Original Article

Long-term effect of corticosteroid treatment during acute COVID-19 infection on pulmonary function test results

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Background: The outbreak of the novel coronavirus 19 has led to unprecedented clinical challenges globally. Various therapeutic and pharmacologic interventions have been proposed, yet evidence of their long-term efficacy remains limited. Corticosteroids (CS) have shown efficacy in the sub-acute phase of the pandemic. This study aims to evaluate the long-term effects on pulmonary function tests (PFTs) in patients treated with CS during acute coronavirus disease 2019 (COVID-19) infection.

Methods: A retrospective study was conducted from February 2020 to March 2021. Clinical and demographic data were extracted from electronic medical records of patients attending the post-COVID outpatient clinic at the Pulmonary Institute of Soroka University Medical Center. A multivariate linear mixed effects model was employed to obtain adjusted estimates for the impact over time.

Results: The study included 405 patients, of whom 155 (38.3%) received CS treatment. Approximately 60% completed two or more follow-up visits. PFTs [forced expiratory volume in the first second (FEV1), forced vital capacity (FVC)] returned to baseline more rapidly (0.9% and 0.85% per month, respectively) in patients treated with CS. This accelerated recovery was observed across all patients, including those with a body mass index (BMI) above 30 kg/m^2 and those with known chronic lung disease.

Conclusions: Systemic CS treatment during acute COVID-19 infection was associated with a faster recovery of PFTs during long-term follow-up, even among subgroups at higher risk of long-term pulmonary damage.

Keywords: Corticosteroid (CS); coronavirus disease 2019 (COVID-19); infection; pulmonary

Submitted Mar 26, 2024. Accepted for publication Jun 25, 2024. Published online Aug 19, 2024.
doi: 10.21037/jtd-24-503
View this article at: https://dx.doi.org/10.21037/jtd-24-503

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Introduction

The outbreak of the novel coronavirus in 2019 triggered unprecedented and unanticipated clinical challenges worldwide (1). The virus, initially identified in Wuhan City, China, for the first time, is capable of human-to-human transmission and has swiftly disseminated worldwide via close human contact or the respiratory droplets, such as sneezing and coughing, of infected individuals (2,3). The severe-acute-respiratory-syndrome-related coronavirus (SARS-CoV-2) pathogen is a single-stranded ribonucleic acid (RNA) respiratory virus that primarily targets the respiratory system (3-5). Acute infection is accompanied by a hyperinflammatory response. The replication of the virus leads to rapid activation of mononuclear macrophages, which produce elevated levels of cytokines, resulting in an amplification of the disease-causing "cytokine storm". Clinical manifestations range from mild illness with symptoms such as fever, cough, and fatigue to critical illness and acute respiratory distress syndrome (ARDS) (2-7). Long-term sequelae of coronavirus disease 2019 (COVID-19) infection include respiratory, cardiovascular, neuromuscular, and cognitive effects (7-9). Several therapeutic approaches were hypothesized to have clinical utility in the treatment of acute COVID-19 infection (10-12). Given its ability to control immune responsiveness and mitigate cytokine hyperactivation, corticosteroid (CS) treatment has demonstrated beneficial outcomes in patients with acute COVID-19 infection, including shortened duration of oxygen requirements, improved radiographic findings, and lower mortality, particularly in severe cases (13,14). Negative impacts of CS therapy include the elongation of viremia and increased risk of superimposed bacterial infections (13,14). Pulmonary function tests (PFTs) provide vital information regarding respiratory metrics such as airflow, lung volumes, and oxygen diffusion (15,16). Studies demonstrate the importance of PFTs in the long-term care of post-COVID-19 patients (17,18).

This study aims to evaluate long-term respiratory outcomes and the physiologic impact of CS treatment in COVID-19 patients. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-503/rc).

Highlight box

Key findings

- Systemic corticosteroid (CS) treatment during acute coronavirus disease 2019 (COVID-19) infection was associated with a faster recovery of pulmonary function tests (PFTs) during long-term follow-up, even among subgroups at higher risk of long-term pulmonary damage.

What is known and what is new?

- CS have demonstrated efficacy during acute COVID-19 infection.
- Our study further corroborates this idea by furnishing evidence that administering steroid treatment during the acute phase of COVID-19 infection correlates with a notably hastened recovery in PFTs.

What is the implication, and what should change now?

- This suggests that CS therapy may offer long-term benefits in managing COVID-19-related pulmonary complications. Healthcare providers should consider the potential advantages of CS treatment in mitigating long-term pulmonary damage among individuals recovering from acute COVID-19 infection.

Methods

Study population and data extraction

This retrospective study utilized data from adult patients who attended the post-COVID outpatient clinic at the Pulmonary Institute of Soroka University Medical Center (SUMC) for customized post-COVID follow-up monitoring, spanning from February 2020 to March 2021. All participants had a confirmed diagnosis of COVID-19, verified by a polymerase chain reaction (PCR) nasopharyngeal swab before their initial visit. Parameters collected encompassed demographic factors (sex, age, employment status), body mass index (BMI), medical and smoking history, hospital admission details (including rehospitalization), COVID-19 treatments (such as CS, anticoagulants, antibiotics, remdesivir), and the mode and duration of mechanical ventilation.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and received approval from the Institutional Review Board of Soroka University Medical Center (approval ID: Sor-0560-20, March 2021). Individual consent for this retrospective analysis was waived due to the determination that the waiver or alteration would not negatively impact the rights and well-being of the subjects, and the research would not be practically feasible without this waiver or alteration.

PFTs (results)

The PFTs conducted in this study utilized the spirometer BRAND/MODEL_YEAR (we don't want to add that because it will looks like an "Advertising" to measure

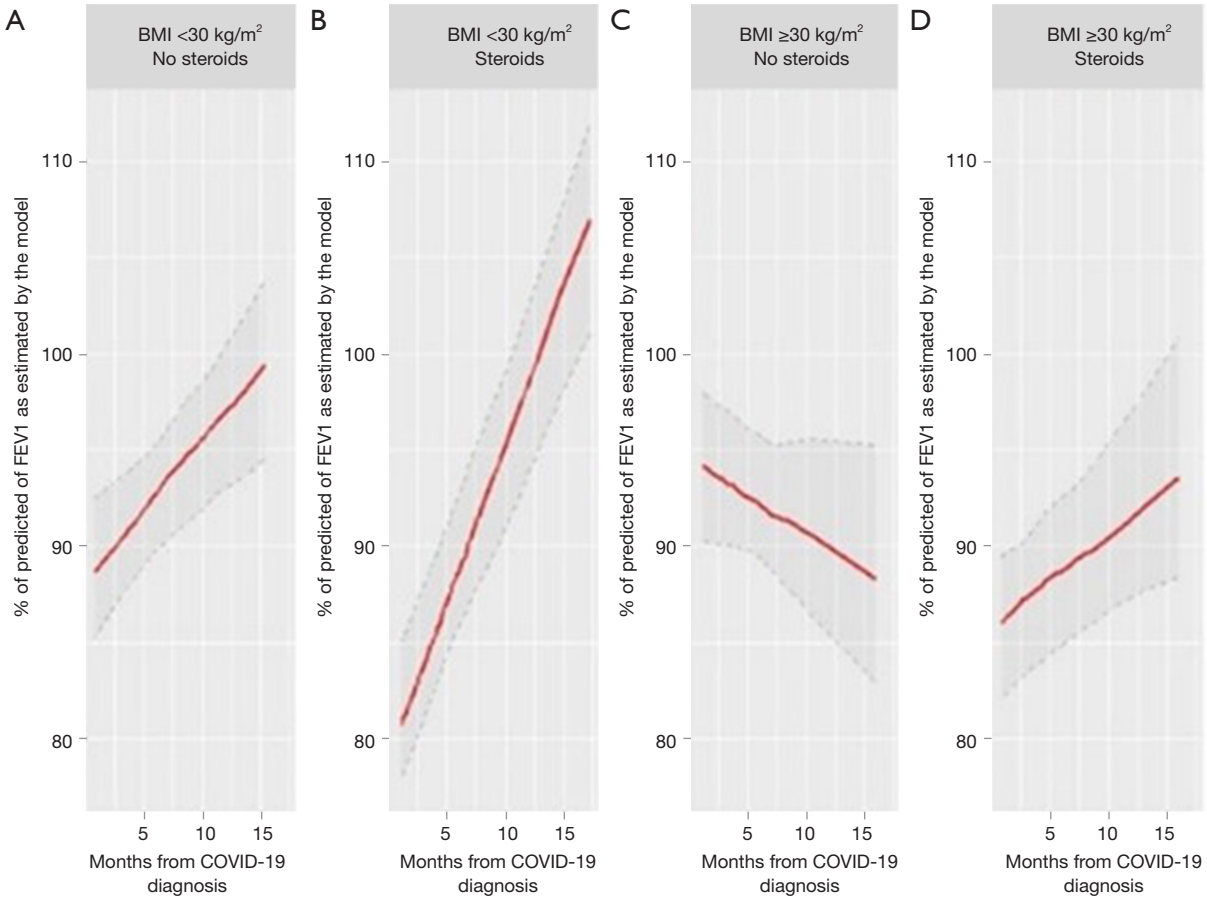

Figure 1 Predicted FEV1 levels *vs.* time (in months) from COVID-19 diagnosis, with 95% confidence limits (in dark grey), (A) for patients with BMI <30 kg/m^2 and not treated with corticosteroids, (B) for patients with BMI <30 kg/m^2 and treated with corticosteroids, (C) for patients with BMI ≥30 kg/m^2 and not treated with corticosteroids and (D) for patients with BMI ≥30 kg/m^2 and treated with corticosteroids. FEV1, forced expiratory volume in the first second; BMI, body mass index; COVID-19, coronavirus disease 2019.

various respiratory outcomes. These tests included the following three parameters:

(I) Forced expiratory volume in the first second (FEV1) (*Figure 1*): this measures the percentage (%) of air expired in the first second of exhalation;

(II) Forced vital capacity (FVC) (*Figure 2*): this represents the volume of air that can be forcibly exhaled from the lungs after taking the deepest breath possible;

(III) FEV1/FVC ratio: this ratio, calculated as the FEV1 divided by the FVC, is known as the FEV1/FVC ratio (the normal value for this ratio typically falls above 0.75–0.85, though it can vary with age).

Administration of steroid treatment

CS treatment encompassed various types, such as prednisone, administered at a dosage of 0.5–1 mg per kg, or a course of dexamethasone at 6 mg.

Statistical analysis

Descriptive data were presented using means and standard deviations for continuous variables, and absolute numbers with percentages for categorical variables. Outcome measures are described with stratification by time from COVID-19 diagnosis, along with the number of visits and follow-up duration. Patients treated with CS were compared univariately to non-treated patients using the *t*-test or Wilcoxon rank sum test for continuous variables, and the Chi-squared test or Fisher's test for categorical variables. A multivariate linear mixed effects model was employed for each outcome to obtain adjusted estimates

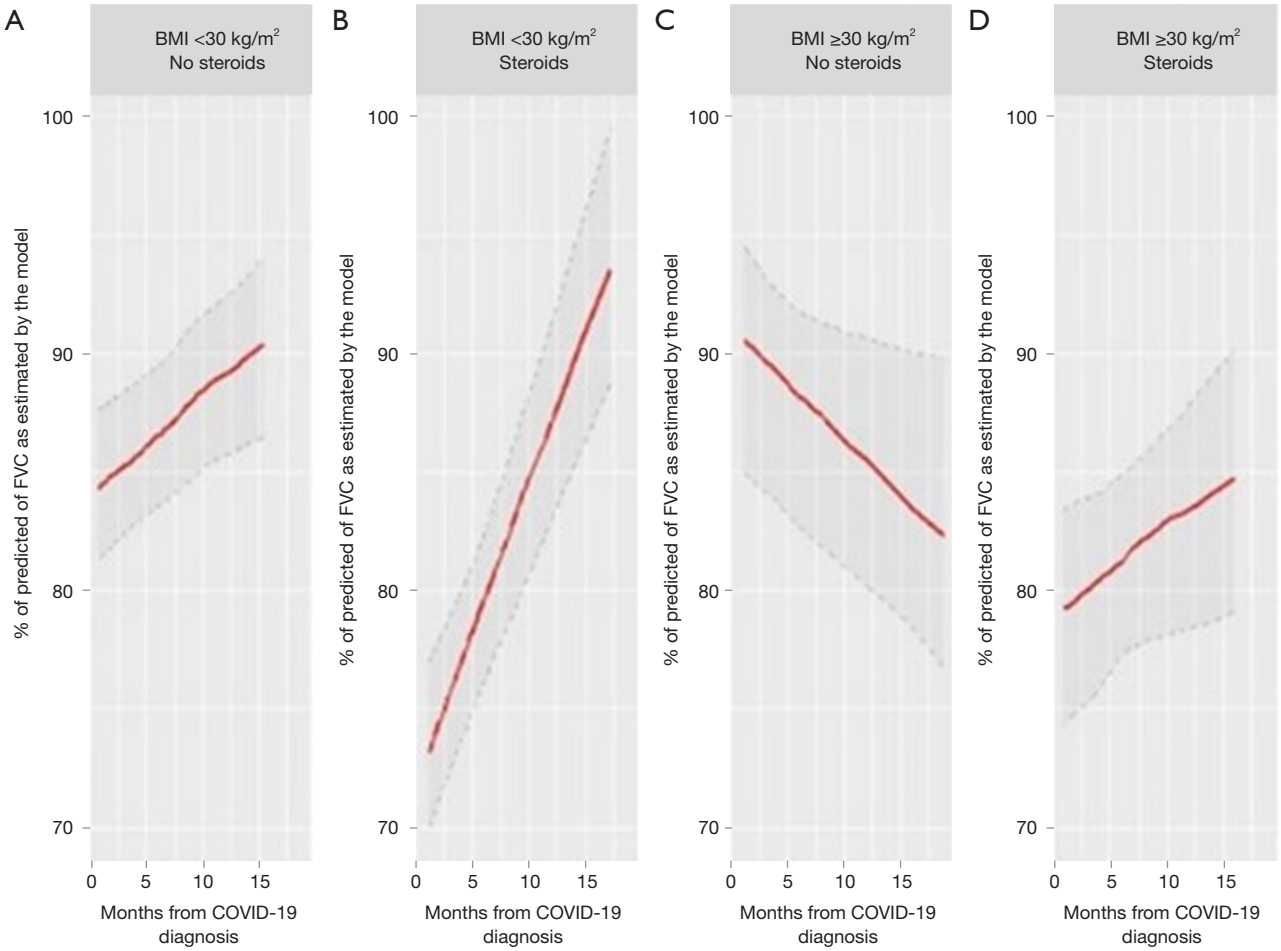

Figure 2 Predicted FVC levels *vs.* time (in months) from COVID-19 diagnosis, with 95% confidence limits (in dark grey), (A) for patients with BMI <30 kg/m^2 and not treated with corticosteroids, (B) for patients with BMI <30 kg/m^2 and treated with corticosteroids, (C) for patients with BMI ≥30 kg/m^2 and not treated with corticosteroids and (D) for patients with BMI ≥30 kg/m^2 and treated with corticosteroids. FVC, forced vital capacity; BMI, body mass index; COVID-19, coronavirus disease 2019.

for changes over time. Differences in trends were assessed by interactions with time. Backward elimination based on Akaike information criterion (AIC) was utilized for model reduction. Predicted values obtained from the models were plotted to demonstrate effects over time. A significance level of 0.05 was employed to denote statistical significance ("P value"). The analysis was conducted using the R statistical software (version 2023) (19).

Results

Patient characteristics

A total of 405 patients were included in the study, with 155 (38.3%) receiving CS treatment (*Table 1*). Among these, females comprised 41%, whereas in the non-treated group, they represented 59%. Treated patients were older, with an average age of 60 years compared to 49.4 years in the non-treated group, while both groups had similar BMI (28 kg/m^2). Smoking history was less prevalent among treated patients (31%) than among non-treated patients (79.2%). Treated patients were more likely to have chronic medical conditions, including diabetes mellitus (31.6% *vs.* 12.4%), hypertension (47.1% *vs.* 24%), chronic kidney disease (9% *vs.* 3.6%), and underlying pulmonary disease (24.5% *vs.* 14.8%). The majority of treated patients (92.9%) were hospitalized, in contrast to only 19.6% of non-treated patients. Additionally, ventilation support was provided to 87.7% of treated patients compared to only 6% of non-

Table 1 Patient demographic, clinical, and outcome characteristics

Characteristic	Total (n=405)	No steroids (n=250)	Steroids (n=155)	P value
Sex				
Male	190 (46.9)	98 (39.2)	92 (59.4)	<0.001
Female	215 (53.1)	152 (60.8)	63 (40.6)	
Age (years)				
Mean ± SD	53.5±15	49.4±14.6	60±13.3	<0.001
<45	111 (27.4)	94 (37.6)	17 (11.0)	<0.001
45–65	206 (50.9)	123 (49.2)	83 (53.5)	
>65	88 (21.7)	33 (13.2)	55 (35.5)	
BMI (kg/m^2)				
Mean ± SD	27.9±6.4	27.6±5.9	28.4±7	0.41
<30	277 (68.4)	176 (70.4)	101 (65.2)	0.32
≥30	128 (31.6)	74 (29.6)	54 (34.8)	
Sector				
Jewish	362 (89.4)	234 (93.6)	128 (82.6)	0.009
Arab	43 (10.6)	16 (6.4)	27 (17.4)	
Employed	285 (70.4)	198 (79.2)	87 (56.1)	<0.001
Smoking				
No	286 (70.6)	179 (71.6)	107 (69.0)	0.01
Past	82 (20.2)	42 (16.8)	40 (25.8)	
Yes	37 (9.1)	29 (11.6)	8 (5.2)	
Pre-DM	40 (9.9)	26 (10.4)	14 (9.0)	0.78
DM	80 (19.8)	31 (12.4)	49 (31.6)	<0.001
Hypertension	133 (32.8)	60 (24.0)	73 (47.1)	<0.001
CHF	32 (7.9)	16 (6.4)	16 (10.3)	0.21
CRF	23 (5.7)	9 (3.6)	14 (9.0)	0.03
Fibromyalgia	36 (8.9)	27 (10.8)	9 (5.8)	0.12
Malignancy	25 (6.2)	13 (5.2)	12 (7.7)	0.41
Lung disease	75 (18.5)	37 (14.8)	38 (24.5)	0.02
Hospitalization	193 (47.7)	49 (19.6)	144 (92.9)	<0.001
Ventilation				
No	254 (62.7)	235 (94.0)	19 (12.3)	<0.001
Oxygen	108 (26.7)	12 (4.8)	96 (61.9)	
High flow/Tubus/ECMO	43 (10.6)	3 (1.2)	40 (25.8)	
Antibiotics	43 (10.6)	12 (4.8)	31 (20.0)	<0.001
Remdesivir	53 (13.1)	2 (0.8)	51 (32.9)	<0.001
% Predicted FEV1	89.1±18.2	92.2±14.7	84.1±21.7	<0.001
% FVC	86.3±16.5	90.4±13.5	80±18.8	<0.001
% DLCO	78.7±19	84.4±16.4	72.2±19.7	<0.001

Data are presented as n (%) or mean ± SD. SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; CHF, congestive heart failure; CRF, chronic renal failure; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusion capacity of carbon monoxide.

treated patients. Treated patients also received higher proportions of other treatments, including anticoagulants (87.7% *vs.* 9.2%), antibiotics (20% *vs.* 4.8%), and remdesivir (32.9% *vs.* 0.8%).

Pulmonary function outcomes

The mean pulmonary test results of treated patients were lower than those of non-treated patients, with FEV1 values of 92.2% compared to 84.1%, FVC values of 90.4% compared to 80%, and diffusing capacity of the lungs for carbon monoxide (DLCO) values of 84.4% compared to 72.2%, respectively.

Visits and follow-up

The number of visits to the post-COVID outpatient clinic ranged between 1 and 6, with a mean of 1.7 [standard deviation (SD) =1] visits per patient. In total, 330 (81.5%) patients visited the clinic once or twice, while the remaining patients visited the clinic at least three times. The time interval between COVID-19 diagnosis and clinic evaluation ranged from 23 days to 20.9 months, with a mean follow-up duration of 6.4 (SD =3.9) months per patient for both groups.

Long-term steroid effects on pulmonary function outcomes

CS treatment was associated with lower baseline levels (at COVID-19 diagnosis) but a faster recovery in FEV1 and FVC measures (see *Table 2* and *Figures 1*,*2*). Patients treated with steroids exhibited FEV1 and FVC levels that were 9.4% and 12.3% lower, respectively, compared to non-treated patients. However, the recovery rate of treated patients was faster, increasing by 0.90% and 0.85% per month, respectively.

A notable difference was observed among patients with a BMI greater than 30 kg/m^2, as those treated with CS demonstrated improvements in PFTs, whereas non-treated patients experienced a decline in their PFT (see *Figures 1*,*2*).

While no relation was found between CS treatment and DLCO, lung disease was associated with a faster recovery of 1.7% per month in DLCO compared to other patients. Additionally, congestive heart failure (CHF) was associated with a deterioration of 2.2% per month in DLCO. Furthermore, individuals aged between 45 and 65 exhibited lower baseline DLCO levels and a recovery rate of 2.3% per month in DLCO compared to other patients (see *Tables 2*,*3*, *Figures 3*,*4*).

Discussion

In recent years, newly emerging virus diseases have posed significant public health threats globally. Over the past two decades, outbreaks of numerous viral diseases, including severe acute respiratory syndrome coronavirus, have been documented. The latest ongoing viral disease, caused by the novel coronavirus, has posed a severe threat to public health worldwide. The initial reporting of the novel coronavirus outbreak to the World Health Organization (WHO) has sparked widespread public concern and has become a focal point within both public discourse and the healthcare system (20,21).

This retrospective single-center study demonstrates the association between glucocorticoid steroid treatment during acute COVID-19 infection and long-term follow-up PFTs. We contribute to a small body of previous research examining the trajectory of lung function as an indicator of respiratory damage during the long-term course, or "long COVID", of the infection. Our cohort comprised COVID-19 recoveries with respiratory involvement of varying severity levels during the acute phase.

We were able to establish a positive relation between CS treatment during the acute period and lung function over time in a diverse population. Our findings align with those of a previous longitudinal study by Aditi S. Shah *et al.* (22), which demonstrated improvement in most pulmonary function measurements between 3 and 6 months after symptom onset for hospitalized COVID-19 patients. However, the previous mentioned study did not specifically investigate the association between medical therapy, including CS treatment, and long-term PFTs. Our study, on the other hand, included a broader cohort comprising both hospitalized and ambulatory COVID-19-infected patients with diverse levels of respiratory severity.

Hägglöf *et al.* also demonstrated improvement in PFTs in 1-year follow-up studies. In Hui Zhang's study, CS therapy was identified as a protective factor for PFT at the 1-year mark (23,24).

In our study, we observed that PFTs, including FVC, FEV1, and DLCO, improved more rapidly in the group treated with CS during the acute illness across all cohorts and various subgroups, including those with mild and severe respiratory illness, restrictive and obstructive lung function abnormalities, high and low BMI, and background chronic respiratory disease.

The rationale for CS treatment stems from the association between inflammatory dysregulation and

Table 2 Long-term steroid effect on pulmonary function outcomes—multivariate analysis results

Variable	FEV1		FVC		DLCO	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
(Intercept)	88.3 (84.7, 91.9)	<0.001	84.2 (80.9, 87.5)	<0.001	91.7 (84.3, 99.1)	<0.001
Time (months)	0.7 (0.4, 1.0)	<0.001	0.4 (0.1, 0.7)	0.01	−0.9 (−2.3, 0.4)	0.18
Steroids	−9.4 (−13.6, −5.3)	<0.001	−12.3 (−16.2, −8.5)	<0.001		
BMI ≥30 kg/m^2	6.3 (2.0, 10.6)	0.004	6.7 (2.7, 10.6)	0.001		
Female	4.5 (1.2, 7.9)	0.008	7.1 (4.0, 10.2)	<0.001		
Age (years)						
>65					−7.2 (−17.3, 3.0)	0.17
45–65					−8.8 (−17.1, −0.6)	0.03
Smoking						
Past					−11.3 (−16.8, −5.9)	0.001
Current					−6.5 (−13.3, 0.3)	0.06
Lung disease	−16.9 (−21.1, −12.6)	<0.001	−8.0 (−11.9, −4.1)	0.001	−13.6 (−20.9, −6.2)	0.004
CHF	−7.6 (−13.7, −1.5)	0.01			3.2 (−7.2, 13.7)	0.55
Ventilation						
Oxygen					−7.0 (−11.9, −2.0)	0.006
High flow/Tubus/ECMO					−17.0 (−22.8, −11.2)	<0.001
Interactions with time (months)						
Time: steroids	0.9 (0.5, 1.4)	0.001	0.9 (0.4, 1.3)	0.001		
Time: BMI ≥30 kg/m^2	−1.1 (−1.5, −0.6)	<0.001	−0.8 (−1.3, −0.4)	0.003		
Time: age >65 years					0.6 (−1.0, 2.3)	0.46
Time: age 45–65 years					2.3 (0.9, 3.7)	0.002
Time: lung disease					1.7 (0.6, 2.8)	0.003
Time: CHF					−2.2 (−3.7, −0.8)	0.004

BMI, body mass index; CHF, congestive heart failure; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; CI, confidence interval.

Table 3 Lung diseases effect on pulmonary function outcomes—multivariate analysis results

Variable	FEV1		FVC		DLCO	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Lung disease						
Obstructive	−11.2 (−15, −7.5)	<0.001	−6.0 (−9.2, −2.7)	0.003	−5.5 (−10.6, −0.4)	0.03
Other	−12.7 (−20, −5.4)	0.007	−10.3 (−16.6, −4.1)	0.001	−5.5 (−14.9, 3.9)	0.25
Restrictive	−24.9 (−34.2, −15.7)	<0.001	−15.2 (−23.1, −7.4)	0.02	−28.8 (−40.7, −17.0)	<0.001

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; CI, confidence interval.

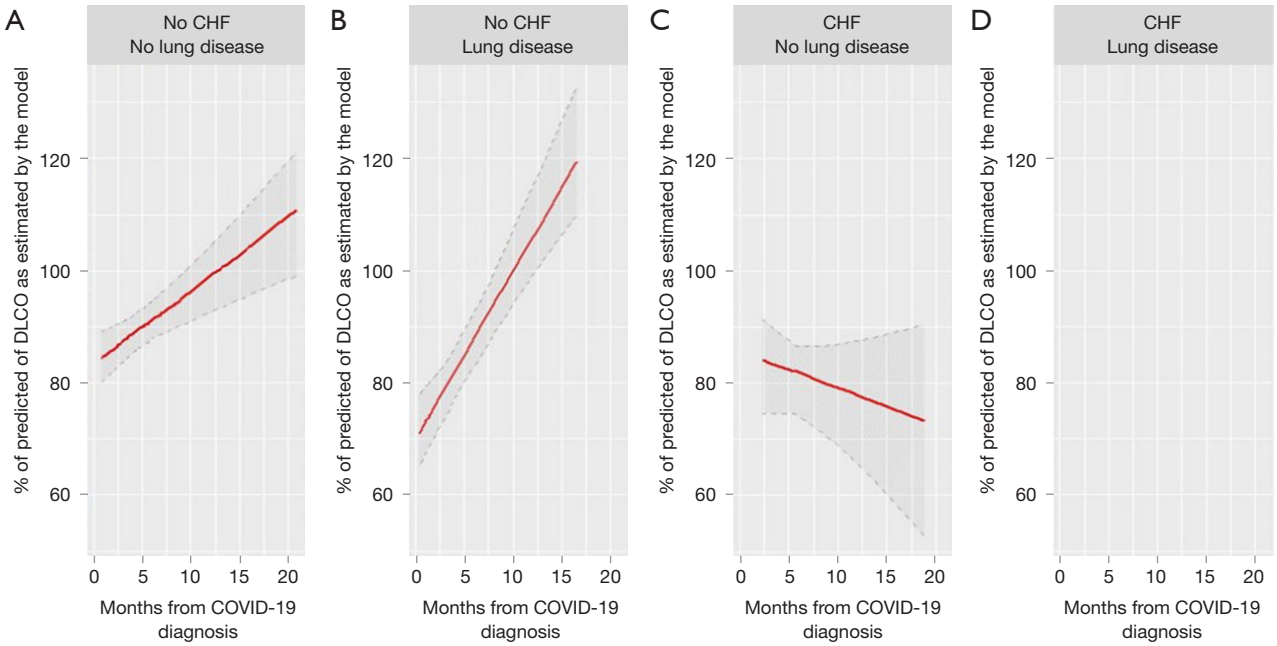

Figure 3 Predicted DLCO levels *vs.* time (in months) from acute COVID-19 diagnosis, with 95% confidence limits (in dark grey), by lung disease and CHF. For patients with no CHF, recovery in DLCO was faster for patients with lung disease. For patients with CHF, DLCO is deteriorating. Predictions were obtained by fitting a multivariate mixed effects model. The plot is shown for patients with baseline levels of all other variables. Only a few CHF patients also had lung disease, data not shown. DLCO, diffusing capacity of the lungs for carbon monoxide; CHF, congestive heart failure; COVID-19, coronavirus disease 2019.

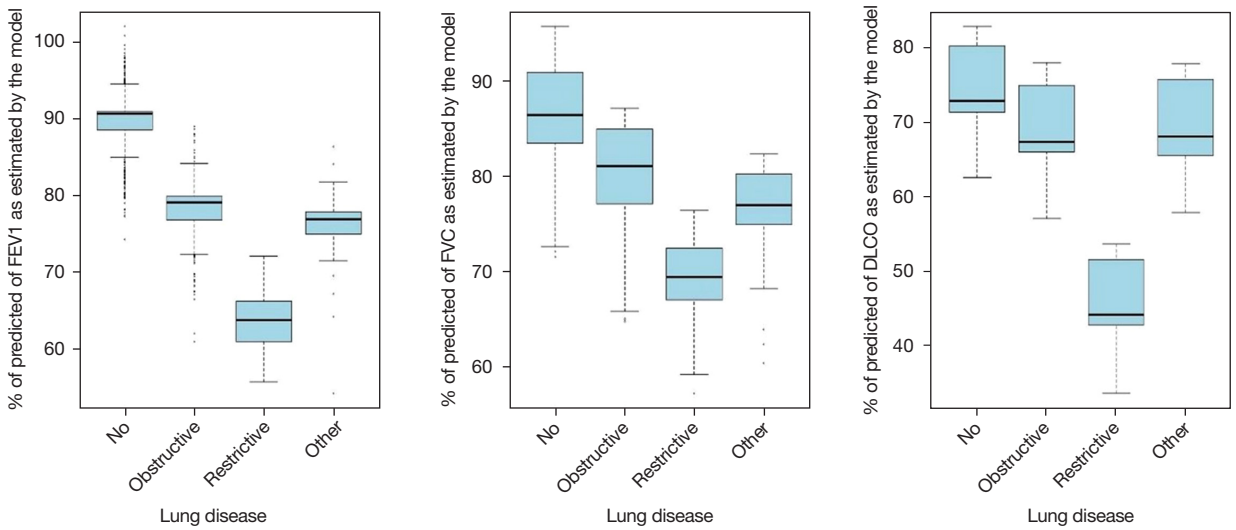

Figure 4 Boxplots of predicted pulmonary outcomes by lung disease subtype. Lung disease patients exhibited lower levels compared to patients without lung disease, with restrictive disease patients demonstrating the lowest levels. Predicted values were obtained by fitting multivariate linear mixed effects models with backward elimination. The plot is shown for patients with baseline levels of all other variables. FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.

adverse clinical outcomes, which serves as a key pathogenic mechanism in severe COVID-19 disease (25). Multiple randomized trials have indicated that systemic CS therapy improves short-term clinical outcomes and reduces mortality among hospitalized COVID-19 patients who require supplemental oxygen (26).

Still, the latest guidelines have identified the need to better evaluate the optimal CS to be used in COVID-19, including the timing and scheme of administration (27). Although CS are not routinely recommended for patients not requiring supplementary oxygen or for outpatients, many centers have administered this treatment during the acute illness. This occurred mainly due to the dynamic presentation and recommendation changes during the pandemic. However, we still do not know the best treatment for these patients.

The retrospective data collection of CS-treated and non-treated patients in our study, along with the long-term follow-up post-acute infection, allows us to better understand the influence of CS treatment. Our study reinforces previous observations and demonstrates in a broader population that those who received CS during the acute illness had a more rapid recovery of their PFTs.

Furthermore, our study showed no significant difference in the recovery rates of individuals with lung disease compared to the general population. This finding supports the observations of Hansen *et al.*, who examined 5,104 patients with COVID-19, including 354 with asthma and 432 with COPD. They found a slightly increased risk of developing severe outcomes of COVID-19 among patients with obstructive lung disease, but this effect disappeared when adjusting for age. There was also no difference among patients with obstructive lung disease as a comorbidity and the rest of the population regarding severe outcomes (28).

More recently, Schlemmer *et al.* described long-term respiratory trajectories after severe COVID-19. Their study supports our results, showing improvement in PFTs over time, including among known chronic respiratory patients (29). Our study aligns with this observation and focuses on steroid treatment during the acute infection to facilitate faster improvement. The lack of sufficient data on the use of steroids in various types of lung diseases highlights a gap in our understanding of tailored treatments for these conditions. Future research should prioritize gathering more comprehensive data to address this issue. Our findings further support the findings.

Finally, the observation that patients with a BMI over 30 experienced a greater rate of recovery is a noteworthy finding. As shown in several other studies, patients with a higher BMI (>24 kg/m^2) are more likely to develop long COVID symptoms. Our findings support those of Schlemmer *et al.*, where obesity was predictive of better respiratory recovery, despite its known detrimental impact on acute COVID-19 prognosis. This may be explained by the findings of Muscogiuri *et al.*, noting the amplification of COVID-19 inflammation among obese subjects via different mechanisms such as cellular tropism and immune system dysfunction. Given that previous data suggested that individuals with a higher BMI were more prone to severe disease, this emphasizes the complexity of COVID-19 and the need for a more nuanced understanding of the interplay between risk factors, comorbidities, and treatment options (29,30).

Our study has several strengths. It involves a long follow-up of diverse respiratory severity COVID-19 patients. Additionally, the study sheds light on special subgroups thought to be at risk for severe COVID-19 complications.

However, this study has several limitations. Given the gap in knowledge on post-acute COVID-19 and the burden on our healthcare system, it was challenging to identify those in need of follow-up, especially during the first waves of the pandemic. Therefore, there was a selection bias of patients who arrived at the post-COVID clinic for follow-up, which might have influenced the results. Additionally, not all discharged patients attended the post-COVID clinic due to reasons such as cultural beliefs, social issues, or improvement or worsening of their condition. One of the consequences is that is no information on whether there are patients who took additional CS course during the examined period. Another limitation was that when examining patients with lung disease as a comorbidity, the subgroups of specific lung diseases were too small to allow for further investigation of the differences between them.

Moving forward, our study provides a foundation for further research and clinical consideration. It is clear that much more studies are needed to refine the use of steroids in COVID-19 treatment, especially in patients with specific lung diseases. Additionally, the relation between BMI and disease severity warrants further investigation to develop a more comprehensive understanding of COVID-19 outcomes in diverse patient populations. Our findings underscore the importance of ongoing research and the need for adaptable treatment strategies.

Conclusions

Since the outbreak of the novel coronavirus in 2019, it has

presented unprecedented and unforeseen clinical challenges on a global scale. Among various theories proposed, the use of CS treatment during acute COVID-19 infection is considered potentially beneficial for patients. Our study reinforces and enhances this notion by providing evidence that the use of steroid treatment during the acute phase of COVID-19 infection is associated with a significantly accelerated rate of recovery in PFTs.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-503/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-503/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-503/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-503/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and received approval from the Institutional Review Board of Soroka University Medical Center (approval ID: Sor-0560-20, granted in March 2021). Individual consent for this retrospective analysis was waived due to the determination that the waiver or alteration would not negatively impact the rights and well-being of the subjects, and the research would not be practically feasible without this waiver or alteration.

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Cite this article as: Boehm Cohen L, Raviv Y, Shalata W, Kasirer M, Reiner Benaim A. Long-term effect of corticosteroid treatment during acute COVID-19 infection on pulmonary function test results. J Thorac Dis 2024;16(8):4994-5004. doi: 10.21037/jtd-24-503