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Original Article

Investigating the effect of pirfenidone on lung CT scans in patients with severe COVID-19 Hospitalized at Shahid Sadoughi Hospital, Yazd, Iran

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Abstract

Background: This study aimed to evaluate the effect of pirfenidone on lung CT scan lesions in patients with severe COVID-19.

Methods: In this cross-sectional study, data were extracted from the electronic medical records of patients with severe COVID-19 who received one of the following treatments: pirfenidone alone (n= 40), prednisolone alone (n= 55), pirfenidone combined with methylprednisolone (n= 18), or supportive care only (n= 32). Chest CT images taken at baseline and two months post-treatment were assessed by a trained radiologist. $p< 0.05$ was considered statistically significant.

Results: The distribution of initial CT scan findings, Comparison of CT scan findings at admission and two months post-discharge, as well as the extent of pulmonary fibrosis and ground-glass opacity (GGO) grades across the groups, showed no statistically significant differences. However, significant differences were observed in CT scan findings and GGO grades between the four study groups at two months post-discharge. Moreover, in both the pirfenidone ($p= 0.00$) and supportive care ($p= 0.01$) groups, the extent of pulmonary fibrosis between admission and two months post-discharge showed statistically significant changes.

Conclusion: In summary, although antifibrotic agents such as pirfenidone may not lead to significant improvement in lung CT scan findings in patients with severe COVID-19, they may help slow the progression of pulmonary fibrosis following the acute phase of the disease.

Keywords: Pirfenidone, Pulmonary fibrosis, COVID-19, CT scan, Prednisolone.

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Acute Coronavirus Disease 2019 (COVID-19) pneumonia can lead to tissue inflammation, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), and even death (1). Among these complications, pulmonary fibrosis is a significant clinical manifestation of severe COVID-19 infection that requires prompt and effective management (2, 3). The development of acute lung injury and pulmonary fibrosis is likely associated with the excessive release of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1-beta (IL-1β), interleukin- 6 (IL-6), and interleukin- 8 (IL-8) (4). Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an oral anti-fibrotic and anti-inflammatory agent approved for the treatment of idiopathic pulmonary fibrosis (5, 6). Given its pharmacological properties, pirfenidone may offer therapeutic benefits in managing pulmonary fibrosis associated with COVID-19 (5, 7-16). Its anti-fibrotic effects are thought to be mediated through the inhibition of apoptosis, suppression of overexpressed transforming growth factor-beta (TGF-β), reduction of connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF), as well as the downregulation of TNF-α and other pro-inflammatory mediators (17).

Considering the prevalence of pulmonary fibrosis in patients with severe COVID-19 and the dual anti-inflammatory and anti-fibrosis actions of pirfenidone, we hypothesized that this drug could play a beneficial role in reducing fibrotic lung damage in COVID-19 patients. Hence, the present study was conducted to evaluate the therapeutic efficacy of pirfenidone on lung lesions, as assessed by chest CT scans, in patients with severe COVID-19 pneumonia.

Methods

Study design and participants: This analytical cross-sectional study was conducted at Shahid Sadoughi Hospital in Yazd, Iran. Retrospective data of patients hospitalized with a diagnosis of severe SARS-CoV-2 infection from February 2020 to August 2022 were collected from the hospital's electronic health records system. Demographic characteristics, clinical manifestations, comorbidities, type of oxygen received, oxygen saturation levels at admission and discharge, duration of hospitalization, primary treatments administered, and laboratory findings were documented for patients who received pirfenidone (N = 40), prednisolone (N = 55), pirfenidone plus prednisolone (N = 18), and supportive care only [Supportive care in this study refers to patients who, following hospital discharge, received supplemental oxygen, adequate nutrition, and nutritional supplements such as vitamin D. These patients did not receive corticosteroids or pirfenidone after discharge (N = 32)].

Chest CT images obtained prior to treatment and two post-discharges were retrieved from the hospital's PACS system and subsequently analyzed. Inclusion criteria were as follows: a) age ≥ 18 years, b) ≤14 days since onset of initial symptoms, c) evidence of bilateral lung involvement on imaging, and d) moderate to severe acute respiratory distress (18). Exclusion criteria included a) elevated liver enzymes (aminotransferase levels > 3-5 times the upper normal limit), b) total bilirubin > 1.5 times the normal range, c) glomerular filtration rate < 30%, d) prior treatment of interstitial lung disease with pirfenidone or nintedanib, e) history of cardiovascular diseases including malignant hypertension or myocardial infarction within the last 6 months, f) unstable angina in the last 6 months, g) history of major cerebrovascular accidents, h) known drug allergy, i) pregnancy, j) breastfeeding, and k) unwillingness of the patient or legal guardian to participate.

All patients had a confirmed diagnosis of COVID-19 via Real-Time polymerase chain reaction (RT PCR) testing from nasopharyngeal swabs, in accordance with clinical diagnostic criteria prior to hospital admission. According to the QUICK COVID-19 SEVERITY INDEX- which evaluates respiratory rate, oxygen saturation, and oxygen flow rate- participants met the criteria for classification as having severe disease.

Treatments: The therapeutic interventions administered included Remdesivir (200 mg on day one, followed by 100 mg daily), Interferon- β, Lopinavir / Ritonavir (Kaletra), Tocilizumab (Actemra), Methylprednisolone (500 -1000 mg for three consecutive days), Colchicine (0.6 mg), Plasmapheresis, and stem cells therapy. Pirfenidone was initiated at 200 mg and titrated up to 600 mg every 8 hours.

Chest computed tomography protocols: Chest CT scans were performed using either a spiral or high- resolution CT (HRCT) scanner (TOSHIBA medical systems, Otawara, Japan; 16 slice Alexion), with 1.2 mm slices obtained in the supine and inspiratory position. Patients were instructed to hold their breath during image acquisition to reduce motion artifacts. CT images were independently evaluated by two trained radiologists. Fibrosis and GGO scoring was based on the CT Severity Score System (CTSS4), in which each of the five lung lobes was assigned a score based on the percentage of involvement: 1 (<5%), 2 (5-25%), 3 (26-49%), 4 (50- 74%), and 5 (> 75%) (11).

Ethical considerations: The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1402.255). All data were kept confidential. Due to the retrospective nature of the requirements for informed consent were waived.

Statistical analysis: Continuous variables were expressed as mean±standard deviation (SD), and categorical variables as frequencies (percentages) for the Independent samples t-tests and chi-square served to compare the differences among the continuous and categorical variables, respectively. A p-value< 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software Version 22.0 (SPSS, Chicago, IL, USA).

Results

Characteristics of the participants: Between February 2020 and August 2022, a total of 145 patients with severe COVID-19 were enrolled in this study. All participants tested positive for SARS-COV-2 by RT-PCR-. The patients were allocated into four groups: 40 received pirfenidone, 55 received prednisolone, 18 received a combination of pirfenidone and prednisolone, and 32 received supportive treatment only.

The mean age of the participants was 58.17±13.47 years in the pirfenidone group, 57.8±13.11 years in the prednisolone group, 54.11±11.11 years in the combination group, and 59.71±10.95 years in the supportive treatment group. No statistically significant difference was observed among the groups in terms of age (P= 0.50). While most baseline characteristics and clinical symptoms were comparable across groups, a significant difference was found regarding the presence of tachypnea (P = 0.00) and the type of oxygen therapy administered (P = 0.003). All other variables, including sex distribution, comorbidities, symptoms, treatments, and laboratory data, were not statistically different among the groups. Full details of baseline variables are provided in table 1.

Table 1. Baseline data of the participants

Variables	Groups				P-value
	Pirfenidone (n = 40)	Prednisolone (n = 55)	Pirfenidone + Prednisolone (n = 18)	Protective treatment (n = 32)	
Age,years	58.17±13.47	57.8±13.11	54.11±11.11	59.71±10.95	0.50
Sex **Female**	23 (57.5)	25 (45.5)	5 (27.8)	15 (46.9)	0.48
Male	17 (42.5)	30 (54.5)	13 (72.2)	17 (53.1)	
Clinical signs					
Cough	30 (20.7)	43 (29.7)	14 (9.7)	24 (16.6)	0.97
Shortness of breath	37 (25.5)	51 (35.2)	17 (11.7)	29 (20)	0.97
Fever	23 (15.9)	35 (24.1)	11 (7.6)	20 (13.8)	0.94
Tachypnea	27 (18.6)	29 (20)	14 (9.7)	10 (6.9)	0.00*
Tiredness	19 (13.1)	22 (15.2)	9 (6.2)	13 (9)	0.81
Myalgia	26 (17.9)	35 (24.1)	13 (9)	18 (12.4)	0.71
Headache	4 (2.8)	7 (4.8)	-	3 (2.1)	0.47
Diarrhea	5 (3.4)	7 (4.8)	2 (1.4)	3 (2.1)	0.96
Nausea	8 (5.5)	6 (4.1)	-	5 (3.4)	0.18
Hyposmia and hypogeusia	7 (4.8)	11 (7.6)	3 (2.1)	1 (0.7)	0.18
Cramp	-	4 (2.8)	-	1 (0.7)	0.21
Rhinorrhea	3 (2.1)	1 (0.7)	-	-	0.17
Comorbidities					
CKD	-	2 (1.4)	-	1 (0.7)	0.55
Smoking	4 (2.8)	5 (3.4)	1 (0.7)	3 (2.1)	0.95
Asthma	3 (2.1)	3 (2.1)	1 (0.7)	2 (1.4)	0.98
Cancer	1 (0.7)	1 (0.7)	-	-	0.76
Hypertension	16 (11)	24 (16.6)	6 (4.1)	10 (6.9)	0.66
Diabetes mellitus	17 (11.7)	20 (13.8)	8 (5.5)	12 (8.3)	0.89
CVD	9 (6.2)	11 (7.6)	2 (1.4)	5 (3.4)	0.72
AIDS	1 (0.7)	-	-	-	0.45
CHF	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	0.86
Liver disease	-	1 (0.7)	-	-	0.64

Comorbidities					
COPD	7 (4.8)	3 (2.1)	1 (0.7)	3 (2.1)	0.23
Drug abuse	1 (0.7)	-	-	2 (1.4)	0.22
Corticosteroid Use	2 (1.4)	-	-	-	0.15
HLP	8 (5.5)	10 (6.9)	4 (2.8)	5 (3.4)	0.94
Treatments					
Remdesivir Use	35 (87.5)	47 (85.4)	17 (94.4)	30 (93.7)	0.46
Interferon	12 (30)	22 (40)	5 (27.7)	9 (28.1)	0.42
Lopinavir / Ritonavir (Kaletra)	1 (2.5)	1 (1.8)	-	-	NS
Tocilizumab (Actemra)	15 (37.5)	35 (63.6)	7 (38.8)	22 (68.7)	0.078
Methylprednisolone	27 (67.5)	35 (63.6)	15 (83.8)	22 (68.7)	0.71
Colchicine Use	20 (50)	38 (69)	15 (83.8)	15 (46.8)	0.071
Plasmapheresis	15 (37.5)	27 (49)	10 (55.5)	11 (34.4)	0.068
Stem cell Therapy	1 (2.5)	4 (7.2)	2 (11.1)	-	0.011
Time from onset to admission	9.54±5.83	7.78±4.85	11.22±7.48	6.89±3.96	0.013
Hospitalization period (days)	11.55±8.31	13.54±8.51	14.33±7.04	10.09±5.96	0.14
Type of oxygen received					
Reservoir bag	22 (55)	36 (65.5)	8 (44.4)	27 (84.4)	0.003*
NIV	10 (25)	8 (14.5)	1 (5.6)	1 (3.1)	
MV	2 (5)	1 (1.8)	4 (22.2)	1 (3.1)	
Reservoir bag + NIV	6 (15)	10 (18.2)	5 (27.8)	2 (6.3)	
Hospitalization **Ward**	16 (40)	24 (43.6)	4 (22.2)	19 (59.4)	0.07
Hospitalization **ICU**	24 (60)	31 (56.4)	14 (77.8)	13 (40.6)	
Laboratory tests					
ESR	57.51±24.60	57.48±24.58	61.64±24.55	51.42±28.34	0.49
CRP	2.57±1.11	2.90±1.09	2.88±1.36	2.85±1.11	0.50
Ferritin	732.20±355.06	851.43±371.45	1049.42±488.98	574.66±495.44	0.51
LDH	852.15±632.10	1033.30±741.88	1117.31±624.95	800.58±363.55	0.61
D-Dimer	1.75±0.44	1.54±0.50	1.68±0.47	1.38±0.49	0.46
IL-6	126.65±144.06	137.33±280.79	40.06±61.85	197.58±433.69	0.019
WBCs	7653.84±3329.52	7730.90±3822.97	10623.52±5000.31	7732.25±3836.87	0.11
LYM	11.16±5.80	13.82±6.92	10.15±3.80	13.22±7.99	0.12
Absolut	825.92±479.99	931.16±420.56	822.58±558.44	884.45±495.91	0.46

- The values are reported as mean ± SD or n (percentage). The p-values were obtained by Chi-square. Abbreviations: CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; AIDS: Acquired Immunodeficiency Syndrome; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; HLP: Hyperlipidemia; NIV: Non-Invasive Ventilation; MV: Mechanical Ventilation; ICU: Intensive Care Unit; ESR: Erythrocyte Sedimentation Rate; CRP: C - reactive protein; LDH: Lactate Dehydrogenase; IL-6: Interleukin-6; WBCs: White Blood Cells; LYM: Lymphocytes.

CT scan findings, pulmonary fibrosis involvement Scale, and GGO Grade: As presented in tables 2 and 4, there were no statistically significant differences among the four study groups regarding CT scan findings and distribution of GGO grades, both at admission and two months post-discharge. However, analysis of pulmonary fibrosis involvement revealed a significant improvement in the pirfenidone group over the two-month follow- up period (P = 0.00). In contrast, patients in the supportive treatment group demonstrated a statistically significant progression of lung lesions (P = 0.01). No statistically significant changes were observed in the prednisolone group or the pirfenidone+prednisolone combination group over the same period (table 3).

Table 2. CT scan findings in the four study groups at admission and two months post discharge

CT lesions		Pirfenidone	Prednisolone	Pirfenidone+ Prednisolone	Protective treatment
Ground glass opacity	Admission	38 (95)	55 (100)	18 (100)	32 (100)
	2 months after discharge	22 (55)	34 (43.6)	11 (61.1)	17 (53.1)
Ground glass opacity+Ground glass opacity with mixed consolidation	Admission	24 (60)	41 (74.5)	13 (72.2)	19 (59.3)
	2 months after discharge	2 (5)	8 (14.5)	2 (11.1)	5 (15.6)
Pleural thickening	Admission	2 (5)	1 (1.8)	-	1 (3.1)
	2 months after discharge	4 (10)	-	-	1 (3.1)
Interlobular septal thickening	Admission	15 (37.5)	12 (21.8)	7 (38.8)	9 (28.1)
	2 months after discharge	8 (20)	19 (34.5)	6 (33.3)	14 (43.7)
Air bronchogram	Admission	14 (35)	23 (41.8)	10 (55.5)	10 (31.2)
	2 months after discharge	2 (5)	4 (7.2)	1 (5.5)	3 (9.3)
Traction bronchiectasis	Admission	10 (25)	7 (12.7)	2 (11.1)	1 (3.1)
	2 months after discharge	9 (22.5)	21 (38.1)	4 (22.2)	6 (18.7)
Fibrotic band	Admission	34 (85)	21 (38.1)	4 (22.2)	7 (21.8)
	2 months after discharge	28 (70)	46 (83.6)	12 (66.6)	26 (81.2)
Bronchovascular bundle distortion	Admission	13 (32.5)	7 (12.7)	3 (16.6)	0 (0.0)
	2 months after discharge	10 (25)	15 (27.2)	5 (27.7)	5 (15.6)
Architectural distortion	Admission	8 (20)	5 (9)	1 (5.5)	0 (0.0)
	2 months after discharge	3 (7.5)	7 (12.7)	3 (16.6)	4 (12.5)
Honeycombing appearance	Admission	5 (12.5)	1 (1.8)	1 (5.5)	1 (3.1)
	2 months after discharge	2 (5)	5 (9)	2 (11.1)	1 (3.1)
P-value		0.05	0.75	0.17	0.71

- The values are reported as n (%). The p-values were obtained by Chi-square.

Table 3. Pulmonary fibrosis involvement SCALE in the four study groups at admission and two months post discharge

Pulmonary fibrosis involvement SCALE		Pirfenidone	Prednisolone	Pirfenidone + Prednisolone	Protective treatment
0	**Admission**	9 (8)	16 (14.2)	9 (8)	15 (13.3)
	2 months after discharge	7 (5.3)	4 (3.1)	2 (1.5)	3 (2.3)
1	**Admission**	1 (0.9)	3 (2.7)	1 (0.9)	3 (2.7)
	2 months after discharge	1 (0.8)	8 (6.1)	1 (0.8)	2 (1.5)
2	**Admission**	1 (0.9)	3 (2.7)	-	3 (2.7)
	2 months after discharge	5 (3.8)	4 (3.1)	2 (1.5)	7 (5.3)
3	**Admission**	4 (3.5)	1 (0.9)	1 (0.9)	1 (0.9)
	2 months after discharge	6 (4.6)	6 (4.6)	4 (3.1)	7 (5.3)
4	**Admission**	4 (3.5)	5 (4.4)	1 (0.9)	1 (0.9)
	2 months after discharge	6 (4.6)	10 (7.6)	1 (0.8)	2 (1.5)
5	**Admission**	2 (1.8)	5 (4.4)	-	2 (1.8)
	2 months after discharge	2 (1.5)	4 (3.1)	-	2 (1.5)
6	**Admission**	1 (0.9)	3 (2.7)	-	1 (0.8)
	2 months after discharge	3 (2.3)	3 (2.3)	-	1 (0.8)
7	**Admission**	2 (1.8)	-	1 (0.9)	1 (0.8)
	2 months after discharge	-	4 (3.1)	-	1 (0.8)
8	**Admission**	2 (1.8)	-	-	1 (0.8)
	2 months after discharge	-	-	-	1 (0.8)
9	**Admission**	-	1 (0.9)	-	-
	2 months after discharge	-	-	1 (0.8)	1 (0.8)
10	**Admission**	3 (2.7)	-	-	-
	2 months after discharge	1 (0.8)	2 (1.5)	1 (0.8)	1 (0.8)
11	**Admission**	-	1 (0.9)	-	-
	2 months after discharge	2 (1.5)	1 (0.8)	1 (0.8)	-
13	**Admission**	-	1 (0.9)	1 (0.9)	-
	2 months after discharge	2 (1.5)	2 (1.5)	-	1 (0.8)
14	**Admission**	1 (0.9)	-	-	-
	2 months after discharge	-	2 (1.5)	-	-
15	**Admission**	1 (0.9)	-	-	-
	2 months after discharge	-	1 (0.8)	-	-
16	**Admission**	1 (0.9)	-	-	-
	2 months after discharge	-	-	2 (1.5)	1 (0.8)
17	**Admission**	2 (1.8)	-	-	-
	2 months after discharge	-	-	-	-
18	**Admission**	-	-	1 (0.9)	-
	2 months after discharge	-	-	-	-
P-value		0.00*	0.28	0.70	0.01**

- The values are reported as n (%). The P-values were obtained by Chi-square.

* Clear trend toward improvement. ** worsening of fibrosis scores.

Table 4. GGO grade distribution in the four study groups at admission and two months post discharge

GGO Grade		Pirfenidone	Prednisolone	Pirfenidone + Prednisolone	Protective treatment
0	Admission	1 (0.7)	-	-	-
	2 months after discharge	14 (10.7)	13 (9.9)	7 (5.3)	10 (7.6)
2	Admission	-	-	-	-
	2 months after discharge	2 (1.5)	-	-	2 (1.5)
3	Admission	-	-	-	-
	2 months after discharge	2 (1.5)	2 (1.5)	-	2 (1.5)
4	Admission	-	-	-	-
	2 months after discharge	1 (0.8)	-	1 (0.8)	1 (0.8)
5	Admission	2 (1.4)	3 (2.1)	-	2 (1.4)
	2 months after discharge	9 (6.9)	14 (10.7)	1 (0.8)	5 (3.8)
6	Admission	2 (1.4)	-	-	-
	2 months after discharge	2 (1.5)	2 (1.5)	1 (0.8)	-
7	Admission	-	-	1 (0.7)	1 (0.7)
	2 months after discharge	-	2 (1.5)	2 (1.5)	-
8	Admission	1 (0.7)	-	1 (0.7)	-
	2 months after discharge	2 (1.5)	1 (0.8)	-	1 (0.8)
9	Admission	-	-	-	2 (1.4)
	2 months after discharge	1 (0.8)	1 (0.8)	-	-
10	Admission	2 (1.4)	5 (3.5)	-	2 (1.4)
	2 months after discharge	4 (3.1)	3 (2.3)	3 (2.3)	6 (4.6)
11	Admission	1 (0.7)	2 (1.4)	-	1 (0.7)
	2 months after discharge	-	-	-	-
12	Admission	1 (0.7)	2 (1.4)	-	3 (2.1)
	2 months after discharge	-	1 (0.8)	-	-
13	Admission	3 (2.1)	1 (0.7)	-	1 (0.7)
	2 months after discharge	-	1 (0.8)	1 (0.8)	-
14	Admission	3 (2.1)	4 (2.8)	1 (0.7)	1 (0.7)
	2 months after discharge	-	2 (1.5)	-	-
15	Admission	4 (2.8)	5 (3.5)	1 (0.7)	3 (2.1)
	2 months after discharge	-	1 (0.8)	1 (0.8)	1 (0.8)
16	Admission	6 (4.2)	2 (1.4)	-	4 (2.8)
	2 months after discharge	-	3 (2.3)	-	-

	GGO Grade	Pirfenidone	Prednisolone	Pirfenidone + Prednisolone	Protective treatment
17	Admission	-	5 (3.5)	1 (0.7)	-
	2 months after discharge	-	-	-	1 (0.8)
18	Admission	3 (2.1)	2 (1.4)	1 (0.7)	3 (2.1)
	2 months after discharge	-	-	-	-
19	Admission	-	3 (2.1)	-	-
	2 months after discharge	-	-	-	1 (0.8)
20	Admission	4 (2.8)	8 (5.6)	3 (2.1)	2 (1.4)
	2 months after discharge	-	-	-	-
21	Admission	2 (1.4)	-	2 (1.4)	4 (2.8)
	2 months after discharge	-	-	-	-
22	Admission	-	2 (1.4)	-	1 (0.7)
	2 months after discharge	-	-	-	-
23	Admission	1 (0.7)	5 (3.5)	4 (2.8)	1 (0.7)
	2 months after discharge	-	-	-	-
24	Admission	1 (0.7)	-	-	-
	2 months after discharge	-	-	-	-
25	Admission	2 (1.4)	6 (4.2)	3 (2.1)	1 (0.7)
	2 months after discharge	-	1 (0.8)	-	1 (0.8)
P-value		0.05	0.91	0.87	0.29

- The values are reported as n (%). The p-values were obtained by Chi-square.

Discussion

The aim of this study was to investigate the effect of pirfenidone on the incidence of pulmonary fibrosis in COVID-19 patients following the acute phase of SARS-CoV-2 infection. The results indicated a significant difference in the rate of pulmonary fibrosis between the pirfenidone group and the supportive care group two months after discharge, compared to the time of hospital admission. Notably, lung lesions worsened in the supportive care group over this period, whereas in the prednisolone and the prednisolone + pirfenidone groups, there was no statistically significant change in lesion severity.

Regarding pirfenidone's potential to improve pulmonary fibrosis and prevent its progression, our findings are in line with previous studies. Boshra et al. (2022) conducted a study on 100 ICU- admitted COVID-19 patients, where 47 patients received standard treatment plus pirfenidone, and 53 received standard treatment alone. They found lower rates pulmonary fibrosis and mortality in the group receiving pirfenidone in addition to standard therapy (11). Another study involving 146 COVID-19 patients (73 in the pirfenidone group and 73 in the standard treatment group) evaluated CT scans four weeks post- treatment. While overall CT findings did not differ significantly between the two groups, the pirfenidone group showed improvement in consolidation, GGO, and reticulation patterns. However, the study also concluded that pirfenidone neither significantly improved nor worsened fibrosis. Importantly, pirfenidone was associated with a significant reduction in IL-2 and TNF-a levels (19). In a separate investigation focused on the effect of pirfenidone on long-term pneumonia following COVID-19, Acat et al. (2021) studied 22 patients (13 treated with pirfenidone+ methylprednisolone and 9 with methylprednisolone alone). They reported that pirfenidone

helped prevent fibrosis progression and facilitated methylprednisolone dose reduction and/or discontinuation, potentially minimizing steroid- associated side effects (12). These findings are consistent with another study on patients with severe COVID-19, in which 17 received pirfenidone and 19 were treated with corticosteroids. The study concluded that earlier initiation of pirfenidone resulted in better clinical and survival outcomes, particularly among high- risk groups such as elderly patients and those with comorbidities (20).

In a 2022 study involving 262 patients with post COVID interstitial lung disease (post-COVID ILD), 135 received corticosteroids and 127 served as controls. The steroid group demonstrated better clinical and functional lung recovery. Although radiological improvement was greater in the steroid group, the difference was not statistically significant (21). In our study, pirfenidone significantly improved pulmonary fibrosis. However, in the group receiving both prednisolone and pirfenidone, the improvement was not statistically significant. This finding contrasts with the results reported by Acat et al. (2021), which may be attributed to the small sample size, inconsistent and insufficient pirfenidone use, or a lack of synergistic interaction between the two drugs in our study. There are two important aspects to consider when evaluating pulmonary fibrosis: a) its extent, which reflects the percentage of lung involvement and b) its severity, determined by the type of lung lesions present.

In assessing the therapeutic effects of medications on lung fibrosis, both factors must be evaluated simultaneously. According to existing research, pirfenidone is an effective agent with anti-inflammatory and anti-fibrotic properties. While It does not reverse established fibrosis (10), it helps prevent the progression and worsening of lung lesions. Therefore, it is recommended for patients with severe COVID-19 during the early stages of the cytokine storm (8, 20). One of the strengths of the present study is the inclusion of a control group that did not receive any antifibrotic treatment. However, several limitations should be noted. First, the sample size was small, and the follow-up period was relatively short.

These limitations highlight the need for further studies with larger sample sizes and longer follow- up intervals, including serial lung CT scans, to better assess the long-term anti-fibrotic effects of pirfenidone on the severity and incidence of pulmonary fibrosis in COVID-19 patients, as well as its impact on recovery outcomes. Accordingly, large randomized controlled trials are warranted. Additionally, after initiating pirfenidone therapy, patients should be monitored every two weeks to assess appropriate therapeutic dosing, monitor for potential drug discontinuation, and detect possible viral reinfection. Finally, it should be noted that the study consisted of patients with severe COVID-19 who were enrolled between February 2020 and August 2022. During this period, widespread vaccination and evolving viral variants may have influenced the clinical course of the disease and, consequently, the study's outcomes. In summary, patients with severe COVID-19 pneumonia require post- discharge treatment to help prevent the development of pulmonary fibrosis. Although antifibrotic agents such as pirfenidone may not lead to significant improvements in CT imaging findings, they may slow the progression of fibrosis in these patients. Overall, the findings of this study suggest that pirfenidone can be considered a therapeutic option for patients with severe COVID-19. However, future research should aim to elucidate the long-term efficacy of pirfenidone in reversing or halting the progression of mild to moderate pulmonary fibrosis following COVID-19 infection.

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Authors' contribution: S. Gholamrezaei, M. Samet, and F. Aghaei Meybodi equally contributed to the conception and design of the research. A. Amelshahbaz, S. Gholamrezaei, N. Namiranian and F. Aghaei Meybodi collected and analyzed the data. S. Samet, A. Amelshahbaz, and N. Namiranian contributed to the interpretation of the data. N. Namiranian, S. Gholamrezaei and F. Aghaei Meybodi drafted the manuscript. All the authors critically revised the manuscript, agreed to be fully accountable for the integrity and accuracy of the work, and read and approved the final manuscript.

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