ORIGINAL ARTICLE

Methylprednisolone in the management of post-COVID-19 interstitial lung disease: A randomized trial (STERCOV-ILD)

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ABSTRACT

Background and aim: Post-COVID-19 Interstitial Lung Disease (ILD) is controversial and need for treatment is unclear. The aim of this study was to investigate the efficacy of methylprednisolone in the management of post-COVID-19 ILD in comparison to standard of care.

Methods: In this multicentre, randomized controlled clinical trial, patients with post-COVID ILD were assigned to two groups: the steroid group received oral methylprednisolone at a dose of 0.5 mg/kg/day, while the control group received supportive therapy. The primary outcome was proportion of patients with functional improvement (defined as the absence of hypoxemia/desaturation during 6MWT) at twelve-weeks.

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Results: A total of 229 patients with post-COVID ILD patients (124 in the steroid group and 104 in the control group) completed the study. At 12-weeks, functional improvement rate was higher in the steroid group compared to the control group (74.2% vs. 55.2%, OR:2.33 [95% CI:1.34–4.06], p=0.0041). Radiological improvement was observed in 61.3% of the steroid group compared to 46.7% of the controls (OR:1.81 [95% CI:1.07–3.06], p=0.037). The mean increase in FVC (7.2% vs 3.7%, p=0.03), 6MW distance (91 vs 41 meters, p<0.001), and SpO2 (2.33 vs 1.21, p=0.002) was significantly higher in the steroid group. Multivariate regression analysis revealed that the following variables were associated with poorer outcomes: smoking (OR:0.932 [95% CI:0.875–0.992], p=0.028), older age (OR:0.951 [95% CI:0.912-0.99], p=0.035), and severe COVID-19 (OR:0.233 [95% CI:0.068–0.799], p=0.029.
Conclusions: Methylprednisolone improved oxygen saturation, FVC, exercise capacity, and radiological resolution in patients with post-COVID-19 ILD compared to the natural course of the disease.

Key words: COVID-19, hypoxemia, interstitial lung disease, methylprednisolone, vital capacity

Introduction

Subsequent radiological assessments of COVID-19 survivors reveal parenchymal and subpleural bands and ground glass opacities (GGOs) (1,2) with some cases progressing to organizing pneumonia and fibrosis (3–5). Functional impairments predominantly present as a mild to moderate reduction in the forced vital capacity (FVC) % predicted (6,7). Some cases may exhibit exercise-induced hypoxemia and reduced six-minute walking distance (6MWD) (8). 10.6% of survivors continuing to experience functional deficits even one year after recovery (9). These findings have recently been termed post-COVID interstitial lung disease (ILD) (10). Post-COVID-19 ILD remains incompletely understood, raising questions about the necessity of treatment. While some authors argue that radiological and functional abnormalities linked to COVID-19 do not endure long term and might regress spontaneously without intervention (11,12), the possibility of incomplete spontaneous recovery necessitates the determination of effective treatment strategies to enhance prognosis. The administration of systemic glucocorticoids hold promise as a treatment avenue for post-COVID-19 ILD. The key factors that initiate ILD after SARS-CoV-2 infection can be associated with an innate immune response, hyperactivation of macrophages, and high level of proinflammatory and profibrotic factor production (13–17). Alveolar epithelial type II cells express and release cytokines and growth factors (14). Glucocorticoids can reduce the synthesis of inflammatory chemicals by preventing translocation of transcription factors, especially Nuclear Factor kappa B (NFκB) (18). Through inhibition of the NFκB pathway, inflammatory cells begin to produce anti-inflammatory cytokines (19). Glucocorticoids reduce the expression of phospholipase A2 (20) synthesis of arachidonic acid metabolites mediate major key steps in the process of inflammation, is inhibited. Also, margination, chemotaxis and phagocytosis by macrophages are inhibited by corticosteroids (21). Unfortunately, systemic glucocorticoids have various side effects, therefore, it is essential to determine whether systemic glucocorticoids are of benefit. The aim of the current study was to investigate the efficacy of methylprednisolone in the treatment of post-COVID-19 ILD compared to the untreated patients who can reflect the natural course of post-COVID-19 ILD.

Methods

Study design and participants

This national, multicentre, a Phase III, 12-week, open-label, randomised controlled trial included individuals with post-COVID-19 ILD (ClinicalTrials.gov, NCT:04988282). The study protocol received approval

from Yüksek İhtisas University Clinical Trials Ethics Committee (Approval Date: 31.03.2021, Number: 2021-01) and adhered to the ethical principles outlined in the Declaration of Helsinki. Inclusion criteria were as follows: 1. Persistent respiratory symptoms at least 90 days after recovery from COVID-19, 2. Hypoxemia during exercise (desaturation by ≥ 4% during a 6-minute walking test (6MWT), 3. A decrease in FVC (< 80% of the predicted value), 4. Sequelae interstitial changes in pre-enrolment thorax high-resolution computed tomography (HRCT)(10). Exclusion criteria: pre-existing ILD predating the pandemic, cystic bronchiectasis, contraindications for systemic corticosteroids, individuals unable to cooperate for pulmonary function tests (PFTs), individuals younger than 18 years, pregnant, or breastfeeding women. Absence of pre-existing ILD was confirmed with pre-pandemic chest CT images of the patients. Previous thoracic radiologic studies of all eligible patients were screened through the national electronical patient database. Informed and written consent was secured from all participants.

Randomisation and intervention

Between May 23, 2021, and November 30, 2021, a total of 262 patients with post-COVID-19 ILD were assigned to one of two arms with an allocation ratio of 1:1 according to the table of random numbers method by a team of two pulmonologists. The arms consisted of standard treatment plus methylprednisolone (steroid group, n:131) and standard treatment alone group (control group, n:131). For the steroid group, oral administration of methylprednisolone was initiated at a dosage of 0.5 mg/kg/day (with a maximum dose: 48 mg/day) for a period of 4 weeks, followed by a gradual reduction of 25% every 2 weeks. The intended duration of steroid therapy was 12 weeks. Prophylaxis for *pneumocystis jirovecii* pneumonia (PJP) was administered to all patients receiving steroid therapy using trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 800/160 mg (double-strength) three times per week, in accordance with institutional protocol. Patients in the control group received symptom-relief treatments including bronchodilators, inhaled corticosteroids, and anti-tussives because there is no standard therapy for post-COVID-19 ILD. At randomization and at the end of the 12-week study period, participants underwent a comprehensive assessment, including the evaluation of persistent COVID-19-related symptoms, modified Medical Research Council (m-MRC) dyspnoea score, oxygen saturation (SpO_2) while breathing room air, PFTs, 6MWT, thorax HRCT, and blood tests (blood sugar, complete blood count, liver and kidney function tests, C-reactive protein, troponin I, D-dimer, fibrinogen, and ferritin). All participants were also invited for follow-up visits at 10 days and 4 weeks post-randomization.

Outcomes

The primary outcome measure was the improvement in functional capacity during exercise, defined as the absence of desaturation during the 6MWT at twelve weeks. The proportion of patients who did not experience desaturation during the 6MWT was compared between the treatment arms at the twelve-week mark. Secondary outcomes included radiological recovery as assessed by HRCT and decrease in dyspnoea severity measured by the mMRC dyspnoea score. Changes in FVC, SpO_2, and 6MWD at twelve weeks were also evaluated and compared between the groups. Additionally, the incidence of all-cause emergency visits, hospitalizations, and mortality rates were calculated. Outcomes were measured by a team including two pulmonologists and a radiologist, who were blinded to the treatment assignments of the participants.

Thorax HRCT

HRCT scans were evaluated at randomisation period. Radiologic patterns were categorized into four groups (1. Mild GGOs, 2. Extensive GGOs, 3. Mild fibrotic bands, 4. Extensive fibrotic bands) according to the predominance of the ground glass or bands. Extension of radiological lesions was classified into two: 'extensive' if there was an involvement more than 25% of lung parenchyma or 'mild' if involvement was less than 25%. The reader assessed the following findings: predominant pattern, septal thickening, and bronchiectasis. The lobes of two lungs were scored on a scale of 0 to 5; with 0 indicating no involvement; and 5, more

than 75% involvement (22). At the end of the study period a follow-up CT scan was obtained. The difference between the randomisation phase and follow up CT scans was assessed.

Statistical analysis

The minimum number of sample size required for the primary endpoints of the current study was determined via G-Power 3.1.9.7 software. Given a significance level of 0.05, effect size of 0.5, and statistical power 0.95; the minimum desired number of participants was calculated as 210 (105 participants in methylprednisolone group, and 105 in the control group). The study conducted descriptive analyses on quantitative variables, including mean and standard deviation calculations. For categorical variables including functional and radiologic improvement and adverse events, proportions were compared using chi-square between the study arms. The significance of the difference in functional tests (SpO_2, FVC, 6MWD) between the groups was investigated after the normality of continuous variables were checked. Parametric tests were used when distributions were normal, non-parametric (Mann-Whitney U) tests were used when not normally distributed. Prespecified subgroup analyses for the primary endpoint were evaluated and logistic regression was used. Multivariable regression model was set up and tested when adjusted for treatment and baseline stratification factors when $p<0.05$. Analyses of primary and secondary endpoints included the patients who completed the study period (n:229), analyses of baseline characteristics contained all randomly allocated participants who did not withdraw the consent (n:251). Statistical significance was set at $p<0.05$.

Results

Baseline characteristics

The baseline characteristics and functional parameters of the 251 assigned patients are summarized in Table 1. 229 patients (n=124 in the steroid group, n=105 in the control group) completed the study period (Figure 1). At the time of randomization in the post-COVID-19 period, the most common symptoms were dyspnoea (n=238, 94.8%), exercise intolerance (n=166, 66%), and fatigue (n=142, 56.6%). The mean ± SD mMRC dyspnoea score was 1.82 ± 0.82, with a mean oxygen saturation of 94.1 ± 3.4% while breathing room air. The mean nadir oxygen saturation during the 6-minute walk test was 82%, and a 6MWD of 374 ± 146 meters. Pulmonary function tests (mean percentage of predicted value ± SD) were as follows: forced expiratory volume in 1 second (FEV1) was 79 ± 19%, FVC was 73 ± 19%, the FEV1/FVC ratio was 87 ± 9%, and the DLCO was 58 ± 21%. The radiological characteristics are shown in Table 2. Three primary patterns were identified on HRCT: GGOs in 35.3% of patients, fibrotic bands in 33.3%, and a mixed pattern of both in 31.3%. The radiological lesions were diffuse, involving more than 25% of the lung parenchyma, in 64.5% of cases. Fibrosis-like changes were observed as follows: interlobular septal thickening in 38.3%, central traction bronchiectasis in 28%, and peripheral cylindrical bronchiectasis in 17.4%. There were no significant differences in baseline spirometry parameters, 6MWD, inflammatory markers, and radiological features between the treatment groups (Table 1 and Table 2). During the acute phase of COVID-19, 73 patients (29.1%) required treatment in the ICU, 133 patients (53%) were treated in hospital wards, and 45 patients (17.9%) were managed as outpatients. During the acute phase of SARS-CoV-2 infection, 191 patients (76.1%) received systemic corticosteroids, while 39 patients (15.6%) were treated with anti-cytokine therapies (Table 3).

Primary and secondary outcomes

At twelve weeks, functional improvement (no desaturation during 6MWT) rate was higher in the steroid group compared to the control group (74.2% vs. 55.2%, OR:2.33 [95% CI:1.34–4.06], p=0.0041) (Table 4). The proportion of patients with an FVC greater than 80% was significantly higher in the methylprednisolone arm (54.1% vs. 33.7%, OR:2.35 [95% CI:1.37–4.03], p=0.0026). Radiological improvement based on HRCT evaluation was observed in 61.3% of the steroid group compared to 46.7% of the control group (OR:1.81 [95% CI:1.07–3.06], p=0.037). Methylprednisolone significantly reduced mMRC dyspnoea

Table 1. Baseline characteristics of the intention-to-treat population.

	Overall (n:251)	Control group (n:121)	Steroid group (n:130)	p
Age, years	60 (12)	60 (12)	59 (11)	0.216
Sex Male Female	 142 (56%) 109 (44%)	 65 (54%) 56 (46%)	 77 (59%) 53 (41%)	0.379
Smoking status Never smoker Active smoker Ex-smoker	 153 (61%) 16 (6%) 82 (33%)	 76 (62.8%) 3 (2.5%) 42 (34.7%)	 77 (59%) 13 (10%) 40 (31%)	0.049*
Cigarettes, package-years	25 (21)	27 (24)	24 (19)	0.63
Body-mass index, kg/m^2	30.5 (6.4)	30.4 (4.8)	30.6 (7.6)	0.614
Comorbidities: Hypertension Diabetes Heart disease Asthma COPD	 111 (44,2%) 74 (29,5%) 40 (15,9%) 20 (8%) 13 (5,2%)	 50 (41.3%) 34 (28.1%) 21 (17.4) 9 (7.4%) 7 (5.8%)	 61 (46.9%) 40 (30.8%) 19 (14.6%) 11 (8.5%) 6 (4.6%)	 0.158 0.545 0.448 0.864 0.761
Modified MRC score	1.82 (0.82)	1.6 (0.7)	2 (0.8)	0.127
Patients receiving home oxygen treatment at baseline	76 (30.3%)	31 (25.6%)	45 (34.6%)	0.135
SpO_2 at baseline	94.1 (3.4)	95.1 (2.4)	93.2 (3.9)	0.06
6MWT distance	374 (146)	388 (151)	360 (140)	0.152
SpO_2 at the end of 6MWT	82 (3.6)	83 (4)	82 (3)	0.788
FEV_1 at baseline (L)	2.28 (0.75)	2.36 (0.82)	2.2 (0.66)	0.106
FEV_1% at baseline	79 (19)	82 (19)	76 (18)	0.07
FVC at baseline (L)	2.6 (0.88)	2.69 (0.97)	2.52 (0.76)	0.158
FVC% at baseline	73 (19)	76 (19)	70 (19)	0.12
FEV_1/FVC% at baseline	87 (9)	87 (8)	87 (10)	0.397
DL_{CO}	58 (21)	58 (20)	58 (22)	0.842
Inflammatory markers C-reactive protein, mg/L D-dimer, mg/dl Lactate dehydrogenase, U/L Ferritin, µg/L Fibrinogen, mg/dL	 18.8 616.4 242.4 311.2 363.9	 17.5 660.6 235 319.4 372.1	 20 574.2 249.3 303.5 356.2	 0.289 0.184 0.262 0.416 0.361

Data are mean (SD) or n (%). *Results are significantly different between the steroid and the control groups (p<0.05). *Abbreviations:* COPD=Chronic obstructive pulmonary disease. DL_{CO}=Diffusing capacity of the lungs for Carbon monoxide. FEV_1=Forced Expiratory Volume at one second. FVC=Forced Vital Capacity. MRC=Medical Research Council. SpO_2=Peripheral oxygen saturation. 6MWT=6 minutes walking test.

score compared with standard care (The mean±SD decrease in mMRC:1.4±0.76 vs 0.7±0.63, p=0,001) (Figure 2). There were no significant differences in all-cause emergency department visits or hospitalizations between the groups (Table 4). One patient in the control group died, no death was seen in the steroid group.

Change in pulmonary functions

Methylprednisolone led to a greater improvement in FVC (mean increase:930 ml vs. 180 ml, p=0.005) and FVC predicted % (mean increase:7.2% vs 3.7%, p=0.03). The mean increase in 6-minute

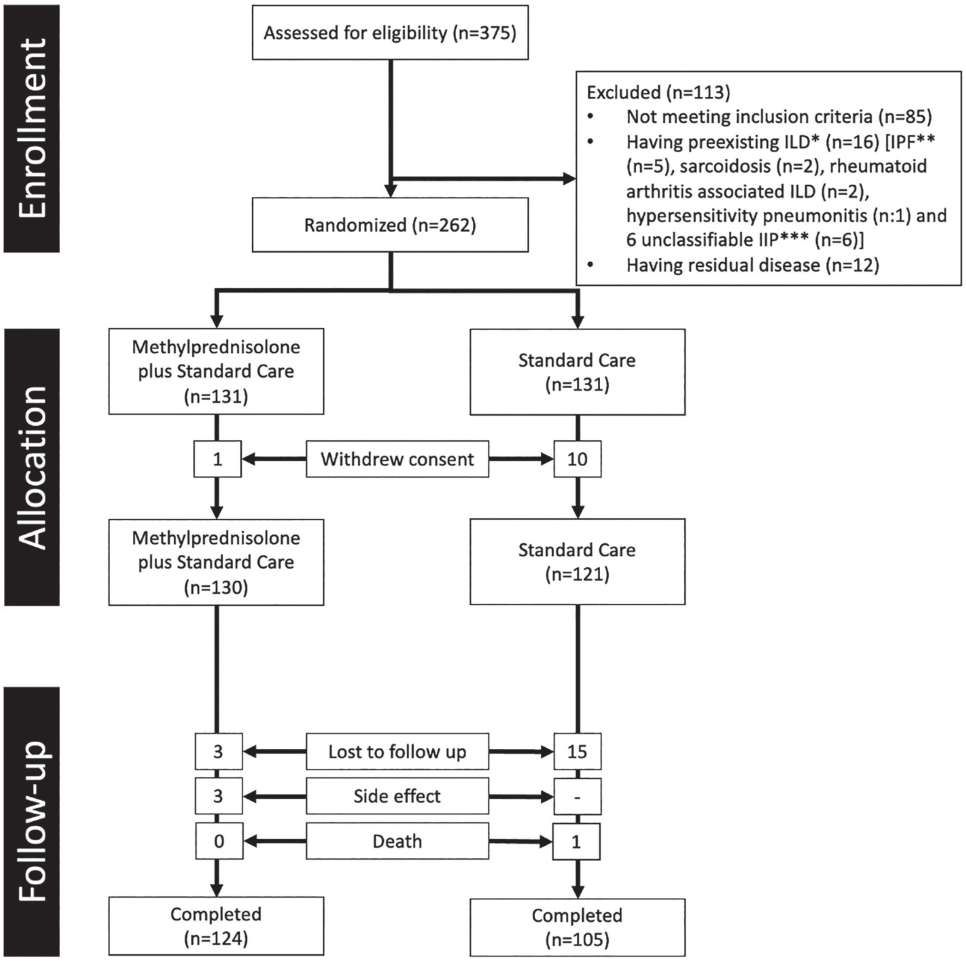

Figure 1. CONSORT diagram.

Table 2. Radiological characteristics of the intention-to-treat population.

Radiological features	Overall population (n = 251)	Control group (n = 121)	Steroid group (n = 130)	P
Radiological pattern type: • Ground glass opacities • Fibrotic bands • Mixt pattern	 35,3 33,3 31,3	 37,9 37,9 24.1	 33,3 29,8 36,8	0.149
Distribution of the lesions: • Peripheral • Peripheral + central	 47.3 52.7	 52.9 47.1	 43 57	0.164
Extension of the lesions: • Mild (≤25 %) • Diffuse (>25 %)	 35.5 64.5	 37.9 62.1	 33.6 66.4	0.528
CT score (mean ± SD)	13.5 ± 5	13 ± 5	14 ± 5	0.164
CT score • ≤15 • >15	 50.7 49.3	 52.9 47.1	 49.1 50.9	0.598

Radiological features	Overall population (n = 251)	Control group (n = 121)	Steroid group (n = 130)	P
Density of ground glass opacities • Mild • Dense	 38.8 61.2	 38.9 61.1	 38.7 61.3	0.987
Septal thickening	38.3	37.9	38.6	0.923
Central traction bronchiectasis	27.9	23	31.6	0.178
Peripheral cylindrical bronchiectasis	17.4	16.1	18.4	0.666

Data are mean ± SD or %.

Table 3. COVID-19 disease severity and treatment modalities during acute infection

	Overall (n:251)	Control group (n:121)	Steroid group (n:130)	p
COVID-19 treatment area Outpatient Ward ICU	 45 (17.9%) 133 (53%) 73 (29.1%)	 23 (19%) 70 (57.9%) 28 (23.1%)	 22 (16.9%) 63 (48.5%) 45 (34.6%)	0.133
COVID-19 severity Outpatient Ward, without O_2 Ward, with O_2 HFNC Non-invasive MV Invasive MV	 45 (17.9%) 10 (4%) 103 (41%) 27 (10.8%) 44 (17.5%) 22 (8.8%)	 23 (19%) 7 (5.8%) 52 (43%) 13 (10.7%) 17 (14%) 9 (7.4%)	 22 (16.9%) 3 (2.3%) 51 (39.2%) 14 (10.8%) 27 (20.8%) 13 (10%)	0.5
Corticosteroid use during acute COVID-19	191 (76.1%)	93 (76.9%)	98 (75.4%)	0.784
Anti-cytokine use during acute COVID-19	39 (15.6%)	15 (10%)	24 (20.8%)	0.25
Antiviral use during acute COVID-19	251	121 (100%	130 (100%)	NA

Data are mean (SD) or n (%). *Results are significantly different between the steroid and the control groups (p<0.05). *Abbreviations:* HFNC=High flow nasal canula. ICU=Intensive care unit. MV=Mechanical ventilation. NA=Not applicable.

Table 4. Primary and secondary outcomes in the steroid and control groups.

	Control group (n:105)	Steroid group (n:124)	Odds ratio [CI 95%]	P value
No desaturation during 6MWT	58 (55.2%)	92 (74.2%)	2.33 [1.34 – 4.06]	0.0041*
FVC ≥ 80% FVC= 60% - 79% FVC <60%	35 (33.7%) 45 (42.6%) 25 (23.8%)	67 (54.1%) 50 (40.2%) 7 (5.7%)	2.35 [1.37 – 4.03] 0.904 [0.53 – 1.53] 0.19 [0.08 – 0.46]	0.0026* 0.878 <0.001*
Dyspnoea No dyspnoea Dyspnoea with an mMRC of 1 Dyspnoea with an mMRC of ≥ 2	 35 (33.3%) 52 (49,5%) 18 (17,1%)	 78 (62.9%) 42 (33,9%) 4 (3,2%)	 3.39 [1.97 – 5.85] 0.52 [0.31 – 0.89] 0.16 [0.05 – 0.49]	 <0.001* 0.024* <0.001*
Radiological improvement	49 (46.7%)	76 (61.3%)	1.81 [1.07 – 3.06]	0.037*
All-cause emergency room visit	7 (7%)	8 (6,4%)	0.91 [0.87-1.14]	0.85
All-cause hospitalisation	4 (3,8%)	6 (4,8%)	1.26 [0.66-1.5]	0.628
All-cause mortality	1 (0,9%)	0	NA	0.477

Data are n (%). *Ratio of patients was found to be significantly different between the steroid and control groups. *Abbreviations:* FVC= Forced Vital Capacity. mMRC= modified Medical Research Council. NA=Not applicable. 6MWT=6 minutes walking test.

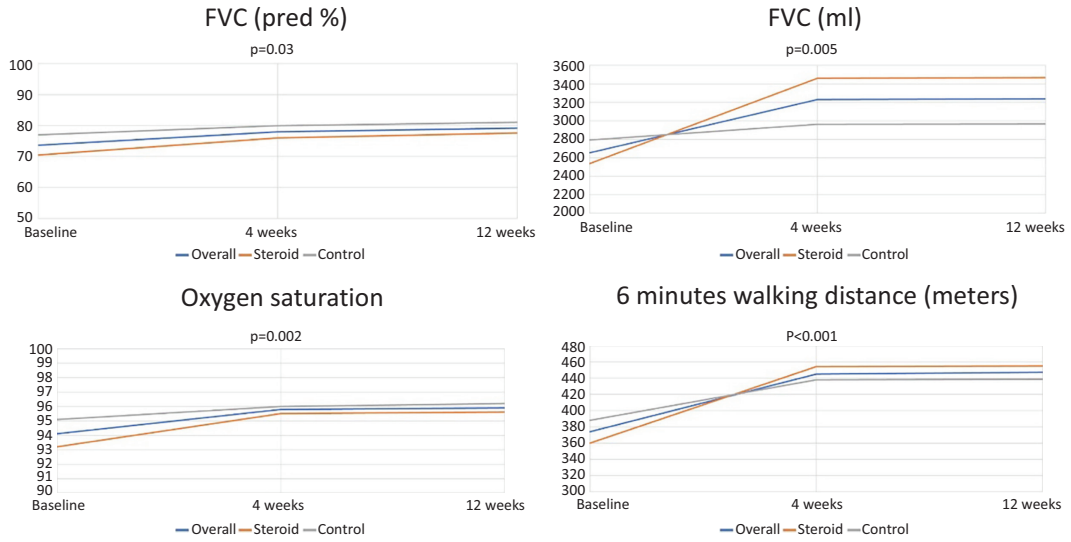

Figure 2. Change in lung functions over time in the treatment arms.

walking distance and oxygen saturation were significantly higher in the steroid group (91 vs. 41 meters, p<0.001; 2.33 vs 1.21, p=0.002; respectively). The change in lung functions is shown in Figure 2.

Uni/multi-variate logistic regression analysis

Several factors were found to be negatively associated with functional improvement at twelve-weeks (Table 5). These included smoking (OR:0.07 [95% CI:0.032–1.28]; p<0.001), advanced age (OR:0.05 [95% CI:0.024–0.112]; p=0.005), interlobular septal thickening (OR:0.688 [95% CI:0.199–2.242]; p=0.04), traction bronchiectasis (OR:0.551 [95% CI:0.242–0.992]; p=0.016), CT score>15 (OR:0.886 [95% CI:0.267–2.944]; p=0.04), and chronic obstructive pulmonary disease (COPD) (OR:0.293 [95% CI:0.082–0.967]; p=0.045). Conversely, patients who had received intravenous vitamin C during the acute phase of COVID-19 exhibited better functional improvement compared to those who had not received it (OR:3.221 [95% CI:1.12–8.49]; p=0.029). Radiological improvement was significantly more likely in patients with GGOs as the dominant radiological pattern compared to those with fibrotic bands (OR:1.552 [95% CI:0.67–3.596]; p<0.001) and those did not require ICU (OR: 2.706 [95% CI:1.031–8.811] (Table 5). Multivariate regression analysis revealed that the following variables were associated with poorer outcomes: smoking (OR:0.932 [95% CI:0.875–0.992], p=0.028), older age (OR:0.951 [95% CI:0.912-0.99], p=0.035), and severe COVID-19 (OR:0.233 [95% CI:0.068–0.799], p=0.029) (Table 5).

Adverse events

Adverse events are summarized in Table 6. Weight gain, hyperglycaemia, hypertension, moon facies, mood alterations, and myopathy were significantly more frequent in the steroid group. 16 patients in the steroid group developed hyperglycaemia and methylprednisolone was stopped temporarily in 6; treatment was restarted after achieving adequate control. Opportunistic infections occurred in three patients in the steroid group: pulmonary tuberculosis, pulmonary aspergillosis, cutaneous herpes zoster. Methylprednisolone was discontinued permanently; patients responded the antimicrobial therapy.

Discussion

STERCOV-ILD is the first randomised controlled trial to search the efficacy of systemic corticosteroids in the treatment of post-COVID-19 ILD comparing with an untreated control group which can reflect the natural course of the disease. Current study revealed that with methylprednisolone both functional

Table 5. Multivariate models for functional and radiological improvement at study endpoint.

Model / covariates, (reference variable)	*Univariate OR* **[95% CI]**	*p*-**values**	*Multivariate OR* **[95% CI]**	*p*-**values**
Functional improvement			Final model	
Study arm (Methylprednisolone vs. standard care)	2.33 [1.34 – 4.06]	**0.0041***	2.88 [2.381 - 9.923]	**<0.001***
Age, years	0.05 [0.024 – 0.112]	**0.005***	0.951 [0.912 - 0.99]	**0.035***
Cigarette smoking, package years	0.07 [0.032 – 1.28]	**<0.001***	0.932 [0.875 – 0.992]	**0.028***
Interlobular septal thickening on HRCT	0.688 [0.199 – 2.242]	**0.04**	1.01 [0.43 – 2.36]	0.514
Traction bronchiectasis on HRCT	0.551 [0.242 – 0.992]	**0.016**	0.395 [0.113 – 1.373]	0.144
CT score greater than 15 (vs less than 15)	0.886 [0.267 – 2.944)	**0.04**	0.971 [0.422 – 2.2]	0.844
Chronic obstructive lung disease	0.293 [0.082 – 0.967]	**0.045**	0.418 [0.078 - 2.247]	0.309
Intravenous vitamin C use during acute COVID-19	3.221 [1.321 – 7.834]	**0.007***	2.89 [1.047 – 8]	**0.041***
Radiologic improvement				
Study arm (Methylprednisolone vs. standard care)	1.81 [1.07 – 3.06]	**0.037***	2.036 [1.039 - 4.184]	**0.042***
COVID-19 severity (non-ICU vs. ICU)	2.706 [1.031 – 8.811]	**0.001***	4.298 [1.251 – 14.774]	**0.021***
Interlobular septal thickening on HRCT	0.452 [0.251 – 0.813]	**0.014**	0.644 [0.278 - 1.492]	0.305
Traction bronchiectasis on HRCT	0.293 [0.162 – 0.554]	**<0.001**	0.679 [0.121 – 3.787]	0.659
Radiological pattern subtype (Ground glass opacities vs. fibrotic bands)	1.552 [0.67 – 3.596]	**<0.001**	1.1 [0.6 – 2]	0.998
CT score greater than 15 (vs less than 15)	0.49 [0.282 – 0.863]	**0.024**	0.857 [0.378 - 1.946]	0.713

* Variable included in the final model.

Table 6. Treatment related adverse events.

Adverse effects	**Control group (n:105)**	**Steroid group (n:124)**	**P**
Weight gain	**3 (2.9%)**	**33 (26.6%)**	**<0.001***
Acne	1 (0.95%)	7 (5.6%)	0.074
Hyperglycemia	**4 (3.8%)**	**16 (12.9%)**	**0.01***
Hypertension	**2 (1.9%)**	**10 (8%)**	**0.03***
Stria	0	0	NA
Moon facies	**1 (0.95%)**	**11 (8.8%)**	**0.008***
Buffalo hump	0	0	NA
Cushing	0	2 (1.6%)	0.502
Hirsutism	0	0	NA
Dyspepsia	13 (12.4%)	20 (16.1%)	0.435
Mood alterations	**1 (0.95%)**	**8 (6.4%)**	**0.04***
Myopathy	**0**	**10 (8%)**	**0.002***
Opportunistic infections	0	3 (2.4%)	0.127

Results are given as n (%). *Results are significantly different between the steroid and the control groups (p<0.05).

and radiological improvement at twelve weeks were significantly better than supportive care. Nonetheless, spontaneous functional and radiological recovery is possible. Methylprednisolone was associated with significant improvements in several key clinical, functional, and radiological parameters in patients with post-COVID-19 ILD. The observed benefits span multiple domains, including symptom relief, oxygenation, exercise capacity, and lung function, suggesting that corticosteroids can play a critical role in enhancing recovery in this patient population. The increase in oxygen saturation and the greater improvement in the 6MWT in the methylprednisolone group indicate a significant enhancement in gas exchange and exercise tolerance. The substantial improvement during 6MWT (no desaturation at exercise) and increase in 6MWD is particularly noteworthy, as it is a strong predictor of functional status and quality of life in patients with ILD. This suggests that corticosteroid therapy has a meaningful impact on physical performance and daily activity levels. Methylprednisolone significantly reduced dyspnoea compared to standard care,

indicating better symptom relief in patients receiving corticosteroids. Dyspnoea is a primary and debilitating symptom, and its reduction is a crucial indicator of clinical improvement. FVC is a critical marker of lung function, reflecting both lung volume and the degree of restriction in ILD. The greater improvement in FVC in the methylprednisolone group suggests that corticosteroids may reduce lung inflammation, leading to improved lung capacity. These overall improvements likely reflect the impact of corticosteroids on reducing pulmonary inflammation, improving lung compliance, and enhancing overall respiratory function. An important and novel aspect of our analysis was the evaluation of the proportion of patients who no longer experienced oxygen desaturation during the 6MWT after 12-weeks of treatment. All patients included in the study experienced desaturation during the 6MWT at baseline, as defined by our inclusion criteria (≥4% drop in oxygen saturation during exertion). Therefore, the proportion of patients who no longer desaturated at 12 weeks directly reflects a meaningful pre–post treatment change across the entire study population. This outcome, while not commonly reported in earlier studies, provides a clinically meaningful and easy-to-interpret functional marker of patient recovery. In contrast to absolute changes in 6-minute walk distance, which may be influenced by multiple factors such as baseline fitness and musculoskeletal condition, the absence of exertional desaturation directly reflects improvement in pulmonary gas exchange and functional reserve. Importantly, the observed improvement in desaturation status in our cohort was paralleled by a significant increase in DLCO values over the same follow-up period. Since DLCO is a sensitive measure of alveolar-capillary membrane integrity and gas transfer efficiency, the concordant improvement in this parameter reinforces our interpretation that resolution of exertional desaturation reflects meaningful physiological recovery in gas exchange. While earlier studies such as by Myall et al. and Mizera et al. reported significant improvements in PFTs and DLCO (23,24), and Dhooria et al. mentioned 6MWD as an exploratory outcome (25), none specifically examined desaturation resolution as a binary, clinically relevant marker. Our results suggest that tracking exercise desaturation status may provide an additional and practical endpoint to guide post-treatment functional assessment. Although the steroid-treated group exhibited a higher proportion of smokers and numerically lower baseline FEV_1, FVC, and 6MWD values, these differences were not statistically significant. Therefore, we do not consider these baseline variations sufficient to explain the observed post-treatment improvements in this group. Moreover, the presence of slightly lower—but statistically comparable—baseline pulmonary function and exercise capacity may in fact highlight the therapeutic efficacy of methylprednisolone. The degree of improvement observed in the steroid group, despite these nonsignificant functional disadvantages at baseline, supports the notion that corticosteroid treatment may have contributed meaningfully to the recovery process. These findings suggest that methylprednisolone could be particularly effective in patients with greater clinical impairment. This study aimed to investigate the factors influencing functional and radiological outcomes in patients with post-COVID-19 ILD. The results of the final analyses reveal several key insights: 1) Negative Association of Smoking with Functional Improvement: This finding aligns with well-established evidence that smoking impairs lung function and hinders recovery from pulmonary diseases, including ILDs. Smoking is known to promote chronic inflammation and oxidative stress in the lungs, which likely exacerbates the damage caused by COVID-19, making recovery more difficult. 2) Age: Older patients generally experience a slower recovery from lung injury and are more prone to the long-term effects of COVID-19. The diminished capacity for tissue repair with age likely contributes to these poorer functional outcomes. 3) Radiological characteristics: Patients with GGOs as the dominant radiological feature demonstrated better radiological improvement compared to those with fibrotic bands. This finding suggests that GGOs may represent more reversible inflammatory processes, whereas fibrotic bands reflect more advanced, irreversible lung damage. This observation is consistent with the natural history of GGOs, which are often reversible and more responsive to anti-inflammatory therapies, including corticosteroids. In contrast, fibrotic bands reflect more permanent structural changes that are less amenable to pharmacological intervention, explaining the lower rate of

radiological recovery in this subgroup. Radiological findings, specifically interlobular septal thickening, traction bronchiectasis, and higher CT scores, were all associated with poorer functional and radiological improvement. These findings suggest that the presence of fibrotic-like changes on HRCT is a key determinant of both functional and radiological recovery. 4) COPD was also associated with reduced functional improvement, which may be due to the additive impact of COPD-related airflow limitation and inflammation on post-COVID-19 lung disease. 5) Vitamin C is known for its antioxidant, anti-inflammatory, and immune-modulatory effects, and its use during acute COVID-19 may have mitigated some of the inflammatory damage to the lungs, enhancing functional recovery. One study found that vitamin C levels are as low as undetectable in more than 90% of the patients with SARS-CoV-2-associated ARDS (26). While the exact mechanism remains uncertain, vitamin C could have helped mitigate oxidative damage, promote better tissue repair, and thereby improve lung function. 6) ICU need: Patients who required ICU care during the acute phase of COVID-19 showed significantly poorer radiological recovery compared to those treated outside the ICU. These findings align with existing literature suggesting that ICU patients, especially those with ARDS or ventilator-induced lung injury, are more likely to experience diffuse alveolar damage and long-term radiological abnormalities (4,6,15). The presence of extensive lung damage likely limits radiological improvement even with corticosteroid treatment. A couple of small number case series which describe the results of prolonged glucocorticoids at discharge in post-acute COVID-19 patients have been published (27,28). Segala and colleagues reported that high-dose intravenous methylprednisolone improved oxygenation in 10 patients with persistent respiratory failure three weeks after COVID-19 (28). Myall and colleagues showed significant clinical and physiologic improvement in patients with post-COVID-19 organising pneumonia with prednisolone 11 weeks after COVID-19 symptom onset (23). In a cohort study of 2,729 COVID-19 survivors, patients who received corticosteroid therapy (n=131) showed significantly greater improvements in pulmonary function, DLCO, radiological abnormalities, and symptoms compared to those managed with noninterventional follow-up. These findings suggest that glucocorticoid therapy may benefit selected patients with persistent post-COVID-19 lung impairment (24). Dhooria and colleagues revealed that high-dose prednisolone was no better than low-dose prednisolone in improving the outcomes in post-acute phase of COVID-19 (25). Posavec et al. conducted a prospective cohort study comparing the effects of corticosteroid therapy of different durations (14 days vs. 3 months) and no corticosteroid use in patients with post-COVID-19 lung abnormalities. They reported no significant benefit of prolonged corticosteroid therapy in terms of radiological improvement, lung function, or symptom resolution at three months; notably, the control group had significantly fewer dyspnea symptoms and higher DLCO values. However, the control group in that study consisted of patients with milder disease and better baseline lung function, which limits comparability between groups. In contrast, our study compared patient groups with similar baseline clinical and functional characteristics, thereby allowing a more reliable evaluation of the efficacy of methylprednisolone treatment (29). Nevertheless, there was no randomised controlled trial designed to investigate the effects of systemic glucocorticoids in treatment of post-COVID-19 ILD by comparing with spontaneous recovery. Our study fills an important knowledge gap related to the require of treatment for patients with post-COVID-19 ILD. The COLDSTER trial contributed important data on corticosteroid dosing in post-COVID-19 ILD by demonstrating that a low-dose regimen (starting at 10 mg/day) was not inferior to a high-dose regimen over a 6-week period in terms of clinical improvement. However, it is important to acknowledge that this trial lacked a non-treatment control group, making it difficult to determine whether the observed improvements were attributable to steroid therapy or the natural resolution of post-viral inflammation. Moreover, steroids were administered very early in the post-acute phase, when spontaneous recovery might still be ongoing, further complicating causal interpretation. Our study differs in that it included a control group and evaluated patients who remained symptomatic and radiologically abnormal well beyond the acute infection phase, providing a clearer

context for assessing treatment efficacy. While our moderate-dose regimen (methylprednisolone 0.5 mg/kg/day) was associated with clinical benefit, it also resulted in significantly higher rates of adverse effects, including hyperglycemia (12.9% vs. 3.8%), weight gain (26.6% vs. 2.9%), myopathy (8% vs. 0%), and mood alterations (6.4% vs. 0.95%). These findings, along with the side effect rates reported in COLDSTER—even in the low-dose arm—highlight the need for a balanced and individualized approach to steroid therapy in post-COVID ILD. The most important strength of our study to have a control group able to show the natural prognosis of post-COVID-19 ILD. The second is the exclusion of pre-existing ILD; previously suspected and/or diagnosed ILD patients, the patients with suspicious radiologic images of ILDs or without thoracic images of pre-COVID-19 period had been excluded. Diagnosis of post-COVID-19 ILD must be assured before starting systemic corticosteroids, the necessity of all four inclusion criteria for the diagnosis of post-COVID-19 ILD is the other strength point of our study. Last, the outcome measures of this study were objective and physiological in nature, such as FVC, 6MWT, and thorax HRCT. These metrics are less susceptible to the subjective evaluation, making it likely that the observed improvements in pulmonary functions and radiological lesions were reproducible. One of the main limitations of our study is the absence of a placebo. We faced ethical and logistical challenges that precluded the use of a placebo. Administering a placebo in place of symptom-relief therapies was deemed inappropriate to withhold active treatments from patients in the control group. Obtaining and distributing placebo tablets posed logistical challenges. Our priority was to provide timely and meaningful data on the efficacy of methylprednisolone for post-COVID-19 ILD. The absence of a placebo introduces the possibility of bias due to the placebo effect. However, we aimed to minimize this bias by focusing on objective outcome measures, such as PFTs and HRCT. In conclusion, the current study highlights the efficacy of oral methylprednisolone in treating post-COVID-19 interstitial lung disease, demonstrating more substantial outcomes compared to the disease's natural course, which may involve spontaneous recovery. The diagnosis of post-COVID-19 ILD and the determination to initiate methylprednisolone should be rooted in comprehensive and meticulous assessments of clinical, functional, and imaging abnormalities.

Conflict of Interest: The authors declare that they have no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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