Pulmonary Fibrosis in COVID-19 Patients

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ABSTRACT

Introduction: Early analysis suggests the prevalence of post COVID 19 fibrosis is approximately a fifth to a third of cured patients and 7%–8% are severe. Initiation and advancement of pulmonary fibrosis is caused by inflammation. **Method:** In brief, the study population included 107 patients with a history of admission with COVID-19 infection diagnosis to Modarres Hospital and Labafinejad Hospital, Shahid Beheshti University of Medical Sciences, from August 2020 to October 2020.All of our participants had at least 2 chest CTs, one on admission time and another at least 6 weeks later for any reason. We evaluated chest CTs for pulmonary fibrosis, presence of pleural and pericardial effusion, crazy-paving pattern, reversed halo sign, air Broncho gram, and cardiothoracic ratio, Aorta to pulmonary artery ratio, epicardial fat thickness, epicardial fat density, and tracheal dimensions. **Results:** The prevalence of pulmonary fibrosis after COVID-19 recovery was 40%. Some lab data like Neutrophil, Lymphocyte, Aspartate Amino Transferase and Lactate Dehydrogenase had significant difference in patients with and without fibrosis. Also severity of pneumonia and fat density was significantly higher in patients with fibrosis. Unfortunately, any of evaluated prescribed medications did not have significant supportive effect in pulmonary fibrosis. **Conclusion:** We found a high prevalence for fibrosis in our study and we demonstrated some factors that can predict this complication in infected patients. None of the used medications could significantly prevent the pulmonary fibrosis development.

Keywords: Pulmonary Fibrosis, COVID-19, Pneumonia.

INTRODUCTION

Large number of patients with novel coronavirus infection (COVID-19,

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SARS-CoV-2) manifest with bilateral ground glass opacities with or without consolidation, mostly in lower lobes in radiologic images [1].

After the COVID-19 pandemic, we will meet increasing number of survived patients who are struggling with the symptoms of the disease, long after they have been completely cured [2]. Various studies have shown that 70-80% of recovered patients even after total recoveryexperience at least 1 chronic symptom [3,4]. Pulmonary fibrosis is an important sequela of ARDS [5]. Previous studies have indicated that about 40% of patients develop to ARDS, and 20% of these cases are severe (6). Early analysis suggests the prevalence of post COVID 19 fibrosis is more than a fifth to a third of cured patients and 7%–8% aresevere [7-9].

Early formation of pulmonary fibrosis could be predicted by irregular interface, parenchymal band,and alveolitisand may contribute to the morbidity and mortality [7,10]. In chest CT, findings for pulmonary fibrosis are as follows: 1- reticular and groundglass opacities; 2-pulmonary consolidation with bronchiectasis; 3- reticular nodular opacities; and 4- fibrosis with other changes [7].

Initiation and advancement of pulmonary fibrosis is caused by inflammation. Duringthe inflammatory stage of disease, matrix metalloproteinase leads to epithelial and endothelial injury. Vascular Endothelial Growth Factor (VEGF), Interleukin-6 (IL-6), Tumor Necrosis Factor Alfa (TNFα), and Transforming growth factor beta (TGF-β) seem to be involved in the fibrosis process [11]. Pulmonary fibrosis mechanism in COVID-19 is different from that of other fibrotic lung diseases, andalveolar epithelial cells instead of the endothelial cells are the site of injury [2].

Although the majority of deaths are due to acute respiratory failure, the fibrosis in later stage scan decreases pulmonary function and the quality of life [12].

In the current study we are going to evaluate the prevalence, the possible risk factors, and the predictive factors for fibrosis in our patients.

METHOD

Participants

In brief, the study population included 107 patients with a history of admission with confirmed diagnosis of COVID-19 infection to Modarres Hospital and Labafinejad Hospital, Shahid Beheshti University of Medical Sciences, from August 2020 to October 2020. Inclusion criteria was as follows: (1) Confirmed diagnosis of COVID-19 with real-time reverse transcriptase polymerase chain reaction (RT-PCR) on the nasopharyngeal specimen; (2) on admission chest CT imaging suggestive for COVID-19 pneumonia; and (3) presence of at least one chest CT 6 weeks after discharge in electronic document due to any cause. Exclusion criteria were as follows: (1) no pulmonary involvement, (2) outpatient treatment, (3) patients with previous lung disease, and (4) poor image quality.

All participants provided written informed consent prior to enrolment and the study was approved by the institutional ethics board of our Hospitals (IR.SBMU.RETECH. REC.1399.1098).

Statistical Analysis

Data analysis was done with SPSS 16.0 statistical software package with a significance level set at $p<0.05$ (two-tailed). Categorical variables were described as frequency rates and percentages, while continuous variables were explained using the mean value. Independent T test, paired T test and Mann-Whitney U test were used for comparison between patients with and without pulmonary fibrosis. Missing values were excluded pending statistical analysis.

CT

All of our 107 participants had at least 2 chest CTs, one on admission time and another at least 6 weeks later for any reason. We did not ask of any patient to do a follow up chest CT. CT was performed using a 64-slice scanner in supine position during quiet deep inspiration. Every chest CT was reportedby two experienced radiologists blinded to clinical and para clinical data of participants. Pulmonary fibrosis patterns were classified as reticular and ground glass opacities; consolidation with bronchiectasis; reticular nodular opacities; and fibrosis with other changes. Furthermore, the presence of pleural and pericardial effusion, crazy-paving pattern, reversed halo sign, and air Broncho gram was assessed (Figure 1).

The right lung was evaluated in the right upper lobe (anterior, posterior, and apical segments), the right middle lobe (medial , and lateral segments), and the right lower lobe (apical, anterior, posterior ,lateral , and medial segments). The left lung was assessed in the left upper lobe (anterior, posterior, and apical segments) and the left lower lobe (apical, anterior, posterior , lateral, and medial segments). Each segment was individually evaluated and based on parenchymal involvement scored from 0 to 5. 0 pointed to no involvement, 1 pointed to1% involvement, 2 pointed to2–25% involvement, 3 pointed to 26–49% involvement,

4 pointed to 50–75% involvement, and 5 pointed to more than 75% involvement. Thenif the segmental involvement was consolidation opacities it was calculated two folds and if groundglass one fold. Then the total CT score was the sum of the individuals' segmental scores, divided to 2. Finally it was reported as percent which was ranged from 0 (no involvement) to 100 (the maximum involvement).
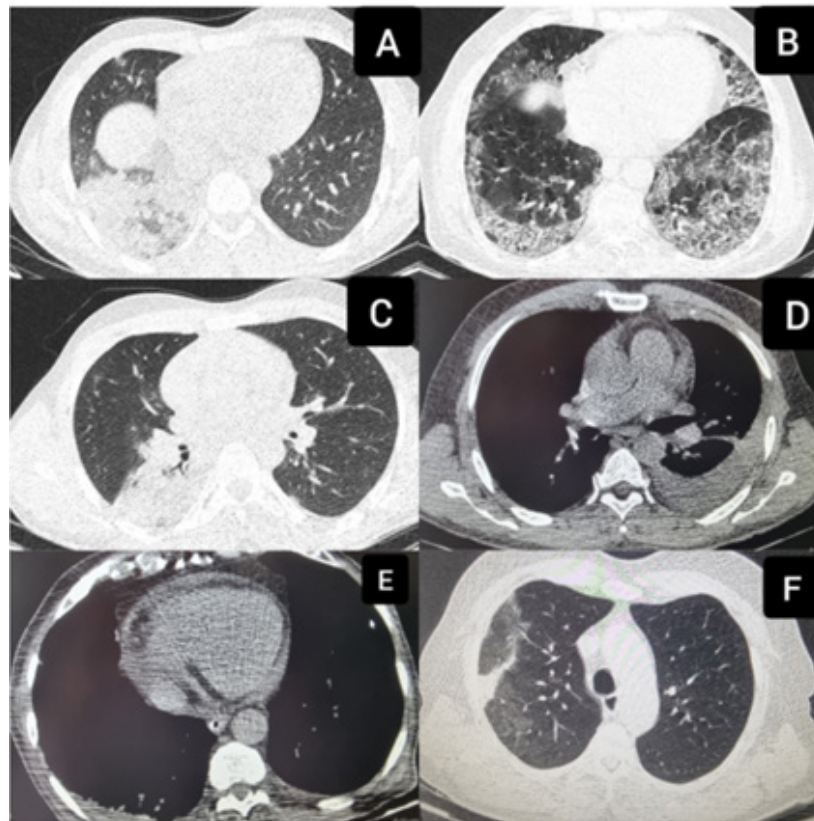

Figure 1. Some abnormalities in patients with COVID-19 infection. (A) Shows a patient with consolidation opacities. (B) Shows demonstrates another patient with crazy paving. (C) Shows consolidation with air bronchogram. (D) Shows an image in patient with plural effusion and (E) Shows pericardial effusion. (F) Shows reverse halo sign.

For cardiothoracic ratio (CTR) we measured the maximum internal diameter of the thoracic cavity (T) then we evaluated the transverse diameter of the heart (the horizontal distance between the left and right borders of the heart to spinous processes of the vertebral bodies) (C). CTR was calculated by the ratio of C to T as percent (Figure 2-E) [13,14].

The diameters of the main pulmonary artery and of the ascending aorta were measured at the level of the pulmonary artery bifurcation (Figure 2-D), according to the procedure described by WELLS et al. [15].

Epicardial fat thickness (EAT) was measured on the right ventricular (RV) anterior free wall on short-axis views. Epicardial fat density was measured by specific software (Figure 2-C).

Transverse and anteroposterior tracheal dimensions were measured below the sternal manubrium notch (Figure 2-A)
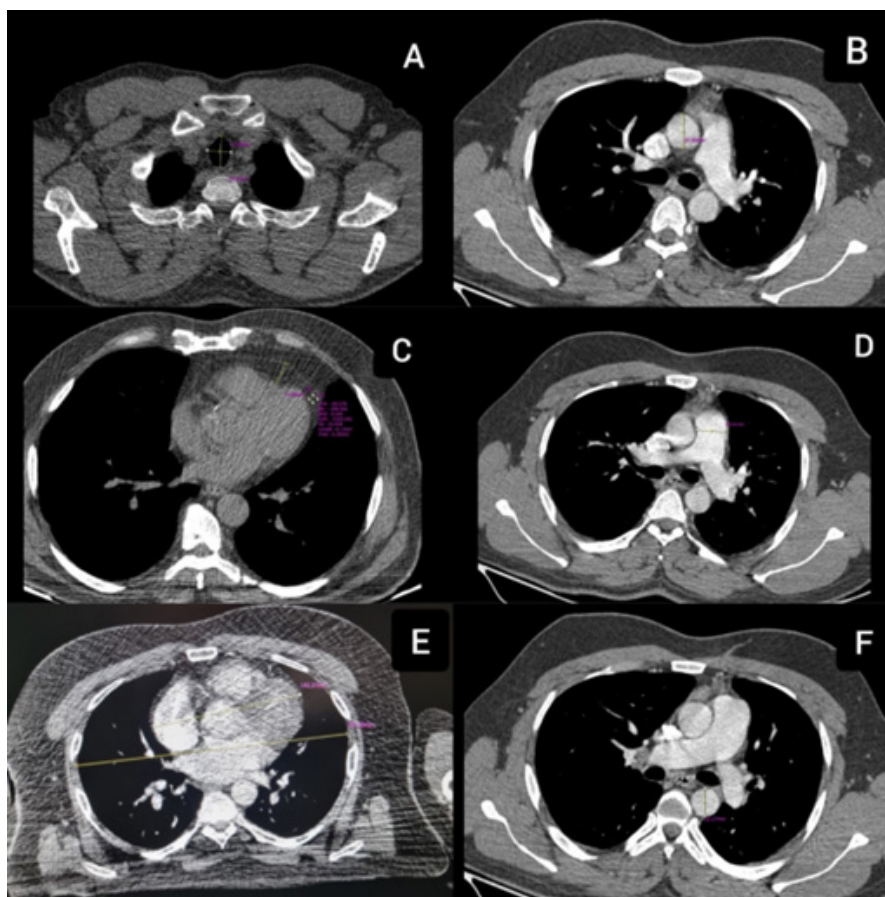
Figure 2. (A) Transverse and anteroposterior tracheal dimensions were measured below the sternal manubrium notch. (B) Aorta measearing at the level of PA biforcation. (C) Epicardial fat density was measured by specific software. (D) The diameters of the main pulmonary artery and of the ascending aorta were measured at the level of the pulmonary artery bifurcation. (E) CTR was calculated by the ratio of C to T as percent. (F) Descending aorta measuring.

RESULTS

Table 1 summarizes the demographic, metabolic and health behavior characteristics of patients. The study population included 107 patients with a history of COVID-19 admission who were evaluated for possible pulmonary fibrosis. Over

ally the prevalence of pulmonary fibrosis after COVID-19 recovery in our patients was 40%. Based on the presence of pulmonary fibrosis we divided our patients in two subgroups. As demonstrated in the table-1, the characteristics' difference between patients with and without pulmonary fibrosis were not statistically significant.

Table 1. Characteristics of participants with a history of COVID-19 infection

	Total	No Fibrosis	Fibrosis	P value
Age	58±13	57±14	59±13	0.45
ICU Admission	13%	9%	18%	0.16
Sex male	59%	59	58%	0.89
CKD	10%	11	9	0.78
DM	22%	25	18	0.43
HTN	32%	34	28	0.48
HLP	5%	5	5	0.9
Smoke	3	5	100	0.15
IHD	14	19	7	0.08
CVA	3	3	2	0.8
VTE	1	0	2	0.22
COPD	7	9	5	0.36

Values are given as means ±SD or percentages; ICU: Intensive Care Unit; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; HTN: Hypertension; HLP: Hyperlipidemia; IHD: Ischemic Heart Disease; CVA: Cerebro Vascular Accident; VTE: Venous Thromboembolism; COPD: Chronic Obstructive Pulmonary Disease.

Table 2 demonstrates radiologic data of our patients in their first and second chest CTs. It indicates that pulmonary involvement was significantly recovered in second chest CT. (p<0.001).

Table 2. Radiographic Data

	First CT	Second CT	P value
Pulmonary involvement	20±16	12±14	<0.001
Heart diameter	124±16	122±16	0.019
Lungdiametr	249±24	250±25	0.111
PA diameter	27±5	27±4	0.364
AO diameter	34±4	33±4	0.1
Fat thickness	5.9±1.7	6.2±1.9	0.016
Fat density	-86±19	-87±18	0.416
TrachealDiameter	20±3	21±6	0.09
CTR	0.50±0.06	0.49±0.06	0.009
P/AO	0.81±0.14	0.83±0.13	0.07

Values are given as means ±SD or percentages; PA: Pulmonary Artery; AO: Aorta; CTR: Cardiothoracic Ratio; P/AO: Pulmonary Artery to Aorta Ratio.

In lab data analysis some inflammatory indicators had significant difference in patients with and without fibrosis. In our experience Neutrophil (74±11%in no fibrosis involvement vs 79±8%, p=0.01 in patients with fibrosis) and Lymphocyte (18±10in no fibrosis involvement vs 14±6 in patients with fibrosis, p=0.03) had significant difference in both groups. Also we realized that the difference in Aspartate Amino Transferase (AST; 39±16in no fibrosis involvement vs 60±47 in patients with fibrosis, p=0.006) and lactate dehydrogenase (LDH;553±273in no fibrosis involvement vs 802±612 in patients with fibrosis, p=0.01) was statistically significant.

In patients with fibrosis development, severity of pneumonia was significantly higher on admission time. (14±11% in no fibrosis involvement vs 30±17% in patients with fibrosis p=<0.001). And fat density was another predictor for fibrosis (-82±20 in no fibrosis involvement vs -91±16 in patients with fibrosis p=0.02).

We evaluated if some types of drugs can prevent fibrosis

improvement. In our study any of prescribed medications (Antibiotic, Remdesivir, Favipiravir, Lopinavir/Ritonavir, Supplements) neither in all patients nor in subgroup analysis did have significant supportive effect in pulmonary fibrosis.

Table 3. Meication effect in pulmonary fibrosis

	Total	No Fibrosis	Fibrosis	P value
Favipiravir	19	17	23	0.44
Remdesivir	32	17	53	0
Floxacins	15	12.5	18	0.38
Meropnem/ Vancomycin	78	70	88	0.02
Azithromycin	21	35	16	0.28
Tavanex	35	23	51	0.003
Tamiflu	7	11	2	0.09
Linezolid	13	12	14	0.82
Vitamin B	12	14	9	0.46
Vitamin C	30	23	39	0.07
Vitamin D	25	12	44	0
Zinc	24	12.5	41	0.001
Interferon	48	36	65	0.003
FFP	2	3	0	0.24
IVIG	2	1	2	0.77
HCQ	4	6	0	0.09
Lopinavir/Ritonavir	8	12	2	0.06

Values are given as percentages; FFP: Fresh Frozen Plasma; IVIG: Intravenous Immune Globulin; HCQ: Hydroxychloroquine.

DISCUSSION

Our study was a retrospective evaluation of possible anticipant factors for pulmonary fibrosis among COVID-19 survivors later after their recovery. Though we may have made a potential selection bias because we have lost more severe cases that had been expired during their hospital admission or early after discharge.

Pulmonary fibrosis caused by SARS is a more common and an important complication. Although many studies have addressed the prevalence of pulmonary fibrosis but these amounts are a little different. Emerging data demonstrated up to 17% prevalence for this sequel [8]. Some other studies indicated that the prevalence of post COVID 19 fibrosis is more than a third of cured patients [9]. A follow up study on 55 patients three months after recovery discovered radiological abnormalities in 39 patients [16]. In Das et al. study it has been reported that 3 months after discharge, residual abnormalities of pulmonary function were observed in 25 % patients [17].

In our study on 107 survivors we found that the prevalence of pulmonary fibrosis after COVID-19 recovery was approximately 40%.

Thilleet al. Showed that pulmonary fibrosis begins early in the course of disease (4% of patientsin first week, 24% in 1 to 3 weeks, and 61% after 3 weeks, developed fibrosis) [18]. We discovered that 9% of patients during hospital admission time, 26% after 2months, 31% after 3months, 35% after 4months, 40% after 5months and 41% after 6months had fibrosis in their imaging.

Although in some studies older ages is taken into account of fibrosis risk factors [19,20] but we could not find a significant statistical difference in age for pulmonary fibrosis.

Another risk factor is disease severity [21]. We reported that severity of pneumonia in patients prone to fibrosis, was significantly higher on admission time. And another finding in chest CT that can predict fibrosis risk is epicardialfat density which in previous studies was considered as a prognostic factor for acute Coronavirus related pnomonia [22].

Smoking is considered as another risk factor [23,24] but we could not prove it. The number of smokers in our experience was very small. Perhaps it has not been mentioned correctly in admission time documents, so we could not evaluate this risk factor.

In Liu et al. and Da et al. studieslab data like lymphopenia, leukocytosis, elevated LD Hand D-dimer had a significant association for fibrosis [25,26]. We demonstrated such association for Neutrophil, Lymphocyte, AST and LDH. But for D-dimer it was not significant. Of note only 50% of our patients were evaluated for D-dimer level during their hospital admission. And these different results may be due to high number of missing data for D-dimer.

We also evaluated some prescribed medications for their potential preventive effects for fibrosis. Unfortunately, any of these medicines did not show significant effect. Perhaps it was due to small number of participants that statistical analysis was impossible based on disease severity. Because prescribed medications were different in various degrees of severity.

It is still unclear why certain individuals are prone to progressive pulmonary fibrosis, though more long-term follow up studies areneeded for evaluating the exact impact of COVID-19 in these organsand seeking for an individualized treatment program.

Study limitations

There are several limitations regarding the present study that should be addressed. This was a small study from two institutions with limited participants. Larger studies with more patients are recommended. Furthermore, our study was on COVID-19 survivors, so the prevalence of severe pneumonia was lower than expected.

We had some missing data. Some documents were incomplete at the time of admission. Also, measures of illness severity such as hemodynamic findings at the time of hospital admission were not available for analysis.

CONCLUSION

Considering large numbers of survivors of COVID19, any sequel will have major health consequence at the population level.Pulmonary fibrosis is an important complication which requires great consideration. We found a high prevalence for fibrosis in our study and we demonstrated some factors that can predict this complication in infected patients. None of the used medications could significantly prevent the pulmonary fibrosis development. Though more studies for identifying associated pathways may result in early diagnosis and individualized treatment for these patients to prevent or reduce irreversible fibrotic damage to the lung.

ACKNOWLEDGEMENT

None

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