VOLUME - 11, ISSUE - 07, JULY - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Radio-Diagnosis

LONG -TERM FOLLOW-UP OF COVID-19 PATIENTS TO ASSESS THE RISK FACTORS FOR THE DEVELOPMENT OF POST-COVID FIBROSIS

Dr. Rajeshkumar Varatharajaperumal*	DMRD,DNB, Department of Radiology, Kovai Medical Center and Hospital, Avanashi Road, Coimbatore, India *Corresponding Author
Dr.Venkatesh Kasi Arunachalam	DMRD,DNB,FRCR,MOI, Department of Radiology, Kovai Medical Center and Hospital, Avanashi Road, Coimbatore, India
Dr . Pudhiavan A	MD, Department of Radiology, Kovai Medical Center and Hospital, Avanashi Road, Coimbatore, India
Dr. Kartheek Guthikonda	DMRD,DNB, Department of Radiology, Kovai Medical Center and Hospital, Avanashi Road, Coimbatore, India
Dr. Gopinath Periyasamy	DMRD,DNB, Department of Radiology, Kovai Medical Center and Hospital, Avanashi Road, Coimbatore, India
Dr.Vijayakumaran Ethiraju	DNB, Department of Radiology, Kovai Medical Center and Hospital, Avanashi Road, Coimbatore, India

ABSTRACT

Purpose: This study aimed to find the risk factors associated with the development of fibrosis in follow-up CT in patients of COVID-19 pneumonia. **Methods:** In this retrospective study, fifty-four patients with RT-PCR proved COVID-19 pneumonia with two chest CTs in a 12-month interval between the initial and follow-up CT were included. Patients were classified into two groups: Patients with complete resolution and patients with fibrosis on follow-up CT. Demographic, laboratory, and therapeutic data and CT findings were compared and analyzed. **Results:** A total of 54 patients (38 men, 16 women) were included in this study. Post-COVID fibrosis and fibrotic-like changes were observed on follow-up CT scans in 34 of the 54 patients (63%). The remaining 20 patients (37%) showed no fibrotic changes with complete resolution. Patients with post covid fibrosis were significantly older than those with normal CT. Males were affected more than females. Patients with post covid fibrosis had more comorbidities when compared with patients without comorbidities. Post-Covid fibrosis patients had a greater frequency of ICU admission, high frequency noninvasive mechanical ventilation(NIV), higher peak levels of C-reactive protein and D-dimer levels, low level of SpO2, and high CT Severity score in initial CT. **Conclusion:** Elderly patients, patients with comorbidities, high CT severity score, longer duration of hospital stay, ICU admission, high CRP and D dimer levels, Patients with NIV were associated with more prevalence of fibrosis in follow up CT.

KEYWORDS : COVID-19; follow up CT, CT severity score, fibrosis, risk factors

INTRODUCTION:

Coronavirus disease was first identified in Wuhan, Hubei province, china, by mid-December 2019 (1,2). The international virus classification commission classified the new coronavirus as severe acute respiratory syndrome coronavirus 2(SARS- CoV-2) on February 12, 2020 (3). Subsequently, the world health organization named this disease as COVID-19 (4). CT chest plays a vital role in the diagnosis of covid 19 infections in addition to RT-PCR. Typical CT features of covid 19 pneumonia are patchy and confluent ground-glass opacities with a peripheral and basal predominance (5,6,7,8). Follow-up of the recovered patients is essential to assess the lung parenchymal changes. In a study done by zou et al., they reported pulmonary fibrosis in 84% of survivors of covid-19 pneumonia during follow-up (9). Our study explores the risk factors associated with the development of pulmonary fibrosis in patients affected with covid 19 pneumonia.

MATERIALS AND METHODS:

The study was done between December 2020 and March 2022. Informed consent was obtained from the patients. The study was approved by institutional ethical committee.

Inclusion criteria:

In this retrospective study, about 54 patients with a history of RT-PCR proven Covid-19 pneumonia with initial CT scan at the time of admission and follow-up CT after twelve months were included.

Data analysis

The demographic characteristics like age, sex, comorbidities (hypertension, diabetes, heart disease, pulmonary disease, and CKD), laboratory findings (CRP and D dimer), history of steroid, duration of hospital stay, ICU admission, Oxygen requirement, and chest CT findings were collected and analyzed retrospectively.

CT acquisition protocol and image interpretation

All CT scans were performed on GE optima CT 520 32 slice CT scanner. The scans were acquired with the patients in the supine position. The following scanning parameters were used: Tube voltage 110–120 kVp, tube current of 100–120 mAs, slice thickness 1.25 mm, and a pitch of 1.5. The images were reconstructed with a slice thickness of 1.25mm and an increment of 0.7 mm. The images were viewed in both lung and mediastinal window settings.

Initial and follow-up CT of all patients were reported by two experienced radiologists. Clinical details were not provided during reporting of follow-up CT. Pulmonary opacities were classified using the Fleischner Society glossary of terms for thoracic imaging [10]. In the initial CT, the following findings were reported: 1. Presence or absence of ground-glass opacities and consolidation with associated findings like interstitial thickening;2. Distribution of lung opacities: Unilateral or bilateral, peripheral or central, and apicobasal predominance 3. Extent and severity of lung involvement. A quantitative scoring system using special software in Syngo-CT pneumonia analysis was used to assess the extent and severity of the disease. Each lobe was scored from 0 to 4 as follows: Less than 5% involvement (score 0), 5-25% involvement(score 1), 25-50% involvement(score 2), 50-75% involvement(score 3), 76-100% involvement(score 4). The total

severity score was calculated by adding a score in each lobe ranging from 0 to 20.

The follow-up CT scan was done in all patients after 6months. Based on the findings, patients were separated as those with and without fibrosis.

Data were analyzed using the SPSS version 21. Both categorical and continuous variables were evaluated. They were expressed as counts /percentages and means/standard deviations, respectively. Fisher's exact test was used to examine the categorical variables. A p-value less than 0.05 was considered statistically significant (Table 1).

Table 1: Comparison of variables in patients with fibrosis to patients with complete resolution of opacities.
p value <0.05 – Significant.

SL. NO	Variables	Pts with fibrosis on follow up CT	Patients with complete resolution of opacities on follow up CT	P value
1.	Comorbidities	72%	22%	0.0011
2.	Spo2	83.3%	27.7%	0.0001
3.	CT severity score	78%	28%	0.0001
4.	Duration of hospital stay	58%	17%	0.0043
5.	ICU admission	47%	11%	0.0143
6.	Steroids	83.3%	66.6%	0.1842
7.	NIV	52.7%	11.1%	0.003

RESULTS:

A total of 54 patients (38 men, 16 women) were included in this study. Post-COVID fibrosis and fibrotic-like changes were observed on follow-up CT scans in 34 of the 54 patients (63%) (Fig.1 and 2). The remaining 20 patients (37%) showed no fibrotic changes (Fig. 3 and 4).

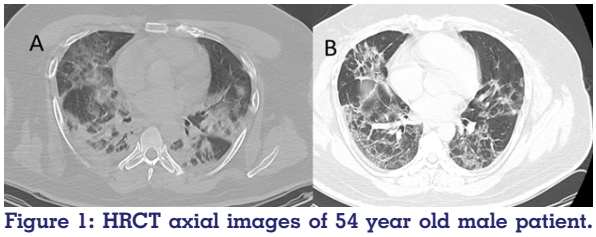

Figure 1: HRCT axial images of 54 year old male patient. Image A shows ground glass opacities and consolidation in both lungs. Image B shows residual ground glass opacities with areas of fibrosis in the form of interstitial thickening.

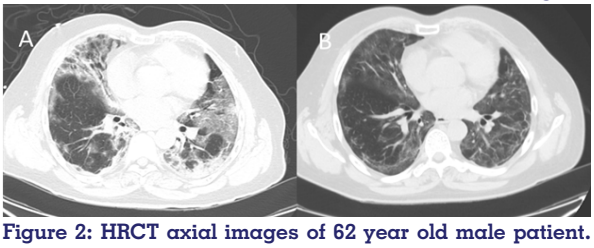

Figure 2: HRCT axial images of 62 year old male patient. Image A shows diffuse extensive ground glass opacities in both lungs. Image B shows residual ground glass opacities with areas of fibrosis in the form of subpleural bands and interstitial thickening

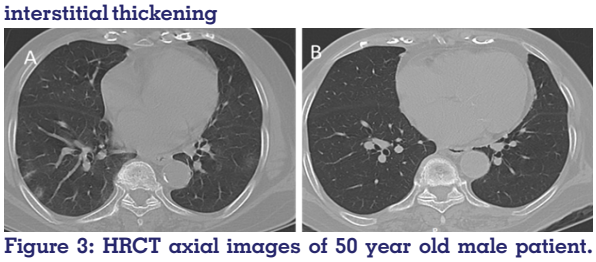

Figure 3: HRCT axial images of 50 year old male patient. Image A shows ground glass opacities in both lungs with peripheral distribution. Image B shows complete resolution

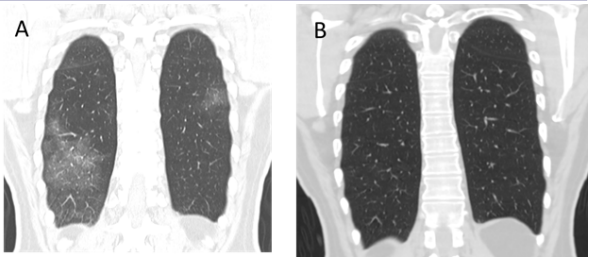

Figure 4: HRCT coronal images of 61 year old male patient. Image A shows ground glass opacities in basal segments of both lungs. Image B shows complete resolution of ground glass opacities without fibrosis.

Patients with post covid fibrosis were significantly older than those with normal CT. 22 patients out of 30 (73.3%) who developed pulmonary fibrosis had ages ranging from 60 to 80-year age group. Low incidence was noted in patients with less than 60 years age group (12 patients out of 24; 50%). Males were affected more than females, as 28 males out of a total of 38 males (73.6%) proceeded to post-COVID-19 fibrosis in comparison to female patients with only eight patients out of 16 complicated with post-COVID-19 lung fibrosis (50%). In addition, patients with post covid fibrosis had more comorbidities (26 of 34 patients[76%] vs. 4 of 20 patients [20%])when compared with patients without comorbidities(P=0.0011).

Post-Covid fibrosis patients had a greater frequency of ICU admission (50% [17 of 34 patients] vs. 10% [2 of 20 participants], P – 0.0143) Patients who showed post covid fibrosis on follow up CT had a longer duration of hospital stay compared with patients with normal follow up CT(21 of 34 patients [61%] vs. 3 of 20 [15%]patients). The mean duration of hospital stay in patients with fibrosis is 12.2+/- 3.8 vs. 6.8 +/- 3.2 days). (p-value = 0.0043).

Post covid fibrosis patients had a greater frequency of steroid administration (30 of 34 [88%] vs 12 of 20 patients[60%], P value-0.1842) and noninvasive mechanical ventilation (19 of 28 patients [52.7%] vs 2 of 20 patients[10%]). P value is 0.003.

Patients with post covid fibrosis showed higher peak levels of C-reactive protein when compared with non fibrotic patients(median, 72 mg/L vs 14 mg/L P = .03) and D-dimer (median, 8.2 mg/L vs 1.5 mg/L P < .001).

SpO2 was less in patients with post covid fibrosis than in non fibrotic patients(30 of 34 patients vs 5 of 20 patients)P value-0.0001 (Mean 86.2 +/-2.1% vs 94.5+/-1.6%).

CT Severity score was more in post covid fibrosis patients than non-fibrotic groups (28 of 34 patients [82%]had high CT severity score vs. 2 of 20 patients[10%]). P-value- 0.0001 (Mean CT score was 12.8+/- 3.8 vs 6.2+/-2.4)

DISCUSSION

The clinical presentation of COVID-19 infection can range from mild symptoms to severe illness that leads to severe lung damage or even mortality [11].

Pulmonary fibrosis in post COVID patients has been recognized as a potentially worrying sequela.

Pulmonary fibrosis results in permanent architectural distortion. It may results in irreversible pulmonary dysfunction [12]. There were many hypotheses explained for the occurrence of pulmonary fibrosis in covid patients. One among them is cytokine storm. The abnormal immune mechanism associated with cytokine storm results in the initiation of pulmonary fibrosis. However, few individuals recover without fibrosis, while few develop progressive

pulmonary fibrosis [13]. Till now, the reasons are unidentified.

In our study, CT chest abnormalities were recorded, initially during admission and later during follow-up after 12 months. The follow-up scan was done explicitly for evaluating the development/progression of pulmonary fibrosis. In our research, many risk factors such as advanced age, sex, cigarette smoking, prolonged ICU admission, and CT severity score were correlated to predict the possibility of development of post-COVID-19 pulmonary fibrosis.

It was found that post-COVID-19 pulmonary fibrosis in follow-up CT was highly correlated to patient age. 22 patients out of 30 (73.3%) who developed pulmonary fibrosis had ages ranging from 60 to 80-years. Our result is similar to the study by Wong et al. [14], who stated that older age group people are more likely to develop pulmonary fibrosis. Low and least incidences were observed in 45–60-year age group (7 patients out of 25; 28%), and 25–45-year age group respectively in his study. This was also correlated with another study done by sansone A et al. [15], in which old age patients were more affected by pulmonary fibrosis.

In our study, males were more subjected to post-COVID-19 pulmonary fibrosis than females. 73% of males developed post covid fibrosis in comparison to 50% of female patients. This is probably secondary to the action of the androgen hormone. The androgen assists the transcription of transmembrane protease, serine 2 gene. This encoded protein primes the spike protein of SARS-Cov-2 thus reduces the antibody response and increases the chance of fusion of the virus and host cells [16].

In our study, patients with post covid fibrosis had a longer duration of hospital stay and with ICU admission. This matches with the study done by Yu et al. [17], who found that patients with post covid fibrosis on follow-up CT were older than those without fibrosis. They found that patients with post covid fibrosis had a longer duration of hospital stay with a higher rate of ICU admission and a higher level of CRP than those without fibrosis.

Post covid lung fibrosis patients had high levels of CRP and D dimer levels during admission. Cytokine storm causes an increase in inflammatory markers.CRP is a protein that is used as an early marker of infection and inflammation. An average level of CRP in the blood is less than 10mg/L. It increases rapidly within 6 to 8 hours and attains its peak in 48 hours from the onset of infection (18,19,20). An increase in D dimer is an indirect manifestation of inflammatory reaction. This occurs due to cytokine storm, which causes the imbalance of coagulation and fibrinolysis (21, 22). D dimer values of more than 1microgram/ml were found to be a poor prognosis for patients with Covid-19 pneumonia (23). Patients with post covid fibrosis showed higher peak levels of C-reactive protein and D- dimer levels when compared with non fibrotic patients in our study. This matches with the study done by Han et al. (24)They observed high levels of CRP and D dimer levels in patients with post Covid fibrosis.

CT severity score has a vital role in the identification of disease progression. Our study found that patients with high CT severity score in the initial CT were more prone to post COVID fibrosis than patients with a low CT severity score. This is similar to the study done by Zhou F. et al. [25], who stated that an increased disease severity score is a reliable indicator of lung tissue destruction and correlates with mortality risk.

Among the variable evaluated in our study, all factors were statistically significant for the development of post covid fibrosis, except steroids. The results of this study can be utilised to select the patients who may need anitfibrotic drugs treatment. Currently, the role of antifibrotic drugs in the prevention and treatment of post-COVID pulmonary fibrosis is not clearly defined. However, these drugs are found to be helpful in patients with acute exacerbations of ILD, thus reducing the pulmonary damage and reducing morbidity and mortality rates in high-risk individuals (26). Larger scale studies have to confirm our study results as well as the role of antifibrotic drugs in preventing or reducing the severity of fibrosis in post COVID patients.

REFERENCES:

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan.China Lancet. 2020; 395: 497-506.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J,et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382: 727-733.
3. V. Coronaviridae Study Group of the International Committee on Taxonomy of The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020; 5: 536-544.
4. Jiang S,Shi Z,Shu Y,Song J, Gao G.F,Tan W,et al. A distinct name is needed for the new coronavirus. Lancet. 2020; 395: 949.
5. 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: 3306-3309.
6. Pan Y, Guan H.Imaging changes in patients with 2019-nCov. Eur Radiol. 2020; 30(7): 3612-3613.
7. Song F,Shi N, Shan F,Zhang Z,Shen J,Lu H, et al. Novel Coronavirus (2019-nCoV) Pneumonia.Radiology. 2019; 2020: 210-217.
8. Chung M,Bernheim A,Mei X,Zhang N,Huang M,Zeng X,et al.CT Imaging Features of 2019 Novel coronavirus (2019-nCoV). Radiology. 2020; 295: 202-207.
9. Zou J-N, Sun L, Wang B-R, Zou Y, Xu S, Ding Y-J, et al. (2021) The characteristics and evolution of pulmonary fibrosis in COVID-19 patients as assessed by AI-assisted chest HRCT. PLoS ONE 16(3): e0248957.
10. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology. 246(3):697–722.
11. Tale S, Ghosh S, Meitei SP et al (2020) Post-COVID-19 pneumonia pulmonary fibrosis. Int J Med 113(11):837–838
12. Ademola S, Simon A, Oyeronke T et al (2020) Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies. Pulmon Med 5:1–10
13. George PM, Wells AU, Jenkin RG et al (2020) Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med 8(8):807–815.
14. Wong K, Antonio GA, Hui DS et al (2002) Severe acute respiratory syndrome: thin-section computed tomography features, temporal changes, and clinicoradiologic correlation during the convalescent period. J Comput Assisted Tomogr 28(6):790–795.
15. Sansone A, Mollaioli D, Ciocca G, Limoncin E, Colonnello E, Vena W, Jannini EA (2021) Addressing male sexual and reproductive health in the wake of COVID-19 outbreak. J Endocrinol Invest. 44(2):223–231.
16. Lee EY, Singh R (2017) Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J RadiolImag 27(3):342–349
17. Minhua Yu, Ying L, Dan X, Rongguo Z, Lan L, Haibo X. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. Korean J radiol. 2020 Jun; 21(6): 746–755.
18. Marnell L, Mold C, Du Clos TW. C reactive protein: ligands, receptors, and role in inflammation. ClinImmunol. 2005;117(2):104 111. 10.1016/j.clim.2005.08.004.
19. Young B, Gleeson M, Cripps AW. C reactive protein: a critical review. Pathology. 1991;23(2):118 124. 10.3109/00313029109060809 .
20. Pepys MB, Hirschfield GM. C reactive protein: a critical update. J Clin Invest. 2003;111(12):1805 1812. 10.1172/JCI200318921.
21. Tang N., Bai H., Chen X. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J. Thromb. Haemost. 2020 DOI: 10.1111/jth.14817.
22. Li X.Y., Du B., Wang Y.S. The key points in the treatment of the acute coronavirus disease 2019 patient. Zhonghua Jie He He Hu Xi ZaZhi. 2020;43(0):E026. cma.j.cn112147-20200224-00159.
23. Zhou F, Yu T., Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062. doi: 10.1016/s0140-6736(20)30566-3.
24. Xiaoyu H, Yanqing F, Osamah A, Na L et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology 2021; 299:E177–E186.
25. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062.
26. George PM, Wells AU, Jenkin RG et al (2020) Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med 8(8):807–815.