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Corticosteroid Therapy Duration and Dosage According to the Timing of Treatment Initiation for Post-COVID-19 Organizing Pneumonia

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COVID-19 can lead to pulmonary complications, including organizing pneumonia. Steroids are essential in treating post-COVID-19 organizing pneumonia. However, research on the clinical benefits of initiating steroid treatment early for this condition is limited. To investigate the steroid initiation time in its association with treatment duration and corticosteroid dose for treating post-COVID-19 organizing pneumonia, we analyzed the data of 91 patients with post-COVID-19 organizing pneumonia at Chonnam National University Hospital between October 2020 and December 2022. Patients were categorized into early and late groups based on time from COVID-19 diagnosis to steroid initiation time for organizing pneumonia. The mean time interval between COVID-19 infection and steroid initiation time for treating organizing pneumonia, was 18.4±8.6 days. Within the early treatment group (treatment initiated $<$ 18.4 days after COVID-19), which included 55 patients, the mean duration of steroid treatment was 43.1±18.3days. In contrast, the late treatment group (initiated $\geq$18.4 days after COVID-19), which consisted of 36 patients, had a longer mean duration of steroid treatment 59.1±22.6 days) ($p < 0.01$). Regarding corticosteroid dosing, the early treatment group had an average dosage of 0.5±0.3 mg/kg/day, in contrast to the late group, which averaged 0.8±0.3 mg/kg/day ($p < 0.01$). Regression analysis showed steroid initiation time significantly influenced treatment duration (β=0.80 , $p < 0.01$) and dosage (β=0.03, $p < 0.01$). The clinical benefits of early steroid treatment for post-COVID-19 organizing pneumonia may lie in its association with reduced steroid treatment duration and dosage.

Key Words: *Post-COVID-19 Organizing Pneumonia; Corticosteroid Therapy; Early Therapeutic Initiation*

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INTRODUCTION

The COVID-19 pandemic has resulted in a wide range of pulmonary complications, including acute respiratory distress syndrome (ARDS) caused by COVID-19 pneumonia and pulmonary fibrosis.[1-3] Notably, in the post-COVID-19 state, which refers to the phase following COVID-19 infection and extends beyond the viral, pulmonary, and hyperinflammatory phases of COVID-19 pneumonia, an organizing pattern of interstitial lung disease (ILD)—known as organizing pneumonia—is frequently observed.[2]

Organizing pneumonia is a form of ILD characterized by radiological findings of consolidation and ground-glass opacity (GGO) predominantly distributed in subpleural areas or bilaterally in the bronchovascular bundle. Additional findings, such as the reverse halo sign or perilobular interlobular septal thickening (known as the arcade sign), may be present.[4]

The increasing incidence of organizing pneumonia in the

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post-COVID-19 state has drawn global attention, with some referring to it as a "hidden pandemic." According to World Health Organization estimates, as of October 2022, there are over 17 million cases of persistent post-COVID-19 symptoms in Europe alone, emphasizing the severity of post-COVID-19 organizing pneumonia.[5]

Patients with post-COVID-19 organizing pneumonia may present with respiratory symptoms, such as dyspnea, chest pain, and dry cough. The severity of symptoms varies, with severe cases requiring high levels of oxygen support.[6,7] While spontaneous resolution is common, empirical administration of corticosteroids is recommended for severe cases or when there is an oxygen demand.[8] Numerous studies have demonstrated a favorable response to empirical corticosteroid treatment, supported by the correlation between radiological and pathological findings of post-COVID-19 organizing pneumonia.[9-14]

However, early detection and management of organizing pneumonia are crucial, as it can progress to long-term lung fibrosis in the post-COVID-19 state.[15] A study investigating ILD with an organizing pattern developing after COVID-19 revealed a statistically significant progression from organization to consolidation in GGOs within the first 2 weeks. Fibrosis was observed to develop subsequently, resulting in increased linear opacity.[16] Therefore, given the nature of the disease, early detection and management of the disease are likely to improve outcomes. However, research on early detection and treatment in clinical settings has been limited in Korea. There has been a lack of research about the clinical benefits of the early initiation of steroids for post-COVID-19 organizing pneumonia.

Therefore, we investigated whether the detection time of post-COVID organizing pneumonia and the initiation time of steroid treatment are associated with the treatment duration and required corticosteroid dose for post-COVID organizing pneumonia.

MATERIALS AND METHODS

1. Data collection

This retrospective study was conducted at Chonnam National University Hospital from October 2020 through December 2022. We initially reviewed the medical records of patients aged 18 years or older who visited the hospital during this period if they met the following criteria: (1) had ongoing respiratory symptoms more than 2 weeks after being diagnosed with COVID-19 (confirmed by either rapid antigen testing or polymerase chain reaction [PCR] analysis) and (2) showed evidence of organizing pneumonia on the initial chest computed tomography (CT) scan and (3) required hospitalization to initiate steroid treatment for organizing pneumonia to control symptoms.

Then, the following patients were excluded to ensure only the inclusion of patients with unequivocal, isolated organizing pneumonia and to verify the long-term outcomes of steroid treatment: (1) those with evidence of significant pulmonary infection, including symptoms, such as fever and purulent sputum, as well as positive results on tests related to infectious pneumonia (e.g., pneumococcal urine antigen test, Gram stain and culture of sputum, respiratory viral PCR, pneumobacter PCR, procalcitonin level of 0.5 ng/mL or higher,[17] or definitive CT findings indicating bacterial pneumonia [e.g., consolidation in the dependent portion or unilateral consolidation]); (2) those with pulmonary edema based on imaging findings; (3) those with coexisting serious medical (e.g., acute myocardial infarction, severe trauma, acute stroke, etc.) conditions requiring oxygen supplementation due to causes other than organizing pneumonia, making it difficult to determine the specific effects of steroids; (4) patients who did not undergo follow-up for $\geq$4 weeks.

The diagnosis of radiographic organizing pneumonia was confirmed by experienced two radiologists with extensive experience in thoracic imaging. They reviewed and described CT findings based on the presence of the following distinctive features: consolidation with subpleural or peribronchial involvement, mid to lower lung zone predominance, perilobular opacities (arcade-like or polygonal shapes with poorly defined borders around secondary pulmonary lobules), opacities showing migration or spontaneous regression, GGO (typically bilateral and patchy), reverse halo sign (GGO surrounded by a crescent or ring of consolidative parenchyma), parenchymal bands (often associated with multifocal consolidation), or reticular opacities with basilar predominance and architectural distortion.[18] These CT findings were classified into categories, such as GGO, consolidation, linear opacity, or mixed categories, and the number of involved lobes was counted to provide a broad classification of organization.[16]

Particularly, to determine the presence or absence of pre-existing underlying ILD, baseline CT scans were obtained and utilized for assessment. In cases where baseline CT scans were not available, the evaluation of the existence of pre-existing ILD was conducted by comparing follow-up CT scans, performed after clinical improvement, with the initial CT scans. This comparison involved an assessment of any remnant lesions to ascertain the presence or absence of underlying ILD.

Additionally, we collected demographic data about these patients, including information about underlying medical conditions, CT findings, prior history of COVID-19 treatment, initial laboratory results, and the SpO2/FiO2 ratio.

2. Data analysis and outcome

We classified patients into either the early or late treatment group based on the mean duration from COVID-19 diagnosis to the initiation of treatment for post-COVID-19 organizing pneumonia. We classified patients into the early treatment group if their intervals were shorter than the mean and into the late treatment group if their intervals exceeded the mean.

The primary outcome measure focused on the time interval from diagnosis and steroid therapy initiation for post-COVID-19 organizing pneumonia to the point of discontinuation during outpatient follow-up. We used this

metric to explore the relationship between the time from post-COVID-19 organizing pneumonia diagnosis to the discontinuation of steroid treatment (Fig. 1). In cases of underlying conditions like adrenal insufficiency requiring baseline steroid doses, cessation was based on reaching a stable physiological threshold.

The secondary outcome aimed to analyze the relationship between the interval from COVID-19 diagnosis and treatment initiation for symptoms associated with post-COVID-19 organizing pneumonia, and the required dosage of steroids during hospitalization (Fig. 1). Steroid requirements during hospitalization were quantified using the following formula:

Steroid requirement during hospitalization
=Total steroid dose/hospitalized days/body weight (mg/kg/days)

This formula was used to determine the mean daily steroid dose per kg of body weight based on the total steroid dose administered during hospitalization and the number of days of administration. Steroid doses were evaluated as equivalent doses of methylprednisolone.

We conducted chi-square analysis to compare non-discrete variables between the two groups. Independent t-tests were used to analyze continuous variables, such as steroid duration and steroid requirement. Statistical significance was indicated by p-values <0.05. Furthermore, to assess the linear relationship between the timing of post-COVID-19 organizing pneumonia treatment and outcomes, we conducted linear regression analysis, considering p-values <0.05 as statistically significant. All analyses were performed using SPSS (Statistical Package for the Social Sciences) Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA).

The study was approved by the Institutional Review Board of Chonnam National University Hospital (IRB No. CNUH-2023-175) and was performed in accordance with the principles of the Declaration of Helsinki.

RESULTS

1. Population

A total of 1,325 patients met the initial screening criteria during the study period spanning from October 2020 through December 2022. However, 1,234 patients were excluded from the analysis due to the presence of bacterial infection, critical medical conditions, or alternative causes of hypoxemia, such as pulmonary edema. Finally, 91 patients were included in the analysis.

2. Baseline characteristics

Among the 91 patients with post-COVID-19 organizing pneumonia, the mean interval from COVID-19 diagnosis to the first hospital visit for steroid treatment was 18.4±8.6 days. With this mean interval as a criterion, patients were categorized into the early treatment group (those with intervals equal to or less than the mean interval from COVID-19 diagnosis to treatment initiation, i.e., <18.4 days) and the late treatment group (those with intervals equal to or greater than the mean interval from COVID-19 diagnosis to treatment initiation, i.e., ≥ 18.4 days), with 55 and 36 individuals, respectively.

The mean patient age was 69.5±13.8 years. The early treatment group had a mean age of 68.9±14.1 years, while the late treatment group had a mean age of 70.6±13.3 years (p=0.57). Furthermore, there were no statistically significant differences between the two groups concerning other factors, such as sex and comorbidities (Table 1).

CT findings at the first treatment visit demonstrated that the early treatment group had a higher propensity for pure GGOs, with 25 cases (44.6%), compared with 6 cases (17.1%) in the late group. Conversely, the late treatment group exhibited relative progression of organization, with 24 patients (68.6%) presenting with mixed findings of consolidation and linear opacities, compared with 17 patients (30.4%) in the early treatment group (p=0.01). Furthermore, there was a higher proportion of patients in the early treatment group exhibiting organization involving up to three lobes, with 16 patients (28.6%) in this category, compared with 4 patients (11.4%) in the late treatment group. Although not statistically significant, the late treatment group showed a trend with a higher proportion of patients having extensive organization across more than three lobes, with 31 patients (88.6%), compared to 40 patients (71.4%) in the early treatment group (p=0.06) (Table 1). Additionally, an analysis of the SpO2/FiO2 ratios (indica-

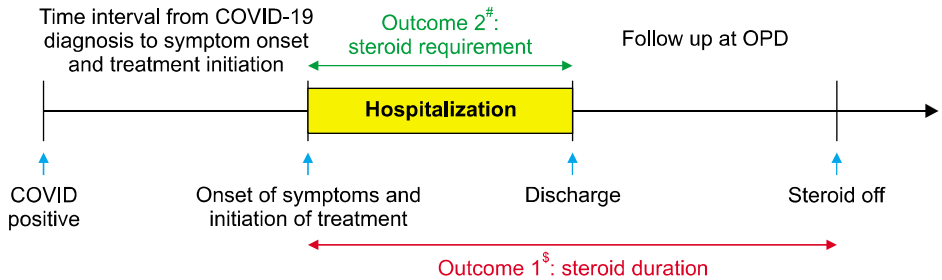

FIG. 1. Timeline of diagnosis, inpatient treatment, and post-discharge follow-up for patients with post-COVID organizing pneumonia. Outcome 1$^{\$}$: time interval from diagnosis and steroid therapy initiation for post-COVID-19 organizing pneumonia to the point of discontinuation during outpatient follow-up (days). Outcome 2$^{\#}$: Steroid requirement, required dosage of steroids during hospitalization (mg/kg/day). OPD: OutPatient Department.

Table 1. Baseline characteristics comparison between the early treatment group and the late treatment group

Variables	Total (n=91)	Early treatment group (n=55)	Late treatment group (n=36)	p-value
Median age (year)	69.5±13.8	68.9±14.1	70.6±13.3	0.57
Male, n (%)	59 (64.8)	35 (62.5)	24 (68.6)	0.56
Comorbidity				
HTN, n/N (%)	32 (35.2)	17 (30.4)	15 (42.9)	0.22
DM, n/N (%)	20 (22.0)	14 (25.0)	6 (17.1)	0.38
DL, n/N (%)	8 (8.8)	5 (8.9)	3 (8.6)	0.95
Chronic kidney disease, n/N (%)	10 (11.0)	7 (12.5)	3 (8.6)	0.56
Liver disease, n/N (%)	8 (8.8)	4 (7.1)	4 (11.4)	0.48
Pulmonary disease, n/N (%)	18 (19.8)	10 (17.9)	8 (22.9)	0.56
COPD, n/N (%)	10 (11.0)	7 (12.5)	3 (8.6)	0.56
ILD, n/N (%)	5 (5.5)	2 (3.6)	3 (8.6)	0.31
Asthma, n/N (%)	2 (2.2)	1 (1.8)	1 (2.9)	0.73
Pulmonary infection[a], n/N (%)	4 (4.4)	1 (1.8)	3 (8.6)	0.12
Etc.[b], n/N (%)	2 (2.20)	1 (1.8)	1 (2.9)	0.73
Recent infection[c], n/N (%)	4 (4.4)	2 (3.6)	2 (5.7)	0.63
Cardiovascular, n/N (%)	15 (16.5)	10 (17.9)	5 (14.3)	0.66
Cerebrovascular, n/N (%)	9 (9.9)	5 (8.9)	4 (11.4)	0.70
Neuroendocrine[d], n/N (%)	6 (6.6)	3 (5.4)	3 (8.6)	0.55
Malignancy, n/N (%)	34 (37.4)	22 (33.9)	12 (34.3)	0.63
Immunosuppressant[e], n/N (%)	31 (34.1)	23 (41.1)	8 (22.9)	0.12
Computed tomography				
Finding				*0.01
Pure GGO, n/N (%)	31 (34.1)	25 (44.6)	6 (17.1)	
GGO and Consolidation, n/N (%)	2 (2.2)	1 (1.8)	1 (2.9)	
Pure Consolidation, n/N (%)	1 (1.1)	1 (1.8)	0 (0.0)	
GGO and Linear opacity, n/N (%)	5 (5.5)	5 (8.9)	0 (0.0)	
With three Sign[f], n/N (%)	9 (9.9)	5 (8.9)	4 (11.4)	
Pure linear opacity, n/N (%)	2 (2.2)	2 (3.6)	0 (0.0)	
Consolidation and Linear opacity, n/N (%)	41 (45.1)	17 (30.4)	24 (68.6)	
Involvement of lung lobes				0.06
N≤3, n/N (%)	20 (22.0)	16 (28.6)	4 (11.4)	
N>3, n/N (%)	71 (78.0)	40 (71.4)	31 (88.6)	
COVID-19 management				
Isolation, n/N (%)	25 (27.4)	30 (54.55)	20 (55.56)	0.91
Antiviral agent[g], n/N (%)	53 (58.2)	34 (60.7)	19 (54.3)	0.55
Dexamethasone, n/N (%)	11 (12.1)	5 (8.9)	6 (17.1)	0.24
Initial parameters				
Time of Initiating steroid treatment (days)[h]	18.4±8.6	14.7±0.7	24.4±11.5	**<0.01
SpO2/FiO2	314.1±137.1	342.4±139.5	268.8±121.8	*0.01
WBC (WBCs/μL)	9359.3±6681.0	8758.9±6125.4	10320.0±7477.5	0.28
CRP (mg/dL)	8.6±7.9	9.9±8.9	6.6±5.4	0.05
KL-6 (U/mL)	725.3±510.1	619.3±404.5	837.5±594.3	0.21

HTN: hypertension, DM: diabetes mellitus, DL: dyslipidemia, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, SpO2: saturation pulse oxygen, FiO2: fraction of inspired oxygen, WBC: white blood cells, CRP: C- reactive protein, KL-6: Krebs von den Lungen-6, GGO: Ground Glass Opacity. [a]Pulmonary infection was defined as any respiratory infection, excluding recent COVID infection within the 3 months. [b]This refers to cases with structural lung issues like bronchiectasis and pneumoconiosis, which are not classified according to diagnostic criteria. [c]Presence of a non-respiratory infection history within the last month. [d]This includes endocrine disorders related to thyroid function abnormalities and dysfunctions in the Hypothalamic-Pituitary-Adrenal Axis or other endocrine hormone irregularities, excluding diabetes. [e]history of using immunosuppressive agents for the treatment of cancer or autoimmune diseases. [f]GGO, consolidation and linear opacity. [g]Antiviral medications such as Remdesivir, Molnupiravir, Nirmatrelvir/Ritonavir, and others used for the treatment of COVID-19. [h]The interval time from COVID-19 diagnosis to the first hospital visit for steroid treatment due to symptoms. *$p<0.05$, **$p<0.01$.

tive of oxygen demand) at initial presentation revealed that these ratios were significantly higher in the early treatment group compared to the late treatment group (342.4±139.5 vs. 268.8±121.8, p=0.01) (Table 1).

3. Outcomes

For the treatment of post-COVID-19 pneumonia, the mean duration of hospitalization was 13.0±8.4 days (13.2±9.4 in the early treatment group vs. 13.0±6.7 days in the late treatment group, p=0.97).

For outcome1, the mean duration of steroid maintenance was 49.4±21.5 days (43.1±18.3 and 59.1±22.6 days in the early and late treatment groups, respectively, $p < 0.01$) (Table 2).

Simple linear regression analysis showed that underlying ILD (p=0.03), neuroendocrine disease (p=0.02), and malignancy ($p < 0.01$) were significantly associated with longer durations of steroid treatment. Additionally, the use of antiviral agents during COVID-19 treatment correlated with shorter durations of steroid therapy ($p < 0.01$). The analysis also found that increased degrees of organization ($p < 0.01$) and extent ($p < 0.01$) seen on CT scans, as well as elevated KL-6 levels (p=0.01), led to longer steroid treatment periods. Furthermore, low SpO2/FiO2 at presentation ($p < 0.01$) and delayed diagnosis and treatment of post-COVID-19 organizing pneumonia ($p < 0.01$) were associated with extended steroid therapy durations, as shown in the linear graph (Fig. 2A).

Multiple regression analysis revealed that the time of diagnosis and treatment of post-COVID-19 organizing pneumonia (β=0.16, $p < 0.01$) as well as the SpO2/FiO2 ratio at presentation (β=−0.45, $p < 0.01$) significantly influenced the duration of steroid treatment (adjusted R square= 0.58). The analysis indicated a linear relationship between these variables and the duration of steroid treatment in patients with post-COVID-19 organizing pneumonia (Supplementary Table 1).

Regarding the secondary outcome, the overall mean steroid dose was 0.6±0.3 mg/kg/day (0.5±0.3 and 0.8±0.3 mg/kg/day in the early and late treatment groups, respectively, $p < 0.01$) (Table 2).

Single regression analysis showed a significant linear relationship between various independent variables and steroid requirements. Patients with ILD (p=0.01) and history of cerebrovascular disease ($p < 0.05$), more extensive organization ($p < 0.01$), and greater extent on CT scans (p=0.01), as well as those presenting with lower SpO2/FiO2 ratios ($p < 0.01$), required higher doses of steroids. This was particularly due to delayed diagnosis and treatment of post-COVID-19 organizing pneumonia ($p < 0.01$), as illustrated in the linear graph (Fig. 2B).

Multiple regression analysis identified several significant predictors of steroid requirements: underlying ILD (β=0.23, $p < 0.01$), cerebrovascular disease (β=0.16, p=0.03), timing of diagnosis and treatment of post-COVID-19 organizing pneumonia (β=0.52, $p < 0.01$), and the SpO2/FiO2 ratio at presentation (β=−0.29, $p < 0.01$). These variables showed a statistically significant linear relationship with steroid needs, with an adjusted R square of 0.34 (Supplementary Table 2).

TABLE 2. Comparison of outcomes between the early treatment group and the late treatment group: hospital days, duration of steroid use, and steroid requirement

Variables	Total (n=91)	Early treatment group (n=55)	Late treatment group (n=36)	p-value
Hospitalization				
Hospital day (=days)	13.0±8.4	13.0±9.4	13.0±6.7	0.97
Steroid agent				
Hydrocortisone, n/N (%)	17 (18.7)	9 (16.1)	8 (22.9)	0.42
Prednisone or prednisolone, n/N (%)	40 (44.0)	23 (41.1%)	17 (48.6%)	0.48
Methylprednisolone, n/N (%)	35 (38.5)	20 (35.7)	15 (42.9)	0.57
Dexamethasone, n/N (%)	23 (25.3)	16 (28.6)	7 (20.0)	0.36
Total steroid dose (mg)[a]	647.3±851.9	474.8±459.3	923.3±1,205.1	*0.04
Steroid requirement (mg/kg/day)[a]	0.6±0.3	0.5±0.3	0.8±0.3	**<0.01
Follow up at OPD				
Follow up duration (days)	37.7±19.1	31.6±14.8	47.4±21.4	**<0.01
Steroid agent				
Hydrocortisone, n/N (%)	45 (49.5)	27 (48.2)	18 (51.4)	0.77
Prednisone or Prednisolone, n/N (%)	91 (100.0)	55 (100.0)	36 (100.0)	1.00
Methylprednisolone, n/N (%)	7 (7.7)	4 (7.1)	3 (8.6)	0.90
Dexamethasone, n/N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Total steroid dose (mg)[a]	109.6±107.8	72.7±67.4	168.5±132.6	**<0.01
Steroid requirement (mg/kg/day)[a]	0.1±0.0	0.1±0.1	0.1±0.0	0.96
Total steroid duration (days)	49.4±21.5	43.1±18.3	59.1±22.6	**<0.01

OPD: outpatient department. [a]The dosage of the steroid was calculated based on the equivalent dose of methylprednisolone. *$p < 0.05$, **$p < 0.01$.

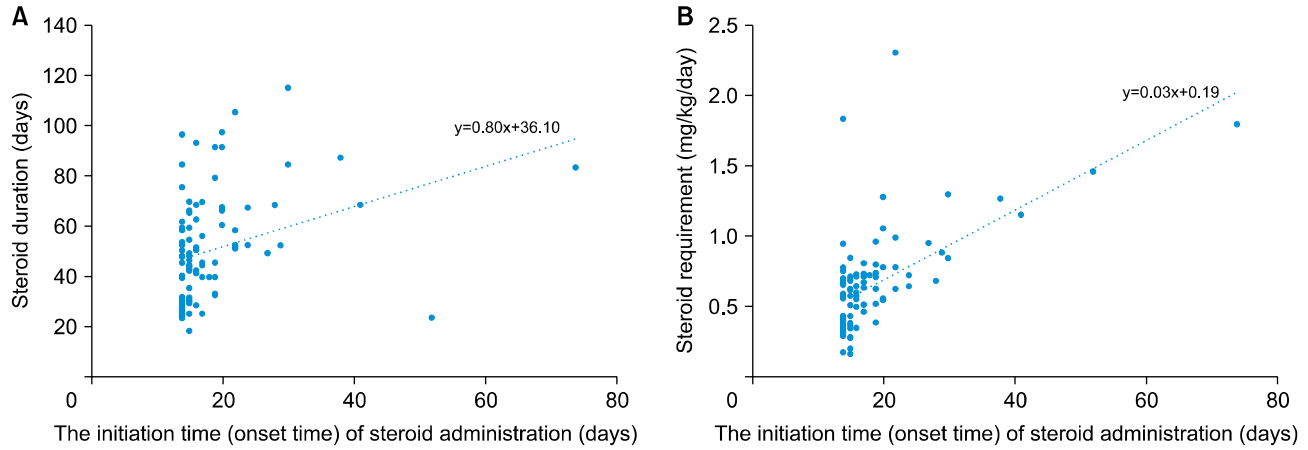

FIG. 2. (A) Linear relationship between steroid initiation time and the duration of steroid treatment. The initiation time (onset time) of steroid administration showed a linear correlation with the duration of steroid treatment (β=0.80, $p<0.01$, R^2=0.32). (B) Linear relationship between the steroid initiation time and the steroid treatment requirement. The initiation time (onset time) of steroid administration showed a linear correlation with the required dosage of the steroid treatment (β=0.03, $p<0.01$, R^2=0.60).

We additionally classified organizing pneumonia into two groups based on SpO2/FiO2 as mild and moderate to severe to compare the requirement of steroid treatment according to severity.[19] We found that the interval between COVID-19 diagnosis and the onset of symptoms due to post-COVID organizing pneumonia, leading to the initiation of treatment, was shorter in the mild group compared to the moderate to severe group (16.3±3.4 days vs. 20.3±11.1 days, p=0.02). Additionally, outcomes such as hospital days (9.3±3.4 days vs. 16.3±10.0 days, $p<0.01$), steroid duration (40.6±14.4 days vs. 59.8±22.5 days, $p<0.01$), and steroid requirement (0.5±0.2 mg/kg/day vs. 0.8±0.4 mg/kg/day, $p<0.01$) were statistically significantly lower in the mild group (Supplementary Table 3).

DISCUSSION

It is acknowledged that corticosteroids—used in the treatment of post-COVID-19 organizing pneumonia—act as immunosuppressants, attenuating the immune processes intrinsic to the organization process. However, functioning as immunosuppressive agents, corticosteroids are recognized to increase susceptibility to opportunistic pathogen superinfections, including multi-drug resistant pathogens. Moreover, they have been implicated in significant side effects, including hemorrhage and major adverse cardiovascular events. Moreover, a multitude of minor adverse effects associated with steroid usage, including hyperglycemia, osteoporosis, psychosis, and muscle weakness, have been extensively documented.[20] Therefore, it is very important to reduce corticosteroid use in the treatment of post-COVID-19 organizing pneumonia to lower the chance of side effects and improve patient outcomes.

We observed that the early treatment group had a statistically significant shorter duration of steroid maintenance and lower steroid requirements compared to the late treatment group, confirmed through linear regression analysis.

In addition to early treatment, multivariable analysis revealed that factors associated with disease severity affect outcomes. For further evaluation, we classified patients using the SpO2/FiO2 ratio as a severity index and confirm the correlation between the severity of the disease caused by organizing pneumonia and steroid requirements. Additionally, we confirmed the relationship between this severity and the time interval between COVID-19 diagnosis and the onset of symptoms due to post-COVID organizing pneumonia, leading to the initiation of treatment. In other words, patients who were diagnosed earlier tended to have milder disease, and earlier initiation of treatment led to a lower steroid requirement.

Related to this, the late treatment group demonstrated relatively advanced organization on CT findings, along with elevated KL-6, an ILD severity marker in baseline characteristics.[21] This suggests that the pronounced organization in the late treatment group may be a mechanism requiring increased steroid intervention.

This suggests the need for early screening for post-COVID organizing pneumonia. Due to the study design, which considers the time of symptom onset as the point of diagnosis and treatment initiation, it is difficult to determine exactly when post-COVID organizing pneumonia developed. However, the correlation between delayed post-COVID organizing pneumonia diagnosis and increased disease severity, which can lead to higher steroid requirements, indicates the need for early screening and timely treatment. Particularly, certain patients may be harboring ongoing organizing pneumonia without subjective perceptions of related symptoms. This is especially relevant for older individuals or those with compromised performance statuses, in whom the organization process may begin early but who may have limited awareness of associated symptoms.[22,23] Consequently, symptom presentation may occur at a later stage, potentially leading to

a delayed initiation of steroid therapy. The timely identification of such patients is crucial for optimizing their management and clinical outcomes.[24]

The importance of the early diagnosis and treatment of post-COVID-19 organizing pneumonia has been emphasized, suggesting the potential need for a more rigorous screening approach. Previously, Bieksiene et al.[15] proposed a 3-week screening criterion following the diagnosis of this condition. However, considering the proportional relationship between the timing of diagnosis and treatment with steroid dosage, we believed that a stricter screening period was necessary. Therefore, we propose setting this criterion at 2 weeks, which is the enrollment criteria of our study.

It is important to note that COVID-19 pneumonia can present CT findings resembling those seen in organizing pneumonia.[25] Implementing a strict 2-week screening period can raise concerns about the potential difficulty in distinguishing between the hyperinflammatory phase of COVID-19 pneumonia and post-COVID-19 organizing pneumonia. However, it is essential to acknowledge that differentiation between these diagnoses is not solely based on a specific time frame but involves overlapping courses of interconnected conditions.[26] Furthermore, it is crucial to recognize that the fundamental aspect of treatment for both conditions relies on utilizing the anti-inflammatory effects of steroid administration. Therefore, instead of emphasizing the distinction between these two entities, which would not significantly alter the treatment plan, the focus should be on the substantial value of early screening in enhancing favorable treatment outcomes.

Evidence supporting early steroid initiation has been mentioned in several studies as well. An et al.[27] found that timely steroid administration may reduce clinical deterioration and improve outcomes. Their study focused on comparing patients with ILD with organizing patterns emerging 1 week after acute COVID-19 and analyzing differences between those receiving steroids and those not. Based on this, our study conducted a quantitative analysis of steroid initiation timing and dosage among users, reaffirming the benefits of early steroid administration.

Therefore, our research suggests that a streamlined approach, focusing on earlier screening and intervention, may improve patient outcomes while reducing the duration and potential side effects of steroid treatment. Further investigations with larger sample sizes and prospective designs are necessary to confirm and expand upon our findings. Such research will play a critical role in establishing management strategies for post-COVID-19 organizing pneumonia, ultimately aiming to enhance patient outcomes.

There were several limitations in our study. Despite our initial screening of approximately 1,300 patients, the application of exclusion criteria significantly reduced the sample size. As a result, the sample size and retrospective design of this single-center study limit its generalizability. Further studies with larger sample sizes will be needed to verify these findings.

Also, as mentioned above, our study classified patients into early and late groups based on the timing of symptom onset and initiation of steroids after hospitalization. However, since the enrolled patients presented with subjective symptoms and were already in a state of progressing organizing pneumonia upon admission, there is a limitation in determining the exact timing of post-COVID organizing pneumonia diagnosis. To compare and analyze the favorable outcomes of early diagnosis and treatment, it would be valid to classify patients into early and late groups based on the time from the accurate diagnosis point to the initiation of steroid intervention.

Furthermore, due to the limitations inherent in this retrospective study, there was a lack of consistency in treatment, as criteria for steroid initiation, tapering, and discontinuation were not based on a fixed protocol but rather on the judgment of the treating physician. Particularly, since only patients who improved with steroid treatment were included, there is a deficiency in analyzing factors determining steroid response and the corresponding in-hospital mortality. Additionally, the study focused on patients with symptoms severe enough to require hospitalization, and steroids were mostly used empirically for symptom control. Therefore, there were limitations in assessing the criteria for steroid initiation and comparing outcomes based on whether steroids were used or not. To overcome these limitations, a large-scale prospective study based on strict protocols for steroid initiation and discontinuation criteria, dosage, and duration is necessary.

Additional limitations of this retrospective study include incomplete documentation related to COVID-19 treatments, including duration and dosage of antiviral and steroid therapies, as well as insufficient records on patients' vaccination statuses and the definite presence or absence of underlying interstitial lung disease, among other factors. Particularly, information on factors like underlying interstitial lung disease or past COVID treatment history, which can influence the steroid treatment duration and requirements for post-COVID organizing pneumonia, could only be obtained through medical records sourced from other hospitals. These limitations make it difficult to accurately assess how these factors relate to steroid requirement and duration.

And, our research did not explore adverse events between the groups. As various literature sources have reported adverse events associated with steroids and demonstrated dose dependency, we might anticipate similar outcomes but, further research is necessary to compare and analyze the outcomes associated with adverse events related to the steroid dose used for the treatment of post-COVID-19 organizing pneumonia.

Furthermore, despite efforts to exclude other diseases such as bacterial pneumonia through the described exclusion criteria to enroll only cases of pure organizing pneumonia, it is inherently limited to completely rule out other conditions based solely on clinical results and CT findings. Consequently, this suggests the need for further prospec-

tive studies.

Lastly, it is well established that cryptogenic organizing pneumonia is associated with a high recurrence rate, with more than 50% of patients experiencing relapse within 1 year.[28] However, we were unable to assess recurrence in this study because we do not have long-term follow-up data.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med 2020;8:807-15.
2. Aronson KI, Podolanczuk AJ. Lungs after COVID-19: evolving knowledge of post-COVID-19 interstitial lung disease. Ann Am Thorac Soc 2021;18:773-4.
3. Konopka KE, Perry W, Huang T, Farver CF, Myers JL. Usual interstitial pneumonia is the most common finding in surgical lung biopsies from patients with persistent interstitial lung disease following infection with SARS-CoV-2. EClinicalMedicine 2021; 42:101209.
4. Tiralongo F, Palermo M, Distefano G, Vancheri A, Sambataro G, Torrisi SE, et al. Cryptogenic organizing pneumonia: evolution of morphological patterns assessed by HRCT. Diagnostics (Basel) 2022;10:262.
5. Bazdyrev E, Panova M, Zherebtsova V, Burdenkova A, Grishagin I, Novikov F, et al. The hidden pandemic of COVID-19-induced organizing pneumonia. Pharmaceuticals (Basel) 2022;15:1574.
6. Achkar M, Jamal O, Chaaban T. Post-COVID lung disease(s). Ann Thorac Med 2022;17:137-44.
7. Cordier JF. Organising pneumonia. Thorax 2000;55:318-28.
8. Siafarikas C, Stafylidis C, Tentolouris A, Samara S, Eliadi I, Makrodimitri S, et al. Radiologically suspected COVID-19-associated organizing pneumonia responding well to corticosteroids: a report of two cases and a review of the literature. Exp Ther Med 2022;24:453.
9. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. Ann Am Thorac Soc 2021;18:799-806.
10. Segala FV, Sgalla G, Salvati F, Berardini L, Negri M, Nardella E, et al. Adjunctive corticosteroid treatment for organizing pneumonia in COVID-19 patients with persistent respiratory failure. Respir Med 2021;187:106571.
11. Khaw CR, Richardson C, Bhowmik A, Agbetile J, Rajakulasingam RK. Use of corticosteroid in persistent post-COVID-19 interstitial lung disease. Ann Am Thorac Soc 2021;18:1599.
12. Ravaglia C, Doglioni C, Chilosi M, Piciucchi S, Dubini A, Rossi G, et al. Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection. Eur Respir J 2022;60:2102411.
13. Rodrigues JP, Júnior R, Pinto M, Santos A, Gerardo R, Miguel A, et al. Organizing pneumonia due to COVID-19: the experience of one year in an intensive care unit. Eur Respir J 2022; 60(Suppl 66):3989.
14. Pogatchnik BP, Swenson KE, Sharifi H, Bedi H, Berry GJ, Guo HH. Radiology-pathology correlation demonstrating organizing pneumonia in a patient who recovered from COVID-19. Am J Respir Crit Care Med 2020;202:598-9.
15. Bieksiene K, Zaveckiene J, Malakauskas K, Vaguliene N, Zemaitis M, Miliauskas S. Post COVID-19 organizing pneumonia: the right time to interfere. Medicina (Kaunas) 2021;57:283.
16. Wang Y, Jin C, Wu CC, Zhao H, Liang T, Liu Z, et al. Organizing pneumonia of COVID-19: time-dependent evolution and outcome in CT findings. PLoS One 2020;15:e0240347.
17. Ito A, Ishida T, Tachibana H, Arita M, Yamazaki A, Washio Y. Utility of procalcitonin for differentiating cryptogenic organising pneumonia from community-acquired pneumonia. Clin Chem Lab Med 2019;57:1632-7.
18. Raghu G, Meyer KC. Cryptogenic organising pneumonia: current understanding of an enigmatic lung disease. Eur Respir Rev 2021;30:210094.
19. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO_2/FIO_2 ratio and the PaO_2/FIO_2 ratio in patients with acute lung injury or ARDS. Chest 2007;132:410-7.
20. Yasir M, Goyal A, Sonthalia S. Corticosteroid adverse effects. Treasure Island:StatPearls Publishing,2024.
21. Bill PM, Castellví I, Martínez-Martínez L, Aparicio F, Franquet T, Vidal OS, et al. Diagnostic value of serum KL-6 in interstitial lung disease: preliminary results from an European cohort. Eur Respir J 2018;52(Suppl 62):PA2959.
22. Ebihara S, Niu K, Ebihara T, Kuriyama S, Hozawa A, Ohmori-Matsuda K, et al. Impact of blunted perception of dyspnea on medical care use and expenditure, and mortality in elderly people. Front Physiol 2012;3:238.
23. Burdon JG, Pain MC, Rubinfeld AR, Nana A. Chronic lung diseases and the perception of breathlessness: a clinical perspective. Eur Respir J 1994;7:1342-9.
24. Bahmer T, Borzikowsky C, Lieb W, Horn A, Krist L, Fricke J, et al; NAPKON study group. Severity, predictors and clinical correlates of post-COVID syndrome (PCS) in Germany: a prospective, multi-centre, population-based cohort study. EClinicalMedicine 2022;51:101549.
25. Kwee TC, Kwee RM. Chest CT in COVID-19: what the radiologist needs to know. Radiographics 2020;40:1848-65.
26. Parotto M, Gyöngyösi M, Howe K, Myatra SN, Ranzani O, Shankar-Hari M, et al. Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations. Lancet Respir Med 2023;11:739-54.
27. An TJ, Lee YJ, Park JE, Lee EG, Kim Y, Kang SY, et al. Benefits of early systemic corticosteroid in clinical deterioration of post-COVID-19 interstitial lung disease. Tuberc Respir Dis (Seoul) 2022;85:358-60.
28. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF, et al. Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. Am J Respir Crit Care Med 2000;162:571-7.