

Comparison of the effectiveness of pirfenidone with corticosteroids in post-COVID fibrosis: A quasi experimental study

Muhammad Rafay Rasheed¹, Kulsoom Farhat², Shabana Ali³, Ikramullah Khan⁴, Rizwan Abdul Malik⁵

Abstract

Objective: To evaluate the effectiveness of corticosteroids with pirfenidone in patients of post-coronavirus disease-2019 pulmonary fibrosis in preventing long-term life-threatening sequelae.

Method: The quasi-experimental study was conducted at the Department of Pharmacology, Army Medical College, Rawalpindi, and the Department of Pulmonology, Pakistan Emirates Military Hospital, Rawalpindi, Pakistan, from January to December 2024, and comprised patients with post-coronavirus disease-2019 pulmonary fibrosis who were divided into Group-A receiving corticosteroids and Group-B receiving a combination of pirfenidone and corticosteroids. Pulmonary fibrosis was diagnosed on the basis of high-resolution computed tomography findings. The participants were subjected to 6-minute walk test and pulse-oximetry, while Warrick scores for pulmonary fibrosis were also noted for each participant at 3 and 6 months. Data was analysed using SPSS 26.

Results: Of the 40 patients, 20(50%) were in Group-A; 12(60%) males and 8 (40%) females with mean age 42.45 ± 11.11 years. The other 20(50%) patients were in Group-B; 13(65%) males and 7(35%) females with mean age 43.15 ± 8.64 years. Group-B showed higher improvement in 6-minute walk test compared to Group-A both at 90 days ($p=0.189$) and 180 days ($p=0.002$). Improvements in Oxygen saturation, Warrick score for fibrosis and fibrosis percentage were significantly higher in Group-B patients at 180-days follow-up as compared to Group-A ($p<0.05$).

Conclusion: The combination of pirfenidone and corticosteroids showed greater improvement in radiological and functional parameters compared to corticosteroids alone.

Keywords: Anti-fibrotic, Corticosteroid, Pirfenidone, Post-COVID pulmonary fibrosis, 6-minute walk test, Warrick score.

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Introduction

New, extremely virulent viruses crossing the animal-human barrier remain a global threat. Severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) has been the latest threat to mankind.¹ The coronavirus disease-2019 (COVID-19) pandemic affected millions of people worldwide, including more than 1.5 million people in Pakistan, with 30,361 reported deaths in the country.² COVID-19 symptoms range from fatigue, body aches and cough to respiratory failure and pulmonary fibrosis (PF). Most patients with severe COVID-19 recover completely both clinically and radiologically, but 25-35% show evidence of persistent functional and structural abnormalities, with 50% patients having ground glass opacities (GGOs) and 21-29% having fibrotic changes as long-term sequelae.³ Multiple studies have concluded that around 60-70% of treated patients presents with the persistence of at least one or more symptoms, and acute respiratory distress

syndrome (ARDS) seems to be the primary prognosticator of PF.⁴

Recent data suggests that in severe COVID-19 patients, the incidence of PF reaches up-to 17%, with more than a third having fibrotic changes.⁵ The most common symptom of PF is persistent dyspnoea accompanied by fatigue, with cough and chest discomfort affecting up-to 20% patients even after 3-6 months of the infection. Radiological evidence and sequelae of post-COVID-19 PF are persistent GGOs on high-resolution computed tomography (HRCT) scan of the chest.⁶ Dyspnoea affects patient's quality of life (QOL), hence assessment and management is pivotal in post-COVID-19 PF. The 6-minute walk test (6MWT), a global assessment tool, is used to assess the severity of dyspnoea and functional exercise capacity, and to quantify rehabilitation outcome for devising the management plan.⁷

For the time being, no completely recognised options are available for the management of post-COVID-19 PF. The main treatment modalities have been antivirals, glucocorticoids, anticoagulants, interleukin-6 (IL-6) inhibitors and supportive management.⁸ However, anti-fibrotic agents, like pirfenidone, have therapeutic role in PF and reduce pulmonary injury, especially in post-COVID-19

¹⁻⁴Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan; ⁵Department of Radiology, Combined Military Hospital, Attock, Pakistan.

Correspondence: M. Rafay Rasheed. e-mail: rafayrasheed88@gmail.com
ORCID ID: 0009-0001-1857-9626

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fibrosis. Pirfenidone is an anti-fibrotic agent having anti-inflammatory properties, and is also used for fibrotic diseases. It mainly acts by inhibiting fibroblast production and suppressing transforming growth factor-beta (TGF-β) and collagen synthesis. It also reduces the production of pro-inflammatory cytokines, like tumour necrosis factor-alpha (TNF-α).⁹

The current study was planned to assess the efficacy of pirfenidone and corticosteroids in post-COVID-19 PF in preventing long-term life-threatening sequelae among Pakistani patients.

Patients and Methods

The quasi-experimental study was conducted at the Department of Pharmacology, Army Medical College (AMC), Rawalpindi, and the Department of Pulmonology, Pakistan Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, from January to December 2024. The last patient was recruited in June 2024 and all follow-ups were completed in December 2024. After approval from the institutional ethics review board, the sample size was calculated using the World Health Organisation (WHO) online calculator¹⁰ with confidence level 95%, margin of error 5% and incidence of post-COVID-19 PF 2%.¹¹ The sample was raised using consecutive non-probability sampling method. Those included were patient of either gender aged 18-70 years having acute illness with symptoms lasting >14 days who had having acute or previous clinical as well as laboratory-confirmed COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) and mild to moderate fibrotic changes on high-resolution computed tomography (HRCT) scan of the chest.

Those excluded were patients having negative RT-PCR or normal HRCT chest despite symptoms, and those who could not undergo HRCT chest due to any reason. Also excluded were patients with severe fibrosis or critically ill patients requiring mechanical ventilation, patients with known asthma, chronic obstructive pulmonary disease (COPD) or any other obstructive or restrictive pulmonary pathology, and those with autoimmune or malignant disorders.

After taking informed consent, the patients were reviewed and diagnosed by pulmonologists with at least three years of clinical experience. The patients were then divided into Group-A and Group-B using the lottery method. Group-A and Group-B patients were given corticosteroids 40mg orally once daily for two weeks, gradually tapering to 5mg per day. In addition, Group-B participants were treated with pirfenidone 267mg two tablets thrice daily. All the patients were called for follow-up at three and six months when

they were reviewed by pulmonologists. Pulse oximetry was noted in each patient at baseline and at each follow-up. Patients having oxygen (O2) saturation equal to or greater than 96% was considered normal. O2 saturation 94-95% was considered mild, 92-93% moderate, and 91% or less was considered severe.¹²

The 6MWT was done at the two follow-ups. The patients were requested to walk at their own pace in a corridor of 30-metre length with marks at every one metre. O2 saturation was observed continuously throughout the test with the help of a pulse oximeter. The test was terminated immediately if the O2 saturation dropped to 90%. Other reasons for termination of the test were dyspnoea, fatigue or chest pain. At the end of the test, O2 saturation, pulse, time and the distance walked by the patients were recorded. The patients were considered to have failed if they had O2 saturation of greater than or equal to 4% compared to the baseline, or if the test was prematurely stopped due to any reason.¹³ Baseline HRCT chest was done and reported by radiologists with at least three years of experience, at the time of recruitment and subsequently at the two follow-ups. The radiological changes were assessed with Warrick score (W-score) for fibrosis as <8=mild, 8-15=moderate and >15=severe. fibrosis percentage was also noted.¹⁴

Data was analysed using SPSS 26. Mean±standard deviation was calculated for quantitative variables, while categorical data was presented as frequencies and percentages. The pulse oximetry test, 6MWD, W-score and fibrosis percentage at baseline and at the two follow-upswere compared between the groups using the independent *t*-test. P≤0.05 was considered statistically significant.

Results

Of the 62 patients assessed, 40(64.5%) were enrolled. Of them, 20(50%) patients were in Group-A; 12(60%) males and 8 (40%) females with mean age 42.45±11.11 years. The other 20(50%) patients were in Group-B; 13(65%) males and 7(35%) females with mean age 43.15±8.64 years.

Table-1: Intergroup comparison of baseline characteristics (n=40).

Variables	Group-A (n=20) mean±SD	Group-B (n=20) mean±SD	p-value
Age, years	42.45±11.11	43.15±8.64	0.825
Gender, n (%)			
Male	12 (60.0)	13 (65.0)	0.752
Female	8 (40.0)	7 (35.0)	
6-Minute Walk Distance (m)	400.00±13.31	401.35±17.75	0.787
Saturation (%)	90.35±1.22	90.80±1.28	0.221
W-Score	14.35±2.32	13.05±1.57	0.045
Fibrosis (%)	31.45±2.58	31.80±5.34	0.794

W: Warrick, SD: Standard deviation.

Table-2: Intergroup comparison of 6MWT.

6MWT	Group-A (n=20) mean±SD	Group-B (n=20) mean±SD	p-value
Baseline	400.00±13.31	401.35±17.75	0.787
90-day	412.95±9.74	417.50±15.59	0.189
180-day, (m)	421.00±6.76	432.85±13.16	0.002

6MWT: 6-minute walk test, SD: Standard deviation.

Table-3: Intergroup comparison of oxygen saturation.

Saturation	Group-A (n=20) mean±SD	Group-B (n=20) mean±SD	p-value
Baseline (%)	90.35±1.22	90.80±1.28	0.221
90-day (%)	92.80±0.76	93.20±0.76	0.087
180-day (%)	93.60±0.68	95.00±0.97	< 0.005

SD: Standard deviation

Table-4: Intergroup comparison of W-score.

W-Score	Group-A (n=20) mean±SD	Group-B (n=20) mean±SD	p-value
Baseline	14.35 ±2.32	13.05±1.57	0.045
90-day	12.65±1.59	11.65±1.89	0.080
180-day	11.30±1.45	9.05±1.31	< 0.005

W: Warrick, SD: Standard deviation.

Table-5: Intergroup comparison of fibrosis percentage.

Fibrosis (%)	Group-A (n=20) mean±SD	Group-B (n=20) mean±SD	p-value
Baseline	31.45±2.58	31.80±5.34	0.794
90-day	27.80±2.60	26.00±5.35	0.187
180-day	25.00±2.20	18.50±4.28	< 0.005

SD: Standard deviation.

Baseline clinical parameters showed no no significant difference between the groups (Table 1).

Group-B showed relatively higher improvements in 6MWT distance compared to Group-A at 90-day ($p=0.189$) and 180-day ($p=0.002$) follow-ups (Table 2).

O₂ saturation improved more in Group-B patients at 90-day ($p=0.087$) and showed significantly significant improvement at 180-day ($p=0.005$) follow-ups (Table 3).

W-score for PF reduced from 14.35±2.32 at baseline to 11.30±1.45 after 180 days of treatment in Group-A patients, while Group-B patients showed higher improvement from baseline 13.05±1.57 to 9.05±1.31 ($p<0.005$) (Table 4).

PF percentage significantly decreased in Group-B patients compared to Group-A patients at both 90-day ($p=0.187$) and 180-day ($p<0.005$) follow-ups (Table 5).

Discussion

The current study found better therapeutic efficacy with the combination of corticosteroid and pirfenidone. It was

observed that in terms of the studied parameters, like 6MWT, pulse oximetry, W-score and PF percentage, combined treatment with corticosteroid and the anti-fibrotic pirfenidone had better improvement compared to corticosteroid alone. As Mishra et al. also reported, PF patients may benefit with the combination of steroid and anti-fibrotic drugs when given in the early phase of the disease, especially in mild to moderate fibrosis.¹⁵ Similarly, Azuma et al. concluded that pirfenidone in pulmonary fibrosis improved pulse oximetry as well as functional capacity of the lung, and prevented the acute exacerbations of Idiopathic Pulmonary Fibrosis (IPF) during nine months of treatment and follow-up ($p=0.006$).¹⁶

In the current study, it was observed that 6MWT and O₂ saturation values were significantly improved in patients who were given the combination of pirfenidone and corticosteroid. Sansores et al. showed pirfenidone in PF was effective in improving dyspnoea, pulse oximetry, 6MWT as well as radiological findings, and the drug was considered safe and therapeutically effective.¹⁷ Methylprednisolone and pirfenidone reduced PF significantly over a course of six months to one year, and led to improved functional capacities in one study.¹⁸ Similar results were reported by Noble et al.¹⁹

In addition, some studies compared clinical efficacy of nintedanib with pirfenidone, and found nintedanib to be a more effective treatment option in PF than pirfenidone.^{20,21}

Zhou et al. concluded that post-COVID-19 PF is challenging to treat, but pirfenidone proved to be an effective treatment in improving 6MWT from 188m to 308m, and improved Total Lung Capacity (TLC) from 1.98L to 2.30L.²² Vitiello et al. showed that anti-fibrotic therapy was effective in preventing progression of PF and accelerating the healing process.²³ Maher et al. observed that patients with unclassified PF benefit from pirfenidone treatment in terms of improved TLC, O₂ saturation, 6MWD, and reduced fibrotic changes with acceptable safety and tolerability profile.²⁴

All these findings imply that dual-drug therapy leads to a uniform and long-term positive change in clinical, functional and radiological measurements, which is an indicator of better treatment effectiveness and possible synergies with combined treatment.

The current study has limitations of being a single-centre study with a limited sample size. In addition, the non-randomised study design, and less control over confounding factors also limited the generalisability of the findings. Multicentre studies with larger sample sizes, randomised study designs, and rigorous control of

confounding factors are needed to confirm the findings.

Conclusion

The combination of pirfenidone and corticosteroids showed greater improvement in radiological and functional parameters compared to corticosteroids alone in the provision of better post-COVID-19 clinical outcomes.

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References

- Bazbaz A, Varon J. Post COVID-19 pulmonary fibrosis - the new pandemic. *Curr Respir Med Rev*. 2025;21:107-8. doi:10.2174/1573398X2102241007101206.
- Khan AA, Abdullah M, Khan R, Kazmi T, Sultan F, Aamir S, et al. Pakistan's national COVID-19 response: lessons from an emergent response to the pandemic. *Front Public Health*. 2024;12:1379867. doi:10.3389/fpubh.2024.1379867.
- Bermudo-Peloché G, Del Rio B, Vicens-Zygmunt V, Bordas-Martínez J, Hernández M, Valenzuela C, et al. Pirfenidone in post-COVID-19 pulmonary fibrosis (FIBRO-COVID): a phase 2 randomised clinical trial. *Eur Respir J*. 2025;65:2402249. doi:10.1183/13993003.02249-2024. Available from: PubMed
- Rai DK, Sharma P, Kumar R. Post COVID 19 pulmonary fibrosis. Is it real threat? *Indian J Tuberc*. 2021;68:330-3. doi:10.1016/j.ijtb.2020.11.003.
- Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol*. 2020;30:3306-9. doi:10.1007/s00330-020-06731-x.
- Hama Amin BJ, Kakamad FH, Ahmed GS, Ahmed SF, Abdulla BA, Mohammed SH, et al. Post COVID-19 pulmonary fibrosis; a meta-analysis study. *Ann Med Surg (Lond)*. 2022;77:103590. doi:10.1016/j.amsu.2022.103590.
- AlBahrani S, AlBarak A, Alqahtani JS, AlGubaisi N, Alkurdi H, Alburaiqi D, et al. Assessing post-COVID-19 functional recovery in healthcare workers: insights from the 6-minute walking test and DLCO analysis. *J Infect Public Health*. 2025;18:102664. doi:10.1016/j.jiph.2025.102664.
- Tanvir M, Wagay I, Nisar S, Ahmed RN, 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;12:53-60. doi:10.4103/cmrip.cmrip_110_21.
- Al-Kuraishy HM, Batiha GES, Faidah H, Al-Gareeb AI, Saad HM, Simal-Gandara J. Pirfenidone and post-Covid-19 pulmonary fibrosis: invoked again for realistic goals. *Inflammopharmacology*. 2022;30:2017-26. doi:10.1007/s10787-022-01027-6.
- Calculator.net. Sample size calculator. Calculator.net; [Online] [Cited 2026 August 27]. Available from: URL: https://www.calculator.net/sample-size-calculator.html?utm_source=chatgpt.com
- Bazdyrev E, Rusina P, Panova M, Novikov F, Grishagin I, Nebolsin V. Lung fibrosis after COVID-19: treatment prospects. *Pharmaceuticals (Basel)*. 2021;14:807. doi:10.3390/ph14080807.
- Wilkerson RG, Annous Y, Farhy E, Hurst J, Smedley AD. Home pulse oximetry monitoring during the COVID-19 pandemic: an assessment of patient engagement and compliance. *Health Policy Technol*. 2023;12:100776. doi:10.1016/j.hlpt.2023.100776.
- Agarwala P, Salzman SH. Six-minute walk test: clinical role, technique, coding, and reimbursement. *Chest*. 2020;157:603-11. doi:10.1016/j.chest.2019.10.014.
- Fessi R, Ourari B, Ben Amar J, Zaibi H, Azzabi S, Baccar MA, et al. High-resolution computed tomography fibrosis score and pulmonary function tests in interstitial lung disease: is there any correlation? *Eur Respir J*. 2018;52: PA2926. doi:10.1183/13993003.congress-2018.PA2926.
- Mishra M, Sindhwani G. Antifibrotics for COVID-19 related lung fibrosis: agents with benefits? *Adv Respir Med*. 2021;89:231-3. doi:10.5603/ARM.a2021.0023.
- Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2005;171:1040-7. doi:10.1164/rccm.200404-571OC.
- Sansores RH, Ramírez-Venegas A, Montiel-Lopez F, Domínguez-Arellano S, Alva-Lopez LF, Falfán-Valencia R, et al. Prolonged-release pirfenidone in patients with pulmonary fibrosis as a phenotype of post-acute sequelae of COVID-19 pneumonia: safety and efficacy. *Respir Med*. 2023;217:107362. doi:10.1016/j.rmed.2023.107362.
- 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:e14961. doi:10.1111/ijcp.14961.
- Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377:1760-9. doi:10.1016/S0140-6736(11)60405-4.
- Kerget B, Çil G, Araz Ö, Alper F, Akgün M. Comparison of two antifibrotic treatments for lung fibrosis in post-COVID-19 syndrome: a randomized, prospective study. *Med Clin (Barc)*. 2023;160:525-30. doi:10.1016/j.medcli.2022.12.021.
- Singh P, Behera D, Gupta S, Deep A, Priyadarshini S, Padhan P. Nintedanib vs pirfenidone in the management of COVID-19 lung fibrosis: a single-centre study. *J R Coll Physicians Edinb*. 2022;52:100-4. doi:10.1177/14782715221103402.
- Zhou X, Yang D, Kong X, Wei C, LvQiu S, Wang L, et al. Case report: pirfenidone in the treatment of post-COVID-19 pulmonary fibrosis. *Front Med (Lausanne)*. 2022;9:925703. doi:10.3389/fmed.2022.925703.
- Vitiello A, Pelliccia C, Ferrara F. COVID-19 patients with pulmonary fibrotic tissue: clinical pharmacological rational of antifibrotic therapy. *SN Compr Clin Med*. 2020;2:1709-12. doi:10.1007/s42399-020-00487-7.
- Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2020;8:147-57. doi:10.1016/S2213-2600(19)30341-8.

Author Contribution:

MRR: Concept, design, drafting and data acquisition.

KF: Concept, design and critical revision.

SA: Data analysis and interpretation.

IK: Writing and accuracy of data critical revision.

RAM: Data acquisition, interpretation and final approval.