The role of tocilizumab therapy in critically ill patients with severe acute respiratory syndrome coronavirus 2

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Abstract

Context: Tocilizumab (TCZ), an interleukin-6 (IL-6) receptor antagonist, has been approved for use in rheumatoid arthritis and cytokine storm syndrome (CSS) associated with chimeric antigen receptor T cells treatment. Although TCZ is currently utilized in the treatment of critically ill coronavirus 2019 (COVID-19) patients, data on survival impact is minimal. Objectives: To assess the mortality rate of patients presenting with COVID-19 who received TCZ for suspected CSS. Methods: This retrospective cohort study was conducted at Henry Ford Health System between March 10, 2020 and May 18, 2020. Data collection began in May 2020 and was completed in June 2020. Patients included in the study required hospital admission and had positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction on nasopharyngeal swab. Eligibility criteria to receive TCZ, per hospital protocol, included any of the following: persistent fever, defined as 38.0 °C for at least 6 hours; a diagnosis of the acute respiratory distress syndrome (ARDS); serum ferritin ≥1,000 (ng/mL) or doubling within 24 hours; D-Dimer ≥5 (mg/L); serum lactate dehydrogenase ≥500 (IU/L); or interleukin-6 level ≥5 times the upper limit of normal. Dosing was initially determined by weight, then changed to a fixed 400 mg per hospital protocol. A comparator cohort was created from patients with COVID-19 and ARDS who did not receive TCZ. Patient survival was analyzed using the Kaplan–Meier method and compared by log rank test. A multivariable cox regression was applied to evaluate the association between TCZ and mortality. Results: One hundred and thirty patients were evaluated in the study, 54 (41.5%) of whom received TCZ. Patients who received TCZ were younger (mean age, 63.8 vs. 69.4 years; p=0.0083) and had higher body mass indices (mean, 33.9 vs. 30.4; p=0.005). Of the comorbid conditions evaluated, heart disease was more common in the comparator group than the TCZ group (27 patients [35.5%] vs. 10 patients [18.5%]; p=0.034). A Kaplan–Meier survival curve demonstrated no difference in survival between TCZ and comparator patients (log rank p=0.495). In the multivariable Cox regression model for mortality at 30 days, treatment with TCZ was not associated with decreased mortality (hazard ratio, 1.1; 95% confidence interval, 0.53–2.3; p=0.77). Lower mean C-reactive protein (CRP) levels were demonstrated within 48 hours of disposition in the TCZ group (mean TCZ, 4.9 vs. mean comparator, 13.0; p=<0.0001). Conclusions: In this cohort study, no difference in survival was observed in critically ill patients treated with TCZ.

Keywords: coronavirus; COVID-19; mortality; survival; tocilizumab.

The coronavirus 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has ravaged the world since it was initially reported in China in December of 2019 [1]. As of April 2021, over 157 million people have been infected and over three million deaths have been reported worldwide [2]. Based on published data, it is estimated that 81% of symptomatic people develop mild to moderate disease, 14% develop severe disease, and 5% develop critical disease associated with respiratory failure,
The reasons certain patients with COVID-19 progress to severe disease remains unclear. Some research [7, 8] has suggested that the progression of the disease to severe form could be caused by cytokine storm syndrome (CSS). CSS is clinically characterized by cytopenia, hyperferritinemia, fever, acute respiratory distress syndrome (ARDS), and if untreated, death [7, 9, 10]. Studies of the previous coronavirus strains, SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV), also demonstrated the increased production and release of proinflammatory cytokines including interleukin 6 (IL-6), interleukin 1β (IL-1β), interferon β (IFN-β), interleukin 12 (IL-12), and tumor necrosis alpha (TNF-α) [11, 12].

The use of corticosteroids and other immunosuppressive therapies in the treatment of infectious conditions associated with CSS or similar proinflammatory syndromes remains limited to patients with bacterial [13] and tuberculous meningitis [14], Pneumocystis jiroveci pneumonia (PJP) [15], and immune reconstitution inflammatory syndrome (IRIS) [16] with HIV. Its use is a controversial and unsettled topic in other conditions. A systematic review [17] of 29 SARS-CoV studies evaluating corticosteroid use determined that 25 were inconclusive and four demonstrated potential harm. A retrospective analysis [18] of 213 patients admitted to our institution with COVID-19 demonstrated that an early course of methylprednisolone initiated at a median time of 2 days after presentation reduced rates of death, ICU transfer, and hospital protocol was amended on March 30, 2020 to a

The primary outcome of this study was mortality at 30 days. Secondary outcomes were hospital length of stay, ICU length of stay, duration on
mechanical ventilation, changes in serologic markers of inflammation (ferritin, C-reactive protein [CRP], LDH, D-dimer, total white blood cell [WBC] count, platelet count), and serologic indicators of organ dysfunction (serum creatinine, liver function studies, creatine phosphokinase, and troponin) associated with COVID-19.

Data collection

Data were collected manually from the electronic medical record and entered into a standardized Excel form (Microsoft, Inc.). A quality control protocol was developed by the research team prior to data collection to ensure a uniform abstraction and entry process. Data collected included demographics (sex, age, body mass index [BMI]), comorbidities [hypertension, diabetes, chronic obstructive pulmonary disease, asthma, renal disease, heart disease, immunocompromised status, smoking], and clinical parameters [highest respiratory support]). The presence of renal disease was categorized as chronic kidney disease stage III–IV or dialysis dependent. An immunocompromised state was defined as infection with human immunodeficiency virus or current immunosuppressive therapy. The initial Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores for patients admitted to the ICU was manually calculated using data from the ICU admission date. APACHE II scores were also calculated at the time of first and second TCZ administration for the group of patients who received two doses.

Laboratory data collected for this study included ferritin, CRP, creatinine, creatinine phosphokinase (CPK), WBC count, platelets, aspartate transaminase (AST), ALT, absolute neutrophil to lymphocyte ratio (NLR), D-dimer, high sensitivity troponin, procalcitonin, and a PaO2/FiO2 (P/F) ratio. The earliest laboratory tests during the first 24 hours after admission were recorded for this study, as were the latest values within 48 hours of discharge. Ferritin and D-dimer values were categorized into ranges as the two hospital laboratories used different references for normal values. All laboratory tests were performed at the discretion of the treating physician.

Treatment data included corticosteroid use (prednisone, methylprednisolone, and dexamethasone) with total duration in days; use of agents potentially targeting SARS-CoV-2 (hydroxychloroquine alone or in combination with azithromycin); use of other antimicrobials, convalescent plasma, intravenous immunoglobulin (IVIG); and anticoagulation use (prophylaxis or therapeutic). Patients in the TCZ group were designated as having antithrombotic therapy if they received at least 3 days of full anticoagulation.

Other clinical events recorded for all patients included use of vasopressors, acute kidney injury, need for continuous renal replacement therapy (CRRT) or hemodialysis, need for oxygen at discharge, cardiac arrest, and presence of positive blood and sputum/tracheal aspirate. CRRT or hemodialysis were initiated at the discretion of the treating nephrologist. In the TCZ group, only infections that occurred after TCZ administration were recorded. Instances of infection documented by an infectious disease specialist were used to distinguish true infection from colonization. Thirty days of follow up in the TCZ group was recorded from the time of TCZ administration.

Statistical analysis

All continuous data are reported using mean and standard deviation, count, median, and range, while categorical data are reported as counts and column percentages (n [%]). Univariate two group comparisons were performed using t-tests for normally distributed continuous variables, Wilcoxon rank sum for continuous variables that were skewed, and chi-square or Fisher’s exact test for categorical variables. Statistical significance was set at p<0.05.

Patient mortality was analyzed using the Kaplan–Meier method and compared by log rank test. A multivariate cox regression was applied to evaluate the association between TCZ and mortality. Variables with a univariate p<0.10 were candidates for inclusion in the final model. Variables included in the analysis were demographics (e.g., age, sex), treatment modalities (e.g., antimicrobial, anticoagulation), laboratory data (CRP, NLR, D-dimer, and WBC), and duration of corticosteroid therapy. TCZ use was accounted for as a time varying exposure to mitigate immortal time bias. The final model was obtained via forward selection process with significance level for entry set at p<0.05. All analyses were performed using SAS 9.4 (SAS Institute Inc.) and SPSS 27 (IBM Corp.).

Results

During the study period, 151 patients were hospitalized with COVID-19 ARDS at the participating hospitals and these consecutive patients were evaluated for inclusion. Of those, 54 (35.7%) received TCZ during the study period and all 54 (100.0%) were included. Ninety seven comparator patients (64.2%) were identified and seventy six (50.3%) were included.

Demographic characteristics

Data for patient demographics, comorbid conditions, and severity of illness are presented in Table 1. The mean age (standard deviation, SD) was 63.8 years (SD, ±11.6; range, 29–87 years) in the TCZ group and 69.4 years (SD, ±11.5; range, 43–90 years) in the comparator group (p<0.01). In the TCZ group, 39 patients (72.2%) were male and 24 (28.9%) were female; in the comparator group, 54 patients (71.1%) were male and 24 (28.9%) were female. Of the comorbid conditions evaluated in this study, heart disease was more common in the comparator group than the TCZ group (27 patients [35.5%] vs. 10 patients [18.5%]; p=0.03). The majority of patients required invasive ventilation during their hospitalization (TCZ group, 47 [87.0%] vs. comparator group, 61 [80.3%] patients; p=0.43). The mean APACHE II score in TCZ survivors (22; 40.7%) was 17.5 (SD, ±5.9) compared with 21 (SD, ±8) in patients who received TCZ but did not survive (21; 38.9%) (p=0.13). In patients who received a second dose of TCZ (17; 31.5%), the mean APACHE II score at first dose was 23.2 (SD, ±8.40) and 25.0 (SD, ±8.71) at second dose (p=0.11). All patients (54; 100.0%) in the TCZ and
comparator groups received corticosteroids (primarily intravenous methylprednisolone; data not available). There was no statistically significant difference between the TCZ group and the comparator group in antibiotic usage (TCZ group, 47 patients [87.0%] vs. comparator group, 66 patients [86.8%]; p=0.97), convalescent plasma (TCZ group, four patients [14.8%] vs. comparator group, nine patients [11.8%]; p=0.62), or antimicrobial use [hydroxychloroquine (TCZ group, 30 patients [55.5%] vs. comparator group, 46 patients [60.5%]), p=0.84; hydroxychloroquine with azithromycin (TCZ group, 13 patients [24.1%] vs. comparator group, 17 patients [22.4%], p=0.84), none (TCZ group, 11 patients [20.4%] vs. comparator group, 13 patients [17.1%], p=0.84]). The difference in rate of anticoagulation use between groups was not statistically significant with either prophylaxis dose (TCZ group, 20 patients [37.0%] vs. comparator group, 24 patients [31.6%]; p=0.31) or therapeutic dose (TCZ group, 34 patients [63.0%] vs. comparator group, 50 patients [65.8%]; p=0.31). Four patients (7.4%) in the TCZ group received IVIG. The majority of patients (38; 70.4%) received a 400 mg TCZ dose, while two (3.7%) received a 600 mg TCZ dose and 14 (25.9%) received an 800 mg dose. For patients who did not receive TCZ, bacterial infection was documented as a reason in 14 (18.4%), while other documented reasons not related to infection were given for 16 (21.1%) and no documented reason was given for 46 (60.5%).

**Laboratory data**

Laboratory results data are presented in Table 2. Differences in admission data did not rise to the level of statistical significance between groups for any category except LDH (TCZ group, 462.6 [SD, ±209.2] vs. comparator group, 394.0 [SD, ±186.5]; p=0.03). Within 48 hours of discharge, mean CRP level was lower in the TCZ group than the comparator group (TCZ, 4.9 ± 6.0 vs. comparator, 13.0 ± 12.0; p=0.01). Mean LDH values within 48 hours of discharge remained higher in the TCZ group than in the comparator group (TCZ, 525.2 [SD, ±440.4] vs. comparator, 444.1 [SD, ±494.4]; p=0.02). There was no difference in the final ratio of arterial oxygen concentration to the fraction of inspired oxygen (P/F) between the two groups (p=0.12). The mean IL-6 level was higher among smokers (58; 52.3%) than nonsmokers (53; 47.7%), though the difference was not statistically significant (smokers, 89.88 [SD, ±163.7] vs. nonsmokers, 71.85 [SD, ±123.2]; p=0.45).

**Table 1: Demographics and comorbid conditions between tocilizumab (TCZ) and comparator groups.**

| Characteristics                       | TCZ group (N=54) | Comparator group (N=76) | p-Value |
|----------------------------------------|------------------|-------------------------|---------|
| Age, years, mean ± SD                  | 63.8 ± 11.6      | 69.4 ± 11.5             | <0.01   |
| BMI, kg/m², mean ± SD                  | 33.9 ± 7.9       | 30.4 ± 6.2              | <0.01   |
| Sex                                     |                  |                         |         |
| Female                                  | 15 (27.8%)       | 22 (28.9%)              | 0.88    |
| Male                                    | 39 (72.2%)       | 54 (71.1%)              | 0.88    |
| Ethnicity, n (%)                        |                  |                         |         |
| White                                   | 24 (44.4%)       | 47 (61.8%)              | 0.07    |
| Black                                   | 25 (46.3%)       | 28 (36.8%)              |         |
| Asian                                   | 2 (3.7%)         | 0 (0.0%)                |         |
| Unknown                                 | 3 (5.6%)         | 1 (1.3%)                |         |
| Interleukin 6 level, pg/mL, mean ± SD   | 108.8 ± 179      | 62.3 ± 105.3            | 0.07    |
| SOFA score, mean ± SD                   | 5.7 ± 2.2        | 6.0 ± 3.2               | 0.96    |
| Symptom onset to admission, days, mean ± SD | 6.9 ± 3.4   | 7.1 ± 4.4               | 0.91    |
| Symptom onset to TCZ dose, days, mean ± SD | 12.6 ± 4.6    |                        |         |
| Admission to TCZ, days, mean ± SD       | 5.9 ± 3.77       |                        |         |
| Corticosteroid duration, days, mean ± SD | 6.5 ± 3.1      | 6.4 ± 2.7               | 0.98    |
| Admission to corticosteroid initiation, mean ± SD | 0.72 ± 1.38 | 0.77 ± 1.7              | 0.85    |
| Highest oxygen need, n (%)              |                  |                         |         |
| Invasive vent                           | 47 (87.0%)       | 61 (80.3%)              | 0.43    |
| Noninvasive vent                        | 3 (5.6%)         | 3 (3.9%)                |         |
| High flow                               | 3 (5.6%)         | 11 (14.5%)              |         |
| Nasal cannula                           | 1 (1.9%)         | 1 (1.3%)                |         |

**Table 2: Comorbid conditions, n (%).**

| Comorbid conditions                     | TCZ group (N=54) | Comparator group (N=76) | p-Value |
|-----------------------------------------|------------------|-------------------------|---------|
| Hypertension                            | 43 (79.6%)       | 55 (72.4%)              | 0.34    |
| Diabetes                                | 26 (48.1%)       | 27 (35.5%)              | 0.15    |
| Asthma                                  | 7 (13.0%)        | 14 (18.4%)              | 0.41    |
| Chronic obstructive pulmonary disease   | 9 (16.7%)        | 18 (23.7%)              | 0.33    |
| Cancer                                  | 6 (11.1%)        | 18 (23.7%)              | 0.07    |
| Renal disease                           | 9 (16.7%)        | 18 (23.7%)              | 0.49    |
| CKD III-V                               | 1 (1.9%)         | 3 (3.9%)                |         |
| ESRD                                    | 10 (18.5%)       | 27 (35.5%)              | 0.03    |
| Heart failure or coronary artery disease | 5 (9.3%)        | 6 (6.6%)                | 0.57    |
| Immunocompromised status                |                  |                         |         |
| Smoking status                          |                  |                         |         |
| Prior user                              | 23 (45.1%)       | 39 (52.7%)              | 0.09    |
| Active user                             | 3 (5.9%)         | 0 (0.0%)                |         |
| Never smoker                            | 25 (49.0%)       | 35 (47.3%)              |         |

BMI, body mass index; CKD, chronic kidney disease; ESRD, end stage renal disease; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TCZ, tocilizumab.
Table 2: Laboratory data.

| Laboratory value       | Tocilizumab group (N=54) | Comparator group (N=76) | p-Value |
|------------------------|--------------------------|-------------------------|---------|
| CRP, mg/dL, mean ± SD  |                          |                         |         |
| Initial                | 13.2 ± 7.4               | 12.6 ± 6.4              | 0.65    |
| Final                  | 4.9 ± 6.0                | 13.0 ± 12.0             | <0.01   |
| N/L ratio, mean ± SD   |                          |                         |         |
| Initial                | 8.6 ± 6.4                | 10.2 ± 8.2              | 0.32    |
| Final                  | 12.5 ± 14.3              | 16.5 ± 18.7             | 0.21    |
| WBC, K/ul, mean ± SD   |                          |                         |         |
| Initial                | 7.7 ± 3.4                | 8.3 ± 5.5               | 0.75    |
| Final                  | 15.3 ± 11.6              | 12.5 ± 7.1              | 0.56    |
| Creatinine, mg/dL, mean ± SD |                  |                         |         |
| Initial                | 1.8 ± 2.1                | 1.7 ± 1.5               | 0.88    |
| Final                  | 2.0 ± 2.1                | 1.7 ± 1.5               | 0.98    |
| CPK, IU/L, mean ± SD   |                          |                         |         |
| Initial                | 535.3 ± 678.5            | 705.8 ± 1,162.9         | 0.18    |
| Final                  | 403.1 ± 750.4            | 245.2 ± 545.8           | 0.09    |
| LDH, IU/L, mean ± SD   |                          |                         |         |
| Initial                | 462.6 ± 209.2            | 394.0 ± 186.5           | 0.03    |
| Final                  | 525.2 ± 440.4            | 444.1 ± 494.4           | 0.02    |
| ALT, IU/L, mean ± SD   |                          |                         |         |
| Initial                | 50.3 ± 67.6              | 32.6 ± 22.2             | 0.15    |
| Final                  | 145.6 ± 491.7            | 54.88 ± 55.8            | 0.11    |
| AST, IU/L, mean ± SD   |                          |                         |         |
| Initial                | 71.7 ± 81.3              | 53.5 ± 37.6             | 0.18    |
| Final                  | 225.6 ± 1,062.5          | 85.25 ± 274.6           | 0.06    |
| Procalcitonin, ng/mL, mean ± SD |                  |                         |         |
| Initial                | 0.5 ± 0.6                | 1.5 ± 6.0               | 0.88    |
| Final                  | 1.5 ± 3.3                | 4.0 ± 13.7              | 0.89    |
| Troponin, ng/L, mean ± SD |                          |                         |         |
| Initial                | 49.9 ± 153.5             | 58.9 ± 147.4            | 0.88    |
| Final                  | 86.4 ± 289.6             | 177.3 ± 700.8           | 0.51    |
| P/F ratio, mean ± SD   |                          |                         |         |
| Initial                | 141.08 ± 94.8            | 151.31 ± 95.7           | 0.18    |
| Nadir                  | 78.07 ± 30.7             | 97.51 ± 38.2            | <0.01   |
| Peak                   | 244.82 ± 93.9            | 284.61 ± 128.9          | 0.11    |
| Final                  | 136.28 ± 62.0            | 166.28 ± 88.8           | 0.12    |
| D-dimer, peak (ug/mL), n (%) |                  |                         |         |
| 0–0.8                  | 4 (7.5%)                 | 2 (2.7%)                | 0.11    |
| 0.81–3.10              | 14 (26.4%)               | 26 (35.1%)              |         |
| 3.11–9.99              | 8 (15.1%)                | 20 (27.0%)              |         |
| >10                    | 27 (50.9%)               | 26 (35.1%)              |         |
| Ferritin, initial (ng/mL), n (%) |                |                         |         |
| <336                   | 6 (12.2%)                | 20 (29.9%)              | 0.14    |
| 336–999                | 19 (38.8%)               | 24 (35.8%)              |         |
| 1,000–1999             | 13 (26.5%)               | 12 (17.9%)              |         |
| >2000                  | 11 (22.4%)               | 11 (16.4%)              |         |
| Ferritin, final (ng/mL), n (%) |                |                         |         |
| <336                   | 5 (11.1%)                | 14 (23.3%)              | 0.19    |
| 336–999                | 21 (46.7%)               | 22 (36.7%)              |         |
| 1,000–1999             | 7 (15.6%)                | 14 (23.3%)              |         |
| >2000                  | 12 (26.7%)               | 10 (16.7%)              |         |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; LDH, lactic acid dehydrogenase; N/R ratio, absolute neutrophil to lymphocyte ratio; P/F ratio, ratio of arterial oxygen concentration to the fraction of inspired oxygen; SD, standard deviation; WBC, white blood cell.
Outcomes

TCZ did not significantly improve overall survival or other secondary outcome measures (Figure 1; Table 3). At 30 days, 22 patients (40.1%) in the TCZ group had survived compared with 33 (43.4%) in the comparator group (p=0.76). There was a trend toward longer mean length of stay in the TCZ group, but the difference was not statistically significant (TCZ, 18.4 [SD, ±11.2] vs. comparator, 15.4 [SD, ±7.9] days; p=0.09). Survival analysis revealed no statistically significant difference in mean hospital length of stay (TCZ group, 21.8 [SD, ±16.6] vs. comparator group, 18.4 [SD, ±8.1] days; p=0.29) or mean duration on ventilator (TCZ group, 10.6 [SD, ±6.5] vs. comparator group, 7.8 [SD, ±5.1] days; p=0.15).

Thirteen patients (24.1%) in the TCZ group received renal replacement therapy compared with two (2.6%) in the comparator group (p<0.01). The difference in the number of patients who had positive blood culture (TCZ group, four patients [7.4%] vs. comparator group, seven patients [9.2%]; p=0.41) was not statistically significant between groups. The most common blood stream pathogen in the TCZ group was candida albicans (three patients; 75.0% of positive cultures), whereas gram positive isolates were the most common in the comparator arm (six patients; 75.0% of positive cultures). Pseudomonas aeruginosa (10 patients [22.0% of 45 total respiratory isolates]) and Staphylococcus aureus (10 patients [22.0%] of 45 total respiratory isolates) were the most common causes of secondary pneumonia. Detailed superinfection data stratified by group are presented in the Supplementary Material.

In the multivariate Cox regression model for mortality at 30 days for the entire sample, treatment with TCZ was not associated with decreased mortality (hazard ratio [HR], 1.18; 95% confidence interval [CI], 0.71–1.96; p=0.516). Underlying renal disease (HR, 2.21; 95% CI, 1.30–3.75; p=0.003) and smoking status (HR, 2.35; 95% CI, 1.34–4.09; p=0.003) were significantly associated with increased mortality. Longer duration of corticosteroid therapy (HR, 0.80; 95% CI, 0.70–0.90; p<0.001) and the use of hydroxychloroquine in combination with azithromycin (HR, 0.37; 95% CI, 0.17–0.81; p=0.012) were

Table 3: Clinical events.

| Characteristics, n (%) | Tocilizumab (N=54) | Comparator (N=76) | p-Value |
|------------------------|--------------------|-------------------|---------|
| Survival at 30 days    | 22 (40.1%)         | 33 (43.4%)        | 0.76    |
| Survival at 14 days    | 31 (57.4%)         | 44 (57.9%)        | 0.95    |
| Vasopressor use        | 35 (64.8%)         | 44 (57.9%)        | 0.43    |
| Acute kidney injury    | 35 (64.8%)         | 46 (60.5%)        | 0.62    |
| Hemodialysis/CRRT      | 13 (24.1%)         | 2 (2.6%)          | <0.01   |
| Cardiac arrest         | 4 (7.6%)           | 3 (3.9%)          | 0.46    |
| CVA                    | 2 (3.8%)           | 1 (1.3%)          | 0.57    |
| Bleeding               | 13 (24.1%)         | 11 (14.5%)        | 0.16    |
| Discharged with oxygen infection | 10 (50.0%) | 12 (38.7%) | 0.43 |
| Blood stream infection | 4 (7.4%)           | 7 (9.2%)          | 0.41    |
| Pulmonary infection (endotracheal aspirates/sputum) | 14 (25.9%) | 23 (30.3%) | 0.71 |

Length of stay, days, mean ± SD

| Event                                | Tocilizumab (N=54) | Comparator (N=76) | p-Value |
|--------------------------------------|--------------------|-------------------|---------|
| Hospital length of stay              | 18.4 ± 11.2        | 15.4 ± 7.9        | 0.09    |
| Survivors hospital length of stay    | 21.8 ± 14.6        | 18.4 ± 8.1        | 0.29    |
| Survivors ICU length of stay         | 16.8 ± 16.5        | 11.8 ± 9.3        | 0.22    |
| Survivors duration on ventilator     | 10.6 ± 6.5         | 7.8 ± 5.1         | 0.15    |
| Survivors ventilator to O2 less than 6 L | 10.5 ± 6.5 | 9.0 ± 6.8 | 0.52 |

CRRT, continuous renal replacement therapy; CVA, cerebrovascular accident; ICU, intensive care unit.

Figure 1: Kaplan–Meier survival curves comparing 30 day survival between Tocilizumab and comparator groups.
associated with a lower rate of mortality. Multivariate analysis is presented in Table 4 and univariate analysis is presented in the Supplemental Material. Boxplots for corticosteroid duration and 30 day outcomes are presented in the Supplemental Material.

### Discussion

We evaluated the role of TCZ on mortality in critically ill patients with COVID-19. Excess cytokine and chemokine release seen in severe COVID-19 is a dysregulated response of both the innate and adaptive immune system in response to infection caused by SARS-CoV-2. Evidence of hyperinflammation caused by this aberrant host response is seen in association with hypoxic respiratory failure in COVID-19. It has been proposed previously that IL-6 is one of the key drivers of this hyperinflammatory response contributing to the perturbation of the balance, tissue damage, and disease severity [10]. Use of humanized monoclonal antibody against IL-6 receptor blocks the signaling by this cytokine and reduces inflammation. The use of humanized monoclonal antibody against IL-6 receptor along with corticosteroids is an attempt to decrease inflammation and restore self-regulation of immune system.

Our study showed no survival benefit at 30 days with TCZ vs. comparator treatment in critically ill patients with COVID-19. This is consistent with the results from three prior randomized controlled trials [27–29] that demonstrated no difference in survival rates. In contrast, two other randomized controlled trials [30, 31] demonstrated survival benefit; however, in both of those trials, the percentage of patients requiring invasive ventilation at the time of randomization to TCZ treatment was less than 30%, far less than the rate in our cohort of 87.0% [30, 31]. Furthermore, in one of those – the Randomized Evaluation of COVID-19 Therapy study [31], which is an ongoing, randomized controlled trial of approximately 4,000 patients – a subsidiary analysis of patients requiring invasive mechanical ventilation at the time of randomization to TCZ treatment revealed no statistically significant difference in mortality or cessation of ventilation [31]. Of the secondary endpoints, we observed significantly lower CRP levels within 48 hours of disposition in the TCZ group (mean CRP, 4.9) than in the comparator group (mean CRP, 13.0; p<0.0001). TCZ blocks IL-6, which has an important role in acute phase response and CRP production [32].

In our cohort, TCZ was administered primarily to patients with critical COVID-19 who required mechanical ventilation. Patients in the TCZ group had higher mean baseline LDH levels, which has been associated with more critical disease and mortality in prior research [6, 33, 34]. Furthermore, the associated in hospital mortality based on APACHE II score at the time of TCZ administration was 25.0% in survivors compared with 40.0% in nonsurvivors. Among the 17 patients who received two doses of TCZ, only two survived, and their associated in hospital estimated mortality associated with their APACHE II score was 40.0% during the first dose and 55.0% at the time of the second dose. This may reflect the severity or refractoriness of the patients’ illness rather than implying a dose dependent toxicity; however, further studies are needed to understand the significance of this finding in our small, critically ill subset of patients.

TCZ has been linked to elevated risk of infection compared with other biological agents, though that study had a much longer duration of treatment than our short term use for CSS in patients with COVID-19 [35]. In our cohort, we did not observe a difference in the overall rate of secondary infection between the two groups. Candidemia was the most common bloodstream infection among patients in the TCZ group; this was also the case in a previous retrospective study of 43 patients [36]. We found that *S. aureus* and *P. aeruginosa* were the most common cause of secondary bacterial pneumonia in patients with COVID-19.

In our cohort, 52% of patients were smokers, and smoking was associated with increased mortality risk (HR, 2.3; 95% CI, 1.34–3.74; p=0.002). A metaanalysis of 11,590 COVID-19 patients demonstrated increased risk of progression of the disease among smokers [37]. In addition, increased risk of ARDS development in smokers has been reported [38, 39]. Elevated IL-6 levels have been shown in both active and former smokers [40]. In our cohort, the mean IL-6 level was higher in smokers than in nonsmokers, though the difference was not statistically significant (p=0.45). The effect of smoking on TCZ efficacy is limited to small studies [41] and larger studies are needed to evaluate it.

Furthermore, our study demonstrated increased mortality among patients with a history of renal disease

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**Table 4:** Cox regression model for 30 day mortality.

| Variable                        | Hazard ratio (95% CI) | p-Value |
|---------------------------------|-----------------------|---------|
| Tocilizumab                     | 1.18 (0.71–1.96)      | 0.516   |
| Hydroxychloroquine              | 0.61 (0.33–1.12)      | 0.109   |
| Hydroxychloroquine + azithromycin| 0.37 (0.17–0.81)    | 0.012   |
| Renal disease<sup>a</sup>       | 2.21 (1.30–3.75)      | 0.003   |
| Smoking<sup>b</sup>             | 2.35 (1.34–4.09)      | 0.003   |
| Corticosteroid duration<sup>c</sup>| 0.80 (0.70–0.90)   | <0.001  |

<sup>a</sup>Renal disease was categorized as having no renal disease or chronic kidney disease stage III–V (including hemodialysis). <sup>b</sup>Smoking was categorized as either nonsmoker or smoker (both active and prior history). <sup>c</sup>Corticosteroid duration was accounted for as a continuous variable. CI, confidence interval.
TCZ was shown to be efficacious and safe in a multicenter study of 371 patients with rheumatoid arthritis and concomitant renal insufficiency [42]. In our study, 13 patients in the TCZ group required renal supplemental therapy. This likely reflects the severity of the illness rather than drug toxicity as the onset of AKI occurred mostly prior to TCZ administration.

Our results showed reduced mortality risk in patients who received hydroxychloroquine in combination with azithromycin (HR, 0.37; 95% CI, 0.17–0.81; p=0.012). Hydroxychloroquine inhibits production of IL-1, IL-6, TNF, and IFNγ [43], which are also implicated in CSS [11, 12]. Azithromycin, a macrolide antibiotic, has also been shown to inhibit IFN-gamma and TNF-alpha in natural killer cells [44]. Moreover, azithromycin has shown synergistic activity against SARS-CoV-2 when combined with HCQ in vitro [45]. The benefit observed in our study could be related to the immunomodulatory effect of these antimicrobial agents; however, our finding is limited by both the retrospective design and a small sample size (n=30) of patients who received this combined treatment. A randomized, controlled trial of 1,561 patients found no survival benefit at 28 days [46]. Cardiopulmonary arrest was observed in seven patients, and the predominant cause of arrest was worsening hypoxia and shock rather than toxicity related to the specific therapeutics [46].

All patients in our study received corticosteroids for a mean duration of 6.5 days. In our multivariate analysis, longer duration of corticosteroid treatment was associated with reduced mortality risk (HR, 0.80; 95% CI, 0.71–0.90; p=0.0003). Previous authors have suggested that inflammation may recur after abrupt discontinuation of corticosteroid therapy because of a subsequent reconstituted systemic inflammation [47]. There was no statistical difference in the mean corticosteroid duration or timing of administration from admission between the TCZ and comparator groups in our study. Given the recent mortality reduction with corticosteroid use documented in a previous study [19], failure of TCZ to show improved outcomes in our study could have been confounded by the corticosteroid usage. A cohort study [48] of 154 mechanically ventilated patients treated with TCZ found a 45% reduction in hazard of death; however, overall corticosteroid use in that study was 25%, in contrast to the 100% rate of use in our cohort.

**Limitations**

Our study had several limitations. The first limitation was the method of selection of patients who received TCZ therapy during their hospitalization. This was done utilizing our hospital guidelines, but there was some variability in how patients were selected and hence, our retrospective study population may incorporate some ordering physician bias. Although the data demonstrated very few statistically significant differences between the TCZ and comparator groups, close examination demonstrated higher initial LDH, BMI, and trends toward higher IL-6 levels, more frequent invasive ventilation use, more frequent vasopressor use, and longer hospitalization in the patients treated with TCZ, which could represent a bias toward treating the sickest patients with TCZ. This would not be inconsistent nor unexpected for the type of off label use addressed in this study; in addition to having a potential benefit of decreasing inflammation, TCZ use also might come with the adverse burden of additional immunosuppression in patients who are already infected and critically ill.

Additionally, our study was retrospective in nature with a small sample size. About 90% of the patients who received TCZ in our study had severe disease with respiratory failure requiring mechanical ventilation; therefore, our data did not assess the potential benefit of TCZ in preventing disease progression in patients with less severe disease. Finally, the use of corticosteroid, antimicrobial, and other treatment interventions in our study are confounding factors.

**Conclusions**

This cohort study showed no improved survival with the use of TCZ in critically ill patients with COVID-19. Our study did not investigate potential efficacy of TCZ when administered earlier in the clinical course of disease or in a less ill subset of patients with COVID-19. More definitive results from randomized clinical trials are needed to fully assess the potential role of TCZ in the treatment COVID-19.

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**Informed consent:** A waiver for consent and approval to include vulnerable population data from incarcerated patients was obtained.

**Ethical approval:** The study was approved by the Henry Ford Institutional Review Board (IRB 13860).

**Disclaimer:** This study describes off label use of tocilizumab.

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