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RISK FACTORS AND INCIDENCE OF PULMONARY FIBROSIS IN PATIENTS RECOVERED FROM COVID-19 PNENUMONIA

Internal Medicine

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ABSTRACT

Background: The first outbreak of novel coronavirus nCoV 19 was reported on December 31, 2019. COVID 19 infection presents from mild fever to severe forms like breathlessness and multi organ failure. COVID produces a hyperinflammatory state and results in pulmonary fibrosis. The reticular changes seen in CT chest were more evident in patients at 2 weeks post symptoms onset and they persisted even after 4 weeks. **Methods:** All patients who were tested positive for COVID 19, had COVID pneumonia with lung infiltrates in chest Xray or requiring oxygen with saturation <95% in room air were considered. Detailed history about comorbidities, onset of symptoms and duration of ICU stay are obtained. These patients are followed up after 1 month of their COVID 19 infection. Patients were asked for any history of new onset COVID symptoms or relapse of existing symptoms. These patients were advised for HRCT chest to look for pulmonary fibrosis after explaining the procedure and side effects. **Results:** In our study, 61% had pulmonary fibrosis in HRCT chest and 39% did not develop pulmonary fibrosis. Elderly patients of male gender with comorbid illnesses like type 2 diabetes mellitus and systemic hypertension and patients who had symptoms of cough and breathlessness, tachypnoea and desaturation developed pulmonary fibrosis in post COVID period. Severe COVID pneumonia patients in ICU who were mechanically ventilated had increased chances of development of fibrosis. Post COVID symptoms like fever, cough and breathlessness were more significant as they present in patients with fibrosis. **Conclusion:** Moderate to severe COVID pneumonia is associated with greater incidence of pulmonary fibrosis and evaluation of these patients and proper follow up should be done for early detection of development of pulmonary fibrosis.

KEYWORDS

INTRODUCTION

SARS CoV-2 is an enveloped virus. The virus with the help of this spike protein gets attached to the angiotensin converting enzyme- 2 (ACE2) receptor which is present on the host cell. This results in endocytosis and viral genome is released into the cells. They replicate with the host cell genomic machinery and replicate which finally forms number of virus particles which are released outside the cells and continue to infect the other normal host cells. Various other organs are involved though lungs are the target organ. They act on type 2 pneumocytes, alveolar macrophages in the lungs. The target cells for the virus in intestines is enterocytes. They also act on basal epithelial cells which are present in nasal passages as they have increased expression of ACE-2 receptors [1]. SARS CoV-2 affects various organs of which lungs are the main target organ. Symptoms include milder forms of cough and running nose to severe forms like acute respiratory distress syndrome. The patients developing ARDS have chronic inflammation resulting in pulmonary fibrosis. COVID produces a hyperinflammatory state and results in release of various inflammatory markers, resulting in various morbid illness which included pulmonary fibrosis. Predominantly, CT findings post SARS infection in lungs include ground glass opacities which are rapidly progressing in nature. The reticular changes seen in CT chest were more evident in patients at 2 weeks post symptoms onset and they persisted even after 4 weeks [2]. A study was done with 15 years follow up of these patients and it was shown that 4.6% of the samples taken in studies showed interstitial abnormality [3].

The extent of fibrosis that occur in people can be varying from one patient to another. But small degree of fibrosis in patients who are of older age and pre-existing lung disease could result in increased morbidity and mortality. Pulmonary fibrosis secondary to COVID-19: a call to arms published by paolo.et al in 2020 on May 15, 2020 quoted that pulmonary fibrosis is a recognised sequalae of ARDS and 40% of the patients with COVID-19 develop ARDS [4]. Another article Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies published by Ademola.et al on 11 August 2020 stated that of 62 patients, fibrotic changes were seen on 21 patients (33.9%) [5]. This study is done to estimate the incidence of pulmonary fibrosis and evaluate the risk factors that are associated with pulmonary fibrosis.

METHODS AND OBJECTIVES

Selection And Description Of Participants

All patients who were tested positive for COVID 19, had COVID pneumonia with lung infiltrates in chest Xray or requiring oxygen with saturation <95% in room air is recognised, and their details are collected. Detailed history about comorbidities, onset of symptoms, ICU stay and duration of stay are obtained. The vitals and chest Xray findings were taken from MRD files and collected. Informed consent is obtained from these patients after explaining the nature of the study.

These patients are followed up after 1 month of their COVID 19 infection. Patients were asked for any history of new onset COVID symptoms or relapse of existing symptoms. These patients were advised for HRCT chest to look for pulmonary fibrosis after explaining the procedure and side effects. The HRCT reports were analysed and compared with the disease severity and various other factors in this study.

Inclusion Criteria

All patients with age >18 years with confirmed COVID-19 positivity by Gene Xpert, COVID RT PCR, SARS CoV Ag test or TrueNat with and presence of infiltrates in chest X-ray or requiring oxygen with saturation of <95% in room air.

Exclusion Criteria

1) Pregnant females
2) Patients with other known causes of Pulmonary fibrosis.

OBJECTIVES

Primary Objective

- To assess the incidence of pulmonary fibrosis and risk factors that increase the chances of pulmonary fibrosis in post COVID patients.

Secondary Objective

- To evaluate the presence of symptoms that persists or relapses after recovery from COVID pneumonia.

Sample Size

Based on the correlation coefficient of age correlated with risk of developing pulmonary fibrosis (r=0.574) observed in ana earlier publication (Pulmonary fibrosis in COVID-19 survivors: Predictive factors and risk reduction strategies, published in Hindawi, 2020) and with 90% power and 95 % confidence, the minimum sample size

comes to 38. I am including 41 samples in my study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage. Continuous variables were presented using mean and standard deviation. Chi-square test/ Chi-square test with continuity correction was used to study the statistical significance of the association of all categorical variables with fibrosis. A p value of <0.05 was statistically significant.

RESULTS

Of the samples taken, 25 samples were male which constituted 61% and 16 samples were female which constituted 39%, suggesting the incidence of moderate to severe pneumonia was more among male gender compared to females in my study. The incidence of fever and cough during COVID pneumonia was more in the samples taken, when compared to all other symptoms of COVID which constituted 68%. Personal history of these patients suggested that 61% were alcoholics and 65.9% were smokers, 68.3% had hypertension while 31.7% did not have hypertension. 61% of the samples had moderate COVID pneumonia while remaining 39% had severe COVID pneumonia. After analysis of HRCT chest of these patients, it was found that 61% of people had fibrosis and 39% did not develop fibrosis [Table 1]. Analysing post COVID symptoms, 63.4% had post COVID cough and 68.3% had post COVID breathlessness.

Association was done between pulmonary fibrosis and various other factors in our study. The mean age calculated among samples was 61.9. In our study, percentage of subjects with age group greater than 61 years was 73.9%. It is found that 56.3% of the females had pulmonary fibrosis and 64% of the males under the study had development of pulmonary fibrosis. 77.8% of the subjects who had COPD in our study was found to have pulmonary fibrosis and 52.2% of the subjects who did not have COPD did not develop pulmonary fibrosis. From the study, 92% of alcoholics and 85% of smokers who had moderate to severe COVID pneumonia developed fibrosis. 79.2% who had tachypnoea and 86.2% who had saturation less than 95% developed pulmonary fibrosis. 93.8% of the subjects who had severe COVID pneumonia had developed pulmonary fibrosis [Table 2], [Figure 2]. Mean number of days in hospital was calculated which was 23.9. It was seen that all patients who were admitted for more than 23.9 days had pulmonary fibrosis in post COVID period and people who had hospital stay for less than 23.9 days had no fibrosis. Considering post COVID symptoms, out of 28 people who had complaints of post COVID breathlessness, 20 patients had developed pulmonary fibrosis which constituted 71%. And 84.6% who had post COVID cough developed pulmonary fibrosis.

DISCUSSION

This study was done using 41 samples which included COVID patients who had desaturation or infiltrates in chest Xray having COVID pneumonia. These patients were followed up after 1 month and HRCT chest was taken to look for fibrosis. Detailed evaluation of these patients including comorbid illnesses, vitals on admission and course of disease in hospital was analysed. Gender distribution in this study showed that male subjects tend to develop pulmonary fibrosis more when compared to females. Symptomatology during COVID infection of these subjects on retrospective analysis showed that fever was found to be predominant in my study population. Though COVID involvement of the lungs are more, in my study, breathlessness was not considered statistically significant as only 58.5% of the samples had breathlessness. This can be contributed to a phenomenon called Happy hypoxia where patients do not give history of breathlessness but on evaluation, they have desaturation with marked infiltrates in chest X-ray. Other presentations like anosmia, fatigue, loose stools, vomiting, rhinitis and headache were minimal and most of the samples did not have the above-mentioned symptoms.

The comorbid profile of the patients taken for study were important as elderly people with multiple comorbid illness were found to have higher morbidity and mortality in various studies. 13 out of 41 samples had type 2 diabetes mellitus which was 31.7% while the remaining 68.3% did not have type 2 diabetes mellitus. This was clinically important as these patients required IV steroids due to lung involvement in this disease. Steroid induced hyperglycemia was looked for and patients were monitored carefully as they are prone to develop risk of diabetic ketoacidosis. Hypertension was found to be present in 68.3%. Chronic obstructive pulmonary disease (COPD) was present in 43,9% of the samples. This is clinically significant as people with COPD develop type 2 respiratory failure and progress faster in developing severe acute respiratory distress syndrome. These people commonly end up in intubation and mechanical ventilation. History of smoking was also asked for in the current study as it was considered important risk factor in development of fibrosis. Of the samples, 65.9% of the patients were smokers. Smoking affects the pulmonary parenchyma and can result in bronchiectasis and emphysema. COVID pneumonia on top of existing lung damage can result in decrease in perfusion and ventilation causing patients to land up in respiratory failure, more towards type 2 respiratory failure. Other comorbid illnesses like chronic kidney disease, chromic liver disease, coronary artery disease and malignancy were taken and were less in number. This is because CKD, CLD and patients with known malignancies had increased rate of mortality that morbidity due to development of multiorgan dysfunction syndrome, disseminated intravascular coagulation and haemorrhagic complications. Hence, they cannot be included in the study. Particularly patients with liver or kidney transplant who are already immunosuppressed had grave prognosis with COVID infection resulting in fast progression of disease and death. Personal history like alcohol consumption was asked for in the study and it showed that 61% were alcoholic and 39% were non-alcoholic. Alcohol consumption results in immune suppression, decreased nutrition and liver damage secondary to which there is faster progression of disease in these patients.

On arrival, vitals of the patients under study were analysed. respiratory rate of these patients had more variation as 58% of the samples had tachypnoea. This is secondary to involvement of parenchyma of the lungs and mismatch of ventilation and perfusion in these patients. 46% of the patients had normal saturation while 53% of 41 samples taken had desaturation and recorded saturation was less than 95% in room air. This can also be attributed to pulmonary parenchymal involvement and presence of infiltrates in chest Xray. All the samples taken for study had infiltrates in chest Xray as inclusion criteria included only patients who had moderate to severe COVID pneumonia, where moderate COVID pneumonia comprised of 61% and severe COVID pneumonia constituted 39% of the samples. The incidence of moderate COVID pneumonia was more than that of severe COVID pneumonia as severe COVID pneumonia was associated with increased mortality and these patients cannot be included in the study. On admission, all the patients taken for study required non-invasive ventilation which included O2 mask, non-rebreathing mask (NRBM) or Bipap, based on severity of desaturation and tachypnoea. These patients were admitted in HDU and later shifted to ICU in case of worsening clinical status. 10 out of 41 patients required intubation and mechanical ventilation and it constituted 24.4% of patients, while 75.6% of the patients did not require invasive ventilation. Almost all patients (40/41) required admission to HDU while remaining 1 patient was admitted directly to ICU. Of them, the percentage of people who worsened after admission and transferred to HDU were 56.1% while remaining 43.9% of the patients were retained in HDU and showed clinical improvement.

The patients were followed up after discharge and evaluated for post COVID symptoms. They were enquired about persisting symptoms since COVID or development of new symptoms after COVID. Fever was present in 24.4%. Incidence of post COVID cough was more in the study as it was 63.4% and 68.3% had symptoms of breathlessness in post COVID period.

These people were followed up after 1 month and advised for High resolution computed tomography of chest. On analysis, it was found that 25 out of 41 patients had pulmonary fibrosis in HRCT chest which constituted 61% while 16 out of 41 patients did not develop pulmonary fibrosis which was about 39%.

Various factors were associated with fibrosis and following results were analysed. The mean age of the patients taken for study was 61.9. 44.4% of the people less than age 62 had fibrosis and 73.9% of patients who were more than 62 years had pulmonary fibrosis. This indicates that age can be considered as one the important risk factor for development of pulmonary fibrosis. Elderly people are more susceptible to infection and have more comorbid illness compared to younger age which makes them more susceptible to morbidity and mortality. Sex was also considered as risk factor for development of pulmonary fibrosis and was identified that pulmonary fibrosis was more predominant in males when compared to females. 67.9% of the patients who presented with fever at the time of COVID infection were found to develop pulmonary fibrosis, 66.7% of the patients who

presented with cough developed pulmonary fibrosis and 66.7% of the patients who had breathlessness during COVID infection had also developed pulmonary fibrosis. 53.8% of the patients who had type 2 diabetes mellitus developed pulmonary fibrosis, 60.7% of the patients who were hypertensive developed pulmonary fibrosis and 54.5% of the patients who had dyslipidaemia developed pulmonary fibrosis. 77.8% of the patients with COPD developed pulmonary fibrosis. 92% of alcoholics developed pulmonary fibrosis as alcohol itself causes general immune suppression. 85.2% of the smokers developed pulmonary fibrosis considering smoking as one of the important risk factors for pulmonary fibrosis. smoking damages pulmonary parenchymal architecture resulting in loss of tissue that participates in ventilation and perfusion in setting of COVID infection.

Association of vitals on admission with development of pulmonary fibrosis was done. 77.8% of the patients who had hypertension on admission had developed pulmonary fibrosis, 68.8% of the patients who had tachycardia developed fibrosis. 79.2% of the patients in this study who had tachypnoea had developed pulmonary fibrosis. 86.4% of the patients who had desaturation with saturation less than 95% in room air, developed fibrosis. Desaturation can be considered significant and patients who had desaturation at the time of admission during COVID infection has higher tendency of developing pulmonary fibrosis. Overall progression of disease to severe COVID pneumonia resulted in increased chances of development of pulmonary fibrosis. 93.8% of patients who developed severe COVID pneumonia developed pulmonary fibrosis and 40% of the patients who had moderate COVID pneumonia had developed pulmonary fibrosis.

Patients who required the need for mechanical ventilation were assessed for development of pulmonary fibrosis in post COVID period and it is seen that 100% of the patients who were intubated during the COVID infection had pulmonary fibrosis. 95.7% of the patients who were admitted in ICU for progression of disease developed pulmonary fibrosis. Increased number of stay in hospital was related to development of pulmonary fibrosis. The mean number of days of admission of COVID patients was taken to be 23.39. Patients who were admitted in hospital for more than 24 days developed pulmonary fibrosis and patients who required hospital stay for less than 24 days did not develop pulmonary fibrosis.

80% of the people who had fever during post COVID period had development of pulmonary fibrosis and 71.4% of the patients who had post COVID breathlessness had development of pulmonary fibrosis. This is due the architectural changes that occur during the process of healing in the lung after the disease.

Hence patients with these risk factors are required to be followed up more frequently for prevention of morbidity. Patients who require O2 requirement at higher rate and faster progression of disease from mild to moderate to severe COVID pneumonia should be predicted for development of fibrosis in post COVID period. Hence these patients should be started on antifibrotics like pirfenidone and nintedanib for prevention of pulmonary fibrosis. The above-mentioned risk factors should be taken into consideration and prioritised for starting antifibrotic medications at earlier stage of the disease.

The most commonly used antifibrotics were pirfenidone and nintedanib. Pirfenidone acts by inhibiting transforming growth factor (TGF)-beta, that controls proliferation and differentiation of cells. It is metabolised in the liver with the help of the enzyme CYP1A2 and hence requires regular monitoring of liver function tests. Nintedanibis a tyrosine kinase inhibitor which inhibits growth factors like vascular endothelial growth factor receptor, fibroblast growth factor receptor and platelet derived growth factor receptor. They bind to ATP binding pocket of these receptors and blocks the proliferation, migration and transformation of fibroblasts.

Table:1

FIBROSIS	FREQUENCY	PERCENTAGE
YES	25	61
NO	16	39
Total	41	100

Table:2

CATEGORY	Fibrosis		p value
	Yes n (%)	No n (%)	
MODERATE (n=25)	10(40)	15(60)	0.001
SEVERE(n=16)	15(93.8)	1(6.3)	

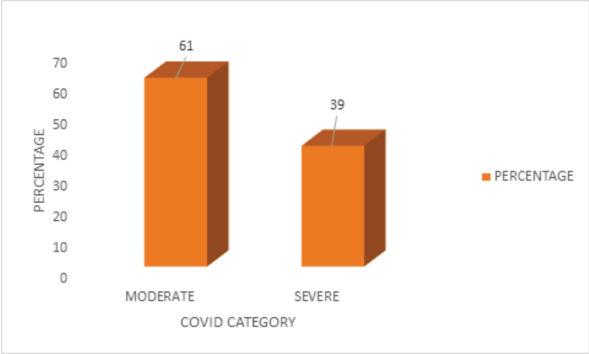

Figure 1 . Incidence Of Pulmonary Fibrosis In Patients Recovered From Moderate And Severe Covid Pneumonia

CONCLUSION

Moderate to severe COVID pneumonia is associated with greater incidence of pulmonary fibrosis and evaluation of these patients and proper follow up should be done for early detection of development of pulmonary fibrosis and prevention of further progression of the disease. Further elderly patients with multiple comorbid illness developing moderate COVID pneumonia should also be treated cautiously as they have high chances of progression of disease resulting in death or significant post COVID symptoms with lung fibrosis. Antifibrotics should be started at early stages of the disease to reduce the development of pulmonary fibrosis.

Limitations

This is a single centred study with limited number of samples which makes it a limitation for studying about various other presentations of the disease. Patients with severe COVID pneumonia had significant mortality and was more seen in patients with chronic liver disease, chronic kidney disease, liver or kidney transplantation. These patients could not be included in this study. The disease pattern and complications and post COVID symptoms in these patients are to be evaluated on detailed study.

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