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Chest CT severity score to forecast clinical requirement of oxygen support in Covid-19 patients

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Abstract
Objectives: All over the world, attempts are made at the early prediction of disease severity of ongoing COVID-19 pandemic and catching early those patients who are likely to develop severe disease and may undergo cytokine storm. Though clinical and laboratory parameters are mainstay in diagnosing severe disease and oxygen requirements, high resolution computed tomographic (HRCT) scanning of the chest is one such promising tool to help identify such a subset of patients very early in the course of COVID-19 disease. The purpose of this research is to find an answer to a question can chest CT severity score (CTSS) on HRCT thorax scan forecast clinical requirements of oxygen support in covid-19 patients?
Methods: During the period from May 2020 to October 15, 2020, 250 patients with confirmed RT-PCR diagnosis of COVID-19 on first or repeat sample and who also underwent HRCT scan of the chest, were retrospectively assigned chest CT severity score (CTSS). Patients were categorized into mild and severe score groups and from data obtained, analysis of how many patients from both groups progress to require oxygen support and intubation?
Results: Out of a total of 250 patients, 175 patients were males and 75 patients were females. The average CT severity score (CTSS) was 19.5. 150 patients belong to mild CTSS group while 100 to severe CTSS group. Overall 180 patients required oxygen support, 100 belong to severe CTSS group while 80 belong to mild CTSS group. In mild CTSS group, 80 patients required low-flow oxygen. In severe CTSS group, 5 patients required low-flow oxygen, 75 required high-flow oxygen and 20 patients needed intubation. 8 out of 20 intubated patients succumbed to death. Overall 28 mortalities were reported of which 22 belong to severe CTSS group. With the Receiver operator characteristics (ROC) analysis, we found the cut off of CTS score. At the score of greater than 13 showed the significant effect on oxygen support with area under curve (AUC) 0.996 (95% CI 0.98 to 1; *P* <0.0001) with 94.4% sensitivity and 100% specificity. We found one another cut off of CTS score (>26) with in-hospital mortality. The Area under curve (AUC) 0.78 (95% CI 0.73 to 0.83; *P* <0.0001) with 70% sensitivity and 81.4% specificity. Intubation, oxygen requirement and mortality are the strongest predictors of CT score. (Regression coefficients 12.65(95% CI 10.05-15.24; *P* <0.0001, 11.04(95% CI 9.5-12.58; *P* <0.0001) and 4.1(95% CI 1.93-6.27; *P* <0.0001 consecutively).
Conclusion: CTSS may be used as a new decisive tool in triaging in-hospital COVID-19 patients. Currently, clinical and laboratory blood parameters guide the requirements of oxygen support in managing severe COVID-19 pneumonia. In the setting of patients overload, there may be delay in prompt clinical judgment and appropriate therapy may be initiated late and hence the poor outcome. Categorizing patients in mild and severe CTSS early in the disease course, even before the marked worsening of clinical parameters may save energy, health resources, help to triage severe patients, and above all may save many lives.

Keywords: COVID-19, high resolution computed tomographic scan, Oxygen support, intubation

Introduction
The novel coronavirus SARS-CoV-2 has spread rapidly across the globe and caused on-going corona-virus disease 2019 (COVID-19) pandemic. The first pneumonia cases were identified in Wuhan, the capital city of Hubei province (China), in December 2019 [1]. As of October 25, 2020, 42,548,289 cases and 1,150,144 deaths have been reported across the globe, and India is one of the worst-hit countries currently [2].
The clinical presentation is variable, ranging from asymptomatic, mild upper respiratory tract

infection (URTI) to severe pneumonia which may progress to acute respiratory distress syndrome (ARDS) with respiratory failure requiring oxygenation support or intubation [3, 4].

Though reverse transcriptase-polymerase chain reaction (RT-PCR) is the confirmatory method for diagnosis, in highly suspected patients with a negative result of RT-PCR, a high resolution computed tomography (HRCT) scan of the chest is the modality of choice [5, 6]. HRCT is a very sensitive radiological modality, playing a vital role in the diagnosis of lung involvement in COVID-19 and monitoring changes during treatment. Radiological patterns of lung involvement on HRCT varies widely in the disease course [7, 8]. Though CT, being limited by specificity (inability to differentiate different viruses), confirmation of diagnosis necessitates nasopharyngeal swabs and virus RNA extraction by RT-PCR [9, 10].

Research is still ongoing to assess the clinical and prognostic implications of various CT scoring systems for lung involvement on CT [11]. Visual assessment or artificial intelligence (AI) based quantitative analysis of the CT exam can be used for this purpose.

Oxygen support is the mainstay of managing severe COVID-19 pneumonia. Among the various drugs tested till now, an increasing number of studies across the world is reporting the role of tocilizumab, a recombinant monoclonal antibody to IL-6 (Interleukin-6) receptor, in treating COVID-19 patients or at risk of developing cytokine storm. [12, 15]. Many of them have shown promising results in proving that treatment with tocilizumab, might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia [16]. Remdesivir, a broad-spectrum antiviral medication has also shown promising but variable results in various studies.

The purpose of this research is to find an answer to a question can chest CT severity score (CTSS) forecast the clinical requirement of oxygen support in COVID-19 patients? Thus able to triage the high-risk patients early in the course of the disease even before laboratory and clinical parameters start to worsen.

Methods

Data collection

We analyzed hospital medical records of those hospitalized patients with confirmed RT-PCR diagnosis of COVID-19 on first or repeat samples. We set cut off of data duration from May 2020 to October 15, 2020. We found 250 patients with severe pneumonia clinically who also underwent an HRCT scan of the chest. Severe pneumonia was considered as at least one of the following: the presence of a respiratory rate of 30 or more breaths per minute, peripheral blood oxygen saturation (SpO2) of less than 93% in room air and a ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) of less than 300 mm Hg in room air according to Chinese management guidelines for COVID-19 (version 6.0) [3, 17].

All CT examinations were performed in the second week from symptoms onset, ranging from day 8 to day 10. We also collected patients' demographics and laboratory findings. Those patients with high CTSS but death before the oxygen support initiation were excluded.

Chest CT analysis and scoring system

All patients underwent a high-resolution non-contrast chest CT with a multidetector 128 slice SOMATOM Definition AS+ (Siemens Healthcare, Germany) CT scanner. The parameters were set at 120 kVp; 100– 200 mAs; pitch, 1-1.2; and collimation, 128 × 0.6. The slice thickness of 1 mm was used after a sharp reconstruction algorithm. All images were viewed with both lung (width, 1200 HU; level, −600 HU) and mediastinal (width, 350 HU; level, 50 HU) settings.

Various CT scoring systems are available for severity scoring of COVID-19 pneumonia depending on the varying degrees of lobar or segmental volume involvements. The lobar scoring system assessed the five lung lobes according to the percentage of the involvement and classified as none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%), with the corresponded score as 0, 1, 2, 3, or 4. The total score is the sum of the five lobe scores (range from 0 to 20) [18]. The segmental scoring system divided the anatomical 18 segments of both lungs into 20 regions, in which the apico-posterior segment of the left upper lobe was subdivided into apical and posterior segmental regions, while the anteromedial basal segment of the left lower lobe was subdivided into anterior and basal segmental regions [19]. Only the ground glass or consolidative lung opacities were considered for evaluation of the 20 lung regions while fibrotic or atelectatic bands were excluded. Scores of 0, 1, and 2 were assigned if parenchymal opacification involved 0%, less than 50%, or equal or more than 50% of each region. The CTSS was defined as the sum of the individual scored in the 20 lung segment regions, which may range from 0 to 40 points. The individual scores in each lung, as well as the total CTSS were higher in severe COVID-19 when compared with mild cases ($P < 0.05$). The optimal CTSS threshold for identifying severe COVID-19 was 19.5 (area under the curve, 0.892), with 83.3% sensitivity and 94% specificity in the study by R Yang *et al.* [19].

With the consensus of two experienced (more than 10 years) radiologists, the segmental scoring system was chosen over the lobar system due to simplicity, less subjectivity, and more reliable reproducibility by visual quantitative evaluation. All the CT images were independently reviewed by both of them, being blinded to the demographics, clinical data, and laboratory indicators. For the ease of interpretation a cut off of 20 was finalized (instead of 19.5 in the study by R Yang *et al.*), a score of < 20 being considered as mild and score >/= 20 being considered as severe. The final score considered was the average of the scores given by two independent radiologists. The scoring performa used is as shown in Table-1.

The decision of giving oxygen support was based on the standard protocol decided by the team of pulmonologists and intensive care specialists of the institute. Patients were considered eligible if they showed SpO_2 of less than 93% and a PaO_2/FiO_2 ratio of less than 300 mm Hg in room air or a more than 30% decrease in their PaO_2/FiO_2 ratio in the previous 24 h during hospitalization. The patients who were given oxygen support were further categorized into low-flow oxygenation (nasal cannula, face mask), high-flow oxygenation (Venturi mask, helmet CPAP) and mechanical ventilation through an endotracheal tube. Outcome in form of discharge or death were also noted.

Statistical analysis

All statistical analysis was performed using SPSS v 24.0

(Chicago, IL, USA). Continuous variables were compared using the unpaired student's t-test or one-way analysis of variance. Continuous variables were summarized as mean ± standard deviation (SD) whereas categorical variables were expressed as percentage of the sample. Multivariate analysis was done for oxygen requirement, intubation and death outcomes. Receiver operator characteristics (ROC) analysis was performed to determine a cut point for CTS score that provides an approximately equivalent sensitivity and specificity for predicting in oxygen support and in-hospital mortality. Group differences associated with a p value ≤0.05 were considered statistically significant.

Table 1: Chest CT severity score

		0/1/2
Right Upper Lobe	Apical segment	
	Anterior segment	
	Posterior segment	
Right Middle Lobe	Medial segment	
	Lateral segment	
Right Lower Lobe	Superior segment	
	Anterior basal segment	
	Medial basal segment	
	Lateral basal segment	
	Posterior basal segment	
Left Upper Lobe	Apical segment	
	Anterior segment	
	Posterior segment	
Left lingular segment	Superior segment	
	Inferior segment	
Left Lower Lobe	Superior segment	
	Anterior basal segment	
	Medial basal segment	
	Lateral basal segment	
	Posterior basal segment	
	Total Score	
0	No involvement	
1	< 50% segment involvement	
2	> 50% segment involvement	
Mild	< 20	
Severe	>/= 20	

Minimum score = 0, Maximum score = 40

Results

Results: Out of a total of 250 patients, 175 patients were males and 75 patients were females. The average CT severity score (CTSS) was 19.5. 150 patients belong to mild CTSS group while 100 to severe CTSS group. Overall 180 patients required oxygen support, 100 belong to severe CTSS group while 80 belong to mild CTSS group. In mild CTSS group, 80 patients required low-flow oxygen. In severe CTSS group, 5 patients required low-flow oxygen, 75 required high-flow oxygen and 20 patients needed intubation. 8 out of 20 intubated patients succumbed to death. Overall 28 mortalities were reported of which 22 belong to severe CTSS group. Multivariate analyses of risk factors for oxygen support, intubation and in-hospital death were also noted (Tables-2-7).

With the Receiver operator characteristics (ROC) analysis, we found the cut off of CTS score. At the score of greater than 13 showed the significant effect on oxygen support with area under curve (AUC) 0.996 (95% CI 0.98 to 1; *P* <0.0001) with 94.4% sensitivity and 100% specificity shown in figure 1. We found one another cut off of CTS score (>26) with in-hospital mortality shown in figure 2. The Area under curve (AUC) 0.78 (95% CI 0.73 to 0.83; *P* <0.0001) with 70% sensitivity and 81.4% specificity. Intubation, oxygen requirement and mortality are the strongest predictors of CT score. (Regression coefficients 12.65(95% CI 10.05-15.24; *P* <0.0001, 11.04(95% CI 9.5-12.58; *P* <0.0001) and 4.1(95% CI 1.93-6.27; *P* <0.0001 consecutively).

Table 2: Gender, age, and CTSS parameters

Variables		Mild CTSS group N=150/250 (60%)	Severe CTSS group N=100/250 (40%)	Total N=250
Gender	M	105(70%)	70(70%)	175(70%)
	F	45(30%)	30(30%)	75(30%)
Age (Average)		54.27±14.23 Y	60.83±11.79 Y	56.89±13.67 Y
CTSS (Average)		13.34±3.8	28.93±5.23	19.58±8.84

Table 3: Oxygen support with outcome and PaO_2/FiO_2 analysis

	No O_2 support	Low-flow O_2	High-flow O_2	Intubation	Overall
Patients	70 (28%)	85 (34%)	75 (30%)	20 (8%)	180 (72%)
Death rate	2 (2.9%)	6 (7.1%)	14 (18.7%)	8 (40%)	28 (15.6)
Discharge/Healing rate	68 (97.1%)	79 (92.9%)	61 (81.3%)	12 (60%)	152 (84.4%)
PaO_2/FiO_2 Range	0	257.99±30.39 208.50-310	188.21±37.28 119.5-301	138.75±29.33 95-203	215.67±54.1 95-310

Table-4: Oxygen support and CTSS parameters

	No O_2 support	Low-flow O_2	High-flow O_2	Intubation	Overall
Patients	70 (28%)	85 (34%)	75 (30%)	20 (8%)	180 (72%)
Mild CTSS group	70 (100%)	80 (94.1%)	0	0	80 (44.4%)
Severe CTSS group	0	5 (5.9%)	75 (100)	20 (100%)	100 (55.6%)

Table 5: Oxygen support and CTSS range

	No O_2 support	Low-flow O_2	High-flow O_2	Intubation	Overall
Patients	70 (28%)	85 (34%)	75 (30%)	20 (8%)	180 (72%)
CTSS </= 10	25 (100%)	0	0	0	0
CTSS > 10 but </= 20	45 (36%)	80 (64%)	0	0	80 (44.4%)
CTSS > 20 but </= 30	0	3 (5.6%)	51 (94.4%)	0	54 (30%)
CTSS > 30 but </= 40	0	2 (4.3%)	24 (52.2%)	20 (43.5%)	46 (25.6%)

Table 6: Oxygen support and inflammatory blood parameters

	No O_2 support	Low-flow O_2	High-flow O_2	Intubation	Overall
Patients	70 (28%)	85 (34%)	75 (30%)	20 (8%)	180 (72%)
CRP (mg/L)+/- SD Range	17.85±4.42	25.46±24.69	41.39±43.19	144.91±79.64	45.37±55.07
	7-32.92	7-143.97	12.19-276.65	76.21-320	7-320
Ferritin (ng/ml)+/- SD Range	91.62±46.61	206.63±225.05	770.56±1250.93	1349±383.36	587.32±609.49
	20-200	12.4-1280	156.87-10000	754-1854	12.4-1994
LDH (U/L)+/- SD Range	187.59±29.57	218.14±61.19	333.16±112.89	435.1±75.89	290.17±114.98
	140-248	144-528	185-551	327-549	114-551
D-Dimer (ng/ml)+/- SD Range	355.47±94.99	389.02±186.62	770.56±1250.93	1021.88±2128.16	618.31±1094.02
	204.1-700.60	193.6-1542.31	156.87-10000	233.87±10000	156.87-10000
IL-6 (pg/ml)+/- SD Range	187.59±29.57	31.95±51.18	127.07±129.64	268.64±110.02	97.88±123.05
	140-248	5-280	7-430	106-436	5-436

Table 7: Multivariate analyses of risk factors for oxygenation support, intubation and in-hospital death

Variable	**Oxygen support**				**Intubation**				**Death**			
	OR	95% CI		P Value	OR	95% CI		P Value	OR	95% CI		P Value
Age	1.88	0.95	3.7	0.07	1.03	0.93	1.15	0.58	1.06	1.009	1.11	0.02
Sex	0.54	0.27	1.09	0.08	1.05	0.11	9.64	0.97	0.68	0.19	2.41	0.55
CRP	0.98	0.898	1.06	0.56	1.01	0.998	1.03	0.09	1.02	1.01	1.03	0.001
D-Dimer	1.001	0.998	1.004	0.49	1	1.0	1.002	0.82	1.001	1	1.002	0.12
LDH	1.02	1.005	1.03	0.005	1.007	0.99	1.02	0.35	1.01	1.003	1.02	0.006
Ferritin	1.02	1.01	1.03	<0.0001	1.001	0.998	1.003	0.53	1.002	1	1.003	0.03
IL-6	1.06	0.99	1.14	0.08	1.004	0.995	1.01	0.36	1.001	0.996	1.007	0.67
CTSS	2.87	1.56	5.28	0.001	2.89	1.32	6.3	0.008	1.19	1.06	1.34	0.004

Discussion

The speed with which the pandemic is spreading across the globe has created panic in the health care system. Flooding of the hospitals, scarcity of ICU beds, ample need for oxygen units, and ventilators are major concerns especially in developing overpopulated countries like India. Thus, triaging is the key to better patient management and outcome.

Chest radiographs, though being a low-cost tool, are limited by low sensitivity in early diagnosis of suspected COVID-19 patients [20, 22]. A High-resolution CT scan of the chest has high sensitivity in the early diagnosis of lung involvements in COVID-19 patients [23-25, Figure-3]. Various scoring systems have emerged and visual as well as many artificial intelligence (AI) based automated volume quantification tools are now available.

The typical imaging manifestations of early COVID-19 are patchy, rounded, peripheral segmental, or subsegmental ground-glass opacities, with or without consolidation [22, Figure 4-5]. Based on typical CT findings proposed in various studies, Yuan *et al.* have proposed a scoring method to screen patients based on the admittance CT scan [11]. More recently, Li *et al.* also described a visual, quantitative analysis of lung damage, based on a "total severity score" to the degrees of parenchymal loss, correlated with a score of clinical severity [26]. Yang R *et al.* in their study devised a semi-quantitative scoring method using the amount of lung opacification involving 20 lung regions as a surrogate for COVID-19 burden [19]. We found that the CTSS was higher in severe when compared to mild cases and the same were the results of their study. High CTSS corresponds to poorly aerated compromised lung areas and hence the severe disease. The segmental scoring system was chosen over the lobar system due to simplicity, less subjectivity, and more reliable reproducibility by visual quantitative evaluation. We strongly believe that this relatively undemanding method could help early triaging and reliably predict the future possibility of developing severe pneumonia, ARDS/cytokine storm and hence the need for oxygen requirement/mechanical ventilation. Artificial intelligence (AI) based automated volume quantification tools are limited in availability, costly and many of them are yet evolving in ensuring consistency.

Currently, clinical and laboratory blood parameters guide the management of patients with severe COVID-19 pneumonia. We found a significant high risk of developing acute respiratory distress syndrome (ARDS) and cytokine storm in patients with high CTSS [Figure 6-7]. By categorizing patients based on mild and severe CTSS, the requirement of oxygen support can be reliably predicted. Lanza *et al.* have studied a similar concept and showed that quantitative chest CT analysis in COVID-19 predicts the need for future oxygenation support and intubation [27]. D Colombi *et al.* also researched on the similar concept to predict adverse outcome [28].

We identified that the severe CTSS correlates with the compromised lung volume and hence serves as a predictor of pulmonary dysfunction as measured by the PaO2/FiO2 ratio, oxygenation support, invasive ventilation and also represented a risk factor for in-hospital mortality. Lanza *et al.*, [27] have made similar observations. Colombi *et al.* [28] have used a similar approach to predict the outcomes of COVID-19. They analyzed volume of well aerated lung and reported good performance of the well-aerated volume (%WAL, − 950, − 700 HU) in predicting the combined outcome of ICU admission and death. Regardless of the quantitative analysis method, it serves as the ideal tool that could be able to predict which patient will need a ventilator soon or who no longer requires one.

The strengths of our study are a sufficient number of patients analyzed, a completely reliable dataset, the high statistical significance of all tests, and a reproducible visual scoring method for rapid triaging decision making.

Following are limitations of our study: 1] Analysis done was retrospective in nature. 2] We did not categorize comorbid conditions and clinical information of the patients. This may explain a few of the patients with mild CTSS ending up with oxygen requirement. 3] We analyzed a single CT study of in-hospital patients done in the second week of symptoms onset. The data was fetched from medical records. Some of the patients or their relatives may have a human error of perception and memory in providing the exact day of symptoms onset. 4] No follow-up scans were considered. 5] CTSS is based on the assumption that lung opacities represent COVID-19 disease burden but histopathological confirmation of the same is lacking. 6] Considering the segmental scoring system over the lobar scoring system was solely departmental protocol decision and no data is available comparing the two methods. 7] CTSS considered was an average of independent blinded analysis of only two experienced radiologists. 8] External validation studies with multicenter larger cohorts are still necessary to determine the validity of CTSS. 9] The decision of giving oxygen support was based on the standard protocol decided by the team of pulmonologists and intensive care specialists of the institute.

Many questions are still unanswered as the disease is new for mankind, yet we are learning and evolving knowledge as fast as we can. We have observations and we have data but nothing 100% concrete. No diagnostic and imaging analysis strategy is the best. No treatment strategy is the best. But with each passing day, we are trying our best for a better understanding of the disease and the world is hopeful.

In conclusion, CTSS may be used as a new decisive tool in triaging in-hospital COVID-19 patients. Currently, clinical parameters guide the requirements of oxygen support in managing severe COVID-19 pneumonia. In the setting of patients overload, there may be delay in prompt clinical judgment and appropriate therapy may be initiated late and hence the poor outcome. Categorizing patients in mild and severe CTSS early in the disease course, even before the marked worsening of clinical parameters may save energy, health resources, help to triage severe patients, and above all may save many lives.

Fig 1: Mild COVID pneumonia. Axial lung window CT image showing focal rounded ground-glass and consolidative opacities in the lower lobe of the right lung. CTSS was 5 in the same patient.

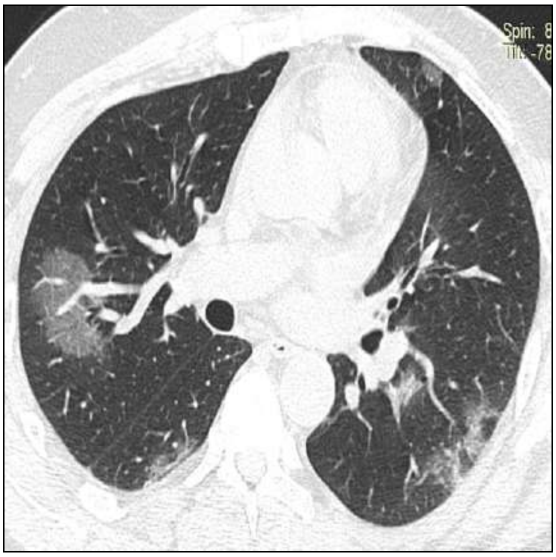

Fig 2: Mild COVID pneumonia. Axial lung window CT image showing few focal ground-glass opacities bilaterally with vascular engorgement sign within opacity in upper lobe of the right lung. CTSS was 7 in the same patient.

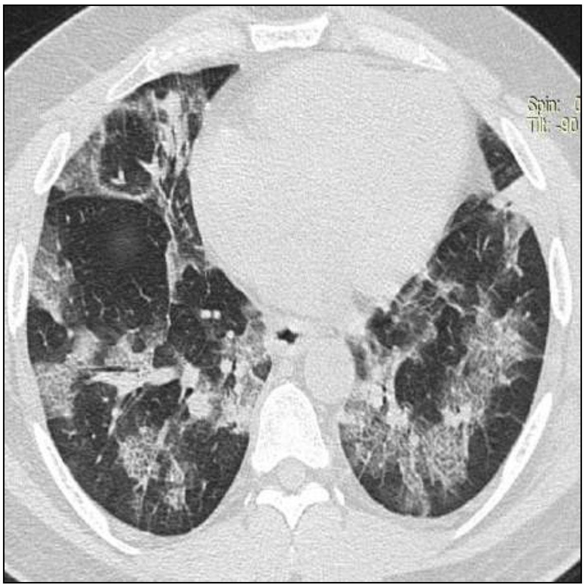

Fig 3: Severe COVID pneumonia. Axial lung window CT image showing multifocal ground-glass opacities and interstitial septal thickening creating crazy-paving appearance. CTSS was 30 in the same patient.

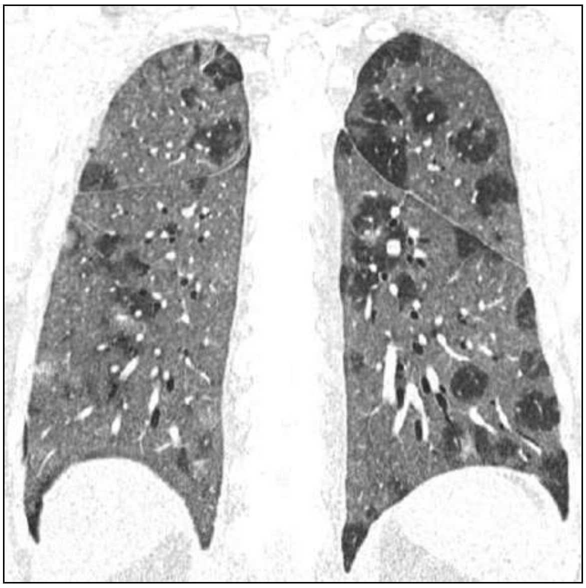

Fig 4: Severe COVID pneumonia. Coronal lung window CT image showing diffuse ground-glass opacities and tractional dilatation of few bronchi. CTSS was 36 in the same patient.

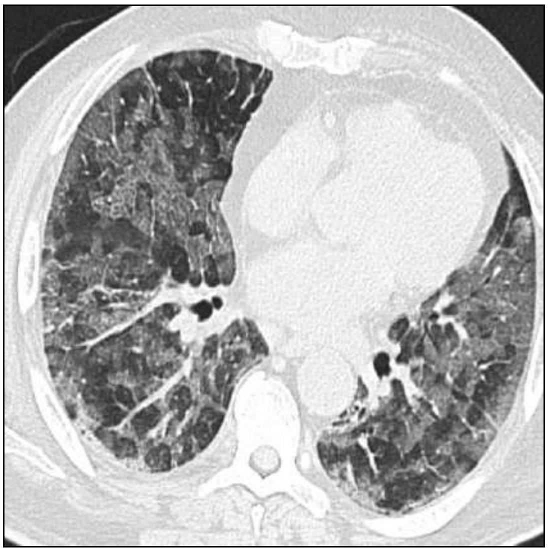

Fig 5: Severe COVID pneumonia with ARDS (Acute Respiratory Distress Syndrome). Axial lung window CT image showing diffuse ground-glass opacities and interstitial septal thickening.

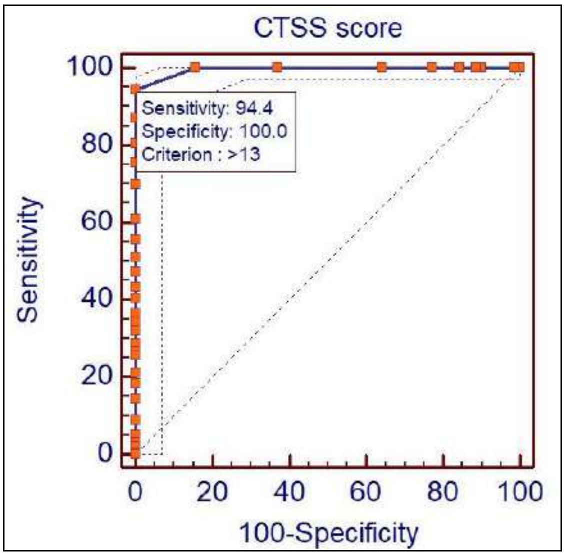

Fig 6: Receiver operating characteristic (ROC) curve showing performance of CTSS as a predictor of oxygen support with 94.4% sensitivity and 100% specificity.

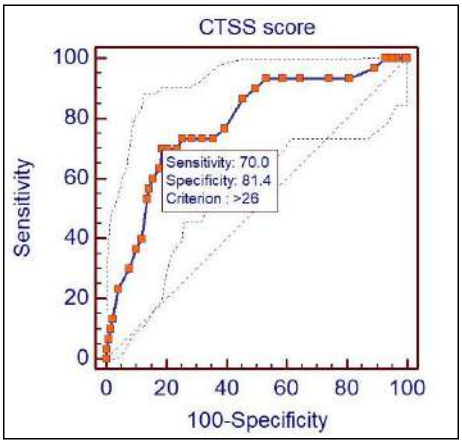

Fig 7: Receiver operating characteristic (ROC) curve showing performance of CTSS as a predictor of mortality with 70% sensitivity and 81.4% specificity.

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Declarations

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