

ORIGINAL PAPER  
RESPIRATORY MEDICINE

# Therapeutic efficacy, mechanical ventilation, length of hospital stay, and mortality rate in severe COVID-19 patients treated with tocilizumab

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**Abstract****Background:** The treatment of severe cases of COVID-19 disease remains a dilemma so far, because there is no approved therapy for it. This study aimed to estimate the therapeutic efficacy of tocilizumab and its role in reducing the need for mechanical ventilation, length of hospital stay, mortality rate for these cases.**Method:** The study included 25 adult patients with confirmed severe COVID-19 infection. Treatment of all patients followed Egyptian Ministry of Health COVID-19 protocol in addition to tocilizumab IV (400-800 mg) as a single dose and then the dose was repeated after at least 12 hours and up to 24 hours from the previous dose. All laboratory and clinical parameters were assessed before and within 24 hours after tocilizumab administration.**Results:** After receiving TCZ, all patients showed significantly lower median IL 6, LDH, CRP, ferritin, TLC at  $P < .001$ , and D-Dimer at  $P = .223$  than their baseline levels. Also, the number of patients who required mechanical ventilation decreased from 11 to 8. Only five patients died after TCZ treatment. A moderate correlation was found between therapeutic failure and death outcomes and mechanical ventilation need at baseline. The median days of hospitalisation (IQR) were 10 (6-16).**Conclusion:** Tocilizumab treatment in patients with severe COVID-19 is safe and has significant therapeutic effects and a significant role in the improvement of all laboratory parameters. Also TCZ plays a significant role in the reduction of the length of stay in hospital and ICU, need for mechanical ventilation, and mortality rate.

## 1 | INTRODUCTION

The COVID-19 patients are very different in the progression of their disease; some of them are asymptomatic, while others may develop a multiorgan systemic failure syndrome. In some studies, the worse outcome and high levels of interleukin 6 (IL-6) that shown in critically ill patients were attributed to cytokine release syndrome (CRS).<sup>1,2</sup>

Acute respiratory distress syndrome (ARDS) is recognised in about 6%-10% of COVID-19 patients with an increased rate of mortality.<sup>3</sup> The inflammatory cytokine release syndrome is the

hallmark of the ARDS, in which the substantial role is attributed to IL-6. Consequently, IL-6 is one of the most significant inflammatory markers released during COVID-19 induced cytokine storm.<sup>4,5</sup> Other inflammatory markers that have been detected in the laboratory abnormalities of COVID-19 patients are increased serum ferritin, C-reactive protein, erythrocyte sedimentation rate, and lymphocytopenia.<sup>6</sup>

D-Dimer is used with IL-6 to estimate severe cases of COVID-19. Consequently, measuring their levels can be very beneficial in the diagnosis of severe COVID-19 patients.<sup>4</sup> Estimating COVID-19

severity can also be defined on the basis of hypoxia ( $\text{SpO}_2 \leq 93\%$ ), respiratory distress, or abnormal blood gas analysis ( $\text{PaO}_2$  50 mmHg).<sup>6</sup>

Currently, antiviral therapy such as hydroxychloroquine, remdesivir, ritonavir, and lopinavir are considered for severe COVID-19 treatment. Lately, steroids such as methylprednisolone have been considered as a standard of treatment.<sup>7</sup>

Tocilizumab (TCZ) is a recombinant monoclonal antibody that antagonises the IL-6 receptor. The ability of TCZ to block inflammatory response mediated with IL-6 in severe COVID-19 patients, made it one of the potential treatments in severe cases. TCZ effect in severe COVID-19 patients has been evaluated in various studies and there was a marked laboratory and clinical improvement of these patients.<sup>8-11</sup>

TCZ is considered a type of biological disease-modifying anti-rheumatic drug. Consequently, it increases the risk of serious infections as it weakens the innate immunity.<sup>12,13</sup> Several studies, carried on COVID-19 patients using TCZ, had different opinions about its adverse effects. One study reported that TCZ treatment did not cause any obvious adverse effects,<sup>8</sup> while another study reported worsened symptoms and severe infection in elderly patients treated with TCZ and attributed this effect to the increased risk of bacterial and viral infection because of the suppression of body immunity.<sup>14</sup>

Until now, tocilizumab is not approved officially in the treatment of COVID-19. We conducted this study to evaluate the therapeutic effect of TCZ and its effect on clinical and laboratory parameters, the mortality rate, and the length of stay in hospital in patients with severe COVID-19.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design and participants

The study included 25 adult patients aged  $\geq 18$  years with confirmed severe COVID-19 infection between June 1, 2020, and June 30, 2020, from Teacher's Hospital, Cairo, Egypt.

### 2.2 | Clinical classification and clinical follow-up

Egyptian Ministry of Health COVID-19 protocol is used as a guideline for triaging and therapeutic management of COVID-19 cases. COVID-19 diagnosis is confirmed by nasopharyngeal swab RT-PCR. Moderate and severe patients are admitted for hospitalization, while mild cases were advised for home care and isolation. Treatment plan included Hydroxychloroquine (400 mg twice on the first day then 200 mg twice for 6 days) as standard therapy to be initiated on admission, steroids (Methylprednisolone 1-2 mg/kg/day) added in case of therapeutic failure or oxygen desaturation on admission. TCZ is considered in severe cases where CRS diagnosis is confirmed, glucocorticoids therapeutic failure, disease progression or persistent oxygen desaturation.

#### What's known

- IL-6 plays the main role in the acute respiratory distress syndrome (ARDS) associated with severe COVID-19 infection. Consequently, serum IL-6 can be considered as an important target in therapeutic management of severe COVID-19 patients.

#### What's new

- Prospective study, carried on 25 adult patients with confirmed severe COVID-19 infection using tocilizumab, showed significant improvement in their case.
- Tocilizumab, as an IL-6 inhibitor, not only lowered IL-6 level but also showed a significant reduction on median LDH, CRP, ferritin, TLC at  $P < .001$  and D-Dimer at  $p = .223$  than their baseline levels.
- Improvement of all laboratory parameters using TCZ was reflected in the reduction of the length of stay in hospital and ICU, need for mechanical ventilation and mortality rate.

Inclusion criteria included the following: (A) COVID-19 infection polymerase confirmed with chain reaction (PCR); (B) pulmonary involvement which was determined by oxygen saturation ( $\text{SaO}_2$ ) of  $< 92\%$  when breathing ambient air, or respiratory rate (RR)  $> 30$ , or  $\text{PaO}_2/\text{FiO}_2$  ratio  $< 300$ .

Patients received TCZ I.V according to their weights (weight  $> 40$  to  $\leq 65$  kg: 400 mg as a single dose, weight  $> 65$  and  $\leq 90$  kg: 600 mg as a single dose; and weight  $> 90$  kg: 800 mg as a single dose; the dose was repeated in  $\geq 12$  to  $< 24$  hours if patient's condition has not improved).

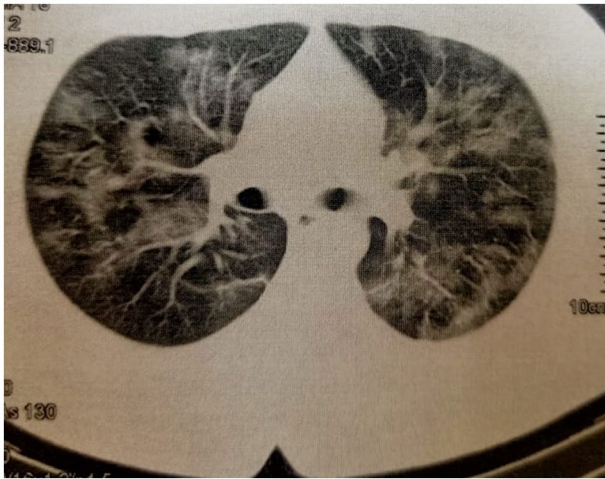
The improvement in symptoms was the primary end-point, while the laboratory and respiratory parameters improvements were the secondary end-points. Pre and post-analysis of clinical response, safety outcomes and laboratory parameters which included D-dimer; C-reactive protein (CRP) values; ferritin; LDH, Absolute Lymphocyte count, TLC and IL-6 levels, were determined within 24hr after TCZ administration for all patients.

### 2.3 | Chest computed tomography

Chest computed tomographic (CT) scans were carried out for COVID-19 patients and analysed (Figure 1). All patients had chest radiology showing more than 50% lesion or progressive lesion.

### 2.4 | Statistical analysis

Descriptive analysis was performed where continuous variables were reported as median with interquartile range (IQR). A Wilcoxon



**FIGURE 1** CT image of a 49-years-old man showing bilateral, ground-glass opacities seen at both lung fields with peripheral basal predominance

Signed Ranks test was used to compare continuous data before and after TCZ administration. Categorical variables were compared using the McNemar test. Correlations between study findings (clinical parameters and outcomes) and baseline patient characteristics were identified with pairwise Kendall rank correlation coefficients. Significance was defined as  $P < .05$ . All tests were performed using SPSS v17.0 (SPSS, Chicago, USA).

## 2.5 | Ethics statement

The study was carried out after approval from the Research Ethical Committee of the faculty of Pharmacy, Beni-Suef University with serial number (REC-H-PhBSU-20014). Informed written consent was taken from each study subject and they were informed that their participation is voluntary and they can withdraw from the study at any time. The study was performed according to the good clinical practices recommended by the Declaration of Helsinki and its amendments.

## 3 | RESULTS

### 3.1 | Demographics and patient clinical features (Table 1)

During the period from 1st of June till 30 of July 2020, 25 patients (21 males), age 55 (46-76) were admitted to the hospital with confirmed COVID-19 diagnosis by nasopharyngeal swab testing using RT-PCR. Patients were categorised into severe cases ( $\text{SaO}_2 < 92\%$ ) according to local MOH protocol. No one showed acute cardiac injury or cardiac arrest at admission. Twelve (48%) patients showed fever (temperature  $> 38^\circ\text{C}$ ) on the day of therapy initiation. The clinical characteristics of patients at baseline were illustrated in Table 1.

**TABLE 1** Baseline demographics

Characteristics	N = 25
Age (y)*	55 (46-76)
Age category, no. (%)	
<50 year	8 (32%)
50-70	13 (52%)
>70	4 (16%)
Gender (Male), no. (%)	21 (84%)
BMI ( $\text{Kg}/\text{m}^2$ )	29.3 (24-25.3)
Max temperature, Celsius	38 (37.5- 39)
Procalcitonin, ng/dL	0.3 (0.16-0.47)
Serum Creatinine, mg/dL	1.1 (1.2-1.7)
Potassium, mEq/L	4.1 (3.6-4.3)
Oxygen saturation ( $\text{SaO}_2$ )	85 (69.5-89.5)
Smoking, no. (%)	2 (8%)
Hypertension, no. (%)	16 (64%)
Diabetes, no. (%)	12 (48%)
Ischemic Heart Disease, no. (%)	8 (32%)
Chronic Kidney Disease, no. (%)	2 (8%)
Asthma, no. (%)	3 (12%)
Hypothyroidism, no. (%)	2 (8%)
Heart failure, no. (%)	1 (4%)
Atrial Fibrillation, no. (%)	2 (8%)
Chronic Obstructive Pulmonary Disease, no. (%)	1 (4%)
Other comorbidities, no. (%)	3 (12%)

Note: Data are expressed as median (interquartile range (IQR)), No. (%).

### 3.2 | Patients comorbidities

Comorbidities were present in most patients and hypertension was the most common one (64%) followed by diabetes (48%) and ischemic heart disease (32%). All patients' comorbidities are illustrated in Table 1.

### 3.3 | CT scan

All patients showed pneumonic radiological findings (ground-glass opacities).

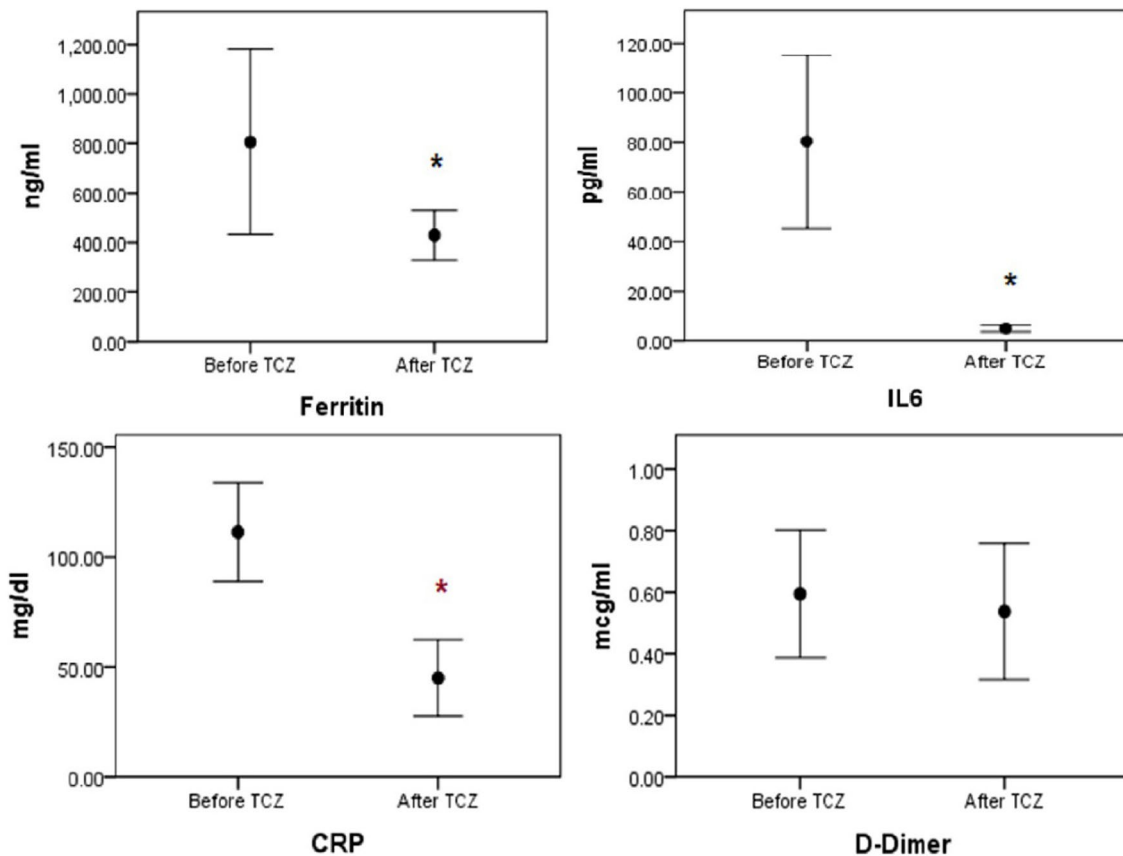
### 3.4 | The effect of tocilizumab on clinical and laboratory parameters (Table 2, Figure 2)

Nineteen (76%) patients required intensive care unit (ICU) admission. After receiving TCZ, all patients showed improvement in symptoms and oxygen saturation. A comparison was set between laboratory findings before and after TCZ administration as showed in Table 2. No adverse effects or complications were recognised

**TABLE 2** Laboratory tests before and after TCZ

Laboratory tests	Before TCZ	After TCZ	Significance (P-value)
Interleukin 6, pg/mL	57 (15.9-114)	4.9 (2-6.8)	<.001
D-Dimer level, $\mu\text{g/mL}$	0.43 (0.24-0.75)	0.3 (0.2-0.84)	.223
Lactate dehydrogenase level, IU/L	518 (409-744)	366 (269.5-469)	<.001
C-reactive protein level, mg/dL	96.6 (80.4-139.2)	29 (10-77.5)	<.001
Ferritin level, ng/mL	487 (369.5-1007.5)	386 (254.5-527.5)	<.001
Total leukocyte count(IQR), cells/ $\mu\text{L}$	10 000 (5350-12850)	7.6 (5.8-10.6)	<.001
Absolute Lymphocyte count, %	9 (5.5-15)	12 (8-20)	.135
Mechanical ventilation, no. (%)	11 (44%)	8 (32%)	.453

Note: Data are expressed as median (interquartile range (IQR)), No. %.



**FIGURE 2** Laboratory results before and after administering tocilizumab (data expressed as mean and SEM, (\*) the difference is significant at  $P < .001$ )

with all patients after receiving TCZ. Patients after receiving TCZ, showed significantly lower median IL 6 (4.9 vs 57 pg/mL), lower median LDH (366 vs 518 IU/L), lower CRP (29 vs 96.6 mg/dL), lower median ferritin level (386 vs 487 ng/mL) and lower median TLC (7.6 vs 10 000) at  $P < .001$  than their baseline levels (pre-TCZ) as shown in Figure 2. Also, patients exhibited lower median D-Dimer level after receiving the drug (0.3 vs 0.43 mcg/mL,  $P = .223$ ) when compared with its baseline level but the difference was not significant.

### 3.5 | Relation between patient demographics, patient comorbidities, and laboratory parameters

Correlations between patient demographics and laboratory finding after TCZ administration were studied. The patient age showed a weak correlation with both TLC and LDH levels post-TCZ ( $r = 0.292$  and  $0.302$ , respectively at  $P < .05$ ), while BMI was weakly correlated with ferritin level after receiving the drug ( $r = -0.410$ ,  $P = .005$ ). Also, weak correlations were found between patient comorbidities and

post-TCZ laboratory findings: hypertension and IL6 ( $r = 0.426$ ,  $P = .013$ ), chronic kidney disease and D-Dimer ( $r = -0.348$ ,  $P < .05$ ) and atrial fibrillation and D-Dimer ( $r = 0.374$ ,  $P = .031$ ).

Correlation between patient demographics and the extent of patient response was displayed where the extent of response was calculated as the difference between pre-lab results and post-lab results (Delta). Weak correlations were identified between age and Delta lymphocyte count ( $r = 0.439$ ,  $P = .028$ ) and between mechanical ventilation need and Delta ferritin ( $r = -0.402$ ,  $P < .05$ ). On the other hand, Delta c-reactive protein was moderately correlated with COPD comorbidity and immunosuppression ( $r = -0.503$ ,  $P = .01$  for both).

### 3.6 | Hospitalisation, mechanical ventilation, and therapeutic failure

The number of patients who required mechanical ventilation, decreased 12 hours after receiving TCZ than before its use (8 (32%) vs 11(44%),  $P = .453$ ). The median days of the hospitalisation (IQR) was 10(6-16) and no one needed vasopressor support during this period. The hospital stay length showed a weak correlation with baseline oxygen saturation ( $r = -0.365$ ,  $P = .014$ ). Therapeutic failure was identified in six (24%) of patients were five (20%) of them died despite the drug use. A moderate correlation was found between therapeutic failure and death outcomes and mechanical ventilation need at baseline ( $r = 0.618$  for therapeutic failure and  $r = 0.657$  for death at  $P < .01$ ). There was no correlation between the therapeutic failure, death outcomes, and the comorbidities of patients.

## 4 | DISCUSSION

In the present study, the effect of TCZ was prospectively observed in the treatment of 25 patients with severe COVID-19. The effects of TCZ on inflammatory markers were observed after a short time from starting TCZ treatment. TCZ not only observed as anti-IL-6 receptor antibody but also made a significant reduction in other inflammatory markers such as LDH, ferritin, D-Dimer and total leukocyte count. This was reflected in decreased number of patients who required mechanical ventilation after receiving TCZ.

All patients with severe COVID-19 who included in the study showed rapid improvement in laboratory and respiratory parameters. This confirms the findings of the previous study that considered TCZ as a safe option for hospitalised adult patients with severe COVID-19 and confirmed its therapeutic benefit through laboratory and respiratory parameters improvement.<sup>15</sup>

Unfortunately, the symptoms of patients with severe COVID-19 usually deteriorate rapidly and even end with respiratory failure. Consequently, the need for oxygen therapy and mechanical ventilation in these patients increases resulting in increasing admission in the ICU and mortality rate of 4.3 to 11% despite of using the recommended standard treatment.<sup>16,17</sup> Also, a previous study reported

a mortality rate of 60.5% in critical cases,<sup>18</sup> while another study, in Italy, reported a 26% ICU mortality rate in critically ill COVID-19 patients.<sup>19</sup> While in the present study the situation was found to be different as only five patients of the 25 ones were died representing about 20% of the studied patients and all of them needed mechanical ventilation and there was no correlation between the mortality rate and the comorbidities of these patients. This is a reasonable ratio compared with other treatments in critical cases.

The present study showed a significant improvement in the level of IL-6 between the hospital admission and after 24 hours of TCZ treatment. Consequently, initial and immediate evaluation of the level of IL-6, upon hospital admission and after initiating treatment, is very important for assessing the disease progression and the worsening of clinical features in COVID-19 patients. This is attributed to the significant role played with IL-6 in the severe respiratory distress in patients with severe COVID-19.<sup>20</sup>

The number of patients who required mechanical ventilation decreased after using TCZ and the length of hospital stay was short as the median days of hospitalisation (IQR) was 10(6-16). This confirms that TCZ administration shortens the length of stay in hospital in severe COVID-19 patients. Also, TCZ reduces the length of stay in ICU in COVID-19 patients with ARDS and this will lead to reducing the risk of invasive mechanical ventilation and death in these patients.<sup>11</sup>

### 4.1 | Limitation of the study

The study did not include a control group in which patients could receive the treatment plan of the Egyptian Ministry of Health COVID-19 protocol without the addition of tocilizumab.

## 5 | CONCLUSION

Our findings indicate that the TCZ treatment of critically ill patients with severe COVID-19 and ARDS has significant therapeutic effects which have been reflected in an improvement in all laboratory parameters especially IL-6 and a reduction of the length of stay in hospital thus in mechanical ventilation and ICU. Also, treatment with TCZ seems to be safe and effective in reducing the mortality rate in severe COVID-19 patients.

### DISCLOSURE

None.

### DATA AVAILABILITY STATEMENT

Data available on request from the authors.

### ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## AUTHOR CONTRIBUTIONS

Conception and design: All authors. Administrative support: All authors. Provision of study materials or patients: All authors. Collection and assembly of data: All authors. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

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