Impact of Corticosteroid Treatment in Patients with Coronavirus Disease 2019

Abstract

Objectives: To assess the efficacy of corticosteroid treatments in patients with coronavirus disease 2019 (COVID-19).

Design, setting: Observational study in the COVID-19 designated hospitals in Wuhu, Anhui province, China, from 24 January to 24 February, 2020.

Participants: Thirty-one patients infected with Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2).

Main outcome measures: Virus clearance time, length of hospital stay (LOS) and duration of symptoms, stratified by patient whether using corticosteroid.

Results: Eleven out of 31 patients received corticosteroid treatment for COVID-19. Cox proportional hazards regression indicated no association between the virus clearance time (HR 1.26, 95% CI [0.58-2.74], p = 0.55), LOS (HR 0.77, 95% CI [0.33-1.78], p = 0.54) and duration of symptoms (HR 0.86, 95% CI [0.40-1.83], p = 0.70) and corticosteroid use. Univariate analysis suggested a possible prolonged virus clearance in patients with chronic hepatitis B (MD 10.6 days, 95% CI (6.21; 15.1), $p < 0.001$), but with only 2 patients that limited the interpretation.

Conclusions: Corticosteroids are widely used in patients with COVID-19, and there was no demonstrable association with therapy provided in patients without ARDS. Co-infection with HBV might delay virus clearance, and this association merits further investigation.

Introduction

In December 2019, a cluster of patients with primary pneumonia caused by a novel coronavirus was reported in Wuhan, China, and then spread rapidly to the whole country and around the world.[1-3] The novel coronavirus was later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which showed 79.5% identity to SARS-CoV that caused the 2003 epidemic of SARS.[4] The corresponding disease, named coronavirus disease 2019 (COVID-19), has clinical manifestations ranging from asymptomatic, mild pneumonia to serious acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS).[5-7] As of this writing, 77,048 cases have been reported in mainland China with a 3.17% mortality rate in general. The mortality rate of 61.5% in critically ill patients is similar to that observed in the Middle East Respiratory Syndrome (MERS), also caused by a coronavirus.[5 8] The mainstay of management of patients with COVID-19 is based on supportive therapy such as fluid management, oxygen therapy, mechanical ventilation and other life support methods.[9]

Previous studies indicate cytokine storm and inflammation induced by uncontrolled immunologic response to a virus is crucial in causing fatal pneumonia following infection with human coronavirus.[10 11] Inhibition of the inflammation improved outcome in animal models infected with SARS and MERS.[12 13] Corticosteroids are commonly used in severe acute respiratory infections of viral etiology due to its anti-inflammatory effect.[14] However, studies of the efficacy of corticosteroids during the SARS and MERS outbreaks showed no improvement in clinical outcomes, but delays in viral clearance and increases in the rates of secondary infections.[8 15 16] A majority of the patients enrolled in these studies were critically ill with ARDS and such patients may have passed the point where adverse outcomes were modifiable with steroids.
The World Health Organization (WHO) has recommended against the routine administration of systematic corticosteroids in patients with COVID-19.[17] Despite this, a consensus statement by the Chinese Thoracic Society recommends the use of corticosteroids, albeit prudently,[18] ideally undertaken in the context of a randomized controlled trial. To accomplish this during an ongoing epidemic is challenging. To facilitate study design, we report the impact of corticosteroid in patients with COVID-19 from accumulated observational clinical data.

Methods

Study design and participants

This is an observational study performed in The Second People's Hospital of Wuhu and Yijishan Hospital, the two designated hospitals for COVID-19 patients. Both are tertiary teaching hospitals, and the only units authorized to admit infectious patients in the city. The hospitals have more than 4000 beds and are in Wuhu, Anhui province, which is around 500 kilometers from Wuhan. Wuhu has a population of about 3.8 million people. The records of admitted patients diagnosed with COVID-19 from 24

January to 24 February 2020 were reviewed. The laboratory confirmation of the infection of SARS-CoV-2 was performed by the local Center for Disease Control using reverse transcription polymerase chain reaction (RT-PCR) as reported previously.[2]

The study was approved by the ethics committee of The Second People's Hospital of Wuhu (Ethics No. 202001).

Data collection

Data extracted from the patient record included age, gender, exposure to Wuhan, comorbidities, symptoms at onset, time from onset of symptoms to hospital admission, vital signs at admission, lab tests during hospitalization, findings on computer tomography (CT), virus clearance time, treatments (duration and dosage), co-infections, and clinical outcomes.

Outcomes and definitions

The primary outcome of interest was time to virus clearance. Secondary outcomes of interest included: duration of clinical recovery, length of hospital stay (LOS).

Viral clearance was confirmed by serial RT-PCR checking samples from throat swab with those having at least two consecutive negative results taken 24 hours apart considered cleared. The virus clearance time, in days, was calculated starting from the onset of symptoms to the date of the first negative RT-PCR test. Clinical recovery was determined by the attending physicians through integration of clinical manifestations, laboratory tests and radiological results. Patients were characterized as having received corticosteroids if they received at least one dose during their hospital stay.

Statistics analysis

Continuous variables were summarized as either means and standard deviations or median and interquartile range as appropriate. Categorical variables were described as frequencies and percentages. The differences between patients receiving and not receiving corticosteroids were analyzed by the Fisher's exact test or the Wilcoxon signed-rank test for categorical variables and the Mann-Whitney *U* test for continuous variables. The association between corticosteroid use and time to outcomes was estimated using survival analysis. Univariable hazard ratios (HR) and 95% confidence intervals (CI) were reported. A $p < 0.05$ was considered statistically significant. All analyses were performed using R software version 3.6.2 (R Foundation for Statistical Computing).

Results

Patient characteristics

There were 31 patients enrolled in the study. The median age was 39 years (IQR, 32-54). Males accounted for 64.5% (n=20) of the study population. The majority of the

patients (21 (67.7%)) had returned from Wuhan, the center of the COVID-19 epidemic, where they most likely had contracted the virus.

Comorbidities were not frequent: 7 (22.6%) patients had hypertension, 2 (6.5%) patients were with chronic hepatitis B virus (HBV) infection (the virus loads were 2,950 and 3,040 copies/ml, and both were receiving entecavir), 1 (3.2%) had diabetes and another (3.2%) had coronary heart disease. Two (6.5%) patients had a history of smoking. No patients reported chronic respiratory diseases, cancer or other chronic diseases.

Clinical, laboratory and radiologic presentations

On admission, patients presented with signs and symptoms of systemic infection with a majority reporting fever, cough and myalgia/fatigue (Table 1). Five (16.1%) reported diarrhea. All patients enrolled in the study were classified as having mild disease: only 4 (16.1%) patients complained of dyspnea, and no patients developed ARDS during the clinical course. The median time from illness onset to admission was 4 (IQR, 2-6) days.

Five (16.1%) patients had leucopenia ($< 4\times10^9$/L), 9 (29%) patients had lymphopenia (1.0×10^9/L), and 2 (6.5%) patients had platelet count less than 100×10^9/L. The level of C reactive protein (CRP) was >10 mg/L in 20 (64.5%) patients, while procalcitonin was within normal levels (0.1-0.5 ng/ml) in the majority (29 (93.5%)). Six (19.4%) patients had elevated alanine aminotransferase (≥ 40 U/L), and 5 (16.1%) patients showed elevated lactate dehydrogenase (≥ 225 U/L). The level of creatine kinase increased (≥ 175 U/L) in 2 (6.5%) patients, while no abnormalities of cardiac troponin (normal range < 0.5 ng/ml) were reported.

Most patients (29 (93.5%)) presented as pneumonia on chest CT; 2 others did not show any abnormalities on chest CT during the whole clinical course. The typical radiological changes were bilateral or bilobular ground glass opacity, and usually progressed within one week (Figure 1). In this study, 20 (64.5%) patients had bilateral involvement on chest CT. The details of the laboratory and radiological results are reported in Table 2.

Treatments

All patients received antiviral treatments as follows: all patients received lopinavir/ritonavir (protease inhibitors) and interferon alpha (an antiviral agent) via inhalation. This combination was used previously in MERS.[19] Five (16.1%) patients received umifenovir on top of the lopinavir/ritonavir and interferon alpha inhalation. Umifenovir blocks viral endocytosis and replication of a large panel of virus and licensed in Russia and China for the treatment and prevention of influenza.[20] Moxifloxacin monotherapy was used as prophylactic antimicrobial treatment in 14 (45.2%) patients with a median time of 6.5 (IQR 3.5-7.0) days.

Corticosteroid management

Corticosteroid (40 mg methylprednisolone once or twice per day) was administered to

11 (35.5%) patients within 24 hours of admission for a median duration of 5 (IQR 4.5-5.0) days (Table 3). Patients who received corticosteroid had more clinical complaints on admission including higher maximum temperature (38.8°C, IQR 38.2-39 vs. 37.8°C, IQR 37-38.1; p = 0.002), myalgia or fatigue (11, 100% vs. 8, 40%; p = 0.004), and cough (10, 90.9% vs. 8,40 %; p = 0.018). Moreover, patients receiving corticosteroid also had higher CRP (84 mg/L , IQR18.65-150 vs. 18.66 mg/L, IQR 4.77-29.63, p = 0.026), lower lymphocyte count (0.99×10^9/L, IQR 0.88-1.29 vs. 1.54×10^9/L, IQR 1.25-1.77, p = 0.012), and more patients had bilateral involvements on chest CT (11, 100% vs. 9, 45%, p =0.009) compared with patients who did not receive corticosteroid (Tables 1 and 2).

Outcomes

At the time of writing, 26 (83.9%) patients recovered from COVID-19 and were discharged well, whilst 5 (16.1%) patients were still hospitalized. The median time to virus clearance was 14 (IQR 11.5-16, range 7-26) days. Median duration of symptoms was 7 (IQR 5-10.5) days. Median of LOS was 18.5 (IQR, 16-21) days. There were no statistically significant differences in virologic or clinical outcomes between patients who received and did not receive corticosteroids. (Table 3). Interestingly, in unplanned analyses, we found an association between co-infection with HBV and prolonged virus clearance (mean difference 10.6 days, 95% CI (6.21-5.1); p < 0.001).

On survival analysis, and the results indicated that the time to virus clearance (HR 1.26, 95% CI [0.58-2.74]; p = 0.55), discharge (HR 0.77, 95% CI [0.33-1.78]; p = 0.54) and clinical resolution symptoms (HR 0.86, 95% CI [0.40-1.83]; p = 0.70) did not differ according to corticosteroid use.

Discussion

Corticosteroid is still widely used in COVID-19 despite the lack of clinical evidence. In our study, 11 (35.5%) patients received corticosteroid, a proportion similar to a previous study.[6] Systematic use of corticosteroid is even higher in critically ill patients with COVID-19, reaching as high as 70%.[5] In our study, patients receiving corticosteroid had more clinical complaints, higher inflammation index, and more abnormalities on chest CT, indicating that corticosteroid use was related to the presence of obvious symptoms on presentation. This practice is consistent to that reported in another study in which 33% patients with symptoms more than 10 days received corticosteroid compared to 17% received in patients with symptoms less than 10 days.[21]

Pathological findings supported ARDS development playing a crucial role in subsequent fatal outcomes of COVID-19,[22] and early admission of corticosteroids might reduce risk of development of ARDS in virus infection.[23] However, in this study, we failed to assess the efficacy of early corticosteroid in preventing ARDS development, because no patients developed ARDS during the clinical course.

The results in our study indicated that the use of corticosteroid did not influence virus clearance time, LOS and duration of symptoms in patients with mild COVID-19.

In univariate analysis, we found an association between co-infection with HBV and prolonged virus clearance (mean difference 10.6 days, 95% CI (6.21-5.1); $p < 0.001$). The small number of HBV co-infected patients (n = 2) does not allow us to make any firm conclusions. However this association has been reported in SARS-CoV infected patients previously.[24] The known T cell dysfunction against non HBV viral infections in chronic HBV infection,[25] might explain why COVID-19 patients had longer virus clearance time. This association merits further study.

There was no evidence to support the use of antiviral as dual or triple combination therapy and all the drugs now using in practice for COVID-19 are based on research in SARS, MERS, influenza or *in vitro* studies.[26] The small sample in our observational study precludes us from making clear statements on these treatments. A recent retrospective observational study compared the treatment of patients suffering from COVID-19 with either umifenovir in combination with interferon alpha inhalation, lopinavir/ritonavir in combination with interferon alpha inhalation and interferon alpha inhalation alone did not show any statistically significant differences among these groups regarding virus clearance time and duration of symptoms.[27] Formal randomized controlled evidence is a necessity to provide definitive guidance on the use of these agents.

There are several limitations in the study. First, the sample size was small, which diminished the power of the inferences that we can make. Second, all the patients included in our study displayed mild disease, which limited the interpretation of results to patients without ARDS, whereas ARDS is the main threat and real challenge in clinical practice. Third, due to limited sample size and the nature of observational study, there were many confounders, and might have distorted interpretation of the results. Despite these limitations, our results provide early findings in the context of a rapidly evolving situation.

In conclusion, in this small observational study of mild COVID-19 patients, overall outcome was good and there was no demonstrable association with therapy provided. Co-infection with HBV might delay virus clearance, and this association merits further investigation. We will continue to assimilate data and recommend a formal review as multiple observational and randomized controlled datasets become available.

Acknowledgements: We thank everyone fighting against the epidemic of COVID-19 all over the world.

Competing interests: No relevant disclosures.

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Characteristics	All patients (n = 31)	Non-corticosteroid (n = 20)	Corticosteroid (n = 11)	*p*
Age, years	39 (32-54)	37 (27-52)	53 (36-57)	0.179
Gender				0.752
Male	20 (64.5)	12 (60)	8 (72.7)	
Female	11 (35.5)	8 (40)	3 (27.3)	
Comorbidities				
Hypertension	7 (22.6)	5 (25)	2 (18.2)	1.000
Diabetes	1 (3.2)	0 (0)	1 (9.1)	0.758
Coronary heart disease	1 (3.2)	1 (5)	0 (0)	1.000
Chronic hepatitis B virus infection	2 (6.5)	2 (10)	0 (0)	0.749
Current smoker	2 (6.5)	1 (5)	1 (9.1)	1.000
Exposure to Wuhan	21 (67.7)	11 (55)	10 (90.9)	0.100
Signs and symptoms				
Fever	25 (80.6)	14 (70)	11 (100)	0.122
Highest temperature, ℃	38 (37.6-38.8)	37.8 (37-38.1)	38.8 (38.2-39)	**0.002**
Cough	19 (61.3)	8 (40)	11 (100)	**0.004**
Myalgia or fatigue	18 (58.1)	8 (40)	10 (90.9)	**0.018**
Headache	4 (12.9)	1 (5)	3 (27.3)	0.226
Diarrhea	5 (16.1)	5 (25)	0 (0)	0.193
Dyspnea	4 (12.9)	1 (5)	3 (27.3)	0.226
Respiratory rate, per minute	20 (18.5-20)	19 (18-20)	20 (19-21)	0.175
Heart rate, per minute	84 (75-95)	82.5 (73.5-94)	84 (79-98.5)	0.321
Systolic pressure, mmHg	127 (122-137)	125.5 (117-137)	128 (125-135)	0.283
Diastolic pressure, mmHg	73 (69.5-78.5)	72.5 (70-86)	73 (68.5-75)	0.369
Peripheral oxygen saturation (%)	98 (96-98.5)	98 (97-99)	97 (95-98)	0.111
Time from illness onset to hospital admission (days)	4 (2-6)	4 (2-5.25)	4 (2-7.5)	0.531

Table 1. Baseline characteristics of patients with coronavirus disease 2019 (COVID-19)

Table 2. Laboratory results and radiological presentations of patients with coronavirus disease 2019 (COVID-19) on admission to hospital

Variables	All patients (n = 31)	Non-Corticosteroid (n = 20)	Corticosteroid (n = 11)	*p*
White blood cell count, $\times 10^9$/L	5.26 (4.28-6.56)	5.2 (4.5-6.16)	5.97 (4.28-6.85)	0.536
Neutrophil count, $\times 10^9$/L	3.12 (2.44-4.19)	3.03 (2.28-3.52)	3.23 (2.66-5.11)	0.256
Lymphocyte count, $\times 10^9$/L	1.39 (0.96-1.64)	1.54 (1.25-1.77)	0.99 (0.88-1.29)	**0.012**
Hemoglobin, g/L	132 (118.5-145)	135 (115.5-148)	131 (124-139.5)	0.695
Platelet count, $\times 10^9$/L	152 (133.5-178.5)	155 (138-169)	150 (122.5-180)	0.577
APTT, second	32.2 (20-36)	32.5 (30.8-36)	31.7 (27.9-34.5)	0.424
D-dimer, mg/L	0.72 (0.49-1.21)	0.7 (0.5-1.2)	0.8 (0.49-1.16)	0.944
Alanine aminotransferase, U/L	21 (15.5-30.5)	24 (15-31.5)	17 (15.5-26)	0.495
Albumin, g/L	41.6 (39.3- 43.3)	41.9 (39.8-43.4)	40.9 (38-42)	0.301
Creatine, μmol/L	70.5 (56.5-78.5)	63 (52.5-75.5)	76 (68-79.5)	0.122
Lactate dehydrogenase, U/L	180 (154-212)	177 (154-194)	212 (158-245)	0.261
Creatine kinase, U/L	48 (41-72)	47.5 (40.5-78)	59 (44.5-66.5)	0.637
Cardiac troponin, ng/ml	0.21 (0.16-0.23)	0.21 (0.13-0.22)	0.22 (0.20-0.24)	0.309
Procalcitonin, ng/ml	0.21 (0.12-0.27)	0.21 (0.11-0.31)	0.21 (0.14-0.23)	0.619
C Reactive Protein, mg/L	23.2 (6.9-90)	18.66 (4.77-29.63)	84 (18.65-150)	**0.026**
Pneumonia	29 (93.5)	18 (90)	11 (100)	0.749
Bilateral involvement on chest computer tomography	20 (64.5)	9 (45)	11 (100)	**0.009**

Table 3. Treatments and clinical outcomes of patients with coronavirus disease 2019 (COVID-19)

Treatments and outcomes	All patients (n = 31)	Non-corticosteroid (n = 20)	Corticosteroid (n = 11)	*p*
Treatments				
Antibiotics	15 (48.4)	7 (35)	8 (72.7)	0.102
Moxifloxacin	14 (45.2)	6 (30)	8 (72.7)	0.056
Duration of moxifloxacin, days	6.5 (3.5-7.0)	7 (5.5-7)	7 (6-8.75)	0.312
Lopinavir/ritonavir + interferon alpha inhalation	26 (83.9)	16 (80)	10 (90.9)	0.780
Umifenovir + lopinavir/ritonavir +interferon alpha inhalation	5 (16.1)	4 (20)	1 (9.1)	
Duration of interferon alpha inhalation, days	15 (10-17)	14.5 (10.5-17)	16 (10.5-17.5)	0.786
Duration of antiviral drug, days	10 (8-11.5)	10 (7.75-13)	9 (8-10)	0.478
Outcomes				
Recovered	26 (83.9)	15 (75)	11 (100)	0.193
Death	0 (0)	0 (0)	0 (0)	NA
Virus clearance time, days	14 (11.5-16)	14 (11-17)	15 (14-16)	0.868
Duration of symptoms, days	7 (5-10.5)	6.5 (4-9.25)	8 (5-12)	0.468
Length of hospital stay, days	18.5 (16-21)	17 (15.5-19.5)	20 (18-21)	0.138
Kidney injury	0 (0)	0 (0)	0 (0)	NA
Liver injury	12 (38.7)	7 (35)	5 (45.5)	0.852

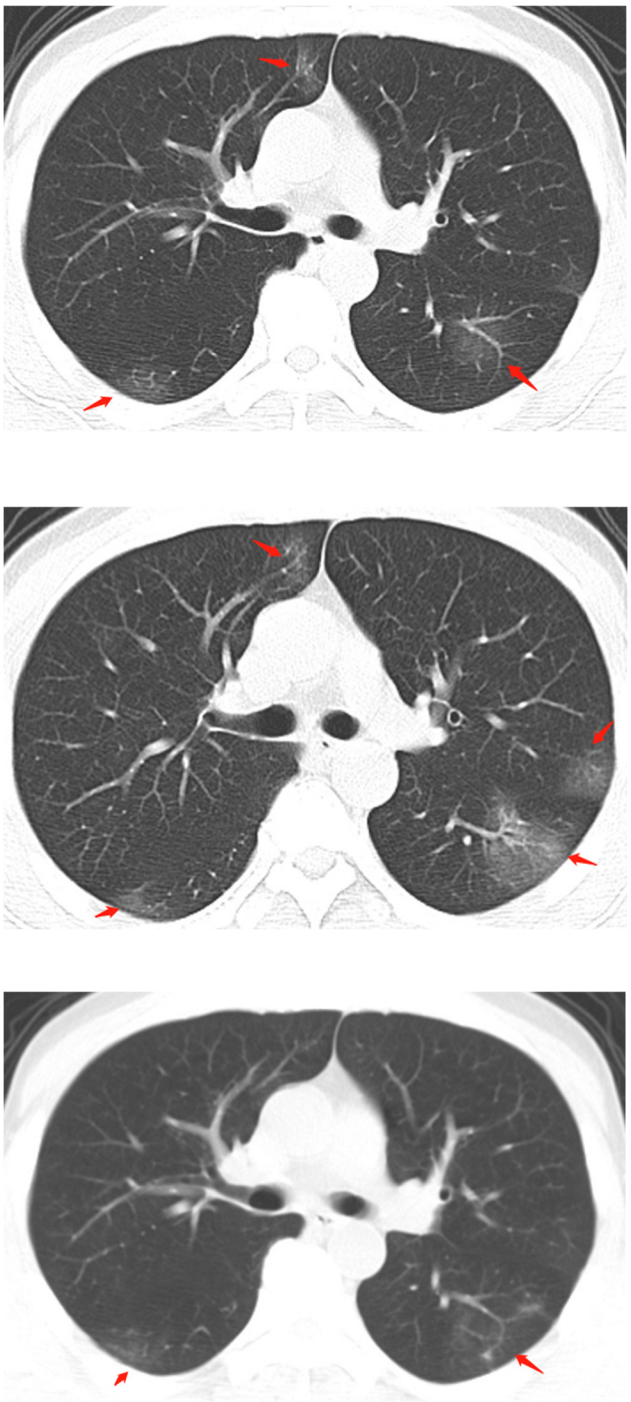

Figure 1: Transverse computer tomography of a patient showing ground glass opacity (red arrows) on multiple lobes near the pleura on admission (top), with progression 3 days later (middle). The previous opacifications have dissipated 20 days after symptom onset (bottom).