

Postacute Sequelae of COVID-19 Pneumonia: 6-month Chest CT Follow-up

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SUMMARY:

At 6-month follow-up chest CT, COVID-19 postacute sequelae were detected in 72% of patients: fibrotic-like changes were the most common residual findings (72%), followed by ground-glass opacities (42%).

KEYS RESULTS:

1. Baseline Lung Severity Score (>14) showed an optimal performance in predicting fibrotic-like changes at follow-up (AUC: .91; sensitivity: 88%; specificity: 80%).
2. Multivariable analysis showed that male sex, cough, lymphocytosis and Quantitative Chest Computed Tomography well-aerated lung volume were significant predictors of fibrotic-like changes at six-month follow-up with an inverse correlation (AUC: .92; sensitivity: 100%; specificity: 73%).

ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19: Coronavirus Disease 2019

RT-PCR: Reverse Transcription Polymerase Chain Reaction

GGO: Ground Glass Opacity

LSS: Lung Severity Score

QCCT: Quantitative Chest Computed Tomography

ROC: Receiver Operating Characteristic

AUC: Area Under the Curve

See also the editorial by Wells and Devaraj.

Abstract:**Background**

The long-term post acute pulmonary sequelae of COVID-19 remain unknown.

Purpose

To evaluate lung injury in patients affected by COVID-19 pneumonia at six-month follow-up compared to baseline chest CT.

Methods

From March 19th,2020 to May 24th,2020, patients with moderate to severe COVID-19 pneumonia and baseline Chest CT were prospectively enrolled at six-months follow-up. CT qualitative findings, semi-quantitative Lungs Severity Score (LSS) and well-aerated lung quantitative Chest CT (QCCT) were analyzed. Baseline LSS and QCCT performances in predicting fibrotic-like changes (reticular pattern and/or honeycombing) at six-month follow-up Chest CT were tested with receiver operating characteristic curves. Univariable and multivariable logistic regression analysis were used to test clinical and radiological features predictive of fibrotic-like changes. The multivariable analysis was performed with clinical parameters alone (clinical model), radiological parameters alone (radiological model) and the combination of clinical and radiological parameters (combined model).

Results

One-hundred-eighteen patients, with both baseline and six-month follow-up Chest CT, were included in the study (62 female, mean age 65 ± 12 years). At follow-up Chest CT, 85/118 (72%) patients showed fibrotic-like changes and 49/118 (42%) showed GGOs. Baseline LSS (>14), QCCT ($\leq 3.75L$ and $\leq 80\%$) showed an excellent performance in predicting fibrotic-like changes at Chest CT follow-up. In the multivariable analysis, AUC was .89 (95%CI .77-.96) for the clinical model, .81 (95%CI .68-.9) for the radiological model and .92 (95%CI .81-.98) for the combined model.

Conclusion

At six-month follow-up Chest CT, 72% of patients showed late sequelae, in particular fibrotic-like changes. Baseline LSS and QCCT of well-aerated lung showed an excellent performance in predicting fibrotic-like

changes at six-month Chest CT (AUC>.88). Male sex, cough, lymphocytosis and QCCT well-aerated lung were significant predictors of fibrotic-like changes at six-month with an inverse correlation (AUC .92).

Impress

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (1).

Chest CT qualitative findings of COVID-2019 pneumonia have been deeply investigated in literature (2), as well as quantitative Chest CT (QCCT) methods (3-5) and semiquantitative lung severity scores (LSS) (6, 7).

Typical Chest CT findings of COVID-19 pneumonia include bilateral and multilobe ground glass opacities (GGOs) with posterior and peripheral distribution associated with consolidations, interlobular septal thickening and subsegmental pulmonary vessels enlargement (> 3 mm) (8).

The short- and mid-term Chest CT outcomes in COVID-19 patients (9, 10) have been reported in some studies, with both qualitative and semiquantitative methods (11-13); fibrosis was a common finding at few weeks from the onset of the symptoms (14-16).

A recent study demonstrated that approximately one-third of COVID-19 survivors showed pulmonary fibrotic-like changes at six-month follow-up Chest CT (17); nevertheless, as a novel pathological entity, further long-term investigations are needed for a full comprehensive knowledge of COVID-19 pulmonary sequelae. Indeed, there is great concern that some of these findings will resolve over time, and are therefore not fibrosis (18).

In fact, for previous different severe viral pneumonias, several studies demonstrated how long-term lung impairment is a common sequelae (19); among them the long-term follow-up study on severe acute respiratory syndrome (SARS) by Zhang et al. (20) and Wu et al. (21) demonstrated the persisting pulmonary interstitial damage several months after recovery.

Thus, the aims of our study are: 1) to prospectively investigate Chest CT late sequelae in patients affected by COVID-19 pneumonia at six-month follow-up and comparing CT features with those present at baseline Chest CT; 2) to evaluate the role of Chest CT and clinical parameters in predicting pulmonary fibrotic-like changes at six-month follow-up.

Material and Methods

Patient Population and Study Design

This prospective study was approved by our local institutional review board and written informed consent was obtained from all study participants.

Patients admitted at Sant'Andrea University Hospital, Rome, Italy, from March 19th, 2020 to May 24th, 2020, with the both following inclusion criteria of (a) selected patients with diagnosis of moderate to severe COVID-19 (22), confirmed by reverse transcription polymerase chain reaction (RT-PCR) who underwent Chest CT and (b) positive baseline Chest CT scans with diagnosis of interstitial pneumonia performed at admission, were prospectively enrolled for a six-month follow-up Chest-CT evaluation.

In order to define the severity of COVID-19 pneumonia, the WHO's interim guidance diagnostic criteria for adults with severe COVID-19 pneumonia were used (22).

Exclusion criteria were as follows: (a) patient death during follow-up interval; (b) refusal of the patient to undergo follow-up Chest CT; (c) severe motion artifacts at first Chest CT.

On the day of follow-up CT, all patients filled out a questionnaire about the long-lasting symptoms after COVID-19, the smoking habit; oxygen saturation was also measured and recorded for each patient.

Patients' demographic characteristics, clinical findings, laboratory results and eventual ventilation support and corticosteroid therapy during the hospitalization were also retrieved from the internal hospital records.

CT Acquisition Technique

All patients underwent six-month (± 14 days) follow-up unenhanced Chest CT scans. Chest CT acquisitions were obtained with the patients in supine position during end-inspiration without contrast medium injection. Chest CT was performed on a 128-slice CT (GE Revolution EVO CT Scanner, GE Medical Systems, Milwaukee, WI, USA). The following technical parameters were used: tube voltage: 120 kV; tube current modulation 100-250 mAs; spiral pitch factor: 0.98; collimation width: 0.625. Reconstructions were made with convolution kernel BONEPLUS at a slice thickness of 1.25mm.

Qualitative Analysis

DICOM data were transferred into a PACS workstation (Centricity Universal Viewer v.6.0, GE Medical Systems, Milwaukee, WI, USA). Two radiologists in consensus (AC and CDD, with 5 and 20 years in thoracic imaging experience respectively), qualitatively analyzed Chest CT images and evaluated the presence of motion artifacts. The following CT findings were recorded: (a) GGOs, (b) GGOs pattern, (c) GGOs location, (d) multilobe involvement, (e) total lobar involvement, (f) bilateral distribution, (g) location of consolidation or GGOs, (h) consolidation, (i) interlobular septal thickening, (j) fibrotic-like changes (reticular pattern and/or honeycombing) (23), (k) bronchiectasis, (l) air bronchogram, (m) bronchial wall thickening, (n) pulmonary nodules surrounded by GGOs, (o) halo sign or reversed halo sign, (p) pleural and (q) pericardial effusion, (r) lymphadenopathy (defined as lymph node with short axis > 10mm) (s) subsegmental vessel enlargement ($\geq 3\text{mm}$) and (t) pulmonary trunk diameter ($< 31\text{mm}$).

All mentioned Chest CT findings were defined as in the Fleischner Society glossary (24).

Lung Severity Score Analysis

The presence of GGOs, consolidation and fibrotic-like changes were semi-quantitatively analyzed in consensus by the same two radiologists above-mentioned, using the LSS ranging from 0 to 40 points, previously used in literature to quantify COVID-19 pneumonia lung impairment (25). Ten segments for each lung were considered; each segment was evaluated 0-2 points on the basis of the area involved, with score 0 for normal parenchyma, 1 for less than 50% segmental involvement and 2 for up to 50% segmental involvement. The final LSS was obtained from the sum of all lung's segments; furthermore, individual segmental scores were added together in total score to perform the statistical analysis.

Quantification Chest CT Analysis

Other two radiologists in consensus (GG and DC, with 3 and 7 years of experience in thoracic imaging respectively) performed QCCT analysis to quantify well-aerated lung by using a dedicated software (Thoracic VCAR v13.1, GE). Attenuation value < -1000 HU was used to exclude trachea air from the analysis, before segmentation. In order to select well-aerated lung for software segmentation, a range between -950 HU and -700 HU density, was selected (26-28). The software automatically calculated the healthy lung

expressed both in percentage and liters; in case of unsatisfactory or incorrect lung segmentation, the radiologists manually adjust the lung contours.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS Inc. Chicago, IL) and MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium). P values $<.05$ were considered statistically significant. All data are expressed as mean \pm Standard Deviation (SD). Categorical variables were described as counts and percentage; qualitative CT findings comparison was performed using the Chi-square test. The comparison between baseline and follow-up LSS and well-aerated lung QCCT analysis were tested with Student's *t* test in case of Gaussian distribution of data, otherwise while Wilcoxon test was applied.

Receiver operating characteristic (ROC) curves and Area under the curve (AUC) were calculated to test the performance of the baseline LSS and QCCT to predict fibrotic-like changes at six-month follow-up Chest CT.

Univariable and backward multivariable logistic regression analysis were used to test clinical and radiological features as predictor of fibrotic-like changes at six-month follow-up. At first, univariable analysis was individually performed on clinical variables: age, gender, comorbidities (dichotomizing with presence/absence), smoking habit (dichotomizing with present and former smoker grouped together and non-smokers), and baseline parameters as cough, dyspnea, fever, CRP, d-Dimer, LDH, lymphocytes, saturation, ventilation support; baseline radiological variables as LSS, pulmonary bilateral involvement, consolidations and well-aerated lung QCCT analysis (L and %). The multivariable analysis was performed on three different models: the clinical model included age, gender, comorbidities, smoking habit, cough, dyspnea, fever, CRP, d-Dimer, LDH, lymphocytes, saturation at admission and ventilation support; the radiological model contained LSS, pulmonary bilateral involvement, consolidations and well-aerated lung QCCT analysis (L and %); finally the combined model comprised all these parameters.

Results

Patient population, clinical data and laboratory findings

From an initial population of 288 patients, 98 (34%) died during the follow-up period, 45 (16%) refused the follow-up Chest CT since already performed elsewhere and 27 (9.4%) patients were excluded for the presence of severe motion artifacts on Chest CT at admission; thus, the final population comprised 118 patients, 56 male (48%), mean age 65 ± 12 years (range 37-84 years). The enrollment flowchart of the study is showed in **Figure 1**.

Twenty-four/118 (20%) patients had smoking habit, 27/118 (23%) had quit tobacco and 67/118 (57%) had never smoked. Twenty-four/118 patients (20%) had one underlying comorbidities, while 58/118 patients (49%) had two or more comorbidities; common comorbidities included hypertension (40/118 cases, 34%), cardiovascular diseases (18/118 cases, 15%) and diabetes mellitus (11/118 cases, 9%).

Ninety-one/118 patients (77%) reported persisting or new symptoms, including cough (22/91, 24%), dyspnea (38/91, 42%), fatigue (7/91, 8%), GI symptoms (15/91, 17%), hair loss (18/91, 20%), decline of visual acuity (11/91, 12%), olfactory and gustatory dysfunctions (13/91, 14% and 18/91, 20%, respectively); 27/118 patients (23%) were asymptomatic and mean oxygen saturation was $97\% \pm 1.97$.

Full data about patients' demographics, clinical records, laboratory findings and eventual ventilation support and corticosteroid therapy are reported in **Table 1**.

Qualitative Analysis

At six-month Chest CT follow-up, 33/118 (28%) presented with normal lungs. Eight-five/118 (72%) patients presented with fibrotic-like changes, 49/118 (42%) with GGOs, peripheral in distribution in 40/118 (34%) cases. Multilobe involvement (≥ 2 lobes) was observed in 45/118 (38%) patients and involvement of all lobes in 16/118 (14%) cases. Interstitial septal thickening was detected in 33/118 (28%) cases and consolidative opacities were observed in 2/118 patient (2%).

All Chest CT findings were reduced at follow-up Chest CT, except for the fibrotic-like changes which was the only feature showing a significant increase (all $p < .05$). Full results about the follow-up Chest CT findings and the comparison with baseline Chest CT findings are shown in **Table 2**.

Chest CT examples of baseline and six-month follow-up are shown in **Figures 2 and Figure 3**.

Lung Severity Score Analysis

At six-month follow-up total LSS was 4.37 ± 5.29 (range 0-20; LSS in right and left lung 2.15 ± 2.68 and 2.22 ± 2.79 respectively), showing a significant decrease compared with the total sum of baseline LSS 15.34 ± 8.32 (range 0-30; LSS in the right and left lung 7.58 ± 4.13 and 7.75 ± 4.71 respectively), (all $p < .001$). A per-segment analysis was also performed and fully reported in **Table 3**.

Quantitative Chest CT Analysis

Six-month follow-up QCCT analysis of well-aerated lung expressed in percentage and liters was $82\% \pm 12.27$ and $3.84 \text{ L} \pm 1.34$, respectively, showing significant differences compared to baseline ($69\% \pm 18.2$ and $2.99 \text{ L} \pm 1.5$, all $p < .001$). An example of baseline and follow-up comparison QCCT analysis is provided in **Figure 4**.

ROC curves and logistic regression

Baseline LSS showed an excellent performance in predicting fibrotic-like changes at six-month Chest CT follow-up with AUC of .91, 95%CI .8-.97, sensitivity of 88% and specificity of 80% when the LSS cutoff was >14 . Baseline QCCT of well-aerated lung, expressed both in liters and percentage, showed an AUC of .88 (95%CI .77-.96, sensitivity of 86%, specificity of 80%, cutoff of $\leq 3.75\text{L}$) and .88 (95%CI .76-.95, sensitivity of 74%, specificity of 100%, cutoff of $\leq 80\%$), respectively, as shown in **Figure 5**.

In the univariable analysis, age >65 (OR, 1.1; 95%CI, 1.03-1.17; $p = .004$) and baseline LSS (OR, 1.15; 95%CI, 1.05-1.25; $p = .003$) have proven to be significant positive independent variables for fibrotic-like changes at six-month follow-up Chest CT (all $p < .05$). On the other side, male gender (OR, .33; 95%CI, .02-1.14; $p = .002$), saturation=96-97 (OR, .13; 95%CI, .02-.95; $p = .04$), the absence of the need for ventilation (OR, .16; 95%CI, .04-.63; $p = .008$), bilateral lung involvement (OR, .28; 95%CI, .06-.92; $p = .04$), pulmonary consolidations (OR, .27; 95%CI, .08-.96; $p = .04$) and baseline QCCT well-aerated lung expressed in liters (OR, .4; 95%CI, .22-.71; $p = .002$) and in percentage (OR, .93; 95%CI, .88-.99; $p = .01$), showed significant inverse correlation for the presence of fibrotic-like changes at six-month follow-up Chest CT (all $p < .05$).

In the multivariable clinical model analysis, the best positive predictors of fibrotic-like changes at six-month follow-up Chest CT were age >65 years (OR, 1.12; 95%CI, 1.03-1.21; p=.007) and the need for mechanical ventilation (OR, 14.02; 95%CI, 1.07-185.55; p=.04). Otherwise, the radiological model showed an inverse correlation between quantified well-aerated lung and fibrotic-like changes (OR, .4; 95%CI, .22-.71; p=.002). Finally, the combined model showed that male gender (OR, .03; 95%CI, .001-.89; p=.04), cough (OR, .08; 95%CI, .01-.88; p=.04), lymphocytosis (OR, .08; 95%CI, .01-.86; p=.04) and QCCT well-aerated lung expressed in liters (OR, .05; 95%CI, .01-1.19; p=.03) were significant predictors of fibrotic-like changes at six-month follow-up with an inverse correlation. Univariable and multivariable logistic regression analysis full results are shown in **Table 4**.

Diagnostic performance of the three models is reported in **Figure 6**. AUC was .89 (95%CI .77-.96, sensitivity 82%, specificity 93%) for the clinical model, .81 for the radiological model (95%CI .68-.9, sensitivity 84%, specificity 67%) and .92 for the combined model (95%CI .81-.97, sensitivity 100%, specificity 73%). Even if the clinical model already performed well, combined model was analyzed too, in order to fully investigate possible stronger results with data derived from different fields of investigation.

Discussion

The results of our study showed that 72% of patients showed fibrotic-like changes at six-month follow-up Chest CT and baseline LSS (>14) was an excellent predictor of fibrotic-like changes (AUC .91). Furthermore, in the multivariable analysis, a model combining clinical and radiological findings reached an excellent diagnostic performance (AUC 0.92). In this model male gender, cough, lymphocytosis and QCCT well-aerated lung expressed in liters showed an inverse correlation with lung fibrotic-like changes.

Even if the clinical model already performed well (AUC .89), we decided to analyze also the combined model to fully investigate possible stronger results with data derived from different fields of investigation.

The percentage of late sequelae of our population at six-month follow-up Chest CT (72%) is in agreement with the study conducted by Zhao et al. (75%) who found that the most common feature at three-month follow-up was interstitial septal thickening (27 % vs our study 28%) (10). On the other hand, our results differ from those of Tabatabaei et al. who reported residual CT findings in 42% of patients examined at three-month follow-up; among them 55% presented residual GGOs (42%) (9). These different results may be related to the younger age of their population and the lower percentage of patients hospitalized in intensive care unit (ICU), compared to our older population with a higher rate of ventilation support needed during hospitalization. In fact, the older age increased the need for ventilation support and might be related with a more aggressive damage on lung parenchyma, with consequent higher percentage of late sequelae (29). Further studies of long-term effects in COVID-19 patients are mandatory to confirm this hypothesis.

A remarkable six-month follow-up study performed by Han et al. (17) showed approximately one-third (35%) of COVID-19 survivors with pulmonary fibrotic-like changes while 62% of patients presented GGOs. In our population, fibrotic-like changes do not arise de novo, but evolved from GGOs and/or consolidations. Discrepancies with our results might be related with demographics differences such as the prevalence of male and younger patients, even if demographic data on fibrosis development are still lacking and confirmation on Chest CT are needed on larger population sample. In addition, all non-fibrotic-like abnormalities have been reduced at six months, probably because almost all our patients have received steroid therapy during hospitalization.

As a novel disease, it is crucial to perform risk stratification of COVID-19 patients already at baseline stage, in order to identify who will be at high risk to develop residual disease hereafter.

In fact, recent studies have found that semiquantitative Chest CT score is a useful tool to stratify the severity of pneumonia and to predict clinical and radiological outcome in COVID-19 patients at short-term follow-up (9, 10, 30). Our baseline LSS showed an optimal performance in predicting residual findings at follow-up Chest CT (AUC .91); seventy-six patients (64.4%) presented a baseline LSS higher than 14. This result supports a similar analysis conducted at three-month follow-up by Tabatabaei et al. (9) and Zhao et al. (10) who demonstrated that patients with residual lung disease had significantly higher CT severity score compared to the group completely healed. Also the total Chest CT score performed by Han et al. (17) showed correlation in predicting pulmonary fibrotic-like changes at six-month follow-up Chest CT, despite some differences between the two lung score performed.

Likewise, baseline QCCT analysis of well-aerated lung demonstrated a good performance to predict residual findings at follow-up Chest CT, expressed in both liters (AUC .88) and percentage (AUC .88). Our results concerning the role of QCCT well-aerated lung support the previous study conducted by Colombi et al. (27) who showed that low rate of well-aerated lung was a predictor of ICU admission or death, and by Lanza et al. (31) who demonstrated that compromised lung volume was a predictor for oxygen support, need for intubation needed and patient death.

In line with the study conducted at short-term follow-up by Yu et al. (14), we found that older age is a potential predictor of six-month fibrotic-like changes. Moreover, we found that fibrotic-like changes at Chest CT follow-up were more frequent in women. In previous mid-term follow-up studies (9, 10) no significant correlation between gender and follow-up fibrotic-like changes were found (32).

Even if the clinical model already performed well (AUC .89), we decided to analyze also the combined model to fully investigate possible stronger results with data derived from different fields of investigation.

Despite the encouraging results, our study had some limitations. First, the relatively small sample size; second, the potential selection bias due to patients' refusal to undergo follow-up CT examinations at our Hospital since already performed in other centers; third, the inter- and intra-reader agreement was not performed.

In conclusion, at six-month follow-up, 72% of patients showed late sequelae, in particular fibrotic-like changes. Baseline LSS and QCCT of well-aerated lung showed an excellent performance in predicting fibrotic-like changes at six-month Chest CT (AUC > .88). Male gender, cough, lymphocytosis and QCCT well-aerated lung (liters) were significant predictors of fibrotic-like changes at six-month with an inverse correlation (AUC .92).

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Tables

Table 1: Patient Population, Clinical Data, and Laboratory Findings

Patients characteristics	Number of patients (n=118)		%	
	Mean age	65 ± 12		
Years (range)	37-84			
Male	56		48%	
Female	62		53%	
Smoking habit				
Smokers	24		20%	
Ex-smokers	27		23%	
Non-smokers	67		57%	
Comorbidities	82		70%	
Hypertension	40		34%	
Cardiovascular disease	18		15%	
DM	11		9.3%	
Others	13		11%	
Ventilatory treatment				
No	31		26%	
Yes	87		74%	
NIV	53		61%	
Mechanical IV	34		39%	
NIV duration (days)	2 ± 0.6			
IV duration (days)	11.3 ± 3.6			
Corticosteroid therapy				
No	7		5.1%	
Yes	111		95%	
Blood test data	Baseline		Follow-up	
	n=118	%	n=118	%
Lymphocytopenia (lymphocyte count <1.1×10 ⁹ /L)	65	55%	27	23%
CRP (increased >0.50 mg/dL)	102	86%	5	4.2%
LDH (increased >220 U/L)	94	80%	34	29%
D-dimer (increased >500 ng/mL)	31	26%	28	24%
Signs and symptoms	Baseline		Follow-up	
	n=118	%	n=118	%
Saturation (mean ± SD)	94.6 ± 2.95		96.9 ± 1.97	
Symptomatic	111	94%	91	77%
Dyspnea	49	42%	38	42%
Cough	51	43%	22	24%
Fever	89	75%	0	0%
GI symptoms	20	17%	15	17%
Fatigue	88	75%	7	8%
Olfactory dysfunction	68	58%	13	14%
Gustatory dysfunction	55	47%	18	20%
Hair loss	0	0%	18	20%
Decline of visual acuity	0	0%	11	12%
Asymptomatic	7	5.9%	27	23%

Abbreviations: DM, diabetes mellitus; GI, gastrointestinal; CRP, C-reactive protein; LDH, lactate dehydrogenase; NIV, non-invasive ventilation; IV, invasive ventilation.

Table 2: Comparison between Baseline and Follow-up Chest CT Findings in COVID-19 Patients

CT findings	Baseline n (%)	Six-month follow-up n (%)	p value
Ground Glass Opacity (GGOs)	102 (86%)	49 (42%)	<.001
Predominantly linear	54 (46%)	47 (40%)	.38
Round	24 (20%)	2 (1.7%)	<.001
Crazy paving	24 (20%)	0 (0%)	<.001
GGOs location (peripheral)	96 (81%)	40 (34%)	<.001
Multilobe involvement (≥2 lobes)	96 (81%)	45 (38%)	<.001
Total lobar involvement	80 (68%)	16 (14%)	<.001
Bilateral distribution	94 (80%)	33 (28%)	<.001
Posterior involvement	94 (80%)	16 (30%)	<.001
Consolidative opacities	80 (68%)	2 (1.7%)	<.001
Interlobular septal thickening	62 (53%)	33 (28%)	.007
Fibrotic-like changes	65 (55%)	85 (72%)	<.001
Bronchiectasis	40 (34%)	29 (25%)	.23
Air bronchogram	38 (32%)	0 (0%)	<.001
Bronchial wall thickening	36 (31%)	5 (4.2%)	<.001
Pulmonary nodules surrounded by GGOs	18 (15%)	0 (0%)	<.001
Halo sign	11 (9%)	0 (0%)	.002
Reversed halo sign	11 (9%)	0 (0%)	.08
Pericardial effusion	27 (23%)	16 (14%)	.13
Pleural effusion	20 (17%)	2 (2%)	<.001
Lymphadenopathy	31 (26%)	5 (4.2%)	<.001
Subsegmental vessel enlargement (≥3mm)	109 (92%)	82 (70%)	.07
Pulmonary trunk diameter (<31mm)	98 (83%)	98 (83%)	.99

Note: All significant p value are highlighted in bold

Abbreviations: GGOs, ground glass opacities

Table 3: Comparison between Baseline and Follow-up Lung Severity Score

LSS	Baseline (mean ± SD)	Follow-up (mean ± SD)	p value
Total Sum	15.3 ± 8.32	4.37 ± 5.29	<.001
Right Lung Sum	7.58 ± 4.13	2.15 ± 2.68	<.001
Left Lung Sum	7.75 ± 4.71	2.22 ± 2.79	<.001
Right lung segments	Baseline LSS (mean ± SD)	Follow-up LSS (mean ± SD)	p value
Anterior	.73 ± .52	.15 ± .36	<.001
Apical	.6 ± .49	.18 ± .39	<.001
Posterior	.9 ± .63	.16 ± .37	<.001
Medial	.56 ± .6	.18 ± .39	.001
Lateral	.71 ± .6	.22 ± .42	<.001
Superior	.88 ± .64	.22 ± .42	<.001
Anterior Basal	0.54 ± .53	.11 ± .32	<.001
Medial Basal	0.62 ± .59	.24 ± .43	<.001
Lateral Basal	0.88 ± .61	.24 ± .43	<.001
Posterior Basal	1.11 ± .64	.39 ± .53	<.001
Left lung segments	Baseline (mean ± SD)	Follow-up (mean ± SD)	p value
Anterior	.75 ± .58	.13 ± .34	<.001
Apical	.56 ± .5	.22 ± .42	<.001
Posterior	.96 ± .67	.15 ± .36	<.001
Superior Lingular	.84 ± .63	.18 ± .39	<.001
Inferior Lingular	.73 ± .59	.34 ± .47	<.001
Superior	.84 ± .72	.2 ± .41	<.001
Anterior Basal	.67 ± .64	.17 ± .38	<.001
Medial Basal	.6 ± .56	.24 ± .43	.001
Lateral Basal	.79 ± .63	.26 ± .44	<.001
Posterior Basal	.96 ± .58	.3 ± .5	<.001

Note: Mean ± standard deviation (SD) of the sum of all single segmental scores (0-2)

Abbreviations: LSS, lung severity score; SD, Standard Deviation

Table 4: Univariable and Multivariable Logistic Regression Analysis: The Relationship between Clinical and Radiological Variables in 118 Patients with Moderate to Severe COVID-19 at Six-month Follow-up CT

Variable	Univariable analysis		Clinical model		Radiological model		Combined model	
	OR(95%CI)	p value	OR(95%CI)	p value	OR(95%CI)	p value	OR(95%CI)	p value
Age	1.1(1.03-1.17)	.004	1.12(1.03-1.21)	.007	-	-	-	-
Gender (=0)	.33(.92-1.14)	.002	-	-	-	-	.03(.001-.89)	.04
Comorbidities	-	-	-	-	-	-	-	-
Smoke*	-	-	-	-	-	-	-	-
Cough (=1)	-	-	-	-	-	-	.08(.01-.88)	.04
Dyspnea	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-
CRP	1.11(.99-1.25)	.067	-	-	-	-	-	-
d-Dimer	-	-	-	-	-	-	-	-
LDH	1.01(.99-1.01)	.072	-	-	-	-	-	-
Lymphocytes	-	-	-	-	-	-	.08(.01-.86)	.04
Saturation (=96)	.13(.02-.95)	.04	-	-	-	-	-	-
Saturation (=97)	.13(.02-.94)	.04	-	-	-	-	-	-
Ventilation (=1)	.16(.04-.63)	.008	-	-	-	-	-	-
Ventilation (=3)	-	-	14.09(1.07-185.55)	.04	-	-	-	-
NIV duration (days)	-	-	-	-	-	-	-	-
IV duration (days)	-	-	-	-	-	-	-	-
LSS	1.15(1.05-1.25)	.003	-	-	-	-	-	-
Bilateral involvement	.23(.06-.92)	.03	-	-	-	-	-	-
Consolidation	.27(.08-.96)	.04	-	-	-	-	-	-
Well-aerated lung (L)	.4(.22-.71)	.002	-	-	.4(.22-.71)	.002	.44(.01-1.19)	.03
Well-aerated lung (%)	.93(.88-.99)	.01	-	-	-	-	-	-

Note: all significant p value are highlighted in bold. *present and former smoker were grouped together. Cox-Snell R² =.45 for combined model.

Gender=0, men; Cough=1, present; Ventilation=1, non-ventilation needed; Ventilation=3, invasive mechanical ventilation.

Abbreviations: Co, coefficient; OR, odds ratio; CI, confidence interval CRP, C-reactive protein; LDH, lactate dehydrogenase; LSS, lung severity score; L, liter; NIV, non-invasive ventilation; IV, invasive ventilation.

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Figures:

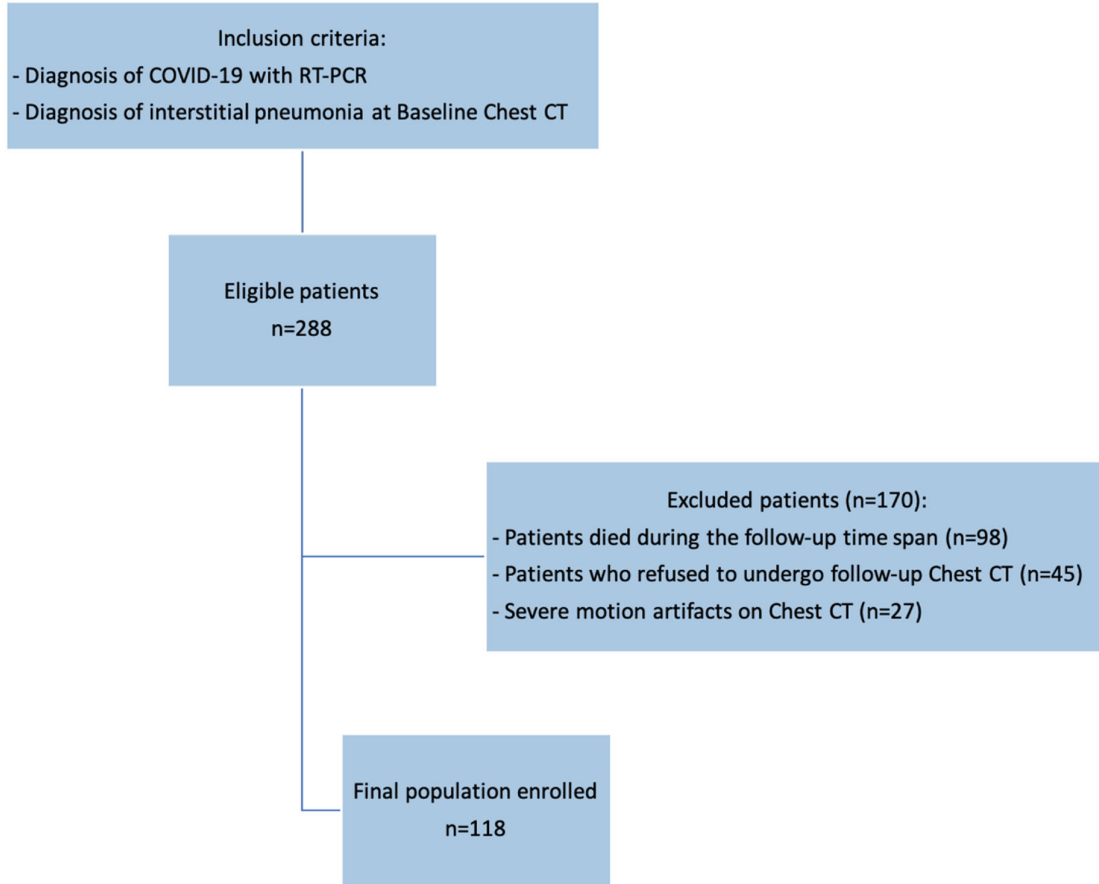


Figure 1. Enrollment flow-chart of the study. From an initial cohort of 288 Patients, 118 patients with both baseline and six-month follow-up Chest CT were enrolled.

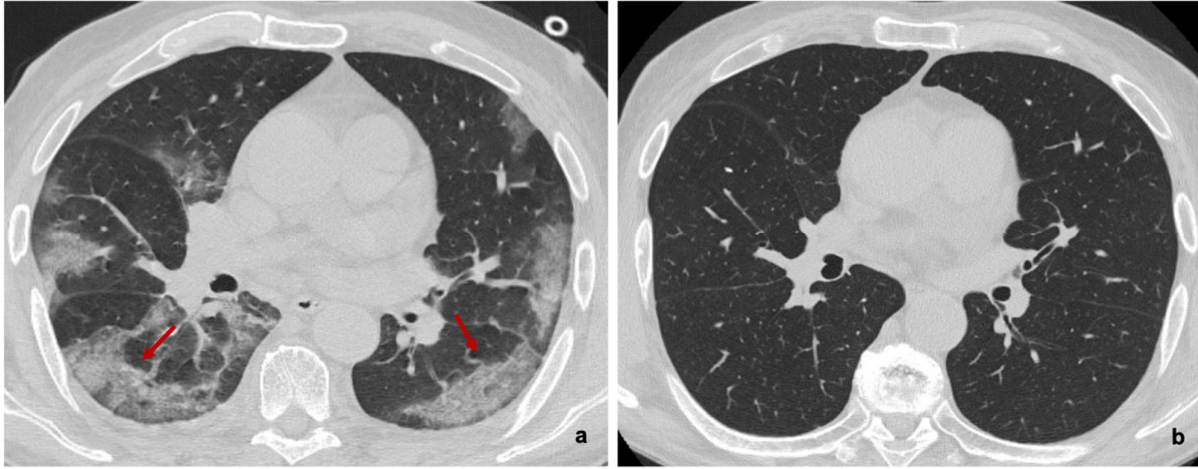


Figure 2. (a) Baseline and **(b)** six-month follow-up axial thin-section unenhanced Chest CT scans of 83-year-old man, former smokers, who presented fever, cough and worsening dyspnea; COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing. **(a)** Baseline scan shows multiple bilateral and confluent ground-glass opacities with predominantly linear pattern and peripheral distribution (red arrows). **(b)** Six-month follow-up scan shows complete resolution of ground-glass opacities without fibrotic-like changes.

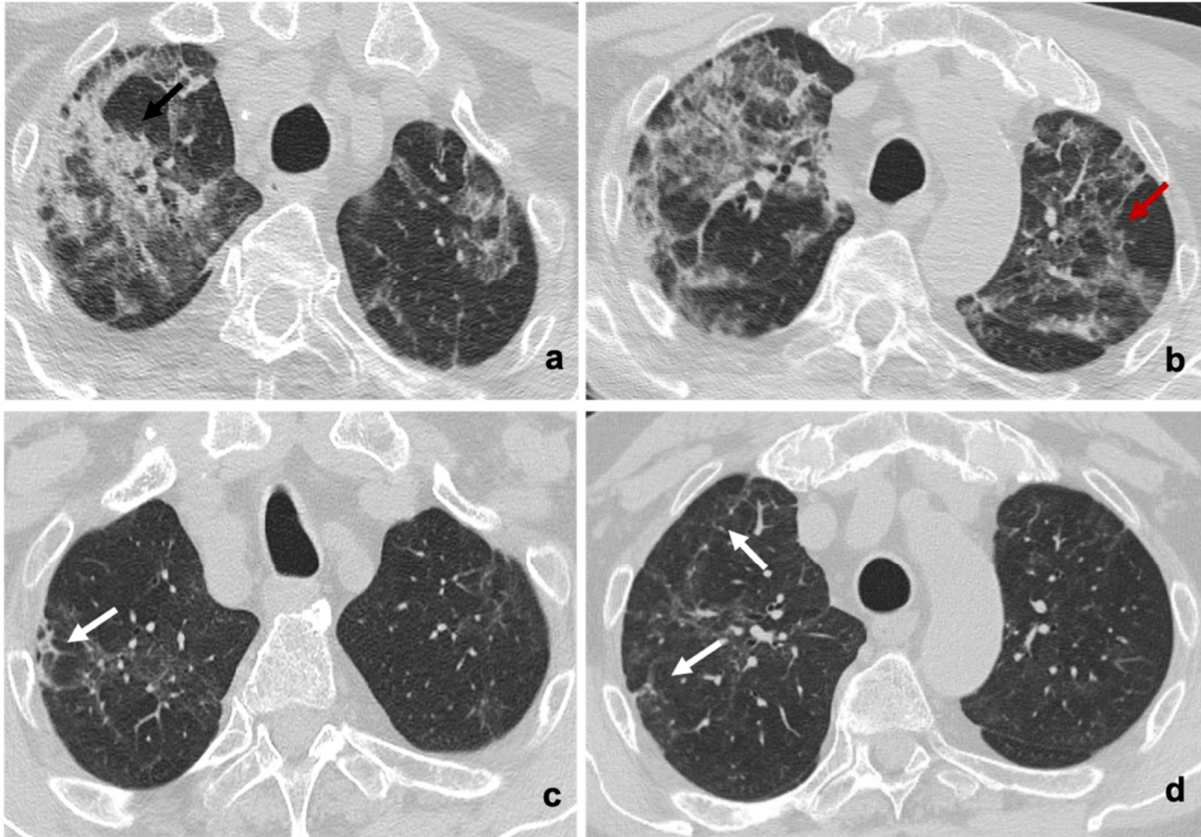


Figure 3. (a,b) Baseline and (c,d) six-month follow-up axial thin-section unenhanced Chest CT scans of 84-year-old man, smoker, admitted to the Emergency Department presenting fever and cough; COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing. (a,b) Images show bilateral consolidative pulmonary opacities (black arrow) with diffuse ground-glass opacities and interstitial septal thickening (red arrow). (c,d) Six-month follow-up scans show residual ground-glass opacities with decreased density compared to baseline, interstitial septal thickening and peripheral fibrotic-like changes (white arrows).

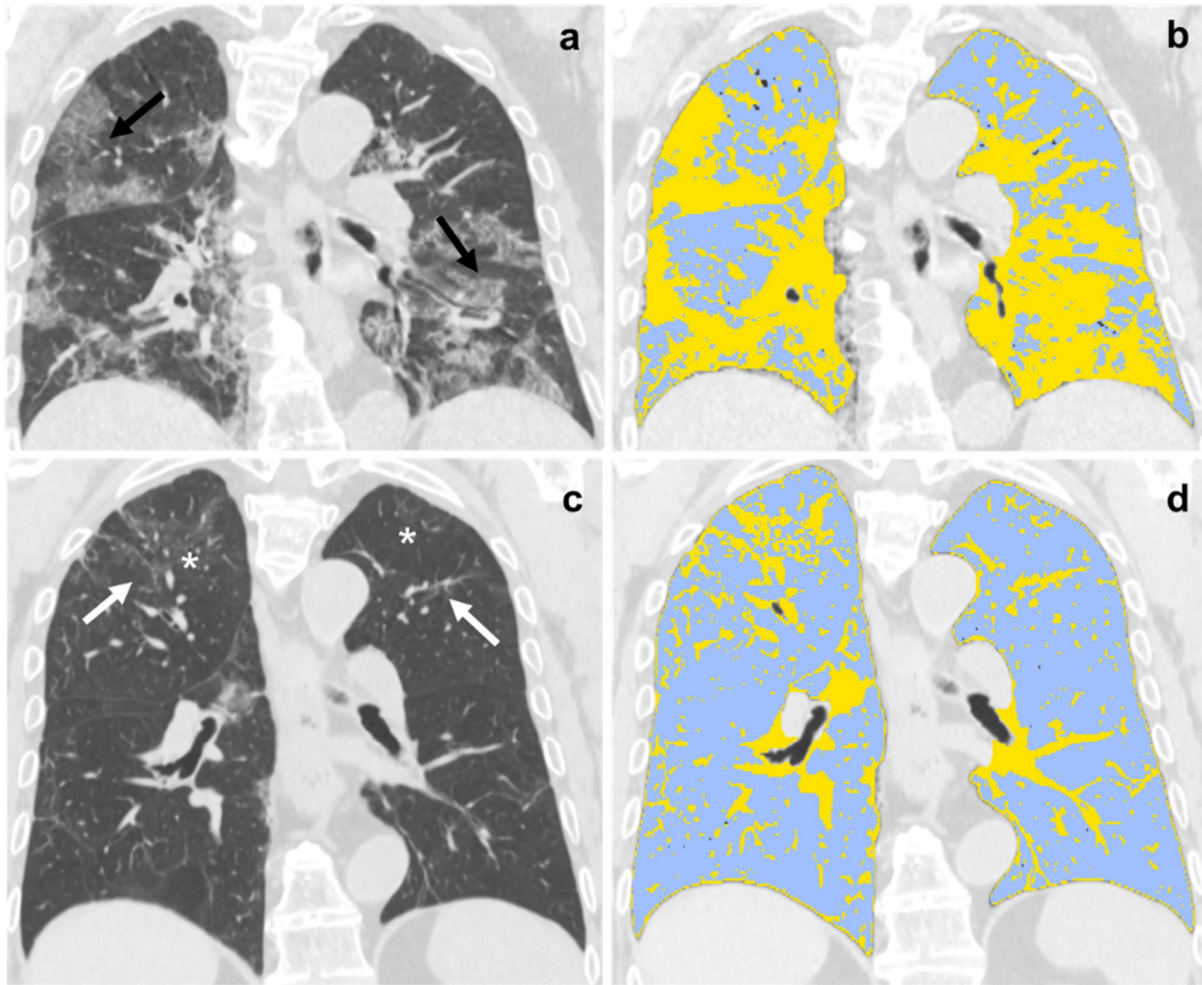


Figure 4. (a,b) Baseline and (c,d) six-month follow-up coronal thin-section unenhanced Chest CT scans of 79-year-old man, admitted to the Emergency Department presenting fever, dyspnea and cough; COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing. (a) Chest CT scan shows bilateral ground-glass opacities tending to consolidation (black arrow). (b) The same scan after Quantitative Chest CT Analysis highlighted in light-blue well-aerated lung (1.5 liters, 50%) and in yellow pulmonary injury of COVID-19 pneumonia. (c) Six-month follow-up scan shows residual fibrotic-like changes (white arrows) and persisting of low-density ground glass (asterisks). (d) The same scan after Quantitative Chest CT Analysis highlighted in light-blue well-aerated lung (3.5 liters, 82%) and in yellow residual findings of COVID-19 pneumonia at six months follow-up.

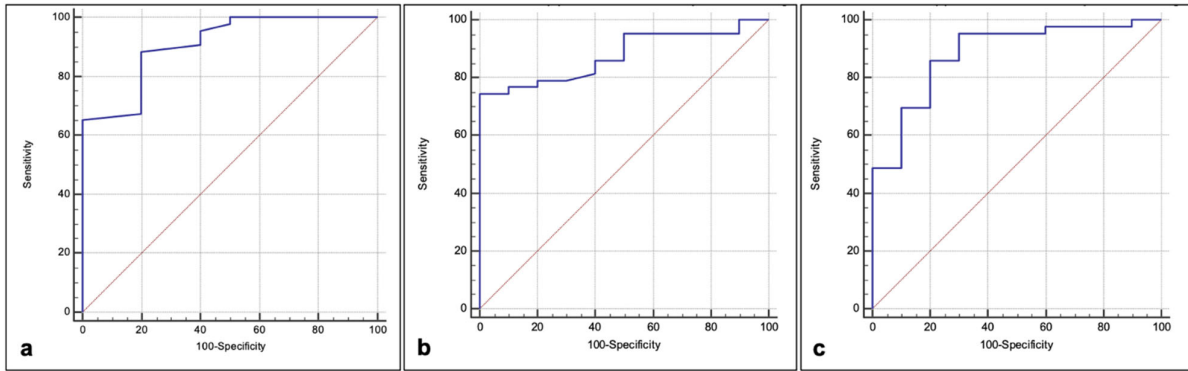


Figure 5. (a) Receiver operating characteristic (ROC) curves tested the performance of baseline lung severity score to predict fibrotic-like changes at six-month follow-up Chest CT, showing an area under the curve (AUC) of .91, 95%CI .8-.97, sensitivity of 88% and specificity of 80% when the cut-off was >14. **(b,c)** ROC curves tested the performance of baseline quantitative Chest CT (QCCT) analysis of well-aerated lung, expressed in percentage **(b)** and Liters **(c)** to predict fibrotic-like changes at six-month follow-up Chest CT: **(b)** with the cut-off of $\leq 3.8L$ an AUC of .88, 95%CI .77-.96, a sensitivity of 86% and a specificity of 80% was found, **(c)** the cut-off of $\leq 80\%$ showed an AUC of .88, 95%CI .76-.95, 74% of sensitivity and 100% of specificity.

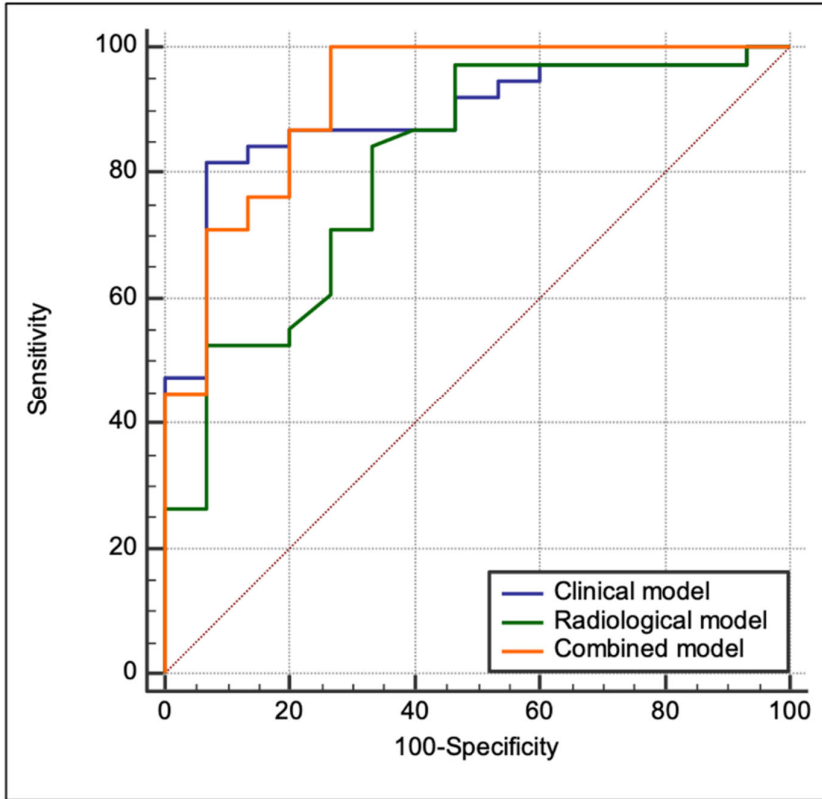


Figure 6. Receiver operating characteristic (ROC) curves tested the performance of clinical (blue line), radiological (green line) and combined model (orange line) in predicting the presence of fibrotic-like changes at six-month follow-up Chest CT. The AUC for the clinical model was .89 (95%CI .77-.96, sensitivity: 82%, specificity: 93%), .81 for radiological model (95%CI .68-.9, sensitivity: 84%, specificity: 67%), and .92 for combined model (95%CI .81-.97, sensitivity: 100%, specificity: 73%).