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# Impact of Timing of Tocilizumab Use in Hospitalized Patients With SARS-CoV-2 Infection

Anup K Singh, Margarita Oks, Gregg Husk, Samuel P Dechario, Bushra Mina, Kanwaljit Singh, Linda Kirschenbaum, Charles M Carpati, Omar Mahmoud, Nader Ishak Gabra, Oki Ishikawa, Erica Altschultz, Varun Shah, Akhilesh Mahajan, Arun Gautam, Brian Birnbaum, Anthony C Antonacci, and Suhail Raoof

**BACKGROUND: SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) continues to be a global challenge due to the lack of definitive treatment strategies. We sought to determine the efficacy of early administration of anti-interleukin 6 therapy in reducing hospital mortality and progression to mechanical ventilation. METHODS: This was a retrospective chart review of 11,512 patients infected with SARS-CoV-2 who were admitted to a New York health system from March to May 2020. Tocilizumab was administered to subjects at the nasal cannula level of oxygen support to maintain an oxygen saturation of >88%. The Charlson comorbidity index was used as an objective assessment of the burden of comorbidities to predict 10-year mortality. The primary outcome of interest was hospital mortality. Secondary outcomes were progression to mechanical ventilation; the prevalence of venous thromboembolism and renal failure; and the change in C-reactive protein, D-dimer, and ferritin levels after tocilizumab administration. Propensity score matching by using a 1:2 protocol was used to match the tocilizumab and non-tocilizumab groups to minimize selection bias. The groups were matched on baseline demographic characteristics, including age, sex, and body mass index; Charlson comorbidity index score; laboratory markers, including ferritin, D-dimer, lactate dehydrogenase, and C-reactive protein values; and the maximum oxygen requirement at the time of tocilizumab administration. Mortality outcomes were evaluated based on the level of oxygen requirement and the day of hospitalization at the time of tocilizumab administration. RESULTS: The overall hospital mortality was significantly reduced in the tocilizumab group when tocilizumab was administered at the nasal cannula level (10.4% vs 22.0%; $P = .002$). In subjects who received tocilizumab at the nasal cannula level, the progression to mechanical ventilation was reduced versus subjects who were initially on higher levels of oxygen support (6.3% vs 18.7%; $P < .001$). There was no improvement in mortality when tocilizumab was given at the time of requiring non-rebreather, high-flow nasal cannula, noninvasive ventilator, or invasive ventilator. CONCLUSIONS: Early use of anti-interleukin 6 therapy may be associated with improved hospital mortality and reduction in progression to more severe coronavirus disease 2019.** *Key words: tocilizumab; COVID19 mortality; interlukin-6.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 169 million people and led to over 3.5 million deaths worldwide.[1] The therapeutic armamentarium has expanded since the start of the pandemic, but the definitive therapy has yet to be determined. This novel infection has a biphasic course that spans ~14 d of acute symptoms. During the first 7 d, there is a mild inflammatory response, with a relatively

Drs Singh, Oks, Mina, Kirschenbaum, Carpati, Mahmoud, Gabra, Ishikawa, Altschultz, Shah, Mahajan, Gautam, Birnbaum, and Raoof are affiliated with the Department of Pulmonary Critical Care and Sleep Medicine, Lenox Hill Hospital – Northwell Health System, New York, New York. Dr Husk is affiliated with Hospital Administration, Lenox Hill Hospital – Northwell Health System, New York, New York. Drs Dechario and Antonacci are affiliated with the Department of Surgery, Lenox Hill Hospital – Northwell Health System, New York, New York. Dr Singh is affiliated with the Critical Path Institute – International Neonatal Consortium, Tucson, Arizona.

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benign clinical course. As the disease progresses, some patients develop a more severe illness, with a profound inflammatory response, the "cytokine storm."[2] In late disease stages, there are increased plasma levels of T-helper type 1 and type 2 cytokines, more specifically interleukin (IL) 2, IL-6, IL-7, granulocyte colony-stimulating factor, and tumor necrosis factor (TNF alpha). This often leads to respiratory deterioration, which requires mechanical ventilation and dialysis, and to further multiorgan failure.

Consequently, there are high SARS-CoV-2-associated mortalities and prolonged hospital and ICU stays. Targeting the aberrant immune response is a therapeutic option and includes immunomodulators (eg, IL-6). IL-6 has been shown to be elevated in patients with SARS-CoV-2 infection, and IL-6-producing monocytes were found to be even higher in ICU patients. Tocilizumab, a humanized monoclonal antibody against the soluble and membrane-bound IL-6 receptor, is a first-line treatment for cytokine release syndrome, which classically occurs as a result of immunotherapy and infections and, similarly, may have potential in the treatment of SARS-CoV-2. We hypothesize that targeting the population of non-critically ill patients who have moderate and severe SARS-CoV-2 disease with off-label anti-IL-6 therapy early in the hospital course would result in lower mortality and prevent progression to mechanical ventilation.

**QUICK LOOK**

**Current knowledge**

The mortality from COVID-19 is significantly higher if mechanical ventilation is required during hospitalization. Effective treatment strategies to reduce the need for intubation for progressive hypoxemic respiratory failure in patients with COVID-10 are still under investigation.

**What this paper contributes to our knowledge**

Using interleuikin-6 antagonists when patients are only requiring nasal cannula level of oxygen support is associated with a decrease in progression to mechanical ventilation, and hence COVID-19 related mortality.

## Methods

### Setting

Patients admitted from March 1, 2020, to May 17, 2020, to 23 hospitals, part of the Northwell Health System, that use a shared electronic medical record system (Sunrise Clinical Manager; Allscripts, Chicago, IL) in the greater New York area were included in this study. All subjects ≥ 18 y old had, via a nasopharyngeal swab sample, polymerase chain reaction-confirmed positive SARS-CoV-2 infection. Subjects who were transferred within the Northwell Health System were counted as a single encounter at the receiving institution. Likewise, we only included the first in-patient admission for subjects with >1 admission within the study period. This work was supported by grants R24AG064191 from the National Institute on Aging of the National Institutes of Health and R01LM012836 from the National Library of Medicine of the National Institutes of Health. The Northwell Health Institutional Review Committee approved this study for publication as a minimum risk retrospective observational cohort study with a waiver of informed consent (20 - 0966).

### Data Sources

For this retrospective observational cohort study, all data were personal health information (PHI) protected and Health Insurance Portability and Accountability Act compliant on a structured query language (SQL) platform, with data repositories maintained within Northwell Health VPN firewalls. Heterogenous internal (electronic medical record: Sunrise Clinical Manager - Allscripts and Northwell Health Consortium COVID Registry) data sources were abstracted, coded, and consolidated into a single view for reporting on patient clinical courses (Outcome Management Systems, Greenwich, Connecticut). Existing and custom-built machine intelligence and natural language processing supplemented our standardized data extraction algorithms for the collection and analysis of actuarial outcome data.

All queries were written by 2 of us (GH, SPD), and the results were validated against the electronic medical record. Charted clinical documentation was used to identify the level of oxygen support required by the subjects during hospitalization. electronic medical record-coded comorbidity and coronavirus disease 2019 (COVID-19) diagnoses, estimated glomerular filtration rate, and orders for dialysis or ultrafiltration were used to identify subjects newly initiated on renal replacement therapy. The records of all subjects with electronic medical record orders for a computed tomography of the chest, with pulmonary embolism protocol

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Drs Singh and Oks contributed equally as first authors.

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Correspondence: Anup K Singh MD, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Lenox Hill, Lenox Hill Hospital – Northwell Health System – New York, NY, Department of Pulmonary Critical Care and Sleep Medicine. E-mail: asingh21@northwell.edu.

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and a venous duplex ultrasound of the extremities were evaluated, and the results were used to identify subjects with pulmonary embolism and deep venous thrombosis. Race and ethnicity data were collected from the electronic medical record by self-report based on predetermined categories. A list of medications was obtained from the medication administration record in the electronic medical record.

### Definitions

Early tocilizumab administration was defined as tocilizumab use in moderate stages of COVID-19, which was defined as requiring a nasal cannula level of oxygen support to maintain an oxygen saturation > 88%. Oxygen support was defined as follows: (1) nasal cannula, up to 6 L/min; (2) non-rebreather mask, up to 15 L/min, at $F_{IO_2}$ 1.0; and (3) noninvasive respiratory support including, BiPAP CPAP and/or HFNC via nasal prongs up to 60 L/min at $F_{IO_2}$ 1.0.

### Variables Assessed

Demographic data collected included age, race, ethnicity, sex, body mass index (BMI), and comorbidities abstracted from the initial admission history. In-patient data collected included SARS-CoV-2-related pharmacologic intervention, laboratory studies, daily maximum level of oxygen support, level of oxygen support during administration of tocilizumab, a need for new renal replacement therapy, and the presence of venous thromboembolism. The primary drug of interest was tocilizumab. We collected data on the level of oxygen requirement at the time of administration of tocilizumab relative to the day of hospitalization. The main intervention of interest was the administration of tocilizumab early in the disease course. Other SARS-CoV-2-related medications used included hydroxychloroquine, azithromycin, and methylprednisolone.

Tocilizumab was administered at 400 mg intravenously as a 1-time dose in most subjects; some subjects received a 1- or 2-time dose at weight-based dosing of 8 mg/kg (up to a maximum of 800 mg). Methylprednisolone dosing was 40 mg intravenously 2 times per day for 5 to 7 d. Azithromycin was administered as an anti-inflammatory agent at 250 mg once a day for 5 d. Hydroxychloroquine was administered as a 1-time dose of 800 mg, followed by 400 mg per day for 4 d (5-d total course). The Charlson comorbidity index was used to predict 10-year survival based on comorbidities. Laboratory variables were collected on admission and daily thereafter, and included C-reactive protein, ferritin, D-dimer, lactate dehydrogenase (LDH), glomerular filtration rate, and neutrophil and lymphocyte counts.

The level of oxygen support was collected on admission and daily thereafter. If a subject had more than one level of oxygen support recorded on the same day, the highest level was recorded. Oxygen supplementation categories included nasal cannula, non-rebreather mask, high-flow nasal cannula, noninvasive respiratory support in the form of BiPAP, and mechanical ventilation. A need for renal replacement therapy was based on a documented estimated glomerular filtration rate of <15 mL/min/1.73 $m^2$ at any point after admission, with concurrent documentation of a higher estimated glomerular filtration rate and no pre-admission need for renal replacement therapy; the decision to dialyze was made by the nephrology and medical ICU teams. A new diagnosis of venous thromboembolism was considered as the presence of pulmonary embolism and/or the presence of deep vein thrombosis in any extremity at any point after admission, with a concurrent absence of any thrombotic event before admission.

### Outcomes

The primary outcome of interest was hospital mortality, with reference to oxygen requirement. The secondary outcomes of interest were (1) progression to mechanical ventilation, (2) prevalence of venous thromboembolism and renal failure in patients who received tocilizumab, and (3) change in inflammatory markers (C-reactive protein, D-dimer, ferritin levels) after tocilizumab administration.

### Statistical Analysis

For the purposes of analysis, the subjects who were admitted were divided into tocilizumab and non-tocilizumab groups. In the tocilizumab group, the subjects received tocilizumab with or without other ancillary medications; and, in the non-tocilizumab group, the subjects received a combination of only ancillary medications. Propensity score matching was used to match the tocilizumab and non-tocilizumab groups to minimize selection bias. We estimated 2 separate propensity score models. The first model included all the subjects in the tocilizumab and non-tocilizumab groups, irrespective of timing of drug administration. The second model only included the subjects who received tocilizumab within 1 week of hospital admission. Propensity score matching was done with the use of a 1:2 matching protocol (without replacement [greedy-matching algorithm], with a caliper width equal to ±0.2 of the SD of the logit of the propensity score).

The groups were matched on baseline demographic characteristics, including age, sex, and BMI; Charlson comorbidity index score; laboratory markers, including ferritin, D-dimer, LDH, and C-reactive protein levels; and maximum oxygen requirement at the time of tocilizumab administration. The primary and secondary outcomes were compared between the 2 matched groups. Mortality outcomes were evaluated based on the level of oxygen requirement and day of hospitalization at the time of tocilizumab administration. Continuous variables are presented as mean

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Table 1. Subject Demographics and Baseline Clinical Characteristics, Unmatched Groups

| Variable | Tocilizumab Group ($n$ = 1,187) | Non-Tocilizumab Group ($n$ = 10,325) | $P$ |
|---|---|---|---|
| Charlson comorbidity index | 4.4 ± 3.1 | 4.6 ± 3.8 | .040 |
| Age, y | 63.8 ± 13.8 | 62 ± 20 | .005 |
| Age range, *n* (%) | | | |
| <40 y | 75 (6.3) | 1,503 (14.6) | <.001 |
| 41–60 y | 382 (32.2) | 2,872 (27.8) | |
| 61–80 y | 590 (49.7) | 4,008 (38.8) | |
| >80 y | 140 (11.8) | 1,942 (18.8) | |
| Sex, *n* (%) | | | |
| Men | 792 (66.7) | 5,730 (55.5) | <.001 |
| Women | 395 (33.3) | 4,595 (44.5) | |
| Race, *n* (%) | | | |
| White | 450 (37.9) | 4,004 (38.8) | .77 |
| Non-white | 737 (62.1) | 6321 (61.2) | |
| Body mass index, kg/m$^2$ | 30 ± 6.7 | 28.9 ± 7.5 | <.001 |
| Body mass index, *n* (%) | | | |
| <30 kg/m$^2$ | 764 (64.3) | 7,431 (71.9) | |
| >30 kg/m$^2$ | 423 (35.6) | 2,894 (28) | |
| Smoking, *n* (%) | | | |
| Smoker | 436 (36.7) | 5907 (57.2) | <.001 |
| Never-smoker | 751 (63.2) | 4418 (42.8) | |
| Medical comorbidities, *n* (%) | | | |
| Cardiac disease | 281 (23.7) | 2,441 (23.6) | .98 |
| Pulmonary disease | 104 (8.7) | 805 (7.8) | .25 |
| Human immunodeficiency virus | 14 (1.2) | 81 (0.8) | .15 |
| Malignancy (any) | 26 (2.2) | 270 (2.6) | .38 |
| Renal disease | 381 (32.1) | 2,652 (25.7) | <.001 |
| Diabetes mellitus | 391 (32.9) | 2,788 (27) | <.001 |
| Maximum $O_2$ requirement 3 d after admission, *n* (%) | | | |
| Room air | 12 (1) | 2,287 (22) | <.001 |
| Nasal cannula | 183 (15.4) | 4,088 (39.7) | |
| Non-rebreather | 623 (52.5) | 2,751 (26.7) | |
| Mechanical ventilation | 309 (26) | 1,011 (9.8) | |
| Ancillary medications, *n* (%) | | | |
| Azithromycin | 611 (51.4) | 4,118 (40.0) | <.001 |
| Hydroxychloroquine | 1,005 (85) | 6,014 (58) | |
| Methylprednisolone | 934 (78) | 3,153 (31) | |
| Maximum laboratory values 3 d after admission | | | |
| Neutrophil-to-lymphocyte ratio | 19.2 ± 19.9 | 11.7 ± 15 | <.001 |
| C-reactive protein, mg/dL | 43.8 ± 72.1 | 38.4 ± 66.7 | |
| Lactate dehydrogenase, U/L | 607 ± 299 | 475 ± 455 | |
| D-dimer, ng/mL | 3497 ± 7856 | 2284 ± 6043 | |
| Ferritin, ng/mL | 2199 ± 4963 | 1564 ± 3779 | |
| Glomerular filtration rate, mL/min/1.73m$^2$ | 70.9 ± 35 | 73 ± 39 | .030 |

Data are presented as mean ± SD unless otherwise indicated.

± SD, and categorical variables are presented as absolute numbers and percentages. Chi-square analysis or Fisher exact tests were used to evaluate categorical variables. Continuous variables were analyzed by using the *t* test and the Wilcoxon rank-sum test. All the analyses were performed with the use of SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

## Results

### Characteristics of the Cohort

There were a total of 11,512 SARS-CoV-2-related sequential admissions from March 1, 2020, to May 17, 2020, in the 12 hospitals of the Northwell Health System that share the same electronic medical records. The baseline

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Table 2. Participant Demographics and Baseline Clinical Characteristics, Propensity-Matched Groups

| Variable | Tocilizumab Group ($n = 939$) | Non-Tocilizumab Group ($n = 1,878$) | $P$ |
|---|---|---|---|
| Charlson comorbidity index score | 4.5 ± 3.1 | 4.6 ± 3.1 | .37 |
| Age, y | 64.1 ± 13.6 | 65.3 ± 13.8 | .02 |
| Men/women, *n* (%) | 627/312 (66.7/33.2) | 1223/655 (65.1/34.9) | .38 |
| Race: white/non-white, *n* (%) | 353/586 (37.6/62.4) | 683/1195 (36.4/63.6) | .68 |
| Body mass index, kg/m$^2$ | 29.7 ± 6.3 | 29.6 ± 6.3 | .71 |
| Smoking, yes/no, *n* (%) | 332/607 (35.6/64.6) | 727/1151 (38.7/61.3) | .08 |
| Medical comorbidities, *n* (%) | | | |
| Cardiac disease | 231 (24.6) | 468 (24.9) | .85 |
| Pulmonary disease | 85 (9) | 175 (9.3) | .81 |
| Human immunodeficiency virus | 12 (1.23) | 12 (0.6) | .08 |
| Malignancy (any) | 22 (2.3) | 42 (2.3) | .85 |
| Renal disease | 309 (33) | 602 (32) | .63 |
| Diabetes mellitus | 316 (33.7) | 620 (33) | .73 |
| Maximum oxygen requirement at 3 d after admission, *n* (%) | | | |
| Room air | 6 (0.64) | 22 (1.17) | .71 |
| Nasal cannula | 146 (15.5) | 289 (15.3) | .92 |
| Non-rebreather | 497 (52.9) | 1053 (56.1) | .07 |
| Noninvasive ventilation | 52 (5.5) | 38 (2) | .11 |
| Mechanical ventilation | 238 (25.4) | 476 (25.4) | .97 |
| Ancillary medication, *n* (%) | | | |
| Azithromycin | 471 (50) | 918 (48.9) | .52 |
| Hydroxychloroquine | 789 (84) | 1692 (90) | <.001 |
| Methylprednisolone | 748 (80) | 1221 (65) | <.001 |
| Maximum laboratory values at 3 d after admission | | | |
| Neutrophil-to-lymphocyte ratio | 19.8 ± 20.5 | 17.4 ± 20.2 | .003 |
| C-reactive protein, mg/dL | 44.7 ± 73.3 | 46.9 ± 75.4 | .46 |
| Lactate dehydrogenase, U/L | 608 ± 300 | 582 ± 682 | .19 |
| D-dimer, ng/mL | 3368 ± 7636 | 2905 ± 7161 | .12 |
| Ferritin, ng/mL | 2126 ± 4325 | 2125 ± 5191 | .99 |
| Glomerular filtration rate, mL/min/1.73 m$^2$ | 71.1 ± 34.9 | 69.4 ± 36.7 | .25 |

Data are presented as mean ± SD unless otherwise indicated.

characteristics of the unmatched and matched cohorts are presented in Tables 1 and 2. A total of 1,187 subjects received tocilizumab and 10,325 did not receive tocilizumab. In the propensity-matched cohort, a total of 939 subjects in the tocilizumab group were matched with 1,878 subjects of the non-tocilizumab group. A total of 218 matched subjects, 119 in the tocilizumab group and 99 in the non-tocilizumab group, were still hospitalized at the end of this analysis, and, hence, mortality outcome data were not available for this subset. In the unmatched patient population, in both the tocilizumab and non-tocilizumab groups, more subjects were in the 61–80 y old age group, men, non-white, and with a BMI $< 30$ kg/m$^2$.

There were more smokers in the tocilizumab group than in the non-tocilizumab group. There were more subjects in the tocilizumab group who required higher levels of oxygen support, including a non-rebreather mask and mechanical ventilation. Diabetes, renal disease, and cardiac disease were the most common comorbidities. Baseline LDH, D-dimer, and ferritin levels, and the neutrophil-to-lymphocyte ratios were higher in the tocilizumab group, and glomerular filtration rate was comparable in both study cohorts (Table 1). Propensity-score matching was based on baseline demographic characteristics, including age, sex, and BMI; Charlson comorbidity index score; laboratory markers, including ferritin, D-dimer, LDH, and C-reactive protein values; and the maximum oxygen requirement at the time of tocilizumab administration. All of these confounders have been proved to increase mortality, and, hence, were matched to maximize the balance of the propensity score. The subjects with missing data were not included in matching to eliminate prediction and biased results.

## Outcomes

The overall mortality in the matched tocilizumab group, excluding the subjects on room air and those who were still hospitalized, was higher than that of the non-tocilizumab group (43.9% vs 36.8%, respectively; $P < .001$) (Table 3).

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Table 3. Mortality per Oxygen Requirement Level, Propensity-Matched Groups†

| Variable | Tocilizumab Group ($n = 809$) | Non-Tocilizumab Group ($n = 1,705$) | $P$ |
|---|---|---|---|
| Subjects were still hospitalized; outcomes not known, *n* | 119 | 99 | |
| Subjects on room air, *n* | 11 | 74 | |
| Overall matched cohort | 355/809 (43.9) | 627/1705 (36.8) | <.001 |
| Subjects on a nasal cannula* | 13/125 (10.40) | 140/638 (21.9) | .002 |
| Subjects on a non-rebreather* | 190/444 (42.8) | 318/820 (38.8) | .17 |
| Subjects on noninvasive ventilation (including CPAP or HFNC)* | 19/38 (50) | 7/20 (35) | .40 |
| Subjects on mechanical ventilation* | 133/202 (65.8) | 162/227 (71.4) | .22 |

Data are presented as *n* /total *n* (%).
*Excluding subjects on room air and without outcomes.
†Matched for age; sex; body mass index; Charlson comorbidity index; ferritin, D-dimer, lactate dehydrogenase, C-reactive protein levels; and maximum oxygen requirement at the time of tocilizumab administration.
HFNC = high-flow nasal cannula

Table 4. Organ Dysfunction per Oxygen Level, Propensity-Matched Groups†

| Variable | Tocilizumab Group ($n = 666$) | Non-Tocilizumab Group ($n = 1522$) | $P$ |
|---|---|---|---|
| Progression to mechanical ventilation | | | |
| All subjects* | 207/666 (31.1) | 378/1,522 (24.5) | .002 |
| Nasal cannula | 8/128 (6.3) | 123/658 (18.7) | <.001 |
| Non-rebreather | 175/494 (35.4) | 248/843 (29.4) | .02 |
| Noninvasive ventilation (including CPAP or HFNC) | 24/44 (54.4) | 7/21 (33.3) | .12 |
| Venous thromboembolism (DVT/PE) | 76/939 (8.1) | 58/1,878 (4.6) | <.001 |
| New hemodialysis | 89/939 (8.8) | 86/1,878 (4.58) | <.001 |

Data are *n*/total *n* (%).
*Excluding subjects on room air and without outcomes.
†Matched for age; sex; body mass index; Charlson comorbidity index; ferritin, D-dimer, lactate dehydrogenase, C-reactive protein levels; and maximum oxygen requirement at the time of tocilizumab administration.
HFNC = high-flow nasal cannula
DVT = deep vein thrombosis
PE = pulmonary embolism

Table 5. Change in Laboratory markers with Tocilizumab Administration

| Laboratory Test | Value at the Time of Tocilizumab Administration | Value 48 h After Tocilizumab Administration | $P$ |
|---|---|---|---|
| C-reactive protein, mg/dL | 32.5 ± 55.4 | 14.9 ± 30.3 | <.001 |
| Lactate dehydrogenase, U/L | 1,995 ± 4,288 | 2,043 ± 3,834 | .12 |
| D-dimer, ng/mL | 637 ± 436 | 750 ± 1,102 | .08 |
| Ferritin, ng/mL | 2,756 ± 5,784 | 3,186 ± 6,458 | .01 |

Data are presented as mean ± SD.

Mortality was significantly lower when tocilizumab was administered at the nasal cannula level (10.4% vs 22.0%; $P = .002$). There was no significant difference in mortality, when tocilizumab was given at the non-rebreather level (42.8% vs 38.8%, respectively; $P = .17$), noninvasive ventilation (50% vs 35%, respectively; $P = .40$), and at the mechanical ventilation level (65.8% vs 71.4%, respectively; $P = .22$). The number of subjects who received methylprednisolone in the nasal cannula group was 70 of 125 and 353 of 638 in the tocilizumab and non-tocilizumab groups, respectively. There was no significant difference in the number of the subjects who received methylprednisolone at the nasal cannula level in the tocilizumab and non-tocilizumab groups (56% vs 55.3%, respectively; $P = .89$). However, the use of methylprednisolone was significantly higher in the tocilizumab group at non-rebreather, noninvasive, and mechanical ventilation oxygen levels.

Administration of tocilizumab at the nasal cannula level decreased the need for mechanical ventilation among all the subjects who received tocilizumab (6.3% in the

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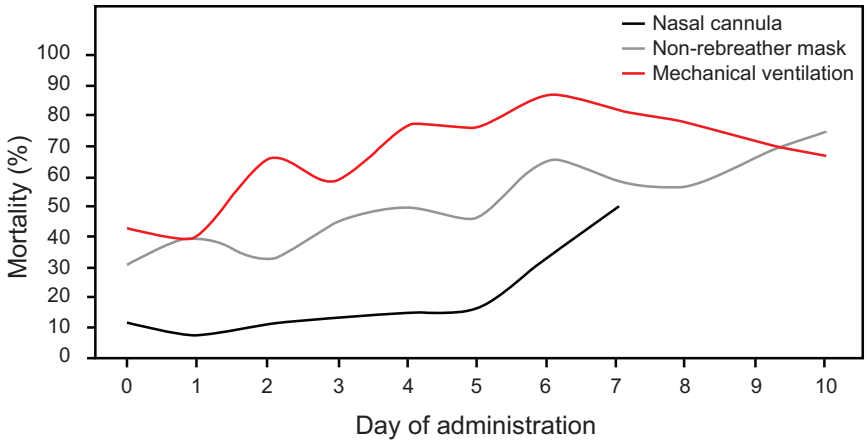


Fig. 1. Mortality (%) at each level of oxygen support vs the day of tocilizumab administration.

tocilizumab group vs 18.7% in the non-tocilizumab group; $P < .001$). A higher percentage of the subjects in the matched tocilizumab group progressed to mechanical ventilation from a baseline of non-rebreather and noninvasive ventilation requirement, except those who received tocilizumab early, at the nasal cannula level ($P < .001$) (Tables 4 and 5). The subjects who received tocilizumab while requiring only the nasal cannula level of oxygen supplementation did not progress to respiratory failure at the level of ventilation (Fig. 1). The subjects in the tocilizumab group had more cases of venous thromboembolism (8.1% vs 4.6%; $P < .001$) and new hemodialysis cases (8.8% vs 4.58%; $P < .001$) versus the non-tocilizumab group (Tables 4 and 5). The levels of C-reactive protein were significantly reduced within 48 h of tocilizumab administration ($P < .001$) (Table 3). The levels of ferritin, LDH, and D-dimer were higher 48 h after tocilizumab administration (Tables 4 and 5).

## Discussion

At the beginning of the COVID-19 surge in New York City, we used tocilizumab in the later phase of disease progression when there was a higher oxygen requirement. At that time, the mortality of patients on mechanical ventilation was high across national and international centers. We hypothesized that early control of the cytokine storm could prevent the progression of respiratory failure and decrease the need for mechanical ventilation, and, hence, may lead to a decrease in mortality. We changed our approach and administered tocilizumab to patients who were early in their disease trajectory. We targeted patients who were requiring only a nasal cannula oxygen level of supplementation to keep oxygen saturation $> 88\%$ at rest. This is considered moderate-stage COVID-19, which can progress quickly to higher levels of oxygen supplementation.

Our system's subject cohort was similar to what has been reported in the literature. Diabetes and renal and cardiac diseases were the top 3 most-frequent comorbidities. The expected survival as per the Charlson comorbidity index, with a score of 4, was ~53% at 10 years (mean ± SD Charlson comorbidity index score in our cohort was 4.5 ± 3.1 vs 4.6 ± 3.1 in matched tocilizumab vs non-tocilizumab groups). Cardiovascular and metabolic comorbidities have been linked with worse outcomes with SARS-CoV-2-related disease, and this has been uniformly reported.[3-5] Likewise, patients who had higher levels of inflammatory markers, including LDH, ferritin, D-dimer, and C-reactive protein, and who received tocilizumab were suspected to be more acutely ill at the time of admission. In our cohort, most of the subjects had a BMI $< 30$ kg/m$^2$. In several studies, a higher BMI was linked with worse outcomes with SARS-CoV-2 disease, including a higher risk of death and ICU admission.[4,6-8] Our cohort was representative of what has been reported in other New York City centers[9] but dissimilar to other states.[10] This discrepancy may be related to regional differences as well as be representative of the changing immunogenicity of the virus because the literature has been published at different times of the pandemic, which points to the possible evolution of the virus.

We evaluated outcomes based on the level of oxygen requirement at the time of tocilizumab administration because it is more clinically useful and eliminates the need for arterial blood gas assessments to make decisions. Administration of tocilizumab at the level of the nasal cannula showed a significant mortality benefit. Although this is considered moderate to severe COVID-19, it is the level of oxygen support that clinically most correlates with disease progression. Mortality associated with tocilizumab administration at the nasal cannula level was half versus the mortality of its matched counterparts in the non-tocilizumab group (10.4% vs 22.0%; $P = .002$). Mortality was decreased by 7 times if tocilizumab was used at the nasal cannula level

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versus the ventilator level (10.4% vs 71.4%) but this may be confounded by specific clinical scenarios because patients who require mechanical ventilation are understood to be more critically ill than those who only require a nasal cannula level of oxygen support. Tocilizumab administration at the nasal cannula level decreased the need for mechanical ventilation by 3-fold versus the control group (6.3% vs 18.7%; $P < .001$). Analysis of these data suggests that tocilizumab was most beneficial at a minimum oxygen requirement of up to 6 L/min through a nasal cannula to keep saturation > 88%. This may be because, within that interim, the cytokine release to SARS-CoV-2 had not yet become rampant enough to overwhelm all organ systems, which allowed anti-IL-6 antagonism to be fully effective. Similarly, Sinha et al[11] concluded that administration of an IL-6 inhibitor before a requirement of $F_{IO_2}$ 0.45 showed a decrease in mortality and a need for mechanical ventilation compared with administration after a $F_{IO_2}$ 0.45 requirement. However, they did not compare tocilizumab administration with a control group.

There was a consistent suggestion of a trend of increasing mortality with each day's delay in tocilizumab administration at all levels of oxygen requirement (Fig. 1). Gupta et al,[12] concluded that mortality among subjects with COVID-19 was lower among those treated with tocilizumab in the first 2 d of ICU admission. There have been smaller-scale observational studies that have shown a mortality benefit with tocilizumab use, but none described a mortality benefit when used early in hospitalization to prevent progression to respiratory failure.[13-15] A small observational study from Spain did show that survivors of SARS-CoV-2 tended to receive tocilizumab earlier in their hospitalization than those who did not, however, the timing intervals were not specified.[16] Unlike our study, Rosas et al[17] did not show any benefit of using tocilizumab in preventing deaths or the need for mechanical ventilation. Likewise, Stone et al[18] were unable to show a statistically significant reduction in the need for mechanical ventilation in the subjects who received tocilizumab at a lesser oxygen requirement. Salvarani et al[19] analyzed subjects with mild ARDS, fevers, and elevated C-reactive protein levels secondary to COVID-19 and the benefit from tocilizumab administration in preventing progression to mechanical ventilation, death, or worsening respiratory failure. Hermine et al[20] suggest a trend toward a reduction in rates of mechanical ventilation when tocilizumab was administered to subjects who required at least 3 L/min of oxygen supplementation via a nasal cannula but no difference in mortality at day 28.

The majority of the subjects in the tocilizumab and non-tocilizumab groups received methylprednisone at some point during their hospitalization. Our data were collected from 23 different hospitals, and the use of a combination of tocilizumab and methylprednisolone was variable. It is now known that dexamethasone has a mortality benefit in patients who require oxygen supplementation, including at the level of mechanical ventilation.[21] Methylprednisolone can be extrapolated to have at least some of this benefit as well and is the recommended corticosteroid of choice if dexamethasone is not available.[22] In our cohort, the use of methylprednisolone did not have any significant confounding effect when administered with tocilizumab at the level of the nasal cannula. Hence, the improved mortality with the use of tocilizumab at the nasal cannula level was independent of the use of methylprednisone. In the CHIC trial,[23] methylprednisolone use, followed by tocilizumab if sufficient respiratory recovery was not achieved, led to better outcomes, including mortality. Recently, a recovery trial group showed that the addition of tocilizumab in subjects with worsening oxygen requirement even after starting a steroid, decreased mortality in hospitalized subjects with COVID-19.[24] Most of the subjects in this group received tocilizumab within 24–48 h of hospitalization and 10 d after onset of symptoms.[24] The CHIC study also supports our hypothesis of better impact of using tocilizumab early in disease process.

The incidence of venous thromboembolism and renal failure that required hemodialysis was significantly higher among the subjects who received tocilizumab. Also, early tocilizumab use did not decrease the incidence of venous thromboembolism and renal failure that required dialysis. Tocilizumab use leads to a temporary increase in IL-6 due to competitive inhibition. An increase in the expression of IL-6 level has been shown to be associated with deep venous thrombosis.[25] Hence, an increased incidence of venous thromboembolism in the tocilizumab group may be due to an increasing IL-6 level after tocilizumab administration. The higher incidence of renal failure that requires renal replacement therapy in our tocilizumab cohort may signal a predominant non-cytokine storm form of injury to the kidneys. The pathogenesis of COVID-19 kidney injury is most likely multi-factorial, with direct viral invasion, renal medullary hypoxia, secondary infections, and drug-induced toxicity.[26] The extent of the inflammatory response may also explain the persistently high levels of LDH, ferritin, and D-dimer, even after administration of tocilizumab. C-reactive protein was the only inflammatory marker that decreased significantly after tocilizumab administration. C-reactive protein has been shown to be an independent predictor of COVID-19 disease severity as well as mortality. [27,28]

The limitations of this study are several-fold. This was an observational retrospective data analysis, which limits the causative conclusions that can be drawn because many unaccounted confounders exist. We were still able to show a mortality benefit with early tocilizumab use at the nasal cannula level of support. The centers that are part of our health system have various organizational structures that may have contributed to some of the better outcomes

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and cannot be accounted for in this type of analysis. Variation in practice styles between the critical care and the non-intensivist teams may have confounded the results as well. The ultimate assessment of a mortality benefit with early tocilizumab use at each respective oxygen support level and its benefit in preventing further respiratory deterioration should be based on a randomized control trial.

## Conclusions

Tocilizumab can significantly decrease COVID19 related mortality if used early in a hospital course. Its use can also halt the progression to mechanical ventilation if administered at nasal cannula level of oxygen support. Further larger randomized controlled trials are needed for confirmation.

### ACKNOWLEDGMENTS

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