

Original Article**Post-COVID Lung Function with Steroid and/or Antifibrotic in A Tertiary Hospital of Bangladesh**

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Abstract

Background: Antifibrotic medication with or without steroid might be beneficial to prevent this post-covid fibrotic event; however, evidence could not establish it yet. **Objective:** To assess the effects of steroid and antifibrotics on the changes of SPO₂ and 6MWD in COVID-19 patients whether antifibrotic has any beneficial effect combined with steroid to improve lung function. **Methods:** This quasi-experimental study was conducted on 76 moderate to severe COVID-19 patients admitted in Sher-e-Bangla Medical College Hospital, Barishal, Bangladesh, between June 2020 and June 2021. After recording the SPO₂ and 6MWD, we gave steroid to 57 patients while the rest 19 patients received steroid and antifibrotic depending on severity. We followed the patients after 1 week, 6 weeks and 12 weeks of discharge to determine their SPO₂ and 6MWD change as outcome variable. **Results:** We recorded nearly 83% improvement (n=63) of post Covid respiratory complains as evidenced by improved SPO₂ of 76.9% from baseline to 96.7% in steroid group and from 74.6% to 95.6% in antifibrotic group (p<0.001). The 6MWD test also improved from 62 meter (p<0.001). Similarly, there was a significant improvement of 6MWD test from 53.1, 125.0 and 133.4 meter in 1st follow up, 2nd follow up and 3rd follow up respectively (p<0.001). On further analysis, we found that the antifibrotic treatment improved SPO₂ and 6MWD test better than steroid only treatment group. **Conclusion:** Antifibrotic treatment with steroid improves pulmonary function better than steroid only in terms of SPO₂ and 6MWD.

Keywords: COVID-19, post-covid lung fibrosis, antifibrotic, pneumonia

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Introduction

Corona virus disease (COVID-19) has been the focus of health care response^{1,2} since its emergence with an unprecedented impact throughout the world. Affecting almost all the organs and systems of the body, the common target has been the lungs, which remained the main cause of hospitalization³ Patients continue to suffer from respiratory illness even after recovery from the disease.⁴ The usual symptoms of dyspnea remains after days to months of hospital discharge.⁵ This could compromise their quality of life affecting their routine daily

performance.⁴ The main risk of post COVID-19 disease or post covid pulmonary complication has been identified as lung fibrosis, the burden of which has been estimated to increase over time.⁶ Doctors and scientists have been experimenting with different intervening options¹ to improve the lung function aiding to a normal daily activity. Out of the tested options, steroid has been used to improve lung function and physical endurance.⁷ In addition, some researchers used vitamin⁸, some used zinc⁹, some also tried with antifibrotic treatment added with steroid therapy.³ Antifibrotic with or without steroid might be beneficial to

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prevent this post-covid fibrotic event though enough evidence is not established yet.

Whatever the management choices the scientists take, the indicator for better functioning lungs are the improvement of vital capacity, FEV1, oxygen saturation (SpO₂), and sub maximal exercise test (6 Minute Walk Distance Test) that entails measurement of distance walked over a span of 6 minutes (6MWD) to evaluate the exercise capacity and physical endurance.^{10,11}

Acat et al.¹² conducted a comparison study between steroid and steroid with antifibrotic to assess lung function. They used FEV1 and FVC values exercise capacity by 6MWD and SpO₂, whereas Guler et al.¹³ use diffusing capacity of the lungs for carbon monoxide (DLCO) in addition to above parameter. Use of 6MWD test and SpO₂ can be considered as the evaluating tools to monitor lung function both in hospital and home setting in resource compromised country like Bangladesh. Researchers used these two parameters and recommended for easy assessment of lung function in post COVID lung complications. As steroid has been a treatment of choice in organizing pneumonia (OP)^{14,15} and COVID has a propensity to turn into OP hence fibrosis, the addition of antifibrotic to severely ill patients might have beneficial outcome in terms of improvement of SpO₂ and 6MWD. Therefore, we proposed this study to assess the effect of antifibrotic with steroid compared to steroid alone in post-covid patients with pulmonary impairment to refute the null hypothesis that antifibrotic treatment has got no role in improving lung function.

Methods

This quasi-experimental study was conducted in Sher-e-Bangla Medical College, Barishal, a tertiary level hospital in Bangladesh, among 76 moderate to severe COVID patients discharged from COVID to respiratory ward from June 2020 to June 2021 excluding patients suffering from asthma, COPD, heart failure and severe anemia. In the respiratory ward, patients with ongoing dyspnea or low SpO₂ (<94%) at rest or exercise induced desaturation or combination of any of these three were assessed clinically to be given only steroid for one group and steroid added with antifibrotic drug for the other. We reviewed the literature^{12,16} to decide for the dose of steroid and antifibrotic treatment. We started oral prednisolone 40mg/day, then gradually tapered to lowest effective dose

assessing the clinical condition of the patients throughout the follow up period. The pirfenidone treatment was increased from 267 mg 12 hourly for one week followed by 534 mg 12 hourly as continuation assessing the clinical condition of the patients. The patients received treatment as long as they didn't recover out of danger. We recorded the patients' SpO₂ and 6MWD during discharge, and followed up thereafter weekly up to the time of their improvement, deterioration or death. The last follow up was after 12 weeks of discharge where we end the study. We analyzed the records during discharge, 1st week and 12th week follow up records of the patients. Improvement was decided after assessing the clinical symptoms including the outcome parameters.

Our data contained information of the patients related to their age, sex, address, SpO₂. Though our primary outcome variable was the change of SpO₂ and 6MWD from discharge, 1st follow up 1 week after discharge and final follow up 12 weeks after discharge, we had a secondary outcome of improvement which was assessed by examining the clinical condition of the patients including the change of SpO₂ and 6MWD.

We entered the collected data in excel where the preliminary cleaning was done. Then we transferred the data in SPSS where we did the final analysis. In SPSS, we recoded the age from ≤40 years and >40 years. We recoded address into Barishal district, outside Barishal district and outside Barishal division. We also deducted the SpO₂ and 6MWD from final follow up values to discharge values to calculate initial change and final change.

We assessed the variables in two intervention groups by the demographic variable. Quantitative variables are expressed as mean±SD, while the qualitative variables are expressed as frequency and percentage. The values of SpO₂ and 6MWD as well as changes from one to another follow up was assessed in these two groups. We plotted a repeated measures graph for the three records in both groups. The qualitative variables were assessed using chi square test. Because there was a compromised normality distribution in the continuous data, we used Mann-Whitney U test for the quantitative variables. The change of SpO₂ and 6MWD was presented in median values for this reason.

Results

Table 1 shows the baseline information of the patients where we find that the characteristics are homogeneously distributed in both the groups (p ns) except SpO₂ where we can see that the antifibrotic group has lesser SpO₂ on admission compared to steroid only group hence they were decided to receive antifibrotic along with steroid. Only 3 patients died during our study, 2 were from steroid group and 1 was from antifibrotic group.

We calculated the SpO₂ and 6MWD test result in three follow up settings (Table 2), where we find that the SpO₂ do not show any difference during discharge (1st SpO₂), but 2nd SpO₂ is better in steroid group than antifibrotic group, while it is just not significantly better in steroid group than antifibrotic group in 3rd SpO₂. In the similar manner, we can find that the steroid group walked better than antifibrotic group in 1st and 2nd 6MWD while it is just missing the significance level in 3rd 6MWD. This picture might indicate that the steroid group gave a better treatment in terms of improved SpO₂ and 6MWD. Therefore, we made a new variable to compute the change of

SpO₂ and 6MWD from 2nd to 1st and from 3rd to 1st follow up. When we compared the change of SpO₂ and 6MWD from between 1st with 2nd and 3rd follow up, we see that and antifibrotic group could improve similar or better than steroid group as evidenced from Table 3. Hence, in ultimate judgement, the antifibrotic group could improve worse patients to the level of steroid group patients or even better than the steroid group in terms of SpO₂ and 6MWD improvement.

We constructed plot against the three follow up measurements of SpO₂ and 6MWD separately for steroid and antifibrotic groups. Figure 1 shows the SpO₂ in 1st, 2nd, and 3rd follow up while Figure 2 shows that 6MWD in such. We observe that the SpO₂ shows a linear improvement of SpO₂ in antifibrotic group compared to steroid group, which shows a small faltering of being linear. While comparing 6MWD, we can see that the improvement is similar in both the groups. While we looked at the plot (Figures 1A, 1B, 2A, 2B) of repeated measures analysis for SpO₂ and 6MWD from 1st, 2nd and 3rd follow up with steroid group and antifibrotic group reveals improvement of SpO₂ more linear than changes of 6MWD.

Table 1: Baseline characteristics of the patients (N=76)

Characteristics	Intervention		All patients	p-value
	Steroid	Steroid+AF		
Age	53.16±14.47	57.05±13.31	54.13± 14.21	0.30
SpO ₂ admission (%)	76.89±13.48	67.53±17.21	74.55± 14.95	0.02
<=40 years	15 (83.3)	3 (16.7)	18 (23.7)	0.35
> 40 years	42 (72.4)	16 (27.6)	58 (76.3)	
Male	23 (71.9)	9 (28.1)	32 (42.1)	0.59
Female	34 (77.3)	10 (22.7)	44 (57.9)	
Barishal district	37 (78.7)	10 (21.3)	47 (61.8)	0.37
Barishal division (but outside Barishal district)	18 (66.7)	9 (33.3)	27 (35.5)	
Outside Barishal division	2 (100)	0 (0)	2 (2.6)	

Table 2: Comparison of outcome variables between the interventions

Outcome variables	Intervention		p-value
	Steroid	Steroid+AF	
1st SpO ₂	94.33±4.24	92.79±4.04	0.17
2nd SpO ₂	95.95±2.27	94.22±3.32	0.02
3rd SpO ₂	96.76±1.80	95.56±2.62	0.08
1st 6MWD	62.34±71.67	25.32±43.08	0.009
2nd 6MWD	136.23±96.43	91.49±114.04	0.009
3rd 6MWD	171.63±117.09	114.74±110.87	0.07

Table 3: Mann-Whitney test to assess the change of SpO₂ and 6MWD between the interventions

Outcome variables	Intervention (Median values)		p-value
	Steroid	Steroid+AF	
Change SpO ₂ 2-1	1.00	1.00	0.99
Change SpO ₂ 3-1	1.00	3.00	0.39
Change 6MWD 2-1	57.00	43.00	0.26
Change 6MWD 3-1	70.00	71.00	0.75

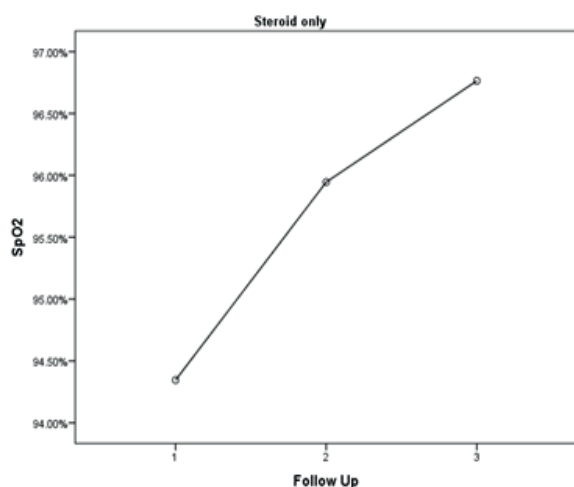


Figure 1A: Repeated measures plot for SpO₂ from 1st, 2nd and 3rd follow up with steroid

Discussion

Our study excavated the better effect of adding antifibrotic treatment compared to steroid only in post covid lung patients. The severely ill patients came back to the level of milder form by antifibrotic treatment compared to those who were receiving steroid only. The baseline parameters were homogeneously distributed between the steroid and antifibrotic group except for low SpO₂ in antifibrotic group. This low SpO₂ is the reason

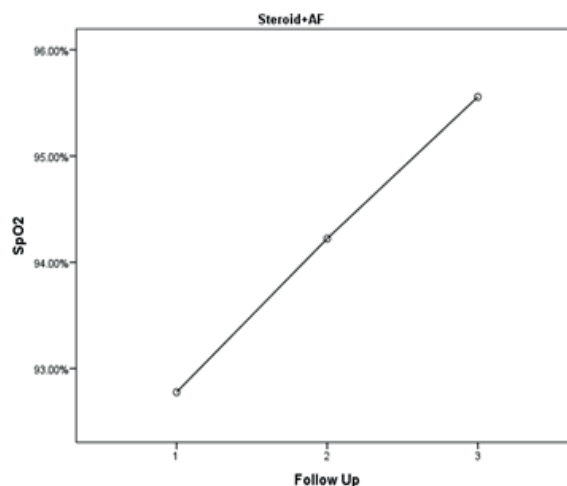


Figure 1B: Repeated measures plot for SpO₂ from 1st, 2nd and 3rd follow up with antifibrotic

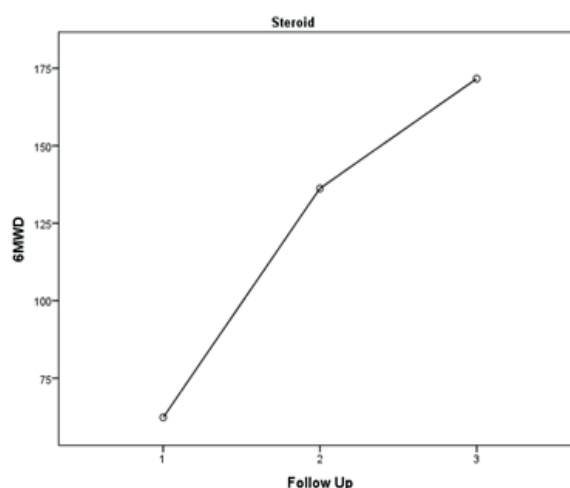


Figure 2A: Repeated measures plot for 6MWD from 1st, 2nd and 3rd follow up with steroid

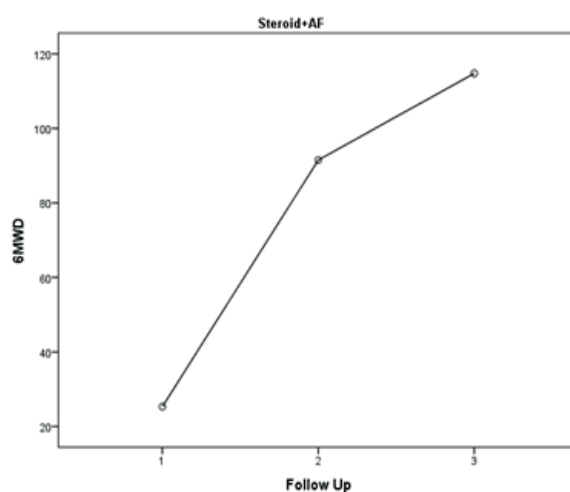


Figure 2B: Repeated measures plot for 6MWD from 1st, 2nd and 3rd follow up with antifibrotic

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that they received antifibrotic added with steroid. In our study, most of the patients were above 40 years. The active family members are in this age group and they have more chance of exposure to infection. Starke et al.¹⁷ also showed the risk of infection hence death increases by age. Population density is an important factor for the spread of COVID-19.¹⁸ We have similar features in patients mostly hailing from Barishal district (62%) in comparison to outside Barishal (38%). Though the population density was not assessed in this study, we assume that Barishal district has more population density being a divisional city thereby recording more patients.

When we looked at the outcome variables comparing the two treatment regimens, we found steroid group showing better record compared to antifibrotic group. This could lead to misinformation that antifibrotic treatment does not work better than steroid (Table 2). But when we assessed the changes of SpO₂ from 1st to 2nd and 3rd visit as well as 6MWD, we can see that the difference is abated away. Rather the antifibrotic group provided better change compared to steroid group in terms of change of SpO₂ and 6MWD from 1st to 3rd visit (Table 3). Repeated measures plot for SpO₂ and 6MWD from 1st, 2nd and 3rd follow up with steroid group and antifibrotic group reveals more linear improvement of SPO₂ than changes of 6MWD.

Acat et al.¹² make comparison between methylprednisolone and pirfenidone plus methylprednisolone group and found FEV1%, FVC and FVC% values were significantly higher in the methylprednisolone plus pirfenidone group compared with the methylprednisolone group, they also conclude that antifibrotic agents can reduce fibrosis of lung after covid infection whereas we try to compare the effect steroid with and without antifibrotic on overall improvement of post COVID lung function in terms of exercise capacity by 6MWD and oxygen saturation by SpO₂. Our result indicates that anti fibrotic has additional beneficial effect improvement of post-COVID lung function.

Our study finding suggests concurrent initiation of antifibrotic added with steroid has momentous benefit on improved lung function over steroid only in severely ill COVID patients. However, Tanvir et al.¹⁹ found that early initiation of antifibrotic in severe COVID infection plays a compelling role than steroid to improve lung function though

they did not find any improvement in 6MWD. In contrast, our study shows significant improvement in 6MWD in antifibrotic group as well along with improved SpO₂. Singhania et al.²⁰ conducted a 3-month follow-up study on pulmonary sequelae of moderate-to-severe COVID pneumonia. They used Remdesivir and steroids for 2 weeks only without employing antifibrotic. After 3 months they found that the fibrosis regressed gradually without any further treatment. They conclude that COVID-19 pneumonia does not induce a fibrotic pathway in the lungs and antifibrotic only can slow down the fibrotic process.

Our study could be compromised with the external validity on the ground of being quasi-experimental. But the evidence that antifibrotic drug has an important role to improve SpO₂ and 6MWD on severely ill post-COVID patients and is being supported by the literature. We may recommend this combined intervention for situation alike. The addition of antifibrotic could bring the severely ill patients back to active life and resume normal function earlier than those who are not receiving the treatment.

Conclusion

Our data showed that an addition of antifibrotic with steroid improves the lung function of the patients. The filling of this knowledge for the COVID treatment could be taken as a measure for any future health crisis involving respiratory system. We recommend further study with a randomized control trial design to verify the effect of our intervention.

Conflict of interest: The authors declare no conflict of interest.

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Ethical approval: We took the ethical clearance from the Ethical Review Committee of Sher-e-Bangla Medical College, Barishal, Bangladesh.

Authors' contribution: MA conceptualized the study; MA, SB planned the design; MA, KZ, HA, KH, EK, FK, SH collected the data; HS, KH entered the data in excel; SB imported the data in SPSS did the analysis. SB, MA, KZ, MB wrote the initial part of the script. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

- Shakoor H, Feehan J, AlDhaheeri A, Ali H, Platat C, Ismail L, et al. Immune-boosting role of vitamin D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas*. 2021;143:1-9.
- Sreepadmanabh M, Sahu A, Chande A. COVID-19: Advances in diagnostic tools, treatment strategies, and vaccine development. *J Biosci*. 2020;45:1-20.
- Salvi SS, Ghorpade D, Dhooi S, Dhar R, Dumra H, Chhajed PN, et al. Role of antifibrotic drugs in the management of post-COVID-19 interstitial lung disease: A review of literature and report from an expert working group. *Lung India*. 2022;39(2):177-86.
- Santus P, Tursi F, Croce G, Simone CD, Frassanito F, Gaboardi P, et al. Changes in quality of life and dyspnea after hospitalization in COVID-19 patients discharged at home. *Multidiscipl Respir Med*. 2020;15(713):1-6.
- Zhang S, Bai W, Yue J, Qin L, Zhang C, Xu S, et al. Eight months follow-up study on pulmonary function, lung radiographic, and related physiological characteristics in COVID-19 survivors. *Sci Rep*. 2021;11(1):13854.
- George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med*. 2020;8(8):807-15.
- Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment. *Ann Am Thorac Soc*. 2021;18(5):799-806.
- Barrea L, Grant WB, Frias-Toral E, Vetrani C, Verde L, de Alteriis G, et al. Dietary Recommendations for Post-COVID-19 Syndrome. *Nutrients*. 2022;14(6):1305.
- Wessels I, Rolles B, Rink L. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. *Front Immunol*. 2020;11:1712.
- Burnfield J, Votto J, Hays A, Stuart M, Lewis L, Prettyman E, et al. Six Minute Walk Test Changes during Long-Term Acute Care Hospital Rehabilitation for Patients Post COVID-19. *Arch Phys Med Rehab*. 2022;103(3):e13-4.
- Directors ABO. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med*. 2002;166:111-7.
- Acat M, Yildiz Gulhan P, Oner S, Turan MK. Comparison of pirfenidone and corticosteroid treatments at the COVID-19 pneumonia with the guide of artificial intelligence supported thoracic computed tomography. *Int J Clin Pract*. 2021;75(12):e14961.
- Guler SA, Ebner L, Aubry-Beigelman C, Bridevaux PO, Brutsche M, Clarenbach C, et al. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J*. 2021;57(4):2003690.
- Jakubec P, Fiserova K, Genzor S, Kolar M. Pulmonary Complications after COVID-19. *Life (Basel)*. 2022;12(3):357.
- Ravaglia C, Doglioni C, Chilosi M, Piciucchi S, Dubini A, Rossi G, et al. Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection. *Eur Respir J*. 2022;60(4):2102411.
- Lam E, Sayedy N, Anjum F, Akella J, Iqbal J. Corticosteroid Therapy in Post-COVID-19 Pulmonary Fibrosis. *Am J Respir Crit Care Med*. 2021;203(9):A2429.
- Romero Starke K, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, Seidler A. The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis. *BMJ Glob Health*. 2021;6(12):e006434.
- Ganasegeran K, Jamil MFA, Ch'ng ASH, Looi I, Peariasamy KM. Influence of Population Density for COVID-19 Spread in Malaysia: An Ecological Study. *Int J Environ Res Public Health*. 2021 Sep 18;18(18):9866.
- Tanvir M, Wagay I, Nisar S, Ahmed R, Maqbool M, Kareem O, et al. Early intervention with anti-fibrotic pirfenidone is effective than corticosteroids in preventing pulmonary fibrosis in severe COVID pneumonia patients. *Curr Med Res Pract*. 2022;12(2):53-60.
- Singhania SVK, Simon C, Raut A, Parvatkar N. Pulmonary sequelae of moderate-to-severe COVID pneumonia, a 3-month follow-up study. *Lung India*. 2021;38(4):397-9.