Predicting lung abnormality and severity in chest CT after COVID-19: Is there a clue based on the clinical spectrum during illness?

Ira Widyaningtiyas[a] , Anita Widyoningroem[b*] , Anggraini Dwi Sensusiati[b]

*Corresponding author, email: anitawidyoningroem@gmail.com
[a]Radiology Resident, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[b]Radiology Department Consultant, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Background: Complaints after COVID-19 have been widely reported, especially those related to the respiratory tract. This situation may be related to the presence of lung lesions even though the patient has been cured as evidenced by negative PCR results. Chest CT scan is a good imaging modality that can be used to follow up post-COVID-19 patients. This study aims to determine the characteristics of a negative post-conversion chest CT scan and the correlation of the clinical spectrum of illness and lesions in a chest CT scan.

Method: This study is an analytic observational type with a retrospective approach. Researchers will examine the medical records of confirmed COVID-19 patients who are hospitalized at Dr. Soetomo and had a negative post-conversion chest CT scan at Dr. Soetomo Hospital. The severity system uses a modified severity level, then a statistical correlation analysis test is carried out with the Spearman Test.

Result: Total sample was 79 patients, with 46 male subjects (58,2 %) and 33 female subjects (41,8 %). From the clinical spectrum of illness, as many as 0% of patients were asymptomatic, 30.4% with mild symptoms, 25.3% with moderate symptoms, 17.7% with severe symptoms/severe pneumonia, and 26.6% with critical symptoms. Of the 79 samples, 93.7% had pulmonary abnormalities. The most abnormalities that were found were fibrosis at 88.6% and ground glass opacity (GGO) at 78.5%.

Conclusion: Even though the patient has been declared cured of COVID-19 with a negative RT-PCR result, there are still abnormalities in the patient's lungs. A significant correlation between clinical spectrum with pulmonary severity was found

Keywords: Clinical spectrum ; Total severity score ; after COVID-19 ; Lung abnormalities ; Chest CT Scan

Introduction

First reported in late December 2019 in China, COVID-19 then spread rapidly around the world since early 2020, and has become a global health problem to date. COVID-19 is a disease caused by a new type of novel coronavirus called Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) (1). Recovery from SARS-CoV-2 infection varies from completely cured to complaints that are still felt for a certain period. Although most will recover completely, others will experience sequelae long after they have recovered from the acute infection with varying severity of symptoms from mild to severe. In a limited study in Indonesia in 2021, it was stated that out of a total of 385 respondents, 256 (66.5%) had persistent COVID-19 syndrome. The most common symptoms were fatigue (29.4%), cough (15.5%), and muscle aches (11.2%) (2). In the evaluation of patients with lung disease after COVID-19, most patients with radiographic abnormalities will have accompanying symptoms, namely shortness of breath with or without coughing, or physiological abnormalities in the lungs (3).

Computed tomography (CT) scan of the chest is a good non-invasive test for the diagnosis and monitoring of COVID-19. Previous studies have addressed the radiological features of the disease at different stages, but post-treatment CT image patterns after PCR conversion have not been extensively elucidated, which is very important not only for understanding the pathophysiology but also for developing management strategies (4,5). Residual lung lesions are usually visible on a chest CT scan, even if the PCR swab is negative. It is usually seen in patients who have a greater inflammatory burden early in the disease, or a more severe clinical spectrum. Ground glass opacity (GGO) is the most common finding after negative conversion (4). Other studies mention that general features include ground-glass opacities (GGO), parenchymal bands, reticular abnormalities, traction bronchiectasis, and mosaic opacities (3).

Based on the Indonesian Lung Doctors Association (PDPI), the clinical syndrome was adapted and then differentiated into asymptomatic, mild, moderate, severe, and critical. Asymptomatic is when the patient had no symptoms. It is said to be mild when there are symptomatic patients without evidence of viral pneumonia or without hypoxia. Patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no evidence of severe pneumonia including SpO2 > 93% with room air were classified in the moderate group. Patients with clinical signs of pneumonia (fever, cough, shortness of breath, fast breathing) plus respiratory rate > 30 breath/min, severe shortness of breath, or SpO2 < 93% on room air were classified as severe/ severe pneumonia. Patients in the critical group are defined as those with acute respiratory distress syndrome (ARDS), sepsis, and septic shock (6).

The purpose of this study was to find characteristics of lung abnormalities after COVID-19 on chest CT imaging and evaluate the correlation between the clinical spectrum with the severity of CT lesions after COVID-19. It is hoped that from this study, it will be easier for radiologists to recognize abnormalities that occur after COVID-19, and clinicians

can estimate lung abnormalities after COVID-19 based on the clinical spectrum during illness, and determine follow-up therapy.

Material and methods

The study conducted was an observational analytic study with a retrospective study design in patients with Covid-19 pneumonia after negative conversion at Dr. Sutomo Hospital, Surabaya. Medical records of 79 patients with confirmed cases of Covid 19 being treated at RSUD Dr. Soetomo Surabaya after negative PCR conversion from 1 June 2020 to 31 December 2021. The clinical spectrum of diseases is divided into asymptomatic, mild, moderate, severe pneumonia, and critical. The CT images were reviewed by one radiologist who was blinded to the clinical data. Chest CT scan is one of the imaging methods used to diagnose and monitor various lung disorders, carried out at the Radiodiagnostic Installation of RSUD Dr. Soetomo by using a CT Scan Phillips 128 slices, Hitachi 16 slices, and Siemens 64 slices. The identification of ground-glass opacity, crazy paving pattern, consolidation, fibrosis, and bronchiectasis according to the terminology of The Nomenclature Committee of the Fleischner Society. The severity of the sequelae is calculated for each lobe and scored through a semiquantitative calculation, then summed and a total score is obtained with a value range of 0-20 which becomes data with an ordinal scale. The data were processed using the Statistical Program for Social Sciences (SPSS) version 26 software and then presented in table form with percentages (%) and tables. Correlation analysis between variables was carried out using the Spearman test with a value of $p < 0.05$ which was considered significant.

Result

In this study, the number of research subjects was 79 samples, male sex as many as 46 people (58.2%), more than female research subjects as many as 33 people (41.8%). Age range of research subjects is between 28 years to 79 years, with an average of 54,82 years.

The clinical spectrum classification is divided into five subject groups, namely asymptomatic, mild, moderate, severe, and critical symptoms. In this study, there were no asymptomatic patients. Patients with mild symptoms were 24 patients (30.4%), patients with moderate symptoms were 20 patients (25.3%), and patients with severe symptoms were 14 patients (17.7%). There were 21 patients (26.6%) with critical symptoms (table 1).

Table 1. Clinical spectrum of research subjects

Clinical Spectrum	Frequency	Percentage
Asymptomatic	0	0
Mild	24	30,4

Moderate	20	25,3
Severe	14	17,7
Critical	21	26,6
Total	79	100

In this study, GGO (Fig. 1A, 2) was obtained in 62 people (78.5%), crazy paving (Fig. 1C) in 20 people (25.3%), consolidation (Fig. 1A) in 35 people (44.3%), fibrosis (Fig. 3) in 70 people (88.6%), bronchiectasis in 32 people (44.5%). The most common lung abnormality in this study was fibrosis. GGO is the second most common lung disorder (table 2).

Table 2. Frequency of lesions found CT images

Lesion characteristics	Frequency	Percentage
GGO		
Y	62	78.5
N	17	21.5
Crazy paving		
Y	20	25,3
N	59	74,7
Consolidation		
Y	35	44,3
N	44	55,7
Fibrosis		
Y	70	88.6
N	9	11,4
Bronchiectasis		
Y	32	40.5
N	47	59.5

Figure 1. Chest CT scan, axial section, lung window of 34 years old male COVID-19 patient, after negative RT-PCR examination. There is still consolidation (A), GGO (B), and crazy paving pattern (C). CT was performed at the interval of 15 days from a positive test, and 4 days from a negative PCR conversion

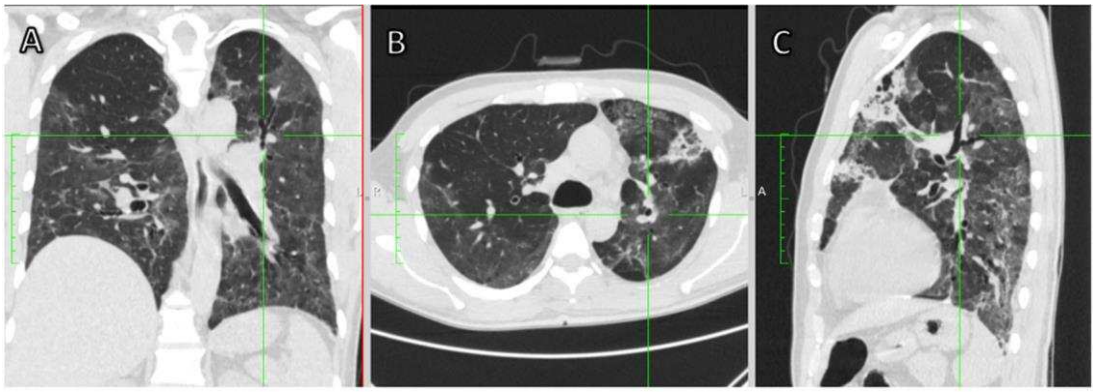

Figure 2. Coronal, axial, and sagittal section, lung window, chest CT scan of 45 years old male, after COVID-19 patient, showed fibrosis, bronchiectasis and GGO.

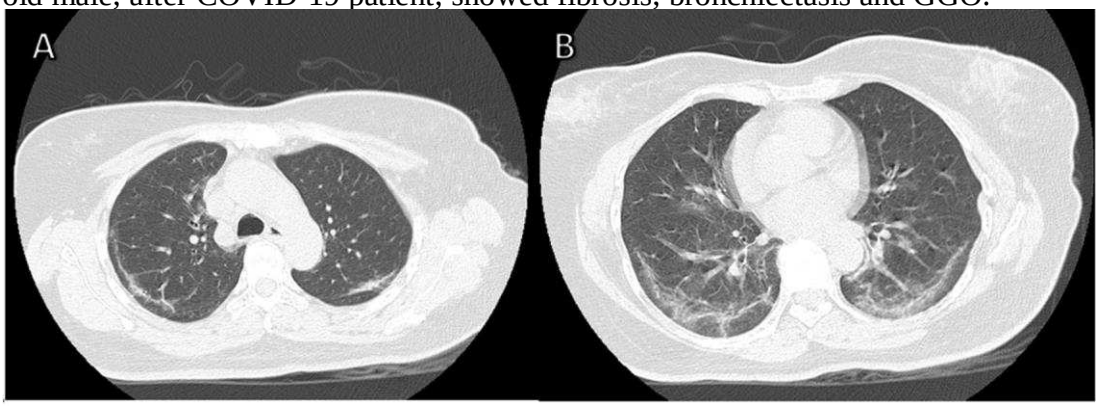

Figure 3. Axial section, lung window, chest CT scan after COVID-19 patient, 47 years old female patient showed fibrosis

In this study, there were 5 people (6.3%) with a severity score of 0 "zero" (without lung disorders). While 74 others (93.7%) with lung disorders with details 25 people

(31.6%) had mild degrees of lung disease with a severity score of 1-7, 36 people (45.6%) had moderate degrees of lung disease with a severity score of 8-14, 13 people (16.5%) had severe lung disorders with a severity score of more than 15 (table 3).

Table 3. CT severity score of research subjects

Severity score	Frequency	Percentage
0 (no abnormalities)	5	6,3
1-7 (mild)	25	31,6
8-14 (moderate)	36	45,6
15-20 (severe)	13	16.5
Total	79	100

The time span for carrying out a CT scan for each subject differed depending on when the PCR was negative and complaints after COVID-19 occurred. Based on the period of a positive test and a CT scan, the fastest time was 7 days and the longest time was 130 days.

Based on the correlation of the non-parametric Spearman rho test and the 2-tailed significance test, a significant correlation was found between the clinical spectrum and CT severity score with a p-value of 0.000 (a significant correlation if the p-value <0.05). The test results also obtained an r-value of 0.585 which means that the strength of the relationship between clinical spectrum and CT severity score of 58.5% is included in the category of moderate relationship.

Discussion

From this study, 46 people (58.2%) were male and 33 people (41.8%) were female. This is in accordance with research analyzed by Roziqo et al., 2022 that men are more susceptible to infection with SARS-CoV-2. This is because male patients have higher expression of angiotensin-converting enzyme 2 (ACE2) due to the influence of male sex hormones, while women are said to be more able to resist the development of SARS-CoV-2 infection (7,8). The lowest age in this research sample is 28 years and the highest age is 79 years, where the average age of the sample is 54 years. With the highest age group being 53-57 years as many as 20 people. In a study by Barek, Azis, and Islam, 2022 (9) it was stated that the elderly or parents of both sexes (≥50 years) are more susceptible to SARS-CoV-2 infection due to weakened immunity and other organ dysfunction. It was also stated

in a study by Sensusiati et al., 2020 (10), that age has a relationship with the mortality of COVID-19 patients.

The Indonesian Lung Doctors Association (PDPI) and four other professions in Indonesia, divide COVID-19 based on the severity of cases into asymptomatic, mild, moderate, severe, and critical symptom (6). In research conducted at RSUD Dr. Soetomo as a referral center, no asymptomatic patients were found. Of the 79 samples, 24 people (30.4%) had mild symptoms, 20 people (25.3%) had moderate symptoms, 14 people (17.7%) had severe symptoms, and 21 people (26.6%) had critical symptoms. In a study by Kwok et al., 2021 (11) in the Asia Pacific area it was said that the majority of COVID-19 patients had mild (40%) or moderate (40%) illness, around 15% were severe, and another 5% developed into critical illness. A large number of critical patients in this study sample was due to the research location being a referral center, so the number of critical patients was higher.

As is found in other coronavirus infections, COVID-19 causes injury to multiple organs and tissues, with extensive lung involvement PCR swab is one of the final markers of COVID-19 infection. However, research by Fu et al., 2020 (4) showed that lung lesions persisted even after RT-PCR conversion which showed an asymmetry between the PCR test and chest CT scan abnormalities in COVID-19 patients after negative conversion. In line with this research, in this study, out of 79 post-negative COVID-19 samples, 74 samples (93.7%) had abnormalities on the chest CT scan while 5 samples (6.3%) had no abnormalities with a severity score of "zero". Most of the 36 samples (45.6%) had a moderate degree of severity. Fibrosis (Fig. 3) was the highest lesion found on a post-conversion CT scan in 70 samples (88.6%). This is in accordance with research by Maranatha et al., 2022 where the incidence of pulmonary fibrosis after COVID-19 is high (93.7%) (12). This is also in line with several other studies that state that fibrosis is the most common sequelae feature of coronavirus infection which is described as caused by viral lung injury, immune response, and activation of repair processes by fibroproliferation (5,13). The study by Roziqo, Widyoningroem and Setiawati, 2022 states that in the final phase (2-3 weeks) when patients usually have negative PCR results, it can be referred to as the fibrosis phase, where the lungs show dense septal and alveolar fibrosis (8). A further study by Ojo et al., 2020 explains that the initial stages of lung injury are followed by acute inflammation and repair efforts by the body's immune response. In the later stage, there is a breakdown of the fibroblastic tissue organized by the fibrinolytic system or remodeling into the stroma coupled with sufficient epithelial and endothelial proliferation to repair if its basement membrane is intact. Concomitantly, however, in severe or prolonged injury with damage to the basement membrane, fibroblast activity persists, changing the organization to persistent and/or progressive fibroblastic tissue. This scar tissue formation is both focal and diffuse, resulting in a disorganized alveolar architecture with excessive extracellular matrix deposition central to the process of pulmonary fibrosis (14). The second most common finding from post-conversion chest CT scans was GGO (Fig. 1B, 2) in 62 people (78.5%).

In a study by Fu et al., 2020 it was stated that GGO remains the most common finding after a negative PCR conversion test, which differs from the findings in the early phase of a mixture with consolidation becoming dominant accompanied by thickening of the bronchial walls and bronchiectasis indicating inflammation of the pulmonary bronchi. Wong et al., 2004 found GGO with the reticular formation and irregular interlobular septal thickening in 91.4% of patients with CT scans within 48 days of treatment for common coronavirus-related infections. The study showed little change in findings at 3 and 6-month follow-up examination (4,15). Fibrosis caused by COVID-19 most often occurs in the chronic or convalescent phase. During the chronic or convalescent phase, bronchial wall inflammation and bronchial obstruction, cause damage to bronchial wall structures, fibrous tissue proliferation, fibrosis, and traction bronchiectasis. The fibrous component gradually replaces the normal cellular component to form the scar (16). Pathologically, the virus in its initial phase attacks the bronchioles and alveolar epithelium, then replicates in the epithelial cells and causes alveolar cavity leakage, then inflammation of the walls or thickening of the alveolar spaces occurs, especially around the lungs or subpleural, giving a picture of GGO. In the peak phase and absorption phase, consolidation lesions are found where inflammation develops in the alveoli and ulceration of the mucosa, the body reacts violently to the inflammatory storm, resulting in widespread alveoli exudating from both lungs. The air in the alveoli has been replaced by the pathological fluid, and the tissue cells then appear as a consolidated appearance (8,16). In this study, there were still many GGO lesions found, and the consolidation lesions were decreasing. In the absorption phase, more than 14 days after the onset of initial symptoms, the infection is controlled gradually and the consolidation is absorbed gradually. However, in this process, extensive GGO can be observed as a demonstration of the consolidation absorption (17). In the healing phase of more than 30 days, there were still GGO lesions and fibrosis. The long-term outcome of the sequelae of COVID-19 is not fully known. In one case study, pulmonary fibrosis disappeared after 65 days after the first onset (12). In a study by Han et al., 2021, a follow-up chest CT scan 6 months after COVID-19 showed that more than a third of patients still had fibrous lesions (13). In another study, follow-up at 3 and 6 months showed findings largely unchanged (4,15). The finding of consolidation in the healing phase requires further investigation, which may not be caused by the COVID-19 process, but caused by other processes and complications, for example, viral or other bacterial pneumonia or neoplastic processes. In this study, the longer the negative PCR time interval with a chest CT scan, the longer it showed fewer lesions. A study by Vijayakumar et al., 2022 showed that abnormalities on a chest CT scan can last up to 12 months after discharge from the hospital. With 81% of participants, having radiological abnormalities decreased between 3-month and 12-month CT scans (18).

Furthermore, the researchers tested the relationship between the clinical spectrum and the severity of the post-conversion CT scan where a moderate correlation was obtained, which means that the more severe the clinical spectrum of the disease, the more severe the

severity of the post-conversion CT scan findings. In the study by Han et al., 2021 it was stated that what influences the onset of fibrosis in post-COVID-19 patients includes acute respiratory distress syndrome (ARDS), which in the PDPI clinical spectrum is classified as a critical condition (13). The study by Nabahati et al., also concluded that severe COVID-19 pneumonia increases the risk of fibrotic lung damage in patients (19). The more the patient is in a state of severe illness, in this case, ARDS, the more likely there is a lung abnormality on post-COVID-19 CT examination.

The limitation of this study is that the CT scan after COVID-19 pneumonia has not become a permanent procedure so the screening results are not at the same time. In addition, we also did not evaluate other factors that might play a role, such as comorbid factors, length of ICU stay and mechanical ventilation, smoking, and chronic alcoholism.

Conclusion

There are still lung abnormalities in after COVID-19 patients, where the most common lesions are fibrosis and GGO. The degree of severity from chest CT imaging after COVID-19 is related to the clinical spectrum during illness.

Acknowledgment

The authors would like to thank all radiology and pulmonary medicine residents who supported this study and the HOR team who assisted with statistical analysis.

Source of funding

This study did not receive any specific grant from funding agencies in the public or commercial sectors.

Conflict of Interest

Nil.

Abbreviations:

COVID-19: Coronavirus disease 2019; CT: Computer Tomography; RT PCR: Reverse Transcription Polymerase Chain Reaction; GGO: Ground Glass Opacity; ARDS: Acute Respiratory Distress Syndrome

References

1. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of covid-19. Viruses. 2020;12(4):1–17.
2. Susanto AD, Isbaniah F, Pratomo IP, Antariksa B, Samoedro E, Harinda F, et al. Original article Clinical characteristics and quality of life of persistent symptoms of COVID-19 syndrome in Indonesia. 2022;12(1):158–68.
3. Solomon JJ, Heyman B, Ko JP, Condos R, Lynch DA. CT of post-acute lung complications of COVID-19. Radiology. 2021;301(2):E383–95.
4. Fu Z, Tang N, Chen Y, Ma L, Wei Y, Lu Y, et al. CT features of COVID-19 patients with two consecutive negative RT-PCR tests after treatment. Sci Rep [Internet]. 2020;10(1):1–6. Available from: https://doi.org/10.1038/s41598-020-68509-x
5. Yasin R, Gomaa AAK, Ghazy T, Hassanein SA, Ibrahem RA latif, Khalifa MH. Predicting lung fibrosis in post-COVID-19 patients after discharge with follow-up chest CT findings. Egypt J Radiol Nucl Med. 2021;52(1).
6. Burhan E, Isbaniah F, Susanto AD, Aditama TY, Soedarsono. Pneumonia Covid: Diagnosis & Penatalaksanaan di Indonesia. Jakarta: PDPI; 2020.
7. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. Intervirology [Internet]. 2021;64(1):36–47. Available from: https://www.karger.com/Article/FullText/512592
8. Roziqo D, Widyoningroem A, Setiawati R. CT Scan finding characteristics of confirmed Covid-19 patients based on clinical symptom onset patterns. Indian J Forensic Med Toxicol [Internet]. 2022;16(1). Available from: https://medicopublication.com/index.php/ijfmt/article/view/17478
9. Barek MA, Aziz MA, Islam MS. Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases. Heliyon [Internet]. 2020 Dec;6(12):e05684. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405844020325275
10. Sensusiati AD, Amin M, Nasronudin N, Rosyid AN, Ramadhan NA, Lathifah R, et al. Age, neutrophil lymphocyte ratio, and radiographic assessment of the quantity of lung edema (RALE) score to predict in-hospital mortality in COVID-19 patients: a retrospective study. F1000Research [Internet]. 2020;9:1286. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33537125
11. Kwok KO, Huang Y, Tsoi MTF, Tang A, Wong SYS, Wei WI, et al. Epidemiology, clinical spectrum, viral kinetics and impact of COVID‐19 in the Asia‐Pacific region. Respirology [Internet]. 2021 Apr 9;26(4):322–33. Available from:

https://onlinelibrary.wiley.com/doi/10.1111/resp.14026
12. Maranatha D, Hasan H, Bakhtiar A, Widyoningroem A, Aryati. Association of TNF-α, TGF-β1, Amphiregulin, IL-2, and EGFR with pulmonary fibrosis in COVID-19. J Infect Public Health [Internet]. 2022 Aug; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1876034122002106
13. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology [Internet]. 2021 Apr;299(1):E177–86. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2021203153
14. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med [Internet]. 2020 Aug 11;2020:1–10. Available from: https://www.hindawi.com/journals/pm/2020/6175964/
15. Wong K, Antonio GE, Hui DSC, Ho C, Chan P, Ng W, et al. Severe acute respiratory syndrome: thin-section computed tomography features, temporal changes, and clinicoradiologic correlation during the convalescent period. J Comput Assist Tomogr [Internet]. 2004;28(6):790–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15538152
16. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. 2020;30(8):4381–9.
17. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology [Internet]. 2020 Jun;295(3):715–21. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2020200370
18. Vijayakumar B, Tonkin J, Devaraj A, Philip KEJ, Orton CM, Desai SR, et al. CT Lung Abnormalities after COVID-19 at 3 Months and 1 Year after Hospital Discharge. Radiology [Internet]. 2022 May;303(2):444–54. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2021211746
19. Nabahati M, Ebrahimpour S, Khaleghnejad Tabari R, Mehraeen R. Post-COVID-19 pulmonary fibrosis and its predictive factors: a prospective study. Egypt J Radiol Nucl Med [Internet]. 2021;52(1). Available from: https://doi.org/10.1186/s43055-021-00632-9