OBSERVATIONAL STUDY

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# Tocilizumab in Coronavirus Disease 2019-Related Critical Illness: A Propensity Matched Analysis

**Prabalini Rajendram, MD**[1]

**Gretchen L. Sacha, PharmD**[2]

**Omar Mehkri, MD**[1]

**Xiaofeng Wang, PhD**[3]

**Xiaozhen Han, MS**[3]

**Vidula Vachharajani, MD**[1]

**Abhijit Duggal, MD**[1]

**OBJECTIVES:** The primary objective was to evaluate ICU mortality at 28 days in patients with severe hypoxemic respiratory failure due to coronavirus disease 2019 infection who received tocilizumab. The secondary objectives were to evaluate ICU-, hospital-, mechanical ventilation-, and vasopressor-free days at day 28 and development of secondary infections.

**DESIGN:** Retrospective, observational, multicenter, cohort study between March 15, 2020, and May 31, 2020. Using propensity score matching based on ICU admission source, C-reactive protein, Sequential Organ Failure Assessment score, vasopressor use, age, race, weight, and mechanical ventilation, patients who received tocilizumab were matched to patients who did not receive tocilizumab.

**SETTING:** Ten hospitals within the Cleveland Clinic Enterprise.

**PATIENTS:** Adult patients admitted to a medical, surgical, neurosciences, or mixed ICU with severe acute respiratory syndrome coronavirus 2 infection.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Four-hundred forty-four patients were included: 342 patients (77%) did not receive tocilizumab and 102 patients (23%) received tocilizumab. Of those, 82 patients in each arm were matched. Before matching, patients who received tocilizumab had higher Sequential Organ Failure Assessment scores (6.1 ± 3.4 vs 4.7 ± 3.6), higher C-reactive protein (21.0 ± 10.2 vs 13.7 ± 9.6 mg/dL), higher frequency of intubation, vasopressor requirement, and paralytics. After matching, characteristics were more balanced and over 85% of patients required mechanical ventilation. ICU mortality was lower in tocilizumab group (23.2% vs 37.8%; risk difference, −15%; 95% CI, −29% to −1%), with more ICU-, hospital-, and vasoactive-free days at day 28 compared with those who did not receive tocilizumab. There was no difference in mechanical ventilation-free days at day 28 or development of secondary infections.

**CONCLUSIONS:** Tocilizumab use was associated with a significant decrease in ICU mortality in critically ill coronavirus disease 2019 patients with severe hypoxemic respiratory failure. Future randomized controlled trials limited to tocilizumab administration in critically ill coronavirus disease 2019 patients, with severe hypoxemic respiratory failure, are needed to support these findings.

**KEY WORDS:** acute hypoxemic respiratory failure; coronavirus disease 2019 critical illness; cytokine storm; tocilizumab



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The viral pneumonia that ensues after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may result in mild, self-limiting symptoms or, in severe cases, progress to acute respiratory distress syndrome (ARDS) and multiple organ failure thought to be a result of a cytokine storm often necessitating ICU utilization (1–5). Five percent to 14% of SARS-CoV-2 positive patients are critically ill requiring ICU admission (1, 5, 6). Triggers for severe illness with SARS-CoV-2 are not completely understood, however, an exaggerated innate immune response has been implicated in rapidly progressive ARDS and cytokine storm.

SARS-CoV-2 enters the target cell via angiotensin-converting enzyme 2, mostly expressed in the alveolar epithelial cells (7–10). The resulting symptomology seems to be determined by the extent of the host's immune system imbalance. Previous studies of SARS revealed that cytokine dysregulation; up-regulation of pro-inflammatory chemokines and cytokines, and down-regulation of early anti-viral cytokines (11–15), is likely the cause of increased vascular permeability and endothelial dysfunction leading to severe inflammatory response and extensive lung damage in addition to hemodynamic instability and hypercoagulability (16–18). Early reports of coronavirus disease 2019 (COVID-19), suggested elevated pro-inflammatory cytokines and chemokines (C-reactive protein [CRP], ferritin, interleukin-6 [IL-6] among many others in patients with severe disease) (19, 20). IL-6 has been implicated in many pathogenic inflammatory states including the cytokine storm following infection with other coronavirus infections (SARS and Middle East respiratory syndrome) (14, 21, 22). As a result, many studies have attempted to study anti-cytokine therapy as a potential therapeutic strategy to mitigate the cytokine storm in COVID-19 (16, 17, 20, 21, 23–32).

Two early single-center studies from Wuhan, China, including patients with COVID-19 pneumonia and cytokine storm, suggested clinical benefit with use of the IL-6 inhibitor, tocilizumab (31, 32). These and other case reports propelled the off-label use of tocilizumab for the treatment of COVID-19 cytokine storm across the world. To date, there have been several case reports (31–33), case series (34–36), retrospective evaluations (25–30, 37), and three recent randomized controlled trials (RCTs) (38–40) of tocilizumab use in COVID-19 critical illness. Although benefit was seen in the retrospective evaluations of tocilizumab, the RCTs conclude no benefit associated with its use, but these studies have not evaluated a severely ill, primarily mechanically ventilated patient population and leave unanswered questions about tocilizumabs efficacy in the critically ill patient population. Our study aims to evaluate the effects of tocilizumab on ICU mortality, biomarker profiles, and clinical outcomes in a propensity score matched population of patients admitted to the ICU with COVID-19–related cytokine storm.

## MATERIALS AND METHODS

### Study Design

This was a retrospective, observational, cohort study conducted at 10 hospitals across the Cleveland Clinic Enterprise. All patients who were admitted to a medical, surgical, neurosciences, or mixed ICU between March 15, 2020, and May 31, 2020, with COVID-19 infection were identified and collected in an internal ICU registry. The study was approved by the Cleveland Clinic Institutional Review Board (Number 20-381).

### Patients

Patients were included if they had polymerase chain reaction (PCR) confirmed SARS-CoV-2 and were admitted to the ICU at the time of tocilizumab administration. Patients were excluded if they received additional doses of tocilizumab more than 48 hours after the initial dose or if they received tocilizumab through a RCT. Patients who received tocilizumab were compared with patients who did not receive tocilizumab (control group) after propensity score matching. All data points were collected through electronic medical record (EMR) database request retrieval and manual abstraction. Data extracted from the EMR included demographics, comorbidities, laboratory values, medication utilization, recorded vital signs, and clinical outcomes. Follow-up continued through June 28, 2020 (28 d after end of study period).

### Outcomes

The primary outcome for our study was ICU mortality. Secondary outcomes included 28-day mortality, ICU- and hospital-free days at day 28, mechanical

ventilation-free days at day 28, vasopressor-free days at day 28, change in Sequential Organ Failure Assessment (SOFA) score, development of secondary infections, and need for renal replacement therapy. We also evaluated the effect of tocilizumab receipt on biomarker levels compared with the control group. ICU and hospital length of stay, mechanical ventilation duration, and vasopressor duration were all calculated as free days at 28 days after ICU admission or tocilizumab administration (for patients who received tocilizumab) (41). Further details on definitions of clinical outcomes are detailed in **eTable 1** (Supplemental Digital Content, http://links.lww.com/CCX/A498).

### Tocilizumab Use

At our institution, in March 2020, a multidisciplinary team reviewed available literature and developed a COVID-19 ICU based treatment algorithm. Based on the lack of data, limitation in tocilizumab supply at that time and pathophysiological plausibility in treatment of chimeric antigen receptor T cell-induced cytokine release syndrome, the multidisciplinary team suggested tocilizumab use for cytokine storm in patients who met the following criteria; PCR documented SARS-CoV-2 infection, CRP greater than 3 mg/dL or ferritin greater than 400 ng/mL, and chest imaging with infiltrates and $Pao_2/Fio_2$ (P/F) ratio less than or equal to 250 mm Hg and positive end-expiratory pressure greater than or equal to 8 mm Hg on mechanical ventilation within 6 hours post-intubation. Tocilizumab was recommended to be dosed at 4–8 mg/kg (maximum dose 400 mg) IV for one dose only and repeat doses were discouraged. In addition to the aforementioned criteria, tocilizumab was restricted to consultation with Infectious Diseases and not all patients who met the criteria received tocilizumab as use was ultimately at Critical Care and Infectious Disease physicians' discretion.

### Statistical Analysis

To reduce the impact of treatment-selection bias in the estimation of treatment effects, propensity score matching was conducted. Variables were selected for inclusion in the propensity score based on potential impact on receipt of tocilizumab and association with ICU mortality (42). The variables included were ICU admission source, maximum CRP, SOFA score at ICU admission, vasopressor use, age, race, weight, and the use of mechanical ventilation during hospital admission. A propensity score density plot and Love plot were generated to examine the balance of propensity score and covariate distribution between the two groups (**eFigs. 1** and **2**, Supplemental Digital Content, http://links.lww.com/CCX/A498) (43). The study variables were described using sample mean with SDs or count with proportions as appropriate, and standardized mean difference (SMD) were reported for comparison between cohorts before and after matching. A multivariable logistic regression evaluating ICU mortality was assessed. Additionally, to account for concern for immortal time bias, a time-dependent covariate Cox regression model with time-dependent indicators of whether a patient received tocilizumab at each point in time were performed for the outcome of time to 28-day mortality (44). Variables included in the multivariable logistic and Cox regression models were selected based on the biologic plausibility to impact mortality. Multicollinearity of included variables was assessed with variance inflation factors, and no factors were deemed to be collinear for either model. To assess the trend of biomarkers (CRP, ferritin, D-dimer, IL-6 levels, and absolute lymphocytes) after initiation of tocilizumab, both raw data with smooth curves using Loess method and plot of fitted line with 95% CI were generated for the two patient groups (tocilizumab and no tocilizumab) separately, in both matched and unmatched patient populations. Linear mixed effect modeling was used to compare the slopes of the fitted lines of the two groups. All analyses were two-tailed and were performed at a significance level of 0.05. R Version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 software (SAS Institute, Cary, NC) were used for all analyses.

## RESULTS

### Patients

There were 453 patients admitted to an ICU with PCR positive SARS-CoV-2 infection. After appropriate exclusion, 444 patients were included: 342 patients (77%) did not receive tocilizumab and 102 patients (23%) received tocilizumab (**Fig. 1**). There were 82 patients who received tocilizumab able to be matched to 82 patients who did not receive tocilizumab.

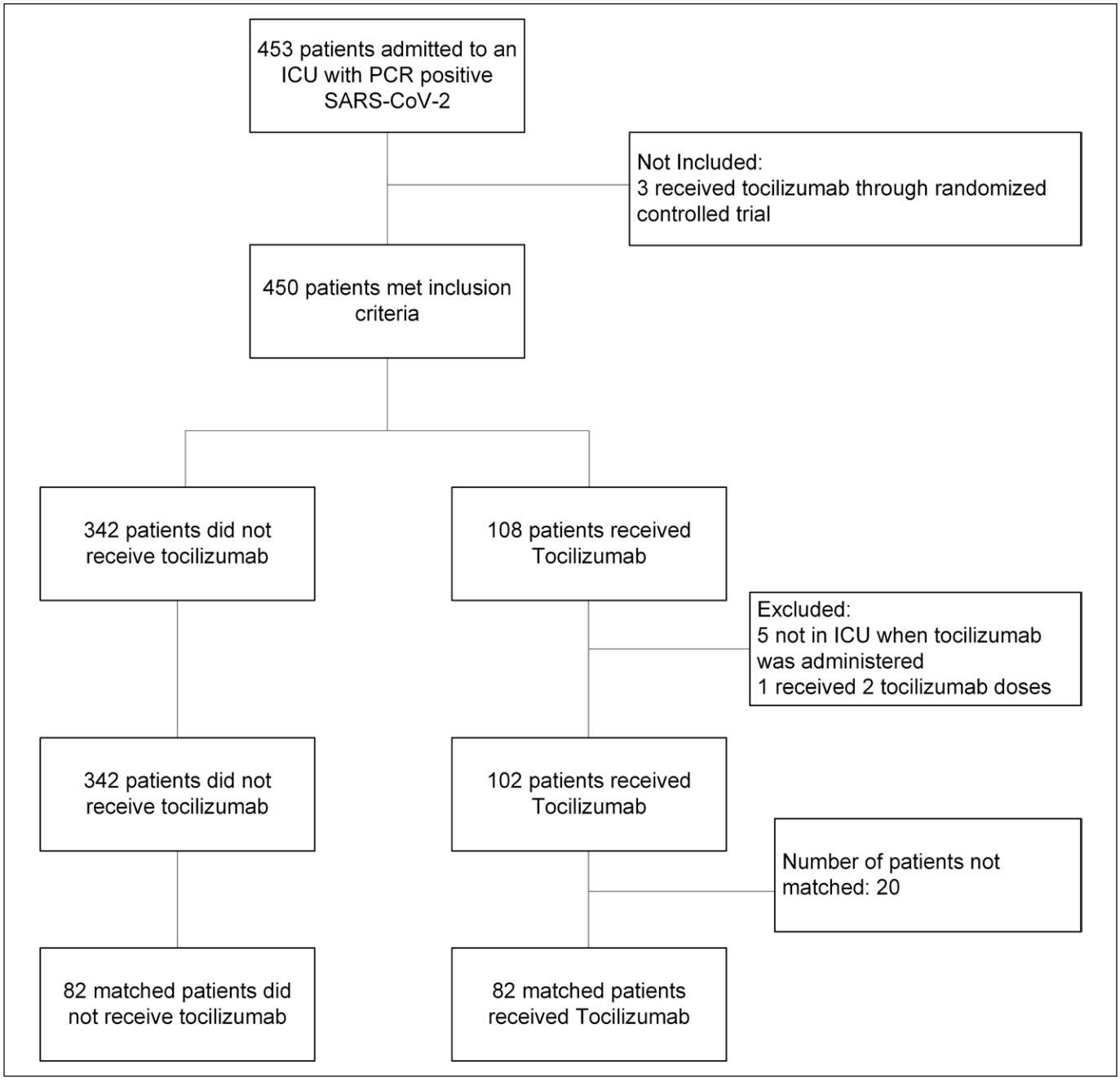


**Figure 1.** Patient inclusion tree. PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## Baseline Characteristics

Before matching, patients who received tocilizumab were younger (62 ± 12 vs 68 ± 14 yr; SMD, 0.44) and more often had no chronic comorbidities. Additionally, the tocilizumab cohort had higher SOFA scores (6.1 ± 3.4 vs 4.7 ± 3.6; SMD, 0.41), baseline CRP concentrations (21.0 ± 10.2 vs 13.7 ± 9.6 mg/dL; SMD, 0.74), frequency of intubation (81.4% vs 33.9%; SMD, 1.10) (**Table 1**), vasopressor use (84.3% vs 41.2%; SMD, 0.99), and paralytic use (52.9% vs 18.7%; SMD, 0.76) at baseline. After matching for ICU admission source (emergency department vs other), maximum CRP, SOFA score at ICU admission, vasopressor use, age, race, weight, and the use of mechanical ventilation during hospital admission, baseline characteristics were more balanced in regards to baseline characteristics and severity of illness (Table 1).

We found no difference in the number of patients who required mechanical ventilation throughout their ICU admission (87.8% tocilizumab vs 85.4% no

**TABLE 1.**
**Clinical Characteristics at Baseline and Throughout Hospitalization Before and After Matching**

| Variable | Before Matching | | | After Matching | | |
|---|---|---|---|---|---|---|
| | Tocilizumab, *n* = 102 | Control, *n* = 342 | SMD | Tocilizumab, *n* = 82 | Control, *n* = 82 | SMD |
| Baseline characteristics at ICU admission | | | | | | |
| Age, yr | 62 ± 12 | 68 ± 14 | 0.44 | 64 ± 12 | 64 ± 13 | 0.04 |
| Male sex, *n* (%) | 58 (56.9) | 204 (59.6) | 0.05 | 48 (58.5) | 55 (67.1) | 0.18 |
| Race, *n* (%) | | | | | | |
| White | 66 (64.7) | 183 (53.5) | 0.24 | 50 (61.0) | 47 (57.3) | 0.11 |
| Black | 29 (28.4) | 134 (39.2) | | 25 (30.5) | 29 (35.4) | |
| Other | 7 (6.9) | 25 (7.3) | | 7 (8.5) | 6 (7.3) | |
| Weight, kg | 99.3 ± 28.3 | 88.6 ± 24.4 | 0.41 | 96.9 ± 27.2 | 96.0 ± 26.4 | 0.04 |
| Body mass index | 34.2 ± 9.2 | 30.2 ± 7.7 | 0.46 | 33.1 ± 8.0 | 31.9 ± 8.3 | 0.15 |
| Hospital location, *n* (%) | | | | | | |
| Main campus | 16 (15.7) | 70 (20.5) | 0.13 | 14 (17.1) | 22 (26.8) | 0.24 |
| Regional facility | 86 (84.3) | 272 (79.5) | | 68 (82.9) | 60 (73.2) | |
| ICU type, *n* (%) | | | | | | |
| Medical ICU | 58 (56.9) | 172 (50.3) | 0.25 | 47 (57.3) | 44 (53.7) | 0.22 |
| Mixed ICU | 41 (40.2) | 143 (41.8) | | 33 (40.2) | 31 (37.8) | |
| Surgical ICU | 0 (0.0) | 3 (0.9) | | 0 (0.0) | 0 (0.0) | |
| Neurosciences ICU | 3 (2.9) | 24 (7.0) | | 2 (2.4) | 7 (8.5) | |
| ICU admission source, *n* (%) | | | | | | |
| Emergency department | 36 (35.3) | 184 (53.8) | 0.51 | 27 (32.9) | 28 (34.1) | 0.39 |
| Regular nursing floor | 51 (50.0) | 103 (30.1) | | 43 (52.4) | 31 (37.8) | |
| Outside hospital | 15 (14.7) | 43 (12.6) | | 12 (14.6) | 21 (25.6) | |
| Other ICU | 0 (0.0) | 5 (1.5) | | 0 (0.0) | 1 (1.2) | |
| Operating room | 0 (0.0) | 6 (1.8) | | 0 (0.0) | 1 (1.2) | |
| Skilled nursing facility | 0 (0.0) | 1 (0.3) | | 0 (0.0) | 0 (0.0) | |
| No chronic comorbidities, *n* (%) | 44 (43.1) | 119 (34.8) | 0.17 | 33 (40.2) | 21 (25.6) | 0.32 |
| Diabetes mellitus, *n* (%) | 39 (38.2) | 122 (35.7) | 0.05 | 33 (40.2) | 34 (41.5) | 0.03 |
| Chronic obstructive pulmonary disease, *n* (%) | 26 (25.5) | 98 (28.7) | 0.07 | 23 (28.0) | 25 (30.5) | 0.05 |
| End-stage renal disease on chronic dialysis, *n* (%) | 4 (3.9) | 18 (5.3) | 0.06 | 3 (3.7) | 6 (7.3) | 0.16 |

(*Continued*)

**TABLE 1. (*Continued*).**
**Clinical Characteristics at Baseline and Throughout Hospitalization Before and After Matching**

| Variable | Before Matching | | | After Matching | | |
|---|---|---|---|---|---|---|
| | Tocilizumab, *n* = 102 | Control, *n* = 342 | SMD | Tocilizumab, *n* = 82 | Control, *n* = 82 | SMD |
| Cirrhosis or hepatic failure, *n* (%) | 2 (2.0) | 19 (5.6) | 0.19 | 2 (2.4) | 4 (4.9) | 0.13 |
| Cancer, *n* (%) | 4 (3.9) | 22 (6.4) | 0.11 | 4 (4.9) | 4 (4.9) | 0.00 |
| Immune suppressed, *n* (%) | 15 (14.7) | 52 (15.2) | 0.01 | 13 (15.9) | 18 (22.0) | 0.16 |
| Acute Physiology and Chronic Health Evaluation III score | 57.6 ± 24.5 | 59.8 ± 27.3 | 0.08 | 58.5 ± 23.6 | 65.7 ± 24.5 | 0.30 |
| Acute Physiology Score | 45.7 ± 23.1 | 44.6 ± 25.0 | 0.05 | 45.5 ± 21.1 | 51.9 ± 25.2 | 0.27 |
| Sequential Organ Failure Assessment score[a] | 6.1 ± 3.4 | 4.7 ± 3.6 | 0.41 | 6.0 ± 3.3 | 6.4 ± 3.6 | 0.11 |
| CRP[a], mg/dL | 21.0 ± 10.2 | 13.7 ± 9.6 | 0.74 | 20.4 ± 10.1 | 17.2 ± 12.3 | 0.28 |
| Ferritin[a], ng/mL | 1,366.2 ± 1,080.6 | 1,968.7 ± 7,351.5 | 0.12 | 1,398.2 ± 1,143.3 | 4,159.9 ± 13,454.1 | 0.29 |
| Lactate dehydrogenase[a], U/L | 508.3 ± 155.9 | 456.1 ± 252.7 | 0.25 | 530.8 ± 157.2 | 528.5 ± 293.2 | 0.01 |
| Interleukin-6[a], pg/mL | 104.2 ± 271.0 | 31.6 ± 52.9 | 0.37 | 46.3 ± 60.5 | 51.3 ± 94.4 | 0.06 |
| Procalcitonin[a], ng/mL | 1.6 ± 2.8 | 2.7 ± 9.1 | 0.16 | 1.8 ± 3.0 | 2.8 ± 4.8 | 0.26 |
| D-dimer[a], fibrinogen-equivalent unit | 4,244.5 ± 7,315.8 | 3,311.9 ± 5,160.0 | 0.15 | 4,352.2 ± 8,123.5 | 4,373.0 ± 6,849.7 | 0.003 |
| Serum creatinine[a], mg/dL | 1.8 ± 1.4 | 2.2 ± 2.7 | 0.19 | 1.7 ± 1.4 | 2.7 ± 3.4 | 0.38 |
| Troponin-T[a], ng/mL | 0.14 ± 0.36 | 0.10 ± 0.29 | 0.10 | 0.14 ± 0.36 | 0.12 ± 0.27 | 0.07 |
| Triglyceride[a], mg/dL | 217.0 ± 190.3 | 162.7 ± 122.8 | 0.34 | 191.9 ± 125.4 | 211.4 ± 193.1 | 0.12 |
| Lactate[a], mmol/L | 1.5 ± 0.51 | 2.3 ± 3.3 | 0.35 | 1.5 ± 0.52 | 1.7 ± 1.4 | 0.21 |
| N-terminal pro-B-type natriuretic peptide[a], pg/mL | 1,863.4 ± 6,001.8 | 4,663.2 ± 10,424.6 | 0.33 | 2,032.5 ± 6,267.2 | 6,530.2 ± 15,950.5 | 0.37 |
| WBC[a], k/uL | 9.8 ± 4.2 | 9.5 ± 5.8 | 0.06 | 9.6 ± 3.9 | 10.2 ± 5.8 | 0.12 |
| Absolute lymphocyte[a], k/uL | 0.89 ± 0.55 | 1.00 ± 0.59 | 0.19 | 0.90 ± 0.56 | 0.83 ± 0.46 | 0.14 |
| Baseline temperature[a], degrees | | | | | | |
| Fahrenheit | 101.3 ± 1.8 | 100.4 ± 1.6 | 0.55 | 101.2 ± 1.8 | 100.8 ± 1.7 | 0.24 |
| Celsius | 38.5 ± 0.98 | 38.0 ± 0.91 | | 38.4 ± 0.98 | 38.2 ± 0.92 | |
| Supplemental $O_2$[a], *n* (%) | | | | | | |
| Baseline noninvasive positive pressure ventilation | 1 (0.98) | 18 (5.3) | 0.25 | 0 (0.0) | 7 (8.5) | 0.43 |
| Baseline invasive ventilation | 83 (81.4) | 116 (33.9) | 1.10 | 66 (80.5) | 54 (65.9) | 0.34 |
| Baseline $Pao_2/Fio_2$ ratio[a] | 132.7 ± 65.1 | 186.7 ± 133.2 | 0.52 | 134.8 ± 68.4 | 149.8 ± 82.2 | 0.20 |

(*Continued*)

**TABLE 1. (*Continued*).**
**Clinical Characteristics at Baseline and Throughout Hospitalization Before and After Matching**

| Variable | Before Matching | | | After Matching | | |
|---|---|---|---|---|---|---|
| | Tocilizumab, *n* = 102 | Control, *n* = 342 | SMD | Tocilizumab, *n* = 82 | Control, *n* = 82 | SMD |
| Medication utilization and laboratories throughout hospitalization | | | | | | |
| Intubated during ICU admission, *n* (%) | 92 (90.2) | 139 (40.6) | 1.22 | 72 (87.8) | 70 (85.4) | 0.07 |
| Maximum CRP, mg/dL | 25.1 ± 11.7 | 19.0 ± 12.5 | 0.51 | 23.6 ± 10.8 | 23.9 ± 14.7 | 0.02 |
| Hydroxychloroquine, *n* (%) | 65 (63.7) | 132 (38.6) | 0.52 | 49 (59.8) | 39 (47.6) | 0.25 |
| Lopinavir/ritonavir, *n* (%) | 7 (6.9) | 1 (0.3) | 0.36 | 6 (7.3) | 1 (1.2) | 0.31 |
| Remdesivir, *n* (%) | 11 (10.8) | 35 (10.2) | 0.02 | 11 (13.4) | 9 (11.0) | 0.08 |
| Azithromycin, *n* (%) | 56 (54.9) | 119 (34.8) | 0.41 | 40 (48.8) | 38 (46.3) | 0.05 |
| Systemic corticosteroids, *n* (%) | | | | | | |
| Hydrocortisone | 36 (35.3) | 48 (14.0) | 0.51 | 28 (34.1) | 21 (25.6) | 0.19 |
| Methylprednisolone | 21 (20.6) | 38 (11.1) | 0.26 | 17 (20.7) | 19 (23.2) | 0.06 |
| Prednisone | 13 (12.7) | 37 (10.8) | 0.06 | 10 (12.2) | 9 (11.0) | 0.04 |
| Vasopressor use, *n* (%) | 86 (84.3) | 141 (41.2) | 0.99 | 66 (80.5) | 69 (84.1) | 0.10 |
| Norepinephrine | 85 (83.3) | 139 (40.6) | 0.98 | 66 (80.5) | 68 (82.9) | 0.06 |
| Epinephrine | 6 (5.9) | 6 (1.8) | 0.22 | 6 (7.3) | 3 (3.7) | 0.16 |
| Phenylephrine | 14 (13.7) | 34 (9.9) | 0.12 | 9 (11.0) | 17 (20.7) | 0.27 |
| Vasopressin | 19 (18.6) | 40 (11.7) | 0.19 | 14 (17.1) | 20 (24.4) | 0.18 |
| Dopamine | 0 (0.0) | 2 (0.6) | 0.11 | 0 (0.0) | 1 (1.2) | 0.16 |
| Maximum norepinephrine dose, µg/min | 27.4 ± 26.0 | 27.6 ± 22.4 | 0.01 | 27.5 ± 27.9 | 27.8 ± 21.4 | 0.01 |
| Paralytics, *n* (%) | 54 (52.9) | 64 (18.7) | 0.76 | 38 (46.3) | 34 (41.5) | 0.10 |
| Intermittent dosing | 41 (40.2) | 47 (13.7) | 0.62 | 31 (37.8) | 24 (29.3) | 0.18 |
| Continuous infusion | 48 (47.1) | 41 (12.0) | 0.83 | 33 (40.2) | 25 (30.5) | 0.21 |
| Inhaled vasodilators, *n* (%) | 5 (4.9) | 7 (2.0) | 0.16 | 4 (4.9) | 5 (6.1) | 0.05 |

CRP = C-reactive protein, SMD = standardized mean difference.
[a]Evaluated within 24 hr of tocilizumab in patients who received tocilizumab and within 24 hr of ICU admission in those who did not receive tocilizumab.

tocilizumab; SMD, 0.07) after propensity matching. However, at the time of ICU admission or tocilizumab receipt, the tocilizumab group had higher frequency of intubation (80.5% vs 65.9%) but lower frequency of receiving noninvasive positive pressure ventilation (0% vs 8.5%). After matching, baseline P/F ratio was 134.8 ± 68.4 for the tocilizumab group and 149.8 ± 82.2 for control group.

### Primary Outcome

Before matching, there was no difference in the primary outcome of ICU mortality between patient cohorts (21.6% tocilizumab vs 21.1% no tocilizumab) (**Table 2**). After matching, however, ICU mortality was significantly lower in the tocilizumab cohort (23.2% vs 37.8%; risk difference, –15%; 95% CI, –29% to –1%). Difference in ICU mortality was not significant after adjustment for SOFA score, Acute Physiology and Chronic Health Evaluation (APACHE) III score, maximum CRP, vasopressor use, age, weight, hospital location, and baseline P/F ratio (odds ratio [OR], 0.67; 95% CI, 0.25–1.81).

### Secondary Outcomes

We found no significant difference in 28-day mortality between patient groups after matching (risk difference, –11%; 95% CI, –25% to 3%). After adjustment for SOFA score, APACHE III score, maximum CRP, vasopressor use, age, weight, hospital location, and baseline P/F ratio, tocilizumab receipt was not associated with 28-day mortality (hazard ratio [HR], 0.56; 95% CI, 0.22–1.43). There were more ICU-free days at day 28 (mean difference, –2.87 d; 95% CI, –5.67 to –0.06 d), hospital-free days at day 28 (mean difference, –3.04 d; 95% CI, –5.28 to –0.08 d), and vasopressor-free days at day 28 (mean difference, –3.31; 95% CI, –6.58 to –0.04) in the tocilizumab cohort (Table 2). There was no difference in mechanical ventilation-free days at day 28 (mean difference, –2.10 d; 95% CI, –5.31 to 1.11 d). The tocilizumab cohort were more likely to be discharged home compared with the control cohort (32.9% vs 17.1%; OR, 3.15; 95% CI, 1.33–7.45). There was no difference in the rates of patients who were discharged to a long-term healthcare facility, hospice, or another hospital.

### Biomarker Trends

There was a significant difference in the predicted slope of CRP ($p < 0.0001$) and ferritin ($p = 0.0005$) between the tocilizumab and control group, however, CRP and ferritin decreased in both cohorts (**Fig. 2**, ***A*** and ***B***). There was no significant difference between the slopes of predicted D-dimer in each patient cohort ($p = 0.99$) (**Fig. 2*C***). IL-6 levels significantly increased in tocilizumab group after its initiation, compared with the control group ($p = 0.037$) (**Fig. 2*D***). Absolute lymphocyte count increased in both patient cohorts, but there was a significant difference in the predicted slopes of patient cohorts ($p < 0.0001$) (**Fig. 2*E***). Biomarker trends for patients before matching are detailed in **eFigure 3** (Supplemental Digital Content, http://links.lww.com/CCX/A498).

### Secondary Infections

Rates of secondary infections were higher in the tocilizumab cohort (26.5% vs 15.8%; risk difference, 11%; 95% CI, 1–20%) before matching. However, after matching, there was no difference in rates of secondary infection (25.6% vs 25.6%; risk difference, 0%; 95% CI, –13% to 13%). Pneumonia was the most common infection type followed by bloodstream infections, occurring in 64.3% and 23.8% of patients, respectively (**Table 3**).

## DISCUSSION

In the current study, a significant reduction in ICU mortality (risk difference of 15%) in critically ill patients with COVID-19 who received tocilizumab was seen after a propensity matched analysis. When censored at 28 days, the mortality difference decreased to 11%. Although not statistically significant, tocilizumab use still indicates clinical benefit in a critically ill patient population. Additionally, tocilizumab receipt was associated with more ICU-, hospital-, and vasopressor-free days at day 28 and a higher likelihood of discharge to home. Exposure to tocilizumab was not associated with increased secondary infections.

Our study focused on tocilizumab use in critically ill patients with severe hypoxemic respiratory failure (P/F < 150 mm Hg). Over 70% of patients were mechanically ventilated at baseline and 90% required mechanical ventilation during their ICU admission. To date, only one other retrospective study included only mechanically ventilated patients receiving tocilizumab for COVID-19 (25). In the current evaluation, both ICU mortality (23.2% vs 37.8%; risk difference, –15%; 95% CI, –29% to –1%) and 28-day mortality (24.4% vs 35.4%; risk difference, –11%; 95% CI, –25% to 3%) were significantly decreased in the critically ill population who received tocilizumab. This is similar to the findings reported by Gupta et al (37), which showed tocilizumab use was associated with 29% reduction in the risk of mortality

## TABLE 2.
## Clinical Outcomes Before and After Matching

| Outcome | Before Matching | | | After Matching | | |
|---|---|---|---|---|---|---|
| | Tocilizumab, *n* = 102 | Control, *n* = 342 | MD/RD (95% CI)[a] | Tocilizumab, *n* = 82 | Control, *n* = 82 | MD/RD (95% CI)[a] |
| ICU mortality, *n* (%) | 22 (21.6) | 72 (21.1) | 1% (–9% to 10%) | 19 (23.2) | 31 (37.8) | –15% (–29% to –1%) |
| 28-d mortality, *n* (%) | 23 (22.5) | 82 (24.0) | –1% (–11% to 8%) | 20 (24.4) | 29 (35.4) | –11% (–25% to 3%) |
| ICU-free days at day 28 | 10.3 ± 8.8 | 15.8 ± 10.9 | –5.50 (–7.57 to –3.43) | 11.1 ± 8.9 | 8.3 ± 9.3 | 2.87 (0.06–5.67) |
| Hospital-free days at day 28 | 7.5 ± 7.3 | 12.1 ± 9.7 | –4.55 (–6.32 to –2.79) | 8.4 ± 7.5 | 5.4 ± 7.1 | 3.04 (0.80–5.28) |
| Vasoactive-free days at day 28 | 17.5 ± 10.1 | 20.7 ± 10.7 | –3.20 (–5.47 to –0.92) | 18.3 ± 10.0 | 15.0 ± 11.2 | 3.31 (0.04–6.58) |
| Mechanical ventilation-free days at day 28 | 13.0 ± 9.7 | 19.2 ± 11.2 | –6.22 (–8.47 to –3.98) | 13.6 ± 10.1 | 11.5 ± 10.7 | 2.10 (–1.11 to 5.31) |
| SOFA score at 72 hr | 7.1 ± 3.3 | 4.4 ± 3.8 | 2.68 (1.91–3.45) | 6.7 ± 3.3 | 7.4 ± 3.6 | –0.63 (–1.72 to 0.46) |
| SOFA score change | 0.95 ± 3.3 | –0.20 ± 2.7 | 1.15 (0.43–1.87) | 0.66 ± 3.3 | 1.01 ± 3.0 | –0.35 (–1.34 to 0.64) |
| Secondary infections[b], *n* (%) | 27 (26.5) | 54 (15.8) | 11% (1–20%) | 21 (25.6) | 21 (25.6) | 0% (–13% to 13%) |
| Need for renal replacement therapy, *n* (%) | 26 (25.5) | 55 (16.1) | 9% (0.1–19%) | 18 (22.0) | 27 (32.9) | –11% (–25% to 3%) |
| Discharge destination, *n* (%)[c] | | | | | | |
| Expired | 22 (21.6) | 86 (25.1) | Reference | 19 (23.2) | 31 (37.8) | Reference |
| Home | 30 (29.4) | 125 (36.5) | 0.94 (0.51–1.74) | 27 (32.9) | 14 (17.1) | 3.15 (1.33–7.45) |
| Skilled nursing facility/ long-term acute care hospital/rehabilitation | 46 (45.1) | 102 (29.8) | 1.76 (0.98–3.16) | 32 (39.0) | 30 (36.6) | 1.74 (0.82–3.71) |
| Another hospital | 1 (1.0) | 7 (2.0) | 0.56 (0.07–4.78) | 1 (1.2) | 3 (3.7) | 0.54 (0.05–5.61) |
| Hospice | 2 (2.0) | 22 (6.4) | 0.36 (0.08–1.63) | 2 (2.4) | 4 (4.9) | 0.82 (0.14–4.89) |
| Still hospitalized | 1 (1.0) | 0 (0.0) | NS | 1 (1.2) | 0 (0.0) | NS |

MD = mean difference, NS = not significant, RD = risk difference, SOFA = Sequential Organ Failure Assessment.

[a]Results compared with mean difference or risk difference with 95% CI as appropriate, unless otherwise specified.

[b]Secondary infections evaluated within the month after tocilizumab administration for patients who received tocilizumab and within the month after ICU admission for those who did not receive tocilizumab.

[c]Comparisons between groups evaluated as odds ratios with 95% CIs with expired as the reference group.

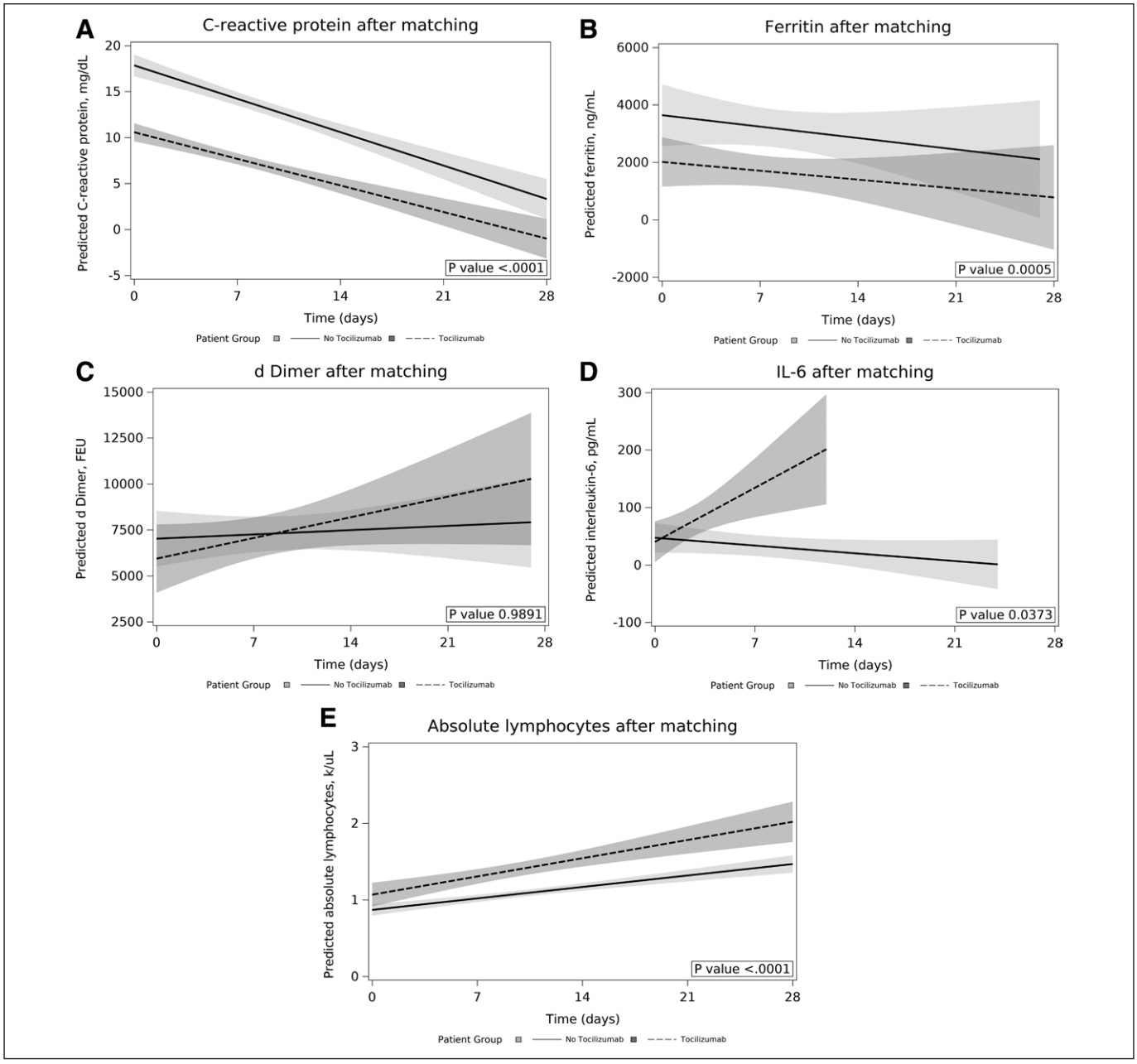


**Figure 2.** Biomarker trends. **A**, C-reactive protein (CRP) after matching. **B**, Ferritin after matching. **C**, D-dimer after matching. **D**, Interleukin-6 (IL-6) after matching. **E**, Absolute lymphocytes after matching. Each figure depicts each specific biomarker in matched patients over time from baseline until 28 d after baseline. Baseline in patients who received tocilizumab is the time of tocilizumab initiation, and baseline in patients who did not receive tocilizumab is the time of ICU admission. The *solid line* in each graph represents the predicted slope of each biomarker (with 95% CI in *light gray shaded area*) in patients who did not receive tocilizumab; the *dashed line* represents the predicted slope of each biomarker (with 95% CI in *dark gray shaded area*) in patients who received tocilizumab. A comparison of the 95% CI slopes of the predicted slopes in patients who received tocilizumab and those who did not receive tocilizumab was conducted for each biomarker. **A**, After matching, a comparison in the predicted slopes revealed a significant difference between the predicted slope of CRP in those who received tocilizumab compared with those who did not receive tocilizumab ($p < 0.0001$). **B**, After matching, a comparison in the predicted slopes revealed a significant difference between the predicted slope of ferritin in those who received tocilizumab compared with those who did not receive tocilizumab ($p = 0.0005$). **C**, After matching, a comparison in the predicted slopes revealed no significant difference between the predicted slope of D-dimer in those who received tocilizumab compared with those who did not receive tocilizumab ($p = 0.99$). **D**, After matching, a comparison in the predicted slopes revealed a significant difference between the predicted slope of IL-6 in those who received tocilizumab compared with those who did not receive tocilizumab ($p = 0.037$). **E**, After matching, a comparison in the predicted slopes revealed a significant difference between the predicted slope of absolute lymphocyte count in those who received tocilizumab compared with those who did not receive tocilizumab ($p < 0.0001$). FEU = fibrinogen-equivalent unit.

## TABLE 3.
## Secondary Infection Development

| Variable | Before Matching | | After Matching | |
|---|---|---|---|---|
| | Tocilizumab, *n* = 102 | Control, *n* = 342 | Tocilizumab, *n* = 82 | Control, *n* = 82 |
| Secondary infection, *n* (%) | 27 (26.5) | 54 (15.8) | 21 (25.6) | 21 (25.6) |
| Time to secondary infection, d | 11.4 ± 6.5 | 9.7 ± 8.1 | 11.6 ± 7.2 | 9.1 ± 6.0 |
| Type of infection[a], *n* (%) | | | | |
| Pneumonia | 16 (59.3) | 27 (50.0) | 13 (61.9) | 14 (66.7) |
| Bloodstream infection | 9 (33.3) | 13 (23.6) | 6 (28.6) | 4 (19.0) |
| *Clostridioides difficile* | 1 (3.7) | 2 (3.7) | 1 (4.8) | 1 (4.8) |
| Urinary tract infection | 3 (11.1) | 14 (25.9) | 2 (9.5) | 3 (14.3) |
| Wound infection | 0 (0.0) | 3 (5.6) | 0 (0.0) | 0 (0.0) |
| Intra-abdominal infection | 1 (3.7) | 0 (0.0) | 1 (4.8) | 0 (0.0) |
| Pathogen[a], *n* (%) | | | | |
| Candida species | 4 (14.8) | 5 (9.3) | 3 (14.3) | 3 (14.3) |
| *C. difficile* | 1 (3.7) | 2 (3.7) | 1 (4.8) | 1 (4.8) |
| Citrobacter species | 1 (3.7) | 2 (3.7) | 1 (4.8) | 2 (9.5) |
| Corynebacterium species | 1 (3.7) | 1 (1.9) | 1 (4.8) | 0 (0.0) |
| *Escherichia coli* | 0 (0.0) | 9 (16.7) | 0 (0.0) | 4 (19.0) |
| Enterococcus species | 1 (3.7) | 4 (7.4) | 0 (0.0) | 2 (9.5) |
| Vancomycin-resistant Enterococcus species | 1 (3.7) | 2 (3.7) | 1 (4.8) | 0 (0.0) |
| Enterobacter species | 1 (3.7) | 1 (1.9) | 1 (4.8) | 0 (0.0) |
| Klebsiella species | 7 (25.9) | 6 (11.1) | 6 (28.6) | 3 (14.3) |
| Methicillin-resistant *Staphylococcus aureus* | 2 (7.4) | 8 (14.8) | 2 (9.5) | 3 (14.3) |
| Methicillin-sensitive *S. aureus* | 1 (3.7) | 7 (13.0) | 1 (4.8) | 3 (14.3) |
| Other Staphylococcus species | 4 (14.8) | 1 (1.9) | 3 (14.3) | 0 (0.0) |
| Pseudomonas species | 3 (11.1) | 8 (14.8) | 2 (9.5) | 1 (4.8) |
| Stenotrophomonas species | 1 (3.7) | 1 (1.9) | 0 (0.0) | 1 (4.8) |
| Other[b] | 2 (7.4) | 6 (11.1) | 2 (9.5) | 1 (4.8) |

[a]Categories are not mutually exclusive as some patients experienced multiple sources of secondary infections and/or polymicrobial infections.

[b]Other pathogens include Acinetobacter species, Actinomyces species, Burkholderia species, Clostridium species, Proteus species, Providencia species, Salmonella species, Serratia species, and Streptococcus species. Patients may have had more than one pathogen from this list. Secondary infections were evaluated within 30 d of tocilizumab administration for those that received tocilizumab and within 30 d of ICU admission for those that did not receive tocilizumab. Denominator for type of infection and pathogens are the number of secondary infections.

in critically ill patients (adjusted HR, 0.71; 95% CI, 0.56–0.92) and Somers et al (25) where tocilizumab use was associated with a 45% reduction in death (HR, 0.55; 95% CI, 0.33–0.90). This is also similar to a recent meta-analysis showing a positive association with tocilizumab on mortality in patients with COVID-19 (pooled OR, 0.47; 95% CI, 0.36–0.60) (45). The aforementioned studies are all retrospective in nature and thus inherently limited. However, they are consistent in their findings indicating benefit with tocilizumab use.

Recent RCTs have not indicated a benefit with tocilizumab use; however, it is important to note that these trials only included patients who were neither critically ill nor mechanically ventilated at baseline. In a study of 131 patients, Hermine et al (38) found that at day 14, 12% (95% CI, –28% to 4%) fewer patients required noninvasive ventilation or mechanical ventilation or died in the tocilizumab group compared with those who received usual care. Notably, this study excluded patients who required ventilation or admission to the ICU. Similarly, a second RCT of 126 patients randomized to either tocilizumab or standard of care excluded patients admitted to the ICU or those who required mechanical ventilation. They found no significant difference in the primary outcome of clinical worsening at day 14 (28.3% tocilizumab vs 27.0 standard care; rate ratio, 1.05; 95% CI, 0.59–1.86) (39). Clinical worsening was defined as occurrence of ICU admission with mechanical ventilation, death from any cause, or P/F less than 150 mm Hg. The last RCT randomized 243 patients to tocilizumab or placebo and also excluded patients who required more than 10 L of supplemental oxygen or mechanical ventilation. This study also revealed no significant difference in preventing intubation or death in moderate COVID-19 (HR, 0.83; 95% CI, 0.38–1.81) (40). Because these RCTs did not include patients requiring noninvasive positive pressure ventilation or mechanical ventilation, they cannot be appropriately applied to critically ill patients with COVID-19 or those requiring mechanical ventilation.

The biological plausibility for the disparate results between the results of the current study and the aforementioned RCTs may be due to the difference in the pathogenesis of COVID-19 occurring at the time of tocilizumab initiation. The RCTs evaluate tocilizumab in the early stages of COVID-19 infection to decrease the effects of IL-6-induced macrophage activation and pulmonary damage. However, it appears tocilizumab does not confer a benefit with early use in patients who have not yet progressed to severe disease and critical illness (38–40) and may indicate that its benefit lies with utilization once a cytokine storm picture develops or later in the course of the disease. This raises questions regarding the utility and efficacy of tocilizumab early in the patient's disease course. Our study suggests the benefit lies with patients who are critically ill and later in their disease course, similar to early findings, which are yet to be published from the tocilizumab arm of the randomized, embedded, multi-factoral, adaptive platform trial for community acquired pneumonia (REMAP-CAP) in patients with COVID-19 trial (46). Additionally, analysis from the tocilizumab arm of the REMAP-CAP trial included data from first 303 critically ill patients with severe COVID-19 who were randomized to receive immune modulation treatments (tocilizumab, sarilumab, anakinra, or interferon) or no immune modulator and evaluated need for organ support in the ICU and hospital survival. The preliminary trial data revealed an OR of 1.87 for improved outcomes with tocilizumab administration (46). Use of other immune modulators is still yet to be evaluated.

Consistent with reported literature, we found a reduction in CRP and ferritin in treatment arms (31, 33). Furthermore, after propensity score matching, patients who received tocilizumab had a greater decrease in CRP and ferritin compared with those who did not receive tocilizumab. Additionally, similar to prior reports in COVID-19 and studies evaluating tocilizumab's use in rheumatoid arthritis and Castleman disease, we found that IL-6 levels increased after tocilizumab administration (31, 36, 47). This increase can be attributed to the decreased IL-6 receptor-mediated clearance (47). It is challenging to attribute a direct causality between biomarkers and ICU outcomes based on findings from the current evaluation due to its retrospective nature and short follow-up. Studies with a longer follow-up are required to determine the prognostic role of IL-6, CRP, and ferritin on mortality and clinical outcomes. Additionally, the current study showed a significant increase in ICU- and hospital-free days with tocilizumab use in patients with COVID-19. As the pandemic is ongoing and healthcare systems grapple with either sporadic or exponential increases in cases that continue to stress the healthcare system and ICU capacity (48), early discharge from the ICU and/or hospital become outcomes of great interest. At a time when

critical care resources are scarce, and healthcare systems need to efficiently increase ICU resources and ventilator availability, our study findings provide a potential therapeutic option that can decrease the burden on ICU resources and create opportunity and space for patients in need of intensive care.

Prior studies have evaluated secondary infections after tocilizumab's utilization and found mixed results, some trials indicating increased risk of infections and other trials showing no association between tocilizumab use and secondary infections. However, after adjusting for confounders, we found that tocilizumab administration was not associated with increased risk of secondary infection (25.6% vs 25.6%; risk difference, 0%; 95% CI, –13% to 13%). It is likely that prior evaluations concluding an increased risk of infection associated with tocilizumab use may be confounded by differences in severity of illness in that patient who received tocilizumab were often sicker than control patients. Ultimately, the risk of secondary infections due to tocilizumab's use should be further evaluated in RCTs.

One of the strengths of our study is that we accounted for confounders and propensity score matching ensured a population that was more homogenous and similar at baseline effectively allowing comparative outcomes between patient cohorts. Our study is not without limitations, the biggest being the observational and retrospective nature of this evaluation. We attempted to account for this by creating a randomized population through propensity score matching and accounting for immortal time bias. Even though we accounted for known confounders, there still exists the possibility that unknown and unaccounted for confounders could still be present and may impact results. To confirm the conclusions of our observation, results of RCTs focusing on tocilizumab's effect on critically ill patients with COVID-19 and ICU outcomes is required.

## CONCLUSIONS

In summary, tocilizumab use was associated with a significant decrease in ICU mortality in critically ill COVID-19 patients with severe hypoxemic respiratory failure. Future RCTs limited to tocilizumab administration to critically ill COVID-19 patients with severe hypoxemic respiratory failure are needed to provide a conclusive answer to these preliminary findings.

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1 *Department of Critical Care, Cleveland Clinic, Cleveland, OH.*

2 *Department of Pharmacy, Cleveland Clinic, Cleveland, OH.*

3 *Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH.*

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*Drs. Rajendram and Sacha contributed equally to this article.*

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*For information regarding this article, E-mail: rajendp@ccf.org*

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