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Gour Prajwaleet P
MD, Government Medical College and Hospital, Nagpur, Maharashtra, India

Tiwari Shreeya A
MBBS, MD (Ongoing), Government Medical College and Hospital, Nagpur, Maharashtra, India

Rajdeo Ravi
DMRD, DNB, Government Medical College and Hospital, Nagpur, Maharashtra, India

Corresponding Author:
Gour Prajwaleet P
MD, Government Medical College and Hospital, Nagpur, Maharashtra, India

Can chest CT severity scoring in covid-19 act as proxy to clinical classification of disease

Gour Prajwaleet P, Tiwari Shreeya A and Rajdeo Ravi

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Abstract

Purpose: To evaluate chest CT pattern in COVID-19 patients and highlight prognostic utility of CT severity score (CTSS) in grading SARS-CoV-2 disease.

Materials and Methods: From May 15th to August 30th2020, retrospective analysis of RT-PCR confirmed 130 COVID-19 patients was done at a tertiary care center in Central India. From the cohort comprising of 81 males and 49 females, 76.92%, 15.38% and 7.69% had clinically mild, moderate and severe disease respectively. CT SS was calculated based on the extent of lobar involvement (0:0%; 1:< 5%; 2:5–25%; 3:26–50%; 4:51–75%; 5:>75%; range 0–5; total score 0–25) and was compared with clinical disease severity using bivariate and agreement analyses. ROC curve was used to evaluate the role of CTSS as a predictor of patients' disease severity.

Results: 59 (45.38%) patients were clinically asymptomatic and 38 (29.23%) patients had no parenchymal abnormality. In the radiologically positive group, 77 (83.69%) patients showed typical CT characteristics. Ground-glass opacification was the main CT pattern seen in 71 (77.17%) patients. Parenchymal changes were commonly observed bilaterally (76.08%) involving posterior more than anterior segments (46.73%) with apicobasilar gradient (lower lobes more than upper lobes). CTSS<8, 8-16 and >16 corresponded to mild, moderate and severe disease respectively. The optimal CTSS threshold for identifying moderate-to-severe patients was 8 (area under the ROC curve 0.8718, $p<0.001$).

Conclusion: Ground-glass opacity is the most common imaging pattern of involvement in COVID-19 pneumonia with predominant bilateral, peripheral, posterior and lower lobar distribution. CTSS can be used as an adjunct to clinical classification to foretell SARS-CoV-2 disease severity.

Keywords: CTSS, COVID-19, GRADING

Introduction

Coronaviruses are a large family of viruses that can cause illness in animals or humans. Respiratory infections in humans ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) have been attributed to several coronaviruses. The most recently discovered coronavirus causes coronavirus disease COVID-19 [1].

The outbreak of COVID-19can be traced to a seafood market in Wuhan city in Hubei Province of China in mid-December, 2019 [2]. WHO (under International Health Regulations) declared this outbreak as a "Public Health Emergency of International Concern" (PHEIC) on 30thJanuary 2020. WHO subsequently declared COVID-19 a pandemic on 11th March, 2020 [3]. India's first case of COVID-19 was reported on 30th January, 2020 in the state of Kerala; the index case was a student who had returned from Wuhan [4]. There has been rampant spread of COVID-19 in India owing to its population, population density and socio-demographic structure. According to Ministry of Health and Family welfare, Government of India, as on September 27, 2020, a total of 9,56,402 active cases have been recorded from 35 states and union territories with total cured or discharged cases being 49,41,627 and deaths tolling to 94,503 [5].

The public health goals have largely shifted from prevention and containment to mitigation of the disease impact. Rapid diagnosis and triage of patients is vital in this regard. Radiological examinations are indispensable component for the early detection, categorization and management of COVID-19. Computed tomography (CT) is the most sensitive radiological technique for the diagnosis of COVID-19.

However it has limited specificity for distinguishing between virus [6, 7]. Early diagnosis is hence mainly performed with nasopharyngeal swabs and virus RNA extraction with real-time reverse transcriptase–polymerase chain reaction (RT-PCR).CT shows diffuse lung alterations ranging from ground-glass opacities to parenchymal consolidations; several radiological patterns are observed at different times throughout the disease course [8, 9].
The purpose of the present study was to identify the lung parenchymal alterations seen in COVID-19 by means of CT examination. The study also aims to evaluate a semi-quantitative CT based approach for grading of severity in COVID-19 which can in turn fasten the patient triage and aid in quicker implementation of precise management strategies.

Methods

This study was approved by the ethics committee of the institution and the requirement for informed consent was waived since the study had no risk and would not adversely affect the subjects' rights or welfare.

Case Selection

We performed a retrospective, single tertiary care center secondary data analysis on a convenience sample of 130 SARS-CoV-2 laboratory confirmed cases between May 15th to August 30th,2020.A confirmed case was defined as a person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms [10]. Laboratory confirmation was done by real time RT-PCR test on oropharyngeal and nasopharyngeal swabs. Patient selection for this study was consecutive, and patients with negative RTPCR test, lung cancer and tuberculosis were excluded from the study.

Clinical Classification

According to "Clinical Management Protocol: Covid-19" given by MoHFW, Government of India, patients were divided into 3 categories based on clinical presentation and parameters- *Mild* disease included patients with uncomplicated upper respiratory tract infection without evidence of breathlessness or hypoxia (normal saturation); *Moderate* disease included pneumonia with no signs of severe disease (presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 90-94%); and *Severe* disease included severe pneumonia (clinical signs of pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 < 90%) and patients clinically classified as having adult respiratory distress syndrome (ARDS) or respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF) [10].

CT Image Acquisition

Chest CT imaging was performed on a 128 slice SIEMENS CT scanner. All patients were examined in supine position. CT images were acquired during a single inspiratory breath-hold. The scanning range was from the apex of lung to costophrenic angle. CT scan parameters: X-ray tube parameters - 140KVp, 234mAs; rotation time - 0.5 second; pitch - 1.0; section thickness - 5 mm; intersection space - 5 mm; additional reconstruction with B80f ultra sharp kernel and a slice thickness of 1 mm. Lung window setting was with a window level of − 600 Hounsfield units (HU) and window width of 1500 HU. Implementation of appropriate infection prevention and control measures were arranged in all cases, consisting of prompt sanitation of CT facility and patient's isolation.

Image Analysis

All the CT images were blinded for clinical data and independently read by one in-training resident and reevaluated by a radiologist with more than 10 years of experience in CT imaging. The following characteristics were considered for the image analysis: (1) density: presence of ground-glass opacities, consolidation, mixed ground-glass opacities and consolidation or crazy paving pattern; (2) others- subpleural atelectasis, pleural effusion, pulmonary nodules and lymphadenopathy (defined as lymph node size of ≥ 10 mm in short-axis dimension); (3) number of lobes affected by ground-glass or consolidative opacities; (4) distribution: peripheral, central or both; (5) lung area involved- anterior, posterior or both(by drawing a vertical line through the midpoint of the diaphragm in the sagittal reconstruction). Ground-glass opacification was defined as hazy increased lung attenuation with preservation of bronchial and vascular margins and consolidation was defined as opacification with obscuration of margins of vessels and airway walls. Crazy paving pattern was described thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacity [11].
According to the consensus statement endorsed by the Society of Thoracic Radiology and the American College of Radiology (ACR), the CT appearance of COVID-19 was further classified into four categories for standardized reporting language - typical, indeterminate, atypical and negative for pneumonia [12].

Quantitative Ct Evaluation Scoring

A semi-quantitative CT severity scoring based on models proposed by Francone M. *et al* &Li K. *et al* [13, 14] was calculated for all patients per each of the 5 lobes considering the extent of anatomic involvement, as follows: 0, no involvement; 1, < 5% involvement; 2, 5–25% involvement; 3, 26–50% involvement; 4, 51–75% involvement; and 5, > 75% involvement. On summing up the acute lung inflammatory lesions involving each lobe the total severity score was tabulated (0 to 25). The resulting global CT score was the sum of each individual lobar score and (0 to 25). When present, other features such as subpleural atelectasis, pleural effusion, nodules and lymphadenopathy were also described [Figure 1-4].

Statistics

Data analysis

Data was coded and analyzed in statistical software, STATA (version 10.2, 2011) and Open Epi (version 3.03, 2013).
Descriptive statistics were used to summarize results for categorical variables by means of frequencies and percentages.
Best cut-off for CTSS was established from ROC (Receiver Operating Characteristic) curve, and AUC (Area Under Curve) was obtained that represents predictive accuracy of the suggested cut-off in discriminating patients by their severity status. Validity measures like Sensitivity, Specificity, PPV, NPC and Diagnostic accuracy were estimated along with 95% Confidence Intervals. Agreement statistic Cohen's kappa (K) was also calculated to find

concordance between CTSS and the reference (gold standard) criteria. Significance of kappa was tested with Z test. A P-value < 0.05 was set for confirming statistical significance.

Results

Clinico-Epidemiological Findings

From May 15th to August 30th, 2020, cohort of 130 patients (81 males and 49 females; sex ratio of female to male 0.60) with a positive RT-PCR test for SARS-CoV-2 underwent HRCT chest examination in our study. 74 (56.92%), 42 (32.3%) and 14 (10.7%) HRCT chest scans were done on day 1 to day 6, day 7 to day 12 and beyond 12 days of clinical illness respectively [Figure 5]. Majority of patients were in their third to fourth decade (mean age 44±1.3 and age range 14 - 75 years).

Of the total enrolled patients, 59 (45.38%) were asymptomatic. Amongst the 71 (54.62%) symptomatic patients, the most common manifestations were fever (38.46%), dyspnea (23.07%) and cough (22.48%). 30 (23.07%) patients had coexisting comorbidities, the most common being hypertension seen in 27 (20.93%) patients followed by diabetes mellitus seen in 17 (13.18%) patients. Based on MoHFW Clinical Management protocol for SARS-CoV2 infection, 100 (76.92%), 20 (15.38%) and 10 (7.69%) patients were classified as having mild, moderate and severe disease respectively.

Demographic and clinical characteristics of the population are summarized Table 1.

CT Findings

In our cohort, 92 (70.76%) CT scans showed lung parenchymal changes and 38 (29.23%) had no such alterations. The CT appearance was classified as *typical* in 77 (59.23%) patients, *indeterminant* in 9 (6.92%) patients and *atypical* in 6 (4.61%) patients as per the guidelines by Society of Thoracic Radiology and the American College of Radiology [12].

The characteristic imaging features of SARS CoV-2 pneumonia on chest CT are tabulated in Table 2. The most common CT pattern of disease observed was GGO seen in (n=71; 54.61%), followed by crazy-paving pattern (n = 32; 24 .61%) and mixed GGO with parenchymal consolidation (n = 16; 12.30%). Other related CT features were found as follows: subpleural atelectasis (n=39; 30.0%), pleural effusion (n = 5; 3.8%), nodules (n=8; 6.1%), lymphadenopathy (n = 5; 3.8%) and miscellaneous (n=9; 6.92%).

In the radiologically positive group, 70 patients (76.08%) showed bilateral lung involvement with 57 (61.95%) patients having changes in more than 2 lobes. Right lower lobe was most frequently involved lobe (n= 74; 80.43%) followed by left lower lobe (n=69; 75%). The distribution of opacities was both peripheral and central in 42 patients (42.85%), purely peripheral in 39 patients (42.39%) and central in 3 patients (3.26%). Posterior lung segments were predominantly involved in our study in total 43 patients (43.67%). Attributes for geographical distribution of opacities are described in Table 3.

Data on CTSS revealed a trend towards lower CTSS values with 90.2% of cases in our cohort having CTSS less than 10. Mean CTSS values for all lung lobes are shown in Figure 6.

ROC curve for CTSS

The ROC curve analysis for CTSS is shown in Figure 7 with its validity measures depicted in Table 4. The area under ROC curve for discriminating patients in mild and moderate-to-severe group was 0.8718 (standard error, 0.03; 95% CI 0.800-0.943; Cohen’s kappa 0.57) and the optimal CT-SS threshold for identifying moderate-to-severe patients was 8, with 89.9% specificity and 67.74% sensitivity. The number of patients with CTSS equal to or greater than 8 was 20 in the moderate-to-severe group and 10 in the mild, while the number of patients with CTSS less than 8 was 10 and 90, respectively, resulting in a positive predictive value (PPV) of 67.74% and a negative predictive value (NPV) of 89.9% for detecting moderate-to-severe disease. We constructed another ROC using information extracted by altering the clinical groups- mild-to-moderate versus severe disease. The CTSS threshold for identifying severe cases was 16, with 99.16% specificity but mere 40.0% sensitivity [Figure 9].

On further statistical evaluation and diagonal correlation we devised CTSS score cut-offs to predict clinical severity where CTSS upto 8 corresponded to mild disease, CTSS 8 to 16 corresponded to moderate disease and CTSS beyond 16 represented severe disease (agreement 80.62%; Cohen’s kappa 0.4936; standard error 0.0714; p=0.001)

Discussion

Radiological evaluation of patients is indispensable part of COVID-19 workup. Chest radiography and CT are widely utilized as imaging tools for detecting COVID 19 infection and pave a path for aftermath of clinical management strategies- from triage to therapy. CT has a higher sensitivity in detecting typical features of SARS-CoV-2 pneumonia and has thus become the forefront modality for disease evaluation [15, 16].

Clinico-epidemiological characteristics in our cohort revealed that almost half of the cases had asymptomatic disease. Similar findings were seen in other studies conducted on Indian population including those done by Mohan A. *et al* and Gupta N. *et al* [17, 18].

The most striking CT feature of COVID-19 is the presence of patchy, rounded ground glass opacities which has been paralleled by studies done by Zhan Ji *et al* and Li Y *et al* [19, 20]. The *typical* pattern of parenchymal involvement by opacities in bilateral and posterior predominant fashion in our study is in concordance with previous reports published by Chung M *et al* [21]. The presence of uncommon features like pleural effusion and lymphadenopathy could be attributed to simultaneous presence of other comorbidities rather than COVID infection. The highlight of this study was the translation of clinical severity into reproducible imaging based grading using CTSS with ROC analysis to validate the objectivity of CT severity scoring [22].

Our study has several limitations- Firstly, at the onset of pandemic all RTPCR positive patients were admitted in our setup regardless of their clinical severity and there was limited literature available for directing imaging aid in these patients. This has a direct impact on the number of scans negative for imaging evidence of SARS-CoV2 pneumonia. Secondly, we chose to analyze the first chest CT obtained on admission; therefore, the studies were not controlled by the number of days since the start of symptoms, which could have implications for interpretation of the CTSS. Thirdly, follow-up CT scans were not obtained patients and thus the full range of disease appearance could not be represented. Lastly, amount of lung opacification due to infection did not

have any histopathological backing for confirmation.
Future research directed towards studies with larger cohorts at multiple centers is needed to determine the validity of CTSS and the proposed threshold before clinical transmutation of its objectivity.
In conclusion, HRCT chest in COVID era should be regarded as a wholesome tool for screening, diagnosis as well as grading of the disease to ensure extensive extraction of its prognostic utility. Our study provides an elementary semi-quantitative method for assessing severity of COVID-19 in the initial chest CT alongwith CTSS based grading system that parallels clinical disease division. The optimal CTSS threshold for indicating moderate-to-severe disease is 8. A CTSS score of less than 16 can rule out severe or critical forms of disease. CTSS could be potentially used not only to expedite triage of patients in need of hospital admission but also to alter the treatment strategies based on imaging evidence. We envisage that such clinico-radiological correlation will go a long way in prompting correct management in scenarios of overwhelming patient volumes with limited PCR testing capabilities and healthcare resources.

Table 1: Demographic and clinical characteristics of cohort.

Characteristic	SARS-CoV-2+ patients (n=130)
Sex	
Male	81 (62.31%)
Female	49 (37.69%)
Age Range	
0-20	3 (2.31%)
21-40	59 (45.39%)
41-60	45 (34.61%)
61-80	23 (17.70%)
>80	0 (0%)
Asymptomatic	59 (45.38%)
Symptomatic	71 (54.62%)
Symptoms	
Fever	50 (38.46%)
Cough	29 (22.48%)
Dyspnoea	30 (23.07%)
Sore throat	15 (11.63%)
Other	13 (10.00%)
Comorbidities	
Hypertension	27 (20.93%)
Diabetes Mellitus	17 (13.18%)
COPD	1 (0.78%)
Other	15 (11.54%)

Table 2: Imaging characteristics of SARS CoV 2 pneumonia on Chest CT.

CT features	No. of patients	% of patients (n=130)	% of radiologically positive patients (n=92)
Main pattern			
Groundglass opacity	71	54.61	77.17
Groundglass + consolidation	16	12.30	17.39
Crazy paving	32	24.61	34.78
Other features			
Subpleural atelectasis	39	30.00	42.39
Pleural effusion	5	3.84	5.43
Nodules	8	6.15	8.69
Lymphadenopathy	5	3.84	5.43
Other	9	6.92	9.78
CT chest characteristic			
Typical	77	59.23	83.69
Indeterminant	9	6.92	9.78
Atypical	6	4.61	6.52
Absent	38	29.23	-

Table 3: Geographical distribution of CT changes and CT Severity Scores in SARS-CoV-2+ patients

Categories	No. of patients	% of patients (n=130)	% of radiologically positive patients (n=92)
Frequency of lung involvement			
Unilateral	22	16.92	23.91
Bilateral	70	53.84	76.08
No of lobes affected			
0	38	29.23	-
1	15	11.53	16.30
2	18	13.84	19.56
3	7	5.38	7.60
4	9	6.92	9.78
5	41	31.53	41.30
>2	57	43.84	61.95
Frequency of lobe involvement			
Right upper lobe	60	46.15	65.21
Right middle lobe	52	40.00	56.52
Right lower lobe	74	56.92	80.43
Left upper lobe	64	49.23	69.56
Left lower lobe	69	53.07	75.00
Distribution			
Peripheral	39	30.00	42.39
Central	3	2.30	3.26
Both	42	32.30	42.85

Lung area			
Anterior	2	1.53	2.17
Posterior	43	33.07	46.73
Both	39	30.00	42.39
CT severity score			
0	39	30.00	-
1-5	51	39.23	55.43
6-10	27	20.76	29.34
11-15	8	6.15	8.69
15-20	4	3.07	4.34
21-25	1	0.76	1.08

Table 4: Validity measures for proposed criteria (CTSS Total score >8) as compared to the gold standard (i.e. Clinical severity)

Parameter	Estimate	Lower - Upper 95% CIs	Method
Sensitivity	67.74%	(50.14, 81.43)	Wilson Score
Specificity	89.9%	(82.4, 94.42)	Wilson Score
Positive Predictive Value	67.74%	(50.14, 81.43)	Wilson Score
Negative Predictive Value	89.9%	(82.4, 94.42)	Wilson Score
Diagnostic Accuracy	84.62%	(77.43, 89.81)	Wilson Score
Likelihood ratio of a Positive Test	6.706	(5.273 - 8.529)	
Likelihood ratio of a Negative Test	0.3588	(0.2942 - 0.4376)	
Diagnostic Odds	18.69	(6.895 - 50.66)	
Cohen's kappa (Unweighted)	0.5764	(0.4045 - 0.7483)	

** p<0.001*

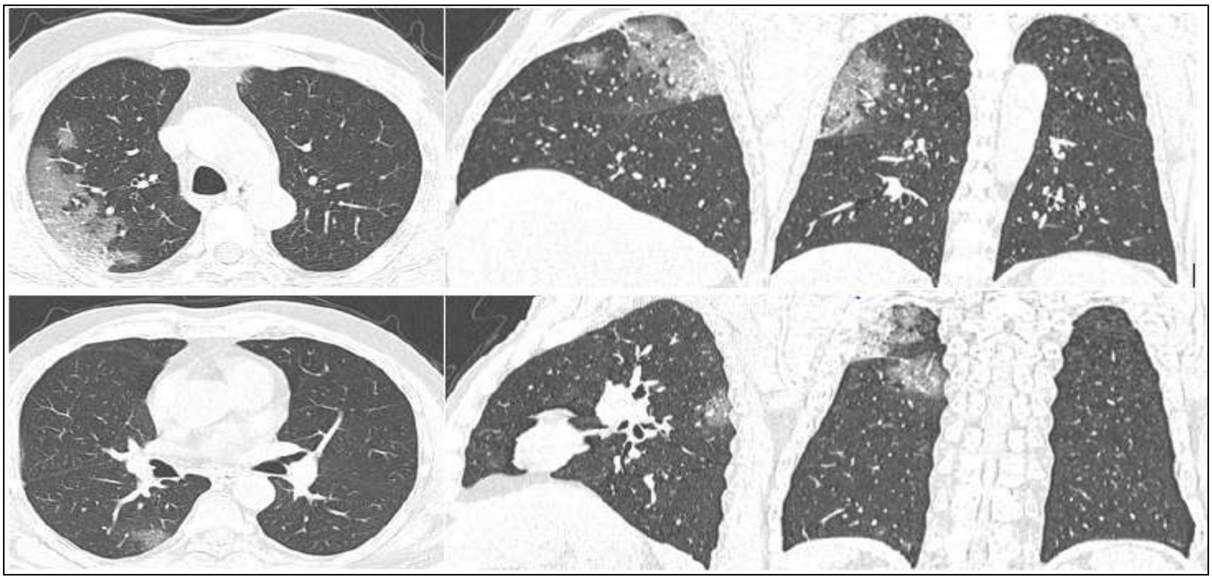

Fig 1: HRCT thorax (A) axial, (B) sagittal and (C) coronal sections of a 55 year male with mild COVID-19 pneumonia show peripheral GGOs in right upper with 5-25% lung parenchymal involvement corresponding to CT score 2. (D) axial, (E) sagittal and (F) coronal sections through right lower lobe of the same patient showed similar GGOs involving <5% of the lobe corresponding to CT score 1. Total CTSS in this case was 3/25.

Fig 2: HRCT thorax (A) axial, (B) sagittal and (C) coronal sections of a 35 year male with mild to moderate COVID-19 pneumonia show GGOs involving 25-50% of the left upper lobe corresponding to CT score 3. Few linear subpleural atelectatic bands also seen in left upper lobe. Similar GGOs were seen in rest of the lung fields with total CTSS 7/25.

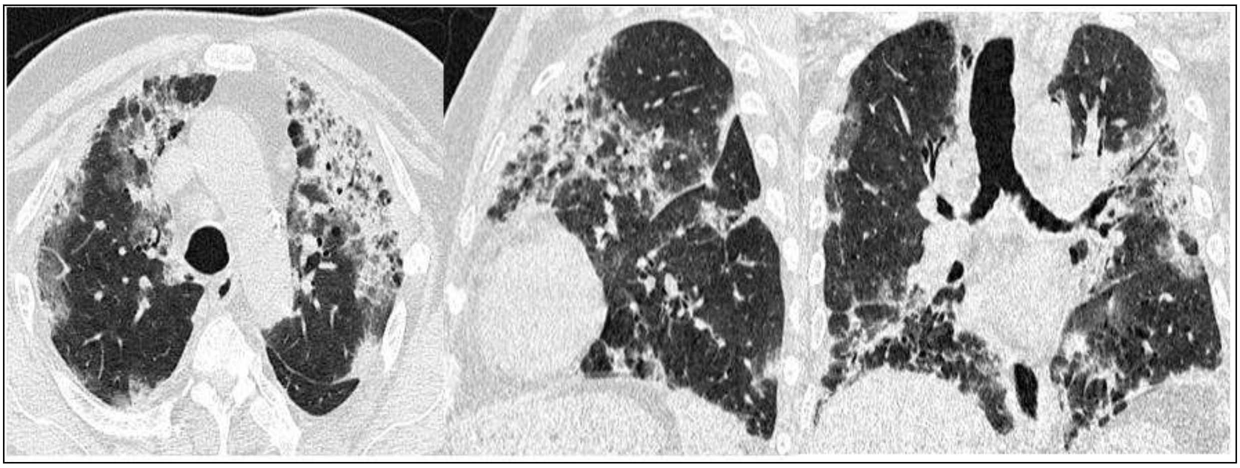

Fig 3: HRCT thorax (A) axial, (B) sagittal and (C) coronal sections of a 72 year male with moderate COVID-19 pneumonia mixed GGO and consolidation pattern in bilateral lungs with prominent inter and intralobar septal thickening and bronchiectasis. Note 50-75% involvement of left upper lobe corresponding to CT score 4. Total CTSS in this case was 14/25.

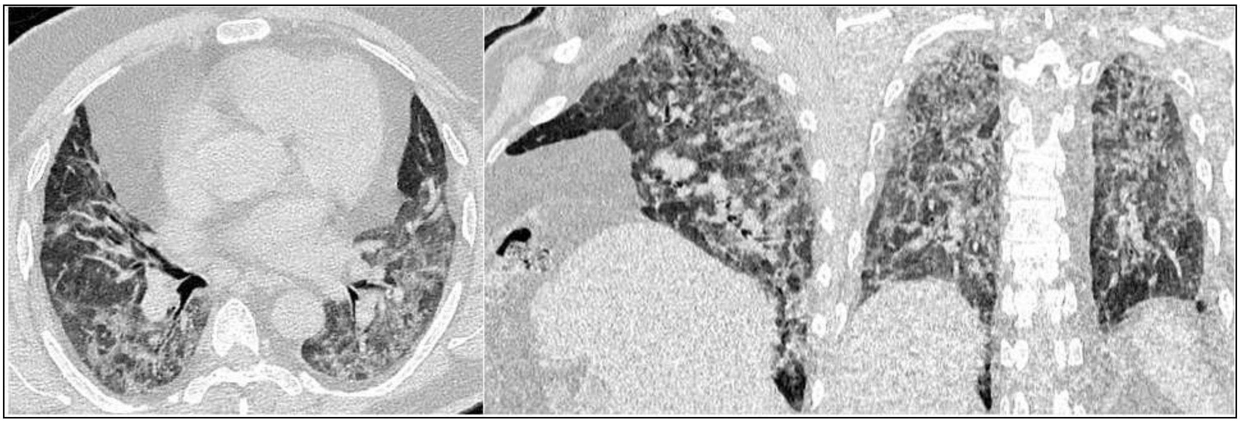

Fig 4: HRCT thorax (A) axial, (B) sagittal and (C) coronal sections of a 67 year male with severe COVID-19 pneumonia show coarse GGOs with inter and intralobular septal thickening in bilateral lung parenchyma. Note more than 75 % involvement of bilateral lower and left upper lobe corresponding to CT score 5 for these lobes. Total CTSS in this case was 22/25**.**

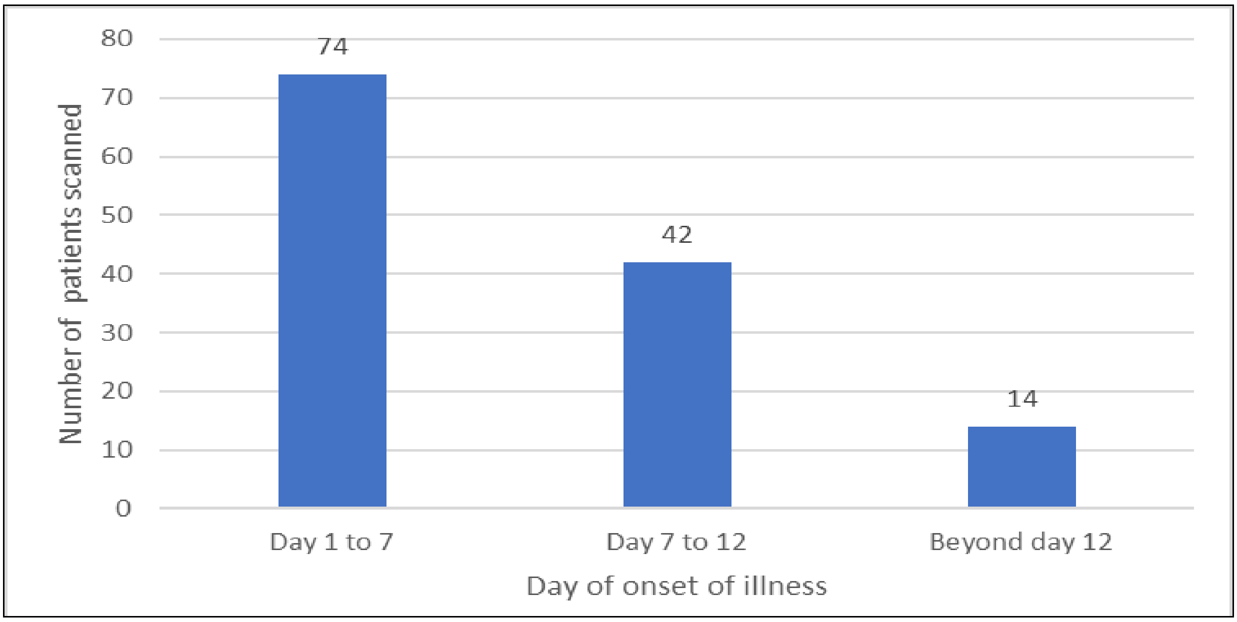

Fig 5: Time distribution of chest HRCT scans based on day of onset of clinical illness.

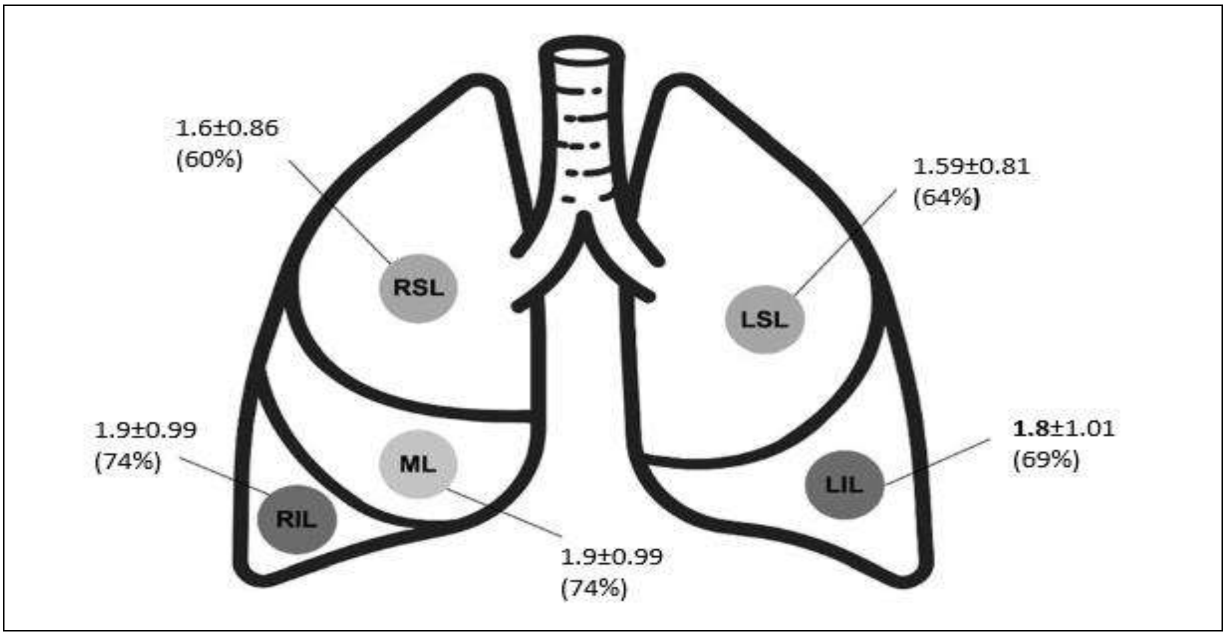

Fig 6: Mean lobar CT severity scores for different lung lobes.

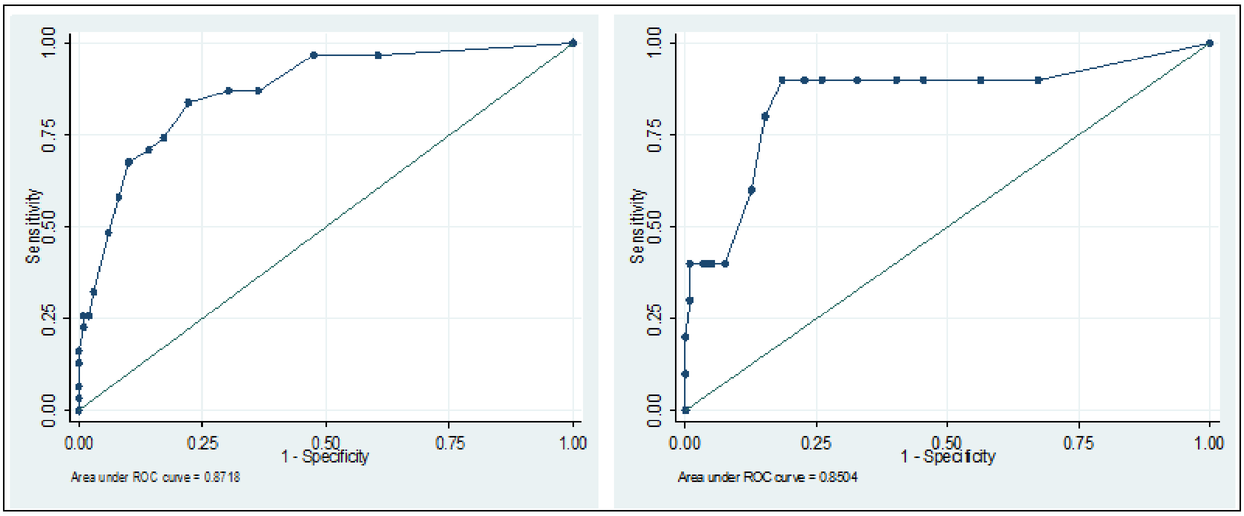

Fig 7: ROC curve analysis for CTSS in (A) mild versus moderate-to-severe group with CTSS cut-off value 8 and (B) mild-to-moderate versus severe group with CTSS cut-off 16.

CTSS	DISEASE CATEGORY
UPTO 8	MILD
8-16	MODERATE
>16	SEVERE

Fig 8: Correlation between CTSS and clinical disease severity

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