Increased secondary infection in COVID-19 patients treated with steroids in New York City

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Summary

Since cytokine release syndrome is considered to be associated with severe cases of COVID-19, steroids are expected to be effective for its treatment. We aimed to investigate the use of steroids and its impact. We conducted a retrospective chart review and analysis of 226 consecutive hospitalized patients with confirmed COVID-19. Patients were divided into those who received steroids (steroid group) and those who did not (no steroid group). Inverse weighted probability weighted analysis was performed to assess the effect of steroids for in-hospital mortality. The steroid group had higher rates of preexisting hypertension and peripheral vascular disease than no steroid group and also had higher lactate dehydrogenase, d-dimer, and inflammatory makers compared to no steroid group (all $P<0.05$). The steroid group had significantly higher rates of multifocal pneumonia than no steroid group at admission (75.4% versus 50.3%, $P=0.001$). Notably, steroid group had higher rates of bacterial infection (25% versus 13.1%, $P=0.041$) and fungal infection (12.7% versus 0.7%, $P<0.001$) during hospital course. After adjustment, steroid did not decrease or increase in-hospital mortality (OR [95% CI]: 1.02 [0.60-1.73, $P=0.94$]). Steroid did not decrease the in-hospital mortality rate. There were increased bacterial and fungal infections with steroid use.

Introduction

Coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has spread globally since December 2019 (1). The World Health Organization declared COVID-19 to be a pandemic on March 11th, 2020, and the number of death due to the COVID-19 pandemic has been rapidly increasing, with total cases exceeding 1.3 million cases to date globally (2). The United States has eclipsed other countries and has the largest number of COVID-19 cases in the world, with more than 1 million confirmed as of May 2nd, 2020, making New York City its epicenter. As of this date, New York State has nearly 590,000 cases (2). Since New York City had its first confirmed COVID-19 patient on February 29th, 2020 and its first confirmed death on March 14th, 2020, the cases have grown at an astounding rate. The total number of deaths has risen exponentially to 18,491, with 172,354 patients suffering from COVID-19 as of May 2nd in New York City. While hospitals and healthcare systems needed to adapt rapidly to the unprecedented spread of viral illness, physicians and healthcare workers struggled to understand the unpredictable consequences of afflicted patients, and the volume and the pace by which they presented.

The clinical manifestations of COVID-19 have ranged quite dramatically from no symptoms whatsoever, to mild cough, fever, and pneumonia, to acute respiratory distress syndrome, multiorgan failure and death (3-5). Since cytokine release syndrome is considered to be associated with severe cases of COVID-19, steroids were expected to be effective for its treatment. Previous observational studies supported this hypothesis, however, they did not assess side effects such as bacterial and fungal infections (6,7). Since the release of RECOVERY trial in June, 2020, steroids use has become favorable in treatment recommendation (8-10). We aimed to

evaluate the effect of steroids use early in this COVID-19 pandemic and to review its impact on in-hospital mortality and outcomes including the secondary infection rate.

Materials and Methods:

Data collection

We obtained the medical records for hospitalized patients with laboratory confirmed COVID-19 in Mount Sinai Beth Israel, which is located in downtown Manhattan (11). The study protocol was approved by the institutional review boards (#20-00436) and conducted in accordance with the principles of the Declaration of Helsinki. Identification of COVID-19 required nasopharyngeal swab, which was tested using polymerase chain reaction. The pathogenic detection was initially detected in Department of Health in New York City and LabCorp, and transitioned into Mount Sinai Hospital's internal lab thereafter. Patients that presented to the hospital with respiratory symptoms or a viral prodrome who had suspicion for COVID-19 were tested and evaluated for admission. Decision to admit was made largely by provider dependent, and not based on any specific predetermined criteria since initially little was known about the disease.

After 502 consecutive COVID-19 tests, the initial hospitalized patient with confirmed detection of SARS-CoV-2 was identified on March 13th, 2020. Subsequently, 226 consecutive hospitalized patients who were confirmed with detection of SARS-CoV-2 by March 31st, 2020 were followed through May 15th, 2020. A retrospective review of patient electronic medical records was evaluated for demographics, clinical course, comorbidities, medications and clinical outcomes by two authors (R.O. and T.M.), mainly. Cases were reviewed to see if criteria were met for systemic inflammatory response syndrome (SIRS), as well as type 1 or type 2 myocardial

infarction. Quick sepsis related organ failure assessment (qSOFA) was also calculated for all those admitted (12,13).

Study design

Patients were divided into two groups, those with steroids initiated (steroid group, 25.2% [N=57]) versus those who were not given steroids (no steroid group, 75.8% [N=169])). Laboratory data and imaging during the hospital stay was collected, and characteristics of hospital stay were also noted. Radiographic findings were reviewed by the attending radiologists. Our institution initially used hydroxychloroquine for moderate cases which was defined as radiologic evidence of pneumonia, or oxygen saturation <94%. Completion of treatment course was defined as 5-day course of hydroxychloroquine, but discontinuation at discharge was also included as completion of treatment (14).

A chronology of time course for clinical deterioration on all patients was reviewed, including incidence of rapid response team (RRT) and code team triggers, whether or not cardiopulmonary resuscitation (CPR) was initiated during the hospital stay, and whether mechanical ventilation was ultimately used. The incidences of bacterial and fungal infection were also collected between steroid versus no steroid group. In addition, these incidences were also assessed with or without tocilizumab among steroid group.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median [interquartile range], as appropriate for the data distribution; categorical variables were expressed as percentages. The changes from baseline in continuous variables were evaluated using Student's *t*-test or Mann-Whitney U test; the χ^2 or Fisher's exact *t*-test was used for analyzing categorical variables. We also analyzed effect of steroids for in-hospital mortality using inverse weighted probability weighted analysis. To estimate a propensity score for the use of steroids, a multivariate logistic regression model was constructed. Considering the total number of people in the steroid group (N=57), six variables were chosen based on prior data. The following covariates were entered for multivariate logistic regression analyses; age, d-dimer, multifocal pneumonia on chest X-ray (either PA film or AP film), use of tocilizumab, use of invasive mechanical ventilator, stay in intensive care unit (ICU). Age and d-dimer were recently reported as independent mortality predictors of COVID-19 patients (15). Though there is no specific X-ray feature of COVID-19, bilateral multifocal opacities or consolidation are common chest X-ray findings (16). Since cytokine release syndrome with elevated interleukin-6 (IL-6) is associated with severe cases of COVID-19, IL-6 inhibitors such as tocilizumab are expected to be effective for its treatment (17,18). Despite controversy on its clinical use, tocilizumab was used for selected patients with COVID-19 early in the hospital course, with rationale that it may prevent disease progression. Mechanical ventilation use is a known to be associated with death in critical COVID-19 patients (19). As a sensitivity analysis to eliminate the imbalance of steroid group versus no steroid group, we analyzed effect of steroid for in-hospital mortality using inverse probability weighted analysis limiting the patients who needed oxygen (N=152, 67.3%). All

statistical calculations and analyses were performed using SPSS (version 24, SPSS, Chicago, IL, USA), with p-values <0.05 considered statistically significant.

Results

Among 226 patients, the mean age was 63.3±16.8 and 57.1% were male. 35.4% were Caucasian, 19.0% was African American and notably, 44.3% were Hispanic. Regarding other demographics of interest, 4.4% were undomiciled, and 6.3% did not have health insurance. Detailed baseline characteristics are shown in Tables 1 and 2. The steroid group had significantly lower oxygen saturation level (94% [88, 96] versus 96% [94, 98], P<0.01) and higher respiratory rate (22 [18, 26] versus 20 [18, 23], P=0.002), and were more likely to have preexisting hypertension, peripheral vascular disease, history of transplant compared to no steroid group (Table 1).

Table 3 describes baseline laboratory findings. The steroid group had a significantly higher baseline neutrophil count, glucose levels, lactate dehydrogenase levels, and d-dimer compared to the no steroid group (all P<0.05). The steroid group also had significantly higher value of baseline inflammatory markers such as C-reactive protein, procalcitonin, ferritin and IL-6 (all P<0.05). Table 3 also describes electrocardiogram and chest X-ray results. Electrocardiograms showed no significant differences (such as T wave inversion) between steroid and no steroid group (Table 3). The steroid group did however have significantly higher proportions of multifocal pneumonia at admission as seen in Table 3 (75.4% versus 50.3%, P=0.001).
Table 4 shows in-hospital treatment and outcomes. Within the steroid group, 63.2% were admitted to ICU during hospital course. RRT was activated for 6.2% of total study cohort. Regarding treatments, the steroid group had higher proportions of hydroxychloroquine and

azithromycin use than the no steroid group (Table 4). Additionally, Tocilizumab was given to 35.1% of steroid group, which was higher than no steroid group (1.8%) during hospital course (Table 4). Notably, the steroid group had higher rates of bacterial infection (25% versus 13.1%, P=0.041) and fungal infection (12.7% versus 0.7%, P<0.001) during hospital course (Table 5).

A subgroup analysis was performed in the steroid group to assess the use of Tocilizumab, which showed no significant difference of either bacterial or fungal infection rate between with Tocilizumab and without Tocilizumab (Table 6). CPR was performed among 5.3% of total patients with one shockable rhythm (1 out of 12 CPR, 8.3%), and death rate for that group was 100%. Of all the patients in the steroid group, 41.8% of patients died, which was 18.4% of total patients (Table 4). To estimate the effect of steroids, inverse probability weighted analysis was performed for adjustment. Interestingly, steroids did not decrease or increase in-hospital mortality (OR [95% CI]: 1.02 [0.60-1.73, P=0.94]). As a sensitivity analysis limiting patients who needed oxygen, steroids did not affect in-hospital mortality in this population either (OR [95% CI]: 0.95 [0.54-1.68, P=0.87]).

Discussion

The salient findings of this cohort study are the followings; 1) we reported a detailed description of clinical characteristics, especially steroid group versus no steroid group in the diverse urban population of New York City 2) the steroid group had higher rates of bacterial and fungal infection during hospital course 3) steroid group had 41.8% of mortality rates 4) steroid use did not show decreased risk of in-hospital mortality after inverse weighted probability weighted analysis.

New York City is the epicenter of COVID-19 crisis in the US (20). Mount Sinai Beth Israel hospital has served the community of lower Manhattan through numerous crises such as 9/11 and the blackout, as well as hurricanes Irene and Sandy (11,21), and now is serving our community during this rapidly evolving COVID-19 pandemic. Our hospital has quickly evolved to a nearly 90% SARS-CoV-2 positive patient census in just a few short weeks and has expanded its volume and ICU capacity to more than triple its functioning census during this time to meet the needs of our community as of May 2nd, 2020. Our study describes the diversity of COVID-19 patient characteristics as well as the population it impacts in New York City. Notably, we included variables such as homelessness, insurance status (which may be a surrogate for access to healthcare), and race/ethnicity. Our data showed that the steroid group had higher baseline lactate dehydrogenase, d-dimer, inflammatory markers such as C-reactive protein, procalcitonin, ferritin and IL-6.

A previous observational study revealed favorable outcome of steroid use in patients with COVID-19 (7). However, a review article concluded that it was due to survivor treatment bias (22). Previous data regarding steroid use in patients with influenza, Severe Acute Respiratory Syndrome, Middle East respiratory syndrome, did not reveal any benefit and rather demonstrated possible harm such as increased mortality, and delayed clearance of virus (23,24). Recently, RECOVERY trial from United Kingdom showed that dexamethasone use decreased 28-day mortality in COVID-19 patients with oxygen support (8). Following studies of steroid use in COVID-19 also reported favorable outcomes in the steroid group (25-27). In addition, these recent trials suggested no association between an increase in the rate of secondary infection and steroid use, and only one fungal infection was reported as related to steroid use. While our data showed no significant difference in mortality between the steroid group and no steroid group, it

did however, show higher rates of bacterial and fungal infection, which is concerning in patients with COVID-19. In addition, our study raises a doubt to RECOVERY trial since our sensitivity analysis of steroid group patients who needed oxygen, steroids did not affect in-hospital mortality in this population. These results could be related to other factors, such as higher age in our steroid group. Indeed, the CoDEX Randomized Clinical Trial applied the same steroid regimen as ours did not reveal significant difference in secondary infection rate (27). Additionally, Tocilizumab use in steroid group did not show significant effect in both bacterial and fungal infection rate.

There are several limitations in our study. This study is conducted in a single center hospital with relatively small sample size. Despite adjustment, we could not eliminate all confounding factors, however, our data is valuable since the data of steroid use is controversial and we showed the higher incidence of bacterial and fungal infections as well as a sensitivity analysis limiting patients who needed oxygen, which improved our robustness.

In conclusions, we reported a detailed description of clinical characteristics, especially steroid group versus no steroid group in the diverse multicultural urban city of New York. Steroids increased the risk of bacterial and fungal infection, however, steroids did not show a decrease in risk of in-hospital mortality after adjustment in our present study. Our study is meaningful since we investigated detailed patient characteristics to help inform physicians who treat COVID-19 patients in other parts of the country and world.

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

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Table 1: Baseline characteristics at admission; No steroid versus steroid

	Categories		P value
	No steroid N=169	Steroid N=57	
Age	64 [51, 76]	70 [59.5, 79]	0.073
Male	59.2% (100/169)	50.9% (29/57)	0.27
BMI	28.3 [23.9, 32.1]	27.4 [24.3, 33.0]	0.92
Race	White 37.0% (61/165) Black 20.6% (34/165) Asian 9.7% (16/165) Other 32.7% (54/165)	White 33.3% (19/57) Black 15.8% (9/57) Asian 21.1% (12/57) Other 29.8% (17/57)	0.16
Hispanic	46.1% (76/165)	39.3% (22/56)	0.38
No Insurance	7.1% (12/169)	3.6% (2/56)	0.34
Medicare	45.0% (76/169)	64.3% (36/56)	0.012
Medicaid	34.3% (58/169)	39.3% (22/56)	0.50
Private insurance	59.8% (101/169)	58.9% (33/56)	0.91
Undomiciled	6.0% (10/168)	0.0% (0/57)	0.060
Shelter	4.8% (8/167)	0.0% (0/57)	0.092
Symptoms			
Fever	64.5% (107/166)	66.7% (38/57)	0.76
Myalgia	14.3% (24/168)	17.5% (10/57)	0.71
Chest pain	19.6% (33/168)	12.3% (7/57)	0.21
Malaise	28.0% (47/168)	26.3% (15/57)	0.81

Sore throat	6.0% (10/168)	10.5% (6/57)	0.25
Runny nose	8.3% (14/168)	12.5% (7/56)	0.47
Shortness of breath	58.3% (98/168)	68.4% (39/57)	0.18
Cough	67.3% (113/168)	78.9% (45/57)	0.095
Sputum	19.9% (27/136)	37.3% (19/51)	0.014
Abdominal pain	11.3% (19/168)	5.3% (3/57)	0.18
Nausea/Vomit	26.2% (44/168)	26.3% (15/57)	0.99
Diarrhea	26.8% (45/168)	17.5% (10/57)	0.16
Black diarrhea	3.3% (3/90)	0.0% (0/32)	0.30
Anosmia	0.6% (1/168)	0.0% (0/57)	0.56
Dysgeusia	0.0% (0/168)	0.0% (0/57)	-
Initial Vital			
Temperature (˚C)	36.7 [36.2, 37.3]	37.2 [36.5, 37.8]	0.012
Heart rate (beat/min.)	96 [81, 111]	99 [84.5, 108]	0.68
SBP (mmHg)	133 [116, 150]	134 [117, 154]	0.42
DBP (mmHg)	80 [68, 88]	75 [65, 85]	0.15
MAP (mmHg)	95.7 [86.5, 108.8]	93.7 [84.2, 105.5]	0.66
RR (/min.)	20 [18, 23]	22 [18, 26]	0.002
SpO_2 (%) at room air	96 [94, 98]	94 [88, 96]	<0.001
SIRS	1 [0.75, 2]	2 [1, 2]	0.20
qSOFA	0 [0, 1]	1 [0, 1]	0.68
Altered Mental Status	10.7% (18/168)	10.7% (6/56)	1.00

Aspirin	25.6% (43/168)	28.1% (16/57)	0.71
Anticoagulation	11.9% (20/168)	8.8% (5/57)	0.52
ACEI	17.9% (30/168)	14.0% (8/57)	0.51
ARB	15.0% (25/167)	26.3% (15/57)	0.053
Steroid use at home	1.2% (2/168)	3.5% (2/57)	0.25
Comorbidities			
Hypertension	54.4% (92/169)	75.4% (43/57)	0.005
Hyperlipidemia	40.2% (68/169)	43.9% (25/57)	0.63
DM	32.0% (54/169)	33.3% (19/57)	0.85
DM with insulin	8.9% (15/169)	8.8% (5/57)	0.27
CKD	11.3% (19/168)	17.5% (10/57)	0.23
COPD	6.5% (11/169)	10.5% (6/57)	0.32
Asthma	8.9% (15/169)	14.0% (8/57)	0.27
CVA	6.5% (11/169)	7.0% (4/57)	0.89
PVD	4.7% (8/169)	12.3% (7/57)	0.048
Dialysis	3.6% (6/169)	1.8% (1/57)	0.50
Cirrhosis	1.8% (3/169)	3.5% (2/57)	0.44
CAD	19.5% (33/169)	21.1% (12/57)	0.80
Previous PCI	11.2% (19/169)	15.8% (9/57)	0.37
Previous CABG	4.7% (8/169)	5.3% (3/57)	0.87
Previous PE/DVT	5.9% (10/169)	5.3% (3/57)	0.85
History of AF	9.5% (16/169)	7.0% (4/57)	0.57
Previous CHF	13.6% (23/169)	8.9% (5/56)	0.36

History of cancer	6.5% (11/169)	10.5% (6/57)	0.32
Active cancer	1.2% (2/167)	0.0% (0/57)	0.41
History of transplant	0.0% (0/169)	3.5% (2/57)	0.014
HIV	5.9% (10/169)	5.3% (3/57)	0.85
Dementia	8.9% (15/169)	7.1% (4/56)	0.69
Schizophrenia	2.4% (4/169)	0.0% (0/57)	0.24
Other psychiatry diseases	15.6% (26/167)	19.3% (11/57)	0.51
Smoker			0.53
Current smoker	3.7% (6/163)	1.8% (1/57)	
Former smoker	25.2% (41/163)	31.6% (18/57)	

Abbreviation: BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, MAP; mean arterial pressure, RR; respiratory rate, SIRS; systematic inflammatory response syndrome, qSOFA; quick sepsis related organ failure assessment, ACEI; angiotensin converting enzyme inhibitor, ARB; angiotensin Ⅱ receptor blocker, DM; diabetes mellitus, CKD; chronic kidney disease, COPD; chronic obstructive pulmonary disease, CVA; cerebrovascular accident, PVD; peripheral vascular disease, CKD; chronic kidney disease, CAD; coronary artery disease, PCI; percutaneous coronary intervention, CABG; coronary artery bypass grafting, PE/DVT; pulmonary embolism/deep vein thrombosis, AF; atrial fibrillation, CHF; congestive heart failure, HIV; human immunodeficiency virus

Table 2: Steroid indication, regimen, and preliminary termination

Indications	%
COVID infection	89.5% (51/57)
Other	10.5% (6/57)
Asthma	3.5% (2/57)
COPD	1.8% (1/57)
Transplant organ	3.5% (2/57)
Gout	1.8% (1/57)
Steroid regimens	**N=57**
Dexamethasone based	84.2% (48/57)
Dexamethasone 20 mg x 5d, 10 mg x 5 d	47.4% (27/57)
Dexamethasone 10-day course, partial	15.8% (9/57)
Dexamethasone plus methylprednisolone	21.1% (12/57)
Prednisone, only	10.5% (6/57)
Methylprednisolone, only	1.8% (1/57)
Methylprednisolone plus prednisone	1.8% (1/57)
Hydrocortisone, only	1.8% (1/57)
Reasons for preliminary termination	
Patient died	15.8% (9/57)
Patient declined	1.8% (1/57)
Adverse events	0.0% (0/57)

Abbreviations
COVID: corona virus disease, COPD: chronic obstructive pulmonary disease, d: day

Table 3: Baseline laboratory findings; No steroid versus steroid

	Categories		P value
	No steroid N=169	Steroid N=57	
Complete blood count			
White blood cell, K/ μ L	6.8 [5.2, 9.0]	7.5 [5.1, 9.6]	0.35

Neutrophil, K/ μ L	4.9 [3.2, 6.6]	5.8 [4.1, 8.1]	0.018
Lymphocyte, K/ μ L	1.0 [0.7, 1.4]	0.9 [0.7, 1.3]	0.11
Hemoglobin, g/dL	13.6 [12.6, 15.0]	13.9 [12.8, 15.2]	0.45
Platelet, K/ μ L	170 [134, 218]	150 [120, 208]	0.18
Biochemistry panel			
Glucose, mg/dL	112 [96, 136]	125 [103, 166]	0.032
BUN, mg/dL	16 [11.5, 24]	20 [12, 27]	0.066
Creatinine, mg/dL	0.95 [0.69, 1.31]	0.98 [0.79, 1.33]	0.33
AST, U/L	37 [27, 52.3]	53 [40, 73]	<0.001
ALT, U/L	28 [19, 46]	39 [23.5, 53.5]	0.032
Total bilirubin, mg/dL	0.5 [0.4, 0.8]	0.5 [0.4, 0.6]	0.33
Albumin, g/dL			0.060
LDH, U/L	345 [256, 451]	448 [326, 593]	<0.001
CPK, U/L	140 [69, 311]	160 [70, 510]	0.71
Coagulation			
PT-INR	1.1 [1.0, 1.2]	1.0 [1.0, 1.2]	0.10
APTT (s)	31.8 [28.7, 36.8]	32.7 [29.2, 36.2]	0.98
D-Dimer, μ g/mL	0.91 [0.58, 1.72]	1.12 [0.74, 2.22]	0.022
Fibrinogen. mg/dL	535 [353, 686]	588 [446, 733]	0.27
Inflammation marker			
CRP or hsCRP, mg/L	60.0 [30.4. 119]	121 [55.0, 190]	<0.001

Procalcitonin, ng/mL	0.11 [0.05, 0.28]	0.24 [0.09, 0.64]	<0.001
Ferritin, ng/mL	500 [273, 1072]	951 [429, 2184]	0.001
IL-6, pg/L	37.9 [19.3, 77.3]	99.9 [53.6, 170]	<0.001
Others			
pH (venous blood gas)	7.41 [7.37, 7.44]	7.39 [7.35, 7.43]	0.048
Lactate, mmol/L	1.3 [1.0, 1.8]	1.55 [1.23, 2.08]	0.019
BNP, pg/mL	33.6 [10.0, 179]	28.2 [10.0, 118]	0.55
Troponin T, ng/mL	0.01 [0.01, 0.04]	0.02 [0.01, 0.06]	0.084
ECG			
AF	4.7% (7/150)	3.6% (2/55)	0.29
PAC	3.3% (5/150)	3.6% (2/55)	0.92
PVC	3.3% (5/150)	3.6% (2/55)	0.92
CRBBB	6.7% (10/150)	5.5% (3/55)	0.75
CLBBB	2.0% (3/150)	0.0% (0/55)	0.29
T wave inversion	9.3% (14/150)	7.3% (4/55)	0.64
ST depression	1.3% (2/150)	0.0% (0/55)	0.39
ST elevation	0.6% (1/169)	3.5% (2/57)	0.096
Chest X ray			
Multifocal pneumonia	50.3% (85/169)	75.4% (43/57)	0.001
Lobular consolidation	0.6% (1/163)	1.8% (1/56)	0.43
Pleural effusion	6.1% (10/164)	10.7% (6/56)	0.25

Abbreviation: BUN; blood urea nitrogen, AST; aspartate aminotransferase, ALT; alanine

aminotransferase, LDH; lactate dehydrogenase, CPK; creatine kinase, PT-INR; prothrombin time-international normalized ratio, APTT; activated partial thromboplastin time, CRP; C-reactive protein, hsCRP; high sensitivity C-reative protein, IL-6; interleukin-6, AF; atrial fibrillation, CRBBB; complete right bundle branch block, CLBBB; complete left bundle branch block, PAC; premature atrial contraction, PVC; premature ventricular contraction

Table 4: In-hospital treatments and outcomes; No steroid versus steroid

	Categories		P value
	No steroid N=169	Steroid N=57	
Initial admission to ICU	9.5% (16/169)	29.8% (17/57)	<0.001
ICU stay	11.8% (20/169)	63.2% (36/57)	<0.001
Activation of RRT	3.6% (6/169)	14.0% (8/57)	0.005
Nosocomial infection	4.1% (7/169)	1.8% (1/57)	0.40
Treatment			
Hydroxychlroquine	79.3% (134/169)	96.5% (55/57)	0.002
Completion hydroxychlroquine	94.8% (127/134)	92.7% (51/55)	0.58
Azithromycin	56.8% (96/169)	75.4% (43/57)	0.012
Steroid pulse	0.0% (0/169)	0.0% (1/57)	1
Toclizumab	1.8% (3/169)	35.1% (20/57)	<0.001
Bacterial infection	13.1% (19/145)	25% (14/56)	0.041
Fungal infection	0.7% (1/144)	12.7% (7/55)	<0.001
Vasopressor	2.4% (4/169)	36.8% (21/57)	<0.001
Phenylephrine	0.0% (0/169)	14.0% (8/57)	<0.001
Norepinephrine	2.4% (4/169)	36.8% (21/57)	<0.001
Vasopressin	0.0% (0/169)	14.0% (8/57)	<0.001
Epinephrine	0.0% (0/169)	3.5% (2/57)	0.014
Dobutamine	0.6% (1/169)	1.8% (1/57)	0.021

Oxygen	56.2% (95/169)	100% (57/57)	<0.001
Nasal Cannula	38.5% (65/169)	12.3% (7/57)	<0.001
Mask	10.7% (18/169)	15.8% (9/57)	0.30
High flow oxygen	2.4% (4/169)	15.8% (9/57)	<0.001
NPPV	1.2% (2/169)	5.3% (3/57)	0.070
IMV	3.6% (6/169)	50.9% (29/57)	<0.001
Tracheostomy	0.0% (0/169)	8.9% (5/56)	<0.001
Dialysis	1.2% (2/168)	10.9% (6/55)	0.001
Liver failure	0.6% (1/168)	1.8% (1/55)	0.42
VT	0.0% (0/169)	0.0% (0/55)	-
NSTEMI type 1	2.4% (4/169)	1.8% (1/57)	0.79
NSTEMI type 2	9.5% (16/169)	21.1% (12/57)	0.062
STEMI	0.6% (1/169)	3.5% (2/57)	0.096
Catheterization	0.6% (1/169)	0.0% (0/57)	0.56
VF/Pulseless VT	0.0% (0/169)	1.8% (1/57)	0.084
CPR	4.1% (7/169)	8.9% (5/56)	0.17
Length of stay	6 [4, 8]	15 [10.5, 19]	<0.001
Death	10.8% (18/167)	41.8% (23/55)	<0.001
Remains in hospital	1.2% (2/169)	3.5% (2/57)	0.25
Remains in ICU	0.0% (0/169)	1.8% (1/57)	0.084

Abbreviation: ICU; intensive care unit, RRT; rapid response team, NPPV; noninvasive positive pressure ventilator, IMV; invasive mechanical ventilator, VT; ventricular tachycardia, NSTEMI;

non-ST elevation myocardial infarction, STEMI; ST elevation myocardial infarction, VF; ventricular fibrillation, CPR; cardiopulmonary resuscitation

Table 5: Infectious profile of no steroid vs. steroid

Type of infection, type of diagnostic test, and detected organisms	No Steroid (N=169)	Steroid (N=57)
Bacterial infection	11.2% (19/169)	24.6% (14/57)
Blood culture	3.0% (5/169)	1.8% (1/57)
Methicillin-sensitive Staphylococcus aureus (MSSA)	1.2% (2/169)	0% (0/57)
Viridans Streptococci	0.6% (1/169)	0% (0/57)
Klebsiella aerogenes	0% (0/169)	1.8% (1/57)
Escherichia coli	1.2% (2/169)	0% (0/57)
Urine culture	2.4% (4/169)	7.0% (4/57)
Escherichia coli	1.8% (3/169)	1.8% (1/57)
Klebsiella pneumoniae	0% (0/169)	3.5% (2/57)
Enterococcus faecium	0% (0/169)	1.8% (1/57)
Streptococcus agalactiae	0.6% (1/169)	0% (0/57)
Enterococcus faecalis	0.6% (1/169)	0% (0/57)
Respiratory culture	0% (0/169)	15.8% (9/57)
Streptomonas multophilia	0% (0/169)	3.5% (2/57)
Methicillin-resistant Staphylococcus aureus (MRSA)	0% (0/169)	1.8% (1/57)
MSSA	0% (0/169)	3.5% (2/57)
Escherichia coli	0% (0/169)	1.8% (1/57)
Pseudomonas aeruginosa	0% (0/169)	1.8% (1/57)
Klebsiella aerogenes	0% (0/169)	1.8% (1/57)
Klebsiella pneumoniae	0% (0/169)	1.8% (1/57)
MRSA nasal swab	3.6% (6/169)	3.5% (2/57)
MRSA	0% (0/169)	1.8% (1/57)
MSSA	3.6% (6/169)	1.8% (1/57)
Other bacterial infection	2.4% (4/169) 1.2% (2/169) liver abscesses, 0.6% (1/169) toe infection, 0.6% (1/169) bacterial vaginosis	0% (0/57)
Fungal infection	0.6% (1/169)	12.3% (7/57)
Candida species	0% (0/169)	7.0% (4/57)

Aspergillus fumigatus	0.6% (1/169)	5.3% (3/57)
Blood test		
Aspergillus Galactomannan, performed	0.6% (1/169)	10.5% (6/57)
Fungiteli, performed	0.6% (1/169)	12.3% (7/57)
Fungiteli positive	Not Available	14.3% (1/7)
No other infectious work up	14.2% (24/169)	1.8% (1/57)

Table 6: Infectious profile of steroid group: tocilizumab vs. no tocilizumab

Type of infection, type of diagnostic test, and detected organisms	Tocilizumab (N=20)	No tocilizumab (N=37)	P value
Bacterial infection	30% (6/20)	21.6% (8/37)	0.536
Blood culture	5% (1/20)	0% (0/37)	
Klebsiella aerogenes	5% (1/20)	0% (0/37)	
Urine culture	10% (2/20)	2.7% (1/37)	
E.coli	5% (1/20)	0% (0/37)	
K. pneumoniae	5% (1/20)	0% (0/37)	
E. faecium	0% (0/20)	2.7% (1/37)	
Respiratory culture	15% (3/20)	16.2% (6/37)	
Streptomonas multophilia	5% (1/20)	2.7% (1/37)	
MRSA	5% (1/20)	0% (0/37)	
MSSA	0% (0/20)	5.4% (2/37)	
E. coli	0% (0/20)	2.7% (1/37)	
P. aeruginosa	0% (0/20)	2.7% (1/37)	
K. aerogenes	5% (1/20)	0% (0/37)	
K. pneumoniae	0% (0/20)	2.7% (1/37)	
MRSA nasal swab	5% (1/20)	2.7% (1/37)	
MRSA	5% (1/20)	0% (0/37)	
MSSA	0% (0/20)	2.7% (1/37)	
Fungal infection	20% (4/20)	8.1% (3/37)	0.219
Candida spp.	15% (3/20)	2.7% (1/37)	
Aspergillus fumigatus	5% (1/20)	5.4% (2/37)	
Blood test	0% (0/20)	2.7% (1/37)	
Aspergillus Galactomannan	0% (0/20)	0% (0/37)	
Fungiteli	0% (0/20)	2.7% (1/37)	