

Outcomes of Tocilizumab Therapy in Severe or Critical COVID-19 Patients: A Retrospective Cohort, Single-Center Study

Hassan Abdelnaby, Wael Aboelhassan, Mohammed Al-Jarallah, Rajesh Rajan, Raja Dashti, Kobalave D. Zhanna, Ahmad R. Al Saber, Ahmed Abd el-Saleem, Islam Ashri, Mohammed Abdullah, Ahmed Mahmud Fouad

Department of Public Health, Community Medicine, Occupational and Environment Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

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ABSTRACT

Objectives: To assess the effectiveness and safety of tocilizumab, a humanized anti-interleukin-6 receptor antibody, in the treatment of critical or severe coronavirus disease 2019 (COVID-19) patients.

Methods: This was a retrospective cohort study of severe or critical COVID-19 patients (≥ 18 years) admitted to one hospital in Kuwait. Fifty-one patients received intravenous tocilizumab, while 78 patients received the standard of care at the same hospital. Both groups were compared for clinical improvement and in-hospital mortality.

Results: The tocilizumab (TCZ) group had a significantly lower 28-day in-hospital mortality rate than the standard of care group (21.6% vs. 42.3%, respectively; $p = 0.015$). 55% of patients in the TCZ group clinically improved vs. 11.5% in the standard-of-care group ($p < 0.001$). Using Cox-proportional regression analysis, TCZ treatment was associated with a reduced risk of mortality (adjusted hazard ratio 0.25; 95% CI: 0.11 – 0.61) and increased likelihood of clinical improvement (adjusted hazard ratio 4.94; 95% CI: 2.03 – 12.0), compared to the standard of care. The median C-reactive protein, D-dimer, procalcitonin, lactate dehydrogenase, and ferritin levels in the tocilizumab group decreased significantly over the 14 days of follow-up. Secondary infections occurred in 19.6% of the TCZ group, and in 20.5% of the standard-of-care group, with no statistical significance ($p = 0.900$).

Conclusion: Tocilizumab was significantly associated with better survival and greater clinical improvement in severe or critical COVID-19 patients.

Keywords: Covid-19, Tocilizumab, Mortality, Survival, Kuwait.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has resulted in a global health crisis with more than 214 million cases and 4.47 million deaths worldwide, as reported by WHO in August 2021. (1, 2)

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COVID-19 shows a heterogeneous clinical presentation, ranging from mild symptoms to generalized vascular disease with multiple organ damage. (3,4) SARS-CoV-2 infection is associated with a dysregulated inflammatory response explained by several pathogenesis pathways. (5) Early reports of COVID-19 highlighted the development of a cytokine storm, described as an excessive production of pro-inflammatory cytokines, particularly IL-6, IL-1 β , and TNF- α , which are correlated with the clinical deterioration and other inflammatory biomarker in patients with severe or critical COVID-19. (6) However, the levels of many pro-inflammatory cytokines in COVID-19 were lower than those seen in other critical illnesses such as cytokine release syndrome, sepsis and acute respiratory distress syndrome, which questions the role of the cytokine storm in COVID-19-induced organ dysfunction. (5,7) Furthermore, hyperferritinemia, lymphopenia with a higher neutrophil-to-lymphocyte ratio (NLR), high lactate dehydrogenase (LDH) levels, and high D-dimer levels were also recorded in COVID-19 patients. (6,8)

IL-6 is an important inflammatory cytokine released by endothelial cells, fibroblasts, T-cells, monocytes, keratinocytes and macrophages during the early phase of infectious inflammations. (6) Excessive IL-6 production plays an important role in the pathogenesis of the extensive lung injury seen in severe or critical COVID-19. (8) IL-6 activity predisposes to thrombotic and microangiopathic vasculopathy through endothelial activation and precipitation of pulmonary immune-mediated thrombosis. It is also a strong inducer of acute-phase reactive proteins that induce hepatocytes to synthesize amyloid A and C-reactive protein (CRP). (8) High plasma IL-6 levels were associated with increased admission to the intensive care units (ICU), and increased mortality among patients with severe or critical COVID-19. (7,9,10) However, recent evidence showed that multiple other mechanisms and pathways were involved in the pathogenesis of COVID-19-related lung injury, such as microangiopathic vasculopathy, and B cell secretion of specific sarsCov-2 antibodies. (5,7)

Many interventions are being evaluated for benefit to COVID-19 patients. (11,12), and much has changed since the initial findings were announced. Given the association between the host immune dysregulation and the level of harm associated with COVID-19, a particular focus is directed towards the beneficial effects of immunomodulatory therapies in mitigating this host-mediated damage. (5,10,11) Accordingly, two landmark trials – RECOVERY and REMAP-CAP – have highlighted the benefit of corticosteroids and tocilizumab, a recombinant humanized monoclonal antibody against IL-6 receptors in reducing mortality and morbidity among severely-ill patients with COVID-19. (13-16) Although early observational studies demonstrated the potential benefit of tocilizumab [17-23], data from patients with severe or critical illness and COVID-19 is lacking. Therefore, the purpose of this study was to assess the effectiveness and safety of tocilizumab use in patients with critical or severe COVID-19.

METHODS

This is a retrospective cohort, single-center study on adult patients (≥ 18 years) admitted to Jaber Al-Ahmad Hospital in Kuwait with a confirmed diagnosis of SARS-Cov-2 infection between March 30th and May 10th, 2020, who fulfilled the

criteria of severe or critical COVID-19. According to the Chinese guidelines for COVID-19 management, severe COVID-19 was defined as the presence of radiological evidence of more than 50% lung infiltrate plus one of the following: (1) respiratory rate ≥ 30 breaths/min; (2) oxygen saturation (SaO_2) $\leq 93\%$ while breathing ambient air at rest or (3) ARDS, defined as the ratio of arterial oxygen partial pressure (PaO_2) to the fraction of inspired oxygen (FiO_2) ($\text{PaO}_2:\text{FiO}_2$) ≤ 300 mmHg. In addition, critical COVID-19 was defined as respiratory failure requiring ventilator support, either invasive or none; septic shock; and/or any organ dysfunction requiring supportive treatment in the ICU. (24) The diagnosis of SARS-Cov-2 infection was confirmed by real time reverse transcription–polymerase chain reaction (rRT-PCR) assays of nasopharyngeal swabs.

The standard of care, issued by the Kuwaiti Ministry of Health, included oxygen therapy, anticoagulants, antivirals (hydroxychloroquine (HCQ), lopinavir/ritonavir, azithromycin), corticosteroids, vitamins, statins, angiotensinogen-converting enzyme (ACE) inhibitors, and/or angiotensin II receptor blockers (ARBs), and was offered to COVID-19 patients based on the existence of contraindications, probable medication interactions, and toxicities. In April 2020, the Kuwaiti Ministry of Health issued the guideline for TCZ administration to adults with severe or critical COVID-19 who are suspected to have cytokine release syndrome, as shown by high CRP (≥ 100 mg/L) or ferritin (≥ 1000 ng/mL) levels, in addition to high LDH (≥ 200 U/L) levels, elevated D-dimer (>250 ng/mL) and need for ICU supportive care with mechanical ventilation for ≤ 48 hours. Exclusion criteria included a concomitant active bacterial infection, neutropenia $< 1000 \times 10^9$ cells/L, baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels by more than five-fold the upper limit of the normal range, and positive testing for hepatitis B virus, hepatitis C virus, or tuberculosis.

Upon approval and due to a shortage of tocilizumab in Kuwait, only 51 patients, admitted between April 15th and May 10th 2020, fulfilled the eligibility criteria for tocilizumab therapy. Among patients admitted to the hospital before the date of tocilizumab availability, only 78 patients who received the standard-of-care had retrospectively fulfilled the eligibility criteria for tocilizumab treatment, and served as a comparison group (Figure 1).

The size of the study groups (i.e. 51 vs. 78) was large enough to detect at least 30% reduction in the in-hospital mortality after administration of TCZ, at a 5% level of confidence and achieved a power of 93.5% (G*Power version 3.1.9.6, Kiel University, Germany). TCZ (Actemra[®], Roche Holding AG, Basel) was reconstituted with 100 mL of 0.9% sodium chloride and injected intravenously at a dose of 4–8 mg/kg over 60 min with a maximum 800 mg per dose. Doses were rounded to the nearest available full vial (80 mg, 200 mg, 400 mg vials). A dose of 4 mg/kg was given to patients with mild baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1 to $3 \times \text{ULN}$, mild neutropenia (1500 to 1000 cell/ mm^3) and baseline thrombocytopenia ($<100,000$ / mm^3). A second dose was injected after 24 hours to patients who showed no improvement in oxygen requirements.

All patients were followed-up for up to 28 days of hospitalization; from the date of TCZ eligibility in the control group and the injection date in the TCZ group. In-hospital mortality and failure of clinical improvement were censored at the last day of follow-up or 28 days, whichever came first. All clinical and laboratory data were retrieved from the hospital's

records at baseline and on days 3, 5, 7, 10, and 14. The primary outcome was in-hospital 28-day mortality. Secondary outcomes were observed 28-day clinical improvement, changes in inflammatory markers by day 14, and 28-day secondary infections confirmed by positive cultures. Clinical improvement was defined as: discharged alive without worsening or at least a 2-point decrease of the WHO disease severity score during the 28 days or maximum follow-up, whichever came first. The WHO severity score is a 4-point ordinal scale defined as: (1) Invasive ventilation defined as patients requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO); (2) noninvasive ventilation defined as patients requiring bilevel positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), high-flow oxygen (O₂), or mid-flow O₂; (3) low-flow O₂ defined as patients requiring nasal cannula or a nonrebreather mask; and (4) ambient air defined as patients requiring room air at the time of tocilizumab administration. (25) Furthermore, TCZ-treated patients were monitored for any adverse effects, incidence of neutropenia (defined as neutrophils < 1500 × 10⁹ cells/L), and secondary infections confirmed by positive cultures.

The Cerrahpaşa-PREDICT score proposed by Eşkazan et al (2021) was used to predict 28-day mortality following tocilizumab treatment in COVID-19 patients. It identified five parameters (platelet count, procalcitonin, SO₂-Room air, D-dimer, and time from symptom onset to tocilizumab use) with specific points assigned to each patient if the parameter was unfavorable. A total score for each patient could be calculated with a cut-off value of 63 or higher, as recommended by the author. (26)

Ethical Approval

The study protocol was approved by the ethical committee for coordination of medical research, Kuwait Ministry of Health (2020/1422), in compliance with the latest version of the Declaration of Helsinki (27).

Statistical Analysis

All data manipulation and analyses were performed using SPSS® Statistics version 24 (IBM Corporation, Armonk, NY, USA). Data normality was tested using the Smirnov–Kolmogorov test. All laboratory variables, body temperature, PaO₂:FiO₂ ratio, ICU stay, and time to hospital admission, which were not normally distributed, were summarized as median (25th–75th percentiles). Patients' age and BMI variables were normally distributed and were summarized as the mean ± standard deviation (SD). Categorical variables were described as frequencies and percentages (%). Associations between categorical variables were tested for statistical significance using Chi-square test or Fisher's exact test as appropriate, while Mann-Whitney or Kruskal-Wallis tests were used for continuous variables. Survival time was tested for normality by Kolmogorov Smirnov test, which yielded non-significant p-value denoting that the survival time was not normally distributed. Accordingly, non-parametric survival analysis was performed using Kaplan-Meier and Cox proportional hazards regression methods. The distributions of survival function were plotted using Kaplan–Meier curve, where the between-group differences were tested for statistical significance using the log-rank test. Hazards ratios (HRs)

and 95% confidence intervals (CIs) were calculated using multivariable Cox proportional hazards models for the 28-day in-hospital mortality and clinical improvement variables. Potential confounders were identified through a series of bivariate analyses of baseline variables where variables with p-values less than 0.10 were included in the Cox models. All assumptions of the Cox proportional regression were met. A p-value of <0.05 was considered statistically significant.

RESULTS

Mean patients' age in the TCZ and control groups was 54.1 and 57.2 years, respectively. Male patients constituted 64.7% and 64.1% of all patients in TCZ and control groups, respectively. No statistically significant differences existed between the study groups regarding the demographic or the baseline clinical and laboratory data as summarized in Table 1.

Median time from hospital admission to the first TCZ dose was 3 days. The mean TCZ dose was 630.3 ± 126.5 mg (6.43 ± 1.84 mg/kg), and only three patients required a second TCZ dose.

The median duration of treatment on ICUs in the TCZ group was significantly shorter than in the standard-of-care group (18 vs. 21 days, respectively, $p = 0.026$, Table 2). The mean survival time in TCZ group was significantly longer than in the standard-of-care group (24.5 days, 95% CI: 22.2–26.3 vs. 20.0 days; 95% CI: 17.7–22.3; Log-rank test p -value=0.046, Figure 2). The unadjusted in-hospital 28-day mortality rate in the TCZ group was significantly lower than in the standard-of-care group: 11 cases (21.6%) vs. 33 cases (42.3%), respectively ($p = 0.015$, Table 2). Further adjustment of potential confounders using Cox proportional regression revealed that tocilizumab therapy was associated with a significantly lower adjusted in-hospital 28-day mortality than the standard of care. Patients who received tocilizumab were 75% less likely to die in hospital within 28 days than patients in the standard of care group (HR: 0.25; 95% CI: 0.11 – 0.61; $p = 0.002$), adjusted for potential confounders listed in Table 3.

The mean time to 28-day clinical improvement in the TCZ group was significantly shorter than in the standard-of-care group (20.5 days; 95% CI: 18.5–22.6 vs. 27.0 days; 95% CI: 26.3–27.8; log-rank test p -value <0.001, Figure 2).

Twenty-eight patients (54.9%) in the TCZ group were clinically improved vs. 9 patients (11.5%) in the standard-of-care group (unadjusted $p < 0.001$, Table 2). Further adjustment of potential confounders using Cox proportional regression revealed that the TCZ group had a significantly higher 28-day clinical improvement rate than the standard-of-care group. Patients receiving tocilizumab were 5 times more likely to clinically improve within 28 days than those treated according to the standard of care (HR: 4.94; 95% CI: 2.03 – 12.0; $p < 0.001$), adjusted for potential confounders listed in Table 4.

In the TCZ group, the percentage of patients who needed invasive ventilatory support significantly decreased from 51% on day 0 to 19% on day 14 ($p < 0.001$) compared to the standard-of-care group (Table 2 and Figure 3).

The median levels of CRP, Ferritin and LDH in patients treated with TCZ showed significant reduction over the first 14 days, compared to insignificant changes in the standard-of-care group: CRP decreased from 246 to 5 mg/L ($p < 0.001$; Figure 4A); ferritin decreased from 1758 to 371 mg/L ($p < 0.001$; Figure 4B); and LDH decreased from 645 to 247 IU/L ($p < 0.001$; Figure 4C). Although PCT and D-dimer did not show significant changes in the TCZ group, they significantly

increased from day 0 to day 14 in the standard-of-care group ($p < 0.001$), with a significant between-group difference at days 7 and 14 ($p < 0.001$; Figures 4D and 4E). Lymphocyte count significantly increased from 0.8 to 1.4 ($p < 0.001$), which was significantly higher than the corresponding increase in the standard-of-care group ($p < 0.001$; Figure 4F)

Regarding TCZ safety, secondary infections were detected in 10 patients (19.6%) in the TCZ group, and in 16 patients (20.5%) in the standard-of-care group, with no statistical significance ($p = 0.900$). Positive cultures included: coagulase-negative *Staphylococcus* in six patients (two in TCZ and four in standard of care); *Staphylococcus epidermidis* in 12 patients (4 on TCZ and 8 on standard of care); *Klebsiella* and *Acinetobacter* in four patients (1 on TCZ, 3 on standard of care); *Klebsiella* in two patients (1 on TCZ, 1 on standard of care); *Enterobacter aerogenes*, AMP C producer in one patient treated with TCZ; *Candida auris* in one patient treated with TCZ; and *Candida parapsilosis* in two patients (1 on TCZ and 1 on standard of care).

Elevated serum ALT or AST levels (more than three times the upper normal values) were reported in 9 (17.6%) TCZ patients and in 20 (25.6%) standard-of-care patients ($p = 0.290$). Serum ALT elevation among TCZ patients was observed on days 3 and 5 of TCZ injection. A transitory neutropenia was noticed in 1 (1.96%) TCZ patient on day 5 after injection and in 1 (1.3%) standard-treatment patient ($p = 0.402$). No infection occurred in the two patients with transitory neutropenia. No anaphylactic reaction was observed during TCZ administration.

The Cerrahpaşa-PREDICT score was calculated with a mean of 35.9 (SD: 31.6; range: 0 – 107). The distribution of patients with unfavorable parameters by 28-day mortality is described in Table 5. Of the 44 patients who died during this study, 28 (63.6%) had a total score of 63 or higher (8/11 deaths in TCZ group and 20/33 in the control group). In our study, the total score had an area under the curve of 0.843 (95% Confidence Interval: 0.768 – 0.901; p -value < 0.001), and the Youden index criterion exceeded 62 (sensitivity 68.2%; specificity 91.8%; positive predictive value 78.8%; negative predictive value 81.2%).

DISCUSSION

This study highlights the outcomes of TCZ therapy in severe or critical COVID-19 patients. Both TCZ and standard-of-care groups were matched in terms of age, gender, BMI, and disease severity to minimize the risk of selection bias. TCZ administration was associated with a significantly lower in-hospital 28-day mortality rate, shorter ICU stay, greater clinical improvement, and higher survival time than the standard of care. The percentage of patients on invasive ventilation decreased significantly from 51% to 19% in the TCZ group. These findings reflect a significant improvement and a high survival rate in patients who received TCZ.

An Italian retrospective study by Guaraldi et al. of 544 severe COVID-19 patients reported a significantly lower death rate in the TCZ group than in the control group (7% vs. 20%, respectively) but lower than that reported by our study. Guaraldi et al. also found a significant decrease in the risk of invasive mechanical ventilation or death (adjusted hazard ratio [aHR]: 0.61; 95% CI: 0.40–0.92; $p = 0.02$). (28) A study by Biran et al. of 764 COVID-19 patients in the ICU reported a

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significant decrease in the mortality rate (HR: 0.71; 95% CI: 0.56–0.89; $p = 0.002$) and risk of mechanical ventilation (HR: 0.63; 95% CI: 0.46–0.85; $p = 0.002$) in the TCZ group compared to the control group. (29) Klopfenstein et al. demonstrated insignificant reduction in the mortality rate in the TCZ group compared to the control group (25% vs. 48%, respectively; $p = 0.066$); however, in terms of death and/or ICU admission, the difference was significant (25% vs. 72%, respectively; $p = 0.002$). (30) Furthermore, in a recently published meta-analysis, IL-6 antagonist therapy was associated with an absolute mortality risk of 22% vs. an assumed mortality of 25% in patients treated with the usual care or placebo. (10)

In contrast, a recent randomized, double-blind, placebo-controlled trial evaluated the efficacy of a single dose of TCZ (8 mg/kg) among moderately ill hospitalized COVID-19 patients. The authors concluded that TCZ is not effective in preventing intubation or death (HR: 0.83; 95% CI: 0.38–1.81; $p = 0.64$). (31) A meta-analysis of seven retrospective studies showed that there is no statistically significant difference between TCZ and standard care regarding all-cause mortality (odds ratio [OR]: 0.62; 95% CI: 0.31–1.22) and ICU admission (relative risk [RR]: 1.51; 95% CI: 0.33–6.78). (32) These inconsistencies in the findings between studies could be attributed to the variations in sample sizes, the control arm of the studies (i.e. comparator group), the severity of COVID-19 in the study group, and differences in co-interventions given to the control group as part of the standard of care at the time of the study.

TCZ-treated patients in our study showed a significant decrease in CRP level by day 14 of the follow-up period. Some reports have identified an inverse relationship between CRP levels and the overall survival rate in COVID-19 patients. Biran et al. suggested that TCZ could exert its effects in patients whose COVID-19 illness is progressing to an inflammatory state (CRP > 15 mg/dL). (29) Toniati et al. reported a rapid and sustained response to TCZ among patients with COVID-19 pneumonia and hyperinflammatory syndrome. (33) Xu et al. showed that CRP levels normalize in 84.2% of severe COVID-19 patients after TCZ administration. (34)

Several studies have highlighted a correlation of ferritin, D-dimer, and LDH levels with COVID-19 severity. In this study, among the TCZ group, we observed a significant decrease in D-dimer, LDH and ferritin levels by day 14, which is consistent with earlier reports by Biran et al. (29). Henry et al. demonstrated an association between elevated LDH levels and worse outcomes in COVID-19 patients (35), however Chen et al. found that even after TCZ administration, D-dimer levels remained high. (36) The high ferritin levels in such patients might be due to the IL-6 receptor blockade, increasing serum IL-6 levels, which contribute directly to ferritin synthesis and accumulation at the injection site, leading to several reactions known as ferritin immunomodulatory effects. (37)

Several studies have recommended PCT as an indicator of COVID-19 severity and prognosis. (6,38–40) Hu et al. showed that PCT levels are four times higher in severe COVID-19 patients than in those with moderate COVID-19. (41) The significant decrease in PCT levels in our TCZ group in comparison to the standard-of-care group ($p < 0.001$) indicated the clinical improvement of this population and supported the aforementioned findings.

Secondary infection, neutropenia, and elevated liver enzymes are the most reported adverse events. In a recent

randomized controlled trial (31), neutropenia in the TCZ group was significantly higher than in the placebo group (13.7% vs. 1.2%, respectively). However, the authors reported an insignificantly different incidence of elevated liver enzymes between TCZ and placebo groups (8.7% vs. 8.6%, respectively). In our study, the occurrence of secondary infections in patients treated with TCZ was comparable to the reported incidence in the standard-of-care group. No significant difference in the incidence of elevated serum ALT or AST levels was found between the groups. Furthermore, only one patient from TCZ group had a transient neutropenia.

This study had several limitations. First, causal association could not be ascertained in this observational study design due to inherent known (e.g. age, pre-existing comorbidities, co-interventions for COVID-19) and unknown confounders. Second, due to the discrepancy between the tocilizumab availability and the number of severe and critical COVID-19, selection of patients for tocilizumab therapy were subject to indication bias. Third, the study reflects a single-center experience in Kuwait with small study groups compared to other studies. Fourth, patients treated earlier in the pandemic may have worse outcomes due to lack of familiarity with the disease and different clinical practices. Fifth, measurements of IL-6 levels were not available for studied patients. Finally, we could not assess long-term safety and adverse effects because of the short follow-up period.

CONCLUSION

Tocilizumab therapy of patients with severe or critical COVID-19 was significantly associated with better survival and clinical improvement compared to the standard of care. Further well-designed RCTs are required to validate these findings.

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Correspondence: Hassan Abdelnaby, Department of Public Health, Community Medicine, Occupational and Environment Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt. Email hassanbadry@med.suez.edu.eg

Table 1. Baseline characteristics of studied COVID-19 patients treated with tocilizumab (TCZ) versus the standard of care.

Parameters	TCZ (n = 51)	Standard of care (n = 78)	p-value
Age (years), Mean ± SD (range)	54.1 ± 14.7 (19 – 88.5)	57.2 ± 13.2 (21 – 84.0)	0.291
Gender, no. (%)			0.944
Male	33 (64.7%)	50 (64.1%)	
Female	18 (35.3%)	28 (35.9%)	
Nationality, No. (%)			0.326
Kuwaiti	30 (58.8%)	39 (50%)	
Non-Kuwaiti	21 (41.2%)	39 (50%)	
BMI (kg/m²), Mean ± SD	29.1 ± 3.2	29.0 ± 4.3	0.505
BMI Class, No. (%)			0.731
Normal	4 (7.8%)	9 (11.5%)	
Overweight	29 (56.9%)	40 (51.3%)	
Obese	18 (35.3%)	29 (37.2%)	
Comorbidities No. (%)			0.280
None	19 (37.3%)	22 (28.2%)	
DM	23 (45.1%)	36 (46.2%)	0.906
HTN	19 (37.3%)	42 (53.8%)	0.065
IHD	4 (7.8%)	7 (9.0%)	1.000
CKD	3 (5.9%)	5 (6.4%)	1.000
COPD	3 (5.9%)	0	0.060
BA	2 (3.9%)	5 (6.4%)	0.703
Others	4 7.8%)	10 (12.8%)	0.374
Charlson's Comorbidity Score, median (IQR)	2 (1–3)	2 (1–4)	0.216
Days from the onset of symptoms to hospital admission	5 (3-7)	6 (4–7)	0.109
Body temperature (C°)	37.7 (37–38)	37.5 (37–37.8)	0.069
Respiratory rate (breaths/min)	33.4 (31 – 38)	34.1 (32 – 37)	0.368
PaO₂:FiO₂ ratio	136.4 (93 – 182)	119.7 (76.0 – 200.0)	0.505
qSOFA	1 (1–2)	1 (1–2)	0.934

Laboratory tests, median (IQR):			
Hemoglobin (g/L)	115.0 (107.0–128.0)	115.0 (104.0–123.0)	0.760
WBCs (10 ⁹ /L)	10.1 (7.2–13.3)	8.6 (6.0–11.5)	0.134
Lymphocyte count	0.8 (0.6–0.8)	0.8 (0.6–1.0)	0.130
Neutrophils	9.0 (5.6–11.2)	7.2 (4.8–10.1)	0.080
Platelets (×10 ³)	301 (203 – 383)	262 (178 – 337)	0.076
Ferritin (ng/mL)	1758 (1300–2413)	1666 (1405–2156)	0.897
CRP (mg/L)	246 (192–392)	204 (157–383)	0.109
LDH (IU/L)	645 (513–815)	605 (479–750)	0.189
D-Dimer (ng/mL)	1775 (1024–3218)	1920 (1475–2895)	0.615
PCT (ng/mL)	0.2 (0.1–0.4)	0.2 (0.1–0.7)	0.840
Serum AST (IU/L)	38.0 (31.0–51.0)	44.0 (29.0–61.0)	0.180
Serum ALT (IU/L)	35.0 (24.0–47.0)	29.5 (21.0–50.0)	0.571
Serum creatinine (μmol/L)	73.0 (56.0–87.0)	78 (67.0–92.0)	0.098
Radiological lung involvement:			
Unilateral	6 (11.8%)	8 (10.3%)	0.788
Bilateral	45 (88.2%)	70 (89.7%)	
Co-interventions, No. (%)			
Antibiotics	49 (96.1%)	74 (94.8%)	0.750
Antiviral (Lopinavir/ritonavir, HCQ)	29 (56.9%)	42 (53.8%)	0.736
Azithromycin	2 (3.9%)	3 (3.85%)	1.000
Glucocorticoids	38 (74.5%)	68 (87.2%)	0.066
Vitamin D	21 (41.2%)	43 (55.1%)	0.121
Therapeutic anticoagulants	51 (100%)	73 (93.6%)	0.156
Statin	9 (17.6%)	21 (26.9%)	0.223
ARB/ACE	11 (21.6%)	20 (25.6%)	0.597
Need for ventilatory support, No. (%)	26 (51.0%)	44 (56.4%)	0.545
ICU admission, No. (%)	43 (84.3%)	63 (80.8%)	0.607

TCZ, tocilizumab; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; CKD, chronic kidney disease; BA, Bronchial Asthma; COPD, chronic obstructive pulmonary disease; GIT, gastrointestinal tract; qSOFA, quick sequential organ failure assessment; ICU, intensive care unit; HCQ, hydroxychloroquine; ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; PaO₂, arterial oxygen partial pressure; FIO₂, fraction of inspired oxygen; WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase; PCT,

procalcitonin; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Numerical variables – median (interquartile range); Categorical variables – frequency (%)

Table 2. Outcome data among studied COVID-19 patients treated with tocilizumab versus the standard of care

Parameters	TCZ (<i>n</i> = 51)	Standard of care (<i>n</i> = 78)	<i>p</i> -value
Length of ICU stay (days)	18.0 (12 – 22)	21 (14 – 28)	0.026*
In-hospital 28-day mortality	11 (21.6%)	33 (42.3%)	0.015*
28-day clinical improvement	28 (54.9%)	9 (11.5%)	0.000*
Need for mechanical ventilation (by day 14)	10 (19.6%)	46 (59.0%)	0.000*
28-day secondary infections	10 (19.6%)	16 (20.5%)	0.900

TCZ, tocilizumab; ICU, intensive care unit.

*Statistically significant test ($p < 0.05$).

Numerical variables – median (interquartile range)

Categorical variables – frequency (%)

Table 3. Cox proportional hazards model for 28-day In-hospital mortality among severe/ critical COVID-19 following Tocilizumab versus standard of care treatments

	Unadjusted HR (95% CI)	p-value
Tocilizumab (vs. standard of care)	0.508 (0.256 – 1.010)	0.054
	Adjusted HR (95% CI)	p-value
Tocilizumab (vs. standard of care)	0.253 (0.105 – 0.613)	0.002*
Age (years)	1.008 (0.967 – 1.050)	0.719
Charlson's comorbidity score	1.088 (0.852 – 1.389)	0.498
Time to hospital admission (days)	1.239 (1.028 – 1.492)	0.024*
qSOFA	1.748 (0.834 – 3.664)	0.139
Need for invasive ventilation (yes vs. no)	1.416 (0.486 – 4.122)	0.523
Antiviral medications (yes vs. no)	0.597 (0.298 – 1.194)	0.144
Glucocorticoids therapy (Yes/No)	1.220 (0.465 – 3.197)	0.686
PaO₂:FiO₂ ratio	0.990 (0.982 – 0.999)	0.025*
Body Temperature (°C)	2.304 (1.320 – 4.019)	0.003*
CRP (mg/L)	1.001 (0.999 – 1.004)	0.281
Serum Creatinine (umol/L)	0.993 (0.98 – 1.007)	0.308
AST (IU/L)	1.013 (0.997 – 1.031)	0.121

^a. -2 Log likelihood = 344.02; Chi-square (*df* = 15) = 58.5; *p* < 0.001.

* Statistically significant HR (*p* < 0.05).

COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; qSOFA, quick sequential organ failure assessment

Table 4. Cox proportional hazards model for 28-day clinical improvement among severe or critical COVID-19 following Tocilizumab versus standard of care treatments

	Unadjusted HR (95% CI)	p-value
Tocilizumab (vs. standard of care)	6.739 (3.168 – 14.33)	<0.001*
	Adjusted HR (95% CI)	p-value
Tocilizumab (vs. standard of care)	4.936 (2.033 – 12.0)	<0.001*
Age (years)	0.99 (0.956 - 1.032)	0.726
Charlson's comorbidity score	0.65 (0.428 - 0.988)	0.044*
Time to hospital admission (days)	0.75 (0.613 - 0.927)	0.007*
Need for invasive ventilation (yes vs. no)	0.38 (0.157 - 0.905)	0.029*
Glucocorticoids therapy (yes vs. no)	0.54 (0.200 - 1.476)	0.232
PaO₂:FiO₂ ratio	1.02 (1.005- 1.031)	0.009*
CRP (mg/L)	1.00 (0.997 - 1.004)	0.817
D-Dimer (ng/mL)	1.00 (1.000 - 1.000)	0.077
AST (IU/L)	0.99 (0.961 - 1.010)	0.234
Platelets (×10³)	0.99 (0.996 - 1.002)	0.554
Hemoglobin (g/L)	0.99 (0.973 - 1.020)	0.760

^a. -2 Log likelihood = 275.7; Chi-square (*df* = 13) = 67.1; *p* < 0.001.

* Statistically significant HR (*p* < 0.05).

COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; AST, aspartate aminotransferase

Table 5. Distribution of patients with unfavorable parameters by the 28-day mortality

Unfavorable Parameters	In-hospital 28-days mortality (n =44)		
	Control (n=33)	TCZ (n=11)	Total
Platelet count $\leq 147 \times 10^9/L$	21 (63.6%)	8 (72.7%)	29 (65.9%)
Procalcitonin ≥ 0.3555 ng/mL	20 (60.6%)	8 (72.7%)	28 (63.6%)
SO ₂ R $\leq 91.5\%$	17 (51.5%)	8 (72.7%)	25 (56.8%)
D-dimer ≥ 2.52 mg/L	29 (87.9%)	7 (63.6%)	36 (81.8%)
Time from symptom start to TCZ use >12 days	6 (18.2%)	4 (36.4%)	10 (22.7%)
Total score ≥ 63 (high-risk for 28-day mortality)	20 (60.6%)	8 (72.7%)	28 (63.6%)

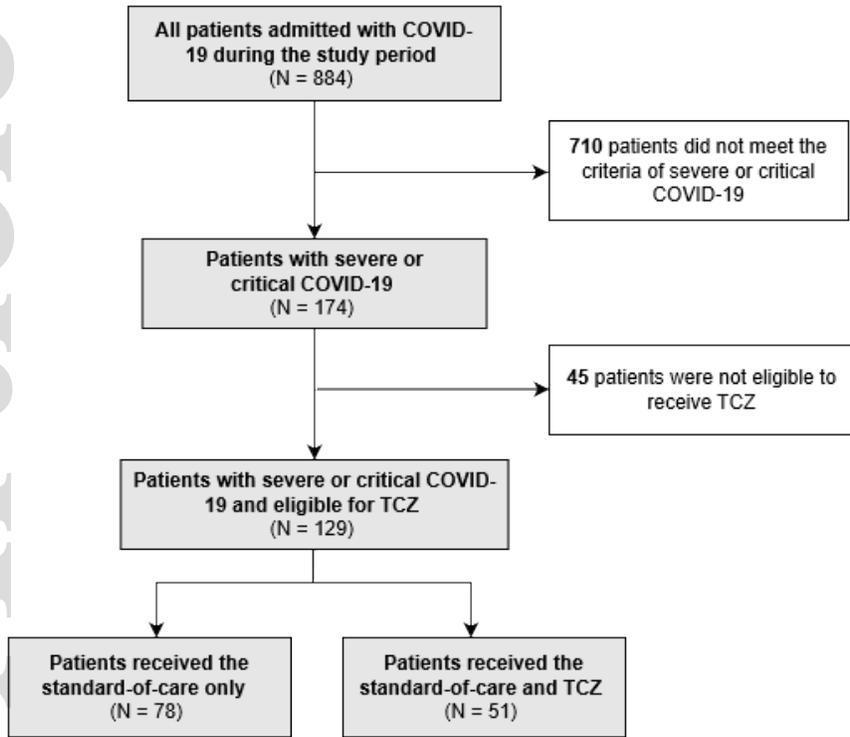
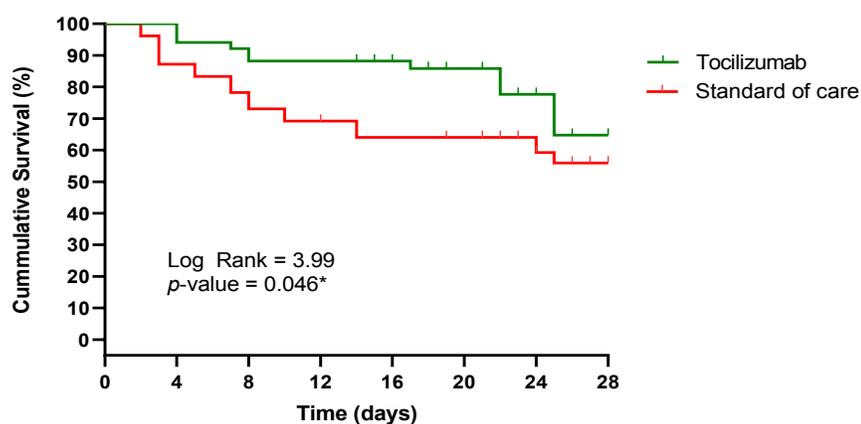
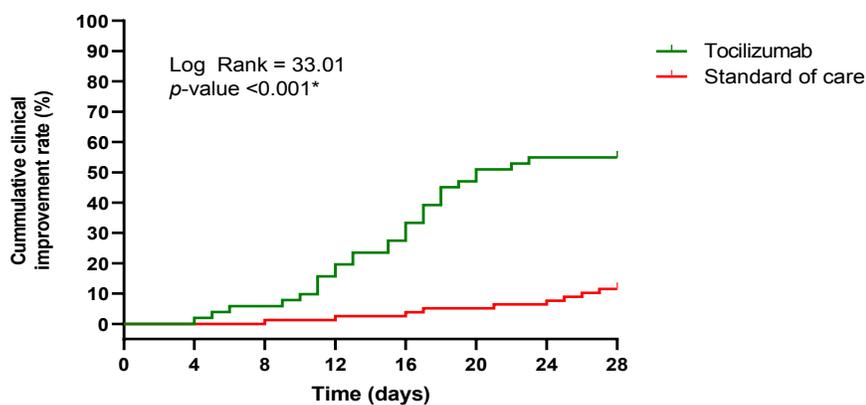


Figure 1. Flow chart of the study population



Number at Risk:

Tocilizumab	51	51	47	45	45	44	42	40
Standard of care	78	68	61	54	50	50	48	45



Number at Risk:

Tocilizumab	51	51	48	43	37	27	23	23
Standard of care	78	78	78	77	76	74	73	69

Figure 2: Kaplan–Meier curves of equality of survival distributions between Tocilizumab- and the standard-of-care treated groups during the 28-day observational period; A: In-hospital mortality, B: Clinical improvement

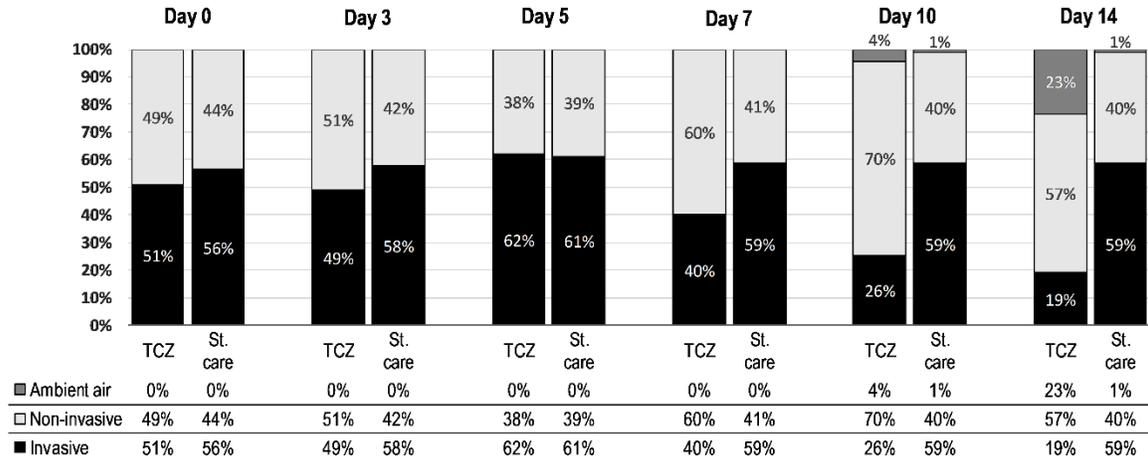


Figure 3: Change in the ventilatory status in the Tocilizumab (TCZ) and the standard-of care (St. care) treated groups during the first 14 days of the observation period

Figure 4A

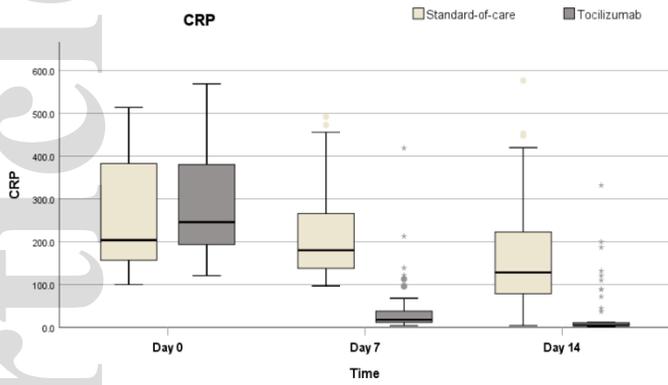


Figure 4B

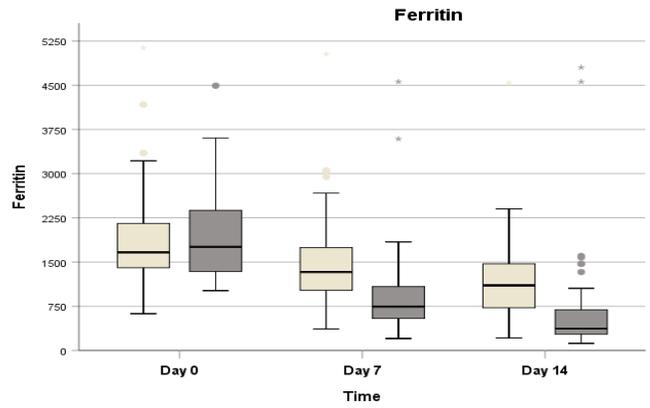


Figure 4C

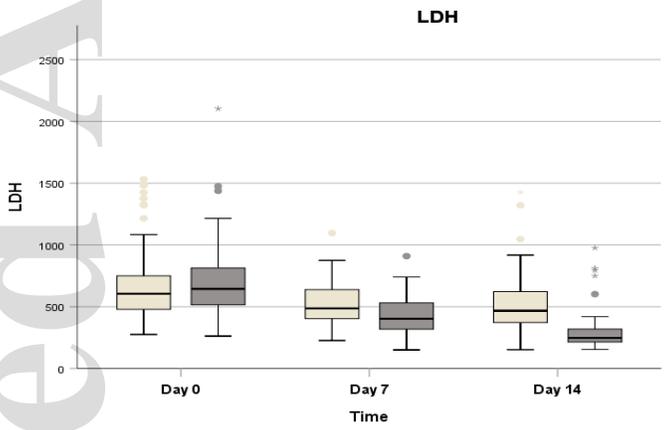


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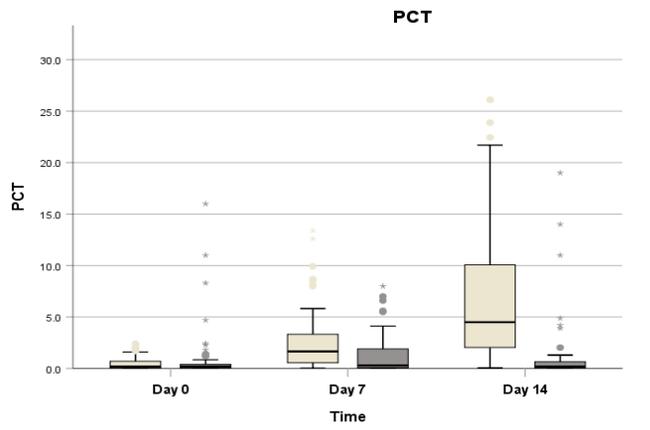


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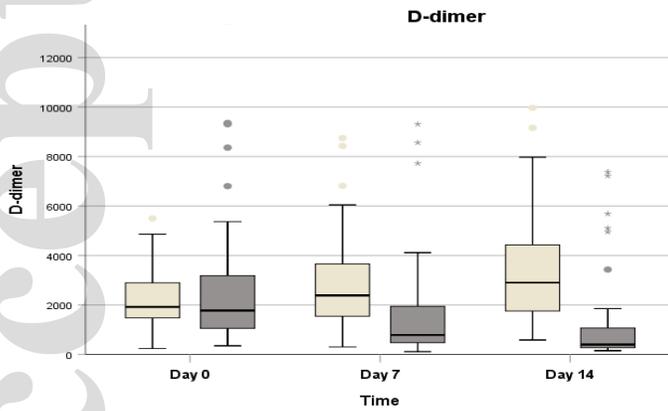


Figure 4F

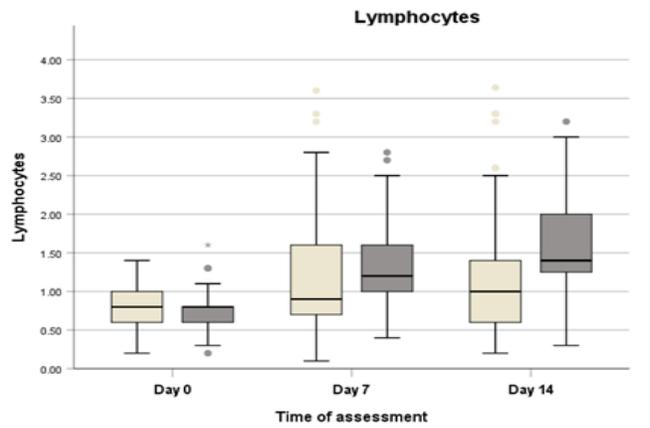


Figure 4. Changes in the inflammatory markers in the Tocilizumab- and the standard-of-care treated groups during the first 14 days of the observation period