Original Article

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Corticosteroid dose escalation in non-ICU COVID-19 patients with worsening lung lesions reduces lesion severity without improving clinical outcomes

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SUMMARY The effect of increasing corticosteroid doses on clinical outcomes and chest findings in patients with coronavirus disease (COVID-19) pneumonia and lung disease remains unknown. We aimed to investigate the effects of increasing steroid dosage on chest lesion area and clinical outcomes in patients with moderate or severe COVID-19 and progressive lung involvement on chest computed tomography (CT). A total of 105 patients with radiological progression during methylprednisolone (MP) therapy either received an increased MP dose (n = 79) or were maintained on the same MP dose (n = 26). These patients were divided into dose-increment and no-change groups according to the MP dose adjustment strategy. Clinical features, changes in CT severity scores within 7 days after steroid adjustment, and outcomes were compared between the groups. Six (7.6%) and one (3.8%) patients in the dose-increment and no-change groups, respectively, had increasing World Health Organization outcome scores 96 h after MP adjustment (P = 0.678). Length of stay [15 days (IQR: 10-24) *vs.* 14 days (IQR: 10-25); P = 0.994] and in-hospital death rate (7.6% *vs.* 3.8%; P = 0.678) showed no significant differences between the groups. Logistic regression analyses revealed that an increased MP dose was significantly associated with improvement in CT lesion area compared with no change in MP dose, but the CT lesions deteriorated subsequently (79.7% *vs.* 53.8%, P = 0.044). In conclusion, increasing the MP dose in patients with worsening CT findings ameliorates CT lesions but fails to prevent serious adverse outcomes.

Keywords coronavirus disease pneumonia, corticosteroid dosage adjustment, outcome, chest CT deterioration

1. Introduction

The coronavirus disease 2019 (COVID-19) epidemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in China occurred in December 2019 (*1*). Antiviral agents (*2*), immunomodulators (*3,4*), and antithrombotic drugs (*5,6*) are alternative agents for heterogeneous patients hospitalized for COVID-19 pneumonia.

Corticosteroids are strong anti-inflammatory drugs used to treat various types of pneumonia, such as influenza and SARS. These drugs were recommended for patients with COVID-19 requiring oxygen supplementation in management guidelines, mainly according to the results of the RECOVERY trial (a randomized, controlled, open-label platform trial, named Randomised Evaluation of COVID-19 Therapy) (*7-9*). In this clinical trial, the dose and duration of dexamethasone administration (6 mg/day for 10 days) were based on previous experience of safely using corticosteroids for asthma and chronic obstructive pulmonary disease (*10,11*). Only patients requiring oxygen supplementation had slightly decreased all-cause mortality in hospitals. The influence of corticosteroid treatment on clinical symptoms and lung lesions remains unknown, but it is correlated with the severity of illness and mortality (*12-14*). Moreover, the optimal dose and duration of corticosteroid therapy have not yet been determined, especially in patients with worsening clinical symptoms or lung lesions.

The RECOVERY trial also assessed the benefit of high- and low-dose dexamethasone administration in patients requiring respiratory support (*15*). This study showed that higher doses of corticosteroids significantly increased the risk of death compared with low doses of corticosteroids. Taboada *et al.* (*16*) showed that treatment with a high dose of dexamethasone reduced clinical worsening, including an increased need for FiO_2 or a score > 4 on the 10-point World Health Organization (WHO) Clinical Progression Scale (*17*).

Patients with COVID-19 require oxygen therapy. However, some studies that used intravenous pulses of methylprednisolone (MP) to treat adults with severe COVID-19 pneumonia showed no decrease in mortality or intubation rate (*18*).

Most studies have focused on investigating the effects of different corticosteroid doses on hypoxic patients by recording the need for oxygen therapy, time free from invasive mechanical ventilation, and mortality. However, the effects of corticosteroid dose adjustment remain undetermined in patients who already received steroid treatment and have aggressive hypoxia or an increased number of lung lesions. The pooled prevalence was 90% for chest computed tomographyn (CT) abnormalities in COVID-19 cases (*19*), with ground-glass opacity, consolidation, septal thickening, crazy-paving pattern, and fibrosis. Chest CT is a potential tool in the diagnosis and prognostication of COVID-19 (*12,14,20*), and the CT severity score is a predictor of mortality and short-term prognosis in these cases (*21,22*). Steroids are thought to reduce pulmonary inflammation in severe pneumonia. However, the effect of steroid treatment to the CT lesions in refractory is undetectable. Here, we aimed to investigate the effects of increasing steroid dose on chest lesion areas and clinical outcomes in patients with moderate or severe COVID-19 and progressive lung involvement on chest CT.

2. Patients and Methods

2.1. Study design

This retrospective clinical cohort study was designed to evaluate the effects of different steroid dose adjustment strategies in patients hospitalized for COVID-19 at Zhongshan Hospital, Fudan University in Shanghai, China.

2.2. Participants

Hospitalized patients were enrolled if they were aged ≥18 years, tested positive for SARS-CoV-2 through real-time polymerase chain reaction, were antigen-positive, had clinically suspected COVID-19 as judged by two experienced attending physicians, had pneumonia, and received corticosteroids between December 14, 2022, and January 26, 2023. The exclusion criteria were failure to undergo chest radiology testing after MP therapy, MP dose reduction after radiological progression, and no radiological progression. The specific inclusion and exclusion criteria are shown in the flowchart (Figure 1).

All patients admitted to our department had moderate or severe illness. Severe illness was defined as SpO_2 < 93%, PaO_2/FiO_2 ratio < 300, respiratory rate ≥ 30 breaths per min, or ≥ 50% lung involvement on chest CT. All patients received standard care, including nirmatelvir/ritonavir (paxlovid) and anticoagulant therapy, according to the current guidelines or evidence at the time of admission. Patients with pneumonia were also administered corticosteroids. Other immunomodulators were rarely used.

All patients underwent chest radiology examinations

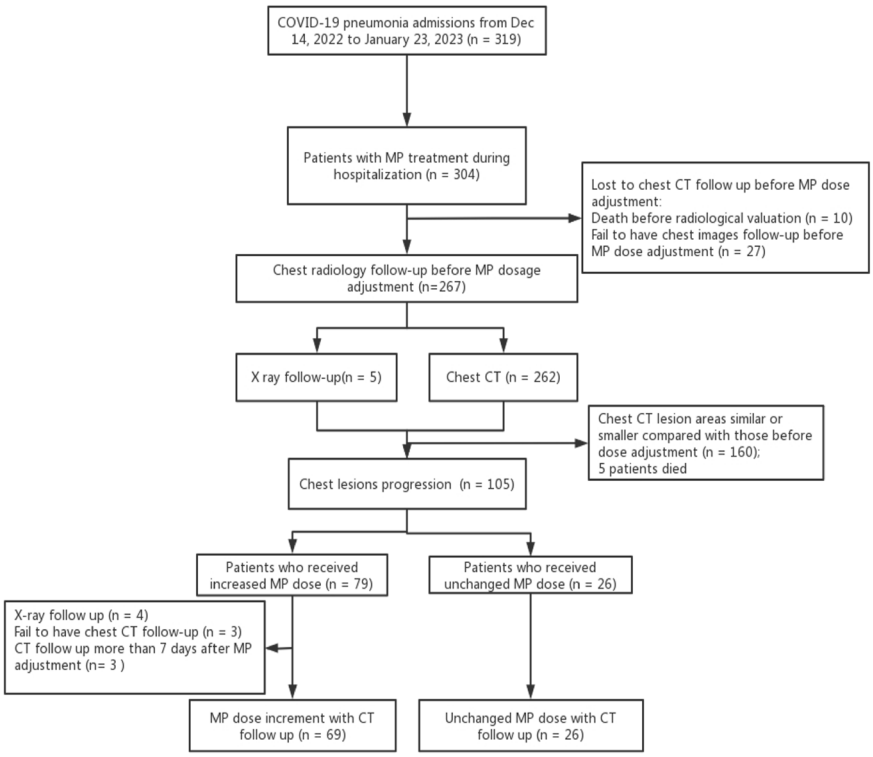

Figure 1. Flow chart.

upon admission and during MP treatment. Progression was defined as lung lesions on chest radiography or CT more than 3 days after MP treatment that were larger than those at admission.

Demographic information, baseline clinical characteristics, complications, and laboratory test results at baseline and follow-up were obtained from the electronic medical records of the patients. Clinical progression was defined as an increase in the level of oxygen supplementation or large chest CT lesions compared with previous ones.

Written informed consent was obtained from all patients before participation in the study. The study was approved by Clinical Research Ethics Committee of Zhongshan Hospital, Fudan University (approval No.: B2023-018).

2.3. CT examination and image evaluation

CT scanning was performed on a 320-slice CT scanner (uCT960+; Shanghai United Imaging Healthcare, Shanghai, China). The CT parameters were as follows: 120 kVp; 300 mAs; detector collimation, 160 × 0.5; pitch, 1.0938; rotation time, 0.5 s; matrix size, 1024 × 1024; field of view, 350 mm; and slice thickness, 1.0 mm, covering the scanning range from the lung apices to the bases.

Most patients underwent chest radiology on admission and every 3-7 days during MP treatment. Two experienced respiratory physicians (with 28 and 22 years of experience), who were blinded to the clinical data, scored and compared the CT findings in consensus. The CT lesions are described using ground-glass opacity, consolidation, patchy consolidation, fibrosis, irregular solid nodules, and interlobular septal thickening (*23*). Meanwhile, the abnormalities including mucoid impactions, focal consolidation, and cavity suggesting bacterial or fungi infection were excluded. The comparison results were divided into three types according to the changes in the lesion area between two adjacent CT images as follows: improvement, no change, and progression. To quantify the extent of lesions, a scoring system was used to assess the abnormal areas. Each of the five lung lobes was scored on a scale of 0 to 5: 0, no involvement; 1, < 5% involvement; 2, 5%–25% involvement; 3, 26%–49% involvement; 4, 50%–75% involvement; and 5, > 75% involvement. Each lobe had a score of 0–5, with a total possible score of 0–25 (*24*).

2.4. Corticosteroid administration

The most common type of steroid was MP; the doses of other types of steroids, such as dexamethasone, were equivalently converted to those of MP. The enrolled participants received MP therapy before or upon admission. The initial dosage was 40–80 mg administered through intravenous injection per day for 10 days, as determined by an experienced physician according to age, complications, hypoxic condition, risk factors, and CT lesion area. Furthermore, the clinicians adjusted the MP dose according to changes in the need for oxygen, breathing rate, symptoms, or CT lesions. Clinical worsening is the worsening of patient condition (increasing need for oxygen and increasing breath rates). The clinicians adjusted the MP dose in patients with clinical worsening or progression of chest CT lesions by increasing the dose by 20–40 mg per day or maintaining the same daily dosage.

2.5. Outcome measures

The primary outcomes of the study were WHO outcome score (WHO Clinical Progression Scale) > 6, length of stay, and in-hospital mortality rate after disease progression (clinical worsening or CT lesion aggression). The WHO outcome scores were assessed for pneumonia aggression 96 h after MP adjustment. This score is based on the level of ventilation required in hospitalized patients, with scores ranging from 4 to 10 (4, room air; 5, oxygen supplementation required; 6, noninvasive positive pressure ventilation usage; 7–9, needing endotracheal intubation; and 10, death). The secondary outcomes of the study were improvement in lung lesion area, reduction in CT severity score within 7 days after MP dose adjustment, and lung lesion reduction, as determined by clinicians.

2.6. Statistical analysis

Categorical data are described using absolute number and percentage, and continuous data are expressed as median (interquartile range [IQR], 25th–75th percentiles), depending on the normality of distribution. Chi-square, Fisher's exact, and Wilcoxon tests were used to measure differences in variables, where appropriate.

The sample size was 69 in group 1 and 26 in group 2, which achieved 77.364% power to result in an odds ratio of the group proportions of 0.297. The proportion in group 1 (treatment group) was assumed to be 0.7530 under the null hypothesis and 0.4752 under the alternative hypothesis. The proportion in group 2 (control group) was 0.7530. The test used was the two-sided Z-Test with unpooled variance. The significance level of the test was 0.05.

A logistic regression model was used to explore the association between the improvement in lung lesions after MP adjustment and the varieties. Multivariate analysis was performed using a multiple logistic regression model that included possible biological variables and varieties at $P < 0.1$. Significance was set at $P < 0.05$, and all tests were two-tailed. Data analyses were performed using SPSS version 25.0.

3. Results

We consecutively included 319 patients with COVID-19 pneumonia; their baseline characteristics are listed in Table S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=232*). The median age was 72 (IQR, 66–82) years; 192 patients (60.2%) were ≥ 70 years, and 207 (64.9%) were men. The most common complications were hypertension (59.2%), diabetes mellitus (35.1%), cardiovascular disease (25.7%), malignancy (15.9%), and chronic kidney disease (14.4%). A total of 144 (44.2%) patients had severe illness and 128 (40.1%) had $PaO_2/FiO_2 \leq 300\%$ on admission. A total of 304 patients who were administered MP therapy were enrolled. The median number of days from onset to initial steroid use was 8 (IQR, 6–10) and the number of days of MP use (≥ 20 mg per days) was 11 (IQR 7.16).

Finally, 105 patients with aggressive lung lesions were enrolled; 79 patients received MP dose increments and 26 received an unchanged dose of MP. Table 1 lists the clinical features of the two groups. No significant differences were observed between the groups in terms of age, sex, or comorbidities. The median daily dose of MP before MP adjustment was 40 mg (40, 60) in the dose-increment group and 58 mg (51, 92) in the no-change group ($P < 0.001$). The number of days from onset to MP adjustment did not differ between the groups [9 (IQR 7–14) days *vs.* 7 (IQR 7–13) days; $P = 0.343$].

3.1. Laboratory findings

The laboratory findings on admission and before MP adjustment are shown in Table 1. Baseline laboratory test results, such as lymphopenia and C-reactive protein (CRP), lactate dehydrogenase, and D-dimer levels, did not differ between the groups. The median oxygen index on admission in the dose-increment group was lower than that in the other group [28.5% (IQR, 230–371) *vs.* 33.6% (IQR, 275–403); $P = 0.105$]. The CRP level was tested when the radiological results worsened in the dose-increment group, and it was significantly higher than that in no-change group [3.2 (5.3–47.6) *vs.* 8.15 (2.5–19.1); $P = 0.029$].

3.2. Clinical outcomes

The clinical outcomes are shown in Table 1. We found that 87.3% and 96.2% patients had a WHO outcome score of < 6 in the dose-increment and no-change groups, respectively ($P = 0.285$). Notably, 12.6% of the patients in the dose-increment group had a WHO outcome score of 6 (need high flow or noninvasive ventilation), which was higher than that in the no-change group (3.8%). The dynamics of the WHO scores after MP dose adjustment in the two groups are shown in Figure 2.

Six of the seventy-nine patients in the dose-increment group and one of the twenty-six patients in the no-change group showed increasing WHO outcome scores 96 h after MP adjustment ($P = 0.678$). In-hospital death occurred in six (7.6%) patients in the dose-increment group and in one (3.8%) patient in the no-change group ($P = 0.180$). Two (2.5%) of the seventy-nine patients in the dose-increment group received invasive mechanical ventilation, whereas none in the other group received the same. The median time to hospital discharge was 15 days (IQR, 10–24 days) in the dose-increment group and 14 days (IQR, 10–25 days) in the no-change group ($P = 0.994$) (Figure 3).

3.3. Series chest CT assessment results

Eventually, 95 patients underwent follow-up chest CT 7 days after CT radiological progression. Clinical features and chest CT score changes are shown in Table S2 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=232*). The median CT score on MP dose adjustment was 10.5 (IQR, 7.8–16.0) in the dose-increment group and 10.5 (IQR, 7.8–16.0) in the no-change group ($P = 0.952$).

Chest CT scanning was conducted before and after MP dose adjustment at an interval of 4 (IQR, 3–5) days in the dose-increment group and 4.5 (IQR: 4–5) days in the no-change group ($P = 0.03$). The CT score changes in the two groups are shown in Figures 4A-4C. We found that 52/69 (75.3%) patients in the dose-increment group and 14/26 (53.8%) patients in the no-change group showed CT score reductions ($P = 0.042$). Meanwhile, 55/69 (79.7%) patients in the dose-increment group and 14/26 (53.8%) in the no-change group showed CT lesion area reductions ($P = 0.012$).

The univariate analysis showed that the time between CT scans and MP dose increment significantly correlated with CT lesion reduction after MP dose adjustment (Table S3, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=232*). The multivariate logistic regression analysis was performed using the CT area reduction and variables including severe illness, immunosuppression, CT scores at MP dose adjustment, time between CT scans, and MP dose increment. The results showed that patients who received increasing MP doses had a proportional benefit in lung involvement reduction compared with patients in the no-change group (odds ratio, 4.235; 95% confidence interval, 1.141–15.718; $P = 0.031$) (Figure 5).

4. Discussion

Treatment with higher doses of steroids decreases clinical worsening, and it may be associated with a significant reduction in mortality (*16,25,26*). However, the efficacy of current steroid dose modulation methods is yet to be demonstrated in patients with lung imaging deterioration who have already received corticosteroids. In this retrospective cohort study involving 105 patients

Table 1. Comparison of clinical characteristics and primary outcomes between groups

	No. total (n = 105)	MP increasing group (n = 79)	MP no-change group (n = 26)	P value
Age (years)	74 (67, 81)	72 (67, 81)	76 (69, 83)	0.286
Sex (male)	68 (64.8)	51 (64.5)	17 (65.4)	0.939
Days from onset to MP dose adjustment (> 14 days)	46 (43.8)	34 (43.0)	12 (46.2)	0.822
Severity on admission				0.823
Moderate	47 (44.8)	36 (45.6)	11 (42.3)	
Severe	58 (55.2)	43 (54.4)	15 (57.7)	
WHO outcome score on MP adjustment				0.285
< 6	94 (89.5)	69 (87.3)	25 (96.2)	
≥ 6	11 (10.5)	10 (12.7)	1 (3.8)	
Diabetes mellitus	39 (37.1)	30 (38.0)	9 (34.6)	0.758
Hypertension	26 (24.8)	20 (25.3)	6 (23.1)	0.818
Malignancy	69 (65.7)	54 (68.4)	15 (57.7)	0.32
Cardiovascular disease	30 (28.6)	21 (26.6)	9 (34.6)	0.432
Chronic kidney disease	13 (12.4)	9 (11.4)	4 (15.4)	0.732
Chronic lung disease	12 (11.4)	7 (8.9)	5 (19.2)	0.149
Immunosuppression	10 (9.5)	7 (8.9)	3 (11.5)	0.706
Mean dose of daily MP before adjustment (mg)	49 (40, 64)	40 (40,60)	58 (51,92)	0.001
Days from onset to MP dose adjustment	13 (10, 17)	13 (10,17)	11.5 (9.8,17.5)	0.964
Days from onset to admission	8 (7, 14)	9 (7,14)	7 (6.5,12.5)	0.343
Oxygen index on admission	295 (241, 379)	285 (230,371)	336 (275,403)	0.105
CT score at adjustment	11 (7, 16)	11 (7,17)	10.5 (7.8,16.0)	0.952
Laboratory data on admission				
lymphocyte count ($\times 10^9$/L)	0.7 (0.4, 1.0)	0.7 (0.5,1)	0.7 (0.4,0.9)	0.472
< 1 × 10^9/L	77 (73.3)	57 (72.2)	20 (76.9)	0.633
≥ 1 × 10^9/L	28 (26.7)	22 (27.8)	6 (23.1)	
Platelet count ($\times 10^9$/L)	163 (117.5, 222.5)	167 (122,228)	157 (109,208)	0.598
CD4 count (cell/μL)	209 (131, 313.5)	221 (131,350)	205 (105,252)	0.266
< 400 (cell/μL)	73 (79.3)	55 (77.5)	18 (85.7)	0.547
≥ 400 (cell/μL)	19 (20.7)	16 (22.5)	3 (14.3)	
D-dimer (mg/L)	0.7 (0.4, 1.7)	0.7 (0.4,1.6)	0.8 (0.4,2.5)	0.456
< 1 mg/L	70 (66.7)	54 (68.4)	16 (61.5)	0.522
≥ 1 mg/L	35 (33.3)	25 (31.6)	10 (38.5)	
Procalcitonin (ng/mL)	0.1 (0.06, 0.16)	0.09 (0.06,0.15)	0.13 (0.08,0.345)	0.056
Serum lactate dehydrogenase (U/L)	289 (227, 344)	286 (223,345)	297 (256,354)	0.173
< 245	30 (29.7)	24 (31.6)	6 (24.0)	0.472
≥ 245	71 (70.3)	52 (68.4)	19 (76.0)	
Serum albumin (gL)	36 (33, 40)	37 (33,40)	36 (33.5,40)	0.849
< 30 (g/L)	8 (7.8)	7 (9.0)	1 (4.0)	0.676
≥ 30 (g/L)	95 (92.2)	71 (91.0)	24 (94.0)	
C-reaction protein (mg/L)				
< 40 (mg/L)	39 (37.5)	28 (35.9)	11 (42.3)	0.559
≥ 40 (mg/L)	65 (62.5)	50 (64.1)	15 (57.7)	
Clycosylated hemoglobin (%)	6.3 (5.9, 7.1)	6.3 (5.9,6.9)	6.2 (5.9,7.35)	0.97
Interleukin 1β (pg/mL)	5 (5, 5)	5 (5,5)	5 (5,5)	0.512
Interleukin 2 (pg/mL)	721 (525, 1007)	735 (545,1023.5)	707 (497,928)	0.507
Interleukin 6 (pg/mL)	7.6 (3.6, 21.6)	7.3 (3.8,16.1)	8.33 (3,33.3)	0.528
Interleukin 8 (pg/mL)	21 (10, 46)	21 (11,44)	21 (8,55)	0.561
Interleukin 10 (pg/mL)	6 (5, 11)	5.4 (5,10.7)	7 (5,17.2)	0.343
Laboratory data before MP adjustment				
lymphocyte count ($\times 10^9$/L)	0.7 (0.5, 0.9)	0.7 (0.5,1.0)	0.6 (0.4,0.8)	0.105
< 1 × 10^9/L	72 (76.6)	50 (73.5)	22 (84.6)	0.292
≥ 1 × 10^9/L	22 (23.4)	18 (26.5)	4 (15.4)	
D-dimer (mg/L)	0.86 (0.45, 1.705)	0.91 (0.43,1.73)	0.81 (0.485,1.485)	0.806
< 1 mg/L	49 (53.3)	35 (52.2)	14 (56.0)	0.748
≥ 1 mg/L	43 (46.7)	32 (47.8)	11 (44.0)	
Serum lactate dehydrogenase (U/L)	290 (230, 359)	287 (220,362)	304 (242.75,339.75)	0.738
Procalcitonin (ng/mL)	0.07 (0.05, 0.1)	0.07 (0.05,0.1)	0.07 (0.04,0.1)	0.628
C-reaction protein (mg/L)	13.6 (4.5, 38.6)	23.2 (5.3,47.6)	8.15 (2.5,19.1)	**0.029**
< 40 (mg/L)	72 (75.5)	47 (69.1)	25 (96.2)	**0.005**
≥ 40 (mg/L)	22 (23.4)	21 (30.9)	1 (3.8)	
Interleukin 1β (pg/mL)	5 (5, 5)	5 (5,5)	5 (5,5)	0.182
Interleukin 2 (pg/mL)	737.5 (514.8, 1060.8)	738 (512.5,1064.5)	618 (439.5,803.5)	0.308
Interleukin 6 (pg/mL)	3.7 (2, 7.7)	3.8 (2.1,10.1)	3.2 (2,5.45)	0.299
Interleukin 8 (pg/mL)	21.0 (12.5, 49.5)	22 (12,39.5)	19 (13,91.5)	0.935
Interleukin 10 (pg/mL)	5.0 (5.0, 6.7)	15 (10,24)	5 (5,8.05)	0.797
Noninvasive ventilation or high flow treatment	14 (13.3)	5 (5,6.75)	1 (3.8)	0.18

Table 1. Comparison of clinical characteristics and primary outcomes between groups (continued)

	No. total (n = 105)	MP increasing group (n = 79)	MP no-change group (n = 26)	P value
Mechanical ventilation requirement	2 (1.9)	2 (2.5)	0	1
Admission to ICU	2 (1.9)	2 (2.5)	0	
Length of stay	15 (10, 24)	15 (10,24)	14 (10,25)	0.994
In-hospital death	7 (6.7)	6 (7.6)	1 (3.8)	0.678
WHO score increment 96 h after adjustment	7 (6.7)	6 (7.6)	1 (3.8)	0.678

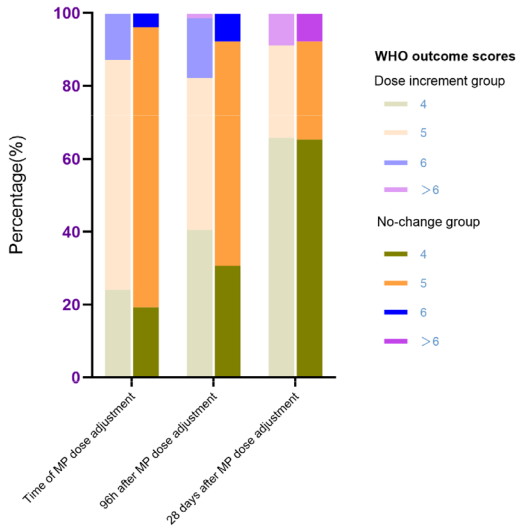

Figure 2. WHO outcome score proportion and dynamics between the groups. Light bar represents the MP dose-increment group; dark bar represents the no-change group. The three sets of bars show the dynamics of WHO outcome score components before and after MP dose adjustment.

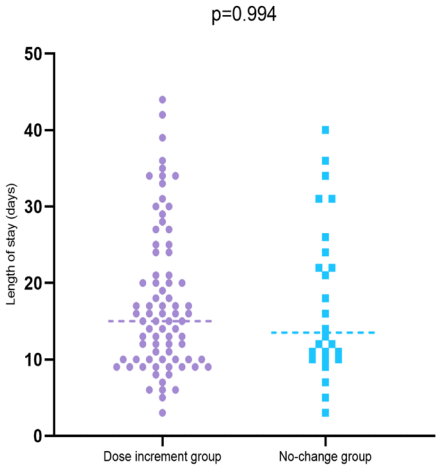

Figure 3. Length of stay in the MP dose-increment and no-change groups.

with COVID-19 with aggressive chest imaging when using steroids, increasing the MP dose was an efficient method for improving lung involvement compared with an unchanged MP dose. Our study provides evidence that MP dose increments prevent radiological progression in patients with deteriorated lung lesions. In our hospital, most participants were older individuals with complications and were at a high risk of progressing to more severe or critical illness. Thus, steroids were the routine therapeutic agents for high-risk patients with moderate-to-severe COVID-19 pneumonia.

We selected MP as the corticosteroid for this study because it has a faster effect and a better penetration in the lung tissue than dexamethasone (*27*). The initial MP dosage in the present study was 40–80 mg per day, depending on the illness severity and severe disease risk. One-third of the patients showed lung lesion deterioration during MP treatment and may have been resistant to steroids (defined as refractory disease) (*28*). This may be due to the low expression of glucocorticoid receptors in these patients. A previous study showed that patients with COVID-19 with high *NR3C1* expression showed a clinical response to corticosteroids (*29*).

Apparently, the beneficial effect of steroid therapy in patients with COVID-19 depends on the selection of the appropriate dose in patients with illness at different levels of severity. A previous study reported that intravenous MP pulse therapy might be beneficial in critically ill patients with acute COVID-19 (*30*). In patients with severe disease, pulsed MP treatment failed to decrease the mortality or intubation rate (*18*). These pulsed-dose therapies have unclear benefits and may slow the clearance of viral RNA and promote further infections (*31,32*). Herein, we propose a steroid treatment strategy in which MP dose is specifically adjusted according to lung involvement to deliver the drug at the right dose to optimize patient benefits. Increasing the MP dose by 20–40 mg per day in patients with COVID-19 with lung lesion deterioration was found to be an effective approach for preventing severe lung lesions.

The rate of CT score reduction before and after the MP dose increment was considerable higher than that in the no-change group. Notably, the sensitivity of CT lesion improvement after MP dose adjustment, as determined by physicians, was higher than that among the CT scoring systems. The reason of this discrepancy may be the area reduction ranging from 1% to 44% for every increase in score of 1 according to the chest CT scoring system. Finally, we selected the lung lesion area reduction as determined by physicians as the secondary outcome and investigated the factors related to this outcome.

Although an increase in the MP dose improved lung involvement in patients, it failed to decrease the

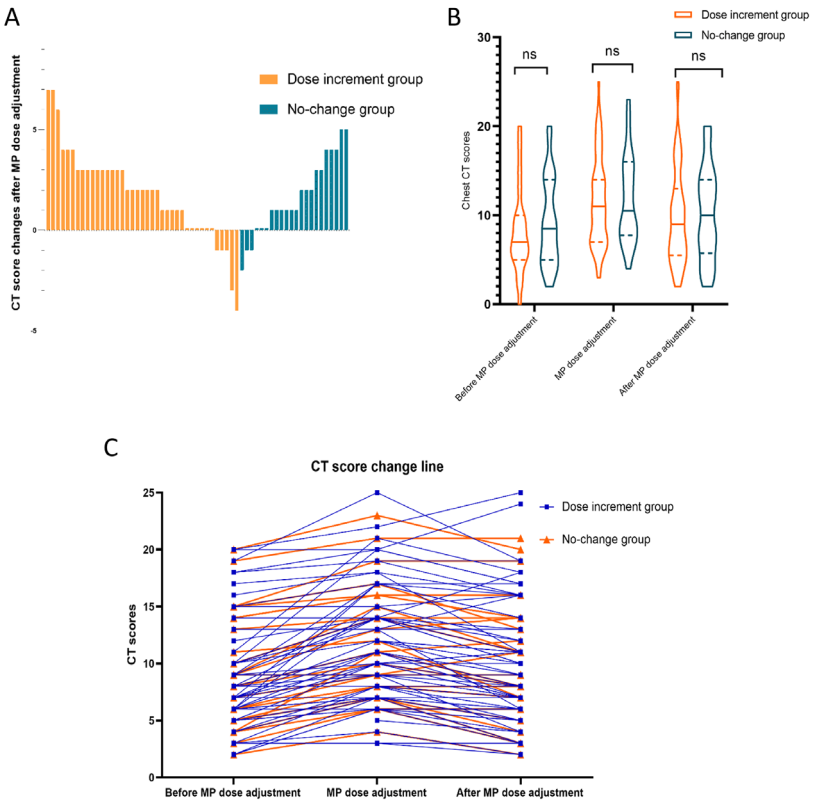

Figure 4. CT score dynamics during MP therapy. A. Chest CT score changes after MP dose adjustment. CT score reduction percentage in the dose-increment group was higher than that in the no-change group. Orange and purple bars represent CT score changes in the dose-increment and no-change groups, respectively. CT score changes showed no significant differences between the groups. **B**. Violin plot showing chest scores between the groups at pre-MP dose adjustment, increasing dose, and post-MP dose adjustment time points. ns, no significant difference between groups. **C**. Spaghetti plot showing CT scores at three time points for 95 patients with available data. Lines connect measurements for individual patients.

	Adjusted OR(95%CI)	p value
Clinical features		
Age(>70y)	1.454(0.445-4.755)	0.535
Sex(male)	1.338(0.364-4.92)	0.662
Days from onset to MP adjustment	0.974(0.888-1.068)	0.57
WHO outcome scores(≥6)	7.105(0.371-136.242)	0.193
Diabetes mellitus	3.616(0.982-13.307)	0.053
Hypertension	1.213(0.254-5.795)	0.808
Malignancy	0.352(0.089-1.391)	0.136
Cardiovascular disease	0.791(0.206-3.039)	0.733
Chronic kidney disease	0.649(0.121-3.487)	0.615
Chronic lung disease	0.424(0.077-2.319)	0.322
Illness Severity(moderate)*	0.539(0.131-2.222)	0.393
Immunosuppression*	0.402(0.069-2.351)	0.312
Mean dose of every MP before adjustment	1.01(0.987-1.033)	0.397
MP dose increasing*	4.235(1.141-15.718)	**0.031**
Chest CT lesion evaluation		
CT score at PM dose adjustment*	0.882(0.751-1.035)	0.123
Time between CT scans conducted*	0.767(0.503-1.169)	0.217

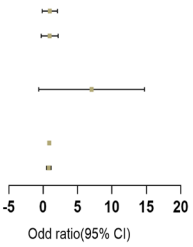

Figure 5. Factors related to CT lesion reduction after MP dose adjustment in patients with COVID-19 with radiological progression. Univariate and multivariate logistic analyses of clinical and CT features of improved lung lesions in non-ICU patients with pneumonia. *factors with $P < 0.2$ in the univariate analysis. Odds ratios are plotted as squares, and the size of each square is proportional to the amount of statistical information available. The horizontal lines represent the 95% confidence intervals.

mortality rate in the current study, which is consistent with the findings of a previous study (*33*). However, unlike previous studies, we investigated the effect of MP dose increment in patients with steroid refractory disease. We hypothesized that the mortality rate in the group that received MP dose adjustment will be low. However, our results contradicted this hypothesis. The main reason for this similar mortality rate may be the

larger proportion of patients with WHO outcome score ≥ 6 in the dose-increment group. The WHO outcome score and serum CRP level at the adjustment stage in the dose-increment group were considerably higher than those in the no-change group. These parameters are associated with increased mortality and exacerbation of COVID-19 (*34,35*).

Even though patients in the dose-increment group did not show significantly lower mortality rates than those in the no-change group, treatment with a higher dose of steroids for at least 10 days significantly reduced mortality in patients with COVID-19, as reported by Taboada *et al.* (*16*) . Further studies should directly investigate the outcomes in a large number of patients with COVID-19 controlled for the same risk factors.

This study had a few limitations. First, because of the small number of aggressive CT patients and the low mortality rate, the mortality rate among the groups was not significantly different. Therefore, we did not conduct Cox regression analysis. Studies with larger cohorts are required. Furthermore, this was an observational study influenced by factors such as the various times of initial MP dosing from onset and loss to CT follow-up. Such factors may have had confounding effects on the outcomes. Finally, we did not follow-up for the effect after discharge among the survivors. Despite these limitations, our study provides a feasible strategy for optimizing steroid therapy in patients with COVID-19 who are not in the ICU.

In conclusion, we demonstrated a strategy for preventing the progression of lung lesions by increasing steroid doses in patients with COVID-19 with refractory pneumonia. We reported the performance of patients with deterioration of lung involvement to demonstrate that our approach may be a remedial measure in refractory patients already using steroids. Treatment may not have been associated with mortality in our patient cohort. This study presents real-life data on the personalized adjustment of steroid doses in patients with COVID-19. A more precise dose adjustment of steroids should be considered in future prospective and larger studies in patients with high risk of illness worsening.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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