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Impact of antifibrotics on post-COVID-19 lung sequelae

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Abstract

Respiratory problems in acute COVID-19 and post-acute COVID-19 syndrome vary greatly, potentially leading to long-term functional difficulties. Off-label usage of antifibrotics, such as pirfenidone, has emerged as a promising treatment for post-COVID interstitial lung problems. Our study aims to assess clinical and radiological lung abnormalities post-COVID-19 and the effect of antifibrotics on the outcome. A retrospective observational study examined data from 90 COVID-19 patients who completed the follow-up period in the post-COVID clinic at the Chest Department, Kasr El Ainy Hospital, from August 2020 to August 2022. Demographic data, comorbidities, exercise tolerance, and chest computed tomography (CT) results were collected 1 and 6 months after the diagnosis. Initial CT scans (1 month following hospital admission) revealed diffuse ground-glass opacities (87.8%) and reticulations (43.3%). After 6 months, 33.3% were back to normal, 41% had persistent reticulations, 22.2% had ground glass opacities, and 3.3% had bronchiectasis. CT scores improved dramatically after 6 months. No significant link was detected between CT score change and off-label use of pirfenidone. Antifibrotic therapy has a modest effect on post-COVID lung problems. One-third of patients showed reticulations as persistent radiological abnormalities, which could guide future treatment choices.

Key words: post-COVID-19 lung abnormalities, antifibrotics, post-acute COVID-19 syndrome, interstitial abnormalities.

Introduction

Coronavirus disease 19 (COVID-19), caused by a new virus (SARS-CoV-2), began in China in late 2019 and spread throughout the world before being declared a pandemic by WHO in March 2020 [1]. Acute COVID-19 is characterized by respiratory symptoms, fever, and gastrointestinal difficulties [2]. Acute COVID-19 patients vary in the length and severity of the disease. Many individuals are asymptomatic, but others require hospitalization and ventilation [3]. However, worldwide, a percentage of patients with acute SARS-CoV-2 infection develop a variety of persistent symptoms that do not resolve over several months [2]. These patients are diagnosed with 'Long COVID' or 'Post-acute sequelae of COVID-19' (PASC) [4]. Patients with a PASC diagnosis are likely to have diverse underlying biological mechanisms driving their symptoms due to SARS-CoV-2-induced organ or tissue harm, as well as related clotting or inflammatory processes during acute COVID-19 [3]. SARS-CoV-2's ability to infect a wide spectrum of human cell types may explain the diverse COVID-19 symptoms [5]. The spike subunit of SARS-CoV-2 interacts with the human angiotensin-converting enzyme 2 (ACE2) receptor to infect and enter host cells [5]. PASC symptoms include fatigue, muscle weakness, sleeplessness, palpitations, persistent rhinitis, dysgeusia, chills, a sore throat, and a headache [4]. Because PASC symptoms are so unique, several therapy techniques may be necessary to manage this complex disorder [6] effectively. Another early study of COVID-19 patients after hospital discharge discovered that more than a third develop lung fibrotic abnormalities, resulting in scarring of the lungs, which may impair gas exchange and exacerbate symptoms of fatigue, dyspnea, and exercise intolerance [7]. Fibrosis is not a typical complication of other viral pneumonia; nevertheless, it has been documented in around 8% of SARS patients and 20% of H7N9 influenza patients [8,9]. Fear of long-term consequences has led to the off-label use of anti-fibrotics in the hope of alleviating and eliminating post-covid interstitial lung problems. Multiple case series have shown that anti-fibrotic medications can improve post-covid lung sequelae [10]. This study aims to assess clinical and radiological lung abnormalities post-COVID-19 and the effect of anti-fibrotics on the outcome.

Materials and Methods

A retrospective observational study that examined data of 90 patients completed follow-up in a post-COVID clinic at the Chest Department, Kasr El Ainy Hospital, Cairo University, between August 2020 and August 2022. Ethical committee approval from the Faculty of Medicine, Cairo University, numbered MD-5-2022.

The inclusion criteria were patients aged 18 and older who confirmed moderate to severe COVID-19 and had a positive reverse transcriptase-polymerase chain reaction nasopharyngeal swab. Patients got standard care therapy according to Egyptian recommendations for managing COVID-19 [11]. All patients were followed up after 6 months of COVID-19 diagnosis. Patients with any interstitial or chronic lung disease, hemodynamic instability, and/or heart failure were excluded. Patients with missing data were also excluded. Data gathered from included were age, smoking history, comorbidities, oxygen saturation as assessed by pulse oximetry or arterial blood gases, length of hospitalization, and duration of oxygen therapy during active infection, if applicable. Data collected during follow-up included medications received, CT chest and oxygen saturation. Steroids (prednisolone 20 mg once daily) and anti-fibrotics (pirfenidone 267 mg TDS) were used for at least three months in the previous six months in a group of patients; another group received steroids only.

CT chest, pulse oximetry for resting oxygen saturation, and stair climbing test for exercise desaturation were obtained one month after the active disease and six months later.

CT chest pattern (diffuse ground glass opacities (GGOs), reticulation, or severe organized pneumonia (OP) pattern) and quantitative assessment of illness severity using a semi-quantitative CT scoring technique were observed and documented.

CT chest score using the semi-quantitative scoring system (CT-SS): Each of the five lung lobes was visually graded from 0 to 5, with 0 indicating no engagement, 1 suggesting less than 5% involvement, two indicating 5-25% involvement, 3 indicating 26-49% involvement, 4 indicating 50-75% involvement, and 5 indicating more than 75% involvement. The total CT score was calculated by adding the individual lobar scores and varied from 0 (no involvement) to 25 (highest engagement) [12].

Statistical analysis

Data were analyzed using the Statistical Program for Social Science (SPSS) version 24. Qualitative data were expressed as frequency and percentage. Quantitative data were expressed as median (IQR) as the data was not normally distributed (The normality test and Kolmogorov-Smirnov & Shapiro-Wilk test were performed).

The following tests were done: Mann Whitney U test (MW) when comparing two groups (for abnormally distributed data), Kruskal Willis test (KW) when comparing between more than two groups (for abnormally distributed data), and the chi-square test was used when comparing non-

parametric data and probability (P-value): P-value < 0.05 was considered significant, a P-value < 0.001 was considered highly important, and a P-value > 0.05 was considered insignificant.

Results

The study comprised data of 90 patients with moderate to severe COVID-19 infection who completed six months for follow-up; the demographic and basic characteristics of all studied patients are shown in Table 1. Table 2 compares the patients' radiological data and oxygenation status collected after one month to data collected after 6 months of active illness.

Off-label use of anti-fibrotic medication was common throughout the post-covid period because of concerns about irreversible lung scarring. In the current study, steroids (prednisolone 20mg once daily) and anti-fibrotics (pirfenidone 267 mg TDS) were used for at least three months in the previous six months in a group of patients 51.1% (n = 46/90), another group received steroids only. Table 3 shows correlation between CT score change (Δ CT score), Δ SO2 (%) and Pirfenidone. Table 4 shows relation between smoking and CT score.This table presents various correlations and clinical outcomes. There was no statistically significant correlation between CT score at admission and smoking (p-value = 0.776), as well as between Δ CT score and smoking (p-value = 0.451).

Discussion

This retrospective observational study examined data of 90 patients previously diagnosed with COVID pneumonia who came for follow-up in the COVID clinic at the Chest Department, Kasr El Ainy Hospital, Cairo University, between August 2020 and August 2022. The studied patients included 49 patients (54.4%) with moderate disease, 34 patients (37.8%) with severe diseases and 7 patients (7.8%) with critical disease.

Regarding demographics, all patients evaluated had a mean age of 57.2 ± 13.07 years, with a 70:30 male-to-female ratio. The male predominance could be attributed to an androgen-driven pathophysiology of SARS-CoV-2, which leads to severe COVID-19 results. Multiple investigations support the hypothesis that estrogen has an immunologic protective effect in females [13]. These findings were comparable to other studies [14,15]. Diabetes was the most common comorbidity in our study. It was present in 42.2% of patients (n=38), with HTN accounting for 38.9% (n=35). It is unclear whether patients with diabetes are particularly vulnerable to COVID-19. However, multiple investigations have found a link between severe COVID-19 infection and DM [16,17]. It was proposed that the angiotensin-converting enzyme 2

(ACE2) could explain this connection [18]. Other studies found hypertension to be the most common comorbidity, followed by type II diabetes [14,19,20]. Hypertension is among the most common chronic disorders. It is hypothesized that hypertensive patients have increased angiotensin-converting enzyme 2 (ACE2) expression, which, while still controversial, may increase susceptibility and severity of COVID-19 [21]. This postulation explains all the research that identified HTN as the primary comorbidity.

The current study found that all patients had an average oxygen saturation of 86.6 ± 5.6%, with a minimum of 65% and a maximum of 96%. The average hospital stay for all investigated patients was 2.2 ± 1.6 weeks, ranging from 1 week to 8 weeks. In all, 69 patients (76.7%) required respiratory assistance, with two (2.9%) on invasive mechanical ventilation, 19 (27.5%) on noninvasive ventilation, 7 (10.1%) on high flow nasal canula, and 41 (59.4%) on O2 mask.

Núñez-Fernández and colleagues found that the average oxygen saturation at hospital admission was 92% (89-97%). The average length of stay for all analyzed patients was 7 (4-13.2) days; 26 patients (13.4%) required invasive mechanical ventilation [22]. COVID-19 hospital stay length varies based on disease severity, patient age, and comorbidities. While the median length of stay often ranges from 7 to 13 days, studies have documented cases with significantly longer hospitalizations, extending up to or beyond 8 weeks [23].

One of the most common long-term effects of COVID-19 pneumonia is the persistence of respiratory symptoms and/or radiological lung abnormalities [14]. The etiology of pulmonary fibrosis in COVID-19 patients comprises dysregulated immunological systems generating generalized epithelial and endothelial damage and an abnormal repair process that leads to pulmonary fibrosis [24-26].

In the present investigation, the baseline CT abnormalities at the time of active infection were 87.8% (n=79) with diffuse GGO patches, 43.3% (n=39) with reticulations, and 12.2% (n=11) with significant OP-crazy pavement. After 6 months, 30 patients (33.3%) recovered to normal, with reticulations being the most common anomaly in 37 patients (41.1%), followed by GGOs in 20 patients (22.2%), and bronchiectasis in three patients (3.3%). We found a decrease in ground-glass opacity but not in other abnormalities such as reticulations or bronchiectasis. These radiological findings were consistent with other studies [14,22].

Six months after hospital discharge, approximately (22%) of our patients continued to have some areas of ground-glass opacity, either reticular lesions (41%) or bronchiectasis (3%), as described by other studies [27], indicating that the mid-term radiological alterations tend to improve or remain unchanged without signs of progression to fibrosis in most patients.

Comparison of CT scores throughout the trial revealed a statistically significant drop in CT scores at 6 months compared to those at 1 month after admission. This data indicates an improvement in the parenchymal affection of the lungs over 6 months after the active infection, as seen by an improvement in the median CT score. As a result, it is unclear whether this improvement is due to a specific treatment regimen.

At 6 months, SO2 saturation was significantly higher (p-value < 0.001) than at admission (median = 88, IQR = 85-90). Similarly, Núñez-Fernández et al. [22] showed considerable improvement in SO2 at 3 and 12 months. These could be explained by the improvement in lung CT with time. SO2 levels were measured one and six months into the current trial while climbing stairs, with significant improvement observed (p-value < 0.001). Early studies examining functional capacity provide information on the propensity to desaturate during field-based exercise testing. Daher et al. found that 60 days after discharge, no patients were severely desaturated on a 6MWT [28]. However, 79% could not accomplish their projected walking distance, and 45% were below the lower limit of normal. Similar findings were observed three months after discharge, 16% of patients had desaturation, with 22% falling below the lower limit of normal walking distance [29].

The management of COVID-19 pulmonary fibrosis is fraught with ambiguity, mainly owing to the lack of available therapy options [24,25]. Anti-fibrotic drugs such as Pirfenidone and Nintedanib have a proven role in fibrotic disorders such as idiopathic pulmonary fibrosis (IPF). By analogy, they can treat post-COVID-19 fibrosis [27,30].

Prednisolone was administered to 84 patients (93.3%) and Pirfenidone to 46 patients (51.1%) three to six months after discharge. The link between CT score change (Δ CT score), Δ SO2 (%) and drug use (Pirfenidone) was not statistically significant between both groups.

Several studies have explored the potential role of anti-fibrotic agents, such as nintedanib and pirfenidone, in managing hospitalized individuals with moderate to severe COVID-19 and those with pulmonary fibrosis following COVID-19 infection.

Vikas et al. described a case study of four individuals who responded effectively to nintedanib therapy for one month [31]. High-resolution computed tomography (HRCT) scans confirmed the presence of lung fibrosis, prompting the start of anti-fibrotic therapy. The degree of pulmonary involvement varied across patients, but all had severe COVID-19 pneumonia and post-COVID pulmonary fibrosis. Jan Michael et al. reported a case of pulmonary fibrosis after severe COVID-19 pneumonia that demonstrated improvement in symptoms, pulmonary function, and HRCT after a six-month course of nintedanib, steroids, and pulmonary rehabilitation [30]. Zhou X. et

al. also reported a case report in which post-COVID pulmonary fibrosis symptoms, pulmonary function, and chest CT imaging improved following two years of pirfenidone treatment [32]. A Chinese experiment found that four weeks of pirfenidone did not significantly reduce lung interstitial lesions in people with severe COVID-19 (according to a CT scan). Pirfenidone therapy did, however, improve anti-inflammatory responses and reduce thrombotic consequences [33]. Ferrara et al. determined that pirfenidone may lessen or prevent the immune-inflammatory response that precedes lung fibrosis [34]. Furthermore, the customized timing of pirfenidone administration reflects its success in preventing pulmonary fibrosis; yet, due to its anti-fibrotic qualities, pirfenidone would cure residual pulmonary fibrotic alterations [35]. A retrospective cohort study examining data from multiple healthcare institutions found that COVID-19 patients with acute respiratory failure who received anti-fibrotic treatment had a notably lower one-year mortality rate than those who did not receive such therapy.This suggests a potential therapeutic benefit, though further validation is needed [36]. Additionally, a review of anti-fibrotic applications in post-COVID-19 pulmonary fibrosis emphasized the need for randomized controlled trials to confirm their effectiveness [37].

In summary, anti-fibrotics's potential therapeutic value in the COVID-19 scenario is questionable for a variety of reasons. First, because there is currently no consensus on therapy selection criteria, the possibility of spontaneous illness resolution over time, reflecting inter-individual heterogeneity, cannot be ruled out. Furthermore, dose regimes and treatment durations have not been consistent throughout the data reported. Furthermore, the daily dose of anti-fibrotic medications may not always meet the required dose for the initial indication (IPF or non-IPF progressive pulmonary fibrosis).

Study limitations

Some limitations must be addressed. First, it was conducted at a single hospital, which, while potentially restricting its external validity, ensures consistency. Specific tests, such as the pulmonary function test, must be performed to produce more reliable results. Finally, the sample size is relatively small.

Conclusions

This study shows that, patients' CT findings, exercise ability, and oxygen saturation improved significantly between one month and six months after COVID-19 pneumonia. Regardless of the anti-fibrotic medication, both CT scores and lung anomalies showed a constant reduction. After

6 months, one-third of the patients returned to normal CT findings, with persistent abnormalities primarily appearing as a reticular pattern. These findings help us understand the post-acute phase of COVID-19 and may guide future treatment options.

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Table 1. Demographic and basic characteristics of all studied patients.

		Studied patients (N = 90)	
Sex	Male	63	70%
	Female	27	30%
Age (years)	Mean ±SD	57.2 ± 13.07	
	Min – Max	21 – 84	
Smoking	No	73	81.1%
	Yes	17	18.9%
Comorbidities	DM	38	42.2%
	HTN	35	38.9%
O_2 saturation (baseline)	Mean ±SD	86.6 ± 5.6	
	Min – Max	65-96	
Hospital stay (weeks)	Mean ±SD	2.2 ± 1.6	
	Min – Max	1-8	
Respiratory support	No	21	23.3%
	Yes	69	76.7%
Respiratory support measures	NIV	19	27.5%
	HNFC	9	13%
	O_2 mask	41	59.4%
Drugs received for >3 months	Steroids	84	93.3%
	Pirfenidone	46	51.1%
Severity of COVID	Moderate	49	54.4%
	Severe	34	37.8%
	Critical	7	7.8%

NIV, noninvasive ventilation; HNFC, high flow nasal cannula; SD, standard deviation.

Table 2. Description of Chest CT, medication received and effort assessment in all studied patients.

			Studied patients (N = 90)	
Chest CT pattern one month after active disease		Diffuse GGO Patches	79	87.8%
		Reticulations	39	43.3%
		Extensive OP - crazy paving	11	12.2%
CT score (one month after active disease)		Mean ±SD	14.2 ± 6.1	
		Min – Max	2-25	
Chest CT pattern after 6 months		Reticulations	37	41.1%
		GGOs	20	22.2%
		Bronchiectasis	3	3.3%
		Normal	30	33.3%
CT score Median (IQR) KW: Kruskal Willis test=141.2.		1 month after active disease	14 (10-18)	p-value < 0.001 is considered highly significant(HS)
		After 6 months	3 (0.75-5)	
SO_2 saturation Median (IQR)(n=90)	one month after active infection	90 (89-92)	KW = 150.7	< 0.001 HS
	After 6 months	95 (93 – 96)		
Stair climbing SO_2 Median (IQR)	One month after active infection	88 (85 – 92.5)	KW = 75.9	< 0.001 HS
	After 6 months	95 (92 -96)		

KW, Kruskal Willis test; HS, p-value < 0.001 is considered highly significant; SD, standard deviation; IQR, interquartile range.

Table 3. Correlation between CT score change (Δ CT score), Δ SO2 (%) and Pirfenidone.

	Pirfenidone		Test	P-value
	Yes (n = 46)	No (n = 44)		
Δ CT score Median (IQR)	84.1 (74.1-100)	80 (56-93.75)	MW = 831	0.191 NS
Δ SO2 (%) Median (IQR)	8 (4.17-10.4)	9.25 (5.3-13.4)	MW = 866.5	0.240 NS

MW, Mann Whitney U test; NS, not significant; SD, standard deviation; IQR, interquartile range.

Table 4. Relation between smoking and CT score.

		Smoking		Stat. test	P-value
		Yes (n = 16)	No (n = 73)		
CT score (one month after active infection)	Median	14.5	14	MW = 593	0.776 NS
	IQR	12.25-18	10-18		
Δ CT score	Median	84.5	82.3	MW = 514	0.451 NS
	IQR	77.1-100	65.4-94.09		

MW, Mann Whitney U test; NS, p-value > 0.05 is considered non-significant.