Effects of Early Corticosteroid Use in Patients With Severe Coronavirus Disease 2019: A Case Control Study

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Abstract

Background

Coronavirus disease 2019 (COVID-19) is associated with acute respiratory distress syndrome, and corticosteroids have been considered as possible therapeutic agents. However, there is limited literature on the appropriate timing of corticosteroid administration to obtain the best possible patient outcomes.

Methods

A retrospective multicenter study was designed to explore the effects of early corticosteroid use on clinical outcomes in 7 tertiary hospitals in South Korea. Twenty-two patients with severe COVID-19 were enrolled, and they were all treated with corticosteroids.

Results

Of the 22 patients who received corticosteroids, 12 patients (55%) were treated within 10 days from diagnosis. There was no significant difference in the baseline characteristics. The initial PaO_2/FiO_2 ratio was 168.75. The overall case fatality rate was 25%. The mean time from diagnosis to steroid use was 4.08 days and the treatment duration was 14 days in the early use group, and 12.80 days and 18.50 days in the late use group, respectively. The PaO_2/FiO_2 ratio, C-reactive protein level, and cycle threshold value improved over time in both groups. In the early use group, the time from onset of symptoms to discharge (32.4 days vs 60.0 days, $P = 0.030$), time from diagnosis to discharge (27.8 days vs 57.4 days, $P = 0.024$), and hospital stay (26.0 days vs 53.9 days, $P = 0.033$) were shortened.

Conclusions

Among patients with severe COVID-19, the early use of corticosteroids resulted in a significant improvement in the time to favorable clinical outcomes.

Background

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in China in late 2019.[1] It has affected almost 25 million people worldwide and resulted in the deaths of more than 850,000 as of August 31, 2020.[2] The majority of infected patients are asymptomatic and showcase only mild symptoms; however, the remainder experience a severe form of the disease. Elderly patients and patients with underlying diseases such as diabetes mellitus, hypertension, and immunosuppressive disorders have considerable morbidity and mortality when co-infected with COVID-19.[3, 4] The overall fatality rate is approximately 0.4–2.0%, but may be up to 50% in patients with life-threatening illnesses,[5] a finding that suggests that it is necessary to use different treatment approaches in these patients.

Severe COVID-19 is accompanied by inflammatory organ injury and causes acute respiratory distress syndrome, shock, or cardiac failure due to elevated levels of inflammatory cytokines and biomarkers. These include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, and D-dimer.[6] Although the main pathophysiology of COVID-19 is not completely understood, excessive inflammation is closely related to the development of pneumonia and rapid progression of the disease. Anti-inflammatory treatments, such as corticosteroids, are therefore, therapeutic options for severe COVID-19.[7]

Several potential therapeutics have been proposed in the early phase of this pandemic, including chloroquine, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, azithromycin, intravenous immune globulin, and convalescent plasma transfusion, but only corticosteroids and remdesivir improve clinical outcome.[8] Although some trials have reported the effectiveness of corticosteroids on the clinical outcomes in patients,[9-11] the correct timing of corticosteroid administration is still unclear. Therefore, we analyzed the effectiveness of corticosteroids in severe COVID-19 cases by dividing them into groups based on early versus late administration.

Methods

Study design and population

This was a retrospective cohort study of patients with severe COVID-19 who received corticosteroid treatment between March 2 and June 30, 2020 in 7 tertiary hospitals in South Korea. We enrolled patients aged ≥ 18 years with laboratory-confirmed SARS-CoV-2 infection and admitted to the ICU. Patients with insufficient clinical data due to hospital transfers were excluded.

Electronic medical records were reviewed for baseline demographics, comorbidities, clinical characteristics, clinical status, laboratory findings, treatment, clinical course, and outcomes. Data were compared before steroid use, 3, 7, and 14 days later.

The study was approved by the Institutional Review Boards of Severance Hospital (Seoul, South Korea), and written informed consent was waived.

Definition

SARS-CoV-2 RNA was assessed by real-time reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs or sputum according to the World Health Organization interim guidance. RT-PCR assays for the *E*, *RdRp*, and *N* genes were performed using the Allplex™ 2019-nCoV Assay (Seegene Inc., Seoul, South Korea). Positive RT-PCR results were defined as a cycle threshold (Ct) value ≤40. The severity was assessed by PaO_2/FiO_2 ratio and categorized into 7 scores based on oxygen supplementation: no limit of activity, limit of activity but no O_2, O_2 with nasal prong, O_2 with facial mask, high flow nasal cannula, noninvasive ventilation, and invasive ventilation.

The patients were divided into 2 groups by time to corticosteroid use. Patients who were treated with corticosteroids within 10 days and after 10 days of confirmation were categorized as the early use group and the late use group, respectively.

CRP concentration was measured in serum using a nephelometric method (Beckman Coulter, Fullerton, CA, USA).

Statistical analysis

All variables are presented as the mean ± standard deviation (SD), unless otherwise indicated. The Mann-Whitney U test, Chi-square (χ^2) test, or Fisher's exact test were used if appropriate. Laboratory findings were analyzed based on a linear mixed model using groups (early or late) and time (after corticosteroid administration). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences version 25.0 (IBM Corporation, Armonk, NY, USA).

Results

During the study period, 22 patients who met the inclusion criteria were categorized into the early use group (n=12) or the late use group (n=10). The baseline demographics and characteristics of each group were similar (Table 1). The mean age of the early use group was 65.6 years and 50% were male. Among them, 7 patients (58.3%) had a history of hypertension. The most common symptoms were fever (75%), cough (50%), sputum (41.7%), dyspnea (41.7%), and fatigue (41.7%). Patients were assessed based on an ordinal scale; 4 patients (33.3%) had a score of 2 (limit of activity but no O_2); 5 (41.7%) had a score of 3 (O_2 with nasal prong), and 3 (25%) had a score of 5 (high flow nasal cannula). Baseline laboratory tests were similar between the two groups. The initial PaO_2/FiO_2 ratio in the early use group was 124.89. The inflammatory markers were elevated; the mean levels of ferritin, ESR, and CRP were 804.22 ± 601.11 ng/mL, 60.00 ± 35.78, and 10.33 ± 8.95, respectively.

Table 1. Comparisons of baseline demographics and characteristics in patients with severe COVID-19

Characteristics	Early use group (n=12)	Late use group (n=10)	*p*-value
Age (years) mean ± SD	65.6 ± 5.6	74.6 ± 4.6	0.056
Sex, No. (%)			
Male	6/12 (50%)	6/10 (60%)	0.691
Coexisting disease, No. (%)			
Hypertension	7/12 (58.3%)	4/10 (30%)	0.392
Diabetes	3/12 (25%)	3/10 (30%)	1.000
Malignant neoplasm	2/12 (16.7%)	1/10 (10%)	1.000
Symptoms			
Fever	9/12 (75%)	7/10 (70%)	1.000
Cough	6/12 (50%)	3/10 (30%)	0.415
Sputum	5/12 (41.7%)	4/10 (40%)	1.000
Dyspnea	5/12 (41.7%)	4/10 (40%)	1.000
Myalgia	5/12 (41.7%)	2/10 (20%)	0.381
Fatigue	5/12 (41.7%)	1/10 (10%)	0.162
Poor oral intake	4/12 (33.3%)	1/10 (10%)	0.323
Initial Score on ordinal scale			0.742
No limit of activity	0	0	
Limit of activity but no O_2	4/12 (33.3%)	4/10 (40%)	
O_2 with nasal prong	5/12 (41.7%)	2/10 (20%)	
O_2 with facial mask	0	0	
High flow nasal cannula	3/12 (25%)	3/10 (30%)	
Non-invasive ventilation	0	0	
Invasive ventilation	0	0	
Baseline score missing	0	1/10 (10%)	
Initial PaO2/FiO_2 ratio	124.89 ± 42.60	133.35 ± 49.40	0.743

COVID-19, Coronavirus disease 2019; SD, standard deviation

The data were expressed as mean ± SD or number (%)

The therapeutic options and timing differences of patients are shown in Table 2. Most patients used methylprednisolone, and only 1 patient used hydrocortisone. Corticosteroids were initiated within a median of 9.75

± 3.64 days of the onset of symptoms, 4.08 ± 2.9 days of the confirmation, and 3.33 ± 3.45 days after hospital admission. The initial dose of corticosteroid administered was 0.8 ± 0.25 mg kg^{-1} day^{-1} methylprednisolone, and patients were treated for 14.00 ± 5.00 days. The total dose administered was 521.6 ± 246.38 mg methylprednisolone.

Table 2. Factors associated with therapeutic option in patients with severe COVID-19

	Early use group (n=12)	Late use group (n=10)	*p*-value
Combination therapy			
Steroid	7/12 (58.3%)	7/10 (77.8%)	0.229
Steroid + Convalescent plasma	5/12 (41.7%)	1/10 (11.1%)	
Steroid + Remdesivir	0	1/10 (11.1%)	
Steroid-related factor			
Time from symptom to steroid use	9.75 ± 3.64	15.70 ± 6.00	0.010
Time from diagnosis to steroid use	4.08 ± 2.99	12.80 ± 1.75	<0.001
Time from hospitalization to steroid use	3.33 ± 3.45	10.00 ± 4.83	0.001
Initial dose*, mg/Kg/day	0.8 ± 0.25	0.9 ± 0.23	0.320
Duration, days	14.00 ± 5.00	18.50 ± 14.76	0.380
Total dose*, mg	521.6 ± 246.38	667.50 ± 606.76	0.490
Score on ordinal scale at steroid start			0.035
O_2 with nasal prong	1/8 (12.5%)	0	
High flow nasal cannula	7/8 (87.5%)	2/5 (40%)	
Invasive ventilation	0	3/5 (60%)	

COVID-19, Coronavirus disease 2019

The data were expressed as mean ± SD or number (%)

*Dose of corticosteroid was calculated based on methylprednisolone.

Laboratory findings before and after corticosteroid use are compared in Table 3. Significant changes in lymphocyte count, lactate dehydrogenase, and inflammatory markers (ferritin, CRP, and procalcitonin) were observed after corticosteroid administration in both groups. The PaO_2/FiO_2 ratio and Ct value improved in both groups. However, when comparing changes between the two groups, there was no significant difference in improvement (Figure 1).

Comparisons of clinical outcomes between the 2 groups are shown in Table 4. A shorter hospital stay in the early use group than in the late use group (26.0 ± 11.4 vs. 53.9 ± 23.0 days, $P = 0.033$). The time from corticosteroid use to discharge was 25.6 days in the early use group and 46.3 days in the late use group, but the difference was not

significant (P = 0.096). In the early use group, there was a correlation between the time between diagnosis and corticosteroid use, and the duration of hospital stay (Figure 2). There was no significant difference in the overall mortality. None of the patients in either group suffered secondary bacterial infection or hyperglycemia.

Table 3. Change in laboratory findings after corticosteroid use

	Early use group (n=12)				Late use group (n=10)			
	Day 0	**Day 3**	**Day 7**	**Day 14**	**Day 0**	**Day 3**	**Day 7**	**Day 14**
WBC count, cells/μL	7496.67 ± 4065.33	9083.33 ± 3157.70	11343.64 ± 5408.91	9762.00 ± 3989.17	8330.00 ± 2953.13	9738.00 ± 2988.52	12063.00 ± 3200.34	10045.56 ± 4728.95
Neutrophil count, cells/μL	706.75 ± 3451.137	7999.33 ± 2943.50	9954.64 ± 5162.74	7918.40 ± 4030.34	6918.10 ± 2844.49	6878.24 ± 2988.34	10142.90 ± 3488.86	8444.31 ± 4657.33
Lymphocyte , cells/μL	756.77 ± 280.28	653.5 ± 247.79	830.20 ± 525.49	901.80 ± 446.39	774.86 ± 31.49	778.2 ± 535.66	906.40 ± 640.20	803.22 ± 451.07
LDH, IU/L	444.30 ± 113.95	366.75 ± 99.70	363.63 ± 95.43	339.43 ± 179.34	394.63 ± 126.97	463.60 ± 201.04	402.63 ± 157.78	367.50 ± 200.63
Ferritin, ng/mL	1423.8 ± 1047.96	966.08 ± 765.58	841.28 ± 465.38	1236.91 ± 975.47	1045.37 ± 895.92	1252.22 ± 1166.20	698.31 ± 167.39	813.22 ± 420.80
CRP, mg/L	16.83 ± 9.76	6.25 ± 7.93	2.95 ± 6.28	3.40 ± 3.44	15.42 ± 8.97	6.61 ± 3.18	2.33 ± 1.58	4.70 ± 2.34
Procalcitonin, ng/mL	0.33 ± 0.28	0.49 ± 0.47	0.17 ± 0.13	0.15 ± 0.25	0.54 ± 0.95	0.23 ± 0.11	0.11 ± 0.03	0.11 ± 0.06
PaO_2/FiO_2 ratio	124.89 ± 42.60	143.42 ± 57.61	157.70 ± 75.48	261.09 ± 134.38	133.35 ± 49.40	220.97 ± 45.61	183.40 ± 29.92	232.77 ± 138.59
Ct value	24.77 ± 8.42	27.31 ± 5.91	29.3 ± 8.85	32.73 ± 5.71	31.5 ± 3.07	24.53 ± 1.31	28.30 ± 7.14	35.40 ± 2.46

WBC, white blood cell; LDH, lactate dehydrogenage; CRP, C-reactive protein; Ct value, cycle threshold

The data were expressed as mean ± SD

Table 4. Clinical outcomes in the early use and late use groups

	Early use group (n=12)	Late use group (n=10)	*p*-value
Time from diagnosis to discharge	27.8 ± 12.2	57.4 ± 22.5	0.024
Time from symptom to PCR negative	28.8 ± 9.0	36.1 ± 13.3	0.168
Time from symptom to discharge	32.4 ± 13.1	60.0 ± 21.5	0.030
Time from corticosteroid use to discharge	25.6 ± 12.4	46.3 ± 22.7	0.096
Hospital length of stay	26.0 ± 11.4	53.9 ± 11.4	0.033
Overall mortality, No./total (%)	1/12 (8.3%)	3/10 (30%)	0.293

Discussion

The COVID-19 pandemic is worsening and spreading across the world. Many treatments have been used, but they have been proven ineffective, so alternative new treatment options are needed[7]. Corticosteroids have long been thought to be effective against patients with acute respiratory distress syndrome, septic shock, and possibly viral pneumonia[12] but this is still controversial. An interim guidance document released on May 27, 2020 by the World Health Organization on clinical management of COVID-19 recommended against the routine use of systemic corticosteroids for the treatment of viral pneumonia. The Infectious Disease Society of America recommends the use of corticosteroids in the context of clinical trials for patients with acute respiratory distress syndrome.[13] However, adherence to this recommendation remained low, and many studies suggesting the opposite result have been released recently. Intravenous dexamethasone reduced 28-day mortality in patients with invasive mechanical ventilation or oxygen alone[9] (RECOVERY clinical trial). Fixed-dose hydrocortisone resulted in improvement in organ support-free days within 21 days[10] (REMP-CAP trial). Intravenous dexamethasone increased the number of ventilator-free days over 28 days[11] (CODEX trial). These clinical trials provide evidence of corticosteroid effectiveness and suggest a safe treatment option for COVID-19.

The pathogenesis of severe COVID-19 is still unclear, but it is believed that it has two overlapping pathologic subsets, similar to other viral pneumonia. In the early stage of infection, as SARS-CoV-2 replicates, mild clinical manifestations such as fever, malaise, and cough are observed. In most of these cases, patients recover without therapeutic support, but in other cases, they progress to severe disease. This is a result of host systemic inflammation rather than direct viral-induced tissue damage. Because sepsis and other critical illnesses occur for approximately 10 days,[3] maladaptive host responses to the viral infection is starts during this period. For this reason, anti-inflammatory therapy such as corticosteroids is not recommended for early use. Many studies have shown that corticosteroids can prolong viral shedding and can cause secondary infections.[14-16] In our study, patients were divided into 2 groups based on the duration of the diagnosis to corticosteroid use on a 10-day basis. Both groups showed increasing Ct values after corticosteroid use. Within each group, the increase was significant, but there was no difference when comparing the 2 groups. Therefore, it can be free from the stigma of inhibition of viral clearance for using corticosteroids in patients with severe COVID-19.

Because corticosteroids generally suppress the immune system response, there is a concern that they can accelerate secondary infections and cause many complications such as diabetes, psychosis, and avascular necrosis.[16] In our study, patients with lymphopenia recovered and inflammatory parameters such as ferritin, CRP,

and procalcitonin also improved after corticosteroid use in both groups, although there was no difference between the 2 groups. Corticosteroid-related complications were not noted.

The mean length of hospital stay varies from 4–11 days in COVID-19 patients and severe and life-threatening COVID-19 patients remain for longer periods.[3, 17] In our study, the early use group stayed in the hospital for 26 days, whereas the late use group styed for 53.9 days. Early corticosteroid use within 10 days after diagnosis did not reduce mortality but reduced hospital stay compared with late use. Thus, it is important to use corticosteroids in patients with severe COVID-19 at the most appropriate time.

Our study had several limitations. First, the sample size was small. It is important to note that the number of patients with severe COVID-19 in South Korea is relatively low. For this reason, the sample size was limited despite the participation of many tertiary hospitals in the study. Second, there was insufficient data on clinical symptoms and missing laboratory findings. Third, the study was performed retrospectively. Therefore, some confounders could not be excluded. Both the dose and duration of corticosteroid use in the study differed for each patient. Fourth, the 10-day-based group was a relatively random request. It should be further subdivided into follow-up studies. Therefore, further large-scale studies in patients with severe COVID-19 are required.

Despite these limitations, this study provides valuable information on the clinical outcomes for patients with severe COVID-19 patients who used corticosteroids. This supports the notion that corticosteroids can be one of the options for treatment of severe COVID-19. It is beneficial to use corticosteroids early within 10 days in severe COVID-19.

In conclusion, corticosteroids can be one of the options for treatment of COVID-19 in patients with severe and life-threatening COVID-19, and early use of corticosteroids is associated with significant improvement in clinical outcomes which are related to a reduction in the length of the hospital stay.

Conclusions

In conclusion, corticosteroids can be one of the options for treatment of COVID-19 in patients with severe and life-threatening COVID-19, and early use of corticosteroids is associated with significant improvement in clinical outcomes which are related to a reduction in the length of the hospital stay.

Abbreviations

COVID-19: Coronavirus disease 2019

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

CRP: C-reactive protein

ESR: Erythrocyte sedimentation rate

Ct: Cycle threshold

SD: Standard deviation

Declarations

Availability of data and materials

All Data and material collected during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions

Conceptualization: Hong GD. Data curation: Kim MH. Formal analysis: Shon YJ. Investigation: Cho YS. Methodology: Baek YJ. Software: Kim JH. Validation: Ahn MY, Kim EJ, Choi H. Visualization: Baek JH, Kim YK. Writing - original draft: Hyun JH. Writing - review & editing: Jeong SJ, Choi JY, Yeom JS. All authors read and approved the final manuscript.

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Ethic approval and consent to participate

The study was approved by the Institutional Review Boards of Severance Hospital (Seoul, South Korea), and written informed consent was waived.

Consent for publication

Not applicable

Competing interests

No competing interests to declare

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Figures

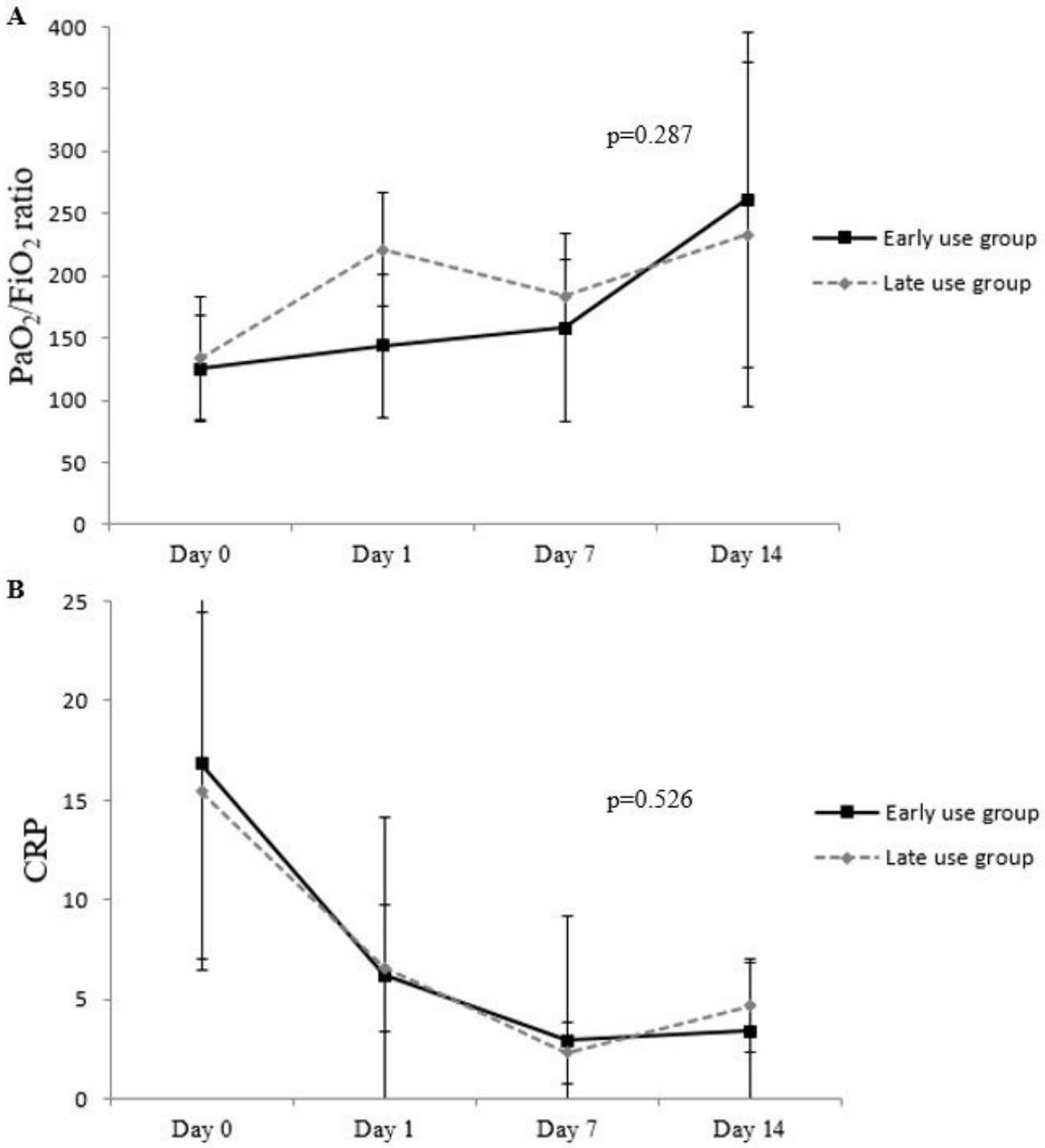

Figure 1

Comparison of clinical response after corticosteroid use. (A) Changes in mean PaFiO2 ration (B) Changes in means CRP. Means were calculated and compared between groups at each time point using a linear mixed model. Error bars represent standard error. CRP, C-reactive protein

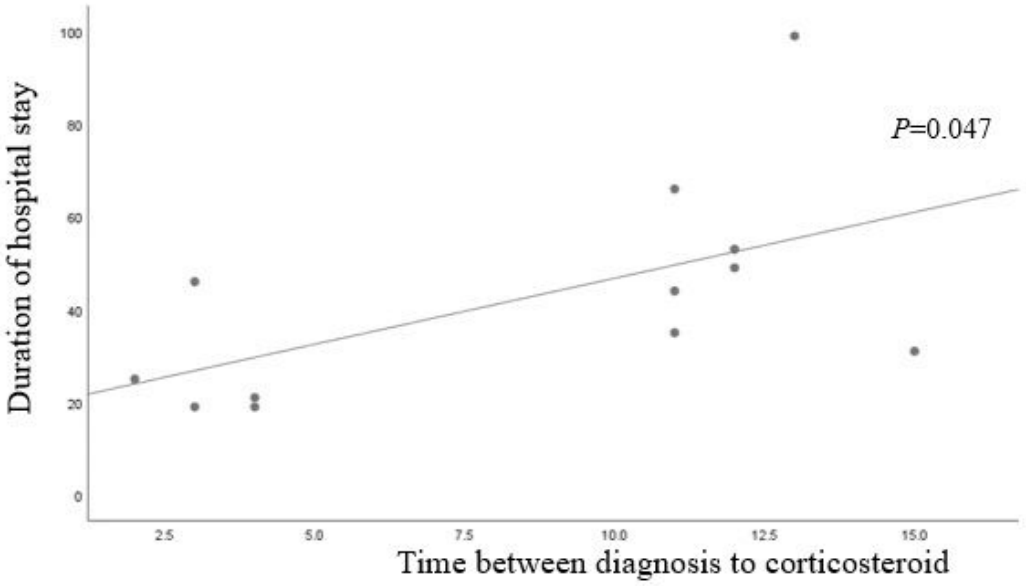

Figure 2

Correlation between time of steroid use and duration of hospital stay in the early use group.