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Coronavirus Pandemic

Lung Fibrosis Sequelae After Recovery from COVID-19 Infection

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes coronavirus diseases 2019 (COVID-19). The SARS-CoV-2 is very contagious and nobody is known to be immune to it. The post-infected lung would leave a scar known as fibrosis, a scar tissue. A study from Wuhan, China suggested the development of fibrosis, though it was too early to label these lung changes as irreversible fibrosis in a time range of 3 weeks. The occurrence of fibrosis indicates a chronic infection which greatly contributes to the hallmark symptom of COVID-19 induced ARDS such as shortness of breath and chest pain. However, many of those studies have not yet explained the condition of the patient's lung after total recovery from the COVID-19. This report demonstrates the clinical symptoms, chest CT scan, spirometry, and blood gas analysis of patient after total recovery from the COVID-19 with appearance lung fibrosis.

Key words: COVID-19; recovery; lung fibrosis.

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Introduction

The outbreak of COVID-19 has affected globally resulting 2,083,033 confirmed cases and 134,603 total deaths with case fatality rate (CFR) 6.5%. In Indonesia, the number of cases has been strikingly increasing for the last two weeks. Data collected in mid-April results in 5.136 confirmed cases and 469 deaths with CFR 9.1% [https://www.coronatracker.com]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes COVID-19. The virus invades the alveolar cells as well as the capillaries and leads to the disease. Similar to any other infection process, debris from the immune reaction which consists of inflammatory cytokines accumulates in the local site and later forming a thick mucus blocking the alveolar from physiologically ventilation process. Damages to capillaries also cause plasma protein leakage, resulting in the accumulation of the protein-rich fluid to the site of injury and lead to a condition known as acute respiratory distress syndrome (ARDS) [1]. The inflammation following ARDS can be reduced if the host immunity work well. Inadequacy of the host immune response leads to worsening a condition of ARDS due to cytokine storm, contributing to the main causes of case fatality [1-3]. Pathologically, lung inflammation including lung infection would end up with fibrotic formation. The occurrence of fibrosis indicates a chronic infection which greatly contributes to the hallmark symptom of COVID-19 induced ARDS such as shortness of breath and chest pain. Many studies have examined the patient's lung conditions during the admission in-hospital based on lung tissue biopsy [3,4]. Hosein *et al*. on his paper compared the occurrence of fibrosis in SARS, MERS, and COVID-19. Fibrosis in SARS was rare and in MERS existed in the one-third patient, whereas in COVID-19 was not yet reported. Recovered patients in MERS whose lung had fibrotic scar account for 33% out of total patients. Additional characteristics from these patients include older ages, prolonged ICU admission, and a greater lung involvement during the acute phase [5]. Another study found that the histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes,

and hyaline membrane formation could indicate strong evidence of ARDS [6]. This was also proven by Luo W *et al*. who conducted a whole right lung biopsy. The result was extensive pulmonary interstitial fibrosis with partly hyaline degeneration, and pulmonary hemorrhagic infarct [7]. CT-Scan imaging is also used in a long-term patient follow up for its findings strongly depending on the time course of infection. A study from Wuhan mentioned that most of the patients admitted in the hospital who were cohortly followed up showed a predominant pattern such as ground-glass opacity, with ill-defined margins, air bronchograms, smooth or irregular inter-lobular or septal thickening, and thickening of the adjacent pleura with the diffuse distribution. Other findings included progressive intra or inter septal thickening, crazy-paving patterns, and interstitial changes. These findings suggested the development of fibrosis, though it was too early to label these lung changes as irreversible fibrosis in a time range of 3 weeks [8]. However, many of those studies have not been explaining the lung patient's condition after total recovery from the COVID-19. A study like this was not conducted in Indonesia yet. Therefore, CT-Scan is highly recommended during follow-up on a long-term phase to observe the finding of permanent lung damage.

Case Report

In mid-March 2020 a 46-year-old man came to a private hospital clinic with symptoms of coughing, runny nose, fever from one week, and headache. Patient with history of close contact with a probable case in his workplace. The patient did not have the comorbid disease, social smoker, works as an office employee, and had no history of any known travel history. Results from patient's last routine medical check-up in 2019 are within normal limits and no respiratory complaints as shown also on CXR examination (Figure 1). The physical examination showed a moderate illness condition (subfebrile, respiratory rate of 20/minutes and peripheral oxygen saturation of 98% in room air). On pulmonary examination, we did not find any abnormalities. A chest x-ray was performed (Figure 2) and completed with a chest CT scan (Figure 3). The ground-glass opacity (GGO) appearance was found in both hemithoraces particularly in the posterior and lateral site. The consolidation appearance along with the fibrosis were also found in posterior site of the bilateral segments. The patient was hospitalized at the private hospital clinic for 2 days and then transferred to the referral hospital for COVID-19. Laboratory finding at referral hospital showed hemoglobin 14,1 g/dl, white cell count 6,290/mcL, and thrombocyte 228,000/mcL. Blood gas analysis showed pH 7,41; PCO_2 30,3 mmHg; PO_2 158,5 mmHg; HCO_3 19,6 mmol/L; BE -5,2 mmol/L and O_2 sat 100% (40% of FiO_2). During hospitalization, the patient required oxygen therapy delivered through nasal cannulae with 5 L/min (40% of FiO_2). The patient was treated with Oseltamivir 75 mg two times a day, Chloroquin 500 mg two times a day, Meropenem 1 gram three times a day, Levofloxacin 750 mg one time a day, cernevit 1 gram one time a day and hepatoproctor agent three times a day. RT-PCR SARS-

Figure 1. Chest X-ray on December 2019 (medical check up file).

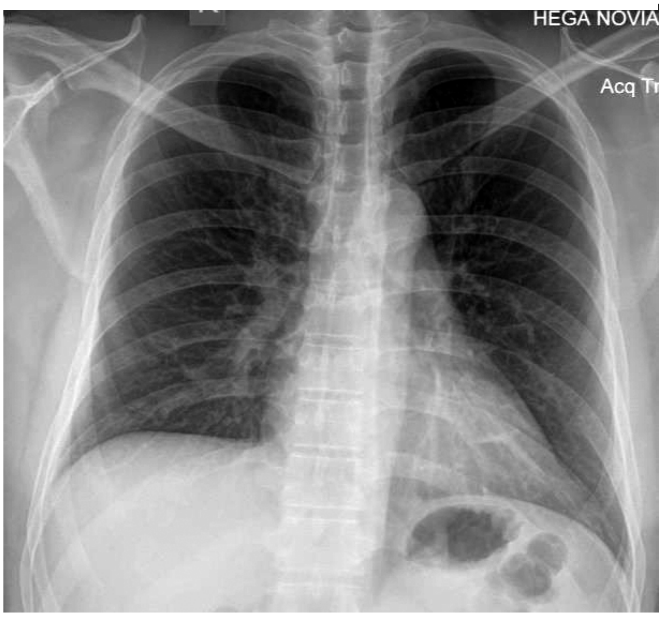


Figure 2. Chest X-ray 18th March 2020 (on the first day come to private hospital) with bilateral pneumonia.

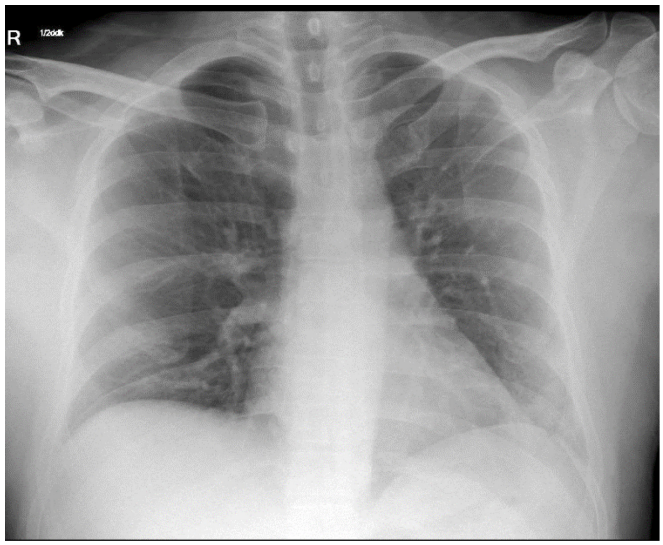
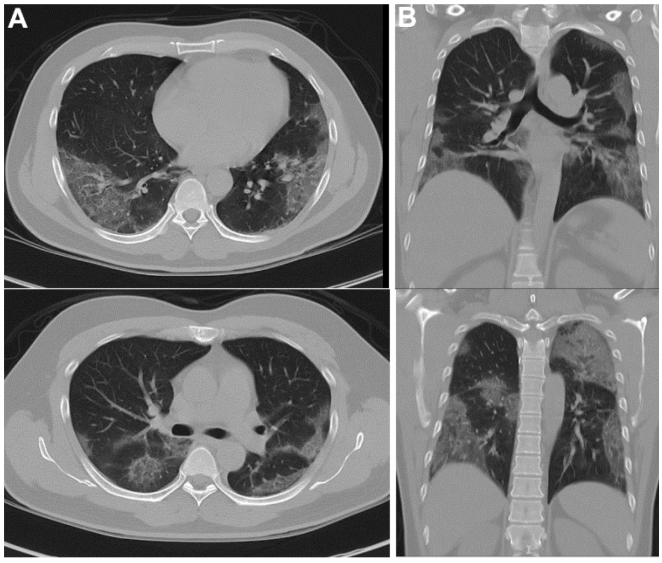


Table 1. Spirometry result of patient in April 2020.

Parameter	Result	Prediction value	%
FVC	1,650	3,710	44.47%
FEV1	1,550	2,950	52.54%
FEV1/FVC	93.88	79.96	

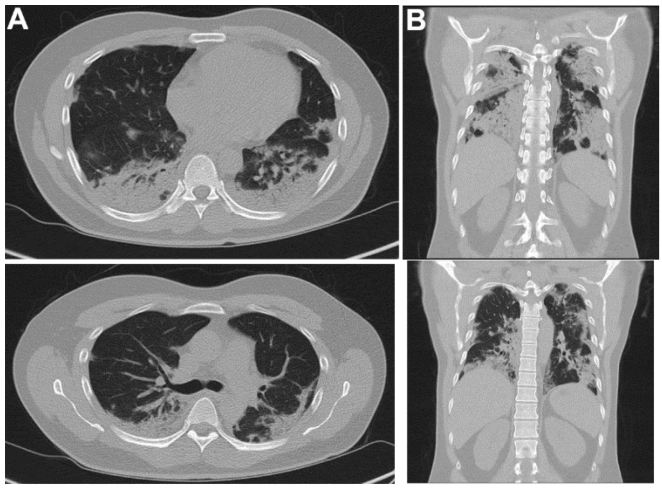
CoV-2 test from nasal and oropharynx swab was positive in 2-period examination. The patient was discharged after 9 days of hospitalization following two negative RT-PCR SARS-CoV-2 for COVID-19 tests (on April, 1st and 2nd). In early April 2020, the patient recovered after being treated at a referral hospital and followed up at the pulmonary clinic at a private hospital with the main complaint of shortness of breath during activity and coughing. The bronchial sound was found in the posterior of the lungs. Blood gas analysis showed pH 7,68; PCO_2 47 mmHg; PO_2 73,7 mmHg; HCO_3 17,5 mmol/L; BE 0,9 mmol/L and O_2 sat 98,3% (in room air). Spirometry examination with moderate restriction results (Table 1). The patient also underwent a chest CT scan with the results showed the appearance of consolidation accompanied by a fibrotic lesion that affects both hemithoraces especially in the posterior and lateral segments. Ground-glass opacity appearance was also found in both of hemithoraces (Figure 4). At the end of May 2020 or two months after the patient had recovered, the patient went to the pulmonary clinic at a private hospital with the result of examination was decrease tightness and improved quality of life. A Chest CT scan was performed with improved results

Figure 3. Axial (A) and coronal (B) view chest CT scan on March, 19th 2020.



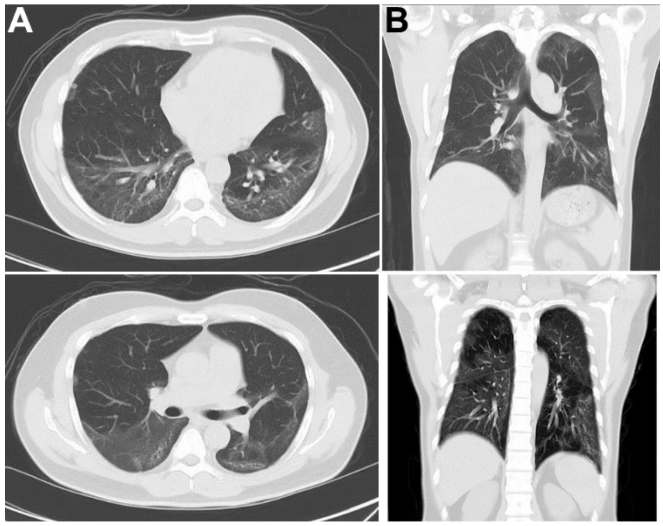
Chest CT scan showed bilateral ground-glass opacity (GGO) appearance especially at posterior and lateral site, consolidation accompanied by fibrotic lesion that affects all posterior segments of lung bilaterally.

Figure 4. Axial (A) and coronal (B) view chest CT scan on April, 6th 2020.



Chest CT scan showed (in the lung window) the consolidation accompanied by fibrotic lesion which affects all posterior and lateral segments in both lungs. Ground-glass opasity was seen in the laterobasal segment of right lung, and the 1st and 2nd of pulmonary segments bilaterally.

Figure 5. Axial (A) and coronal (B) view chest CT scan on May, 30th 2020.



Consolidation of the apical segment, part of the anterior segment, lateral segment of the right pulmonary mediate lobe; apicoposterior segment, left lung inferior segment and almost both of lingula and mediate lobe are thinner compared to previous CT scan. Multiple fibrotic parenchimal bands and mild dilatation of the distal bronchial branches were found especially in the posterior segment of the inferior and mediate lobes of both lungs.

Table 2. Spirometry result of patient in May 2020.

Parameter	Result	Prediction value	%
FVC	2,550	3,710	68.93%
FEV1	2,550	2,950	86.61%
FEV1/FVC	100	79.63	

Table 3. Comparison of spirometry results in April and May.

Parameter	Result	
	April (after recovery)	May (2 month after recovery)
FVC	1,650 (44.47%)	2,550 (68.93%)
FEV1	1,550 (52.54%)	2,550 (86.61%)
FEV1/FVC	93.88	100

compared to the Chest CT scan in early April 2020, where the fibrotic consolidation becomes thinner (Figure 5). Spirometry results showed improvement compared to spirometry in early April 2020 (Tables 2 and 3), but still restrictive pattern (FVC= 68,93% predicted). Since April 2020, patiens was given a low dose of Azithromycin 250 mg once daily and use Metered Dose Inhaler combination of long-acting (LABA) beta$_2$-agonist plus corticosteroid.

Discussion

Pathological changes of lungs during COVID-19 in-hospital progress and after recovery is already reported by some previous studies in other countries, but the occurrence of lung fibrosis and the predictors of which group of people will likely develop lung fibrosis after recovery is still rarely reported. Some of the most common imaging features found in COVID-19 patients are ground-glass opacity, crazy-paving pattern, and consolidation [9]. Imaging features after recovery of COVID-19 is still underreported, but it was reported that a large number of patients had no abnormalities on the imaging results post-recovery, yet many were found to have obvious residual parenchymal abnormalities on follow-up chest CT scans [10]. A serial CT scan was done in this patient to observe the progression of imaging features during hospitalization until after recovery. This patient had relatively mild symptoms and did not fall into acute respiratory distress syndrome (ARDS). Upon coming to the clinic for the first time for his COVID-19 symptoms, a chest x-ray and CT scan were done. Chest x-ray results could only show bilateral pneumonia, whereas CT scan results found bilateral ground-glass opacity (GGO) appearance especially at the posterior and lateral site, consolidation accompanied by a fibrotic lesion that affects all posterior segments in both lungs. CT scan is reported to be more sensitive in finding lung abnormalities in COVID-19 infected patients, therefore it is preferable to use to observe the evolution of lung abnormalities during and after recovery of COVID-19 infection [11]. Image findings on chest CT scan in COVID-19 patients vary from normal (particularly in the early stages) to unilateral or bilateral peripheral consolidation and diffuse ground-glass opacities in severely affected patients. These image findings might be subtle and overlap with those encountered in other viral pneumonia such as influenza, organizing pneumonia, eosinophilic pneumonia, and other acute lung injuries. As the disease progresses, the image findings found in the chest CT scan also evolving [11]. In a study of the early cases in China, imaging features related to the disease progression were divided into several phases based on the number of days from appearance of initial symptom to initial CT scan results: early (0 to 2 days); intermediate (3 to 5 days); and late (6 to 12 days). In this study, it was found that 56% of patients with early-stage had a normal chest CT scan and only 4% of patients with late-stage had normal chest CT scan results [12]. According to that study, this patient would be categorized as a late-stage patient at the time he went to the clinic and got the initial chest CT scan, in which he already experienced symptoms one week prior coming to the clinic, and lung abnormalities were already found in the results of the CT scan. The findings of bilateral ground-glass opacity (GGO), consolidation, and fibrotic lesions were also consistent with the findings of a study by Pan F *et al.* that reported during progressive stage (5-8 days after initial symptoms), infection rapidly aggravated and extended from unilateral abnormalities to bilateral multi-lobe distribution with diffuse GGO and more other findings such as crazy-paving pattern and consolidation [13]. CT scan results in the first week after hospital release and recovery status showed consolidation accompanied by a fibrotic lesion that affects all posterior segments and

several lateral of both lungs and ground-glass opacity in several segments of both lungs, with patient's chief complaint of shortness of breath during activity and coughing. Although the number of lung fibrosis occurrence in recovered COVID-19 patients is still not well reported, a study by Yu *M et al.* reported half of its patients who were already in discharged from the hospital showed evidence of fibrosis, such as irregular interface and parenchymal band, in the CT scan results. Initial and worst-state CT scan results were compared to examine the process of COVID-19 pneumonia and image findings that might indicate the formation of fibrosis after discharge. The results found that the most common initial CT scan findings in COVID-19 were pure GGO, GGO with consolidation, interstitial thickening, crazy paving, irregular interface, and parenchymal band. As the disease progressed, more segments were involved with larger lesions diameter that eventually exhibited more irregular interface and parenchymal band on worst-state CT scan than initial CT scan. As for the latest follow-up CT scan after discharge, typical features such as interstitial thickening and crazy paving were almost absorbed, but evidence of fibrosis, such as irregular interface and the parenchymal band were still existing. These results indicate that lesions other than fibrotic lesions such as irregular interface and parenchymal band, with the exception residual GGO, will be resolved earlier, though fibrotic lesions could resolve later [10]. Predictors of lung fibrosis occurrence are still not well known. The patient in this case was male in his middle forties with mild symptoms, no comorbidities, and hospitalization duration of 9 days. In the study by Yu M *et al*., it was revealed that fibrosis happened in the older patient, with patients in the fibrosis group median age, 54.0; IQR: 49.0–65.3, and non-fibrosis group median age, 37.0; IQR: 30.5–52.5. The patients with hypertension have the highest proportion in the fibrosis group as compared to the non-fibrosis group, although it is not statistically significant. More patients in the fibrosis group had dyspnea and higher respiratory rate than those in the non-fibrosis group, indicating that patients with evidence of fibrosis after discharge had worse lung function at the time of illness onset. The increased inflammatory reaction could lead to pulmonary fibrosis during recovery, indicated by higher levels of CRP and IL-6. It was also found that patients with fibrosis had a longer period of hospitalization than those without fibrosis and also a higher rate of admission to the intensive care unit [10]. Two months after the recovery (end of May 2020), the CT scan result of the patient showed an improvement as compared to the chest CT scan in early April 2020, in which the fibrotic consolidation becomes thinner. The patient also experienced reductions in tightness and improved quality of life. This is consistent with several studies that reported fibrosis lesions would eventually start to resolve [10,13]. Lung fibrosis is known as the sequelae of ARDS. Available data indicate that about 40% of patients with COVID-19 develop ARDS, and 20% of ARDS cases are severe, thus COVID-19 patients who suffer ARDS would more likely develop lung fibrosis and will be resolved in a few than those who did not [10].

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