Research Article

Tocilizumab Plus Corticosteroid in Elderly Patients Hospitalized With COVID-19 Pneumonia: A Retrospective Cohort Study

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Background. Tocilizumab is prescribed with corticosteroids to treat COVID-19; however, the benefits and risks of this combination are not understood, especially in older patients.

Objectives. To determine whether adding tocilizumab to corticosteroids decreases the incidence of mechanical ventilation in older patients compared to corticosteroids alone. Secondary objectives were to assess the mortality and improvements in the respiratory status.

Methods. This retrospective cohort study was conducted at a community hospital. Patients over 65 years old diagnosed with COVID-19 between March 2020 and March 2021 were screened. Patients receiving tocilizumab in addition to corticosteroids versus patients on corticosteroids were placed into treatment and comparison groups. Chi-square statistics and odds of being placed on a ventilator within 28 days, in-hospital mortality, and the improvement in the respiratory status were calculated.

Results. Of 1,651 patients screened, 355 met the inclusion criteria (176 treated patients and 179 patients in the comparison group) The incidence of being placed on a ventilator within 28 days was of 20% and 11% (OR=2.0; p=0.016) for the treatment and the comparison groups, respectively. Patients in the treatment group had 2.4 times the odds of dying (p<0.001). Patients in the treatment group had 0.9 times the odds of improvement in respiratory status (p=.628).

Conclusion and Relevance. There was no difference in the incidence of mechanical ventilation by day 28 between the patients who were on tocilizumab and those who were not. Increased mortality was seen in those who received tocilizumab and corticosteroids. The addition of tocilizumab to corticosteroids did not provide any improvement in the respiratory status and may have been harmful to older patients.

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Background

Early in the Coronavirus Disease 2019 (COVID-19) Pandemic, there was limited evidence on the efficacy of various medications used to treat pneumonia connected with SARS-COV-2.[1] Among patients hospitalized with COVID-19 pneumonia, patients requiring invasive mechanical ventilation and those above 65 years of age were at the highest risk of mortality.[2]

Early observational studies suggested that patients who developed a more severe disease with COVID-19 often had elevated inflammatory markers and cytokines.[3] Among the inflammatory cytokines, interleukin-6 (IL-6) was identified as a potential therapeutic target for COVID-19. Tocilizumab is a monoclonal antibody directed against IL-6 that has been theorized to reduce the inflammation and the progression to a more severe disease associated with COVID-19.[1][4] The immunomodulatory effects of corticosteroids in reducing systemic inflammation have also been proposed as a potential adjunctive treatment in patients with COVID-19.[1][5][6] However, the immunosuppressive properties of tocilizumab and corticosteroids can predispose patients to secondary infections, especially the vulnerable geriatric patients who often have multiple comorbidities and are on many medications.[7][8] There are also concerns with potential drug-drug interactions, drug-disease interactions, and potential harms associated with the changes in pharmacokinetics and pharmacodynamics of medications in geriatric patients.[9][10][11]

There were several studies that established the use of tocilizumab and dexamethasone in COVID-19 pneumonia.[12][13][14][15] The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial concluded that the use of dexamethasone in COVID-19 patients requiring supplemental oxygen was associated with a lower mortality rate.[12] The largest open-labeled randomized controlled trial on the use of tocilizumab conducted by the RECOVERY Collaborative group reported that weight-based dosing of tocilizumab in hospitalized patients with hypoxia and systemic inflammation was associated with lower all-cause mortality, higher hospital discharge rate, and a lower rate of mechanical ventilation.[13] However, no difference in mortality was seen in a subgroup analysis of patients aged under 70 and those aged 80 and above.[13] About 82% of patients in the study received adjunctive corticosteroids.[13] In addition, a meta-analysis by Lim and colleagues including 13 controlled trials and 24 case-control studies demonstrated a trend of mortality reduction with

tocilizumab, with no difference in rates of mechanical ventilation with tocilizumab or corticosteroids.[14] A cohort study by Biran and colleagues showed a decrease in mortality with a fixed dose of 400 mg tocilizumab in adult patients needing support in the intensive care unit (ICU) as compared with placebo, suggesting that a fixed dose may be sufficient for therapeutic benefits.[15] We hypothesized that a non-weight-based, fixed dose of tocilizumab in combination with adjunctive corticosteroids in geriatric patients may mitigate the risk of drug-induced adverse reactions while maintaining therapeutic effects in treating COVID-19 pneumonia.

As a substantial number of studies have not examined tocilizumab at 400 mg in combination with corticosteroids in elderly patients, the purpose of this study was to fill this knowledge gap and evaluate if tocilizumab at 400 mg in combination with corticosteroids would reduce the incidence of mechanical ventilation among elderly patients without an increase in mortality or adverse effects when compared to treatment with corticosteroids alone.

Methods

Study design

This was a retrospective, single-center, observational cohort study to evaluate the effects of tocilizumab in hospitalized elderly patients with COVID-19 pneumonia. Electronic health records (EHR) of patients admitted to the hospital between March 1, 2020, and March 31, 2021, were screened for eligibility. Tocilizumab was administered as a single fixed dose of 400 mg along with either methylprednisolone or dexamethasone. The choice of corticosteroids was based on availability and prescribers' discretion. No patients included in this study were vaccinated against COVID-19. Additionally, some patients in this study received other agents including hydroxychloroquine, azithromycin, doxycycline, or remdesivir as part of their care in the hospital. This investigation received an exemption from the hospital and Western Institutional Review Board and was conducted in accordance with the tenets espoused in the Declaration of Helsinki.[16]

Study Population

Eligible patients were aged 65 years and older and hospitalized with a positive COVID-19 polymerase chain reaction (PCR) test. Patients were excluded if they were mechanically ventilated prior to the initiation of treatment, received prior treatment with tocilizumab or corticosteroids, were

hospitalized for less than three days or deceased within three days of hospitalization, had a history of hypersensitivity reaction to tocilizumab or corticosteroid, history of lung diseases including asthma, chronic obstructive pulmonary disease (COPD), emphysema, and pulmonary fibrosis. Other exclusion criteria were baseline hepatic injury as defined by an alanine transaminase (ALT) or aspartate transaminase (AST) of three times the upper limit of the normal range (normal AST: 6 to 40 units/liter; ALT: 8 to 40 units/liter), thrombocytopenia (defined as a platelets count of less than 50,000 per cubic millimeter), and neutropenia (defined as neutrophil count less than 1,000 counts per cubic millimeter). Patients were also excluded in case of prior use of other immunomodulators including sarilumab, siltuximab, or baricitinib.

Outcome Measures

The primary outcome was the incidence rate of mechanical ventilation at 28 days since hospital admission. The secondary outcomes were in-hospital mortality rate; and respiratory support reduction at 28 days as defined by a reduction from a higher level to a lower level of respiratory support. Patients receiving supplemental oxygen with noninvasive positive-pressure ventilation (NIPPV) with bi-level positive airway pressure (BIPAP), continuous positive airway pressure (CPAP), or average volume-assured pressure support (AVAPS) were considered as receiving a higher level or respiratory support than patients receiving support with high flow nasal cannula (HFNC), non-rebreather mask (NRB) or Venturi mask. Safety outcomes were the incidence of hepatic injury as defined by an ALT or AST of three times the upper limit of the normal range, bacteremia, and fungemia as identified by positive blood cultures through day 28.

Data Source

Demographic information was based on documentation in the EHR. Respiratory support data at baseline and after treatment were collected from the respiratory flowsheet. The types of respiratory support were grouped based on the World Health Organization (WHO) Clinical Progression Scale for COVID-19 (Appendix A) as: nasal cannula; HFNC, NRB, Venturi mask; BiPAP, CPAP, AVAPS, collectively as noninvasive positive-pressure ventilation (NIPPV); and mechanical ventilation. The oxygen saturation at presentation and the time to progression onto mechanical ventilation were obtained from the same flowsheet. Comorbidities were identified based on the International Classification of Diseases (ICD) 10^{th} edition diagnosis code documented on the EHR or from the

provider's notes. C-reactive protein (CRP) levels were obtained from the laboratory result sheet. The use of hydroxychloroquine, azithromycin, doxycycline, or remdesivir was confirmed by medication orders and administration records. In-hospital mortality was confirmed by expiration notes from providers on current admission in the EHR. Cases of hepatic injury were obtained from laboratory results of liver function tests. Cases of bacteremia or fungemia were recorded based on microbiology lab results.

Statistical Analysis

We estimated that recruiting 174 patients in each group would provide at least an 80% power to detect a between-group difference of 40% in the primary outcome. As for descriptive statistics, means (standard deviations) and medians (interquartile range) were calculated for quantitative data, and frequencies and percentages for categorical data. Data were then analyzed for normal distribution using normal probability plots and the Anderson-Darling (AD), Shapiro-Francia (SF), and Shapiro-Wilk (SW) normality tests. Data were not normally distributed and thus the Wilcoxon-Mann-Whitney test was used to examine differences in continuous variables. Pearson's chi-square test was used to test categorical variables. Multivariable logistic regression was performed to assess the odds of being placed on a ventilator. A manual likelihood ratio test (backward elimination) approach was used for model building. An alpha of 0.15 was used for model building and an a priori alpha of 0.05 was used for significance testing. Kaplan-Meier curves were generated to compare whether there was statistical evidence of a difference between treatments. The Harrington-Fleming test was used to compare survival curves. An additional time-to-event (mortality/survival) analysis was done to assess whether there was a difference in mortality between treatment groups.

In April 2019, the American Statistical Association (ASA) formally and strongly advocated abandoning the following terms, "statistical significance", "significantly different," "$p<0.05$," and "nonsignificant". In accordance with this statement by the ASA, researchers drew no conclusions with respect to "statistical significance". The statistician used R v4.0.3 in the analysis.

Results

Patient population

Of the 1,651 patients admitted for COVID-19 during the study period, 355 patients were included in the final analysis, with 176 patients in the tocilizumab and corticosteroid (treatment) group and 179 in the corticosteroid monotherapy (comparator) group (Figure 1).

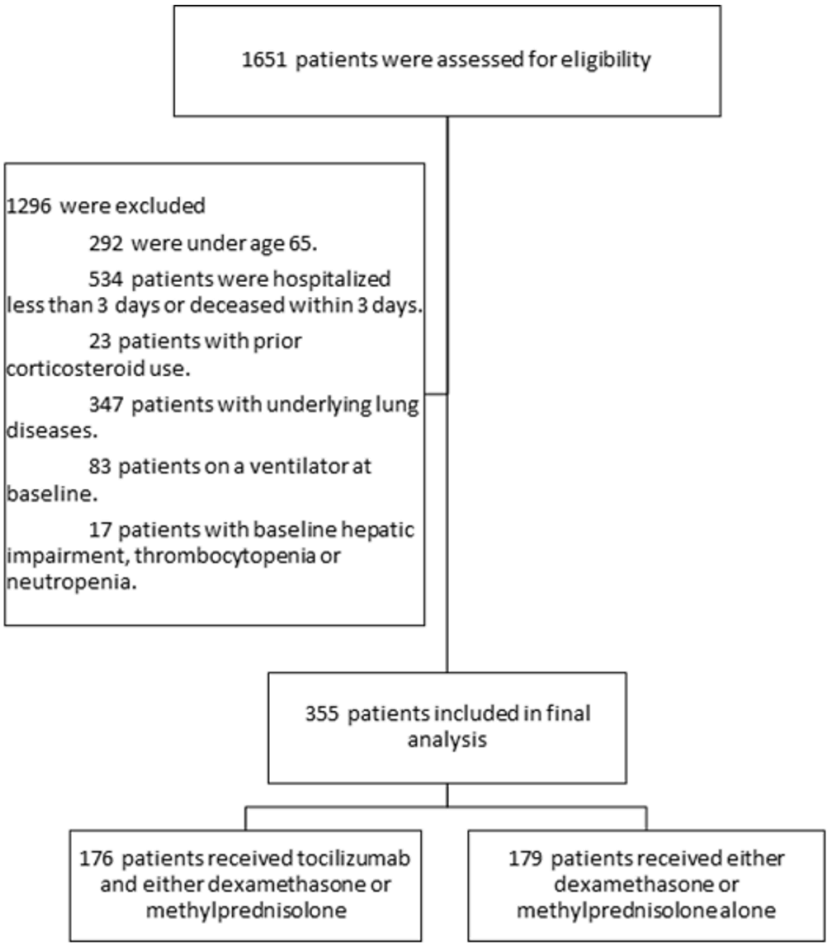

Figure 1. CONSORT flow diagram of patient recruitment for a quality improvement project investigating Tocilizumab plus corticosteroids vs. corticosteroids at one community hospital in the Northeastern, US (n=355).

The baseline demographic and disease characteristics were illustrated in Table 1. There were 47% of men in the treatment group as compared to 50% in the comparator group. The mean (±SD) age in each

group was 78±9.0 years and 78±8.5 years, respectively. In the overall population, the majority of the patients were White, followed by Black, Asian, and Hispanic. More patients in the treatment group were on higher levels of respiratory support: 29% vs. 62% on nasal canula, 45% vs. 18% on high flow nasal cannula/nonrebreather mask/Venturi mask, 26% vs. 20% on noninvasive positive pressure ventilation (NIPPV) at baseline. The median oxygen saturation on admission was 95% in the treatment group and 95% in the comparator group. Comorbidities were balanced between the two groups, except for heart failure and hypertension, which were more prevalent in the comparator group. Over 80% of patients in both groups had a CRP level of over 75 mg/L. The median CRP level was 146 mg/L in the treatment group as compared to 140 mg/L in the comparator group. More patients in the treatment group received hydroxychloroquine and azithromycin; the comparator group had more patients on doxycycline and remdesivir. The treatment group received a median dexamethasone equivalent dose of 67.5 mg as compared to 56 mg in the comparator group.

Characteristics	Tocilizumab plus Corticosteroids (n = 176)	Corticosteroids Only (n = 179)
Male [n (%)]	83 (47)	89 (50)
Age [M (SD)] (years)	78 (9.0)	78 (8.5)
Age group [n (%)]		
65-84 years	121 (69)	126 (70)
≥ 85 years	55 (31)	53 (30)
Race [n (%)]		
White	126 (72)	124 (69)
Black	30 (17)	40 (22)
Hispanic	7 (4)	7 (4)
Asian	13 (7)	8 (5)
Baseline respiratory support [n (%)]		
Nasal cannula	51 (29)	111 (62)
HFNC/NRB/Venturi mask	79 (45)	32 (18)
BiPAP/CPAP/AVAPS (NIPPV)	46 (26)	36 (20)
Comorbidities [n (%)]		
Diabetes	75 (43)	67 (37)
Hypertension	102 (58)	130 (73)
Coronary artery disease	29 (17)	21 (12)
Heart failure	17 (10)	31 (17)
Chronic kidney disease	29 (17)	21 (12)
Obesity	15 (9)	18 (10)
Oxygen saturation [n (%)]	95 (5.0)	95 (7.5)
Distribution – [n (%)]		
≥ 90	149 (85)	138 (77)

Characteristics	Tocilizumab plus Corticosteroids (n = 176)	Corticosteroids Only (n = 179)
75 – 89	25 (14)	37 (21)
< 75	2 (1)	4 (2)
C-reactive protein level (mg/L) [Mdn (IQR)]	146 (128.52)	140 (108.96)
Distribution [n (%)]		
≥ 75	141 (80)	138 (82)
< 75	35 (20)	31 (18)
Other treatments [n (%)]		
Hydroxychloroquine	118 (67)	50 (28)
Azithromycin	154 (88)	112 (63)
Doxycycline	0 (0)	30 (17)
Remdesivir	37 (21)	69 (39)
Corticosteroid doses [Mdn (IQR)]	67.5 (46)	56 (37.5)

Table 1. Baseline demographics and characteristics of patients receiving Tocilizumab plus corticosteroids and corticosteroids at one community hospital in the Northeastern, US (n=355)

[c] *Doses of corticosteroids are expressed in dexamethasone equivalent doses.*

Abbreviations: SD, standard deviation; IQR, interquartile range; HFNC, high flow nasal cannula; NRB, nonrebreather mask; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; AVAPS, average volume-assured pressure support; NIPPV, noninvasive positive-pressure ventilation.

Primary outcome

On day 28, 36 patients (20.5%; 95% confidence interval [CI], 14.8% to 28.4%) in the tocilizumab and corticosteroid group and 20 patients (11.2%; 95% [CI], 7.2% to 17.3%) in the corticosteroid monotherapy group were intubated and placed on mechanical ventilation [odds ratio, 1.4; 95% CI, 0.69 to 2.66; p= 0.76 by Fleming-Harrington test]. Results were shown in Table 2 and Figure 2.

Outcomes	Tocilizumab plus corticosteroids (N=176)	Corticosteroids only (N=179)	Odd ratio [a]	Difference [a]	*p*
Ventilation [a, b]	20 % (14.8%, 28.4%)	11 % (7.2%, 7.3%)	1.4 (0.69 to 2.66)	NA	0.76
In-hospital mortality [a, c]	32 % (25.0%, 42.0%)	17 % (11.7%, 24.0%)	NA	16% (6.2% to 25.0%)	<0.001

Table 2. Primary and secondary outcomes at Day 28 of patients receiving Tocilizumab plus corticosteroids and corticosteroids at one community hospital in the Northeastern, US (n=355)

Abbreviations: CI, confidence interval; NA, not applicable.

[a] 95% Confidence interval

[b] Primary outcome

[c] Secondary outcome

Secondary outcomes

Over the 28-day study period, 57 patients (32.4%; 95% [CI], 25.0% to 42.0%) deceased in the tocilizumab group, and 30 patients (16.8%; 95% [CI], 11.7% to 24.0%) deceased in the comparator group (OR: X; 95% CI: X to X; p = X).

In terms of respiratory status improvement, there was no statistical evidence of a difference between the two groups for patients receiving any of the three levels of respiratory support at baseline. There was no difference in respiratory support reduction in patients receiving nasal cannula at baseline (treatment 52.5% vs. 44.6% comparator, p = 0.516). Over 70% of patients in both groups receiving HFNC/NRB/Venturi masks at baseline required a lower level of respiratory support at the end of the study period (74.5% vs 81.5%, p = 0.680). On day 28, there was no difference in respiratory support reduction in patients on NIPPV at baseline (82.1% vs. 88.3%, p = 1.00).

Overall adverse effects occurred in 30.1% of the treatment group and in 8.4% of the comparator group. The rate of hepatic injury was 19.3% in the treatment and 0.6% in the comparator group. Through day 28, bacteremia occurred in 17 patients (9.7%) in the treatment group as compared to 11 patients (6.1%)

in the comparator group. Fungemia was observed in two patients (1.1%) in the treatment group as compared to three patients (1.7%) in the comparator group.

Adverse Effects	Tocilizumab plus corticosteroids (N = 176)	Corticosteroids only (N = 179)
Hepatic injury [n (%)]	34 (19.3)	1 (0.6)
Bacteremia [n (%)]	17 (9.7)	11 (6.1)
Fungemia [n (%)]	2 (1.1)	3 (1.7)
None [n (%)]	123 (69.9)	164 (91.6)

Table 3. Adverse events through Day 28 in the safety population of patients receiving Tocilizumab plus corticosteroids and corticosteroids at one community hospital in the Northeastern, US (n=355)

Discussion

This retrospective cohort study in older patients hospitalized with COVID-19 pneumonia showed that the combination of tocilizumab and corticosteroid did not appear to prevent the progression to mechanical ventilation in elderly patients as compared to corticosteroid monotherapy. The combination was also associated with a higher in-hospital mortality, a similar extent of respiratory status improvement, and more cases of hepatic injury and bacteremia.

Data available from other randomized controlled trials generated mixed results regarding the use of tocilizumab in patients with COVID-19 pneumonia. The Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) trial reported tocilizumab was associated with more organ-support-free days and a lower mortality rate than no treatment for severe COVID-19 patients in the ICU.[17] Approximately 70% and over 90% of patients received corticosteroids before and after the publication of the RECOVERY trial, respectively.[17] However, about 20% of patients were not confirmed to have COVID-19 and the researchers did not specify whether the organ-support-free days were continuous or the sum of the days that the patients were off organ support.[17] Furthermore, among survivors, the median organ-support-free days were similar between the tocilizumab and control groups.[17] The Boston Area COVID-19 Consortium (BACC) Bay study, which evaluated the effect of a single dose of tocilizumab as compared to placebo,

reported no difference between the use of tocilizumab at 8 mg/kg and placebo in the time to intubation or death.[18] However, this study was conducted before the RECOVERY trial.[12] As a result, no patients in the BACC Bay Study received dexamethasone. Additionally, the BACC Bay study population had an imbalanced distribution of elderly patients between the two groups. The median age of patients in the tocilizumab group was 61.6 years as compared to 56.5 years in the placebo group.[18] The Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia (COVACTA) trial evaluated the use of tocilizumab with weight-based dosing 8 mg/kg up to 800 mg versus placebo and showed no benefit of tocilizumab in clinical status as defined by a reduction in the WHO Clinical Progression Scale for COVID-19 pneumonia.[19] Less than 20% of patients in this study received corticosteroids, with more patients in the placebo group receiving steroids when compared to the tocilizumab group.[19] The COVACTA trial also included patients of various severities such as severe hypoxia and mechanical ventilation at baseline, which could potentially confound the true benefits of tocilizumab.[19] The Evaluating Minority Patients with Actemra (EMPACTA) trial concluded treatment with tocilizumab was associated with a lower risk of mechanical ventilation and death in COVID-19 patients who had a high probability of deteriorating.[20]

To the best of our knowledge, we were the first group to study the combination of tocilizumab and corticosteroids in elderly patients. Our findings were consistent with previous studies in that tocilizumab at 400 mg did not result in a lower incidence of mechanical ventilation.[18][19][21] In terms of mortality, our results were different from the findings in previous cohort studies.[15][21][22][23] Previous cohort studies demonstrated mortality benefits of tocilizumab regardless of weight-based dosing or a fixed dose of 400 mg, proportion of patients on adjunctive corticosteroid therapy, or baseline clinical status and disease progression.[15][21][22][23] Of note, these studies included patients from all age groups, with a median age of under 65 years. The discrepancy in the findings was likely multifactorial. Firstly, we studied the effects of tocilizumab and corticosteroids specifically in the older population, which often only accounted for a small portion in other studies. Secondly, we took a similar approach as the EMPACTA trial,[20] in that we selected patients who were hypoxic at baseline but were not yet mechanically ventilated, whereas previous studies also included patients who were already on mechanical ventilation at baseline.[15][19][21][22][23] Thirdly, all the patients in our comparator group received corticosteroids, which was not achieved in previous studies.[15][21][22][23] In addition, all patients with baseline lung diseases were excluded from our study to control for

confounding variables. A meta-analysis by Ssentongo and colleagues reported no increase in the mortality due to COVID-19 in patients with asthma or COPD,[24] but the cohort study by Narain and colleagues suggested asthma was associated with a higher mortality rate.[22] We also performed a parallel subgroup analysis for surviving patients who were not placed on a mechanical ventilator throughout the study period. Both the combination and corticosteroid monotherapy groups demonstrated similar efficacy in weaning patients to a lower level of respiratory support. The addition of tocilizumab did not appear to improve the patients' respiratory status regardless of what type of respiratory support the patient was on at baseline.

Only a few previous studies collected safety data on adverse effects.[18][19][20][21][22] For secondary infections, our findings were consistent with those in other studies.[18][19][20] In our study, there were similar rates of bacteremia and fungemia between the treatment and comparator groups. A lower dose of tocilizumab did not appear to be linked to fewer secondary infections, though two other cohort studies reported that weight-based dosing of tocilizumab up to 800 mg was associated with higher rates of new infection[21] and bacteremia.[22] Previous studies observed similar rates of hepatic injury between the treatment and control groups.[18][19] However, we observed more cases of hepatic injury in the tocilizumab and corticosteroid combination group. Tocilizumab is also associated with gastrointestinal (GI) perforation among patients receiving therapy for rheumatoid arthritis.[25] [26] With gastrointestinal bleeding being a known complication of corticosteroids,[27] there is a concern for a higher risk of GI complications with the combination of corticosteroids and tocilizumab. However, no cases of GI bleeding or perforation were found in our study.

Measures were implemented to control some of the confounding variables in this study. During the time of this study, no protocol for the initiation of tocilizumab had been adopted yet. The decision to initiate tocilizumab was highly dependent on the providers' clinical judgment of the disease's severity. This was evident from the fact that more patients in the tocilizumab and corticosteroid combination group required higher levels of respiratory support at baseline than those in the corticosteroid monotherapy group. To minimize the effect of this confounder, patients' oxygen saturation levels at the first presentation were collected to stratify the severity of the disease at baseline between the two groups. There was minimal difference in the baseline oxygen saturation levels, as shown in Table 1.

There were also some limitations to this study. Firstly, due to the retrospective nature of this study and the lack of randomization, the timing for tocilizumab administration was not well controlled. Time to treatment initiation varied among patients due to the lack of guidance and available literature. With our intention-to-treat approach, all patients who had received tocilizumab at the prespecified dose were included for analysis. Secondly, excluding patients with baseline lung diseases could have affected our generalizability. As a large proportion of the population has been vaccinated against COVID-19, patients who otherwise require hospitalization with COVID-19 pneumonia would likely be those with lung diseases at baseline.[2] Thirdly, we grouped patients based on their level of respiratory support in accordance with the WHO Clinical Progression Scale to categorize the severity of the disease. The fraction of inspired oxygen with each form of respiratory support was not calculated. Fourth, the administration of other agents with varying levels of evidence was imbalanced between the two groups. There were more patients in the combination group who received hydroxychloroquine and azithromycin, whereas more patients in the corticosteroid monotherapy group received doxycycline and remdesivir. Hydroxychloroquine alone or with azithromycin was a common treatment approach for the early phase of the pandemic, though more recent studies reported hydroxychloroquine had little or no effect on COVID-19 mortality than control.[28][29] There was no statistical evidence of a difference in mortality between patients treated with hydroxychloroquine as compared to no hydroxychloroquine exposure in subgroup analysis (Appendix B). Remdesivir was associated with faster time to recovery and clinical improvement in hospitalized patients with hypoxia,[30][31] but the trials did not evaluate the effects or perform a subgroup analysis on the progression to mechanical ventilation or mortality in specifically geriatric population.[30][31] The actual effects of those agents on our patient population and results were uncertain.

Conclusion

There was no difference in the incidence of mechanical ventilation with tocilizumab and corticosteroid combination as compared to corticosteroid alone, but it was associated with a clinically-important higher in-hospital mortality, similar effects on patients' respiratory status, and more cases of hepatic injury and bacteremia in older patients. Additional prospective, randomized controlled trials are needed to evaluate the effects of tocilizumab and corticosteroid combination in elderly patients.

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Conflicts of Interest

The authors disclosed that they do not have any potential conflicts of interest.

Appendix A

Disease Severity	Descriptor	Score	
Uninfected	Uninfected, no viral RNA detected	0	
Ambulatory, mild	Asymptomatic, viral RNA detected	1	
	Symptomatic, independent	2	
		Symptomatic, assistance needed	3
Hospitalized, moderate	Hospitalized, no oxygen	4	
	Hospitalized, oxygen by mask or nasal prongs	5	
Hospitalized, severe	Hospitalized, oxygen by non-invasive ventilation or high flow	6	
	Mechanical ventilation, $pO2/FiO2 \geq 150$ or $SpO2/FiO2 \geq 200$	7	
		Mechanical ventilation, $pO2/FiO2 < 150$ or $SpO2/FiO2 < 200$ or on vasopressors	8
	Mechanical ventilation, $pO2/FiO2 < 150$ or $SpO2/FiO2 < 200$ and on vasopressors, dialysis or ECMO	9	
Dead	Dead	10	

WHO Clinical Progression Scale

Abbreviations: pO2, partial pressure of oxygen; SpO2, oxygen saturation; ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen.

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