New grading system for post-COVID-19 pulmonary fibrosis based on computed tomography findings

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Abstract

Background: There is currently no objective computed tomography (CT)-defined grading system for coronavirus disease (COVID-19)-related pulmonary fibrosis. We propose a CT-based radiological scale that adapts the histological fibrosis scale to pulmonary fibrosis CT findings, to evaluate possible predictive factors for the degree of fibrosis in these patients.

Methods: A new radiological fibrosis grading system was created based on existing histological fibrosis scales. One hundred forty-seven COVID-19 patients with any degree of fibrosis on CT were evaluated. Smoking status, the presence of hypertension, the duration of hospital stays, the presence of comorbid diseases, and the levels of prognostic and predictive factors for COVID-19 were evaluated, and how these parameters affected the fibrosis scores was examined.

Results: Of 147 patients, 17.7% had grade 1, 17% had grade 2, 51.7% had grade 3, and 13.6% had grade 4 fibrosis. ANOVA revealed statistically significant relationships between the fibrosis scores and lactate dehydrogenase values, lymphocyte count, C-reactive protein level, and length of hospital stay. Smoking, advanced age, hypertension, and male sex showed significantly higher scores for fibrosis.

Conclusions: Using our CT-defined lung fibrosis grading system, we could predict the severity of fibrosis as well as the resultant lung pathology in COVID-19 patients. Thus, disease exacerbation and development of permanent severe fibrosis can be prevented using the appropriate treatment methods in high-risk patients.

Abbreviations: COVID-19 = coronavirus disease, CT = computed tomography.

Keywords: chest tomography, COVID-19, grading system, predictive factors, pulmonary fibrosis

1. Introduction

The coronavirus disease (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in a worldwide health crisis after first being reported in the Hubei province of China on December 31, 2019. Currently, the number of cases detected in the COVID-19 pandemic, which has spread around the world, is 123 million, while deaths stand at 2.7 million.15

SARS-CoV2 primarily affects the respiratory system and causes atypical pneumonia, progressing to acute respiratory distress syndrome (ARDS). Pulmonary fibrosis represents a chronic and progressive tissue repair response, leading to irreversible scarring and remodeling of the lung.12-4 Pulmonary fibrosis was first graded histologically by simple classification methods used in asbestos patients and subsequently using the Ashcroft scale.13

The WHO reports that 80% of patients infected with SARS-CoV-2 will develop mild symptoms; 14%, severe symptoms; and 6%, critically ill. Studies have shown that hypertension (HT), lymphopenia, an elevated neutrophil count, increased lactate dehydrogenase (LDH) levels, high C-reactive protein (CRP) levels, and increased D-dimer levels are all associated with severe cases.14

Various imaging methods have been used for both diagnosis and follow-up. The most valuable method is computed tomography (CT) of the chest. Chest CT exposes infiltration patterns of the disease as well as detects the disease severity.7-10 However, to our knowledge, there is no objective CT-defined grading system for COVID-19-induced pulmonary fibrosis. We propose a CT-based radiological scale that adapts the histological fibrosis scale to pulmonary fibrosis CT findings in patients, by evaluating the relationship between the degree of fibrosis and the predictive factors such as HT, lymphopenia, an elevated neutrophil count, increased LDH levels, high CRP levels, and increased D-dimer levels.

2. Methods

2.1. Participants

This retrospective study was approved by the Marmara University, Faculty of Medicine, Ethics Committee (Date: 05.02.2021, Protocol number: 09.2021.222) and was carried out in accordance with the Declaration of Helsinki.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Chest CT of 1809 patients who were hospitalized with a diagnosis of COVID-19 between March 2020 and February 2021 were examined prior to discharge from hospital. Amongst these patients, 147 with any degree of fibrosis on CT were included in the study. Patients who died due to COVID-19 (n = 45) and those with pulmonary fibrosis findings on CT diagnosed prior to COVID-19 infection (n = 24) were excluded from the study. Eighty-four men and sixty-three women aged from 31 to 97 years (mean 63.5 ± SD: 14.2 years) were included. Polymerase chain reaction (PCR) tests for all patients were positive for COVID-19. Patients were discharged from the hospital following recovery from their illness and respiratory symptoms.

2.2. Imaging technique

All patients underwent high-resolution chest CT using a 128-CT scanner (Ingenuity Core 128, Philips Healthcare, Cleveland, OH) with exposure parameters of 120kV and 50 mAs, without the use of contrast media. The area between the lung apex and the diaphragm was scanned in the supine position in the axial plane, at full inspiration without contrast. Images were reconstructed with 1.5 and 4 mm collimation.

2.3. Chest CT evaluation

A new radiological fibrosis grading system was created based on the histological fibrosis grading of the Ashcroft study. According to these CT findings, pulmonary fibrosis was categorized into 5 groups: grade 0: normal parenchyma; grade 1: minimal fibrosis (thickening of alveolar or bronchiolar walls) (Fig. 1); grade 2: reticulation (interlobular and intralobular septal thickening) (Fig. 2); grade 3: subpleural linear streaks or parenchymal band (Fig. 3); and grade 4: parenchymal distortion and volume loss (Fig. 4). Minimal fibrosis was defined as thickening of the alveolar and bronchiolar walls. Interlobular septal thickening was defined as smooth thickening of the interlobular septa and peribronchovascular interstitium. Subpleural linear streaks or parenchymal bands were defined when streaks ran parallel to the lung parenchyma and bands were oriented vertically to the pleura. Distortion and volume loss were defined when structural deterioration and shrinkage of the lungs were present (Table 1).

2.4. Comparison of clinical parameters

The neutrophil count, lymphocyte count, CRP level, LDH level, and D-dimer level were investigated as biochemical prognostic and predictive factors for COVID-19 infection. The values of these parameters on the first day of hospitalization were recorded. The following were considered normal values: neutrophil count, 1500 to 8000; lymphocyte count, 1000 to 4800; CRP level, 0 to 3; LDH level, 90 to 250; and D-dimer level, 0 to 0.5. The average values of these parameters were calculated, and their relations with fibrosis scores of the patients were evaluated. In addition, smoking, duration of hospital stays, and the presence of comorbid diseases such as hypertension, diabetes, coronary artery disease, and chronic obstructive pulmonary
disease were evaluated. The effects of these parameters on fibrosis scores were analyzed.

2.5. Statistical analysis

Descriptive statistics in the form of mean and standard deviation were calculated for age range, days of hospital stay, neutrophil count, lymphocyte count, CRP level, LDH level, and D-dimer level. These data were analyzed using a variance analysis method and one-way ANOVA, according to their fibrosis score values separately. Later, the patients were divided into separate groups according to tobacco use and presence of hypertension, diabetes, coronary artery disease, and chronic obstructive pulmonary disease. The mean fibrosis score differences between these groups were analyzed using Pearson Correlation Test and the P values of the pearson chi-square value were recorded. A two-tailed P value of ≤ .05 was considered statistically significant. The IBM SPSS version 21.0 (IBM, Armonk, NY) statistical package was used for the analysis.

3. Results

In our study, 147 COVID-19 patients with fibrosis findings on CT were evaluated. Eighty-four patients were men (57.1%) and 63 were women (42.9%). The average age of female patients was 63.5 years and of male patients was 63.4 years. Of the 147 participants, 26 patients (17.7%) had grade 1, 25 (17%) had grade 2, 76 (51.7%) had grade 3, and 20 (13.6%) had grade 4 fibrosis findings on CT (Table 2).

The mean values found in the descriptive analysis are listed in Table 3. In the ANOVA evaluation of the parameters, a statistically significant relationship was found between the fibrosis scores and LDH levels (P = .001), lymphocyte count (P = .01), CRP level (P = .04), and length of hospital stay (P = .006). There was no significant relationship between fibrosis scores and neutrophil counts (P = .39) and D-dimer levels (P = .58).

Smoking, advanced age, hypertension, and male sex were correlated with statistically significant higher scores of fibrosis. There was no significant effect of comorbidities other than HT on fibrosis scores. The P and Pearson correlation scores are given in Table 4.

4. Discussion

In our study, we scored CT-defined pulmonary fibrosis findings in inpatients who developed lung fibrosis due to COVID-19 infection. Our results determined that an increase in the fibrosis score was correlated with prognostic and predictive factors, reflecting the course of the COVID-19 disease.

To our knowledge, there is no radiological grading system in the literature that evaluates lung fibrosis on CT in COVID-19 patients. Ashcroft et al. rated lung fibrosis histologically in their study[1]; we designed a novel radiological classification.
Sixty-five percent of the patients in the study group showed grade 3 and 4 fibrosis findings, whereas 35% showed early fibrosis findings of grades 1 and 2. Various studies have reported the relationship between some prognostic and predictive factors for COVID-19 infection and the severity of disease.[6,11,12] We investigated the relationship between these prognostic and predictive factors and the degree of fibrosis, based on the assumption that high degrees of fibrosis observed on chest CT were associated with more severe disease pathology. Because of the correlation between these parameters, we suggest that early and appropriate treatment could stop the progression of fibrosis and prevent respiratory distress that may occur after the disease. Fibrosis is impossible to reverse, as seen in idiopathic pulmonary fibrosis (IPF) patients, but the progress can be stopped. This study includes a more detailed perspective for these patients’ treatment.

Based on laboratory data from the study conducted by Guan et al, the severity of COVID-19 was associated with high LDH levels.[10] In addition, Guan et al and Gorbalenya et al found a significant relationship between the severity of the disease and lymphopenia and elevated CRP values.[11,12] In our study, we observed a significant relation between pulmonary fibrosis findings and high LDH levels, lymphopenia, and high CRP levels. This significant correlation validates the grading system we developed for predicting the disease severity. Neutrophil counts and D-dimer levels also determine the severity of the disease.[6,11,12] However, in our study, no significant relationship was found between these values and our grading system. Future studies with a higher number of patients may show a potential correlation.

The most important and objective parameter to evaluate the severity of the disease was the duration of hospitalization. As the severity of COVID-19 infection increases (with variants), the recovery and hospitalization periods of patients change. Our analysis found that the patients who stayed in the hospital longer had a higher fibrosis score (P = .006). This confirms our CT-defined fibrosis grading system. This grading system will predict the average length of hospital stay and need for inpatient services.

Many studies on COVID-19 have shown the relationship between disease severity and male sex, advanced age, smoking, and the presence of HT.[10,13,14] In our study, we compared the above parameters to the patients’ fibrosis scores to evaluate the reliability of our grading system. Our findings are consistent with the existing literature, with a significant positive correlation between disease severity and the following variables: male sex, age >55 years, smoking, and hypertension.

We performed an objective correlation with chest CT scans of COVID-19 patients and clinical findings. With this grading system, CT images of both COVID-19 patients and those with other respiratory diseases can be evaluated more uniformly and accurately. This study has a few limitations. Although the number of inpatients in our hospital was high, the sample size was small due to the mortality rate and patient recovery. In future studies, larger sample sizes should be recruited by designing a multicenter prospective study, and pulmonary function tests may be added for additional validation measures.

Pulmonary fibrosis can develop in patients with severe COVID-19 and respiratory distress may develop after recovery in patients with fibrosis, affecting their quality of life. With our CT-defined lung fibrosis grading system, we could collect information about the potential severity of fibrosis as well as the course of the disease. In this way, we believe that the increase in disease severity and the development of permanent severe fibrosis can be prevented with appropriate treatment methods in high-risk patients. In addition, new information can be obtained by adapting this grading system to different diseases that result in fibrosis in the lung.

Author contributions

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