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Role of Computed Tomography in Detecting Lung Changes in Post-COVID-19 Patients

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INTRODUCTION

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coronavirus 2 (SARS-CoV-2) that causes Coronavirus Disease 2019 (COVID-19) has spread worldwide. According to pathological investigations, COVID-19 causes damage to several tissues and organs, including the lungs, and this pattern is comparable to that of other coronavirus infections, such as the Middle East respiratory syndrome infection (MERS-CoV) and SARS-CoV [1].

Chest CT is essential for COVID-19 diagnosis, monitoring, problem detection, and prognostication. While chest CT scans are useful for identifying COVID-19 problems such as heart failure, lung fibrosis, pulmonary embolism, and acute respiratory distress syndrome (ARDS), their role in prognostication needs more research [2].

Information from earlier coronavirus infections revealed that COVID-19 individuals might have significant fibrotic complications. On the other hand,

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not much is known regarding the long-term lung alterations following infection of COVID-19. Examining pulmonary alterations on follow-up chest CT scans every six months and investigating the risk variables for lung fibrotic-like alterations in individuals who have been cured of severe COVID-19 pneumonia are the goals of many investigations [3,4].

We aimed to outline the lasting impacts of COVID-19 in patients following their release from the hospital and to pinpoint the possible risk factors—such as the severity of the disease—that may be correlated with these effects.

Patients:

METHODS

This prospective Cohort study was performed at the Radiodiagnosis Department, Faculty of Medicine, Zagazig University between April 2022 and september 2022 at Zagazig University Hospitals. Verbal and written informed consent was collected from all individuals after an explanation of the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB#9397/30-3-2022).

Cases with the following criteria were included in the study: (1) cases that were confirmed to have SARS-CoV-2 infection through throat and nasopharyngeal swab samples analyzed using RT-PCR. (2) cases that were diagnosed with moderate or severe COVID-19 pneumonia.

Cases with the following characteristics were excluded: (1) mild COVID-19 pneumonia; (2) unavailable Chest CT scan on admission; and (3) inadequate CT image quality.

Determining the severity of COVID19 pneumonia by the **National Health Commission of China 2019**: mild: manifestation is mild and cannot be detected by imaging, moderate: mild to high fever and opacities can be detected by plain x-ray or CT chest, severe: stressful respiration, respiratory rate higher than 30/min, in resting state, oxygen saturation less than 93 %, opacities can be detected by plain x-ray or CT chest and PaO2/FIO2 less than 300(partial pressure of oxygen in arteries/fraction of inspired oxygen)

Methods:

This prospective Cohort study was performed at the Radiodiagnosis Department, Faculty of Medicine, Zagazig University on 120 cases with moderate to severe COVID-19 who have been released from the hospital following COVID-19 treatment as inpatients between April 2022 and september 2022 at Zagazig University Hospitals. RT-PCR was performed to establish the presence of SARS-CoV-2 using throat swab samples. Involvement levels range from 0 to no involvement, to (1) <5%, (2) 6-25%, (3) 26-49%, (4) 50-75%, and $(5) > 75%$. The maximum CT score was 25, which was assessed as the sum of the individual lobar scores. The score over time and the evolution tendency of the pattern were assessed [6]. The cases were divided into two groups according to the pulmonary severity score: group 1 with Score <18 and group 2 with Score \geq 18. Additionally, based on their survival, they were classified into survivors and nonsurvivors.

All cases were subjected to complete history taking, full clinical and laboratory examination (CBC, CRP, serum ferritin, D Dimer, IL6, ESR, kidney and liver functions), and imaging, including non-contrast CT chest at 0 and 6 months [5].

CT protocol and image interpretation

We used a Siemens 16-detector CT scanner to perform chest CT imaging. All participants were positioned in a supine position and instructed to perform a single inspiratory breath hold for CT examination. The lung's apex to the costophrenic angle was the scanning range. The CT scan specifications were as follows: pitch of 1.0, rotation duration of 0.5 seconds, x-ray tube parameters of 120 kVp and 350 mAs, extra reconstruction using a sharp convolution kernel, and a slice thickness of 5 mm.

The patterns of CT scans were described using terms developed by the Fleischner Society, which included consolidation reticular pattern, and ground-glass opacity (GGO) [5]. A semi-quantitative scoring technique was utilized to evaluate the quantitative CT in accordance with prior research findings. Based on lung involvement area percentage, the 5 mm lung window was scored. Every lobe was visually rated for lung involvement percentage on a scale of 0 to 5.

Involvement levels range from 0 to no involvement, to (1) <5%, (2) 6-25%, (3) 26-49%, (4) 50-75%, and (5) > 75%. The maximum CT score was 25, which was assessed as the sum of the individual lobar scores. The score over time and the evolution tendency of the pattern were assessed [6].

Statistical Analysis:

Statistical analysis was done using SPSS version 28 (IBM Co., Armonk, NY, USA). Quantitative parametric data were presented as mean \pm standard deviation (SD), while quantitative non-parametric data were presented as median with interquartile range (IQR). Classified into two groups based on the opacity score and their survival. Mann-Whitney U test was used to compare 2 independent groups for quantitative data that not normally distributed

Categorical variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test, while the repeated results were compared using Cochran's Q test. The overall survival analysis was conducted using Kaplan-Meier curve analysis to assess the survival probability and the expected duration of time until an event (mortality) occurs. Logistic regression was carried out to evaluate the different factors associated with the incidence of fibrotic-like changes. P-value $\langle 0.05 \rangle$ was considered statistically significant.

RESULTS

This study included 120 moderate and severe COVID-19 cases (69 males and 51 females) with a mean age of 51.16 ± 8.85 years. Out of 120 cases, 23.3% were smokers, 10% were hypertensive, 8.3% were diabetic, 2.5% had hepatic disease, 1.7% had COPD and only 0.8% had renal disease. All the studied patients had positive PCR. The most common symptom at discharge was cough elicited by most patients (77.5%), followed by dyspnea in 70.8%, tachycardia in 63.3%, then fever in approximately half of patients (50.8%). According to CT at admission, more than half of patients (65%) had an opacity score \geq 18 (Table 1).

Regarding investigations at admission there were significant differences between pulmonary opacity score groups as regard; oxygen saturation tends to be significantly lower in groups with score \geq 18, while inflammatory markers were higher in groups with score \geq 18. CRP, D-dimer, LDH, IL6, Procalcitonin were higher in groups with score \geq 18 with p values were >0.001,

Although SGPT/ALT results were near normal range or very mild increased, there were significant higher readings in groups with score ≥ 18 (Table 2).

There were highly statistically significant differences among score groups regarding GGO, with the percentage of cases lower in the score<18 groups, while GGO was higher in a group with a score ≥ 18 as presented in 100% of the group with p-value ≤ 0.001 .

Also, interlobar pleural traction was statistically significantly higher in the group with a score ≥ 18 (p= 0.02). On the other hand, consolidation was present in 28.5% of cases in a group with a score <18, which was substantially lower than the other group ($p < 0.024$) (Table 3).

There were significant differences between opacity score groups regarding outcome (Oxygen support on discharge and hospital stay) $(P<0.05)$ (Table 4).

Based on non-contrast CT chest results at admission and 6 months post-discharge, the rate of GGO, consolidation, pleural effusion, reticular pattern, nodules or masses, and traction bronchiectasis findings were substantially varied between the two scans (P<0.05) (Table 5).

The comparison between the survivors and nonsurvivors in terms of their CT findings at admission revealed no statistically significant difference (Supplementary Table 1).

The survival rate among the patients with opacity score <18 was 97.6% in a mean time of 21.5 days (95%CI: from 20.7 to 22.38), while the survival rate among the patients with opacity score ≥ 18 was 89.7% in a mean time of 27.5 days (95%CI: from 25.1 to 29.9) as demonstrated by Kaplan-Meier analysis (Supplementary Table 2).

Based on univariate logistic regression findings, age (P<0.001) and hospital stay (P<0.001) were significant predictors of the incidence of fibrotic-like changes. Smokers ($P=0.002$), diabetic patients ($P=0.018$), and hypertensive patients $(P=0.004)$ had remarkably higher odds of having fibrotic-like changes than the nonsmokers, non-diabetic and non-hypertensive patients, respectively. Patients with anosmia (OR: 4.213, 95%CI: 1.026 to 17.299, P=0.046), body-ache (OR: 6.083, 95%CI: 1.469 to 25.192, P=0.013) and diarrhea (OR: 6.395, 95%CI: 1.542 to 26.524, P=0.011) had significantly higher odds of having fibrotic like changes compared to the ones with no such symptoms. Patients on non-invasive (OR: 28.235, 95%CI: 3.189 to 249.977, P=0.003) or invasive MV (OR: 60, 95%CI: 5.045 to 713.612, P=0.001) had markedly higher odds of having fibrotic like changes as compared to those on O2 mask (Supplementary Table 3).

Case 1: A 55-year-old female presented with symptoms including fever, cough, expectoration, dyspnea, and body ache. The patient had a risk factor of diabetes (Fig. 1).

Case 2: A 55-year-old male presented with symptoms including fever, anosmia, body ache, and dyspnea (Fig. 2).

Table (2): Comparison between patient groups according to opacity score as regard investigations at admission and discharge

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Table (3): Comparison of different score groups as regard CT findings at admission

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Table (4): Comparison between patient groups according to opacity score as regarding the Outcome

Table (5): CT findings over 6 months of discharge of the studied patients

significant difference, *: Statistically significant as P value<0.05, GGO: Ground-glass opacity*.*

Figure (1) (A) High-resolution CT chest axial cuts at admission revealed bilateral scattered opacities of consolidations (air bronchogram) with GGOS. CT score 22. (B) A chest CT after six months revealed bilateral diffuse reticular opacities, nodular opacities, and peripheral and subpleural atelectatic bands.

Figure (2) (A) High-resolution CT chest axial cuts at admission reveal bilateral consolidations (air bronchogram) and atelectatic bands. CT severity score 21. (B) CT chest after six months revealed diffuse bilateral reticular opacities, traction bronchiectasis, and fibrotic bands.

DISCUSSION

Following the 2003 SARS outbreak, several patients made a full recovery. Nonetheless, at 4–6 months following hospital admission, radiological abnormalities were found in over 70% of SARS cases who recovered [7], and earlier research had documented long-term pulmonary effects [8].

Thus, this may prompt physicians to ask a crucial question: Do COVID-19 patients who are recovering have any long-term pulmonary sequelae? The COVID-19 survivors' impacts have received little attention up to this point [9], and more study needs to be done on the long-term radiological alterations. Thus, this study aimed to outline the lasting impacts of COVID-19 in cases following their release from the hospital and to pinpoint the possible risk factors that may be correlated with these effects of a 6-month follow-up chest CT in COVID-19 cases.

This study was conducted on 120 moderate and Severe COVID-19 patients who were PCR positive for COVID-19 who admitted to Zagazig University hospitals with a mean age of 51.16 ± 8.85 years. All the studied patients had positive PCR at admission.

Regarding investigations at admission there were significant differences between opacity score groups as regard; oxygen saturation tends to be significantly lower in groups with score \geq 18, while inflammatory markers were higher in groups with score ≥ 18 . CRP, D-dimer, LDH, IL6, Procalcitonin were higher in groups with score ≥ 18 with p values were >0.001 ,

Although SGPT/ALT results were near normal range or very mild increased, there were significant higher readings in groups with score ≥ 18

This was in agreement with studies by Yu et al. [10] and McGroder et al. [11], who reported that elevated IL-6, lactate dehydrogenase, and CRP have been linked to worse fibrosis at follow-up.

Also, Huang et al. [12] and Zou et al. [13] Noticed that at follow-up, higher levels of albumin, white blood cell count, and D-dimer have been linked to poorer fibrosis.

As regards symptoms, the most common symptom at discharge was cough elicited by most patients (77.5%), followed by dyspnea in 70.8%, tachycardia, and then fever in approximately half of patients.

This was in agreement with Ali and Ghonimy [14], who found that the majority of cases (75%) presented with a dry cough; dyspnea, and diarrhea affected one third of cases.

As regards CT findings at the admission of different pulmonary score groups, regarding GGO there was highly significant difference between two groups, with the percentage of cases that had GGO lower in the score<18 groups, while GGO was higher in a group with a score ≥ 18 with p-value <0.001. Also, interlobar pleural traction was statistically significantly higher in the group with a score ≥ 18 (p= 0.02). On the other hand, consolidation was significantly lower in group with score < 18 than the other group ($p < 0.024$).

Our findings were in line with Chen et al. [15], who found that percentage of GGO consolidation, and interlobar pleural traction increased in the severe COVID-19 patients.

As regards the outcome of studied patients: In terms of oxygen support there was high statistically significant difference between two groups:

In group with a Score ≥ 18 more patients needed noninvasive mechanical ventilation, invasive mechanical ventilation and more days at hospital more than the other group, with substantial variance between groups. The mortality rate was 2.4% in cases with a Score <18 and 10.3 % in patients with a score \geq 18.CT findings over six months of discharge of the studied patients: Based on non-contrast CT chest results at admission and 6-months post-discharge, the rate of GGO findings was substantially varied between the two scans (P<0.001) being higher at admission (67.5%) as compared to post-discharge scan in which the extent of ground-glass was completely attenuated, similarly for the incidence of consolidation and pleural effusion. Regarding interlobar pleural traction, it was higher after six months from discharge compared to scans at admission, with remarkable variance between the two scans. In terms of reticular pattern, it was significantly different according to CT between the two examinations, after six months being significantly higher. Regarding fibrotic-like change manifested by traction bronchiectasis, it was significantly different according to CT between the two examinations (as it wasn't detected in any patient at admission, while it was detected in 9.01% after six months are significantly increased after 6 months than admission.

This finding match with Chen., et al [15] who found slight irregular linear opacities were still visible a year

after discharge, along with subpleural lines and reticulation, which appeared in the GGO areas about a month after release. Additionally, they discovered that the prevailing pattern on CT scans evolved with time. In particular, the degree of consolidation reached its maximum (40.2%) during the third week following the beginning of symptoms and then declined. The most prevalent aberrant patterns from the time of symptom onset to 12 months following hospital discharge were pure GGO or GGO with reticular pattern. Only 13.0% of the lung zones had pure GGO, and 8.1% had GGO with reticular pattern at the conclusion of the 1-year follow-up.

In contrast, Solomon et al. [16] found that only 4% of the 48 survivors of severe COVID-19 who underwent 3-month scans showed normal imaging results. 89% of cases had GGO, and 67% had fibrosis-related symptoms. Patients had anomalies in their pulmonary function tests (reductions in lung volumes and DLco) and increased CT severity ratings.

The majority of residual abnormalities were found in regions where baseline scans revealed GGO with reticulation. That was due to all patients in this study being mechanically ventilated, different sample sizes, and different demographics of the patients included in this study.

Zhang et al. [17] also noticed that in early recovery of COVID-19 cases (within 30 days of sickness start), a gradual drop in CT scores has been previously reported. Lesion absorption and recovery happened more frequently in the first 12 months following infection. Subsequently, they stabilized over the next 15 years in the prior 15-year follow-up research involving serial CT images in SARS-infected individuals. Therefore, lengthier follow-up research is needed to determine how long the residual opacities would last following COVID-19.

John et al. [18] noticed that one significant complication of severe respiratory infections in individuals is the development of pulmonary fibrosis. Since Antonio et al. [3] noticed the significant fibrotic effects observed after contracting MERS-CoV and SARS-CoV-1, questions have been raised over the frequency and durability of lung fibrosis following COVID-19. Based on earlier research, 35% of cases cured of severe COVID-19 at six months following illness onset had lung fibrotic-like alterations.

Ali and Ghonimy [14] found that the mild group revealed less risk for post-COVID-19 fibrosis, seen only in 18.4%, whereas the severe group revealed higher prevalence of post-COVID-19 lung fibrosis seen in 42.8% of cases as in our study that included all patients with severe COVID19.

Based on the findings of univariate logistic regression, age $(P<0.001)$ and hospital stay $(P<0.001)$ were significant predictors of the incidence of fibrotic like changes. Smokers (OR: 10.07, 95%CI: 2.382 to 42.574, P=0.002), diabetic patients (OR: 12.375, 95%CI: 1.533 to 99.872, P=0.018), hypertensive cases (OR: 8.952, 95%CI: 2.038 to 39.327, P=0.004) had remarkably elevated odds of having fibrotic like changes than the non-smokers, non-diabetic and nonhypertensive patients respectively. Patients with anosmia (OR: 4.213, 95%CI: 1.026 to 17.299, P=0.046), body-ache (OR: 6.083, 95%CI: 1.469 to 25.192, P=0.013) and diarrhea (OR: 6.395, 95%CI: 1.542 to 26.524 , P=0.011) had significantly higher odds of having fibrotic like changes compared to the ones with no such symptoms. Patients on non-invasive (OR: 28.235, 95%CI: 3.189 to 249.977, P=0.003) or invasive MV (OR: 60, 95%CI: 5.045 to 713.612, P=0.001) had markedly elevated odds of having fibrotic like changes as compared to those on O2 mask. This was in agreement with Ali and Ghonimy [14] found that Following the COVID-19 pandemic, pulmonary fibrosis was significantly more common in patients between the ages of 60 and 75 (43.3%), with a somewhat greater frequency in the 45–60 age group (28%), compared to the 25–45 age group (20%).

This also matches a study by Wong et al. [19], which reported that pulmonary fibrosis is more common in older adults after MERS. The 45–60 age group had the lowest incidence (25–28%), whereas the 25–45 age group had the lowest incidence (20%).

Cigarette smoking was another risk factor; the results of this study indicated that smokers had a significantly greater prevalence of post-pulmonary fibrosis than non-smokers.

Our results were in agreement with Ali and Ghonimy [14], who stated that out of the 30 smoker cases, 60% had post-pulmonary fibrosis. Also, Vardavas C.I. et al. [20] found that compared to non-smoker patients, smokers are 1.4 times more likely to experience severe COVID-19 symptoms, 2.4 times more likely to require MV and ICU admission, and 2.4 times more likely to die.

Also, Chen et al. [15] investigated the risk factors for lingering abnormalities in radiography one year following discharge. Patients were split into two groups based on whether their CT scans showed any residual lesions one year after discharge ($n = 17$) or not $(n = 19)$. Clinical and epidemic traits were contrasted between the two subgroups. Older patients ($p = 0.01$) and those with a history of current smoking, hypertension, decreased SaO2, and secondary bacterial infections during the acute phase were more likely to

have lasting radiological abnormalities. Age was a risk factor linked to residual radiological aberrations at one year following discharge, according to multivariable logistic regression analysis. A predictor of residual radiologic opacities was found to be age.

Also, Song et al. [21] reported that older (more than fifty years) COVID-19 cases showed more consolidation lesions compared to younger patients. Wang et al. [22] found that compared to younger cases $(\leq 45$ years), the older cases' mass of lung involvement was much more severe and increased later. In a study by Han,et al.,2021, that was 6-month follow-up chest CT results after severe COVID-19 pneumonia, notice that after SARS-CoV-2 infection, older age (> 50) was found to be the independent risk factor for fibrotic-like alterations. Also, Yang et al. [23] and Suleyman et al. [24] found that a potential relationship exists between the age of cases and the severity and result of COVID-19. It is yet unknown why older COVID-19 cases typically recover more slowly and are sicker overall.

Studies by Cherry et al. [25] and Ooi et al. [26] from various viral infections involving the lungs indicate that after being released from the hospital, functional and radiologic deficits continue. The reticular aberrations were first observed at two weeks, when the CT aberrations were at their most severe, in the initial SARS-CoV outbreak in 2003, which included 8000 verified cases and a 9% fatality rate. On follow-up scans after discharge, fibrosis was observed in 50–60% of cases despite the GGOs and consolidations gradually improving.

Older individuals who had been hospitalized for a longer period and had greater acute phase lactate dehydrogenase levels were more likely to have fibrosis. Also, Huang et al. [12] have found that older age, male gender, and underlying comorbidities have been correlated with worse fibrosis at follow-up

Yu et al. Yu et al. [10] And Lerum et al. [27] have found that ICU admission, longer hospital stays, the need for MV, and the duration of MV have been related with increased fibrosis at follow-up

CONCLUSION

Six-month follow-up CT showed lung fibrotic-like changes in more than one third of patients who survived moderate and severe COVID-19 pneumonia. These changes were associated with older age, longer in-hospital stays and higher initial chest CT score.

These results support that those with severe disease need post-discharge care. Longer follow-up studies in a larger population are necessary to understand the full spectrum of health consequences from COVID-19

No potential conflict of interest was reported by the authors.

the severity of illness and blood leucocyte telomere

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