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Outcomes of patients with COVID-19 pneumonia treated with moderate and high dose corticosteroids

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ABSTRACT

Introduction: The mortality related to coronavirus disease-2019 (COVID-19) develops due to hyper immune response in most of the patients. The use of corticosteroids (CS) is reported to be effective in decreasing mortality and maintaining a better prognosis but the results of some studies are against the use of CS due to delayed virus clearing, adverse effects, and insignificant effect on clinical course and outcome. We aimed to evaluate the effect of CS use in hospitalized COVID-19 pneumonia patients on clinical course and mortality.

Material and Method: Demographic and laboratory data, history for CS treatment, need for oxygen support, duration of hospitalization and/or ICU follow up, and mortality of inpatients with COVID-19 pneumonia treated between 15.03.2020 and 15.06.2021 at Sultan 2. Abdülhamid Han Training and Research Hospital were collected. The whole cases were divided into two groups as CS group (who were given CS) and the control group (who did not receive CS). All parameters were compared between the two groups.

Results: A total of 185 patients (122 CS group and, 63 control group) were included in the study. The patients in the CS group were younger than the controls (median age was 63 (30-91) years and 71 (34-91) years respectively, p<0.001). In the CS group compared to controls, the number of cases followed in ICU and intubated was lower (55 [45.1%] cases vs. 53 [84.1%] cases, p<0.001 and 40 [32.8%] cases vs. 53 [84.1%] cases, p<0.001, respectively) but, the time for ICU and hospital stay was longer (13 [1-32] days vs.6 [1-29] days, p<0.001 and 11 [5-44] days vs. 9 [4-35]days, p=0.005, respectively). The number of cases who died was less in the CS group compared to controls significantly (35 [28.7%] cases vs. 53 [84.1%] cases respectively, p<0.001).

Conclusion: CS treatment may be related to better prognosis and less mortality in COVID-19 pneumonia inpatients although it may prolong the time for ICU follow up and hospitalization.

Keywords: COVID-19, pneumonia, corticosteroid, mortality

Our research's data was presented in 9. International Medicine and Health Sciences Congress as 'Oral Presentation' on March 2022.

INTRODUCTION

The mortality due to coronavirus disease-2019 (COVID-19) was explained by multi-organ failure developed as a result of severe hyper immune response named "cytokine storm" in most of the patients (1,2). The idea for the use of corticosteroids (CS) in management of hospitalized COVID-19 patients was supported by the information from previous studies that it might have beneficial effects in overcoming both hyper inflammation and adult respiratory distress syndrome (ARDS). The use of CS is reported to be effective on decreasing mortality and resulting in a better outcome (3-10). In contrast, some studies reported that CS use was associated with delayed virus clearing and did not improve survival, reduce hospitalization duration or intensive care unit (ICU) admission rate and/or use of mechanical ventilation (11,12). In this retrospective, observational study we aimed to evaluate the effect of CS use in hospitalized COVID-19 pneumonia patients on clinical course and mortality.

MATERIAL AND METHOD

Adult inpatients aged over 18 years, treated for COVID-19 pneumonia in the Sultan 2. Abdülhamid Han Training and Research Hospital between 15.03.2020 and 15.06.2021 were included in the study. COVID-19 pneumonia was diagnosed based on polymerase chain reaction (PCR) positivity in nasopharyngeal swab or lower respiratory tract samples and radiological findings consistent with COVID-19

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pneumonia on chest computed tomography (CT). This study was approved by Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.05.2021, Decision No: B.10.1.TKH.4.34.H.GP.0.01/179). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. The following data were obtained from the hospital's medical records: Data on demographic information, smoking status, comorbidities (hypertension [HT], respiratory disease [chronic obstructive pulmonary disease or asthma], coronary artery disease [CAD],congestive heart failure [CHF], atrial fibrillation [AF], obesity, cancer, renal disease, diabetes mellitus [DM] and, autoimmune- neurodegenerative disease), duration of CS treatment, number of cases followed in ICU, duration of ICU stay and hospitalization, SpO_2 (peripheral oxygen saturation) level, pulse rate, body temperature, number of cases intubated, cases treated with nasal, mask, reservoir mask oxygen and high flow nasal cannula oxygen (HFNCO), immunosuppression (related with chemotherapy, previous CS use, tocilizumab treatment and, sepsis), severity of COVID-19 according to oxygen need, need for oxygen treatment at time of hospitalization and day 1,3 and, 7 and, number of cases died at hospital.

The patients were divided into two groups: those treated with corticosteroids, defined as CS group, and those not, defined as control group. The groups were compared in terms of demographic, clinical, laboratory data and, outcome.

At the first few months of pandemics the treatment with CS was not included in the treatment regimen of COVID-19 patients. The control group was consisted from inpatients hospitalized before the start of CS use for COVID-19 with respiratory distress. The CS group included in-patients treated with CS. The CS treatment was started when the patients suffered from respiratory distress and had a SpO_2 level below 90% in room air at rest/on effort. The dose of CS was, an equivalent dose of0.5-1 mg/kg methylprednisolone/day for 5-7 days in mild cases (who were followed up with nasal oxygen) and 250mg-500mg/day methylprednisolone for 3 days followed with 0.5-1mg/kg/day methylprednisolone which was temporarily decreased and stopped in days/weeks according to the clinical severity. The clinical severity of COVID-19 was determined according to oxygen as follows: mild(room air), moderate (nasal oxygen), severe (reservoir mask oxygen) and, very severe (HFNCO/MV[mechanical ventilation]).

Statistical Analysis

Patient data collected in the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 package program (Statistical Package for the Social Sciences, Chicago, IL, USA). Discrete data was given as frequency and percentage. The variables were not normally distributed so the median (range) for continuous data was given as descriptive value. "Mann Whitney U test" was used to compare the two groups. "Pearson Chi-Square Test" was used to compare two categorical groups. "Logistic Regression Analysis" was used to examine the risk factors for mortality and intensive care unit admission. The effect of CS use on survival was examined with Kaplan Meier test and Log Rank test. The results were considered statistically significant when the P value was less than 0.05.

RESULTS

A total of 185 patients (122 CS group and, 63 control group) hospitalized with SARS-CoV-2 pneumonia were included in the study. The comparison of demographic and clinical features was shown in **Table 1**. Patients in the CS group were younger (median age was 63 [30-91] years and 71 [34-91) years, p<0.001).The distribution of both sexes was similar (79 [64.8%] cases in the CS group and 38 [60.3%] cases in the control group were males, p=0.553). The smoking history was less frequent in the CS group (6 [4.9%] cases were current, 7 [5.7%] cases were ex-smoker and 109 [89.3%] cases were none smokers in the CS group while 9 [14.3%] cases were current, 7 [11.1%] cases were ex-smoker and,47 [74.6%]cases were nonsmoker in controls, p=0.028). Among comorbidities obesity was more and DM was less common in CS group (14 [11.5%] vs 0 [0%], and, 34 [27.9%] vs. 29 [46%], p=0.003 and, p=0.013, respectively). The median duration of steroid treatment was 8 (2-31) days. In CS group, the number of cases followed up in ICU and intubated was lower (55 [45.1%] cases vs. 53 [84.1%] cases, p<0.001 and 40 [32.8%] cases vs. 53 [84.1%] cases, p<0.001 respectively), while median time for ICU and hospital stay was longer (13 [1-32] days vs. 6 [1-29] days, p<0.001 and 11 [5-44] days vs.9 [4-35] days, p=0.005 respectively). Cases treated with HFNCO were similar between two groups (30 [24.6%] cases in CS group vs. 23 [36.5%]cases in controls, p=0.127). Immunosuppression due to chemotherapy, previous CS use, tocilizumab treatment and, sepsis were similar between CS and control group (2 [1.6%] cases vs.2 [3.2%] cases, 9 [7.4] cases vs. 2 [3.2%] cases, 18 [14.8%] cases vs. 5 [7.9%] cases, 30 [24.6%] cases vs. 9 [14.3%] cases, p=0.606, p=0.337, p=0.273 and, p=0.150 respectively). Distribution of cases according to oxygen need were similar between CS and control group (Moderate: 78 [63.9%] cases vs. 40 [63.5%] cases, severe: 37 [30.3%] cases vs. 22 [34.9%] cases and, very severe: 7 [5.7]) cases vs. 1 [1.6%] case, p=0.381). The number of cases died were significantly less in CS group (35 [28.7%] cases vs. 53 [84.1%] cases, p<0.001).

Number of cases needed oxygen treatment at time of hospitalization was more in CS group (Nasal oxygen: 60 [49.2%] cases vs.21 [34.4%] cases, mask oxygen16 [13.1%] cases vs.11 [18%] cases, reservoir mask oxygen:21 [17.2%] cases vs.1 [1.6%] case, HFNCO:4 [3.3%] cases vs. 12 [19.7%] cases, MV:1 [0.8%] case vs.1 [1.6%] case respectively, p<0.001).

Table 1. Clinical and demographic features of the two groups

	CS group (N=122)	Control (N=63)	P value
Age (min-max)	63 (30-91)	71 (34-91)	<0.001
Sex			0.553
Male	79 (64.8)	38 (60.3)	
Female	43 (35.2)	25 (39.7)	
Smoking status			0.028
None smoker	109 (89.3)	47 (74.6)	
Smoker	6 (4.9)	9 (14.3)	
Ex-smoker	7 (5.7)	7 (11.1)	
Comorbidities			
HT	66 (54.1)	37 (58.7)	0.548
Respiratory disease	22 (18)	14 (22.2)	0.627
Coronary artery disease	34 (27.9)	17 (27)	0.898
AF	8 (6.6)	5 (7.9)	0.766
Obesity	14 (11.5)	0 (0)	0.003
Cancer	9 (7.4)	5 (7.9)	1
Renal disease	6 (4.9)	8 (12.7)	0.078
DM	34 (27.9)	29 (46)	0.013
Autoimmune-Neurodegenerative disease	7 (5.7)	2 (3.2)	0.720
Duration of steroid treatment (days)	0	8 (2-31)	NA
Number of cases followed in ICU	55 (45.1)	53 (84.1)	<0.001
Time for ICU stay(days)	13 (1-32)	6 (1-29)	<0.001
Time for hospitalization(days)	11 (5-44)	9 (4-35)	0.005
Number of cases intubated	40 (32.8)	53 (84.1)	<0.001
Cases treated with HFNCO	30 (24.6)	23 (36.5)	0.127
Immunosuppression			
Chemotherapy	2 (1.6)	2 (3.2)	0.606
Previous CS use	9 (7.4)	2 (3.2)	0.337
Tocilizumab treatment	18 (14.8)	5 (7.9)	0.273
Sepsis	30 (24.6)	9 (14.3)	0.150
Severity of COVID-19 according to oxygen need			0.381
None	20(16.4)	15(24.6)	
Moderate (nasal)	78 (63.9)	40 (63.5)	
Severe (Reservoir mask)	37 (30.3)	22 (34.9)	
Very severe (HFNCO/MV)	7 (5.7)	1 (1.6)	
Outcome			<0.001
Survival	87 (71.3)	10 (15.9)	
Death	35 (28.7)	53 (84.1)	

* n (%) or median (minimum-maximum). HT: Hypertension, AF: Atrial fibrillation, DM: Diabetes mellitus, ICU: Intensive care unit, HFNCO: High flow nasal cannula oxygen, CS: Corticosteroid, MV: Mechanical ventilation.

On day 1 the median SpO_2 was similar between two groups (88% [72-93] in CS group and, 88% [62-93] in controls, p=0.477). The oxygen need was less in CS group compared to controls (nasal oxygen:55 [45.1%] cases vs. 26 [41.9%] cases, mask oxygen: 18[14.8%] cases vs. 12[19.4%] cases, reservoir mask oxygen: 34 [27.9%] cases vs. 5 [8.1%] cases, HFNCO: 7 [5.7%] cases vs. 2 [3.2%] cases and, MV 2 [1.6] cases vs. 14 [22.6%] cases, p<0.001). The median pulse rate, body temperature, number of leukocytes and, number of lymphocytes were lower in CS group compared to controls (81 [53-135]/min. vs. 88 [59-134]/min. and, 36.5 [35-40]°C vs.36.8 [35.2-39]°C, 7.2x10^3/ml [2.4-24.5] vs. 10.3×10^3/ml [3-55.6], 0.73 [0.13-18.7]×10^3/ml vs. 1[0.1-51.6]×10^3/ml, p=0.047 and p=0.021,p=0.001, p=0.007 respectively). The median serum CRP, IL-6, and ferritin levels were similar between CS group and controls (120.6 [2-350] mg/dl vs.133.5 (3-318] mg/dl, 35.7 [2-297] vs.18 [6-202] and, 729.6 [24.5-2000] vs.356.7 [20.7-36872.5], p =0.602, p=0.518 and, p=0.086 respectively). The median D-Dimer level was lower in CS group (0.6 [0.01-4.8] ng/dl vs.0.9 (0.05-5.7] ng/dl, p=0.028).

On day 3, the median SpO_2 was similar between two groups (93 [70-99%] in CS group and 92 [79-100%] in controls, p=0.875). The need for oxygen support was less in CS group (nasal: 46 [37.7%] cases vs. 9 [14.8%] cases, mask: 9 [7.4%] cases vs. 5 [8.2%] cases, reservoir mask: 22 [18%] cases vs. 5 [8.2%] cases, HFNCO: 19 [15.6%] cases vs. 5 [8.2%] cases and, MV: 10 [8.2%] cases vs. 29 [47.5%] cases, p<0.001). The median pulse rate was similar between two groups, while the body temperature was lower in CS group significantly (81.5/min [50-137] and 36 [35-38]°C in CS group and, 91/min. [43-127] and, 36.5 [35.5-40.3]°C in controls, p=0.099 and, p<0.001 respectively). The median number of leukocytes and lymphocytes were similar (10.36 [2.37-24.14] ×10^3/ml and, 0.65 [0.17-18.34]×10^3/ml in CS group and, 10.08 [1.59-38.6]×10^3/ml and, 0.87 [0.12-14.75]×10^3/ml in controls, p=0.965 and, p=0.098 respectively). The median serum CRP and D-Dimer level was lower in CS group (64.1 [1.6-280.87] vs. 16.6 [2-202], and, 0.57 [0.01-8.43] vs. 0.89 [0.04-4.38], p=0.027 and p=0.039 respectively).The median IL-6 and, ferritin level was similar between two groups (77.7 [2-307] and 706 [87.2-2000] in CS group and, 30.8 [7.71-501] and, 461 [60-100000] in controls, p=0.108 and, p=0.124 respectively).

On day 7 the median SpO_2 value was higher (94 [74-100%] vs. 90 [49-99%], p<0.001) while the median number of cases needed oxygen support was lower in CS group(nasal: 25 [20.5%] cases vs.4 [6.6%] cases, mask: 19 [15.6%] cases vs. 4 [6.6%] cases, reservoir mask: 18 [14.8%] cases vs. 7 [11.5%] cases, HFNCO: 16 [13.1%] cases vs. 2 [3.3%] cases and, MV: 23 [18.9%] cases vs. 41 [67.2%] cases, p<0.001). The median pulse rate was lower in CS group (81 [36.3-140]/min. vs. 91 [36-131]/min., p=0.017) while the median body temperature was similar between two groups (36.4 °C [34.9-39.1°C] in CS group and, 36.5°C [36-39.5°C] in controls, p=0.121).The median number of leukocytes and lymphocytes were also similar (9.69 [2.92-26.25]×10^3/dl and, 0.8 [0.15-18.32] ×10^3/dl in CS group and, 12.1[4.07-213.13]×10^3/dl and, 0.79 [0.1-158.28]×10^3/dl in controls, p=0.202, p=0.873, respectively). The median serum CRP level was lower in CS group (21.48 [0.1-285.69] vs. 89.55 [4.1-326], p<0.001). The median IL-6, D-Dimer and ferritin level were similar (36.90 [2.82-5689], 0.99 [0.01-8.05] ng/ml and, 669 [47.48-2000] in CS group and, 43.3 [5.85-733], 1.44 [0.12-194] ng/ml and, 540.92 [103-1106,9] in controls, p=0.571,p=0.193, p=0.119 respectively) (**Table 2**).

The effect of CS use on survival was examined with Kaplan Meier test and Log Rank test and showed the significant positive effect of CS treatment on survival (**Figure 1**).

Table 2. Oxygen need and laboratory data of two groups

	CS group (N=122)	Control (N=63)	P value
Oxygen need on admission			<.0.001
None	20 (16.4)	15 (24.6)	
Nasal	60 (49.2)	21 (34.4)	
Mask	16 (13.1)	11 (18)	
Reservoir mask	21 (17.2)	1 (1.6)	
HFNCO	4 (3.3)	12 (19.7)	
MV	1 (0.8)	1 (1.6)	
DAY 1			
SpO_2	88 (72-93)	88 (62-93)	0.477
Oxygen need			<.0.001
None	6 (4.9)	3 (4.8)	
Nasal	55 (45.1)	26 (41.9)	
Mask	18 (14.8)	12 (19.4)	
Reservoir	34 (27.9)	5 (8.1)	
HFNCO	7 (5.7)	2 (3.2)	
MV	2 (1.6)	14 (22.6)	
Pulse/minutes	81 (53-135)	88 (59-134)	0.047
Body temperature	36.5 (35-40)	36.8 (35.2-39)	0.021
Number of leukocytes ($\times10^3$/ml)	7.2 (2.4-24.5)	10.3 (3-55.6)	0.001
Number of lymphocytes ($\times10^3$/ml)	0.73 (0.13-18.7)	1 (0.1-51.6)	0.007
CRP (mg/dl)	120.6 (2-350)	133.5 (3-318)	0.602
IL-6	35.7 (2-297)	18 (6-202)	0.518
D-Dimer (ng/ml)	0.6 (0.01-4.8)	0.9 (0.05-5.7)	0.028
Ferritin	729.6 (24.5-2000)	356.7 (20.7-36872.5)	0.086
DAY 3			
SpO_2	93 (70-99)	92 (79-100)	0.875
Oxygen need			<0.001
None	16 (13.1)	8 (13.1)	
Nasal	46 (37.7)	9 (14.8)	
Mask	9 (7.4)	5 (8.2)	
Reservoir mask	22 (18)	5 (8.2)	
HFNCO	19 (15.6)	5 (8.2)	
MV	10 (8.2)	29 (47.5)	
Pulse	81.5 (50-137)	91 (43-127)	0.099
Body temperature	36 (35-38)	36.5 (35.5-40.3)	<0.001
Number of leukocytes ($\times10^3$/ml)	10.36 (2.37-24.14)	10.08 (1.59-38.6)	0.965
Number of lymphocytes ($\times10^3$/ml)	0.65 (0.17-18.34)	0.87 (0.12-14.75)	0.098
CRP(mg/dl)	64.1 (1.6-280.87)	77.7 (2-307)	0.027
IL-6	16.6 (2-202)	30.8 (7.71-501)	0.108
D-Dimer(ng/ml)	0.57 (0.01-8.43)	0.89 (0.04-4.38)	0.039
Ferritin	706 (87.2-2000)	461 (60-100000)	0.124
DAY 7			
SpO_2	94 (74-100)	90 (49-99)	<0.001
Oxygen need			<0.001
None	21 (17.2)	3 (4.9)	
Nasal	25 (20.5)	4 (6.6)	
Mask	19 (15.6)	4 (6.6)	
Reservoir mask	18 (14.8)	7 (11.5)	
HFNCO	16 (13.1)	2 (3.3)	
MV	23 (18.9)	41 (67.2)	
Pulse (/min.)	81 (36.3-140)	91 (36-131)	0.017
Body temperature (°C)	36.4 (34.9-91)	36.5 (36-39.5)	0.121
Number of leukocytes ($\times10^3$/ml)	9.69 (2.92-26.25)	12.1 (4.07-213.13)	0.202
Number of lymphocytes ($\times10^3$/ml)	0.8 (0.15-18.32)	0.79 (0.1-158.28)	0.873
CRP(mg/dl)	21.48 (0.1-285.69)	89.55 (4.1-326)	<0.001
IL-6	36.90 (2.82-5689)	43.3 (5,85-733)	0.571
D-Dimer (ng/ml)	0.99 (0.01-8.05)	1.44 (0,12-19,4)	0.193
Ferritin	669 (47.48-2000)	540.92 (103-1106,9)	0.119

n (%) or median (minimum-maximum). HFNCO: High flow nasal cannula oxygen, MV: Mechanical ventilation, SpO_2: Peripheral oxygen saturation, CRP: C-reactive protein, IL-6: Interleukin 6

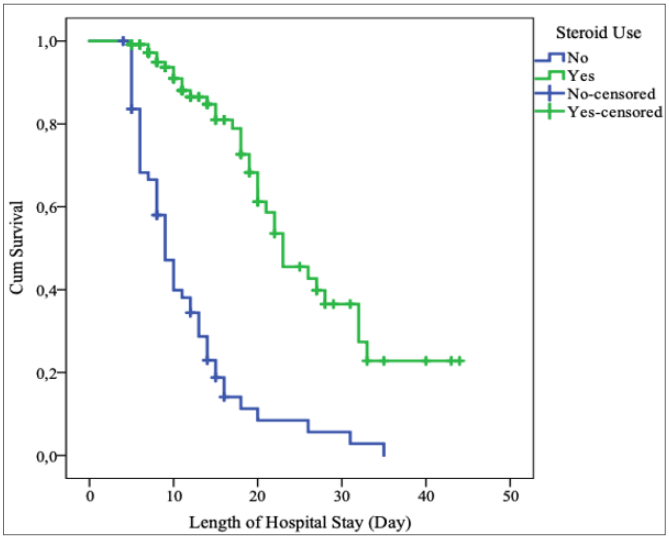

Figure 1. Kaplan–Meier curves of cumulative survival rate for patients administered with and without corticosteroids

DISCUSSION

In this retrospective observational study, the use of CS was related with better prognosis and increased survival in hospitalized patients with COVID-19 pneumonia. Primary endpoint was hospital mortality rate which was significantly lower in CS group although DM and obesity were more frequent in this group. On the other hand CS group was younger than controls. There are several studies reported that both DM, obesity and older age increased the COVID-19 related morbidity and mortality (1,2,13-16). Our findings about positive effect of CS on mortality was compatible with the results of several previous studies (6-10). A meta-analysis including more than 20,000 patients confirmed a beneficial effect of CS treatment on short-term mortality and a reduction in need for MV in hospitalized COVID-19 patients (10). But there are few studies against the use of CS which reported that the CSs did not maintain beneficial clinical outcome and decreased hospital mortality but resulted in adverse effects such as bacterial superinfections and delayed viral clearance (12). As we did not have detailed data on PCR conversion time and complications related to CS treatment we only focused on the effect of the treatment on clinical course and survival rate.

Secondary endpoint was the clinical course. Although the ratio of cases with oxygen need on admission was more in the CS group, on follow up the oxygen need was less and, laboratory parameters related to worse prognosis and mortality were lower in CS group. This may be explained with the potent anti-inflammatory effect of CS.

The number of cases transferred to ICU was more in the control group. CS treatment may prevent the worsening of the cases and decrease the need for ICU follow-up.

Liu et al. (3) reported that although the early start of CS treatment before the need for oxygen support is beneficial, there were no significant differences in hospital mortality rates between patients with and without CS treatment. In our study, we did not furtherly analyze the effect of CS treatment in relation to time of initiation of the treatment but we showed the positive effect of CS on morbidity and mortality.

The duration of hospitalization and ICU follow up was shorter in controls. This may be due to adverse effects of CS such as bacterial superinfections or hyperglycemia which may result in the need for extra treatment and prolonged hospital stay. Also, the ratio of the patients who needed oxygen treatment on admission was more in CS group, so the longer hospital stay may be due to the presence of more severe patients in the study group compared to controls.

There are several studies evaluating the effect of CS treatment on COVID-19 pneumonia, but the results may be confusing and include some bias due to the varying indication, dose and, duration of CS treatment and, different mortality measures (hospital mortality, 28 days mortality, etc.). It was reported that CS might have beneficial effects to reduce the hyper inflammatory response and result in clinical improvement in patients with ARDS (17). On the other hand, the adverse effects, such as delayed viral clearance, opportunistic fungal and bacterial superinfections, and hyperglycemia have to be kept in mind during making the decision to start CS treatment and follow-up. It was reported that CS treatment did not improve survival, reduce hospital stay or ICU admission rate and/or use of mechanical ventilation and prolonged viral clearance (11,12).

This study had a few limitations. The study group was heterogeneous including a large spectrum of patients from mild to very severe cases. The sample size was small so subgroup analysis could not be performed. The patients who received CS were younger which may affect the clinical course and mortality in a positive manner. The adverse effects and complications such as secondary bacterial infections were not evaluated which may be related to clinical outcome and mortality

CONCLUSION

CS treatment is related to a better prognosis and less mortality in inpatients with COVID-19 pneumonia. In addition, it may prolong the duration of hospitalization and ICU follow up. So the decision for CS treatment should be made carefully.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.05.2021, Decision No: B.10.1.TKH.4.34.H.GP.0.01/179).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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