ORIGINAL ARTICLE

The outcome of 12-week corticosteroid therapy in COVID-19-related diffuse interstitial lung abnormalities

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ABSTRACT

Introduction: The efficacy of long-course corticosteroid therapy in treating COVID-19-related diffuse interstitial lung abnormalities (DILA) needs to be better understood. We aimed to investigate the benefits of 12-week corticosteroid treatment in COVID-19-related DILA by evaluating computed tomography (CT) lung severity scores.

Materials and Methods: This retrospective, single-centre observational study included patients aged 18 years or older admitted with moderate to severe COVID-19 pneumonia who received 12 weeks of oral prednisolone between January 2021 and December 2021. We recorded clinical parameters, baseline CT scores and post-treatment, modified Medical Research Council (mMRC) dyspnoea scale and pulmonary function tests.

Results: A total of 330 patients were analysed. The mean (standard deviation, SD) age was 54.6 (14.2) years, and 43% were females. Three-point nine per cent (3.9%) require non-invasive ventilation (NIV), while 14.6% require mechanical ventilation (MV). On follow-up at 12 weeks, the CT patterns showed improvement in ground-glass opacities, perilobular density and consolidation. There was an improvement in the mean (SD) CT score before and after prednisolone therapy, with values of 17.3 (5.3) and 8.6 (5.5), respectively (p<0.001). The median mMRC was 1 (IQR 0-1), and 98.8% had a radiological response. The common side effects of prednisolone therapy were weight gain (13.9%), hyperglycaemia (1.8%) and cushingoid habitus (0.6%).

Conclusion: A 12-week treatment with prednisolone showed significant improvement in CT scores with minimal residual dyspnoea and was relatively safe. Longer duration of steroids may be beneficial in moderate to severe COVID-19-related DILA.

KEYWORDS:
Corticosteroid, prednisolone, COVID-19, SARS-CoV-2, diffuse interstitial lung abnormalities

INTRODUCTION

The clinical spectrum of COVID-19 ranges from asymptomatic to severe pneumonia or acute respiratory distress syndrome (ARDS). Prolonged respiratory symptoms or persistent hypoxemia can occur in a subset of patients with COVID-19 pneumonia due to direct viral pathogenicity and hyperimmune response triggering, leading to the destruction of lower respiratory tract airways and alveolar and vascular endothelium. Following COVID-19 infection, persistent parenchymal change is associated with prolonged respiratory symptoms and functional impairment.

Computed tomography (CT) imaging reveals that the abnormalities in these patients often show a combination of ground-glass opacities, perilobular densities and patchy multifocal consolidation consistent with a pattern of organising pneumonia (OP). Histopathologically, this represents diffuse alveolar damage, capillary injury and organising pneumonia. It should be emphasised that most pathological data was from post-mortem specimens and may not reflect survivors' disease course. Transbronchial lung biopsy has been carried out in patients with persistent radiological consolidation in COVID-19 pneumonia and found to have pathological findings of OP.[1]

Steroids have been shown to reduce the inflammation associated with OP, resulting in symptom resolution, improvement in gas exchange and potentially preventing the progression of early parenchymal abnormalities to irreversible fibrosis. However, steroids are associated with adverse effects such as delayed viral clearance, hyperglycaemia and increased susceptibility to infections. Some authors advocate high-dose steroid treatment regimens for a minimum of six months, as proposed for cryptogenic organised pneumonia. However, the question remains whether less intense treatment could resolve the disease in non-idiopathic cases of OP. In COVID-19, studies indicate that the judicious use of corticosteroids in severe COVID-19 may benefit certain patient cohorts but do not recommend routine treatment.[2,3]

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The post-COVID-19 pulmonary sequelae continue to evolve. A prolonged immunologic phase could follow the initial phase of viral replication.[4] Studies mainly concentrate on the role of anti-inflammatory agents during the acute immunologic phase, and little is known about the prolonged use of nonspecific immune modulators such as corticosteroids in patients with COVID-19-related diffuse interstitial lung abnormalities (DILA). Despite the evidence supporting the benefits of corticosteroids in COVID-19, the optimum dose and duration of corticosteroid therapy in different clinical situations and stages of COVID-19 are still being determined due to the substantial heterogeneity of the disease.

During the COVID-19 pandemic, data on the efficacy of corticosteroids have been limited. However, the pandemic has been a powerful stimulus for clinical research addressing the benefits of prolonged corticosteroids for improving lung parenchyma abnormalities and preventing possible fibrosis. To obtain a more comprehensive understanding of the clinical outcomes of COVID-19 treated with long courses of steroids, we conducted a retrospective study analysing CT imaging based on the severity score and the clinical parameters.

MATERIALS AND METHODS

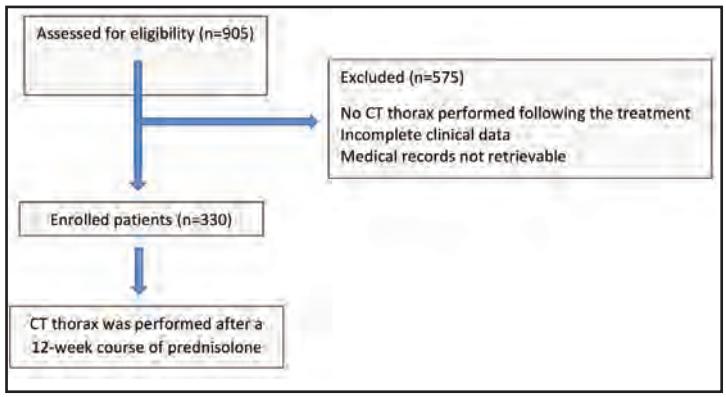
Study Design and Participants

This study was a single-centre, retrospective, cross-sectional analysis of patients with moderate to severe COVID-19 pneumonia treated with a 12-week course of prednisolone at the Teaching Hospital Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz (UKM-HCTM). The study period spanned from January 2021 to December 2021, during the second peak of the COVID-19 pandemic. Inclusion criteria for the study were patients who tested positive for COVID-19 with a positive nasopharyngeal specimen at real-time reverse transcription polymerase chain reaction (RT-PCR) and who received a 12-week course of corticosteroids (prednisone 0.5mg/kg taper over 12 weeks) with available CT thorax before and after corticosteroid treatment. Exclusion criteria included patients who did not undergo CT before and after treatment or incomplete or irretrievable data. This study adhered to the Declaration of Helsinki and was approved by the ethics committee of the UKM-HCTM (HTM-2021-023). The ethics board waived informed consent as the study was retrospective.

Data collection

Data collection involved using a standardised data collection form to retrieve information from the patient's case notes and electronic health record system. Baseline demographic data, clinical history, comorbidities, vital signs, classic COVID-19 symptoms, laboratory values on the day of admission, radiological characteristics, spirometry data, and treatment administered for COVID-19 were manually collected. The chest HRCT images were retrieved and evaluated using picture archiving and communication systems (PACS). Two physicians reviewed the data, and a third physician was consulted to adjudicate any differences in interpretation between the two primary researchers.

Enrolment flow chart of patients with moderate to severe COVID-19:



Lung Imaging Acquisition and CT Quantitative Evaluation

All subjects underwent HRCT (Toshiba Aquilion 640 slices) thorax scan in the supine position during end inspiration. The detailed parameters for CT acquisition were reconstructed at 1.0mm slice thickness, with a 1 mm increment and a sharp reconstruction kernel.

The severity of lung involvement was assessed using a previously described quantitative 25-point CT severity score that is an effective tool in estimating the severity of COVID-19 lung involvement.[5]

CT Severity Score

- A quantitative and a qualitative CT imaging analysis was performed by two blinded expert radiologists with respective 5 years of thoracic imaging experience. Final scores were determined by consensus in case of an inconsistency.
- The CT findings were reported according to the Radiological Society of North America expert consensus document on reporting chest CT findings related to COVID-19.[6]
- Pulmonary abnormalities were quantitatively estimated using a scoring system that assigned a score of 0 to 5 to each of the five lung lobes based on the extent of involvement: 0, no involvement; 1, < 5%; 2, 5-25%; 3, 26-49%; 4, 50-75%; and 5, >75% involvements. Maximum total score was 25.[5]
- The sum of the individual lobar scores constituted the total CT score, which ranged from 0 (no involvement) to 25 (maximum involvement).

The following CT descriptive terms were used: ground glass opacity (GGO), consolidation, interseptal lobar thickening, reverse halo pattern, reticulation or parenchymal band and crazy paving pattern. The chest CT was performed within 2 weeks following the completion of the prednisolone treatment.

Pulmonary Function Tests

In accordance with the American Thoracic Society/European Respiratory Society guidelines, certified technicians conducted outpatient pulmonary function tests within 2 weeks following the completion of the prednisolone treatment.[7] The analysis included forced expiratory volume

Table I: Demographic and baseline clinical characteristics of patients with diffuse interstitial lung abnormalities following COVID-19.

Characteristic	n=330
The severity of the disease, no (%)	
Category 4	285 (86)
Category 5	45 (14)
Gender	
Male: Female	1.3: 1
Age, mean (SD), y	54.6 (14.2)
Age group, No. (%), y	
<18	2 (0.6)
18-29	16 (4.9)
30-39	35 (10.6)
40-49	60 (18.2)
50-59	80 (24.2)
60-69	89 (27)
≥70	48 (14.5)
Duration of symptoms, mean (SD), days.	6.07 (2.75)
Smoking history, No. (%)	
Current-smoker	21 (6.4)
Former-smoker	25 (7.6)
Comorbidities, no (%)	
a. OSA/OHS	6 (1.8)
b. COPD	4 (1.2)
c. Bronchial asthma	10 (3)
d. ILD	0 (0)
Non-respiratory comorbidities	
a. Diabetes mellitus	130 (39.4)
b. Hypertension	183 (55.5)
c. Obesity	22 (6.7)
d. Autoimmune diseases	4 (1.2) RA, MNG, SLE, ITP
e. CKD	14 (4.2)
No comorbidities	73 (22.1)
Pneumothorax/pneumomediastinum, no (%)	9 (2.7)
Initial prescribed treatment, no (%)	
Dexamethasone	65 (19.7)
Methylprednisolone	168 (50.9)
Baricitinib	58 (17.6)
Tocilizumab	50 (15.2)
Tofacitinib	5 (1.5)
Favipiravir	92 (27.9)
Hospital stay, mean (SD), days	16.22 (10.22)

Definition of abbreviations: OSA/OHS = obstructive sleep apnoea/obesity hypoventilation syndrome; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; CKD = chronic kidney disease; COVID-19 = coronavirus disease 2019.

in 1 second (FEV_1), forced vital capacity (FVC), FEV1/FVC ratio, diffusing capacity of the lungs for carbon monoxide (DLCO) adjusted to haemoglobin, DLCO/alveolar volume (VA), and forced expiratory flow 25-75 (FEF25-75). An abnormal value was defined as lower than 80% predicted. Pulmonary function tests (PFTs) with reduced FVC or total lung capacity (TLC) (<80% predicted) but normal or improved FEV1/FVC (>70%) were classified as restrictive ventilatory impairment, while DLCO <80% predicted was considered as diffusion capacity impairment.[8]

Treatment Protocol

Patients diagnosed with DILA are administered systemic corticosteroids when presenting with any of the following indications: i) moderate to severe COVID-19 pneumonia; ii) requiring oxygen supplementation; iii) resting hypoxia with SpO2 <90%. The use of corticosteroids is based on the treatment protocol for inflammatory interstitial lung diseases, such as organising pneumonia and hypersensitivity pneumonitis.[9,10] Although guidelines suggest administering corticosteroids at a dose of 0.5-1mg/kg prednisolone and gradually tapering the dosage over several weeks to months, we have modified the steroid (prednisolone) regime by prescribing 0.5mg/kg body weight over 4 weeks, followed by 20mg daily for 4 weeks, 10mg daily for 2 weeks, and 5mg daily for 2 weeks. Therapeutic interventions were conducted in accordance with the multidisciplinary consensus guidelines on diagnosing and treating COVID-19 established by our centre. In the acute phase of the illness, COVID-19 treatment was initiated upon admission at the discretion of attending physicians, guided by clinical symptoms and CT images.

Outcome of the Treatment

The primary composite outcome was a change in CT scores after a 12-week course of prednisolone therapy. The secondary outcomes assessed were related to prednisolone therapy and included changes in lung physiology and clinical parameters.

Statistical Analysis

In this study, we compared the severity of DILA before and

Table II: Admission symptoms, laboratory values, initial and maximum respiratory support from patients with DILA following COVID-19.

Admission symptoms and laboratory values	n=330
Admission symptoms, no (%)	
Cough	228 (69.1)
Dyspnoea	163 (49.4)
Sore throat	13 (3.9)
Fever	268 (81.2)
Anosmia	21 (6.4)
Diarrhoea	55 (16.7)
Laboratory values on the day of admission, mean (SD)	
Leucocytes, 109/L	8.44 (3.78)
Absolute neutrophil count, 109/L	6.48 (3.57)
Absolute lymphocyte count, 109/L	1.34 (0.68)
Absolute monocytes count, 109/L	0.68 (1.07)
Neutrophils lymphocytes ratio (NLR)	6.06 (4.99)
Platelet count, 109/L	225.83 (94.28)
C-reactive protein, mg/dl	16.4 (77.23)
Ferritin, ug/L	2054.88 (2443.35)
Lactate dehydrogenase, U/L	533.95 (388.87)
D-dimer, µg/ml	3.65 (30.44)
Alanine aminotransferase, U/L	53.33 (42.59)
Alkaline phosphatase, U/L	82.54 (48.34)
Albumin, g/l	32.42 (4.90)
Bilirubin, umol/l	12.68 (8.82)
Blood urea nitrogen, mmol/L	6.14 (6.13)
Creatinine, umol/l	109.76 (123.06)
PaO2/FiO2, mmHg on presentation, mean (SD)	236.6 (107.08)
RS on presentation, no (%)	
Nasal prong	145 (43.94)
Rebreather mask (FM+VM)	81 (24.55)
High-flow non-rebreather mask	44 (13.33)
HFNC	11 (3.33)
CPAP	5 (1.52)
BiPAP	3 (0.91)
MV	8 (2.42)
Maximum RS, no (%)	
Nasal prong	82 (24.85)
Rebreather mask (FM+VM)	66 (20)
High-flow non-rebreather mask	78 (23.64)
HFNC	38 (11.52)
CPAP	5 (1.52)
BiPAP	8 (2.42)
MV	48 (14.55)

Definition of abbreviations: PaO2/FiO2: arterial oxygen tension/inspiratory oxygen fraction; RS: respiratory support; FM: Face mask; VM: Venturi mask; HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure; BiPAP: Bilevel positive airway pressure; MV: mechanical ventilation.

Table III: Results after structured assessment of patients with DILA treated with a 12-week course of prednisolone after COVID-19.

Parameter	n=250
mMRC upon clinic follow-up (IQR)	1 (0-1)
6 MWT distance, m	274.34 (75.92)
6 MWT desaturation (SpO_2 dropped > 3%), no %	47 (18.88)
Full lung function test	
FEV_1, L	2.18 (0.62)
FEV_1, % of predicted	84.34 (16.76)
FVC, L	2.62 (0.74)
FVC, % of predicted	74.91 (14.68)
FEV_1/FVC, % median	82.48 (7.73)
FEF 25-75, L	2.77 (1.16)
FEF 25-75% predicted	97.05 (37.59)
DLCO adj, L	17.83 (7.41)
DLCO adj, % of predicted	81.77 (36.2)
DLCO/VA, L	4.36 (0.99)
DLCO/VA, % of predicted	108.31 (22.64)

Definition of abbreviations: 6MWT = 6-minute walk test; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; MRC = Medical Research Council; SpO_2 = oxygen saturation as measured by pulse oximetry; TLCO = transfer factor of the lung for carbon monoxide. Data are presented as mean + standard deviation unless otherwise stated.

Table IV: CT pattern at baseline and after a 12-week course of prednisolone.

CT pattern	Baseline n (%)	After a long course of prednisolone n (%)
GGO	323 (97.88)	314 (95.15)
Perilobular density	269 (81.52)	107 (32.42)
Consolidation	239 (72.42)	11 (3.33)
Crazy paving	42 (12.73)	4 (1.21)
Septal thickening	10 (3.03)	2 (0.67)
Parenchymal band/reticulation	28 (8.48)	184 (55.76)
Reverse halo sign	14 (4.24)	0

Table V: Baseline CT score versus CT score after a 12-week course of prednisolone therapy.

Lobe involved	Baseline CT score	CT score after prednisolone therapy	p-value)
RUL	3.30 (1.28)	1.54 (1.18)	p<0.001
RML	2.94 (1.43)	1.41 (1.12)	p<0.001
RLL	3.91 (1.09)	1.83 (1.25)	p<0.001
LUL	3.26 (1.27)	1.57 (1.20)	p<0.001
LLL	3.92 (1.10)	1.82 (1.31)	p<0.001

Definition of abbreviations: RUL = right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe. Data are presented as mean (SD).

Table VI: Analysis of the confounding factors.

CT score	Ventilated	Not ventilated	p-value
Baseline CT score	18.5 (5.3)	17.3 (5.3)	0.646
CT score after treatment	10 (6.2)	8.6 (5.5)	0.724
	With tocilizumab	Without tocilizumab	
Baseline CT score	20.1 (5.2)	16.8 (5.1)	<0.001
CT score after treatment	9.5 (6)	8.5 (5.4)	0.225
	With baricitinib	Without baricitinib	
Baseline CT score	17.1 (4.9)	17.3 (5.4)	0.786
CT score after treatment	9 (5.5)	8.5 (5.5)	0.589

Notes: The result is presented as mean (standard deviation).

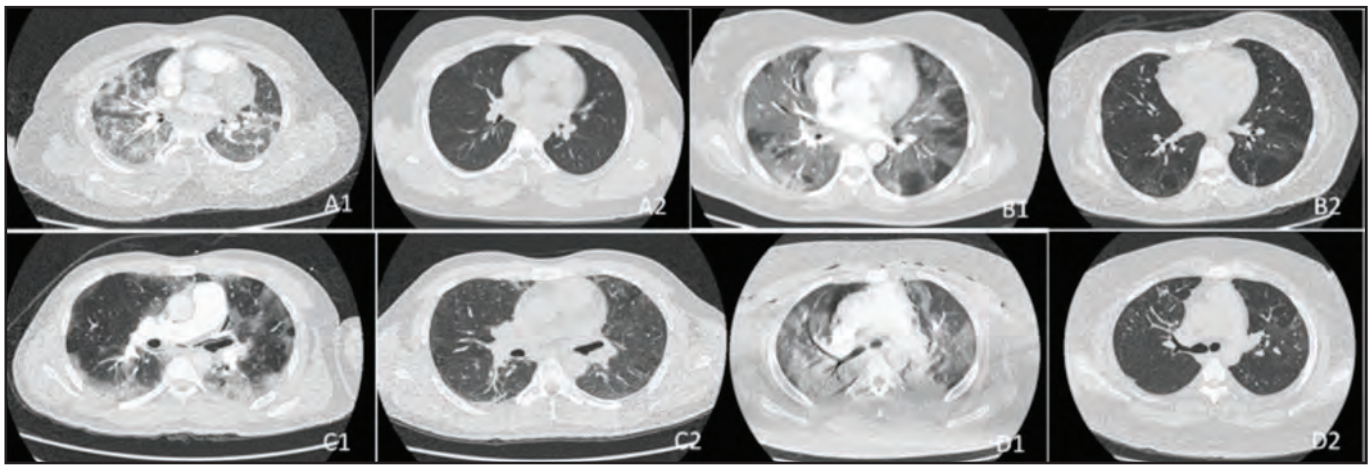


Fig. 1: Axial chest HRCTs suggest a significant improvement in CT scores after CS therapy. (A1) Pre-CS: consolidation and perilobular density of RML, RLL, and LLL. (A2) Post-CS: minimal linear parenchymal bands. Reduction of CT score, consolidations and perilobular density. (B1) Pre-CS: extensive GGO and the arcade-like all lobes. (B2) Post-CS: residual GGO and linear parenchymal bands. Reduction of CT score and GGO. (C1) Pre-CS: peripheral consolidation and GGO of all lobes. (C2) Post-CS: GGO and reticulation. Reduction of CT score, consolidations and GGO. (D1) Pre-CS: extensive consolidation of all the lobes, pneumomediastinum and subcutaneous emphysema. (D2) Post-CS: complete regression of consolidations and pneumomediastinum with residual reticulation. Reduction of CT score and resolution of consolidation and pneumomediastinum.

Definition of the abbreviation: CS, corticosteroid; GGO, ground glass opacity; HRCT, high-resolution computed tomography; LLL, left lower lobes; RML, right middle lobe; RLL, right lower lobe.

after a 12-week course of prednisolone therapy by analysing the CT scores and exploring the association between these variables. Categorical data were presented as numbers and percentages, while continuous variables were expressed as median and interquartile range (IQR) or mean and standard deviation. The Student's t-test was used for normally distributed continuous variables, and the Mann–Whitney U test was used for non-normally distributed continuous variables. The changes in CT scores were assessed using an independent samples T-test. Adverse events and radiology findings were reported descriptively. Categorical variables were compared using a chi-squared test or Fisher's exact test, as appropriate. Pearson's correlation coefficient and Cox regression examined the relationship between variables. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (version 26; SPSS, Chicago, IL, USA).

RESULTS

Demographic Data

The present study assessed a cohort of 905 patients, of which 575 were excluded based on predetermined criteria that included no CT thorax performed following prednisolone treatment, incomplete clinical data, or medical records not retrievable. The mean (SD) age of the enrolled patients was 54.6 (14.2) years, with a range spanning from 14 to 84 years. Females constituted 43% of the cohort. The prevalence of current smokers was 6.4%, whereas non-smokers and former smokers accounted for 86% and 7.6% of the cohort, respectively. Tables I and II outline patients' demographic and baseline clinical characteristics with DILA following COVID-19.

Clinical Characteristic

On presentation, 268 (81.2%) patients manifested fever, while nearly half presented with cough and dyspnoea (69.1% and 49.4%, respectively). The mean (SD) duration from symptom onset to deterioration was 6.95 (4.61) days. Of the cohort, 257 (77.9%) had pre-existing medical conditions, with hypertension being the most common comorbidity (n=183, 55.5%). Among respiratory comorbidities, bronchial asthma was the most prevalent, observed in 10 (1%) patients. Fifty-eight (17.6%) patients were diagnosed with pulmonary embolism during the acute phase of COVID-19.

Upon presentation to the emergency department, 297 (90%) required oxygen supplementation, and 48 (14.6%) required mechanical ventilation, with a mean (SD) duration of ventilation of 8.73 (6.65) days. Throughout hospitalisation, methylprednisolone was the most frequently administered therapy (50.9%). The mean (SD) hospital stay was 16.22 (10.22) days, with 11 patients (3.3%) staying for five days or less, 101 (30.6%) for 6-11 days, 97 (29.4%) for 11-15 days, and 121 (36.7%) for more than 16 days. Twelve (3.64%) patients required home oxygen upon discharge.

The side effects of long-course steroids include weight gain, uncontrolled diabetes mellitus, infection (one pulmonary tuberculosis, one MSSA bacteraemia, one herpes infection) and others (two cushingoid, three hair loss, two acnes, one insomnia, two dyspepsia)

Laboratory Parameter

At the time of presentation, 16 (4.8%) patients had leucopenia, 98 (29.7%) had lymphopenia, eight (2.4%) had neutropenia and 59 (17.9%) had thrombocytopenia. Of the total cohort, 322 (97.6%) patients had lactate dehydrogenase levels > 220 U/L, 313 (94.8%) had CRP levels >1mg/dL, and 31 (9.4%) had D-dimer levels >4µg/mL. The mean (SD) ferritin level was elevated at 2054.88 (2443.35) µg/L. Liver enzymes were elevated (>2 times the upper normal limit) in 53 (16.06%) patients. There was no significant correlation between the baseline CT score and the NLR, CRP, and ferritin levels upon the initial presentation to the hospital.

Pulmonary Function Test

A total of 250 (75.8%) patients underwent full lung function testing after receiving a 12-week prednisolone treatment (Table III). The mean post-treatment values for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and diffusing capacity of the lungs for carbon monoxide (DLCO) was 2.18 L (84.4% predicted), 2.62L (74.9% predicted), and 17.83L (81.8% predicted), respectively. Of the patients, 163 (65.2%) had FVC impairment (FVC <80% predicted). Impairment of FEV1/FVC (FEV1/FVC <0.7) was observed in 13 (5.2%) patients. Mild DLCO impairment was present in 71 (28.4%) patients, moderate impairment in 46 (18.4%), and severe reduction in DLCO in 3 (1.2%) patients. After treatment, there were significant negative correlations ($p<0.05$) observed between CT scores and DLCO ($p=0.003$), FVC ($p=0.004$), as well as FEV1 ($p=0.042$), with higher CT scores being associated with lower values of DLCO, FEV1, and FVC.

Radiological Features

We found a complete radiological response in four (1.2%) subjects. The three most common baseline CT patterns were GGO (323, 97.9%), perilobular density (269, 81.5%) and consolidation (239, 72.4%). Following a 12-week course of prednisolone treatment, the most common CT patterns observed were GGO in 314 patients (95.2%), parenchymal band/reticulation in 184 patients (55.8%) and perilobular densities in 107 patients (32.4%). The patterns of lung changes are depicted in Table IV.

CT Severity Score

In terms of oxygenation and length of stay (LOS), patients with a higher baseline CT score (CT score >10) had significantly worse parameters than those with a lower CT score (CT score ≤10): the median (IQR) PaO2/FiO2 ratio on presentation was lower [230 (145-300) vs. 300 (236-365), $p<0.001$], and the median duration of hospitalisation was longer [14 (10-21) vs. 10 (7-12) days, $p<0.001$].

The mean (SD) CT scores at baseline and after treatment for each lung lobe were depicted in Table V. The mean (SD) baseline total CT score was 17.3 (5.27), and after treatment, it was 8.61 (5.48). There was a significant improvement in the mean (SD) CT severity score after a 12-week course of prednisolone treatment compared to the baseline score [8.6 (5.5) vs. 17.3 (5.3), $p<0.001$]. Figure 1 depicts the change in CT findings before and after treatment in patients with post-COVID-19 DILA.

DISCUSSION

While most COVID-19 patients manifest mild symptoms, a significant portion may experience prolonged inflammation that results in persistent respiratory symptoms and imaging abnormalities, as documented in prior studies.[11-12] The COVID-19 virus can trigger the secretion of cytokines, which can lead to severe alveolar injury. The question of whether prolonged corticosteroid therapy should be utilised to treat diffuse parenchymal abnormalities in COVID-19 patients remains a highly debated topic. Lung autopsy findings have shown diffuse alveolar injury with cellular fibromyxoid exudate, interstitial mononuclear inflammatory infiltration and hyaline membrane formation, resembling acute respiratory distress syndrome (ARDS).[13] These findings suggest that increased immune and inflammatory responses mediate the COVID-19 virus infection and that the severity of the disease is correlated with immune factor concentrations. This study describes the clinical and radiological outcomes observed in a large cohort of patients with moderate to severe COVID-19 DILA following their initial hospitalisation. The patients were administered 12-week course of oral prednisolone to avert the onset of pulmonary fibrosis and permanent functional deficits.

Corticosteroids are a class of immunosuppressive drugs that exhibit anti-inflammatory properties, reducing systemic inflammation. In COVID-19 pneumonia, corticosteroids can have beneficial and deleterious effects depending on the stage of infection. Early administration of corticosteroids may suppress host antiviral activity and promote viral replication and alveolar epithelial cell cytopathic damage. However, in the later stages of infection, corticosteroid therapy can reduce proinflammatory cytokines, enhance anti-inflammatory cytokines and pro-resolving lipids, improve epithelial barrier integrity, decrease lung vascular permeability, and promote alveolar oedema fluid clearance. Studies reported administration of corticosteroids in the hyperinflammation stage in COVID-19 patients may suppress the cytokine storm and improve oxygenation, but the results were inconsistent.[14-16]

It has been reported that CT evidence of air trapping corresponds to postviral constrictive bronchitis, while GGO corresponds to post-OP and post-DAD fibrosis.17 Cryptogenic OP has been studied to understand the clinical and imaging patterns of OP in COVID-19.[18] OP is typically highly responsive to steroids, with opacities that improve or resolve with treatment, although residual fibrosis may occur. This residual fibrosis often has a pattern that resembles nonspecific interstitial pneumonia with basilar predominant reticulation, traction bronchiectasis, and subpleural sparing.[19]

Several randomised trials suggest that systemic corticosteroids enhance clinical outcomes and reduce mortality among hospitalised COVID-19 patients requiring supplemental oxygen.[20,24] However, managing COVID-19-related DILA remains unclear. Some physicians take a 'wait-and-see' approach, while others administer prolonged corticosteroids to patients with persistent symptoms and DILA.[22] Duration of corticosteroid use ranges from 3 to 11 weeks, and studies have shown that this treatment improves clinical symptoms, oxygenation, and radiological abnormalities. Glucocorticoids have been reported to improve diffuse parenchymal lung abnormalities in symptomatic COVID-19 patients, though the complete radiological response is rare.[22] Approximately 22% of severe COVID-19 patients show radiological improvement at 12 weeks, with 38% showing improvement at six months.[23] A meta-analysis suggests that corticosteroids are associated with lower mortality among critically ill patients, whether or not they receive invasive mechanical ventilation.[24] The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial found that 6mg/d of dexamethasone led to a 2.8% absolute reduction in mortality, with the most significant benefit observed in patients receiving invasive mechanical ventilation or oxygen alone. However, potential harm was noted in patients not requiring oxygen.[25] A study indicated that administering oral methylprednisolone at 0.5mg/kg/day for 4 weeks improved radiological abnormalities, oxygen saturation, FVC and 6-minute walking distance in post-COVID-19 ILD.[26] The question remains whether post-COVID-19-related DILA will resolve spontaneously or due to the effects of corticosteroid therapy. Some patients may require more extended corticosteroid therapy to achieve symptomatic relief and radiological improvement. In this study, patients with COVID-19-related DILA and hypoxic respiratory failure were given a trial of corticosteroids in tapering doses over 12 weeks.

Chest CT plays an important role in both diagnosing COVID-19 pneumonia and assessing the extent of lung involvement. Several studies have demonstrated a strong correlation between the 25-point CT score and the clinical severity and outcome of COVID-19 infection.[5] Additionally, these studies have found a positive association between CT scores, inflammatory markers, and oxygen requirement, which helps define the severity of the disease.[5] Quantitative CT analysis has proven to be a valuable tool for monitoring the severity of COVID-19 pneumonia and evaluating treatment response, with consistently high reproducibility in results.[26] Study also demonstrated strong interrater reliability between radiologists regarding the CT score.[27] Our study assesses corticosteroid treatment response in COVID-19 using quantitative CT analysis. Our findings indicated that prednisolone therapy had a beneficial effect in expediting the recovery of compromised lung function in patients with moderate to severe COVID-19 pneumonia, as evidenced by the CT score.

The reported CT sequelae commonly observed after COVID-19 infection include pulmonary interstitial changes, which include ground-glass opacities (GGO) and irregular lines that may persist for beyond six months.28 Additionally, more severe cases of COVID-19 have been linked to increased fibrosis, bronchial dilatation, parenchymal bands, and coarse subpleural reticulation. A study indicated that patients who survived ARDS caused by COVID-19 were more likely to exhibit fibrotic changes. These survivors tended to be older, male, with lower BMI, longer duration of oxygenation requirement (MV or HFNC duration), and worse sedative status.[29,31] Another study revealed that persistent interstitial lung abnormalities were still evident in 2-year follow-up CT scans, with approximately one-fifth showing fibrotic

abnormalities.28 In the present study, the most common CT findings were the peripheral distribution, GGO, consolidation, and crazy-paving pattern. However, whether all these radiographic lesions eventually resolve, become permanent, or progress over time remains uncertain based on this data and the available medical literature.

In COVID-19, pulmonary function tends to improve over time, although it may persistently remain impaired in some patients for several months or even years.[32,33] The reduction of respiratory function observed after COVID-19 were more pronounced in patients who developed ARDS. In our group of patients, approximately half exhibited a decline in DLCO during follow-up, and those with higher CT scores showed greater DLCO impairment. These findings align with previously reported studies. Autopsy findings from COVID-19 cases have shown varying degrees of alveolar destruction and interstitial fibrosis, which may partially account for the impaired DLCO. Interestingly, a small percentage of patients with no residual imaging abnormalities displayed a decrease in DLCO. We hypothesise that this group of patients might have residual microcapillary or alveolar abnormalities post-COVID-19 infection. The residual dyspnoea in our patient cohort underscores the need for specific attention to address this issue. Patients experiencing persistent dyspnoea and impaired DLCO or DILA should be offered pulmonary rehabilitation to improve their lung function.

It is worth mentioning that although only a small percentage of the study cohort received tocilizumab (15.25%) and baricitinib (17.6%), there was an observed improvement in the CT score post-treatment (Table VI). However, this result should be approached with caution since even those who didn't receive tocilizumab or baricitinib also exhibited some improvement in CT scores after treatment, likely attributable to prednisolone treatment. This observation aligns with another study where no significant differences were noted in CT scores 14 days post-treatment with tocilizumab.[34] The authors of that study suggested that the semi-quantitative assessment of lung involvement, relying on visual scoring of lobar extent, might have limitations in detecting subtle density changes, especially in short follow-up assessments.[34] While baricitinib has demonstrated effectiveness in reducing the need for invasive mechanical ventilation and mortality in COVID-19 patients, there hasn't been any study specifically examining its impact on CT scores.[35] Another factor analysed for potential confounding effects was the CT scores between ventilated and non-ventilated patients. Although the baseline CT score was higher in the ventilated group, the difference did not reach statistical significance (Table VI). However, it's noteworthy that the baseline CT score proved to be informative, as a previous study demonstrated that semiquantitative chest CT analysis at hospital admission accurately identified patients who were less likely to respond well to non-invasive positive pressure ventilation.[36]

In the absence of a control arm in our study, we conducted a comprehensive literature review focusing on the natural course of post-COVID-19 CT changes and studies utilising a similar CT severity scoring system to evaluate the progression of CT findings. A study involving patients treated with a combination of methylprednisolone and tocilizumab revealed mean (range) CT scores for categories 4 and 5 COVID-19 during hospitalisation and 3-month follow-up to be 14.7 (6.5-24) versus 8.3 (2.5-20) and 16.9 (11-22.5) versus 10.4 (3.5-18.5), respectively.37 Another study administering steroids during the acute phase of COVID-19 demonstrated mean (SD) CT scores based on ground-glass opacities (GGO) and consolidation patterns at baseline and 18 months as 20.9 (11.2) vs. 11.1 (5.6) and 7.7 (6.8) vs. 1 (1.7), respectively.[38] Studies focusing on COVID-19 patients with bilateral pulmonary involvement treated with a combination of steroids and intravenous immunoglobulins indicated CT scores at baseline and 8-week follow-up of 10.8 (4.3) vs. 14.5 (6.5), respectively.[39] Meta-analysis indicated that about 32% of the patients had residual CT abnormalities of ground glass opacity and fibrotic-like 1 year after COVID-19.[40] Compared to these studies, our patient cohort exhibited notable improvement in CT scores following 12 weeks of prednisolone treatment.

LIMITATION

This study has several limitations, including its retrospective design and the fact that it was conducted at a single centre, which may introduce selection biases. Additionally, the study only included a subgroup of patients who received 12 weeks of corticosteroid and underwent post-treatment CT scans, potentially limiting the generalizability of the findings to the larger population of COVID-19 patients with diffuse interstitial lung abnormalities.

CONCLUSION

We observed that a 12-week course of systemic corticosteroids resulted in radiological improvement in moderate to severe COVID-19-related diffuse interstitial lung abnormalities (DILA) cases. We found the safety profile of corticosteroid usage to be acceptable. However, corticosteroid therapy should be individualised and tapered off as soon as clinical stability and radiological improvement are achieved. It is unclear if COVID-19-related organising pneumonia or DILA is linked to the risk of progressive pulmonary fibrosis or if corticosteroid treatment might lower the risk. Still, these ideas should be carefully looked at in future studies.

Figure 1. Change in CT findings before and after treatment with a 12-week course of prednisolone in patients with post-COVID-19 diffuse interstitial lung abnormalities.

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