*Clinical Infectious Diseases*

MAJOR ARTICLE

# Tocilizumab for Treatment of Mechanically Ventilated Patients With COVID-19

**Emily C. Somers,[1,2,3,a] Gregory A. Eschenauer,[4,a] Jonathan P. Troost,[5] Jonathan L. Golob,[1] Tejal N. Gandhi,[1] Lu Wang,[6] Nina Zhou,[6] Lindsay A. Petty,[1] Ji Hoon Baang,[1] Nicholas O. Dillman,[7] David Frame,[4] Kevin S. Gregg,[1] Dan R. Kaul,[1] Jerod Nagel,[7] Twisha S. Patel,[7] Shiwei Zhou,[1] Adam S. Lauring,[1] David A. Hanauer,[8] Emily Martin,[9] Pratima Sharma,[1] Christopher M. Fung,[10] and Jason M. Pogue[4]**

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA, [2]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan, USA, [3]Department of Obstetrics & Gynecology, University of Michigan, Ann Arbor, Michigan, USA, [4]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA, [5]Michigan Institute for Clinical & Health Research, University of Michigan, Ann Arbor, Michigan, USA, [6]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA, [7]Department of Pharmacy, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA, [8]Department of Learning Health Sciences, University of Michigan, Ann Arbor, Michigan, USA, [9]Department of Epidemiology, University of Michigan, Ann Arbor, Michigan, USA, and [10]Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan, USA

**(See the Editorial Commentary by Cheng and Hill on pages e455–7.)**

***Background.*** Severe coronavirus disease 2019 (COVID-19) can manifest in rapid decompensation and respiratory failure with elevated inflammatory markers, consistent with cytokine release syndrome for which IL-6 blockade is an approved treatment.

***Methods.*** We assessed effectiveness and safety of IL-6 blockade with tocilizumab in a single-center cohort of patients with COVID-19 requiring mechanical ventilation. The primary endpoint was survival probability postintubation; secondary analyses included an ordinal illness severity scale integrating superinfections. Outcomes in patients who received tocilizumab compared with tocilizumab-untreated controls were evaluated using multivariable Cox regression with propensity score inverse probability of treatment weighting (IPTW).

***Results.*** 154 patients were included, of whom 78 received tocilizumab and 76 did not. Median follow-up was 47 days (range, 28–67). Baseline characteristics were similar between groups, although tocilizumab-treated patients were younger (mean: 55 vs 60 years), less likely to have chronic pulmonary disease (10% vs 28%), and had lower D-dimer values at time of intubation (median: 2.4 vs 6.5 mg/dL). In IPTW-adjusted models, tocilizumab was associated with a 45% reduction in hazard of death (HR, .55; 95% CI, .33–.90) and improved status on the ordinal outcome scale [OR per 1-level increase, .58; .36–.94). Although tocilizumab was associated with an increased proportion of patients with superinfections (54% vs 26%; $P < .001$), there was no difference in 28-day case fatality rate among tocilizumab-treated patients with versus without superinfection (22% vs 15%; $P = .42$). *Staphylococcus aureus* accounted for ~50% of bacterial pneumonia.

***Conclusions.*** In this cohort of mechanically ventilated COVID-19 patients, tocilizumab was associated with lower mortality despite higher superinfection occurrence.

**Keywords.** COVID-19; SARS-CoV-2; interleukin-6; tocilizumab.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), has caused a global pandemic with over 6.7 million infections and 390 000 deaths as of 5 June 2020. Up to 20% of patients with COVID-19 develop severe illness characterized by worsening dyspnea and the need for supplemental oxygen [1]. Patients may further progress to respiratory failure, acute respiratory distress syndrome (ARDS), multiorgan dysfunction, and death. Hyperinflammation may contribute to this deterioration, resulting in elevations in C-reactive protein (CRP), ferritin, lactate dehydrogenase, D-dimer, and various proinflammatory cytokines including interleukin-6 (IL-6) [1–6]. This profile resembles that seen in cytokine release syndrome (CRS) associated with chimeric antigen receptor (CAR) T-cell therapy and hemophagocytic lymphohistocytosis [4, 5, 7]. In CRS, IL-6 blockade with tocilizumab has resulted in rapid improvement in respiratory and hemodynamic parameters [8], and the US Food and Drug Administration has approved its use for CAR T-cell–associated severe or life-threatening CRS.

As a result, adjunctive therapy with either IL-6 receptor antagonists (tocilizumab, sarilumab) or IL-6 antagonists (siltuximab) has been proposed as treatment for severe, progressive COVID-19. While multiple case series have suggested a potential role for tocilizumab [9–13] or siltuximab (preprint) [14], these reports are hampered by incomplete reporting, short durations of follow-up, and lack of control groups. Furthermore, infection is a concern with IL-6 blockade, and cases of viral myocarditis [15] and candidemia [16] with tocilizumab have been reported. As secondary infection has been associated with increased mortality in COVID-19 [3], controlled data are necessary to evaluate the risks and benefits of these therapies.

Received 5 June 2020; editorial decision 29 June 2020; accepted 9 July 2020; published online July 11, 2020.

[a]E. C. S. and G. A. E. contributed equally to this work.

Correspondence: E. C. Somers, University of Michigan, 2800 Plymouth Rd, NCRC B14-G236, Ann Arbor, MI 48109-2800 (emsomers@umich.edu).

**Clinical Infectious Diseases® 2021;73(2):e445–54**



DOI: 10.1093/cid/ciaa954

At our institution, IL-6 blockade with tocilizumab is considered for patients with severe COVID-19 and suspected hyperinflammation based on rapidly worsening respiratory status and elevated inflammatory markers, with the majority of usage occurring in patients requiring mechanical ventilation. Using our COVID-19 Rapid Response Registry infrastructure, we performed an observational study of outcomes in patients with COVID-19 requiring mechanical ventilation, comparing those treated with tocilizumab with those who were not.

## METHODS

Within the Michigan Institute for Clinical and Health Research, we developed a COVID-19 Rapid Response Registry for clinical characterization of persons with SARS-CoV-2 infection. The registry includes core items from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterization Protocol [17, 18]. This analysis follows STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations [19]. Ethics approval was obtained by the Institutional Review Board of the University of Michigan (HUM00179261).

### Study Population

Patients were eligible for inclusion in this analysis if they were admitted to Michigan Medicine from 9 March–20 April 2020 for severe COVID-19 pneumonia, had a reverse transcriptase–polymerase chain reaction–positive SARS-CoV-2 test, and required invasive mechanical ventilation (the first COVID-19 cases in Michigan were identified in early March 2020). Follow-up continued through 19 May 2020. Patients were excluded if they were younger than 16 years, were intubated for conditions unrelated to COVID-19, or were enrolled into a randomized controlled trial (RCT) for sarilumab. This analysis focuses on comparative outcomes of mechanically ventilated patients who received tocilizumab and those who did not. Untreated patients who died prior to the opportunity to receive tocilizumab treatment per institutional criteria (within 48 hours of intubation) were excluded to minimize immortal time bias [20].

### Tocilizumab Exposure

During the study period, preference was given to enrollment in an IL-6 inhibitor (sarilumab) clinical trial. However, given strict trial eligibility criteria and protocol requirements (eg, timed phlebotomy and repeated SARS-CoV-2 testing), tocilizumab was considered in patients ineligible for the trial or when trial enrollment was not feasible due to logistical constraints (eg, outside of enrollment hours or on nonstudy units). Criteria for tocilizumab usage were developed by the institutional Antimicrobial Stewardship Program and Division of Infectious Diseases. In general, tocilizumab was recommended for consideration in patients with rapid respiratory deterioration and evidence of hyperinflammation. Guidance was slightly modified during the study period based on drug availability, whether the sarilumab trial was active, and experiences of the treating team. None of these changes were substantial (usage criteria as of 19 May 2020 in Supplementary Methods). Adherence to this guidance was not enforced or mandatory, as within our large Infectious Diseases Division providers had varying views on the use of investigational or repurposed agents such as tocilizumab. The language in the guidance was intentionally nonprescriptive, saying that tocilizumab "May be considered . . . " and cautioning that " . . . the evidence for benefit is weak, and a risk for potential harm exists." Ultimately, individualized decisions on tocilizumab usage were made by the attending infectious diseases physician. The standard tocilizumab dose was 8 mg/kg (maximum 800 mg) × 1; additional doses were discouraged.

### Outcomes

The primary outcome was survival probability after intubation. A secondary endpoint assessed status at day 28 on a 6-level ordinal scale of illness severity, including bloodstream infection and pneumonia: (1) discharged alive, (2) hospitalized/off ventilator without superinfection, (3) hospitalized/off ventilator with superinfection, (4) hospitalized/mechanically ventilated without superinfection, (5) hospitalized/mechanically ventilated with superinfection, and (6) deceased.

### Covariates

Data were obtained via electronic health record queries and manual abstraction and included demographics, comorbidities, hospitalization dates, transfer status, laboratory values, microbiology results, concomitant medications, mechanical ventilation dates, oxygenation variables, and discharge status. The pulse oximetric saturation ($SpO_2$)/fraction of inspired oxygen ($FiO_2$) ratio was substituted for the partial pressure of arterial oxygen ($PaO_2$)/$FiO_2$ ratio, which has been validated in patients with ARDS [21]. All positive blood and respiratory cultures were assessed by an infectious diseases physician to adjudicate infection versus colonization. Infections were included if they occurred after intubation and more than 48 hours after hospitalization. Additionally, only infections occurring after administration of tocilizumab were considered in the treatment group. For patients who transferred from an outside hospital, length of stay, intubation date, and tocilizumab administration characteristics at that facility were manually abstracted from admission notes. For those intubated at Michigan Medicine, the lowest $PaO_2$ to $FiO_2$ ratio in the first 12 hours after intubation was also recorded.

Relevant laboratory values at times of presentation and intubation were abstracted. For transfer patients already on mechanical ventilation, the most extreme laboratory values in the

first 24 hours after transfer were considered as values at time of intubation. For patients intubated at Michigan Medicine, the most extreme values ±24 hours from intubation were considered. For patients who received tocilizumab, only laboratory values pre-tocilizumab were considered.

#### Other COVID-19–Directed Therapies

Based on available evidence and lack of enrolling clinical trials at local onset of the pandemic, hydroxychloroquine 600 mg every 12 hours × 2 doses, then 200 mg every 8 hours was recommended as standard management at the beginning of the study period. Once remdesivir studies were activated, hydroxychloroquine was formally removed from our guidelines on 26 March 2020, and treatment with hydroxychloroquine was rare after these changes. Adjunctive corticosteroid use was generally not recommended, but use in patients with ARDS was at the discretion of the critical care physician.

#### Statistical Analysis

Descriptive characteristics were provided using means and standard deviations or medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Kaplan-Meier survival curves were used to describe post–ventilator-onset outcomes and time-varying stacked bar plots were applied to demonstrate the 6-level ordinal outcome by elapsed day. Univariate prediction ability of each covariate on the time to death and ordinal outcome at day 28 were explored using Cox proportional hazards models and proportional odds models, respectively. Proportional odds assumption was assessed via Score test. Multiple imputation (MI) [22] was used to impute missing laboratory values for inclusion in sensitivity analyses: 25 imputations by fully conditional specification were made based on age, sex, race, ethnicity, transfer status, history of hypertension, congestive heart failure, chronic pulmonary disease, and chronic renal disease. To address nonrandomized treatment allocation, we calculated propensity scores by multivariable logistic regression with tocilizumab treatment as the binary outcome and potential confounding factors associated with both outcome and treatment assignment. Using such propensity scores, we applied inverse probability of treatment weighting (IPTW) to create a pseudo-study cohort, where the weighted version can balance off the covariate bias and mimic a randomized treatment assignment situation: the IPT weights for tocilizumab-treated patients = 1/p (treated); for untreated patients = 1/(1 − p [treated]) [23–25]. All analyses were conducted in univariate and multivariable fashion, and before and after IPTW. Sensitivity analyses were performed by thresholds of age, CRP, and D-dimer, and stratified analyses by sex and transfer versus nontransfers. Analyses were performed in SAS version 9.4 (SAS Institute) and R version 4.0.0 (R Foundation for Statistical Computing).

## RESULTS

#### Cohort Characteristics

Of 484 cases admitted during the study period for COVID-19, 34 were excluded based on enrollment in a sarilumab RCT (NCT04315298). Also excluded were 293 who did not require mechanical ventilation, 2 untreated patients who died within 24 hours of intubation, and 1 infant. Thus, this study included 154 patients requiring mechanical ventilation: 78 treated with tocilizumab and 76 untreated (Figure 1). Median follow-up time was 47 days (range, 28–67 days).

Patient characteristics as a function of treatment are shown in Table 1. In general, the 2 groups were well balanced, and patients were similar with regard to sex, race, most comorbidities, and concomitant therapies. Tocilizumab-treated patients were younger (mean, 55 vs 60 years; $P = .05$) and less likely to have either chronic pulmonary disease (10% vs 28%; $P = .006$) or chronic kidney disease (35% vs 49%; $P = .08$). The majority of patients in both groups were transfers from an outside facility, with a higher number of transfers (74% vs 58%; $P = .04$) in the untreated group.

Laboratory values at time of intubation are shown in Table 1. Tocilizumab-treated patients had lower D-dimer (median, 2.4 vs 6.5 mg/dL; $P = .005$) and higher serum albumin concentrations (mean, 3.5 vs 3.1 g/dL; $P < .001$). Of patients intubated after admission at Michigan Medicine, median $PaO_2$ to $FiO_2$ ratios were lower in the tocilizumab group (median, 155 vs 198; $P = .001$). The timing of mechanical ventilation (Table 1) did not differ between the 2 groups, with the majority of patients being intubated either within 48 hours prior to transfer or during the first 24 hours of admission. Tocilizumab was most commonly administered within 24 hours of intubation, with a minority of use (26%) occurring more than 48 hours after intubation. While administration of a second dose of tocilizumab was generally not recommended, 4 patients in the tocilizumab group received a second dose (timing of administration post–initial dose: 1 day [2 patients], 2 days [1 patient], 6 days [1 patient]).

Propensity score distributions stratified by actual treatment group and diagnostics are shown in Supplementary Figure 1; odds ratios for tocilizumab receipt by variables included in the propensity score model are presented in Supplementary Table 3. Balancing pre- and post-IPTW is shown in Supplementary Table 4.

#### Survival

Survival probability was significantly higher among tocilizumab-treated compared with untreated patients, as displayed by Kaplan-Meier estimates ($P = .0189$) (Figure 2). Based on Cox proportional hazards models, tocilizumab was associated with a lower hazard of death, after adjusting for demographics (model A: hazard ratio [HR], .54; 95% confidence

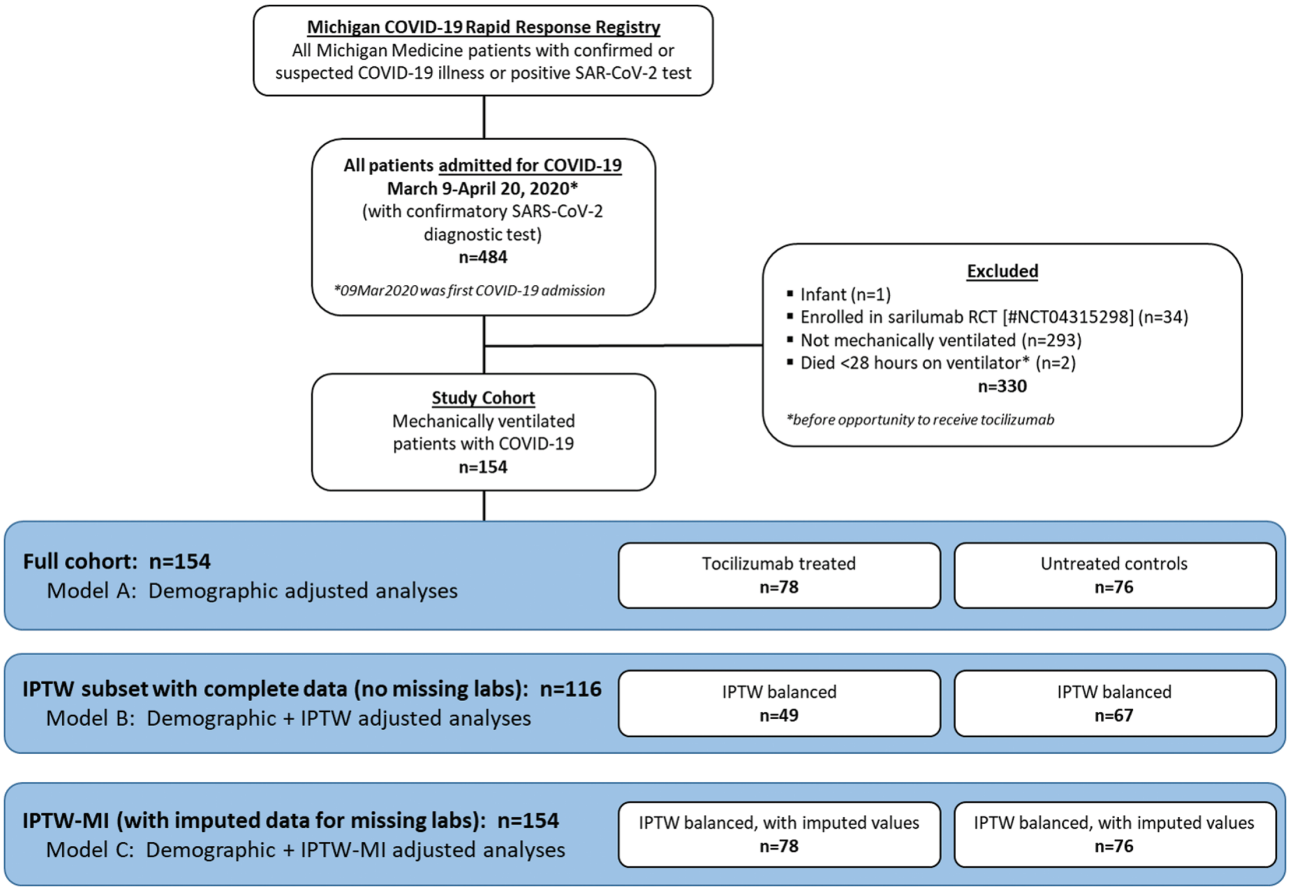


**Figure 1.** Study cohort flow chart. Abbreviations: COVID-19, coronavirus disease 2019; IPTW, inverse probability of treatment weighting; MI, multiple imputation; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

interval [CI], .29–1.00), when further IPTW-adjusted for the cohort subset with complete laboratory data (model B: n = 116; HR, .55; 95% CI, .33–.90; IPTW-Kaplan-Meier; Supplementary Figure 2), and when IPTW-MI adjusted (with imputed laboratory data) in the full cohort (model C: HR, .54; 95% CI, .35–.84) (Table 2, Supplementary Table 6). In stratum-specific sensitivity analyses including transfer patients from outside facilities (HR, .54), direct admits (HR, .41), patients with CRP values greater than 150 mg/L (HR, .48), D-dimer values greater than 1.2 mg/dL (HR, .42), and various age cutoffs (<60, <70, or <75 years; HRs, .55–.59), as well as when adjusted for intravenous methylprednisolone use (HR, .49), similar findings persisted (Supplementary Figure 3, Supplementary Table 6). Case fatality rate at 28 days was also lower for tocilizumab-treated patients (18% vs 36%; $P = .01$) (Table 2).

#### Superinfections

Patients who received tocilizumab were more than twice as likely to develop a superinfection than untreated controls (54% vs 26%; $P < .001$), driven primarily by a large increase in ventilator-associated pneumonia (45% vs 20%; $P < .001$) (Table 2). There was no difference between groups with regard to timing of infection, incidence of bloodstream infections, or development of more than 1 infection. The causative microbiology of superinfections was similar between groups. *Staphylococcus aureus* accounted for approximately 50% of the bacterial pneumonias in both groups. Case fatality rates at day 28 were similar among tocilizumab-treated patients who had a superinfection and those who did not (8/37 [22%] vs 6/41 [15%]; $P = .42$).

#### Ordinal Outcome Integrating Effectiveness and Infection Data

Stratified by treatment group, Figure 3A depicts the daily distribution of status on the 6-level ordinal scale through day 28, while Figure 3B displays individual patient trajectories. Tocilizumab administration was associated with improved status in the demographic- and IPTW-adjusted proportional odds models (odds ratio [OR] per 1-level increase in outcome scale), which was statistically significant for both of the models with IPTW (model A/demographic-adjusted: OR, .60 [95% CI, .34–1.08]; model B/demographic + IPTW: OR, .58 [.36–0.94]; model C/demographic + IPTW-MI: OR, .60 [.39–.91]) (Table 2, Supplementary Table 7, Supplementary Figure 4). During the study period, 56% of patients who received tocilizumab were discharged alive compared with 40% of untreated patients ($P = .04$). Among the 17 patients in

**Table 1. Characteristics of the Cohort**

| | Overall (n = 154) | Tocilizumab Treated (n = 78) | Untreated (n = 76) | *P* |
|---|---|---|---|---|
| Baseline characteristics | | | | |
| Age,[a] years | 58 ± 14.9 | 55 ± 14.9 | 60 ± 14.5 | .05 |
| Female, n (%) | 52 (34) | 25 (32) | 27 (36) | .65 |
| Race, n (%) | | | | .48 |
| Black | 81 (53) | 38 (49) | 43 (57) | |
| White | 41 (27) | 24 (31) | 17 (22) | |
| Other | 32 (21) | 16 (21) | 16 (21) | |
| Weight,[a] kg | 99 ± 28.5 | 101 ± 31.1 | 97 ± 26.2 | .36 |
| BMI,[a] kg/m$^2$ | 34.1 ± 9.5 | 34.7 ± 10.1 | 33.4 ± 8.8 | .40 |
| NEWS[b,c] (n = 61) | 7 (4–8) | 7 (5–8) | 6 (4–8) | .31 |
| Outside hospital transfer | 101 (66) | 45 (58) | 56 (74) | .04 |
| Transfer on mechanical ventilation | 74 (48) | 31 (40) | 43 (57) | .04 |
| Comorbid conditions | | | | |
| Hypertension | 102 (66) | 50 (64) | 52 (68) | .57 |
| Congestive heart failure | 36 (23) | 16 (21) | 20 (26) | .39 |
| Chronic pulmonary disease[d] | 29 (19) | 8 (10) | 21 (28) | .006 |
| Pre-existing requirement for long-term oxygen therapy | 4 (3) | 1 (1) | 3 (4) | .36 |
| Asthma | 31 (20) | 16 (21) | 15 (20) | .90 |
| Sleep apnea | 41 (27) | 18 (23) | 23 (30) | .31 |
| Diabetes | 25 (16) | 10 (13) | 15 (20) | .24 |
| Chronic kidney disease | 64 (42) | 27 (35) | 37 (49) | .08 |
| Chronic liver disease | 2 (1) | 1 (1) | 1 (1) | .99 |
| Solid-organ transplant | 9 (6) | 7 (9) | 2 (3) | .09 |
| Laboratory values at time of intubation | | | | |
| Temperature,[a] °F | 100.5 ± 1.8 | 100.7 ± 1.8 | 100.3 ± 1.7 | .17 |
| $PaO_2/FiO_2$[b,e] (n = 80) | 165 (136.5–231.5) | 155 (129.0–188.0) | 198 (163.0–240.0) | .001 |
| White blood cell count[a] (n = 142), $10^9$/L | 13.2 ± 6.5 | 12.1 ± 6.6 | 14.1 ± 6.2 | .06 |
| Absolute lymphocyte count[a] (n = 121), $10^9$/L | 0.8 ± 0.4 | 0.9 ± 0.4 | 0.7 ± 0.4 | .09 |
| Albumin[a] (n = 141), g/dL | 3.2 ± 0.5 | 3.5 ± 0.4 | 3.1 ± 0.5 | <.001 |
| C-reactive protein[b] (n = 135), mg/L | 220 (125–293) | 185 (112–278) | 231 (141–299) | .28 |
| D-dimer[b] (n = 129), mg/dL | 4.7 (1.6–11.8) | 2.4 (1.1–6.1) | 6.5 (2.4–18.9) | .005 |
| Ferritin[b] (n = 129), ng/mL | 1418 (692–2139) | 1262 (738–1804) | 1524 (512–2263) | .83 |
| Lactate dehydrogenase[b] (n = 123), IU/L | 606 (484–828) | 627 (536–865) | 589 (418–757) | .27 |
| Aspartate aminotransferase[b] (n = 140), IU/L | 72 (49.5–119) | 66 (51–107) | 80 (48–133) | .98 |
| Alanine aminotransferase[b] (n = 140), IU/L | 50 (29.5–79) | 50 (31–68) | 52 (27–86) | .87 |
| Alkaline phosphatase[b] (n = 140), IU/L | 79.5 (59–111) | 76 (56–105) | 83 (60–115) | .32 |
| Total bilirubin[b] (n = 140), mg/dL | 0.6 (0.4–1.0) | 0.6 (0.4–0.9) | 0.6 (0.4–1.0) | .99 |
| Concomitant medications/interventions during hospitalization, frequency (%) | | | | |
| Hydroxychloroquine | 35 (23) | 20 (26) | 15 (20) | .38 |
| Remdesivir | 4 (3) | 2 (3) | 2 (3) | .99 |
| NSAIDs | 53 (34) | 25 (32) | 28 (37) | .53 |
| Acetaminophen | 146 (95) | 76 (97) | 70 (92) | .14 |
| ACE inhibitors or angiotensin receptor blockers | 22 (14) | 11 (14) | 11 (15) | .95 |
| Vasopressors | 140 (91) | 71 (91) | 69 (91) | .96 |
| Therapeutic anticoagulation | 109 (71) | 59 (76) | 50 (66) | .18 |
| Corticosteroid usage | 38 (25) | 23 (29) | 15 (20) | .16 |
| Methylprednisolone infusion | 24 (16) | 14 (18) | 10 (13) | .41 |
| Oral prednisone | 14 (9) | 9 (12) | 5 (7) | .28 |
| Prone positioning | 36 (23) | 24 (31) | 12 (16) | .03 |
| ECMO | 10 (6) | 5 (6) | 5(7) | .97 |
| Timing of mechanical ventilation, n (%) | | | | |
| At outside hospital | 74 (48) | 31 (40) | 43 (57) | .85 |
| Within 24 hours of transfer | 19 (26) | 7 (23) | 12 (28) | |
| 24–48 hours prior to transfer | 22 (30) | 10 (32) | 12 (28) | |
| >48 hours prior to transfer | 33 (45) | 14 (45)[f] | 19 (44)[f] | |

**Table 1. Continued**

| | Overall (n = 154) | Tocilizumab Treated (n = 78) | Untreated (n = 76) | *P* |
|---|---|---|---|---|
| At Michigan Medicine | 80 (52) | 47 (60) | 33 (43) | .26 |
| In first 24 hours after presentation | 52 (65) | 28 (60) | 24 (72) | |
| 24–48 hours after presentation | 7 (9) | 6 (13) | 1 (3) | |
| >48 hours after presentation | 21 (26) | 13 (28) | 8 (24) | |
| Timing of tocilizumab treatment | | | | |
| Treated at outside hospital | … | 3 (4) | … | |
| Treated >24 hours prior to intubation | … | 6 (8) | … | |
| Treated within 24 hours of intubation | … | 37 (47) | … | |
| Treated 24–48 hours after intubation | … | 12 (15) | … | |
| Treated >48 hours after intubation | … | 20 (26)[g] | … | |

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; NEWS, National Early Warning Score; NSAID, nonsteroidal anti-inflammatory drug; $PaO_2/FiO_2$, partial pressure of arterial oxygen/fraction of inspired oxygen.

[a]Values are means ± SDs.

[b]Values are medians (IQRs).

[c]NEWS score calculated in a subset of patients who were not on mechanical ventilation on transfer or intubated in the Emergency Department at Michigan Medicine (n = 37 tocilizumab, 24 untreated).

[d]Chronic pulmonary disease includes chronic bronchitis, chronic obstructive pulmonary disease, emphysema, cystic fibrosis, bronchiectasis, interstitial lung disease, pre-existing requirement for long-term oxygen therapy.

[e]For patients intubated at Michigan Medicine, value represents the worst $PaO_2/FiO_2$ value within 12 hours of intubation.

[f]Among those ventilated >48 hours prior to transfer from an outside hospital, length of ventilation prior to transfer was tocilizumab (mean, 5.4 days; median, 4.7 [IQR, 3.6, 7.7]) and untreated (mean, 6.4 days; median, 5.8 [IQR, 4.0, 7.0]) (*P* = .40).

[g]Among the 20 patients receiving tocilizumab >48 hours after intubation, timing after intubation was a median of 3.9 days (IQR, 2.7, 7.6); 19 of these 20 patients were transfers from outside hospitals.

each group remaining hospitalized at the end of follow-up, the majority had come off mechanical ventilation: 14 of 17 (82%) treated with tocilizumab and 9 of 17 (53%) untreated.

## DISCUSSION

In this observational, controlled study of patients with severe COVID-19 necessitating mechanical ventilation, receipt of tocilizumab was independently associated with improved survival. Importantly, however, tocilizumab was also associated with increased incidence of secondary bacterial pneumonia. While this did not appear to negatively influence ultimate outcome, and case fatality rates were similar in infected and uninfected tocilizumab-treated patients, this finding highlights the need for adequately powered RCTs further evaluating efficacy and safety of tocilizumab in COVID-19.

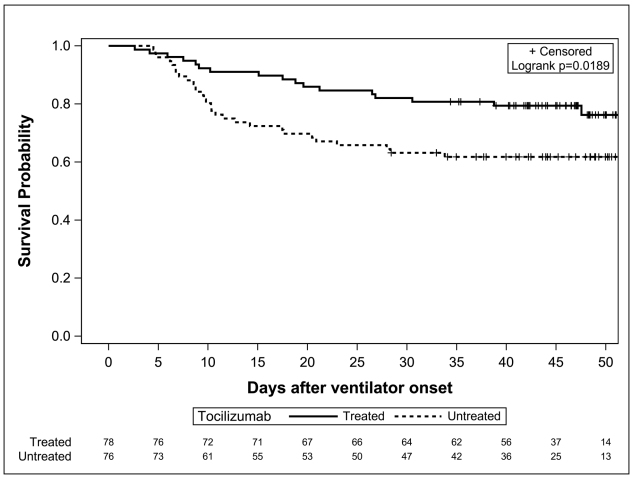


**Figure 2.** Kaplan-Meier estimates for probability of survival as a function of time since mechanical ventilation onset, stratified by tocilizumab treatment (n = 154; n = 46 deaths).

Respiratory failure in severe COVID-19 is frequently characterized by high serum IL-6 concentrations [26]. Excessive IL-6 can induce lung epithelial cells to increase inflammatory responses, leading to increased macrophage response and ultimately pulmonary damage. IL-6 may also be a significant contributor to thrombosis, having been associated with both tissue and vascular endothelial cell injury, and contributing to platelet aggregation and angiotensin II microvascular dysfunction [27, 28]. Conversely, as a critical cytokine in organizing T-cell responses to infections, IL-6 may play a beneficial role in COVID-19. It may suppress viral reactivation [29], protect against superinfection, and facilitate lung repair and remodeling after viral injury [30]. Thus, our approach was to administer tocilizumab in patients who were rapidly desaturating or recently intubated in an attempt to optimize the timing of administration for maximal benefit. Our dosing strategy (single, high dose of 8 mg/kg) was an attempt to saturate receptors to rapidly inhibit IL-6 signaling but also allow more rapid clearance in order to not interfere with tissue remodeling and limit immunosuppression.

Our results support these hypotheses. Given the heterogeneity in tocilizumab treatment decisions between providers at our institution, the 2 groups in this analysis were largely

**Table 2. Outcomes, Including Superinfections, Stratified by Treatment**

| | Tocilizumab Treated (n = 78) | Untreated (n = 76) | *P* |
|---|---|---|---|
| Case fatality rate, n (%) | | | |
| 14-day | 7 (9) | 20 (26) | .005 |
| 21-day | 11 (14) | 25 (33) | .006 |
| 28-day | 14 (18) | 27 (36) | .01 |
| Discharged alive by end of follow-up, n (%) | 44 (56) | 30 (40) | .04 |
| Length of stay (among discharged),[a] days | 20.4 (13.8–35.8) | 22.9 (16.3–28.5) | .31 |
| Duration of mechanical ventilation,[a,b] days | 13.8 (7.1–27.5) | 13.0 (8.1–23.5) | .94 |
| Hazard ratios (95% CI) for tocilizumab vs control | | | |
| Model A: demographic adjusted | .54 (.29, 1.00) | Ref | .05 |
| Model B: demographic + IPTW adjusted (n = 116) | .55 (.33, .90) | Ref | .02 |
| Model C: demographic + IPTW-MI adjusted | .54 (.35, .84) | Ref | .01 |
| Odds ratios (95% CI) for proportional odds model for tocilizumab vs control (day 28) | | | |
| Model A: demographic adjusted | .60 (.34, 1.08) | Ref | .09 |
| Model B: demographic + IPTW adjusted (n = 116) | .58 (.36, .94) | Ref | .03 |
| Model C: demographic + IPTW-MI adjusted | .60 (.39, .91) | Ref | .02 |
| Superinfection data | | | |
| Patients with a superinfection, n (%) | 42 (54) | 20 (26) | <.001 |
| 28-day case fatality rate[c] | 8 (22) | 5 (28) | .61 |
| Patients with pneumonia, n (%) | 35 (45) | 15 (20) | <.001 |
| Patients with bloodstream infection, n (%) | 11 (14) | 7 (9) | .34 |
| Time from intubation to first infection,[a] days | 9.8 (4.5–15.8) | 7.7 (3.9–14.4) | .13 |
| Patients with >1 infection | 10 (13) | 7 (8) | .47 |
| Causative microbiology, n (%) | | | |
| Microbiology of pneumonia[d] | (n = 41) | (n = 22) | |
| *Staphylococcus aureus* | 21 (51) | 11 (50) | |
| Methicillin susceptible | 15 (71) | 5 (45) | |
| Methicillin resistant | 6 (29) | 6 (55) | |
| *Pseudomonas aeruginosa* | 5 (12) | 4 (18) | |
| Multidrug resistant | 4 (80) | 3 (75) | |
| *Escherichia coli* | 4 (10) | 1 (5) | |
| ESBL producing | 1 (25) | 0 | |
| *Klebsiella aerogenes* | 4 (10) | 1 (5) | |
| *Klebsiella pneumoniae* | 3 (7) | 1 (5) | |
| *Serratia marcescens* | 3 (7) | 0 (0) | |
| *Senotrophomonas maltophilia* | 2 (5) | 0 (0) | |
| Other[e] | 7 (17) | 5 (23) | |
| Microbiology of bloodstream infections[d] | (n = 12) | (n = 8) | |
| Coagulase-negative staphylococcus | 4 (33) | 3 (38) | |
| *Enterococcus* spp. | 3 (25) | 2 (25) | |
| *Candida* spp. | 3 (25) | 1 (13) | |
| Other[f] | 4 (36) | 2 (28) | |

Abbreviations: CI, confidence interval; ESBL, extended-spectrum beta-lactamase; IPTW, inverse probability of treatment weighting; MI, multiple imputation; Ref, reference.

[a]Values are medians (interquartile ranges).

[b]Limited to those who were extubated alive during the study period (n = 94).

[c]Limited to patients with infection in first 28 days: 37 tocilizumab treated vs 18 tocilizumab untreated.

[d]There were 41 unique cases of pneumonia in 35 tocilizumab-treated patients and 22 unique cases in 15 untreated patients; there were 12 unique bloodstream infections in 11 tocilizumab-treated patients and 8 unique bloodstream infections in 7 untreated patients; pathogen numbers can add up to >100% due to polymicrobial infections.

[e]In tocilizumab patients: n = 1 *Acinetobacter baumannii, Citrobacter koseri, Corynebacterium striatum, Haemophilus influenzae, Proteus mirabilis, Pseudomonas putida,* and *Streptococcus pneumoniae.* In untreated patients: n = 1 *Aspergillus fumigatus, Acinetobacter baumannii, Enterobacter cloacae, Proteus mirabilis,* and *Streptococcus pneumonia.*

[f]In tocilizumab patients, n = 1 methicillin-susceptible *Staphylococcus aureus, Streptococcus mitis, Escherichia coli,* and *Klebsiella pneumoniae*; in untreated patients n = 1 methicillin resistant *Staphylococcus aureus* and *Enterobacter cloacae.*

comparable with regard to factors impacting COVID-19 outcomes. Although there were slight imbalances with regard to age, baseline D-dimer, CRP, comorbid chronic pulmonary disease, and transfer status, we utilized rigorous methods for observational data accounting for these factors and treatment propensity. Tocilizumab remained associated with better outcomes across modeling strategies. Furthermore, results remained consistent across various sensitivity analyses,

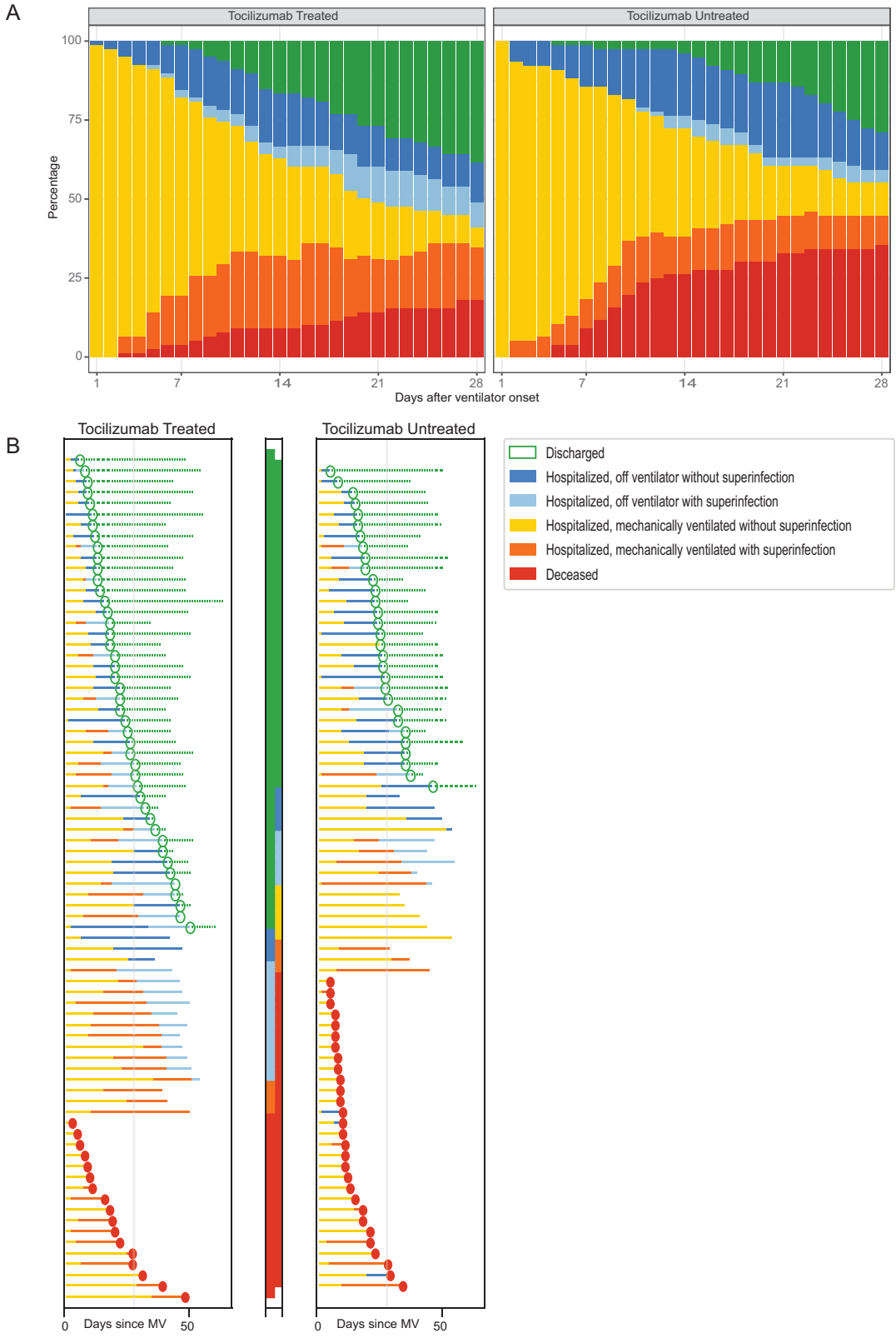


**Figure 3.** Patient status post–ventilator onset on a 6-level ordinal scale integrating superinfection occurrence, stratified by tocilizumab treatment. *A*, The distribution of patient status, by number of days after onset of mechanical ventilation through day 28 of follow-up. *B*, Individual patient trajectories on the 6-level ordinal scale over the study period. Each row represents changes in individual patient status from time of onset of mechanical ventilation until event (death) or end of the study period (19 May 2020). Horizontal lines correspond to elapsed time, with colors corresponding to clinical status of the patient. Solid circles represent death, and hollow circles represent discharge from hospital (alive). The middle panel indicates the most recent patient status. Gray vertical lines mark 28-day follow-up. Abbreviation: MV, mechanical ventilation.

including when patients were stratified according to D-dimer and CRP thresholds previously associated with mortality [6], by outside hospital transfer/direct admission status, and when restricted to various age groups.

In addition to the survival advantage, receipt of tocilizumab was associated with improvement on a 6-point ordinal scale that incorporated mechanical ventilation, development of superinfection, and discharge from the hospital (OR, ~.6; $P \leq .03$ for IPT-weighted models). This improvement in illness severity level with receipt of tocilizumab is reflected in the statistically significant increase in patients discharged home over the study period (56% vs 40%; $P = .04$); while 17 patients in each group remained in the hospital at the end of follow-up, only 3 of 17 (18%) of tocilizumab-treated patients remained on the ventilator compared with 8 of 17 (47%) of untreated controls (Figure 3B). This consistent advantage across the ordinal scale provides support for the observed benefit associated with tocilizumab in this cohort and furthermore has significant resource conservation implications.

Importantly, these data also reinforce concerns with superinfection risk due to IL-6 inhibition. To date, the risk of superinfection in mechanically ventilated patients with severe COVID-19 remains poorly described and the incremental risk associated with a single dose of tocilizumab is not well characterized. We demonstrated that superinfection was common in this population, with 39% developing a pneumonia or bloodstream infection. Furthermore, tocilizumab was associated with higher occurrence of infection (54% vs 26%; $P < .001$), driven primarily by the development of ventilator-associated bacterial pneumonia in 45% of patients receiving tocilizumab. Interestingly, we also identified an association between severe COVID-19 infection and staphylococcal pneumonia, as approximately half of the cases in both the tocilizumab and control group were due to *S. aureus*.

Although these data are observational, several strengths of the study warrant comment. First, this analysis utilizing a Rapid Response Registry informed by an internationally designed clinical characterization protocol [18] represents the first well-controlled, comparative analysis assessing the safety and effectiveness of tocilizumab for severe COVID-19. In order to address potential confounding by indication or other imbalances between groups, propensity scoring and multivariable models were utilized, as well as sensitivity analyses. Across various analytic strategies, results consistently indicated benefit associated with tocilizumab. Additionally, median follow-up time for the cohort was 47 days (range, 28–67 days), with all patients followed for at least 28 days, representing a substantially longer observation period than many COVID-19 treatment studies to date, and indicative of sustained benefit. Furthermore, all secondary infections were reviewed by an infectious diseases physician to ensure accurate reporting.

However, this analysis is not without limitations. First and foremost, RCT data will be critical for confirming the perceived benefits from this observational study and better quantify risks. Second, there were incomplete data for laboratory variables, although we used contemporary methods for imputing missing data. Third, for patients transferred from outside hospitals, variations in the initial period of care (prior to transfer) cannot be fully or consistently characterized; however, the vast majority of transfers occurred directly from outside emergency departments that were over capacity. It should also be noted that, for transfer patients, we do not have information on tocilizumab usage criteria at the outside hospitals, although only 3 patients received tocilizumab outside of our institution. Fourth, we focused on the impact of tocilizumab 8 mg/kg × 1 in mechanically ventilated patients. This study does not address the potential role of tocilizumab earlier in illness for preventing mechanical ventilation, the optimal dose of tocilizumab, the potential utility of multiple doses, or the role of IL-6 serum concentrations (which were not routinely available) in predicting tocilizumab response, all of which are important questions that warrant further investigation. Further, though tocilizumab administration was guided by institutional criteria, usage in this clinical care setting was not dictated by a firm study protocol, and therefore was not completely standardized. Finally, while all patients in our cohort had a minimum follow-up time of 28 days, additional follow-up will be valuable to determine the full course of hospitalization for the 34 remaining inpatients, and to characterize long-term sequelae for survivors in this cohort.

In conclusion, tocilizumab was associated with improved survival, despite higher occurrence of superinfections, in a cohort of patients with COVID-19 requiring mechanical ventilation. These data are encouraging and can help inform clinical practice while results from RCTs of IL-6 inhibitors are awaited.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Acknowledgments.*** The authors acknowledge the Michigan Institute of Clinical and Health Research (MICHR) infrastructure and staff for their extraordinary support and teamwork in creation of the COVID-19 Rapid Response Registry. Special thanks to Dr Elizabeth LaPensee and the MICHR Interdisciplinary Research Initiatives team, Shari Sidener for database management, Jane Bugden for project management, and Janine Capsouras for administrative support. They also thank Aubrie Andrews, Brandon McCoy, Alyssa Nielsen, Peter Link, and Thomas Mobley for technical support, as well as Chiu-Mei Chen, MA, MS, with support from the Michigan Medicine Department of Emergency Medicine and the Joyce and Don Massey Family Foundation. Finally, the authors thank Dr George Mashour for critical review of the manuscript. This work is dedicated to the memory of Maureen Peck Nielsen.

***Disclaimer.*** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institutes of Health, Centers for Disease Control and Prevention, or the Department of Health and Human Services.

***Financial support.*** This work was supported by the National Institutes of Health (grant numbers UL1TR002240; 1K12HL133304; to C. M. F.); the Centers for Disease Control and Prevention (grant number U01IP000974); and an American Society for Transplantation and Cellular Therapy New Investigator Award (to J. L. G.).

***Potential conflicts of interest.*** J. P. T. reports stock in Proctor & Gamble and General Electric; A. S. L. reports being a paid consultant on antivirals for Sanofi and a paid member of a clinical trial steering committee for Baloxavir for Roche; E. M. reports being a paid consultant for Pfizer on RSV and receipt of research funding from Roche. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **2020**; 382:1708–20.
2. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med **2020**; 180:1–11. doi:10.1001/jamainternmed.2020.0994.
3. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intens Care Med **2020**; 46:846–8.
4. Moore BJB, June CH. Cytokine release syndrome in severe COVID-19. Science **2020**; 368:473–4. doi:10.1126/science.abb8925. Epub 2020 Apr 17.
5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Specialty Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet **2020**; 395:1033–4.
6. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ **2020**; 369:m1966. doi:10.1136/bmj.m1966.
7. Zhong J, Tang J, Ye C, Dong L. The immunology of COVID-19: is immune modulation an option for treatment? Lancet Rheumatol **2020**; 2:e428–36.
8. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood **2013**; 121:5154–7.
9. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci **2020**; 117:10970–5. doi:10.1073/pnas.20056.
10. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol **2020**; 38:529–32.
11. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol **2020**; 92:814–8.
12. Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med **2020**; 76:31–5.
13. Klopfenstein T, Zayet S, Lohse A, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Médecine Mal Infect **2020**; 50:397–400. doi:10.1016/j.medmal.2020.05.001.
14. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. medRxiv [Preprint]. 20 June **2020.** Available at: https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v4.
15. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report. Chest **2020**; 158:e15–19. doi:10.1016/j.chest.2020.04.024.
16. Antinori S, Bonazzetti C, Gubertini G, et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun Rev **2020**; 19:102564.
17. Dunning JW, Merson L, Rohde GGU, et al; ISARIC Working Group 3, ISARIC Council. Open source clinical science for emerging infections. Lancet Infect Dis **2014**; 14:8–9.
18. ISARIC Clinical Characterization Group. Global outbreak research: harmony not hegemony. Lancet Infect Dis **2020**; 3099:30440.
19. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening The Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology **2007**; 18:805–35.
20. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol **2008**; 167:492–9.
21. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health; National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest **2007**; 132:410–7.
22. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res **2007**; 16:219–42.
23. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math Model **1986**; 7:1393–1512.
24. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. Int J Radiat Oncol **2012**; 84:1078–85.
25. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med **2015**; 34:3661–79.
26. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev **2020**; 19:102537.
27. Senchenkova EY, Russell J, Yildirim A, Granger DN, Gavins FNE. Novel role of T cells and IL-6 (interleukin-6) in angiotensin II-induced microvascular dysfunction. Hypertension **2019**; 73:829–38.
28. Bester J, Pretorius E. Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity. Sci Rep **2016**; 6:32188.
29. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. Front Microbiol **2019**; 10:1057. doi:10.3389/fmicb.2019.01057. eCollection 2019.
30. Yang ML, Wang CT, Yang SJ, et al. IL-6 ameliorates acute lung injury in influenza virus infection. Sci Rep **2017**; 7:43829.