%) | 0 (0%) | 1 (4.76%) | 0 | 1 | 0 (0–28.04) | 0.41 |
| | Cardiac arrest | 15 (36.06%) | 13 (61.9%) | 2 (9.52%) | 13 | 2 | 4.67 (1.06–42.65) | 0.023* |
| Infections or infestations | Fungemia | 8 (19.04%) | 8 (38.09%) | 0 (0%) | 8 | 0 | Zero denominator | 0.013* |
| | Catheter-related infection | 7(16%) | 6 (28.27%) | 1 (4.76%) | 6 | 1 | 4.31 (0.52–198.42) | 0.158 |
| | Lung infection | 11 (26.19%) | 10 (47.61%) | 1 (4.76%) | 11 | 1 | 7.91 (1.15–340.41) | 0.016* |
| Respiratory, thoracic, and mediastinal disorders | Grade 4 adult respiratory distress syndrome | 15 (36.06%) | 13 (61.9%) | 3 (14.28%) | 13 | 3 | 3.12 (0.85–17.04) | 0.065 |
| Vascular disorders | Shock | 16 (38.09%) | 13 (61.90%) | 3 (14.29%) | 13 | 3 | 3.12 (0.85–17.04) | 0.065 |
| Metabolism and nutrition disorders | Hyperglycemia[Ψ] | 30 (71.43%) | 21 (100%) | 9 (42.86%) | 106 | 49 | 1.56 (1.09–2.23) | 0.009* |
| Gastrointestinal disorders | Gastric hemorrhage | 4 (9.52%) | 4 (19.04%) | 0 (0%) | 18 | 0 | Zero denominator | <0.001* |
| Total number of events[‡] | | | | | 188 | 61 | 2.22 (1.65–3.01) | <0.001* |

**TABLE 3: Adverse events.**

All cardiac arrests were grade 5.

‡Excludes deaths and infections to avoid duplication.

ΨBlood sugar > 180 mg/dL.

*p-value < 0.05 was considered significant.

HDD: high-dose dexamethasone; TCZ: tocilizumab; CTCAE: Common Terminology Criteria for Adverse Events.

## Discussion

Steroids have been extensively used and evaluated since the beginning of the pandemic. Several cohort studies described varied findings, either favorable or unfavorable, promoting confusion especially when it concerns the dose of steroids [8-10]. The first RCT on the role of steroids in COVID-19 has recommended

that dexamethasone 6 mg once daily for 10 days decreased mortality [12]. A recent RCT on HDD has shown therapeutic benefit at doses of 20 mg per day in critically ill patients with COVID-19 [13]. Treatment with HDD was beneficial in lowering mortality and the period of mechanical ventilation in critically ill patients with non-COVID-19 ARDS [18]. Despite these promising results, there is still uncertainty regarding the role of HDD in COVID-19. Several meta-analyses have claimed TCZ to be a safe and effective drug in reducing the risk of death [19-21]. In a low- to middle-income country with scarce TCZ supply amidst the pandemic, we surmised that HDD would be an easily accessible, low-cost, and potentially effective treatment option. At moderate or high doses, it has not been linked with detrimental effects [12,13]. Hence, we sought to compare the therapeutic effectiveness of HDD and TCZ in COVID-19.

VFDs were selected as the principal outcome as it takes into account mortality and the period of ventilation together in a manner that summarizes the net effect of an intervention on these parameters [22]. The major difference between recent RCTs and our study is that patients with clinical worsening within 48 hours of receiving standard care were treated with HDD or TCZ, as a rescue, second-line therapy [11-13,19-21]. Characteristically, ARDS presents with a profound pulmonary and systemic inflammatory reaction within 48 hours, giving rise to aggravated pulmonary inflammation and fibroproliferation [23]. Failed efforts to halt the self-perpetuating tissue inflammation within a specified time lead to the subsequent suppression of lung function and increased chances of mortality. Therefore, we ensured that all the randomized patients unresponsive to standard care received immediate rescue therapy within 48 hours of worsening ARDS.

Notably, our findings show that HDD was associated with high 28-day mortality and was poorly tolerated. There was a significantly higher incidence of adverse events, especially new infections. This high incidence was beyond the predetermined limits of futility, fostering a very weak probability of a large trial. Our findings have unveiled the ineffectiveness and poor safety of HDD therapy in COVID-19 ARDS with $PaO_2/FiO_2 < 200$. Hence, as decided by the institute clinical management board, the trial was stopped immediately after the prespecified interim analysis.

Our study results favor the use of TCZ in moderate to severe COVID-19. Several RCTs examining the role of TCZ in COVID-19 reported conflicting results [24,25]. These trials differed considerably in study design, illness severity of enrolled patients, and imbalances in the use of steroids between study groups. The RECOVERY trial reported all-cause mortality of 31% among patients allocated to the TCZ arm and 35% in the usual care arm (rate ratio: 0.85; 95% CI: 0.76-0.95; p = 0.0028) [11]. Our study had an all-cause mortality rate ratio of 0.21 (95% CI: 0.02-0.93; p = 0.022); however, our study was never powered to detect this outcome. Nevertheless, IL-6 inhibitors also have the potential to suppress the host immune response and could hypothetically raise the probability of acquiring secondary infections. In our trial, we did not witness a greater risk of infection or adverse events with TCZ use. These findings support previous RCTs about the safety of TCZ in COVID-19 [11,24,25].

Our study has certain limitations. First, the trial was discontinued after the first interim analysis, at a limited sample size; hence, the precision of the treatment effect estimates might be low than anticipated. However, it would be prudent to note that this interim analysis sample size was calculated to be valid for demonstrating a large effect size with adequate power when it came to VFDs as the primary outcome measure. A larger sample size, no doubt, would have been able to detect the differences in the effects of HDD or TCZ on mortality. Second, the study lacks a control arm. We did not compare outcomes against a control group that should have received only the standard care. Third, a different dose of dexamethasone might have provided a different result; therefore, the outcomes portrayed in this study should be linked only to the particular dose administered. Despite the above limitations, our robust study design and results add necessary evidence to the scientific community. Our findings await subsequent clarification from ongoing clinical trials on different doses of dexamethasone [26-28].

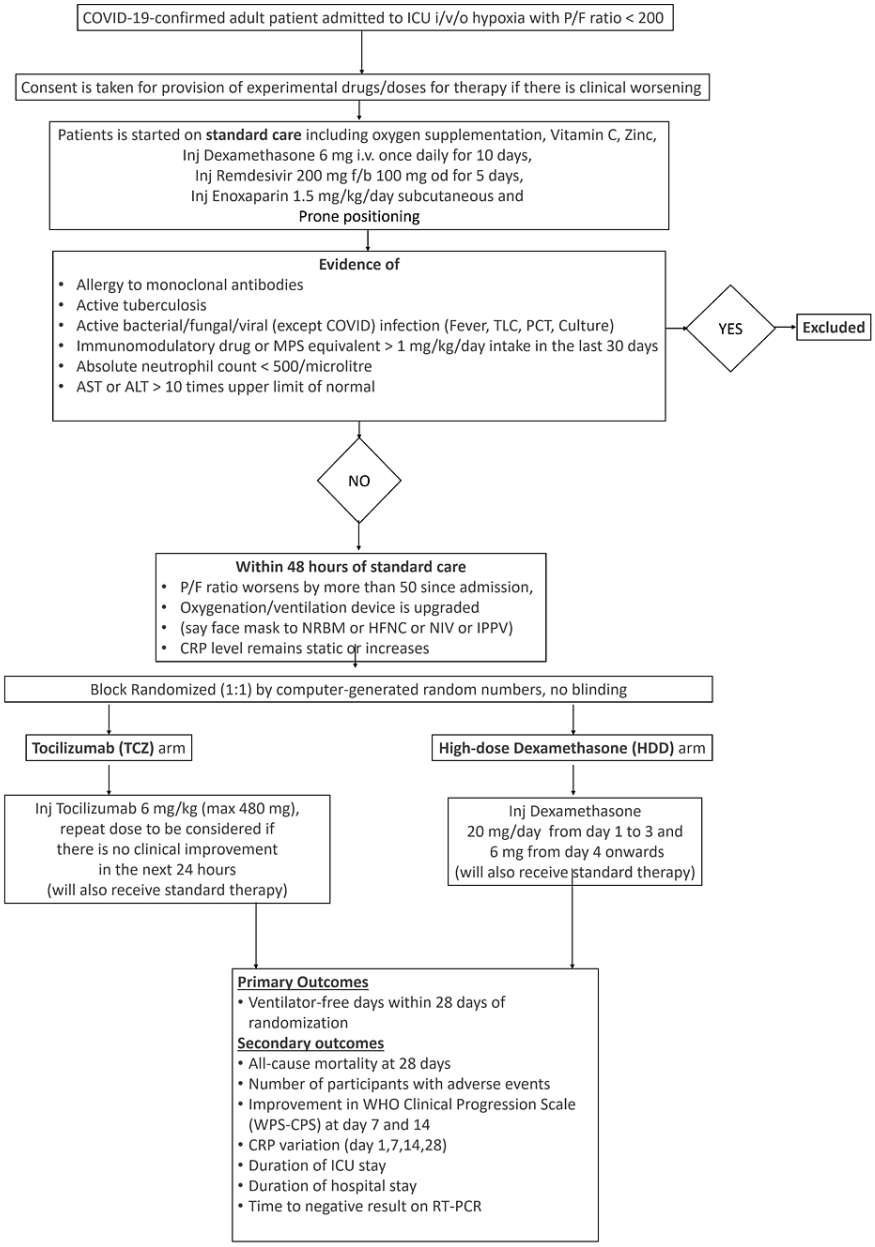
## Conclusions

Our study findings discourage the use of high doses of dexamethasone in the management of moderate to severe COVID-19 ARDS. The routine use of such high doses to mitigate the inflammatory cytokine storm in these patients might worsen outcomes possibly due to a high rate of secondary infections and therefore cannot be recommended.

From this study, we can conclude that tocilizumab is associated with a decreased mortality, reduced need for invasive mechanical ventilation, and a higher probability of successful hospital discharge in comparison with high-dose dexamethasone when used in the context of mitigating the adverse effects of the cytokine storm.

## Appendices

The study protocol that was initially proposed has been represented in the following flowchart (Figure *4*), and the a priori statistical analysis plan is depicted in Figure *5*.




## FIGURE 4: The proposed study protocol.

$PaO_2/FiO_2$: partial pressure of arterial oxygen to fraction of inspired oxygen; f/b: followed by; MPS: methylprednisolone; TLC: total leucocyte count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; WHO-CPS: World Health Organization Clinical Progression Scale; NRBM: non-rebreather mask; HFNC: high-flow nasal cannula; NIV: noninvasive ventilation; IPPV: invasive positive pressure ventilation.

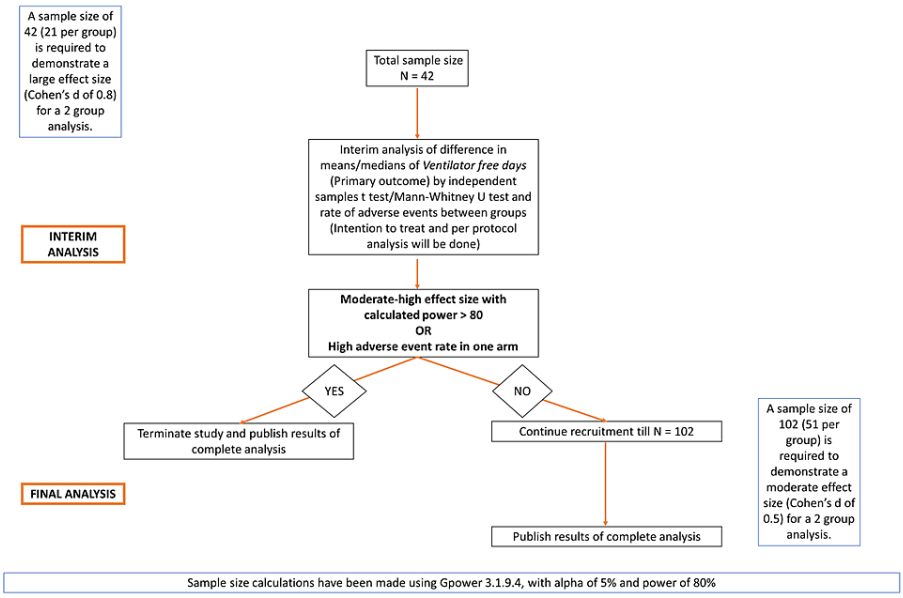



**FIGURE 5: Statistical analysis/interim analysis plan.**

The course of biomarkers is shown in Table *4* as the median difference between various time points. The relationship between the biomarkers and $PaO_2/FiO_2$ ratio is shown in Figure *6*. Figure *7* depicts the median and interquartile range of the various biomarkers between groups as violin plots, and Figure *8* illustrates the correlation scatterplot between the markers and $PaO_2/FiO_2$ ratio, which shows the Spearman rank correlation coefficients. CRP appears to have the best negative correlation with the $PaO_2/FiO_2$ ratio.

| Outcomes | High-dose dexamethasone (n = 21) | Tocilizumab (n = 21) | p-value** |
|---|---|---|---|
| CRP (mg/dL), median difference between time points (95% CI) | | | |
| Baseline to treatment day | 35 (-10.88 to 80.88) | 36 (-5.03 to 77.03) | 0.93 |
| Treatment day to 24 hours | -16.4 (-61.11 to 28.31) | -53.5 (-96.21 to -10.71) | 0.116 |
| Treatment day to 48 hours | -32.9 (-75.83 to 10.03) | -73.5 (-111.16 to -35.84) | 0.038* |
| Treatment day to day 3 | - 48.49 (-93.62 to -3.36) | -95.33 (-126.86 to -63.79) | 0.014* |
| Treatment day to day 4 | - 51.51 (-104.05 to 1.04) | -102.88 (-131.55 to -74.20) | 0.004* |
| Treatment day to day 7 | -51 (-111.99 to 9.99) | -108.54 (-136.85 to - 80.22) | 0.001* |
| Treatment day to day 10 | - 54.42 (-108.03 to -0.80) | -109.91 (-145.52 to -74.30) | 0.002* |
| Treatment day to outcome day | - 57.1 (-111.02 to -3.18) | -110.36 (-137.23 to -83.48) | 0.008* |
| Ferritin (ng/mL), median difference between time points (95% CI) | | | |
| Baseline to treatment day | -53.8 (-539.43 to 431.84) | 151 (-276.89 to 578.89) | 0.428 |
| Treatment day to 24 hours | -62 (-575.75 to 451.75) | -72.1 (-543.9 to 399.7) | 0.327 |
| Treatment day to 48 hours | -59.7 (-539.28 to 419.88) | -159 (-545.61 to 227.611) | 0.333 |
| Treatment day to day 3 | - 141.7 (-651.60 to 368.20) | -179 (-547.59 to 189.59) | 0.428 |
| Treatment day to day 4 | - 166.7 (-671.02 to 337.62) | -114 (-1394.34 to 1166.34) | 0.428 |
| Treatment day to day 7 | -150 (-693.09 to 393.09) | -333 (-705.78 to 39.78) | 0.274 |
| Treatment day to day 10 | - 111.7 (-638.47 to 415.07) | -361 (-778.4 to 56.4) | 0.122 |
| Treatment day to outcome day | - 269.4 (-936.06 to 397.27) | -461 (-790.71 to -131.29) | 0.333 |
| D-Dimer (ng/mL), median difference between time points (95% CI) | | | |
| Baseline to treatment day | -514.8 (-2205.57 to 1175.97) | 47 (-2053.98 to 2147.98) | 0.064 |
| Treatment day to 24 hours | -474.06 (-2062.58 to 1114.46) | 772 (-809.9 to 2353.9) | 0.011* |
| Treatment day to 48 hours | 75.8 (-1513.10 to 1664.70) | 771 (-901.35 to -2443.35) | 0.554 |
| Treatment day to day 3 | 71.8 (-1180.89 to 1324.49) | 152 (-1278.13 to 1582.13) | 0.155 |
| Treatment day to day 4 | 214.58 (-1398.48 to 1827.64) | -114 (-1394.34 to 1166.34) | 0.285 |
| Treatment day to day 7 | -68.2 (-1182.07 to 1045.67) | -357 (-1559.94 to 845.94) | 0.148 |
| Treatment day to day 10 | - 307.7 (-1585.92 to 970.52) | -440 (-1979.02 to 1099.02) | 0.094 |
| Treatment day to outcome day | - 288.2 (-1639.72 to 1063.32) | -675 (-1838.18 to 488.18) | 0.213 |

**TABLE 4: Course of biomarkers in our study population.**

*p < 0.05 was considered significant; **Mann–Whitney U-test for comparing change from baseline to treatment day and from treatment day to indicated time point between treatment groups (the negative sign indicates a decrease from each earlier mentioned time point). Median differences and 95% CIs have been derived from quantile regression.

CRP: C-reactive protein.

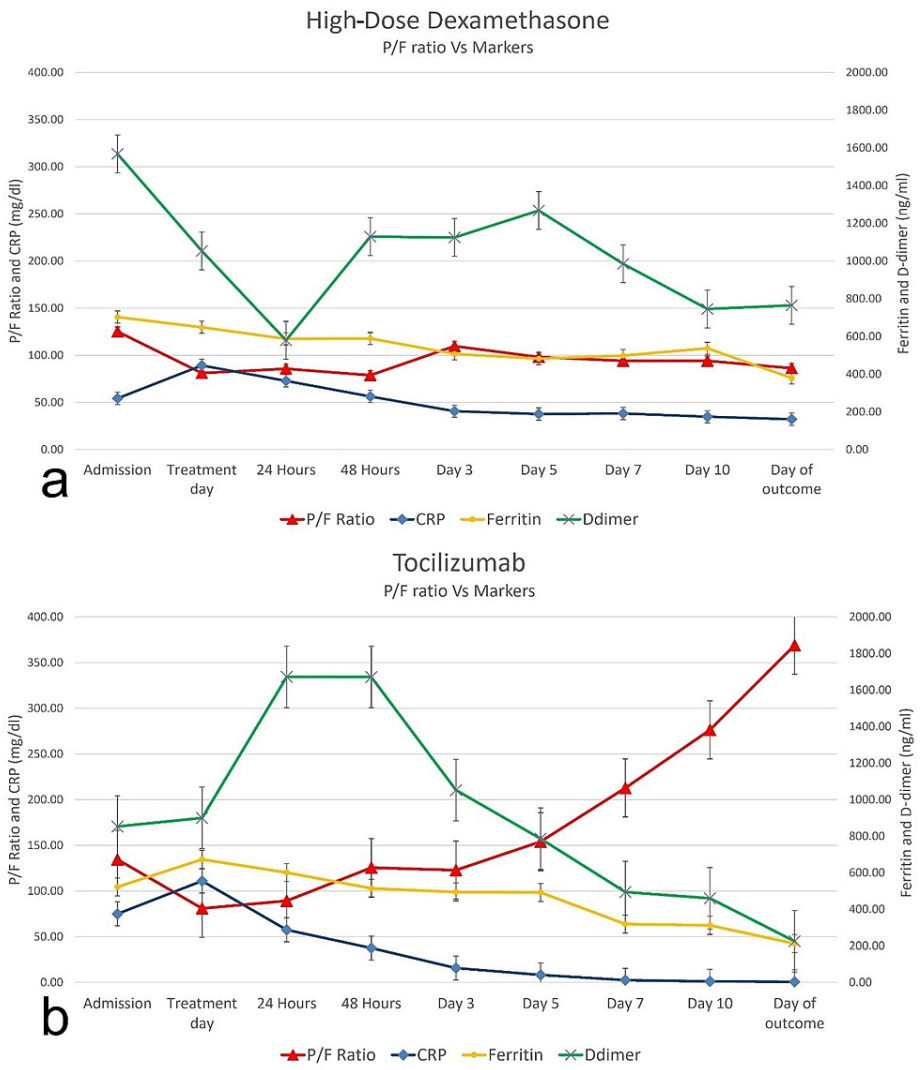



**FIGURE 6: Trend of PaO2/FiO2 (P/F) ratio with biomarkers in each group (median values and standard errors have been plotted).**

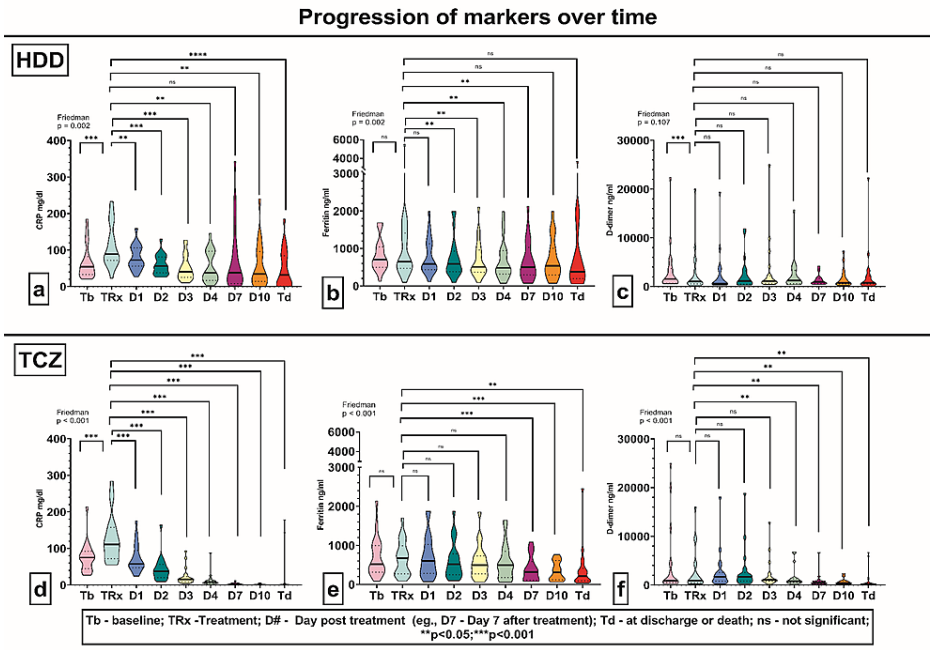



**FIGURE 7: Panel of violin plots showing progression over time of CRP (a and d), ferritin (b and e), and D-dimer (c and f): a, b, and c for the high-dose dexamethasone (HDD) group, and d, e, and f for the tocilizumab (TCZ) group. Pairwise comparisons are with the Wilcoxon signed-rank test.**

CRP: C-reactive protein.

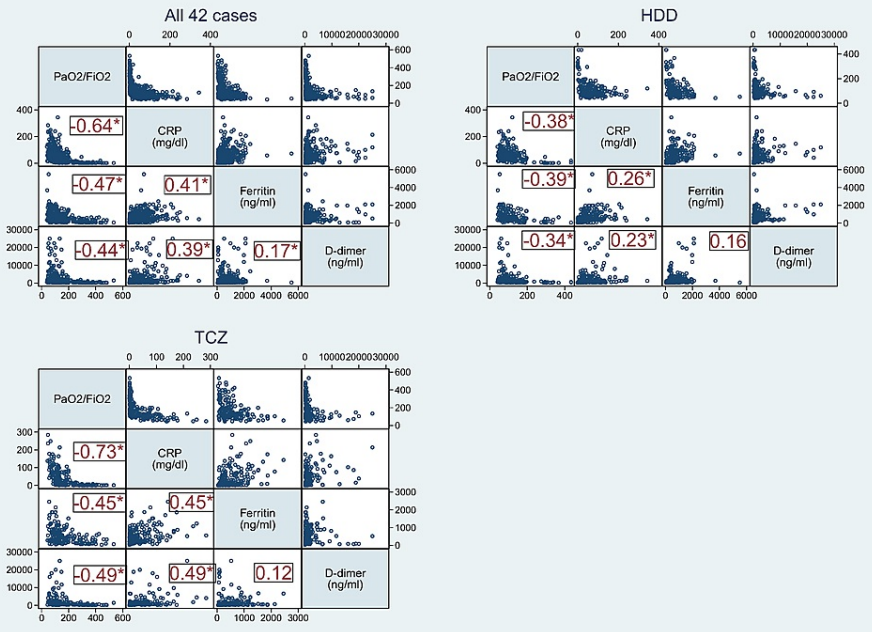



**FIGURE 8: Scattergraph showing correlations between PaO2/FiO2 ratio, CRP, ferritin, and D-dimer in all cases and by groups.**

HDD: high-dose dexamethasone; TCZ: tocilizumab; CRP: C-reactive protein; non-axial numbers (maroon): Spearman rank correlation coefficients; *: p-value < 0.05.

Table 5, Table 6, and Table 7, and Figure 9 and Figure 10 show the results of the survival analysis and competing risks regression.

| Dependent variable | Time variable | Measured result | Values | 95% CI | Statistical test | Extended mean |
|---|---|---|---|---|---|---|
| Discharge | Days posttreatment | Mean time HDD | 17.80 (underestimated) | 15.19–20.41 | Log rank p value < 0.0001 | 24.33 |
| | | Mean time TCZ | 10.85 | 9.72–11.93 | | 10.85 |
| | | Median time HDD | 20 | 13–infinity | | |
| | | Median time TCZ | 10 | 9–13 | | |
| Expiry | Days posttreatment | Mean time HDD | 16.87 | 15.10–18.63 | Log rank p value = 0.839 | 16.87 |
| | | Mean time TCZ | 15.05 (underestimated) | 13.83–16.26 | | 69.99 |
| | | Median time HDD | 17 | 15–19 | | |
| | | Median time TCZ | Not computed | 13–infinity | | |
| RT-PCR negative status | Days posttreatment censored at 28 days if expired | Median time HDD | 12 | 11–14 | Log-rank p-value = 0.0059 | |
| | | Median time TCZ | 10 | 9–10 | | |
| WPS improvement by a score of 1 | Days posttreatment censored at 28 days if expired | Mean time HDD | 17.90 (underestimated) | 12.80–23 | Log-rank p-value = 0.0024 | 46.50 |
| | | Mean time TCZ | 6.48 (underestimated) | 3.40–9.55 | | 7.61 |
| | | Median time HDD | Not computed | 3–infinity | | |
| | | Median time TCZ | 4 | 3–6 | | |

**TABLE 5: Survival analysis outcomes (Kaplan–Meier estimates).**

p < 0.05 was considered significant; N.B., where median survival time could not be computed in any one group, the restricted means and extended means have been provided for careful interpretation, if necessary.

HDD: high-dose dexamethasone; RT-PCR: real-time polymerase chain reaction; TCZ: tocilizumab; WPS: WHO Clinical Progression Scale.

| Dependent variable | Time variable | Measured result | Values | 95% CI | p-value | LR Chi-squared compared to null | Prob>Chi-squared compared to null | phtest Schonfeld residuals prob>Chi-squared (p-value) |
|---|---|---|---|---|---|---|---|---|
| Discharge | Days posttreatment | HR TCZ | 5.153 | 2.090–12.702 | 0.001 | 14.93 | <0.001 | 0.5614 |
| | | Adjusted# HR TCZ | 5.106 | 1.628–16.009 | 0.005 | 18.38 | 0.053 | 0.5185 |
| Expired | Days posttreatment | HR TCZ | 0.843 | 0.159–4.471 | 0.841 | 0.04 | 0.839 | 0.5501 |
| | | Adjusted# HR TCZ | 0.315 | 0.034–2.899 | 0.308 | 9.57 | 0.144 | 0.678 |
| WPS improvement by a score of 1 | Days posttreatment censored at 28 days if expired | HR TCZ | 3.18 | 1.39–7.27 | 0.006 | 14.64 | 0.0001 | 0.5038 |
| | | Adjusted# HR TCZ | 3.69 | 1.34–10.15 | 0.024 | 18.71 | 0.032 | 0.5203 |

**TABLE 6: Cox proportional hazards model estimates.**

$p < 0.05$ was considered significant; #adjusting for the variables $PaO_2/FiO_2$ ratio at baseline, days from symptom onset at intervention, C-reactive protein (CRP), total leukocyte count (TLC), and neutrophil/lymphocyte (N/L) ratio at intervention.

HR: hazard ratio; TCZ: tocilizumab; WPS: WHO Clinical Progression Scale.

| Dependent variable | Competing interest | Time variable | Measured result | Values | 95% CI | p-value | Wald Chi-squared compared to null | Prob>Chi-squared compared to null |
|---|---|---|---|---|---|---|---|---|
| Discharge | Expiry | Days posttreatment | Sub-HR TCZ | 4.269 | 1.906–9.565 | <0.001 | 12.44 | 0.0004 |
| | | | Adjusted# sub-HR TCZ | 5.856 | 1.488–23.037 | 0.011 | 26.49 | 0.0002 |
| Expiry | Discharge | Days posttreatment | Sub-HR TCZ | 0.119 | 0.024–0.584 | 0.009 | 6.89 | 0.0087 |
| | | | Adjusted# sub-HR TCZ | 0.085 | 0.016–0.435 | 0.003 | 21.83 | 0.0013 |

**TABLE 7: Competing risks regression.**

$p < 0.05$ was considered significant.

HR: hazard ratio; TCZ: tocilizumab.

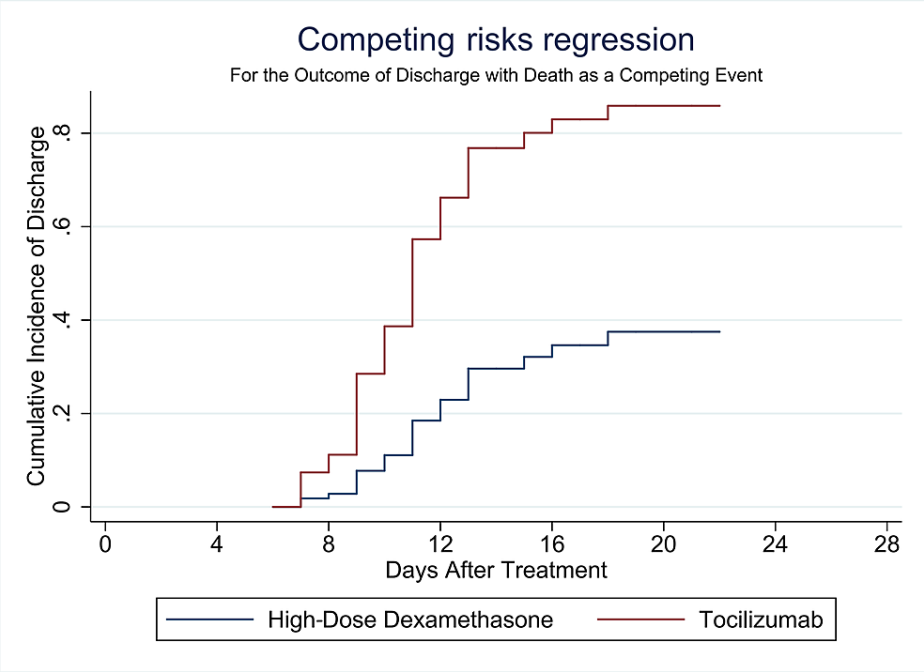



**FIGURE 9: Competing risks regression curves for the outcome of discharge.**

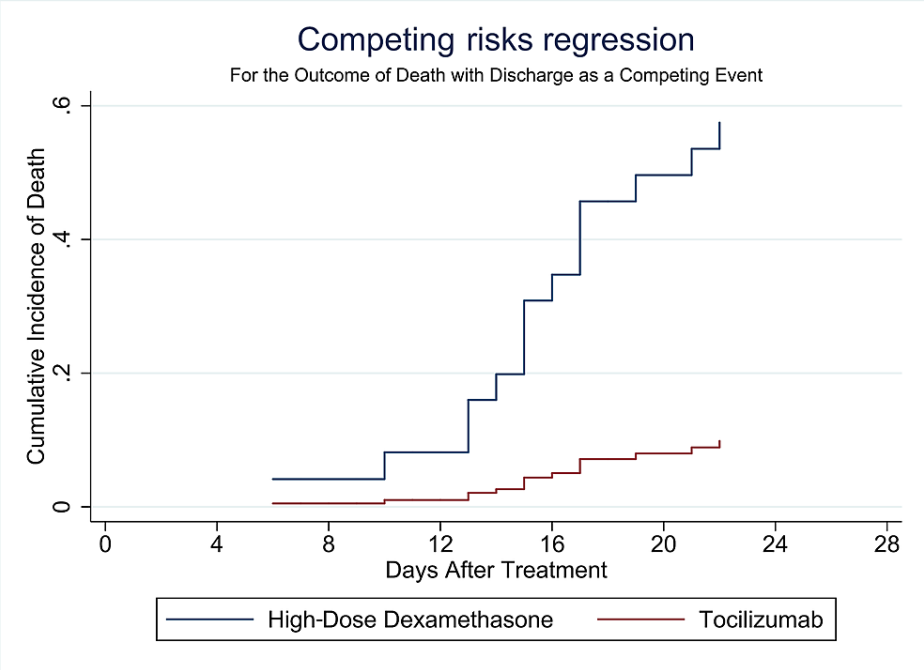



**FIGURE 10: Competing risks regression curves for the outcome of death.**

## Additional Information

### Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. Institutional Ethics Committee issued approval INT/IEC/2021/SPL-697. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no

financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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