doi • 10.5578/tt.20219811
Tuberk Toraks 2021;69(2):217-226
Geliş Tarihi/Received: 03.10.2020 • Kabul Ediliş Tarihi/Accepted: 12.04.2021

RESEARCH ARTICLE
KLİNİK ÇALIŞMA

Corticosteroid use in COVID-19 pneumonia

Özlem ERÇEN DİKEN[1] (ID)
Fatma YILDIRIM[2] (ID)
Pınar YILDIZ GÜLHAN[3] (ID)
Şevket ÖZKAYA[4] (ID)
Meltem ŞİMŞEK[5] (ID)
Cihan YÜCEL[1] (ID)
Sinem BERİK SAFCI[1] (ID)
Pelin Pınar DENİZ[1] (ID)
Müge COŞKUN ÇELİK[6] (ID)
Devrim AKDAĞ[6] (ID)
Adem DİRİCAN[7] (ID)

[1] Clinic of Chest Diseases, Health Sciences University, Adana City Training and Research Hospital, Adana, Turkey
[1] *SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Adana, Türkiye*
[2] Clinic of Chest Diseases, COVID Intensive Care Unite, Health Science University Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
[2] *Sağlık Bilimleri Üniversitesi Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, COVID Yoğun Bakım Ünitesi, Ankara, Türkiye*
[3] Department of Chest Diseases, Düzce University Faculty of Medicine, Düzce, Turkey
[3] *Düzce Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Düzce, Türkiye*
[4] Department of Chest Diseases, Bahçeşehir University Faculty of Medicine, İstanbul, Turkey
[4] *Bahçeşehir Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, İstanbul, Türkiye*
[5] Clinic of Internal Medicine, Health Science University Dışkapı Yildirim Beyazit Research and Education Hospital, COVID Intensive Care Unite, Ankara, Turkey
[5] *Sağlık Bilimleri Üniversitesi Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, COVID Yoğun Bakım Ünitesi, Ankara, Türkiye*
[6] Health Science University, Adana City Training and Research Hospital, Clinic of Anaesthesiology and Reanimation, Adana, Turkey
[6] *SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi, Anestezi ve Reanimasyon Kliniği, Adana, Türkiye*
[7] Clinic of Chest Diseases, Samsun Medikal Park Hospital, Samsun, Turkey
[7] *Samsun Medikal Park Hastanesi, Göğüs Hastalıkları Kliniği, Samsun, Türkiye*

Cite this article as: *Erçen Diken Ö, Yıldırım F, Yıldız Gülhan P, Özkaya Ş, Şimşek M, Yücel C et al. Corticosteroid use in COVID-19 pneumonia. Tuberk Toraks 2021;69(2):217-226.*

Yazışma Adresi (Address for Correspondence)

Dr. Pınar YILDIZ GÜLHAN
Düzce Üniversitesi,
Göğüs Hastalıkları Anabilim Dalı,
DÜZCE - TÜRKİYE
e-mail: pinaryildiz691@hotmail.com

ABSTRACT

Corticosteroid use in COVID-19 pneumonia

Introduction: *Coronavirus disease 2019 (COVID-19) has a 1-2% fatality rate, where no specific treatment has yet been defined. Although corticosteroids are recommended for selected COVID-19 patients without acute respiratory distress syndrome (ARDS) and septic shock, there is no consensus regarding patient subgroups, dose, and duration. In this study, it was aimed to examine the contribution of corticosteroid treatment to the management of COVID-19 pneumonia without ARDS, septic shock both in acute and recovery setting.*

Materials and Methods: *The study population was divided into two as those who used corticosteroids during the recovery phase (who did not develop sufficient radiological or clinical improvement) and those who did so during the activation phase (non-ARDS/ septic shock condition, clinical, laboratory or radiological progression).*

Results: *We identified 47 patients, 26 of which were males, and mean age was 60.5 ± 16.5 years. Seventeen patients were found to receive corticosteroids during the recovery phase and the rest (n= 30) during the activation period. After corticosteroid therapy, we found reduction of increased pre-treatment levels of D-dimer, ferritin, fibrinogen, CRP, increment of decreased pre-treatment lymphocyte count and saturation. Complete symptomatic improvement was detected in 6.9% and 17.6% of the patients in the activation phase and recovery phase, respectively. Complete radiological improvement was found in 11.5% and 35.3% of the patients in the activation phase and recovery phase, respectively. While corticosteroid treatment was initiated on day 4.2 ± 2.6 and continued for a mean of 5.9 ± 2.8 days in the activation group, it was started on day 8.1 ± 11.3 and administered for 7.8 ± 3.8 days in the recovery group. In both groups, methylprednisolone was given at a median dose of 40 mg/day.*

Conclusion: *Short-term low-dose corticosteroid therapy may improve clinical, radiological, laboratory outcomes in the management of COVID-19 pneumonia during the activation period without ARDS and non-septic shock and during recovery period with no satisfactory response. Further randomized controlled studies will be useful in demonstrating its efficacy.*

Key words: *COVID-19; methylprednisolone; corticosteroid*

ÖZ

COVID-19 pnömonisinde kortikosteroid kullanımı

Giriş: *Koronavirüs hastalığı 2019 (COVID-19), henüz spesifik bir tedavi tanımlanmayan %1-2'lik bir ölüm oranına sahiptir. Akut respiratuvar distres sendromu (ARDS) veya septik şok olmayan seçilmiş COVID-19 hastaları için kortikosteroidler önerilse de, hasta alt grupları, dozu ve süresi konusunda fikir birliği yoktur. Bu çalışmada kortikosteroid tedavisinin ARDS veya septik şok olmaksızın COVID-19 pnömoni yönetimine katkısını hem akut hem de iyileşme ortamında incelemeyi amaçladık.*

Materyal ve Metod: *Çalışma popülasyonu, iyileşme aşamasında kortikosteroid kullananlar (yeterli radyolojik veya klinik iyileşme geliştirmeyenler) ve aktivasyon döneminde (ARDS dışı/septik şok durumu, klinik, laboratuvar veya radyolojik progresyon olarak ikiye ayrıldı).*

Bulgular: *Yirmi altısı erkek ve yaş ortalaması 60,5 ± 16,5 yıl olan 47 hasta belirledik. On yedi hastanın (%36,2) iyileşme aşamasında, geri kalanının (n= 30) aktivasyon döneminde kortikosteroid aldığı tespit edildi. Kortikosteroid tedavisinden sonra, artan tedavi öncesi D-dimer, ferritin, CRP seviyelerinde azalma ve tedavi öncesi lenfosit sayısında ve satürasyonda azalma olduğunu bulduk. Aktivasyon fazında ve iyileşme fazında sırasıyla hastaların %6,9 ve %17,6'sında tam semptomatik iyileşme tespit edildi. Aktivasyon fazında ve iyileşme fazında sırasıyla hastaların %11,5 ve %35,3'ünde tam radyolojik iyileşme saptandı. Kortikosteroid tedavisine 4,2 ± 2,6 gün başlanıp aktivasyon grubunda ortalama 5,9 ± 2,8 gün devam edilirken, iyileşme grubunda 8,1 ± 11,3 gün başlandı ve 7,8 ± 3,8 gün uygulandı. Her iki grupta da metilprednizolon medyan 40 mg/gün dozunda verildi.*

Sonuç: *Kısa süreli düşük doz kortikosteroid tedavisi, ARDS ve septik olmayan şok olmayan aktivasyon döneminde ve tatmin edici yanıt alınamayan iyileşme döneminde COVID-19 pnömonisinin tedavisinde klinik, radyolojik ve laboratuvar sonuçları iyileştirebilir. Diğer randomize kontrollü çalışmalar kortikosteroidlerin etkinliğini göstermede faydalı olacaktır.*

Anahtar kelimeler: *COVID-19; metilprednizolon; kortikosteroid*

INTRODUCTION

An outbreak began in December 2019 in Wuhan, China, which was caused by a novel virus (initially 2019-nCoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1-3). Later, the name of the 2019-nCoV disease was accepted as coronavirus disease 2019 (COVID-19). In COVID-19, more than 16% of the patients have been reported to develop acute respiratory distress syndrome (ARDS) with a fatality rate of 1-2% and no specific treatment (4). The first case in our country was reported on March 11, 2020. During the COVID-19 pandemic, drugs such as hydroxychloroquine, favipiravir, remdesivir, lopinavir-ritonavir, which were shown to be safe and in vitro effective against SARS-CoV have been used in treatment. Many studies are ongoing on the efficacy and safety of these drugs in COVID-19.

Another therapeutic option in the treatment of COVID-19 may be corticosteroid treatment, for which several studies are underway; and in fact, it is used in some patient groups. Based on indirect evidence in systematic reviews in SARS-CoV-1, the guideline by Infectious Diseases Society of America (IDSA) has conditionally recommended against the use of corticosteroids in COVID-19 patients admitted to the hospital (5). It was not included in the routine treatment. In the COVID-19 guideline published by the Turkish Ministry of Health (MoH) and frequently updated by ongoing evidence in the literature, corticosteroids were initially recommended at a dose 1

mg/kg in refractory shock and ARDS patients. In our country, several centers have reported using corticosteroids on COVID-19 pneumonia apart from ARDS and refractory shock, based on clinical experience. Beside the activation phase of COVID-19 pneumonia, a rapid clinical and radiological response has also been reported when corticosteroids are initiated upon unsatisfactory clinical and radiological response in the recovery period. The timing, dosage, and effects of corticosteroid use on the course of treatment remains uncertain. Overdose or inadequate treatment may lead to non-standard approaches in clinical practice of glucocorticoids. While clinical studies on corticosteroid treatment are ongoing across the world during the pandemic, the results have started to be published (6).

In this study, we aimed to examine the contribution of corticosteroid treatment to the management of COVID-19 pneumonia without ARDS or septic shock in acute setting and in the recovery phase.

MATERIALS and METHODS

After obtaining approval from the ethics committee, we retrospectively examined medical records of patients who received corticosteroid treatment due to COVID-19 pneumonia without ARDS or septic shock between 20 March and 30 May of 2020. The patients were either RT-PCR positive or negative.

We recorded COVID-19-associated symptoms including cough, fever, and dyspnea. We analyzed relevant laboratory parameters (C-reactive protein [CRP], lymphocyte, D-dimer, ferritin, and fibrinogen) and saturation, which may be associated with the prognosis of COVID-19. We also collected data on radiological findings that may be associated with COVID-19, i.e., ground glass and consolidation (7-9).

The study population consisting of hospitalized COVID-19 pneumonia patients were divided into two as Group 1 and Group 2. Group 1 included those who were started on corticosteroids due to progression of poor prognostic clinical, radiological, or laboratory markers (CRP, ferritin, lymphocyte, D-dimer) in non-ARDS or non-septic condition (activation phase). Group 2 included the patients who were initiated on corticosteroids during the recovery phase upon unsatisfactory radiological or clinical improvement despite no clinical, radiological, or laboratory progression. Patients were administered hydroxychloroquine, favipiravir, and low-molecular-weight heparin as standardized clinical practice. Patients who were given tocilizumab, anakinra or other additional treatment during the activation period were not included in the study. The activation phase was determined as seven days from the onset of the symptom, and the recovery phase after 14 days.

We collected data on baseline clinical, laboratory, and radiological parameters as well as the timing of initiation, duration, and dose of corticosteroids. Other therapies and any adverse effects were recorded. Clinical, laboratory, and radiological responses to the treatment were also evaluated, where the laboratory assessment was based on a single value analyzed between the third and fifth day from the start of the treatment. We calculated the difference between the baseline and control values. Clinical and radiological responses were also based on the assessment recorded between the third and fifth day. Response was rated as partial, complete or none by the physician who was responsible for the follow-up of the particular patient. While clinical partial and complete responses were defined as decreased and no complaints, respectively; radiological responses were defined as partial or complete resolution in infiltration in the chest X-ray or thorax computed tomography (CT).

Statistical Analysis

Statistical evaluations were performed through the Statistical Package for the Social Sciences 22.0 software (SPSS, Chicago, IL, United States). Categorical and continuous variables were expressed as number and percentages or mean, median, standard deviation, minimum, and maximum values; where appropriate. The normality of parametric variables was analyzed via Kolmogorov-Smirnov test. The comparison between the groups were analyzed through chi-square and Mann-Whitney U test. An overall Type-I error level of 5% was used to infer statistical significance.

RESULTS

We identified 47 patients, 26 (55.3%) of which were males and the mean age was 60.5 ± 16.5 years. A positive RT-PCR test was detected in 31 (66.0%) patients. Seventeen patients (36.2%) were found to receive corticosteroids during the recovery phase (Group 2) and the rest (n= 30) during the activation period (Group 1). A total of 33 patients (70.2%) received corticosteroid treatment in the ward setting while the remaining were administered in the intensive care unit (ICU) due to active disease other than ARDS and septic shock. At the time of corticosteroid

initiation, 28 patients (59.6%) had cough, 13 (27.7%) had fever, and 31 (66.0%) had dyspnea.

Forty patients (85.1%) had bilateral involvement on thorax CT at onset of the corticosteroid treatment. The involvement was in the form of ground-glass pattern in 34 patients (72.3%) and consolidation in 28 patients (59.6%). Representative CT findings of patients with partial and complete response after corticosteroid treatment was shown in Figure 1 and Figure 2 for the activation and recovery phases.

Corticosteroid treatment was initiated on day 5.6 ± 7.8. While 40 mg/day was given to 43 patients (91.5%), other patients received 60 mg, 80 mg, 120 mg, or 250 mg (n= 1 for each). Corticosteroid treatment was continued for an average of 6.6 ± 3.3 days. Sixteen patients (34.0%) were treated for five days. The response to corticosteroid was obtained on a mean 3.6 ± 1.8 days. A total of 33 patients (70.2%) were under favipiravir treatment. Mortality occurred in only one (2.1%) case. Mean length of hospital stay after the onset of corticosteroid therapy was 8.4 ± 6.2 days.

After corticosteroid therapy, we found reduction of increased pre-treatment levels of D-dimer, ferritin, fibrinogen, CRP and increment of decreased pre-treatment lymphocyte count and saturation. The study groups did not differ in terms of the improvement in these parameters (Table 1).

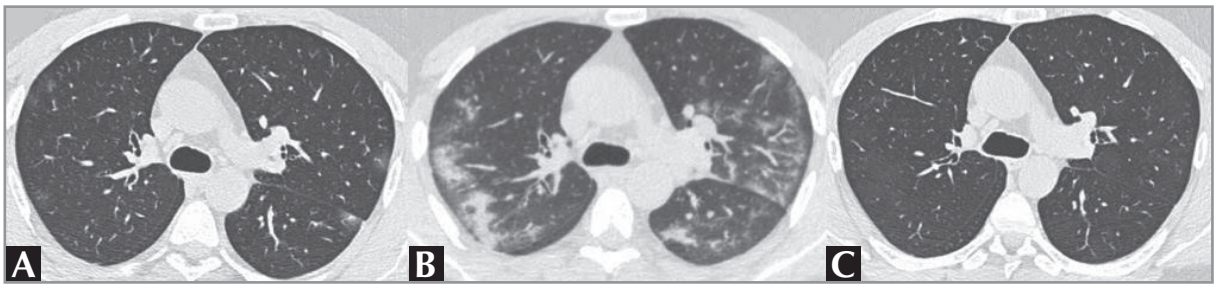

Figure 1. CT findings of patients with partial and complete response after corticosteroid treatment is shown in Figure 1 for the activation phases.

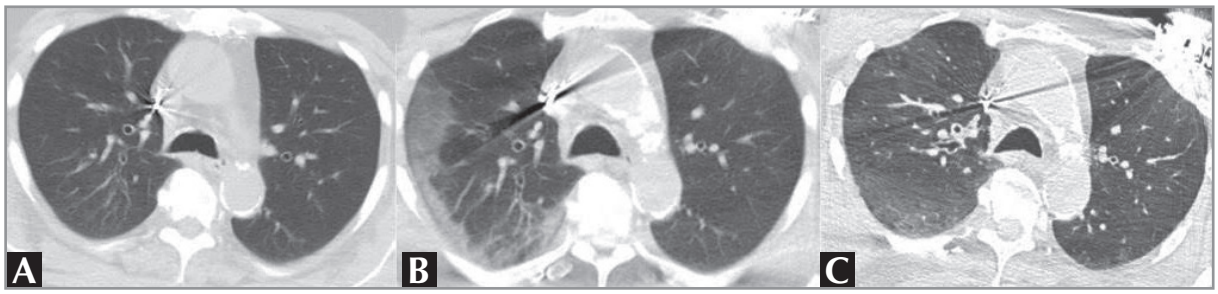

Figure 2. CT findings of patients with partial and complete response after corticosteroid treatment is shown in recovery phases.

Table 1. Laboratory values before and after steroid treatment and difference between baseline and post-treatment levels in activation and recovery time groups

			Difference between baseline and post-treatment		
	Baseline	**Control**	**Activation time**	**Recovery time**	**p***
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
D-dimer	472.74 ± 920.30	423.32 ± 506.90	-183.88 ± 539.54	141.85 ± 889.62	0.623
Lymphocyte	1100.20 ± 573.37	1288.20 ± 624.02	-288.90 ± 563.55	-21.80 ± 646.26	0.250
Ferritin	593.51 ± 814.29	513.53 ± 593.63	987.33 ± 1734.27	-220.40 ± 1004.41	0.247
Fibrinogen	533.86 ± 166.43	397.22 ± 136.96	147.64 ± 174.19	219.57 ± 131.01	0.375
CRP	99.20 ± 90.54	83.47 ± 121.11	26.18 ± 152.71	108.43 ± 154.29	0.64
Saturation	88.14 ± 6.20	94.28 ± 3.15	-6.68 ± 6.71	-5.88 ± 5.84	0.758

Group 1 which included patients in the activation phase had equal distribution of male and female patients (n= 15 for each). Mean age was 61.2 ± 17.4 years. Fifteen of the 30 patients in Group 1 (50.0%) had never smoked. More than half of the patients (53.3%) in Group 1 had comorbidities: hypertension (n= 12, 40.0%), diabetes (n= 6, 20.0%), atherosclerotic heart disease (n= 8; 26.7%), asthma (n= 1, 3.3%), and chronic obstructive pulmonary disease (COPD) (n= 3; 10.0%). Cough and fever were present in 21 patients (70.0%) and seven patients (23.3%) in Group 1, respectively. In Group 1, corticosteroid was initiated during the activation period of the disease upon dyspnea in 27 patients (90.0%) and evidence of hypoxemia in 23 patients (76.7%). In the total of Group 1 patients; corticosteroid therapy was started in 29 (96.7%) due to clinical progression, in 23 (76.7%) due to radiological progression, and in 19 (65.5%) due to progression in laboratory parameters. Ten patients (33.3%) were found to receive corticosteroids in the ICU setting.

In Group 1, one patient (3.3%) had no symptomatic improvement, two had complete improvement (6.6%) and 27 patients (90%) had partial improvement. Three patients (10.0%) had no radiological improvement on day five. For those with radiological improvement, 11.5% had complete resolution and 88.5% had partial resolution. After corticosteroid therapy, a patient had elevated procalcitonin level, which was successfully treated with piperacillin plus tazobactam. Seven patients were receiving piperacillin plus tazobactam before initiation of the corticosteroid therapy; hence, it was not considered as a secondary complication. Three patients developed hyperglycemia, which was controlled with crystallized insulin. These patients were already under oral antidiabetic drugs due to established diabetes, and did not need insulin after cessation of corticosteroid therapy. No fatal outcome was observed in Group 1. Corticosteroid treatment was initiated on mean 4.2 ± 2.6 days. Methylprednisolone was administered at a median dose of 40 mg/day for a mean of 5.9 ± 2.8 days. The mean length of hospitalization was 8.6 ± 6.4 days after the onset of corticosteroid therapy.

Male patients constituted 64.7% (n= 11) of the Group 2, i.e., those in the recovery phase. Mean age was 59.2 ± 15.1 years. Fifteen patients (88.2%) had never smoked. Ten patients (58.8%) had comorbidities: hypertension (n= 6, 35.3%), diabetes (n= 5, 29.4%), atherosclerotic heart disease (n= 3; 17.6%), asthma (n= 1, 6.3%), and COPD (n= 3; 17.6%). Corticosteroid was initiated upon dyspnea in four patients (23.5%) and evidence of hypoxemia in 10 patients (58.8%) after considering these manifestations as an unsatisfactory recovery. All 17 patients (100.0%) were detected to have radiological and clinical improvement on day five. Clinical improvement was regarded as complete in three patients (17.6%) and partial in the rest (82.4%) whereas complete radiological improvement was seen in six patients (35.3%) and partial in the remaining eleven patients (64.7%). After corticosteroid therapy, a patient was found to have elevated procalcitonin level, which was successfully treated with piperacillin + tazobactam. Six patients were detected to receive piperacillin + tazobactam before the start of the corticosteroid treatment; therefore, it was not considered as a complication of the treatment. Five patients had elevated blood glucose levels, which was controlled with crystallized insulin. These patients were already under oral antidiabetic medication due to pre-existing diabetes, and did not need insulin after corticosteroid therapy was ceased. One fatal event was found to occur in Group 2. Corticosteroid treatment was initiated on day 8.1 ± 11.3. Methylprednisolone was administered at a median dose of 40 mg/day for a mean of 7.8 ± 3.8 days. The mean length of hospitalization was 8.2 ± 5.9 days after the onset of corticosteroid therapy.

DISCUSSION

In our study, it was seen that most of our patients were started on corticosteroids upon radiological or clinical progression. The therapy was administered to the rest due to insufficient improvement in the recovery period. We observed improvement in laboratory values and saturation parameters of the patients who were initiated corticosteroids. Corticosteroid treatment was associated with both improved clinical, laboratory, and saturation parameters and radiological response. Corticosteroids were started in the group that did not respond to other standard treatments, so the response was attributed to corticosteroid treatment, rather than other therapies.

Corticosteroid treatment was started on an average of 5.6 ± 7.8 days. We saw that physicians preferred corticosteroids in the group that did not receive radiological and clinical responses before corticosteroid therapy was included in the Turkish MoH guidelines. Corticosteroid was included to the guideline

for the management of patients with severe pneumonia on the updated version of August 2, 2020. Afterwards, we started to use corticosteroids for our patients if they had severe pneumonia. Further studies will reveal the clinical effect and adverse effect profile. In our study, no serious adverse effects were observed in patients receiving corticosteroids. The patients who developed hyperglycemia were intervened with short-acting insulin therapy. No uncontrolled side effects were observed. This might be explained by short-duration and low-dose of administered corticosteroids; therefore, care should be taken in long-term treatments. Corticosteroid treatment was given to the patients at a dose of 40 mg/day to most of the patients for 5.9 ± 2.8 days during the activation period and for 7.8 ± 3.8 days during the recovery period.

Studies specifically investigating the role of corticosteroids in the treatment of acute COVID-19 are limited. They have been used frequently in China for patients with COVID-19 pneumonia to prevent the development of ARDS (10-13). A systematic review has reported 15 studies, 13 of which concluded no benefit with corticosteroid use (14). One randomized controlled trial (RCT) has reported delayed viral clearance of SARS-CoV-1 viral load with corticosteroid use. The same review has also been reported in a subgroup of ARDS patients. One small RCT of 24 patients using low-dose methylprednisolone for two days has reported possible improvement in ARDS. However, two large-sized studies have shown little or no effect in critically ill patients with respiratory failure. The authors have concluded that despite the widespread use of corticosteroids during the SARS pandemic, there was no clear evidence of benefit and that administration of corticosteroids early in the disease process might have delayed viral clearance before viral replication was controlled. IDSA Committee has considered the certainty of direct evidence as very low due to potential bias, inconsistency, and lack of information. The committee has conditionally recommended against the use of corticosteroids in patients admitted to the hospital based on indirect evidence from systematic reviews in SARS-CoV (5).

COVID-19 pneumonia can be seen in different degrees of severity, from mild pneumonia to critical illness. It can be severe especially in those with underlying diseases and in advanced ages. The Turkish MoH guideline included treatment recommendations based on the severity of the disease. The recommendation on the beginning of the outbreak was to administer corticosteroids at 0.5-1.0 mg/kg dose in cases with ARDS or resistant shock.

Most cases of COVID-19 are asymptomatic or have mild illness. However, a substantial number of patients develop respiratory disease that needs hospitalization. The disease may progress into critical illness requiring prolonged mechanical ventilation (15,16).

Its pathophysiological features from autopsy studies include diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis (17). Although improvement with corticosteroid therapy has been shown in COVID-19 patients by some studies (18, 19), the efficacy of corticosteroids in COVID-19 has not been established yet. The RECOVERY study has suggested use of 6 mg/day up to 10 days in COVID-19 patients requiring respiratory support, with no claim regarding its effect in the patients without respiratory failure (6). In our study, the effect of corticosteroids on patients in the recovery period without respiratory failure was also examined. We observed improvement in laboratory, radiological, and clinical findings in most patients. No serious side effects were observed. Owing to its anti-inflammatory activity, corticosteroids may be reasonable in patients whose recovery period feature unsatisfactory clinical, radiological, or laboratory improvement. For avoiding side effects, it should be administered at minimal effective dose with shortest duration. In our study, the median dose was 40 mg methylprednisolone given for less than 10 days. In patients with mild hypoxemia or who develop clinical, radiological, or laboratory progression, we also detected improvement in these parameters upon initiation of corticosteroids in a short period of time.

Preliminary findings from the RECOVERY trial have reported reduced 28-day mortality and length of hospital stay with 6 mg/day dexamethasone up to 10 days plus respiratory support with invasive mechanical ventilation or oxygen treatment, compared to the standard treatment in COVID-19 patients. The benefit of dexamethasone could not be demonstrated in the group without respiratory failure. It was reported to be beneficial when inflammatory lung injury begins seven days after symptom onset. Physiological, laboratory, and virological data were not collected in the RECOVERY study (6). In our study, corticosteroid was

also administered to the group that did not need respiratory support, where we also observed improvement in laboratory parameters.

Low-dose corticosteroids can restore oxygenation and reverse lung tissue injury with their immunosuppressive effects (20). In the most updated version of the guideline by Turkish MoH, a recommendation for dexamethasone 6 mg/day was included for cases with severe pneumonia (21). In our study, methylprednisolone treatment was mostly administered at a dose of 40 mg/day.

To our knowledge, there was no study that reported the effect of corticosteroid use in the recovery phase of COVID-19 pneumonia on overall improvement. The radiological findings of COVID-19 pneumonia are similar to those of many other diseases that cause organized pneumonia. The types and extent of radiological findings vary according to the stage of infection. The dominant finding of organized pneumonia in the radiological findings of COVID-19 is the presence of ground-glass appearance (22). This is followed by mixed ground-glass opacity and consolidation with lower lobe and peripheral distribution. In addition, ground-glass opacity observed in the first week gradually transforms into ground-glass and consolidation in the second week, and increased linear opacities in the third week. These findings are similar to the publications reporting radiological progression by the second week and radiological improvement after the second week (23,24). Histopathologically, early and advanced stage is characterized by injured alveolar epithelium and leaked and coagulated inflammatory component, fibrin deposition, and matrix, followed by gradual recession and resorption in the late disease course (25); which may explain the primary CT findings in organized pneumonia pattern.

Pathological examinations of pulmonary tissues in COVID-19 reveal interstitial mononuclear inflammatory infiltration with predominance of lymphocytes. Cytokines play an important role in pathophysiology and clinical findings. Inflammatory response caused by excessive cytokine release observed with T-cell and monocyte/macrophage activation increases vascular permeability and leads to exudative fluid accumulation in the alveoli, causing respiratory failure. Cytokine storm is a condition that requires urgent treatment, which should be diagnosed and treated early. It was also recommended to be treated by our national guideline, under the definition of macrophage activation syndrome (MAS). Cytokine inhibitors such as tocilizumab and other treatment options are recommended in MAS. While corticosteroids are recommended in cases with ARDS and resistant shock, there is no sufficient data regarding their use in the recovery period in the absence of MAS; and therefore, not recommended for this indication (21). In our study, instead of the very high values of ferritin, D-dimer, and CRP values that we experienced in MAS during the activation period, we preferred corticosteroids in patients with moderate elevation of these parameters when we did not give tocilizumab. In patients where we started corticosteroids during activation, the improvement was mostly partial both in radiological and clinical aspects.

Several investigators have observed and recently reported the effect of corticosteroid use in the recovery period of influenza A (H7N9) virus infection (26,27). We experienced the use of corticosteroids during the recovery period in COVID-19 pneumonia in some centers in our country. Patients benefited from low-dose corticosteroid therapy in the recovery period when they had exertional dyspnea, or failed to return pre-existing saturation level, or had incomplete radiological resolution. Symptom relief, improved saturation, and radiological response were achieved in a short time in this patient group.

Abnormal tissue repair is seen during the recovery period of pulmonary infections. If left untreated with on time corticosteroids, the pathological appearance of the organizing pneumonia may progress into interstitial pulmonary fibrosis. During the recovery period, the immune response in the tissue enters into the inflammatory repair phase.

It remains unelucidated whether the use of corticosteroids has a beneficial effect in patients with prolonged pulmonary inflammation and persistent radiological shadows. These cases are mostly treated with antibiotics with suspected secondary bacterial infection. In fact, it might be consistent with the clinical and radiological findings of the abnormal tissue repair that may be seen as organizing pneumonia pathologically and could be treated with corticosteroids.

Lung tissue repair after viral infections may accompany abnormal type 2 immune response. Th2 that promotes the chemotaxis of neutrophils form the cytokine environment and M2-type macrophage activation. Transforming growth factor-b, epidermal growth

factor-2, and fibroblast growth factor-2 facilitate the transformation of epithelial cells into mesenchymal cells through cytokine release such as neutrophils and macrophages and activate fibroblasts. A significant amount of collagen fibers becomes deposited and eventually leads to a fibrosis (28,29). This mechanism is consistent with evidences from clinical trials. While the underlying mechanism of abnormal tissue repair in the influenza virus is unclear, there is not sufficient information about this mechanism in COVID-19 yet due to more recent experience. However, our clinical observation in the follow-up of patients with COVID-19 pneumonia implies the lack of complete radiological improvement, which may manifest itself as exertional dyspnea and mostly low saturation values. Although it has not been yet observed whether the patients recover with fibrosis in long-term, we are concerned that the healing process involve fibrosis with a consequent permanent effort dyspnea and deteriorated quality of life, even requiring long-term oxygen therapy. Anecdotal evidences so far indicate such concern that many clinicians may prefer use of corticosteroids upon unsatisfactory radiological or clinical improvement during recovery period.

A systematic review has investigated 73 studies and 21350 COVID-19 patients (40% severely ill, 51.3% intensive care unit and 35.3% was mechanically ventilated patients) and has shown that corticosteroids have beneficial effects and reduces mortality in severely ill COVID-19 patients (30).

Bartoletti et al. have indicated that corticosteroid treatment might not be associated with a lower mortality rate, but when they investigated only patients with PaO_2/FiO_2 <200 mmHg, they observed lower mortality (31).

In a randomized controlled study using methylprednisolone for short time period (0.5 mg per kg for five days) on COVID-19 patients under invasive mechanical ventilation treatment has found that methylprednisolone does not reduce mortality. However, in this study, methylprednisolone was used for a short time period and opposite to our study, they included only patients under invasive mechanical ventilation (32).

Papamanoli et al. have investigated 447 patients with severe COVID-19 pneumonia (patients on high - flow oxygen; FiO_2 ≥50%). Patients who received an average of 160 mg methylprednisolone and those who did not receive corticosteroids were compared. As a result, they stated that corticosteroids reduce the need for mechanical ventilation and use less intensive care resources without more complications (33).

The timing, dosage, and course of treatment with corticosteroids are not clear in the recovery period after viral pneumonia. Excessive or inadequate treatment may result in non-standard approaches with respect to corticosteroid use in clinical practice. During the recovery period, our patients received corticosteroids at a median dose of 40 mg/day for an average of less than 10 days, where no serious adverse effects were detected.

We experienced the use of corticosteroids during the recovery period in COVID-19 pneumonia and also in cases where disease activation occurred other than in the form of ARDS or septic shock. The limitations of our study include its retrospective nature and non-RCT design. We believe that this study, being a retrospective preliminary analysis, may serve a base for further prospective RCTs.

In our study, short-term, low-dose corticosteroid therapy contributed to the discharge of patients with COVID-19 pneumonia in a short time without serious side effects. Early initiation of corticosteroid therapy provided clinical, radiological, and laboratory improvement in patients who had no response for these parameters in the active disease state of COVID-19. We also suggest short-term use of low-dose corticosteroids in patients who did not respond adequately during the recovery period. RCTs will provide more convincing results about efficacy and safety. Short-term and low-dose corticosteroid therapy should be considered in patients with COVID-19 pneumonia.

Ethical Committee Approval: The study was approved by both the Ministry of Health and the Local Ethics Committee (Adana City Hospital Local Ethic Committee approval document dated 03.06.2020 and numbered 901).

CONFLICT of INTEREST

The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ÖED, FY, PYG, ŞÖ, MŞ

Analysis/Interpretation: ÖED, FY, PYG, ŞÖ, MŞ

Data Acqusition: All of authors

Writing: ÖED, FY, PYG, ŞÖ

Clinical Revision: All of authors

Final Approval: All of authors

REFERENCES

1. *Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229): 1054-62.*
2. *Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. Infection. 2020; 48(2): 155-63.*
3. *Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 2020; 323(13): 1239-42.*
4. *Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing) 2020; 6(10): 1192-8.*
5. *Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis 2020: ciaa478.*
6. *Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19 - Preliminary Report. N Engl J Med 2021; 384(8): 693-704.*
7. *Zeng F, Li L, Zeng J, Deng Y, Huang H, Chen B, et al. Can we predict the severity of coronavirus disease 2019 with a routine blood test? Pol Arch Intern Med 2020; 130(5): 400-6*
8. *Ferrari D, Motta A, Strollo M, Banfi G, Locatelli M. Routine blood tests as a potential diagnostic tool for COVID-19. Clin Chem Lab Med 2020; 58(7): 1095-9.*
9. *Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol 2020; 30(8): 4381-9.*
10. *Wang Y, Jiang W, He Q, Wang C, Liu B, Zhou P, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv 2020.*
11. *Liu Y, Sun W, Li J, Chen L, Wang Y, Zhang L, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv 2020.*
12. *Sun F, Kou H, Wang S, Yun L, Houyu Z, Wenjing L, et al. Medication patterns and disease progression among 165 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective, observational study. Ann Transl Med 2020; 9(4): 306.*
13. *Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; 180(7): 934-43.*
14. *Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006; 3(9): e343.*
15. *Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054-62.*
16. *Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020; 71(15): 748-55.*
17. *Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 2020; 20(10): 1135-40.*
18. *Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C. GLUCOCOVID investigators. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). Wien Klin Wochenschr 2021; 133(7-8): 303-11.*
19. *Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020; 43(3): 183-4.*
20. *Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D; Lille COVID-19 ICU and Anatomopathology Group. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. Intensive Care Med 2020; 46(6): 1124-6.*
21. *Rebuplic of Turkey Ministry of Health. COVID-19 Interim Guidance (T.C. Sağlık Bakanlığı COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi) 2020. Available from: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf?type=file*
22. *Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-NCoV). Radiology 2020; 295(1): 202-7.*
23. *Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; 20(4): 425-34.*
24. *Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on Chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 2020:200370.*
25. *Roberton BJ, Hansell DM. Organizing pneumonia: a kaleidoscope of concepts and morphologies. Eur Radiol 2011; 21(11): 2244-54.*
26. *Liu H, Li J, Chen M, Su J. Glucocorticoid treatment of suspected organizing pneumonia after H7N9 infection: a case report. Medicine (Baltimore) 2019; 98(34): e16839.*
27. *He H, Wang H, Li X, Tang X, Sun B, Tong Z. Successful management of refractory respiratory failure caused by avian influenza H7N9 and secondary organizing pneumonia: a case report and literature review. BMC Infect Dis 2019; 19(1): 671.*

28. *Yoo JK, Kim TS, Hufford MM, Braciale TJ. Viral infection of the lung: host response and sequelae. J Allergy Clin Immunol 2013; 132(6): 1263-76.*

29. *Meneghin A, Hogaboam CM. Infectious disease, the innate immune response, and fibrosis. J Clin Invest 2007; 117: 530-8.*

30. *Cano EJ, Fonseca Fuentes X, Corsini Campioli C, O'Horo JC, Abu Saleh O, Odeyemi Y et al. Impact of corticosteroids in coronavirus disease 2019 outcomes: systematic review and meta-analysis. Chest. 2021; 159(3): 1019-40.*

31. *Bartoletti M, Marconi L, Scudeller L, Pancaldi L, Tedeschi S, Giannella M, et al; PREDICO Study Group. Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicentre study. Clin Microbiol Infect 2021; 27(1): 105-11.*

32. *Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2021; 72(9): e373-e381.*

33. *Papamanoli A, Yoo J, Grewal P, Predun W, Hotelling J, Jacob R, et al. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. Eur J Clin Invest 2021; 51(2): e13458*