A Propensity-Matched Cohort Study of Tocilizumab in Patients With Coronavirus Disease 2019

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Objectives: To determine the impact of tocilizumab, a monoclonal antibody against the interleukin 6 receptor, on survival in patients with coronavirus disease 2019.

Design: Observational cohort study of patients hospitalized with coronavirus disease 2019 between March 1, 2020, and April 24, 2020. A propensity-matched (1:1) analysis was used to compare patients who received tocilizumab to controls who did not. Competing risk survival analysis was used to determine the primary outcome of time to mortality, and adjusted log-linear and logistic regression for secondary outcomes.

Setting: Three hospitals within the NYU Langone Health system in New York.

Patients: Consecutive adult patients hospitalized with coronavirus disease 2019.

Intervention: Tocilizumab 400-mg IV once in addition to standard of care or standard of care alone.

Measurements and Main Results: Data from 3,580 severe acute respiratory syndrome coronavirus 2 positive qualifying hospitalized patients were included, of whom 497 (13.9%) were treated with tocilizumab. In the analysis of tocilizumab-treated patients and matched controls, fewer tocilizumab-treated patients died (145/497, 29.2%) than did controls (211/497, 42.4%). In the adjusted competing risk regression model, tocilizumab therapy was associated with improved survival relative to controls (hazard ratio = 0.24, 95% CI = 0.18–0.33, $p < 0.001$). Tocilizumab-treated patients and controls had similar adjusted time to discharge from hospital (hazard ratio = 0.96, 95% CI = 0.78–1.17, $p = 0.67$). However, they had longer adjusted ICU length of stay (rate ratio = 3.1, 95% CI = 2.5–3.7, $p < 0.001$) and a higher adjusted infection rate (odds ratio = 4.18, 95% CI = 2.72–6.52, $p < 0.001$) than controls.

Conclusions: Tocilizumab therapy was associated with significantly improved survival in coronavirus disease 2019 patients. This survival benefit was associated with increased ICU length of stay and increased infection rate, even as more patients in the tocilizumab group were rescued from rapid death. A prospective, randomized, placebo-controlled trial is needed to confirm these findings.

Key Words: coronavirus disease 2019; hyperinflammation; interleukin 6; respiratory failure; survival; tocilizumab

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The novel 2019 coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which causes the respiratory illness known as coronavirus disease 2019 (COVID-19), rapidly evolved into a global pandemic (1). Many patients with COVID-19 progress to hypoxic respiratory failure with development of the acute respiratory distress syndrome (ARDS) in 30–40% (2, 3). In early cohorts, mortality rates in those with ARDS exceeded 50%, and there remain few validated therapeutic options beyond supportive care (2–4).

A consistent finding in those with COVID-19 and respiratory failure is the elevation of the inflammatory cytokine interleukin 6 (IL-6), which also predicts of mortality among those with severe disease, making inhibition of IL-6 an attractive therapeutic option (2, 3, 5–7). IL-6 is known to be a driver in other systemic inflammatory states, such as the cytokine release syndrome (CRS), particularly following chimeric antigen receptor (CAR) T cell therapy. CRS responds rapidly to the IL-6 receptor antagonist tocilizumab

leading our institution and others to begin empirically utilizing this agent off-label in patients with severe COVID-19 (8).

To date, clinical experience of tocilizumab in patients with COVID-19 is largely limited to case series. Encouraging results have been reported with decreasing oxygen requirements, improvement in radiologic findings, and seemingly improved mortality; however, all these studies lacked a comparator arm (9–14). Two recent reports have included a comparator group of patients not receiving tocilizumab and similarly found a significant decrease in risk of mechanical ventilation and mortality associated with tocilizumab. However, these reports were limited by either small sample size, variable tocilizumab dosing and administration, or inadequate adjustment of covariates in the analysis, leading to likely confounded association (15, 16). Thus, we performed a retrospective, propensity-matched study to evaluate the effect of tocilizumab compared with standard of care in hospitalized patients with COVID-19.

MATERIALS AND METHODS

Study Design

We performed a retrospective, observational cohort study of patients admitted to one of three hospitals within the NYU Langone Health (NYULH) system. The study was reviewed by the NYU Grossman School of Medicine Institutional Review Board and a waiver of informed consent was granted due to its retrospective nature (i20-00426).

Patients

Consecutive patients who were hospitalized between March 1, 2020, and April 24, 2020 were reviewed for a positive SARS-CoV-2 polymerase chain reaction by nasopharyngeal swab. All patients who received tocilizumab based on drug administration records were included in the analysis. A control group consisting of patients who were SARS-CoV-2 positive but did not receive tocilizumab was selected using propensity score matching as described below. Patients were excluded if they were enrolled in a trial of another IL-6 pathway antagonist. Patients in clinical trials of other agents (remdesivir, hydroxychloroquine, or convalescent plasma) were included in this analysis.

Study Variables

All data were extracted from the electronic health record and manually validated. Demographic variables included age, sex, race (categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian, multiracial/other, and unknown), smoking status, and body mass index (BMI). Preexisting comorbidities included hypertension, heart disease, diabetes mellitus, chronic lung disease, solid organ transplant, leukemia, and lymphoma. Laboratory variables included inflammatory markers (ferritin, C-reactive protein [CRP], D-dimer, and lactate dehydrogenase), serum creatinine, and liver enzymes. Medication use included those used to treat COVID-19 (antivirals and corticosteroids) and those indicating more severe critical illness (vasopressors and neuromuscular blockers). Clinical data included vital signs and

oxygen support. Secondary infections were identified based on positive blood, urine, and sputum cultures.

Intervention

Use of tocilizumab was not standard of care, nor were patients randomly selected. Enrollment into randomized clinical trials of other IL-6 pathway antagonists was prioritized; however, clinical trial availability varied among our three sites. If a patient was not a candidate for these trials, a multidisciplinary team (pulmonary/critical care and clinical pharmacy) reviewed patients for tocilizumab based on general criteria developed as institutionwide guidance and available to all providers via an online portal (**Table S1**, http://links.lww.com/CCX/A426). Patients with active infection, acute hepatitis, or active gastrointestinal process were excluded from tocilizumab. Tocilizumab was given as a dose of 400 mg once with the option for a second dose. However, second doses were rare. All doses were given intravenously. The single dose of 400 mg was selected based on a limited supply of tocilizumab at the onset of the COVID-19 pandemic and the desire to distribute equitably available stock among critically ill patients. As an increased supply of tocilizumab was procured, nonintubated patients were increasingly offered tocilizumab, in addition to critically ill patients, with the aim of abrogating inflammation early and preventing progression to invasive respiratory support. Furthermore, COVID-19-targeted therapy, including antivirals and corticosteroids, was at the discretion of the attending physician, but was generally consistent across the healthcare system through systemwide guidelines distributed to all providers. Mechanical ventilation was at the discretion of the attending physician and consistent with existing guidelines for the management of ARDS. All ICUs, including those newly formed during the pandemic, had at least one physician experienced in critical care and mechanical ventilation. Prone positioning was recommended as tolerated for all nonintubated patients; in mechanically ventilated patients, prone positioning was uniformly implemented for patients who met criteria based on established guidelines for patients with ARDS. All patients admitted to the hospital routinely receive venous thromboembolism prophylaxis with either subcutaneous unfractionated heparin or enoxaparin, unless otherwise contraindicated. Guidelines developed during the pandemic recommended the empiric use of therapeutic anticoagulation if there was high suspicion for venous thromboembolism (hypoxia not otherwise explained, tachycardia not otherwise explained, lower extremity swelling, or D-dimer > 6× upper limit of normal [~1500]); otherwise, standard prophylactic anticoagulation was used.

Outcomes

Our primary outcome was time to inpatient mortality since receiving tocilizumab. Secondary outcomes included time to discharge from the hospital, median length of ICU stay, and the prevalence of secondary infections.

Propensity Score Matching

To address confounding and other sources of bias arising from the use of observational data, we estimated a propensity score for the likelihood of treatment with tocilizumab and matched patients

treated with tocilizumab to those not treated with tocilizumab using a 1:1 ratio without replacement, according to the estimated propensity scores (17). In the logistic regression model used to estimate propensity scores, we included demographic variables, comorbidities, as well as therapies and laboratory markers 24 hours prior to administration of tocilizumab. These included hydroxychloroquine, azithromycin, lopinavir/ritonavir, nitazoxanide, corticosteroids, neuromuscular blockade, vasopressors, CRP, D-dimer, ferritin, IL-6, and extracorporeal membrane oxygenation (ECMO). We also ensured that the days from hospitalization to tocilizumab administration matched the length of stay for the control group using a rolling entry strategy (18). The month indicator (before and after April 1) was included to ensure that the rapidly evolving treatment protocol for COVID-19 treatment was balanced between the two groups. Propensity score matching was implemented using a nearest neighbor strategy. Quality of matching was assessed using standardized mean difference. Matched patients were considered for outcome analysis. Day of the first administration of tocilizumab and the corresponding matched hospitalization day for the matched controls were considered the baseline for time-varying variables.

Statistical Analysis

We summarized continuous variables using median and ranges, and categorical variables using frequency and proportions, overall and stratified by tocilizumab. Missing on-admission variables were imputed using multiple imputation; laboratory markers that were not measured were categorized into quartiles with a missing category. We used propensity score matching to match patients who received tocilizumab to the control patients who did not. Unadjusted and adjusted competing risk regression models were used to compare the primary outcome of time to inpatient mortality; discharge was considered a competing event, to account for differential censoring of patients still hospitalized and those already discharged (19). Covariates from the propensity score model with a standardized mean difference greater than 0.15 postmatching were included in the adjusted model. Patients who were still hospitalized at the time of analysis were censored, with June 18, 2020 as last day of follow-up.

For secondary outcome analysis, we used linear regression to compare the log-transformed length of ICU stay and logistic regression to compare infection rates between the matched groups. Competing risk regression was also used to analyze time to discharge, with inpatient mortality as the competing event. As an exploratory analysis, we also assessed the association of steroids with time to mortality on the matched cohort. All tests were two-tailed at a significance level of 0.05, unadjusted for multiplicity. R software (Version 3.6.1, with libraries "MatchIt," "cmprisk," and "survival," R Foundation, Vienna, Austria) was used for the analysis.

RESULTS

Baseline Demographics and Clinical Characteristics

We identified 3,580 SARS-CoV-2 positive patients admitted to the NYULH system between March 1, 2020, and April 24, 2020. The patients in the cohort had a mean age of 64 (interquartile range [IQR], 52–75). A majority (60.1%) of the patients were male. The study population comprised 43.4% White, 15.4%

African-American, 6.8% Asian, and 34.5% other/unknown subjects. A detailed description of the demographic and clinical characteristics of the overall cohort is provided in the supplementary appendix (**Table S2**, http://links.lww.com/CCX/A426). Missing data were most common for BMI (22.7%) and laboratory markers that were not measured for a subset of patients. In the study cohort, 497 patients received tocilizumab for the treatment of COVID-19. We identified an equal number of propensity-matched control subjects. The standardized mean difference (**Table S3**, http://links.lww.com/CCX/A426), computed to assess the quality of matching, indicated overall a good balance of covariate distribution between the groups with a mean standardized difference under 0.15 for most variables. The standardized mean difference exceeded 0.15 in absolute measure for CRP, D-dimer, ferritin, and IL-6 levels at baseline; vasopressor use at baseline; treatment with azithromycin; days in hospital prior to tocilizumab administration; and any steroid use during hospitalization.

The baseline characteristics of patients who received tocilizumab and those who did not in the propensity score-matched sample are described in Table S3 (http://links.lww.com/CCX/A426). The patients in the tocilizumab group had a mean age of 60.2 years. A majority (70.8%) of the patients were male. They comprised 44.7% White, 14.7% African-American, 7.4% Asian, and 33.2% other/unknown subjects. The tocilizumab group was similar to the matched controls with respect to smoking status; BMI; and prevalence of hypertension, diabetes, heart disease, chronic lung disease, and history of solid organ transplantation.

Therapeutic Interventions on Matched Groups

Patients in the tocilizumab group received the study drug at a median of 3 days after hospitalization (IQR, 2–5). At baseline, a higher percentage of patients in the tocilizumab group had received azithromycin (90.5% vs 85.9%). A higher percentage of matched control patients received vasopressors at baseline (9.7% vs 5.6%). Patients who received tocilizumab also received steroids more often during hospitalization compared with matched controls (51.7% vs 25.2%). Tocilizumab-treated patients received a higher cumulative dose of corticosteroids during the hospital stay, expressed as methylprednisolone equivalents, when compared with matched controls (median, 350 vs 125 mg). Tocilizumab and matched control patients received similar levels of oxygen support at baseline. Three patients in the tocilizumab group and two controls received ECMO therapy at baseline.

Outcomes in the Matched Study Groups

Fewer tocilizumab-treated patients died (145/497, 29.2%) when compared with matched controls (211/497, 42.5%) (Table 1). After adjusting for covariates for which the standardized mean difference exceeded 0.15, tocilizumab was associated with improved survival relative to matched controls (HR = 0.24, 95% CI = 0.18–0.33, $p < 0.001$) (**Fig. 1** and **Table 2**). A total of 332 tocilizumab-treated patients and 283 controls experienced clinical improvement and were discharged from the hospital. Twenty tocilizumab-treated patients remained in the hospital at the time of the last follow-up and three of the surviving control patients remained in hospital (Table 1). The adjusted time to discharge from hospital was

TABLE 1. Study Outcomes Postmatching, Overall and Stratified by Tocilizumab Status

Outcome	Total (IQR/%) (n = 994)	On Tocilizumab (IQR/%) (n = 497)	Not on Tocilizumab (IQR/%) (n = 497)	p[a]
Death, n (%)	356 (35.81)	145 (29.18)	211 (42.45)	< 0.001
Discharged, n (%)	615 (61.87)	332 (66.80)	283 (56.94)	0.002
Still hospitalized, n (%)	23 (2.31)	20 (4.02)	3 (0.60)	0.001
Secondary infection, n (%)	224 (22.54)	171 (34.41)	53 (10.66)	< 0.001
Bloodstream infections, n (%)	87 (8.75)	69 (13.88)	18 (3.62)	< 0.001
Pneumonia, n (%)	158 (15.90)	129 (25.96)	29 (5.84)	< 0.001
Urinary tract infections, n (%)	55 (5.53)	40 (8.05)	15 (3.02)	0.001
ICU length of stay (d), median (IQR)	9.39 (3.37–20.14)	13.8 (6.18–23.2)	3.59 (1.26–7.93)	< 0.001
Time to death (d), median (IQR)	8 (4–15)	16 (9–26)	5 (3–9)	< 0.001
Time to discharge (d), median (IQR)	8 (4–18)	16 (11–31)	4 (3–6)	< 0.001
Time to any infection, median (IQR) (d)	9 (4–14)	10 (5–15)	4 (1–8)	< 0.001
Time to bloodstream infection (d), median (IQR)	10 (5.5–16)	12 (7–16)	6.5 (1.75–10.75)	0.010
Time to pneumonia (d), median (IQR)	10 (7–16)	12 (7–17)	5 (1–9)	< 0.001
Time to urinary tract infection (d), median (IQR)	7 (1.5–16)	13.5 (2–19.5)	1 (1–6)	0.001

IQR = interquartile range.

[a]All comparisons are unadjusted.

similar for tocilizumab-treated patients and controls (HR = 0.96, 95% CI = 0.78–1.17, p = 0.67) (Fig. 1; and **Table S5**, http://links.lww.com/CCX/A426). Multivariable linear regression analysis showed that tocilizumab-treated patients had a three times longer ICU length of stay than controls (95% CI = 2.5–3.7 d, p < 0.001) (**Fig. 2** and **Table 3**). Furthermore, steroids use did not have survival benefit in the matched cohort (**Fig. S1**, http://links.lww.com/CCX/A426).

Adverse Events

In a multivariable logistic regression model, secondary infections occurred at a higher rate in tocilizumab-treated patients than in controls (34.4% vs 10.7%, odds ratio [OR] = 4.18, 95% CI = 2.72–6.52, p < 0.001) (Fig. 2 and Table 3). This was explained by a higher prevalence of bloodstream infections (13.9% vs 3.6%, OR = 3.85, 95% CI = 2.08–7.46, p < 0.001), pneumonia (25.9% vs 5.8%, OR = 5.96, 95% CI = 3.47–10.66, p < 0.001), and urinary tract infections (8% vs 3%, OR = 2.39, 95% CI = 1.20–4.92, p = 0.014) in tocilizumab-treated patients. Infections occurred later during the course of hospitalization in tocilizumab-treated patients (10 d; IQR, 5–15) than in controls (4 d; IQR, 1–8).

DISCUSSION

In this study, we retrospectively reviewed the treatment of hospitalized COVID-19 patients across the NYULH system with tocilizumab, a soluble IL-6 receptor antagonistic monoclonal antibody. The main finding was a significant survival benefit in patients receiving tocilizumab as compared with propensity-matched controls. The survival benefit was associated with increased length of stay in the ICU and an increased rate of secondary infections.

Cytokine storm has been implicated in the pathogenesis of COVID-19 disease with higher levels of inflammatory cytokines, specifically IL-6, found in critically ill patients (3, 5, 6). The resultant inflammatory process leads to progressive hypoxemic respiratory failure often necessitating oxygen support and mechanical ventilation (20). Inhibition of inflammatory cytokines by antibodies such as tocilizumab may mitigate respiratory compromise and improve the survival of patients with severe disease.

Tocilizumab has been shown to be effective in the treatment of CRS, particularly in the setting of CAR T cell therapy (21). A small, single-arm, retrospective study from China published early during the COVID-19 pandemic demonstrated dramatic improvement in fever, laboratory parameters, and oxygen support in COVID-19 patients who received tocilizumab (9). This report piqued interest in tocilizumab use as the pandemic spread to Italy and the United States. Subsequently, several other studies on tocilizumab were published. However, they all suffered from similar limitations of a lack of comparator arm and small sample size (10–13). More recently, two observational cohort studies have improved the evidence of benefit for tocilizumab by incorporating a comparator group and attempting to control for imbalances between the groups. Consistent with prior reports, these two studies found a reduction in the risk of death or mechanical ventilation associated with tocilizumab, with an accompanied increased risk of infection (15, 16). Our experience is the largest cohort published to date. We performed propensity matching and competing risk regression models postmatching to control for imbalances between the groups. We found that receipt of tocilizumab was associated with improved survival. This allowed critically ill patients, who would
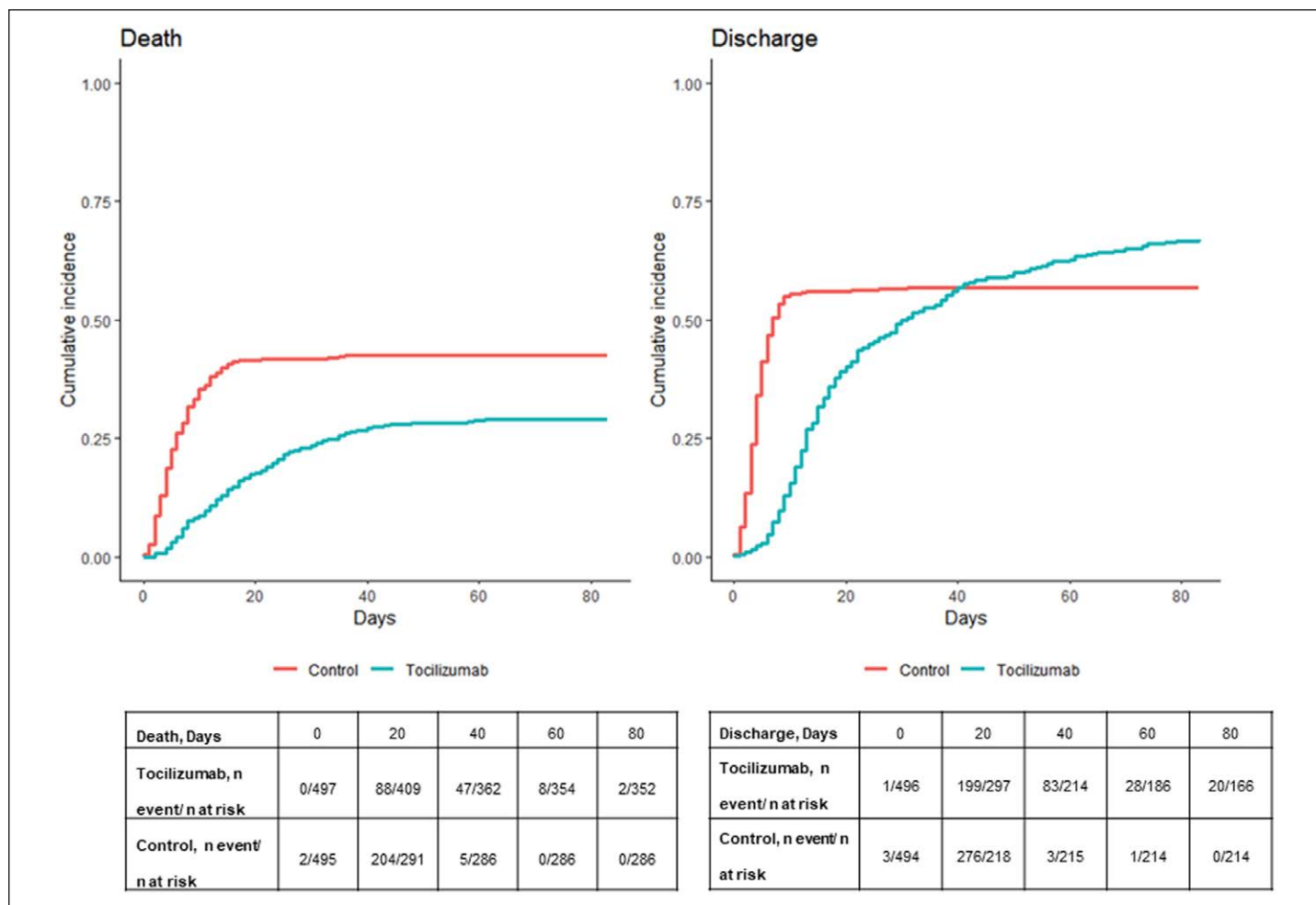
Figure 1. Cumulative incidence curves for time to mortality with discharge as a competing event, and for time to discharge with mortality as a competing event.

have otherwise died, to survive the initial inflammatory insult, progressing to a sustained critical illness characterized by lung injury and prolonged hypoxemic respiratory failure. As a result, patients who received tocilizumab also had much longer durations of mechanical ventilation and ICU length of stay. It is unclear the impact this will have on quality of life, and future studies will be needed to address long-term outcomes.

A recent press release from Roche (Basel, Switzerland, no published data are available) suggested that tocilizumab in the multicenter randomized COVACTA trial (NCT04320615) did not reach its primary end point of improved clinical status for patients with severe COVID-19-associated pneumonia (22). A review of the inclusion criteria listed on ClinicalTrials.gov for this trial reveals that enrollment was dependent on the clinical findings of SARS-CoV-2-associated pneumonia and not on the biochemical evidence of severe inflammation. Two-thirds of the patients in our study who received tocilizumab had a predosing CRP level of greater than 95 mg/L, indicating that our study population was skewed toward a hyperinflammation phenotype, supporting the mechanism of action of tocilizumab. Based on the minimal data mentioned in the press release, it would also appear that our patients (both tocilizumab-treated and matched controls) had notably higher rates of mortality and days on mechanical ventilation, suggesting higher

levels of critical illness than the COVACTA trial. Although ordinal scale end points have been common in phase III COVID-19 trials and may increase power in studies with smaller samples, a time-to-event analysis may be preferred in a critically ill patient population when many patients have not met the outcome at the specified follow-up interval (23, 24). This was true in our cohort where many patients, particularly in the tocilizumab group, had not reached the primary end point by the 28-day follow-up period used in the COVACTA trial. Although randomized controlled trials remain the gold standard of evidence, our study contributes to the rapidly evolving body of literature as it shows a significant improvement in survival in a large population of patients receiving a consistent level of critical care.

A major confounder that should be accounted for in any analysis of COVID-19-infected patients is the concomitant administration of corticosteroids. Recently reported findings of the UK RECOVERY study demonstrated significant improvement in survival in COVID-19 patients who were treated with dexamethasone, particularly those on mechanical ventilation (25). These findings were in contrast to prior published data, and thus, corticosteroid use was not considered in many early studies of tocilizumab (26). Steroid use (drug, dose, and duration) was highly variable at our institution during the early course of the pandemic. Additionally,

TABLE 2. Competing Risks Regression Comparing Time to Inpatient Mortality Between Tocilizumab and Matched Control Group

Variable	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Tocilizumab	0.55 (0.45–0.67)	< 0.001	0.24 (0.18–0.33)	< 0.001
Steroid use			2.22 (1.72–2.87)	< 0.001
Pretocilizumab vasopressors			1.45 (1.10–1.91)	0.008
Azithromycin			0.76 (0.55–1.03)	0.079
Days in hospital			0.95 (0.92–0.97)	< 0.001
C-reactive protein, mg/L				
0–34			1.0 (Reference)	
35–94			1.4 (0.36–5.44)	0.63
95–192			3.31 (0.91–12.05)	0.069
193+			6.1 (1.67–22.34)	0.006
Unmeasured			2.17 (0.59–8.08)	0.25
D-dimer, ng/mL				
0–343			1.0 (Reference)	
344–752			1.8 (0.89–3.66)	0.10
753–2207			3.87 (1.97–7.58)	< 0.001
2,207+			4.67 (2.41–9.04)	< 0.001
Unmeasured			2.71 (1.43–5.17)	0.002
Interleukin 6, pg/mL				
0–6			1.0 (Reference)	
7–21			1.02 (0.36–2.89)	0.97
22–86			1.87 (0.72–4.89)	0.20
87+			2.23 (0.94–5.31)	0.07
Unmeasured			1.58 (0.69–3.6)	0.28
Ferritin, ng/mL				
0–483			1.0 (Reference)	
484–990			0.96 (0.52–1.75)	0.89
991–1917			1.14 (0.64–2.02)	0.65
1,917+			1.31 (0.74–2.32)	0.35
Unmeasured			1.23 (0.64–2.36)	0.53

the likelihood of a patient receiving steroids and the cumulative dose they received was affected by how long the patient survived. Thus, we were unable to control completely for this important variable. However, we found similar corticosteroid utilization as other cohorts, with more patients who received tocilizumab also receiving corticosteroids (13, 15, 16). Despite this imbalance, steroids did not appear to offer additional survival benefit when administered after tocilizumab in the matched cohort leading us to conclude this did not account for the difference in outcomes between the two groups.

Tocilizumab has relatively few adverse effects, but the most concerning is the risk for secondary infection with additional immunosuppression in critically ill patients (21). Indeed, secondary infections were common in ours and other studies (15, 16). Types of infection were diverse in our tocilizumab population with an increased rate of blood stream infections, urinary tract infections, and pneumonias. However, this trade-off must be taken in the context of the earlier death in the control group. Additionally, it is unclear from our analysis if infections contributed to, or were the result of, prolonged stay in the ICU in the patients who received tocilizumab.
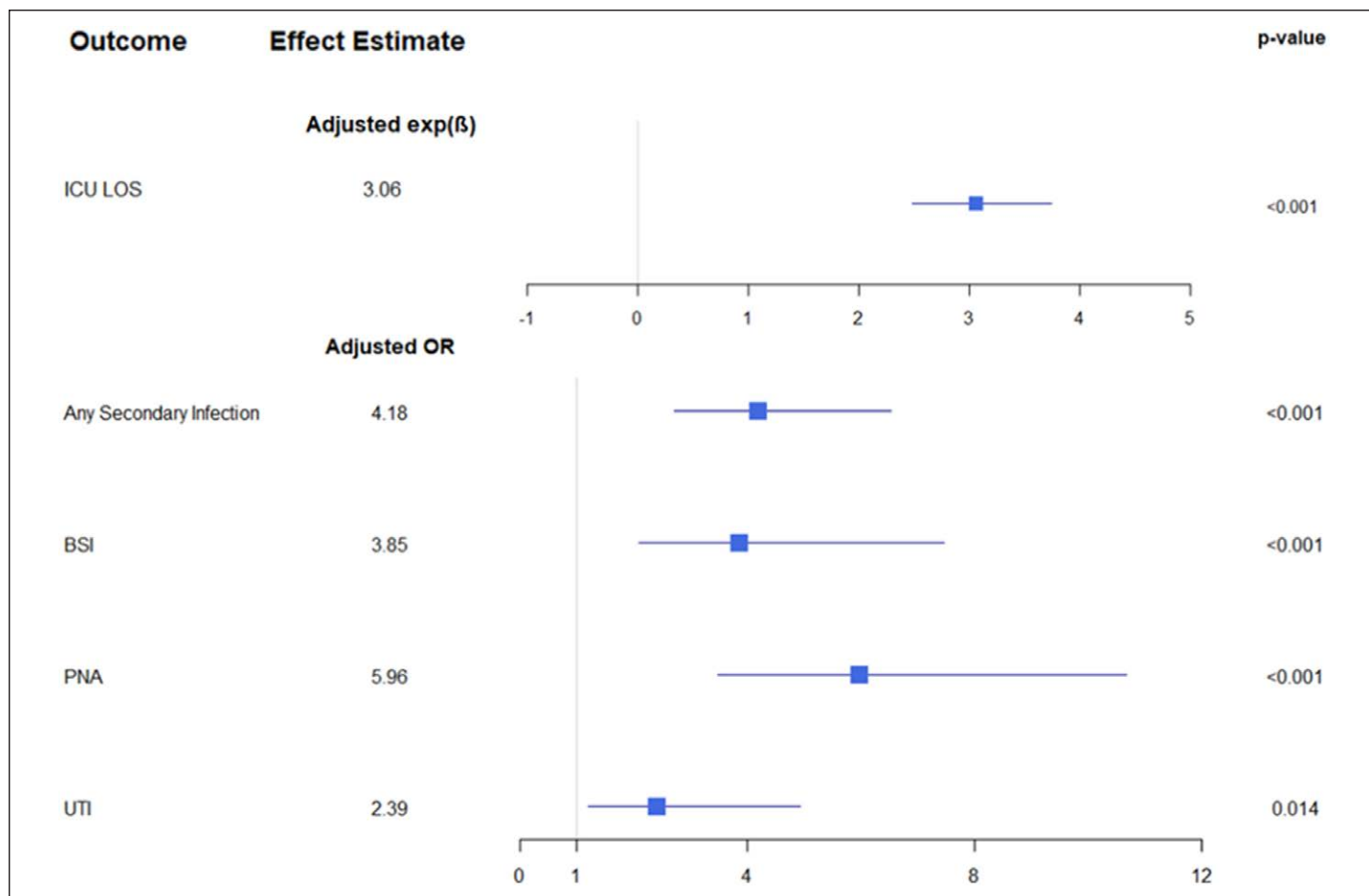
Figure 2. Effect estimates comparing secondary events between tocilizumab and matched control group. [a]Adjustment covariates include use of steroids, use of vasopressors before tocilizumab administration, use of azithromycin, days in hospital, categorical C-reactive protein, categorical D-dimer, categorical interleukin-6, and categorical ferritin. [b]For ICU length of stay (LOS [d]), exponentiated effect size is coefficient from the log-linear regression with log-transformed outcome reported, whereas for the binary outcomes of infection, bloodstream infection (BSI), pneumonia (PNA), and urinary tract infection (UTI) odds ratio (OR) from logistic regression are reported.

TABLE 3. Effect Estimates Comparing Secondary Events Between Tocilizumab and Matched Control Group

Outcome	Unadjusted[b]		Adjusted[a,b]	
	Effect Estimate (95% CI)	p	Effect Estimate (95% CI)	p
ICU length of stay (d)	2.66 (2.22–3.22)	< 0.001	3.06 (2.48–3.74)	< 0.001
Any secondary infection	4.39 (3.15–6.22)	< 0.001	4.18 (2.72–6.52)	< 0.001
Bloodstream infection	4.29 (2.57–7.53)	< 0.001	3.85 (2.08–7.46)	< 0.001
Pneumonia	5.66 (3.75–8.8)	< 0.001	5.96 (3.47–10.66)	< 0.001
Urinary tract infection	2.81 (1.57–5.32)	0.001	2.39 (1.20–4.92)	0.014

[a]Adjustment covariates include use of steroids, use of vasopressors before tocilizumab administration, use of azithromycin, days in hospital, categorical C-reactive protein, categorical D-dimer, categorical interleukin 6, categorical ferritin.

[b]For ICU length of stay (d) exponentiated effect size coefficient from the log-linear regression with log-transformed outcome is reported whereas for the binary outcomes of infection, bloodstream infection, pneumonia, and urinary tract infection odds ratio from logistic regression is reported.

Limitations of our study include its retrospective nature and lack of randomization. We attempted to correct for the variable clinical course of COVID-19 infection through the use of propensity score matching and a rolling entry strategy; however, the possibility remains of imperfect comparisons. Guidelines for the management of many aspects of care of the COVID-19 patient were updated frequently and distributed systemwide. Still, we were unable to control for all of these treatments such as frequency and duration of prone positioning or anticoagulation. The availability of anti-IL-6 clinical trials and usage of off-label

tocilizumab varied among NYULH hospitals potentially biasing the patient population. Although the tocilizumab and the control groups were matched for corticosteroid usage prior to tocilizumab administration, tocilizumab-treated patients received a higher cumulative dose of corticosteroids during the hospital stay than controls. However, we controlled for corticosteroid use, both pre- and posttocilizumab, and did not find that corticosteroids affected outcomes in those receiving tocilizumab. Secondary infections were defined only according to positive microbiologic culture and thus may have been overestimated due to capturing colonization or contamination.

CONCLUSIONS

In summary, in this retrospective, propensity-matched cohort study, IL-6 receptor blockade with tocilizumab was associated with significantly improved survival in patients with COVID-19 pneumonia. This survival benefit was associated with an increase in ICU length of stay and an increased rate of infection. Ultimately, we await the results of randomized, placebo-controlled trials to determine the impact of tocilizumab and other IL-6 pathway inhibitors on COVID-19. In addition, it is hoped that these trials will inform us on the optimal timing of administration and disease severity for the use of these promising anti-inflammatory agents.

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