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# Characteristics of the First 102 Severe COVID-19 Cases Treated With Convalescent Plasma or Tocilizumab or Both in Al-Nahdha Hospital, Oman

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## Abstract

**Background:** In the absence of an effective vaccine, the coronavirus disease (COVID-19) continues to cause more deaths. Evidence on the effectiveness of various COVID-19 management plans is inconclusive. This paper describes the characteristics of the first 102 severe COVID-19 in-patients treated with Convalescent Plasma (CP) therapy or Tocilizumab or both at Al-Nahdha hospital in Muscat, Oman. Additionally, differences in requiring critical care were explored across the treatment groups.

**Methods:** Data of all the positive cases in Al-Nahdha hospital were retrieved from the electronic health information system retrospectively from April 1st to July 31st 2020. The required information was recorded in a bespoke sheet and exported to SPSS for further analysis. The primary outcome was defined as improved (discharged home) vs worsening (requiring critical care).

**Results:** Out of the 102 severe cases of COVID-19 admissions, 20.6%, 59.8% and 20.6% received CP, Tocilizumab and both respectively. In average, CP was introduced at day 3.7(4.8) whereas Tocilizumab at day 7.8(5.1) from admission. The between-group differences in the proportion of patient who improved vs worsened were not significant ($P = 0.7$). However, the within-group difference in the proportion of patient who improved vs worsened was significant in the Tocilizumab treatment group ($P = 0.03$). All socio-demographics were not significantly different across the treatment groups. Most improvements in the studies parameters [CBC (total WBC, Lymph and neutrophil counts), oxygen and immune response "cytokine storm" parameters] post-treatment was attributed to the use of Tocilizumab. There was a statistically significant difference in the mean hospital stay between the improved and worsened cases across all treatment categories [at the population level: 8.2(5.0) improved vs 4.7(3.7) worsened-$P < 0.001$].

**Conclusions:** Results from this study provided baseline information about the characteristics of confirmed COVID-19 cases in Al-Nahdha hospital who received CP, Tocilizumab or both. Results obtained seems to be promising in preventing critical care, especially for Tocilizumab. However, further randomized studies are needed.

## Keywords

Covid-19, Oman, clinical, characteristics, convalescent plasma, tocilizumab

## Introduction

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China[1,2] in December 2019 and was declared as a pandemic by World Health Organization (WHO) in March 2020.[2] As of July 31st, 2020, a total of more than 17 million confirmed cases and more than 690,200 deaths had been reported worldwide.[1,2] Meanwhile, a total of approximately 79,000 confirmed cases and 434 deaths were reported in Oman according to reports from the Oman Ministry of Health in July 2020[3]; currently,

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evidence around the effective treatment for this disease is inconclusive. Drugs, such as Remdesivir showed some effectiveness in shortening the time to recovery in hospitalized COVID-19 patients.[4,5] Other treatments such as corticosteroid—Dexamethasone showed reductions in COVID-19 deaths among seriously ill patients.[6-8] On the other hand, studies involving hydroxychloroquine and other agents such as Kaletra (Lopinavir/Ritonavir) failed to show effectiveness in reducing morbidities and mortalities. In the absence of an effective vaccine, there is an urgent need to look for an alternative strategy for COVID-19 treatment, especially among severe patients.

Over the past 2 decades, Convalescent plasma (CP) therapy was successfully used in the treatment of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and the 2009 H1N1 pandemic with satisfactory efficacy and safety.[6,9,10] A meta-analysis from 32 studies of SARS coronavirus infection and severe influenza showed a statistically significant reduction in mortality rates following CP therapy, compared with placebo or no treatment (odds ratio, 0.25; 95% confidence interval, 0.14–0.45).[11] Due to the similarities among SARS, MERS, and COVID-19,[12] CP therapy might be a promising treatment option for severe COVID-19 cases.[12] Thus COVID-19 recovered patients with a high neutralizing antibody titer may be encouraged to donate their plasma to be used as therapy for the severe COVID-19 cases.

The severity of COVID-19 is linked to the virus-induced cytopathic effects cited as an "inflammatory cytokine storm."[13] Patients with COVID-19 have increased plasma concentrations of inflammatory cytokines [tumor necrosis factor α (TNF-α), interleukins (IL) 2, 7, and granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and interferon-γ-inducible protein].[14] Consequently, this massive reaction causes multiple organ failure including interruptions in the alveolar gas exchange process leading to high mortalities of severe COVID-19 patients.[14] Tocilizumab is the first marketed IL-6 blocking antibody through targeting IL-6 receptors and hence has potential in reducing mortality of severe or critical COVID-19[15] diagnosed patients by blocking the inflammatory reactions of the cytokine storm. The results of tocilizumab treatment are inspiring. The temperature of all the patients returned to normal very quickly. The respiratory function and all other symptoms improved remarkably.[16]

Nevertheless, the benefits of CP therapy or Tocilizumab or both in COVID-19 remain uncertain.[6,14] Hence, this study in Al-Nahdha hospital explores the characteristics of severe COVID-19 in-patients treated with CP therapy or Tocilizumab or both. Additionally, differences in the proportion of patients who improved vs worsened were compared across these treatment groups was examined.

## Methods

This retrospective study was conducted at Al-Nahdha hospital, in Muscat, Oman, from April 1st to July 31st 2020. Al-Nahdha hospital provides in-patients and out-patient services for Muscat region, the capital of Oman. It has a total of 142 beds for in-patients and 12 beds for daycare services. The hospital covers multiple specialities (head & neck surgery, Ophthalmology, Dermatology, Dental/Oral and Maxillofacial Surgery, Internal medicine and Pediatrics).

Eligibility criteria included: a) age of at least 18+ years, b) a laboratory-confirmed diagnosis of infection with Acute Respiratory Distress Syndrome (ARDS) caused by SARS-CoV-2, c) admitted for the treatment of COVID-19 complications, d) have severe or life-threatening COVID-19, or judged by the treating physician to be at high risk of progression to severe or life-threatening disease, and e) willing to give informed consent provided by the patient or the relative.

Severe COVID-19 was defined by one or more clinical presentations including shortness of breath (dyspnea), respiratory frequency $\geq$ 30/min, blood oxygen saturation $\leq$ 93%, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, lung infiltrates > 50% within 24 to 48 hours.[17] In addition, life-threatening COVID-19 was diagnosed based on signs of respiratory failure, septic shock, or multiple organ dysfunction or failure.

Eligibility for CP or Tociluzumab treatments for the severe COVID-19 cases were based on criteria from the Oman Ministry of Health.[17] CP was administered as 200-500 mL divided over 2 days, 24 hours apart. Tocilizumab, on the other hand, was prescribed to patients with abnormal findings in chest imaging, or Blood O2 saturation $\leq$ 93%, or/and rapidly worsening gas exchange requiring >6L/min of O2.

Further, hyper-inflammatory markers suggestive of cytokine storm were identified to aid early initiation of the Tociluzumab treatment including ferritin > 300 micrograms/L, LDH >250 U/L, D-dimer (>1 mg /L), and serum IL-6 $\geq$3$\times$ upper limit (routine IL monitoring not required). Notably, infectious disease consultants were consulted for the initiation of the treatments, and follow up the management plans.

### Data Collection

Data were collected from the hospital electronic system, including:

*Demographics:* age, gender, nationality

*Baseline characteristics:* obesity, smoking, alcohol consumption

*Risk factors:* diabetes, hypertension, other co-morbidities

*Respiratory parameters pre (day 0) and post-treatment* (24 hrs and before discharge),

Laboratory parameters pre (day 0) and post-treatment (24 hrs and before discharge), (absolute lymphocytic *count (ALC), CRP, LDH, ferritin, D-dimer, IL-6, PH and lactate),*

*Other medications used to treat admitted COVID-19 patients*

*Radiological features: chest x-ray: unilateral infiltrate, bilateral with < 50% infiltrate, extensive > 50% infiltrate*

*Hospitalization: total length of stay*

### Sample Size

All severe cases were included from April 1st to July 31st 2020.

### Ethics

The study was approved by the Regional Research and Ethics Committee (supplementary file 1).

### Analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's $\chi^2$ tests (Fisher's exact tests for expected cells of less than 5). For continuous variables, mean and standard deviation were used to summarize the data, while analyses were performed using t-test. Abnormally distributed variables were summarized using median and interquartile range and analyzed using the Wilcoxon Mann-Whitney test. Statistical analyses were conducted using SPSS v20 version. The dependent variable was dichotomized to "improved" defined as discharged from hospital and "did not improve" defined as died or transferred for critical care, and results were compared across the studied variables. Average point estimation (imputation technique) was utilized to replace any missing value, which has the benefit of not changing the sample mean for that variable. Differences in post-pre-treatment parameters were calculated, and results were categorized as "no change" if the difference was 0, "improved" if the difference was a minus number and/or "worsened" if the difference was a positive number.

## Results

### Sociodemographic

One hundred two cases were included in the study [20 participants received plasma (19.6%), 61 received Tocilizumab (59.8%), and 21 received both (20.6%)]. Overall, males (81.4%, n = 83 vs 18.6%, n = 19 females) were dominant across all the treatment groups. Mean age was 52.2(15.2). More than half of the study population were Omanis (68.6%, n = 70). The categories of other nationalities are shown in Figure 1.

### Primary Outcome

Overall, the proportion of patients who improved vs worsened was not statistically significant across the treatment groups ($P = 0.7$) (Table 1) or any of the studied sociodemographic characteristics. However, within-group differences in the proportion of patients who improved vs worsened were statistically significant in the Tocilizumab treatment group (59.0%, n = 36 vs 41.0%, n = 25, $P = 0.03$). There were only 3 deaths at Al-Nahdha among those who worsened (n = 3/43, 6.97%) in which 2 of them were from the CP treatment group and one from the group who received both treatments.

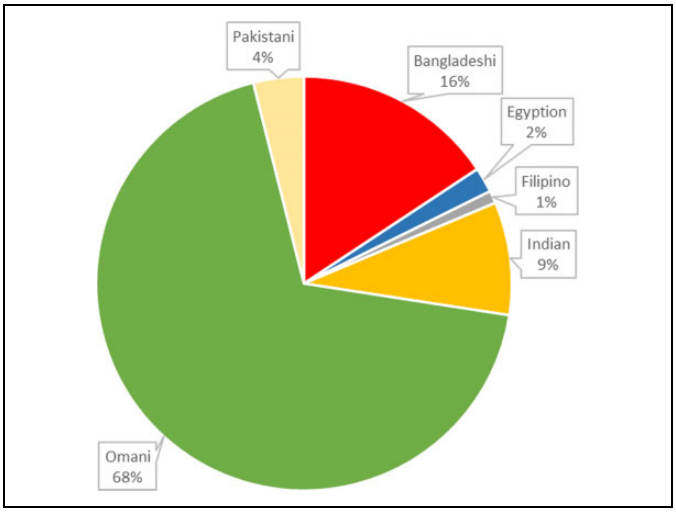


**Figure 1.** Percentage of non-Omani per nationalities.

### History of Risk Factors

A modest group of patients reported diabetes (44.1%, $n = 45$) and hypertension (40.2%, $n = 41$). More than one fifth (21.6%, $n = 22$) of the patients were obese and very few of them had Coronary artery disease (4.9%, $n = 5$), Heart failure (2.9%, $n = 3$), Chronic kidney disease (9.8, $n = 10$), Asthma (2.9%, $n = 3$), Interstitial lung disease (0.9%, $n = 1$), Chronic obstructive pulmonary disease (0.9%, $n = 1$), or old Tuberculosis (0.9%, $n = 1$). The proportion of these risk factors was not significant between the treatment groups or across the studied variables.

### Symptoms and Diagnosis

Most patients presented with fever (84.3%, $n = 86$), dry cough (90.2%, $n = 92$) and shortness of breath (92.2%, $n = 94$). Chest pain (6.9%, $n = 7$), and other non-specific symptoms were uncommon (diarrhea (28.4%, $n = 29$), vomiting (10.8%, $n = 11$) or sore throat (11.8%, $n = 12$). The differences in proportion in presented symptoms were not significant between the worsened and improved patients across the treatment groups.

### Radiology

Overall the majority of patients (67%, $n = 68$) had bilateral lung infiltrates. The proportion of patients with extensive lung infiltrates was significantly higher in patients who worsened vs those who improved (35%, $n =$ vs 20% respectively $P = 0.04$) (Figure 2).

### Mean Change in CBC (total WBC, Lymph and Neutrophil Counts), Oxygen and Immune Response "Cytokine Storm" Parameters

Overall, between-group (improved vs worsened) differences in the mean changes in the studied parameters, after the treatment was introduced from baseline, were not significant across all

**Table 1.** Proportion of Patients Who Improved versus Worsened by Treatment Groups.

| | Population (n = 102) | | Plasma (n = 20, 19.6%) | | Tocilizumab (n = 61, 59.8%) | | Both (n = 21, 20.6%) | |
|---|---|---|---|---|---|---|---|---|
| Improved | 59(57.8) | Within-group differences | 12(60) | Within group differences | 36(59.0) | Within group differences | 11(52.4) | Within group differences |
| Worsened | 43(42.2) | 0.5 | 8(40.0) | 0.05 | 25(41.0) | 0.03 | 10(47.2) | 0.7 |

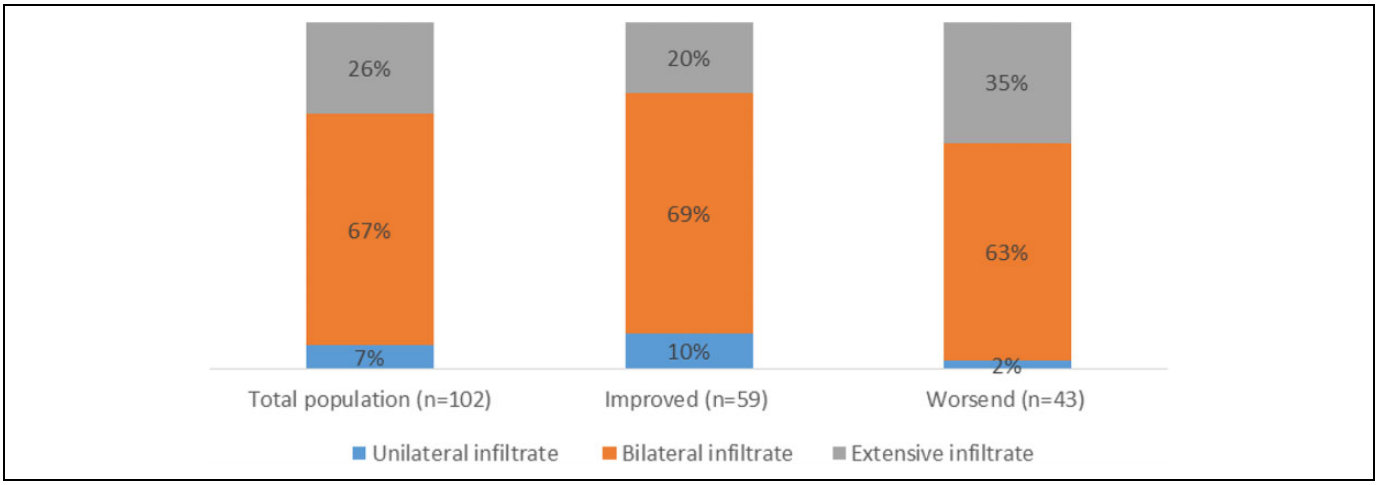


**Figure 2.** Chest X-ray findings in participants who improved and worsened (required critical care).

treatment groups (Table 1) or any of the studied variables. However, most improvements in the parameters were attributed to patients who received Tocilizumab (Figure 3).

### *Severity*

Most of the patients (93%, $n = 40$) who did not improve had severe ARDS (PaO2/FiO2 <100) and only 7%, $n = 3$ had either mild or moderate ARDS (Figure 4).

### *Cytokine Storm Syndrome [Ferritin: >600, LDH > 250, DD > 1 and IL-6 > 3× Upper Limits]:*

Eighteen patients were severely ill with all the criteria in place more than half were from the category who received Tocilizumab (56%, $n = 10$), followed by both (28%, $n = 5$) and then plasma (17%, $n = 3$).

### *Treatment*

In average, plasma was introduced at day 3.7(4.8) from admission, whereas Tocilizumab was introduced at day 7.8(5.1). All patients received steroid, antibiotics and Heparin. However, Mean number of doses of hydroxychloroquine, Kelatra, interferon, hydrocortisone, dexamethasone, and heparin was significantly higher in patients who improved compared to those who did not improve [5.2(6.5) vs 1.74(3.3) P = 0.03, 4.3(5.5) vs 1.9(3.4) P = 0.02, 0.6(1.1) vs 0.4(0.8) P = 0.04, 8.4(11.3) vs 3.5(6.8) P = 0.01, 4.9(4.5) vs 2.1(2.3) P = 0.04, 11.8(6.8) vs 5.2(5.6) P = 0.02] respectively (Figure 5).

### *Hospital Stay*

There was a statistically significant difference in the mean hospital stay between the improved and worsened cases across all treatment categories [at the population level: 8.2(5.0) improved vs 4.7(3.7) worsened-$P < 0.001$, for Plasma group 9.8(2.3) improved vs 4.1(2.9) worsened-$P < 0.001$, for Tocilizumab10.9 (5.2) improved vs 4.7(4.4) worsened-$P \leq 0.001$, for both 11(3.3) improved vs 5.3(1.9) worsened-$P = 0.001$].

## Discussion

This descriptive study looked at the characteristics of the first 102 patients with pneumonia admitted at Al-Nahdha hospital who received Plasma, Tocilizumab or both and their clinical outcome whether improved or worsened. Generally, the population was mostly males, and the mean age was 52 years. More than half of the population were Omanis. Results from this study showed that between-group differences in the proportion of patients who improved vs worsened across the 3 treatment groups were not significant. It is therefore fair to say that the differences in the effect of using CP or Tocilizumab or both on preventing the need for critical care were not different. Additionally, the lack of randomised control studies in the literature makes this comparison inconclusive.[18,19] However, there was a borderline to strong significant within-group difference in the proportion of patients who improved vs worsened in the CP treatment group (P = 0.05) and Tocilizumab (0.03), respectively. This finding supports the potential clinical benefits of these drugs in lowering the rates for critical care. None the less, it is important to note that many countries are facing a shortage

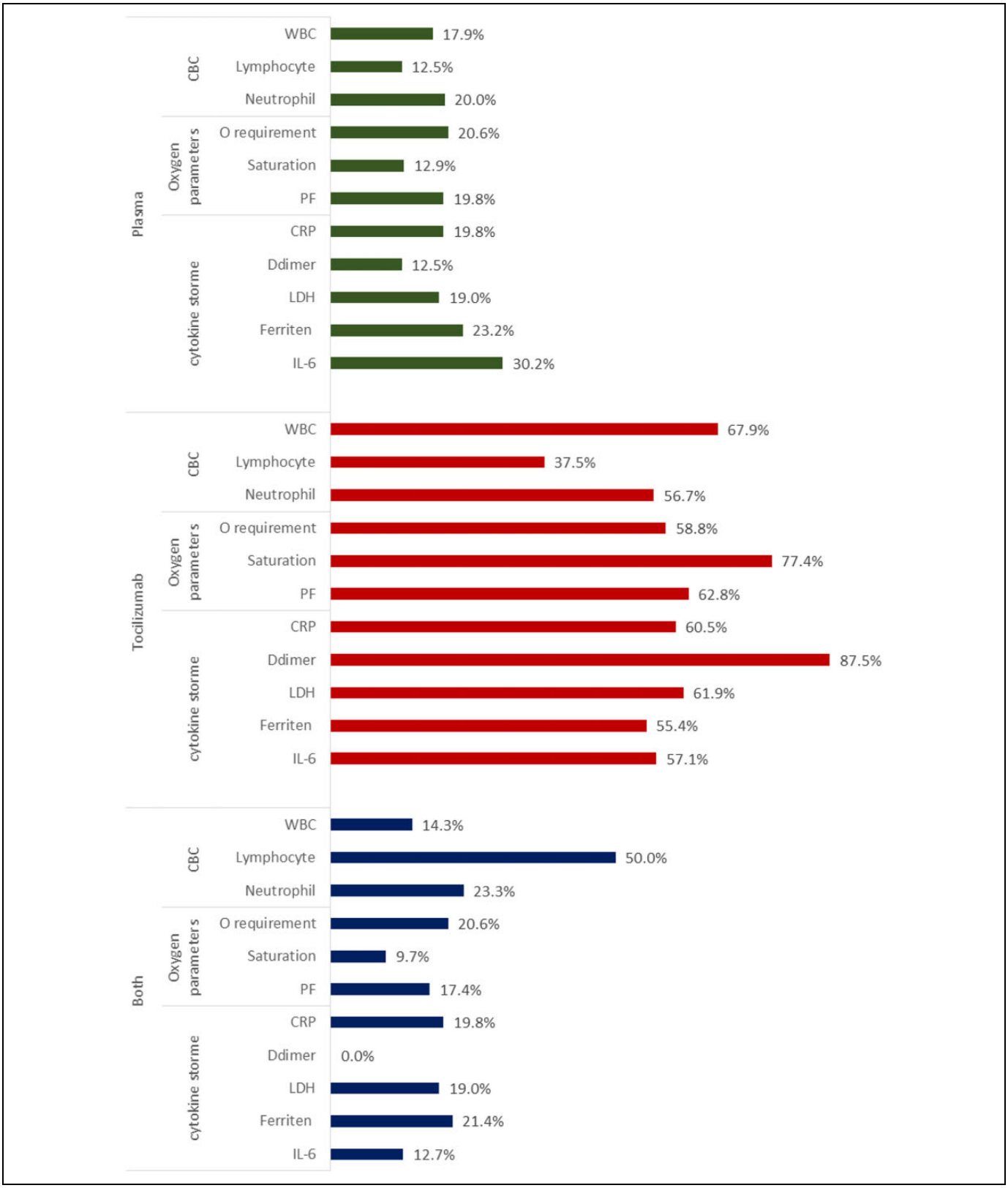


**Figure 3.** Improvements in CBC (total WBC, lymph and neutrophil counts), oxygen and immune response "cytokine storm" per treatment group.

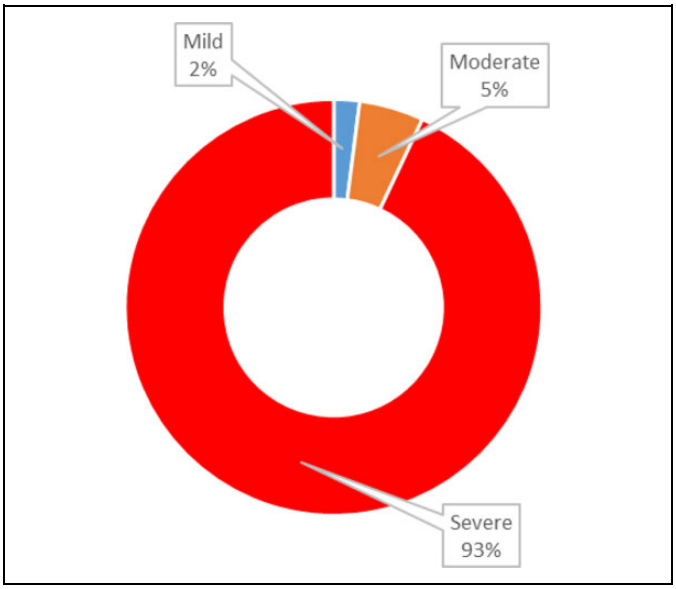


**Figure 4.** RDS categories among the study participants.

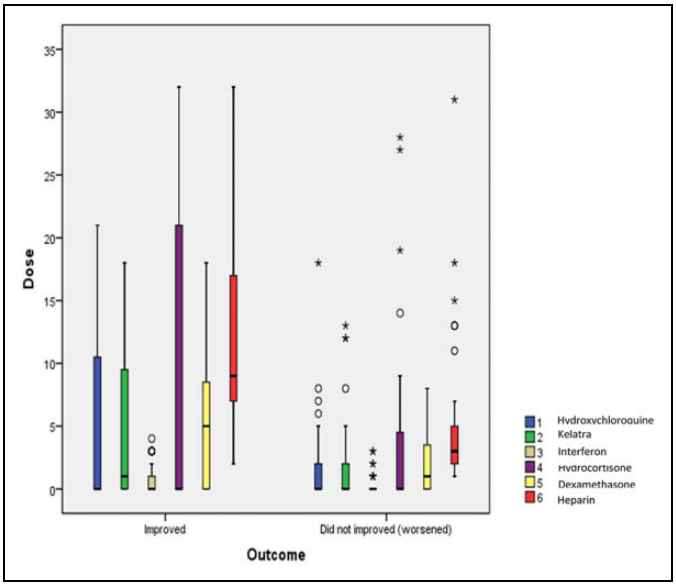


**Figure 5.** Mean number of doses of hydroxychloroquine, Kelatra, Interferon, Hydrocortisone, Dexamethasone, and Heparin in the patients with COVID-19 who improved vs those who worsened.

of mechanical ventilators.[18,19] This shortage could lead to difficult clinical choices about which patients to prioritize for treatment. Consequentially, a treatment that reduces ICU admission is highly relevant not only to ameliorate the prognosis of the hospitalized patients but also to allow more patients to receive intensive care when needed. Similarly, a cohort study on the use of CP of over 35,000 hospitalized patients with COVID-19 in the USA reported significant associations between using CP with lower observed rates of 7-day and 30-day mortality.[19] Other recent exploratory study reported potential therapeutic benefits of CP in the management of COVID-19.[20] Another study involving a course of high-dose methylprednisolone, with or without Tocilizumab, showed a significant acceleration in respiratory recovery, lower hospital mortality and reduced likelihood of invasive mechanical ventilation in COVID-19-associated cytokine storm syndrome.[21] However, no longitudinal studies were reported in the current literature that compared the use of CP or Tocilizumab or both. Interestingly, this study showed that the overall improvements in the studied parameters post-treatment (CP, Tocilizumab or both) were mostly attributed to the Tocilizumab group. Similar studies Tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0.61, 95% CI 0.40–0.92; $p = 0.020$). 24 (13%) of 179 patients treated with Tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone ($p < 0.0001$).[22] Thus, longer follow-up and larger sample sizes were recommended to better understand the prognostic role of IL-6 concentrations and other biomarkers in patients with COVID-19 pneumonia who are treated with Tocilizumab.

In average, CP was introduced at day 3.7(4.8) whereas Tocilizumab at day 7.8(5.1) from admission. This finding was expected because Tocilizumab competitively blocks IL-6 receptors to relive the cytokine storm, which usually happens at the latter stages of the disease. Longer hospitalization was noted in patients who improved because patients who worsened were transferred to other hospitals for critical care and thus antibiotics, steroids, Kelatra and Heparin were introduced for longer duration in the improved patients.

### *Limitations of the Study*

This study has several limitations. First, it is not a randomised comparison, and thus confounding effect cannot be ruled out. The patients who received CP or Tocilizumab or both treatments were mainly selected based on the availability of the drug and adjustments in the national COVID-19 management guidelines (which was changing over the recruitment phase).

Another limitation is that some of the biomarkers of inflammation and coagulation were not available for all patients. Using the average imputation technique to deal with the missing values may have jeopardized the data. Finally, the side effects of the treatments were not explored.

On the other hand, this study has strengths that need to be highlighted. First, it included patients from a real-life hospital setting. Second, the introduction of the treatments was closely monitored as it was introduced under strict drug administration protocols. Additionally, results from this study have informed further research to consider the effectiveness of the COVID-19 treatment protocols.

## Conclusion

This is the first study in Oman that explored the compared the use of CP or Tocilizumab or both in severe cases of COVID-19. Despite lack of effect between the treatment groups on the

proportion of patients who improved vs worsened, this study showed significant within-group differences in the proportion of patients who improved vs worsened in mostly the Tocilizumab treatment group. Results from this study indicate that both treatments might be capable of reducing the risk of invasive mechanical ventilation in patients with severe COVID-19 pneumonia. However, despite promising results, randomised studies are warranted.

## Authors' Note

SA supervised the analysis of this data, interpreted the data and wrote the manuscript. MO, NA, and TA reviewed, participated in data collection and data analysis. ZA, TA, SA, and MA reviewed the manuscript and finalized references. All authors read and approved the final manuscript. Data generated from this study is not available for public use. However, it is available from the corresponding author on reasonable request and approvals from the Oman Ministry of Health. Ethical approval was obtained from the Regional Research Committee in the Ministry of Health based on secondary data collection.

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## Declaration of Conflicting Interests

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## Supplemental Material

Supplemental material for this article is available online.

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