


## RESEARCH ARTICLE

# Early use of tocilizumab in the prevention of adult respiratory failure in SARS-CoV-2 infections and the utilization of interleukin-6 levels in the management

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**Abstract**

Respiratory failure in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appears related to cytokine release syndrome that often results in mechanical ventilation (MV). We investigated the role of tocilizumab (TCZ) on interleukin-6 (IL-6) trends and MV in patients with SARS-CoV-2. In this longitudinal observational study, 112 patients were evaluated from 1 February to 31 May 2020. TCZ was administered followed by methylprednisolone to patients with >3L oxygen requirement and pneumonia severity index score  $\leq 130$  with computed tomography scan changes. IL-6, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimer, and procalcitonin were monitored on days 0, 3, and 6 of therapy. Statistical analyses were performed with significance  $\leq 0.05$ . Eighty out of 112 SARS-CoV-2-positive patients (45 males, 56.96%; 34 females, 43.04%) were included in this study. Seven patients expired (8.75%) and nine patients required MV (11.25%). Median IL-6 levels pre-administration of TCZ was 342.50 (78.25–666.25) pg/mL compared with post-administration on day 3 (563; 162–783) pg/mL ( $P < .00001$ ). On day 6, the median dropped to 545 (333.50–678.50) pg/mL compared with day 3 ( $P = .709$ ). CRP, ferritin, LDH, and D-dimer levels were reduced after TCZ therapy. Early use of TCZ may reduce the need for MV and decrease CRP, ferritin, LDH, and D-dimer levels. The sequential use of methylprednisolone for 72 hours seems to potentiate the effect and prolong the suppression of the cytokine storm. IL-6 levels may be helpful as a prognostic tool.

**KEYWORDS**

early treatment, IL-6 levels, mechanical ventilation, outcomes, SARS-CoV-2

## 1 | INTRODUCTION

The major pathological hallmark of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the activation of a cytokine release syndrome.<sup>1</sup> It has been suggested that this syndrome is the product of excess inflammatory chemokine release, a few of which are interleukin-6 (IL-6), IL-1 $\beta$ , and tumor necrosis factor- $\alpha$ .<sup>1–3</sup>

IL-6 is of particular interest as it is the main cytokine responsible for activating cytokine release syndrome (CRS) and is secreted by stromal and immune cells.<sup>4,5</sup> High expression of IL-6 resulting in CRS has been observed in all three coronavirus subtypes, SARS-CoV-1, Middle East respiratory syndrome, and now SARS-CoV-2.<sup>5</sup> Thus, IL-6 levels could be useful in predicting the severity of SARS-CoV-2.<sup>2,6,7</sup> This is supported by one study, which concluded with statistical

significance that patient with SARS-CoV-2 mortality was higher with increasing mean IL-6 values.<sup>1</sup> Hence, physicians should monitor IL-6 levels and use it as a prognostic guide for SARS-CoV-2 disease. However, due to its IL-6 inhibition and ability to limit the extent of proinflammatory states, we propose the use of tocilizumab (TCZ) in an attempt to avoid worsening respiratory failure which may require intubation due to its IL-6 inhibition and potential ability to limit the extent of the proinflammatory state. TCZ is a humanized anti-IL-6 receptor monoclonal antibody that is broadly effective in targeting the two types of IL-6 receptors, membrane-bound (mIL-6R) and soluble (sIL-6R), ultimately blocking both the classical and trans-signaling IL-6 pathways.<sup>4</sup> Our study examines the role of IL-6 in evaluating SARS-CoV-2 disease progression and TCZ's efficacy in preventing or reducing the number of patients placed on mechanical ventilation (MV).

## 2 | METHODS

### 2.1 | Literature search, study design, and participants

PubMed, Google Scholar, and Medline were used for database collection and literature review on SARS-CoV-2 disease, IL-6, and TCZ. SARS-CoV-2-positive patients from four different hospitals in El Paso, Texas were included within this longitudinal observational study from the period of 1 February to 31 May 2020. One hundred and twelve SARS-CoV-2-positive patients were evaluated in this study. Our inclusion criteria were patients with positive SARS-CoV-2 polymerase chain reaction (PCR), >18 years old, oxygen (O<sub>2</sub>) supplement of >3L, pneumonia severity index (PSI) score ≤130 with computed tomography (CT) scan changes. Exclusion criteria were negative SARS-CoV-2 PCR, mechanically ventilated patients, end-stage comorbid conditions, such as cardiomyopathy, cardiac arrhythmia, cancer, septic shock, end-stage renal disease, O<sub>2</sub> supplement of <3L, PSI score >130.

### 2.2 | Procedures

TCZ 4 mg/kg/day q12hr was given to patients within the first 24 hours of hospitalization followed by methylprednisolone 60 mg q8hr for 72 hours. No medications were added to the treatment except for methylprednisolone. Demographic data, medical history, and clinical outcomes were collected from all patients included in this study. Labs monitored on days 0, 3, and 6 included IL-6, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimer, procalcitonin, complete blood count, complete metabolic panel, and blood and urine cultures if fever occurred. All patients had chest x-rays or CT scans upon admission and subsequent imaging studies as needed. The duration of hospital stay was monitored for each patient.

## 2.3 | Statistical analysis

Data were retrieved from electronic health records and computed using Excel 365 version. The Excel-computed data were imported into statistical software, Stata/IC 16.0 for data analysis. Descriptive statistics were presented in frequency and percentages. Shapiro-Wilk normality test for continuous variables showed that the distribution of data was non-normal, therefore, median (interquartile range) were used as values for the summary statistics. The Wilcoxon signed-rank test was used for associating differences in median values for selected independent variables before and after TCZ treatment. Fisher's exact test was used for associating categorical variables with values less than 5. An observation is said to be statistically significant if  $P \leq .05$ . The National Heart, Lung, and Blood Institute's<sup>8</sup> study quality assessment tool was used to analyze the validity of the referenced literature case studies in Table 1.

## 3 | RESULTS

Eighty out of 112 SARS-CoV-2-positive patients (45 males, 56.96%; 34 females, 43.04%) were included in this study. The general socio-demographic characteristics, medical history, and clinical presentations of patients with SARS-CoV-2 treated with TCZ are summarized in

**TABLE 1** National Heart, Lung, and Blood Institute<sup>8</sup> criteria for quality assessment of previously published SARS-CoV-2 studies

Criteria <sup>a</sup>	Study			
	Luo et al <sup>9</sup>	Di et al <sup>10</sup>	Michot et al <sup>11</sup>	Zhang et al <sup>12</sup>
1.	+	-	-	-
2.	+	+	+	+
3.	+	+	+	+
4.	+	+	N/A	N/A
5.	+	+	+	+
6.	-	-	-	-
7.	CD	CD	CD	CD
8.	+	-	-	-
9.	+	-	-	-
Quality rating <sup>b</sup>	7	4	3	3

Abbreviations: (+), yes; (-), no; CD, cannot determine; NA, not applicable; NR, not reported; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>National Heart, Lung and Blood Institute<sup>8</sup> Criteria included the following: (a) Was the study question or objective clearly stated?; (b) Was the study population clearly and fully described, including a case definition?; (c) Were the cases consecutive?; (d) Were the subjects comparable?; (e) Was the intervention clearly described?; (f) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?; (g) Was the length of follow-up adequate?; (h) Were the statistical methods well-described?; (i) Were the results well-described?

<sup>b</sup>Quality rating<sup>8</sup> was determined to be good (7-9), fair (4-6), or poor (≤3).

**TABLE 2** General sociodemographic characteristics, medical history, and clinical presentations of SARS-CoV-2 patients treated with TCZ

Characteristics	Frequency (n = 80)	Percentage (%)	Characteristics	Frequency (n = 80)	Percentage (%)
Age			Fever		
<30 <sup>R</sup>	37	46.84	Yes	53	73.61
30-64	39	49.37	No	19	26.39
≥65	37	46.84	Cough		
Median values (IQR)	63 (51, 72)		Yes	49	68.06
Sex			No	23	31.94
Male	45	56.96	Shortness of breath		
Female	34	43.04	Yes	62	86.11
Race/ethnicity			No	10	13.89
Hispanic	44	57.14	Other symptoms		
White/Hispanic	25	32.47	Yes	42	58.33
White/non-Hispanic	3	3.90	No	30	41.67
White/none listed	2	2.60	Total number of symptoms		
White	1	1.30	≤2	20	27.78
Black/non-Hispanic	1	1.30	3 or more	52	72.22
Caucasian	1	1.30	Median values (IQR)	3 (2-5)	
Diabetes			Bacterial coinfection		
Yes	37	51.39	Yes	12	15.00
No	35	48.61	No	68	85.00
Hypertension			Multiorgan damage		
Yes	47	65.28	Yes	10	12.50
No	25	34.72	No	70	87.50
Hyperlipidaemia			Travel history		
Yes	18	25.00	Yes	11	15.71
No	54	75.00	No	59	84.29
Other comorbidities			Contact history		
Yes	31	43.05	Yes	34	48.57
No	41	56.94	No	36	51.43
Total number of comorbidities					
≤2	46	63.89			
3 or more	26	36.11			
Median values (IQR)	2 (1-3)				

Abbreviations: IQR, interquartile range; n, number of patients; %, percentage of patients; R, reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.

Table 2. The median age was 63 (51-72) years. We have categorized the age into three age groups: <30 years (46.84%), 30 to 64 years (49.37%), and ≥65 years (46.84%). Most patients were Hispanic (44, 57.14%), followed by White/Hispanic (25, 32.47%), which can be mainly

attributed to the fact that the population of El Paso is predominately Hispanic. In assessing the number of patient comorbidities during the initial presentation, those with ≤2 illnesses were 63.89%, and those with 3 or more illnesses were 36.11%, with a median of 2 illnesses (1-3).

**TABLE 3** Clinical outcomes among SARS-CoV-2 patients treated with TCZ

Clinical outcomes	Frequency (n = 80)	Percentage (%)
Mortality		
Yes	7	8.75
No	73	91.25
Use of mechanical ventilation		
Yes	9	11.25
No	71	88.75

Abbreviations: n, number of patients; %, percentage of patients; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.

The majority of these comorbidities were hypertension (65.28%) and type II diabetes mellitus (51.39%). In addition, the total number of symptoms on admission were  $\leq 2$  symptoms (27.78%), and 3 or more clinical symptoms (72.22%), with a median of 3 symptoms (2-5). Shortness of breath was the most common presenting symptom (86.11%) followed by fever (73.61%) and cough (68.06%), respectively. Bacterial coinfection was noted in 12 patients (15%) and a limited number of patients encountered Multiorgan damage (10, 12.50%). Recent travel history was reported in 11 patients (15.71%) and 34 patients had positive contact history (48.43%). Clinical outcomes in terms of mortality and use of MV among SARS-CoV-2 patients treated with TCZ are summarized in Table 3. Nine patients (11.3%) were placed on MV, of which 7 (8.7%) expired. The duration of hospital stays ranged from five to 10 days for all patients.

As acute SARS-CoV-2 results in elevated IL-6 levels, we used TCZ in the treatment of these patients. Therefore, the level of IL-6 was monitored before and after the use of TCZ as shown in Table 4. The median IL-6 levels before the administration of TCZ on day 0 was 342.50 (78.25-666.25) pg/mL compared with after administration of TCZ on day 3, 563 (162-783) pg/mL ( $P < .00001$ ), reflecting a significant increase in the level post-TCZ use. There was a drop in the median to 545 (333.50-678.50) pg/mL on day 6 after TCZ treatment, which is considered an 18-point reduction from the median of day 3; however, it did not show any statistical significance (either increase or decrease) in comparison to day 3 ( $P = .709$ ). However, in comparing

day 0 to day 6, we noted a statistically significant increase post-TCZ ( $P = .006$ ). This elevation can be explained by the ongoing cytokine storm.

Other laboratory findings of SARS-CoV-2 patients treated with TCZ were studied before and after the use of the medication as summarized in Table 5. CRP levels were above the normal range initially before TCZ treatment in most patients and significantly dropped after TCZ therapy in the following days. The median values of CRP at first reporting following TCZ use on day 3 and sequentially on day 6 were significantly decreased compared with pre-TCZ therapy, which dropped from 11 (6-18.75) mg/L on day 0 to 5 (2-13) and 2 (1-4) mg/L on days 3 and 6, respectively ( $P < .00001$ ).

Ferritin and LDH showed no statistically significant reduction between day 0 before TCZ therapy and immediately after TCZ on day 3. However, both showed a statistically significant reduction in their median values on day 6 compared with before the initiation of the medication. Ferritin decreased from 595 (311.25-1022.50) to 432.50 (234-676) ng/mL ( $P = .001$ ). LDH dropped from 364 (278-543) to 328 (234-432) U/L ( $P = .008$ ).

D-dimer did not show any statistical significance before and after TCZ therapy, but there was a statistically significant drop in between day 3 and day 6 following initiation of TCZ. On day 6, D-dimer was 1.2 (0.66-1.84) mcg/mL compared with 1.2 (0.92-2.05) mcg/mL on day 3 ( $P = .03$ ).

Procalcitonin levels were noted to be within the normal range as expected in most of our study population.

In addition, the association of sociodemographic characteristics, medical history, and clinical presentations, with clinical outcomes in terms of mortality and use of MV is illustrated in Table 6. It is interesting to note that patients with SARS-CoV-2 who have had secondary bacterial coinfections showed a statistically significantly higher proportion of deaths than those without coinfections (57.14% vs 42.86%;  $P = .008$ ). Also, SARS-CoV-2-positive patients who experienced multiorgan damage were more susceptible to higher mortality (85.71% vs 5.48%;  $P < .0001$ ).

## 4 | DISCUSSION

In this study of 80 patients, the population was predominately Hispanic and male with presentations of hypoxemia requiring  $>3L O_2$

Variables	Days	Median (IQR)	Wilcoxon signed rank	P value
IL-6	IL-6 d 0 (pre)	342.50 (78.25-666.25)	5.022	$<.00001^*$
	IL-6 d 3 (post)	563.00 (162-783)		
IL-6	IL-6 d 0 (pre)	342.50 (78.25-666.25)	2.750	.006*
	IL-6 d 6 (post)	545 (333.50-678.50)		
IL-6	IL-6 d 3 (post)	563.00 (162-783)	0.374	.709
	IL-6 d 6 (post)	545 (333.50-678.50)		

Note: IL-6, normal 0.0-12.2 (pg/mL)

Abbreviations: IQR, interquartile range; (pre), before TCZ use; (post), after TCZ use; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.

\*Statistically significant ( $P \leq .05$ ).

**TABLE 4** Interleukin-6 (IL-6) levels of SARS-CoV-2 patients before and after TCZ treatment

**TABLE 5** Laboratory findings of SARS-CoV-2 patients at before and after TCZ treatment

Variables	Days	Median (IQR)	Wilcoxon signed rank	P value
C-reactive protein (CRP)	CRP day 0 (pre)	11 (6-18.75)	5.720	<.00001*
	CRP day 3 (post)	5 (2-13)		
	CRP day 0 (pre)	11 (6-18.75)	6.744	<.00001*
	CRP day 6 (post)	2 (1-4)		
	CRP day 3 (post)	5 (2-13)	6.362	<.00001*
	CRP day 6 (post)	2 (1-4)		
Ferritin	Ferritin day 0 (pre)	595 (311.25-1022.50)	0.003	.998
	Ferritin day 3 (post)	558 (368-1009)		
	Ferritin day 0 (pre)	595 (311.25-1022.50)	3.225	.001*
	Ferritin day 6 (post)	432.50 (234-676)		
	Ferritin day 3 (post)	558 (368-1009)	4.536	<.00001*
	Ferritin day 6 (post)	432.50 (234-676)		
Lactate dehydrogenase (LDH)	LDH day 0 (pre)	364 (278-543)	0.969	.333
	LDH day 3 (post)	366 (265-502)		
	LDH day 0 (pre)	364 (278-543)	2.645	.008*
	LDH day 6 (post)	328 (234-432)		
	LDH day 3 (post)	366 (265-502)	3.280	.001*
	LDH day 6 (post)	328 (234-432)		
D-dimer	D-dimer day 0 (pre)	1.065 (0.65-2.3)	0.321	.748
	D-dimer day 3 (post)	1.2 (0.92-2.05)		
	D-dimer day 0 (pre)	1.065 (0.65-2.3)	1.426	.154
	D-dimer day 6 (post)	1.2 (0.66-1.84)		
	D-dimer day 3 (post)	1.2 (0.92-2.05)	2.080	.038*
	D-dimer day 6 (post)	1.2 (0.66-1.84)		

Note: CRP, normal <8.0 (mg/L); ferritin, normal 12 to 300 for males, 12-150 for females (ng/mL); LDH, normal 109 to 245 (U/L); D-dimer, normal <0.5 (mcg/mL).

Abbreviations: (pre), before TCZ use; (post), after TCZ use; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.

\*Statistically significant ( $P \leq .05$ ).

and chest x-rays showing bilateral infiltrates. All patients had evidence of initial elevation of CRP, ferritin, LDH, and D-dimer in keeping with similar findings in published literature. These inflammatory biomarkers all were reduced by day 6 post-TCZ therapy. In contrast, IL-6 levels appeared to be markedly elevated by day 6 of the disease process. However, patients who were given IL-6 inhibitor tended not to progress to MV as 88.75% from our study population did not use MV. This study suggests that TCZ followed by methylprednisolone is useful in the early stages of respiratory distress secondary to SARS-CoV-2. Additionally, IL-6 may be a good indicator for management of the cytokine storm. Moreover, we noted that the addition of steroids appeared to help in reducing the progression of the cytokine storm and the short administration course of steroids has minimized the possible side effects of the medication. We were unable to determine if TCZ would be sufficient alone to treat these patients as the steroids could have enhanced the effects of TCZ.

Currently, the only certain mainstay treatment is not well defined and much of the therapy is based on supportive care.<sup>13</sup> Early treatments included steroids, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, IL-6 inhibitors (TCZ), ivermectin, or other IL-1 inhibitors.<sup>4,7,13-16</sup> This study focuses on the early use of

TCZ, which is a humanized monoclonal antibody that acts by antagonizing both mL-6R and sIL-6R IL-6 receptors, thus inhibiting subsequent proinflammatory effects.

TCZ currently has been used in the treatment of rheumatoid arthritis and CRS from chimeric antigen receptor T-cell therapy.<sup>3,13</sup> These studies showed a resolution of severe fevers, resolution of CRP levels, reduction in the oxygen demand, and improvement in the ground glass opacifications seen on CT scans.<sup>13</sup>

The recommended dose of TCZ is 4 to 8 mg/kg or 400 mg IV 1× dose and an optional second dose 12 hours later not to exceed an 800 mg total dose. Caution is also recommended for immunocompromised patients due to a higher susceptibility of bacterial infection, neutropenia, and thrombocytopenia following TCZ therapy.<sup>13,17</sup> Interestingly, we did not observe any side effects that required stopping TCZ therapy that could be attributed to the short course of the therapy.

In this group of patients, we noticed a few significant findings that were consistent with previous studies including elevated IL-6 levels in acute CRS and elevated CRP, LDH, ferritin, and D-dimer levels.<sup>9-12</sup> As expected, procalcitonin levels were not markedly elevated except when there appeared to be a secondary bacterial

**TABLE 6** The association of sociodemographic characteristics, medical history, and clinical presentations with SARS-CoV-2 clinical outcomes in term of mortality and use of MV

Variables	Mortality			P value	Use of mechanical ventilation			P value
	Yes (n = 7) Freq (%)	No (n = 73) Freq (%)	Total Freq (%)		Yes (n = 9) Freq (%)	No (n = 71) Freq (%)	Total Freq (%)	
Age								
<30 <sup>R</sup>	0 (0)	3 (4.17)	3 (3.80)	.439	0 (0)	3 (4.29)	3 (46.84)	.815
30-64	2 (28.57)	37 (51.39)	39 (49.37)		4 (44.44)	35 (50)	39 (49.37)	
≥65	5 (71.43)	32 (44.44)	37 (46.84)		5 (55.56)	32 (45.71)	37 (46.84)	
Sex								
Male	2 (28.57)	43 (59.72)	45 (56.96)	.133	7 (77.78)	38 (54.29)	45 (56.96)	.286
Female	5 (71.43)	29 (40.28)	34 (43.04)		2 (22.22)	32 (45.71)	34 (43.04)	
Total number of comorbidities								
3 or more	1 (14.29)	25 (38.46)	26 (36.1)	.410	2 (25)	24 (37.50)	26 (36.11)	.702
≤2	6 (85.71)	40 (61.54)	46 (63.89)		6 (75)	40 (62.50)	46 (63.89)	
Total number of symptoms								
3 or more	5 (71.43)	47 (72.31)	52 (72.22)	.998	6 (75)	46 (71.88)	52 (72.22)	.995
≤2	2 (28.57)	18 (27.69)	20 (27.78)		2 (25)	18 (28.13)	20 (27.78)	
Bacterial coinfection								
Yes	4 (57.14)	8 (10.96)	12 (15)	.008*	1 (11.11)	11 (15.49)	12 (15)	.996
No	3 (42.86)	65 (89.04)	68 (85)		8 (88.89)	60 (84.51)	68 (85)	
Multiorgan damage								
Yes	6 (85.71)	4 (5.48)	10 (12.50)	<.0001*	2 (22.22)	8 (11.27)	10 (12.50)	.312
No	1 (14.29)	69 (94.52)	70 (87.50)		7 (77.78)	63 (88.73)	70 (87.50)	
Travel history								
Yes	1 (14.29)	10 (15.87)	11 (15.71)	.998	2 (28.57)	9 (14.29%)	11 (15.71)	.302
No	6 (85.71)	53 (84.13)	59 (84.29)		5 (71.43)	54 (85.71%)	59 (84.29)	
Contact history								
Yes	3 (42.86)	31 (49.21)	34 (48.57)	.996	3 (42.86)	31 (49.21%)	34 (48.57)	.998
No	4 (57.14)	32 (50.79)	36 (51.43)		4 (57.14)	32 (50.79%)	36 (51.43)	

Abbreviations: Freq, frequency; MV, mechanical ventilation; n, number of patients; R, reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.  
\*Statistically significant ( $P \leq .05$ ).

pneumonia. The commonality of the data seems to point towards the use of coronavirus inflammatory indices (CRP, LDH, ferritin, D-dimer, and normal procalcitonin) in these patients to predict acuteness, severity of illness, and prognosis.<sup>9-12</sup>

In both Luo et al<sup>9</sup> and Zhang et al<sup>12</sup> case series, all patients demonstrated elevated IL-6 levels in addition to other proinflammatory markers, such as CRP, LDH, ferritin, and D-dimer from the time of admission through their hospitalization.<sup>9,12</sup> These four case series, although small in sample size and with limited patients, suggest that TCZ may be efficacious in improving these clinical paradigms and may reduce the need for hospitalization and MV. This is given that 15 out of 20 (75%) of their collective patients improved clinically following treatment as shown in Table 7.

TCZ functions by inhibiting the IL-6 receptor resulting in an increased level of unbound IL-6 as was seen in our study.<sup>18</sup> However, our patients' average IL-6 levels initially increased through day 3 of therapy and stayed elevated until around the day of discharge. It appears that the early use of TCZ may result in a reduction of CRS,

thus reducing the possibility of MV.<sup>19</sup> We seemed to observe this in most of the patients in this study wherein there appeared to be a reduction in the number of patients who were intubated. We find this encouraging as once they are intubated, the rates of mortality and morbidity in this population appear to be high.<sup>14,20</sup>

Previous studies did not have complete laboratory data documented as we did in this study. We also believe that the inflammatory indices seen in our study may prove to be helpful in the diagnosis and treatment of these patients. Issa et al<sup>21</sup> supports our conclusions that TCZ use is beneficial in reducing fevers, shortening hospital duration, and improving patients' respiratory and proinflammatory markers.<sup>21</sup> Additionally, Issa et al<sup>21</sup> reports an association between elevated IL-6 levels and severe SARS-CoV-2 cases.<sup>21</sup> Our study is unique, however, in that we apply this association by measuring and using IL-6 levels as a prognostic indicator.

Although the use of corticosteroids is a conventional therapy in treating cytokine storms, their use in viral pneumonia remains controversial.<sup>9,13,15</sup> A meta-analysis demonstrates that corticosteroid

**TABLE 7** Clinical courses of 20 TCZ-treated patients with SARS-CoV-2 originally presented in four literature case series

Pt	Author	Age/sex	Comorbid history	Exposure history	Clinical signs	First; last IL-6, pg/mL	First; last CRP, mg/L	Other labs	Intubation	Outcome
1	Di Giambenedetto et al <sup>10</sup>	71/M	HTN	NR	Flu-like symptoms, dyspnea	NR	117; NR	Multiple enlarging areas of consolidation	NR	Resolved
2		45/M	None	NR	Fever, dyspnea, chest pain	NR	151; 13	Reduced diaphragm in right lower lobe, bilateral interstitial pneumonia	NR	Resolved
3		53/M	HTN	NR	Flu-like symptoms, dyspnea	NR	250; 92	Interstitial bilateral pneumonia	NR	Resolved
4	Luo et al <sup>9</sup>	73/M	HTN	NR	"Critically ill"	16.4; 5000	199.9; 51.8	NR	NR	Mortality on day 7
5		62/M	None	NR	"Critically ill"	32.7; 2230	257.9; 12.8	NR	NR	Mortality on day 6
6		62/M	HTN	NR	"Critically ill"	73.6; 5000	175.8; 17.9	NR	NR	Mortality on day 6
7		74/M	HTN, history of stroke	NR	"Critically ill"	392; 396.8	177.6; 2.8	NR	NR	Clinical stabilization
8		72/M	HTN	NR	"Critically ill"	24.4; 172	32.2; 1.1	NR	NR	Clinical stabilization
9		73/M	None	NR	"Critically ill"	31.9; 269.4	253.1; 5	NR	NR	Clinical stabilization
10		65/M	HTN, history of stroke	NR	"Critically ill"	46.8; 3628	126.9; 93.5	NR	NR	Disease aggravation
11		66/F	History of stroke	NR	"Seriously ill"	72.7; 133.1	96.1; 5.7	NR	NR	Clinical stabilization
12		73/M	HTN, DM	NR	"Seriously ill"	76.7; 119.1	91; 3.4	NR	NR	Clinical stabilization
13		77/M	HTN, DM	NR	"Seriously ill"	46.5; 45.7	10.7; 0.5	NR	NR	Clinical stabilization
14		65/F	HTN, DM	NR	"Seriously ill"	21.4; 197	97.7; 1.3	NR	NR	Clinical stabilization
15		77/M	HTN, DM	NR	"Seriously ill"	19.7; 108.8	26.3; 0.5	NR	NR	Clinical improvement
16		75/M	None	NR	"Moderately ill"	71.1; 66.6	91.2; 2.5	NR	NR	Clinical stabilization
17		77/M	None	NR	"Moderately ill"	627.1; 249	160.2; 2.1	NR	NR	Clinical stabilization
18		80/F	None	NR	"Seriously ill"	112.8; 704.7	180.6; 6.3	NR	NR	Disease aggravation
19	Michot et al <sup>11</sup>	42/M	RCC-metastatic sarcomatoid clear cell	NR	Fever, cough	NR	225; 33	Bilateral patchy ground glass opacities, partial regression of infiltrates and ground glass opacities	NR	Recovered on day 12
20	Zhang et al <sup>12</sup>	60/M	Symptomatic multiple myeloma treated with chemotherapy	Travel and work history in Wuhan, China	Chest tightness, dyspnea	121.59; 117.1	3.14; NR	LDH (U/L): 202; NR procalcitonin (ng/mL): 0.9; NR multiple ground glass opacities with bilateral subpleural pneumatoceles	NR	Recovered on day 42

Note: All 20 patients presented in these four literature case series were treated with TCZ and methylprednisolone.

Abbreviations: CRP, C-reactive protein; DM, diabetes mellitus; HTN, hypertension; IL-6, interleukin-6; LDH, lactate dehydrogenase; NR, not reported; RCC, renal cell carcinoma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.



monotherapy may reduce hospitalization time but increases the risk of hyperglycemia and mortality.<sup>15</sup> However, we found it to be effective in treating CRS after the use of TCZ.<sup>15</sup> The 72-hour steroid therapy was chosen to be hopefully an additive to the IL-6 inhibitor in prolonging the suppression of CRS and decreasing long-term steroid effects.<sup>9,16</sup>

Some of the limitations of this study include (a) cultural diversity of the patients, (b) lack of a control group, (c) lack of long-term follow up over 4 weeks, and (d) the addition of steroids could have possibly enhanced the robust effects of the IL-6 inhibitor, creating a bias as to which drug was effective.

## 5 | CONCLUSIONS

This study was designed as a pilot study to examine the clinical outcomes in patients with SARS-CoV-2 infection in early respiratory failure using TCZ. Although not definitive, it appears to show that the early use of this drug, when used in patients requiring >3L O<sub>2</sub>, reduced the cytokine storm and inflammatory response in the majority of patients. This reduction in CRS appeared to decrease the need to mechanically ventilate these patients, thus reducing the mortality and morbidity. In addition, this study suggested that the use of SARS-CoV-2 inflammatory indices, such as CRP, LDH, ferritin, and D-dimer are useful when used regularly and in a structured manner.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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