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Research Article

Post-Covid Lungs Fibrosis: An Worrying Experience of Covid19 Survivors!!

SM AA Mamun[1]*, Zafor Iqbal[2], Sanaullah Sarker[3], QT Islam[4], Arif Mahmud[5] and Sania Ahsan[6]

[1]Senior Consultant of Respiratory Medicine, Evercare Hospitals, Dhaka, Bangladesh

[2]Consultant, Intensive Care Unit, Evercare Hospitals, Dhaka, Bangladesh

[3]Senior Specialist of Respiratory Medicine, Evercare Hospitals, Dhaka, Bangladesh

[4]Professor of Medicine, Popular Medical College, Dhaka, Bangladesh

[5]Public Health Specialist and Deputy Director of Evercare Hospitals, Dhaka, Bangladesh

[6]Senior Consultant of Radiology and Imaging, Evercare Hospitals, Dhaka, Bangladesh

***Corresponding Author:** SM AA Mamun, Senior Consultant of Respiratory Medicine, Evercare Hospitals, Dhaka, Bangladesh.

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Abstract

Introduction: Patients recovering from confirmed COVID-19, particularly moderate to severe disease, those who needing HDU/ICU support with HFNC and MV, experienced different symptoms ranging from tiredness, fatigue to severe exertional dyspnea. HRCT of Chest of these patients showing persistent radiological abnormalities simulating progressive fibrotic lung disease. Lung function including DLCO revealed moderate to severe reduction of CO transfer factor. In case of patients recovered from moderate to severe COVID-19 pneumonia, lung injury and fibrosis is a big problem and it is one of the most worrying long-term complications. We observed that lung fibrosis was documented in previous SARS and MERS pathology, and current observational studies suggests that pulmonary fibrosis could also complicate infection by SARS-CoV-2.

Objective: The objective of our study is to early segregation of patients who have potential to develop such serious complication, thus giving a chance for early detection of post-COVID-19 lung fibrosis and to prevent or at least modify such disabling complication by proper and early intervention.

Results: From April 2020 to June 2021, 110 patients at Evercare hospitals Dhaka Bangladesh, who had admitted in HDU and ICU with florid clinical manifestations and confirmed COVID-19 by RT-PCR, were evaluated by follow-up HRCT of chest and symptoms scoring. Different radiological signs and residual fibrotic changes in follow up HRCT was considered. CT severity score (CT-SS) is a good predictor for disease progression, that leads to pulmonary fibrosis.. In our study we have taken mild to moderate group (CT-SS of 1-17) and severe group (CT-SS of 18-25).

There are no documented predisposing factors that may directly influence the development of post-COVID-19 lung fibrosis, some predicting factors such as old age, multiple comorbidity, long term cigarette smoking and prolong HFNC or mechanical ventilation may be the inciting factors.

Conclusion: Early detection of potential cases of post-COVID-19 lungs fibrosis may give us the opportunity to prevent or at least modify such disabling condition.

Keywords: COVID-19; Fibrosis; Antifibrotic

Background

The outbreak of the novel coronavirus (SARS-CoV-2), responsible for the coronavirus disease-19 (COVID-19), was first reported in Hubei province, China, on December 31, 2019. After this outbreak, increasing number of patients worldwide who have survived COVID-19 continue to battle the symptoms of the illness, long after they have been clinically tested negative for the disease. As the physicians are fighting day and night with this pandemic to save lives, another challenging part is to manage post Covid19 sequelae after surviving of patients, which may vary from fatigue and body aches to lung fibrosis.

Postcovid lung fibrosis is one of the important consequences of COVID-19 pneumonia, and it is one of the most worrisome long-term complications. This fibrosis may lead to non-reversible lung dysfunction. Such permanent lung changes of previous COVID infection (SARS, MERS) still not completely understood and should demand further research.

Aim of the Study

The aim of this study is to determine the early predicting factors of lung injury and fibrosis, to find out the risk factors, course of disease and treatment option for post covid pulmonary fibrosis. Patients of old ages, requiring HDU or ICU support and mechanical ventilation, are at the highest risk to develop pulmonary fibrosis. At present, no fully proven treatment options are available for post COVID 19 lungs damage and fibrosis

Methods

Study design

Total 110 patients including 72 males (65.45%) and 38 females (34.55%) with age range from 20 to 88 years old were enrolled in this cross-sectional prospective study at Evercare hospitals, Dhaka Bangladesh, during the period from 18 April 2020 to 30 June 2021 admitted in HDU and ICU. The male versus female ratio was designed to 1.8 :1. Different age group were, 20 - 45 years old 28 patients, from 46 to 60 years old were 35 patients, and those ranging from 60 to 88 years old were 47 patients. 45 patients received HFNC, 23 patients has high flow oxygen mask and 42 patients undergone Mechanical ventilation. All patients were properly scrutinized for full clinical data taking including age, sex, contact history, and current presenting complaint during follow up.

Inclusion criteria

- Molecular Laboratory Confirmed Covid 19 RT PCR positive patients.
- Admitted to Covid HDU and Covid ICU of Evercare hospitals.
- Having positive CT chest findings were included in this study.

HRCT chest was done 3 weeks after from covid19 positivity to assess degree of recovery and residual fibrotic changes. Further follow up at the end of 2nd month and 3rd months for patients with persisting dyspnea and having fibrotic changes in earlier HRCT of chest.

Exclusion criteria

- Pregnant women,
- Advanced ILD patients as per previous HRCT of chest,
- Patients with advanced Bronchiectasis, and
- Patients with chronic medical condition such as uncontrolled DM, hypertension, and autoimmune disease.

Results

This prospective cross sectional study included 110 patients (72 males, 38 females) with age ranging from 20 to 88 years with confirmed diagnosis by PCR-positive COVID results and admitted in HDU and Medical ICU of Evercare hospitals from 18 April 2020 to 30 June 2021. Among them 68 patients was treated in HDU (45 Patients with HFNC and 23 patients with High flow mask) and 42 patients (in ICU) necessitates Mechanical ventilation but survived and discharged.

Figure 1: Gender wise distribution of admitted Covid19 patients.

Gender wise admission data		
Gender	**Total admission**	**Percentage**
Male (72)	72	65.45%
Female (38)	38	34.5%
Total Admission	110	100%

Table 1: Percentage of male and female patients admitted Covid ICU and HDU.

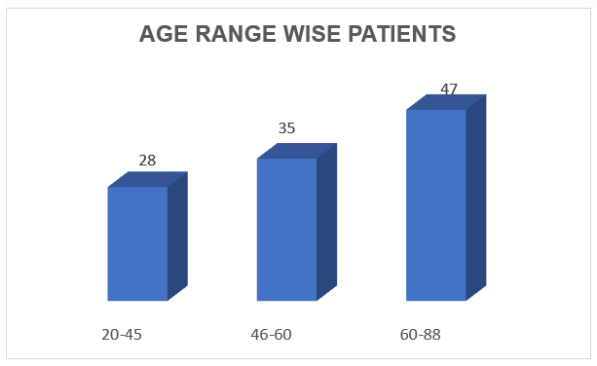

Figure 2: Age Distribution of admitted Covid19 patients.

Age range wise patients Data		
Age group	**Number of patients**	**(%)**
20-45	28	25.45%
46-60	35	31.81%
60-88	47	42.72%
Total	110	100%

Table 2: Percentage of patients according to age.

Although all age groups are at risk of contracting COVID-19, older people face significant risk of developing severe disease and need hospital admission. In our study 47 patients was in 60 to 88-year age group followed by 35 in 45 - 60-year age group and 28 was in 25 - 45-year age group.

Support needed

At initial presentation, during admission 1st HRCT of Chest was performed, then follow-up CT chest was done after 3 weeks from 1st positivity to assess degree of recovery and residual fibrotic changes. Further follow-up at 4 - 6 weeks and 9 - 12 weeks for patients with residual symptoms and/or residual lung fibrotic changes with or without further Chest Scanning. Total 30 Patients gave history of heavy cigarettes smoking (27.3%). (More than 20 pack years).

Figure 3: Distribution of patients with different support and facility.

Category	Number of Patients	%
HFNC	45	40.90
High flow mask	23	20.90
Mechanical ventilation	42	38.18
Total	110	100%

Table 3: Percentage of patients according to facility and support.

Common clinical presentation was dry cough, which was seen in 80 patients (75%); 58 patients suffered from moderate to severe dyspnea (56%), 55 patients had fever (50%), and 35 patients presented with diarrhea (31%)

Number of patients	Clinical history
80 (73%)	Dry cough
58 (53%)	Dyspnea
55 (50%)	Fever
35 (31%)	Diarrhea

Table 4: Clinical history of patients enrolled in our study.

Lung fibrosis developed in Post-COVID-19 patients was found maximum in patients age ranging from 60 to 88-year age group (26/60 patients; 43.3%) followed by mild higher prevalence in 45 - 60-year age group (7/25 patients; 28%), than 25 - 45-year age group (5/25 patients; 20%). Patients who have history of cigarettes smoking showed much higher incidence of post-pulmonary fibrosis than those have no smoking history. As from the 30 smoking patients, 20 developed post-pulmonary fibrosis.

The patients having minimum lung injury, marked as mild group (CT-SS of 1 - 17) (48 patients) showed lower tendency for post-COVID-19 fibrosis seen only in 14 patients (29.1%) whereas the severe group (CT-SS of 18 - 25) (62 patients) showed greater incidence of post-COVID-19 pulmonary fibrosis seen in 32 patients (51.6%).

Figure 4: A 67-year-old ex- smoker male patient presented with fever for 5 days, exertional dyspnea, and dry cough diagnosed as positive for COVID-19 by PCR. Admitted in Covid ICU. CT-SS was 16/25. On HRCT (A,B) done 14th day of admission. Follow up HRCT (C,D) was done after 6 weeks and 12 weeks from start of symptoms, revealed bilateral pulmonary fibrotic changes in the form of fibrotic bands, peribronchial thickening, traction bronchiectasis but improved in comparison to previous one (after getting antifibrotic therapy).

Discussion

The severity of COVID19 ranges from asymptomatic infection, through mild flu-like symptoms, to severe COVID19 disease that can rapidly progress to respiratory distress requiring intensive care treatment and mechanical ventilation and can ultimately result in respiratory failure and death. In different study including the expert panel of World Health Organization (WHO), it is estimated that 80% of SARS-CoV-2 infections are mild, 15% develop severe symptoms, and 5% will become critically ill.

Recent studies have shown that the infection fatality rate (IFR) from COVID-19 varies substantially across geographical locations, which may reflect the variation in population age [1,2]. Increased age is a major contributing factor to mortality from COVID-19 [3]. Furthermore, increased age is associated with higher risk of hospitalization following COVID19 infection. Adults over 65 years of age represent 80% of hospitalizations and have a 23-fold greater risk of death than those under 65. Whereas it is not yet established, why elderly people are more at risk and age is an independent risk factor, evidence suggest that declining of immunological response with aging may be most important factor. For the immune system to effectively suppress and eliminate SARS-CoV-2 virus, it must perform four main tasks: (a) recognize, (b) alert, (3) destroy and (d) eliminate. Each of these mechanisms are known to be dysfunctional and increasingly heterogeneous in older people [1].

In addition to increased age, various other factors are now well documented to increase risk of death from COVID-19 including gender (males have higher mortality), ethnicity, obesity, and pre-existing medical conditions including diabetes, chronic respiratory, cardiac and liver diseases, reduced kidney function, hematological malignancies, and neurological diseases.

Interstitial lung disease (ILD) is a group of disorders that includes various diffuse parenchymal lung diseases characterized by inflammation and scarring. ILD often characterized by shared features of inflammation and/or fibrosis [4]. But the term pulmonary fibrosis is a pathological outcome of acute and chronic inflammation of lungs, in which normal regulation of tissue repair is compromised [5,6]. The pathogenesis of pulmonary fibrosis involves repeated microinjury to the alveolar epithelium that leads to an aberrant and ineffective repair response and epithelial dysfunction, which results in the trans differentiation, activation and expansion of fibroblasts/myofibroblasts [7].

Great advances have been made in recent years in the understanding of the underlying pathogenesis of pulmonary fibrosis.

A combination of genetic, environmental and aging factors is involved in the initiation of the fibrotic processes, which likely begins many years before clinical manifestations become apparent [8]. Predisposing factors like smoking, dust inhalation and asbestos exposure are also associated with increased risk of IPF [9].

The development of pulmonary fibrosis is often reported as an important sequelae to severe or persistent lung damage after respiratory tract infections [10]. Fibrosis is also a known sequelae of Acute Respiratory Distress Syndrome [11] and although many ARDS patients survive the acute phase of the illness, a substantial proportion of patients who have a longer disease duration (>3 weeks) will die as a result of progressive pulmonary fibrosis.

Whereas, direct relationship between respiratory viral infection and development of progressive fibrosis has not yet been confirmed, evidence from the previous global SARS outbreaks with SARS-CoV and Middle East Respiratory Syndrome (MERS) shows a clear link between coronavirus infection, persistent impairment of lung function and abnormal radiological findings consistent with pulmonary fibrosis [12,13]. Evidenced suggest that Influenza viruses like H1N1 and H5N1 a promote the development of pulmonary fibrosis [14,15] and Cytomegalovirus and Epstein-Barr virus play as viral cofactors in the development of IPF [16].

The incidence of lung injury and fibrotic pulmonary changes following SARS-CoV-2 infection is likely to be high than other viral pneumonia. It is estimated that, the total global burden of fibrotic lung disease will be significantly higher in next decade.

As per worldometer 196 million people have already been affected by COVID-19 in this world pandemic, majority have been marked as mild form of infection. Only about 15% will get a severe COVID-19 pneumonia, and 5% will progress to ARDS, meaning that almost 30 million will have severe pulmonary involvement. Although majority of them will recover without residual lung damage, a significant number of patients will suffer chronic sequelae [17]. As there is not a completely proven treatment of post-COVID 19 pulmonary fibrosis; the use of common and proven anti-fibrotic drugs, that are used in IPF, is rationale to start in the early acute phase of severe disease with ARDS with hope to reduce further lung damage and fibrosis [18].

In our study, Its found that post-COVID-19 pulmonary fibrosis is significantly related to patient age ranging from 60 to 88-year age group. This is matching to study by Wong., *et al*. [19], who stated that older people are more likely to develop pulmonary fibrosis following MERS. It was observed that incidence of developing fibrosis is less in 45 - 60-year age group, and 25 - 45-year age group showed least incidence; this was also noticed by Das KM., *et al*. [20] that correlated age with MERS and SARS-CoV 2 pulmonary fibrosis development.

In our study male are more affected than female in developing lung fibrosis, In one study in Egypt, 15 males out of total of 40 males proceeded to post-COVID-19 fibrosis (37.5%) in comparison to female patients with only 10 patients complicated with post-COVID-19 lung fibrosis (25%). This may be explained by the effect of androgen which promotes the transcription of transmembrane protease, serine 2 gene. That encoded protein primes the spike protein of SARS-Cov-2, thus impair antibody response and facilitate fusion of the virus and host cells [21].

Cigarette smoking is another important risk factor for developing post covid fibrosis. Study showed that cigarette smoker had much higher incidence of post-pulmonary fibrosis than non-smoking one. As from our study, out of the 30 smoking patients, 18 developed post-pulmonary fibrosis (60%), Vardavas C.I., *et al*. [22] mentioned that smokers are 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to need ICU admission and mechanical ventilation or die compared to non-smokers patients.

CT severity score (CT-SS) is a good predictor for disease progression, that leads to pulmonary fibrosis. In study published in Egyptian Journal of Radiology and Nuclear Medicine, we found that the mild group (CT-SS of 1 - 17) showed less preponderance for post-COVID-19 fibrosis whereas the severe group (CT-SS of 18 - 25) showed higher incidence of post-COVID-19 pulmonary fibrosis. That is matching with the study of Zhou F., *et al*. [23] who stated that increased disease severity is a reliable indicator of lung tissue destruction and correlates with mortality risk.

Conclusion

A significant number of patients will be at risk for long-term complications following severe COVID-19 pulmonary disease, due to the high prevalence of respiratory failure and the need for HFNC or MV. The understanding of long-term pulmonary complication in COVID-19 survivors is limited at present time, but increasingly emerging as top priority for the medical community.

Patients who experience long term cardiopulmonary complications following their acute illness may place enormous demands on a healthcare system that is already struggling with limitations in providers and resources. Survivors of COVID-19 who develop persistent pulmonary disease will require long term specialty care; therefore, all clinicians should render keen interest in understanding post-COVID-19 pulmonary fibrosis. It is time demanded that we begin proactively collecting and analyzing objective pulmonary data from COVID-19 survivors in controlled studies in order to identify potentially modifiable clinical risk factors or employ risk mitigation strategies to help protect patients from progression to Post covid pulmonary fibrosis.

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