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COVID-19 Chest CT Quantification: Triage and Prognostic Value in Different Ages

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Objective: We evaluated the triage and prognostic performance of seven proposed computed tomography (CT)-severity score (CTSS) systems in two different age groups.

Design: Retrospective study.

Setting: COVID-19 pandemic.

Participants: Admitted COVID-19, PCR-positive patients were included, excluding patients with heart failure and significant pre-existing pulmonary disease.

Methods: Patients were divided into two age groups: ≥65 years and ≤64 years. Clinical data indicating disease severity at presentation and at peak disease severity were recorded. Initial CT images were scored by two radiologists according to seven CTSSs (CTSS1-CTSS7). Receiver operating characteristic (ROC) analysis for the performance of each CTSS in diagnosing severe/critical disease on admission (triage performance) and at peak disease severity (prognostic performance) was done for the whole cohort and each age group separately.

Results: Included were 96 patients. Intraclass correlation coefficient (ICC) between the two radiologists scoring the CT scan images were good for all the CTSSs (ICC=0.764-0.837). In the whole cohort, all CTSSs showed an unsatisfactory area under the curve (AUC) in the ROC curve for triage, excluding CTSS2 (AUC=0.700), and all CTSSs showed acceptable AUCs for prognostic usage (0.759-0.781). In the older group (≥65 years; n=55), all CTSSs excluding CTSS6 showed excellent AUCs for triage (0.804-0.830), and CTSS6 was acceptable (AUC=0.796); all CTSSs showed excellent or outstanding AUCs for prognostication (0.859-0.919). In the younger group (≤64 years; n=41), all CTSSs showed unsatisfactory AUCs for triage (AUC=0.487-0.565) and prognostic usage (AUC=0.668-0.694), excluding CTSS6, showing marginally acceptable AUC for prognostic performance (0.700).

Conclusion: Those CTSSs requiring more numerous segmentations, namely CTSS2, CTSS7, and CTSS5 showed the best ICCs; therefore, they are the best when comparison between two separate scores is needed. Irrespective of patients' age, CTSSs show minimal value in triage and acceptable prognostic value in COVID-19 patients. CTSS performance is highly variable in different age groups. It is excellent in those aged ≥65 years, but has little if any value in younger patients. Multicenter studies with larger sample size to evaluate results of this study should be conducted.

Keywords: Area Under Curve; Computed Tomography; COVID-19; Intraclass Correlation Coefficient; ROC Curve; Quantification

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Because of the primary involvement of the respiratory system, computed tomography (CT) of the chest is recommended in suspected COVID-19 cases.[1] CT finding in the early phase (up to 5 days after the onset of symptoms) mostly consists of peripheral ground glass opacity (GGO) in the lungs. In progressive phase (5 to 8 days after symptom onset), is characterized by increased GGO, which may be accompanied by interlobular septal thickening (crazy-paving pattern). Peak phase (9 to 13 days after symptom onset) is characterized by progressive consolidation. Halo and reverse halo signs may also be seen in this stage. In the late stage (≥14 days after symptom onset) gradual decrease of consolidation and GGO opacities occurs, while signs of fibrosis (including parenchymal bands, architectural distortion, and traction bronchiectasis) may appear.[2] Lung involvement in COVID-19 can be quantified by chest CT with some triage and prognostication value.[3-11] Optimizing initial triage of patients could help to decrease adverse health impact of the disease through better management of clinical problems and healthcare systems' load via efficient prioritization of cases and timely discharge of admitted patients.[11] At least seven scoring systems using chest CT have been proposed to quantify lung involvement in COVID-19 which are summarized in Table 1,[1-10] and we use the term CT severity score (CTSS) to refer to them with numbers 1-7 referring to a specific scoring system. We introduced STSS5 as a possible tool to be implemented for triage and prognostic purposes.

Zhao et al[2] used a CTSS based on dividing the lungs into the upper, middle, and lower zones; each scored 0-4 based on the percentage of involvement (CTSS1).[2] They stated that mean CTSS1 was significantly higher in the severe/critical group than in the mild/moderate group of patients (12.86 vs. 5.34).[3] Zhou et al[4] used a CTSS with the same zonal concept, further dividing each zone into anterior and posterior divisions with a maximum of 48 scores (CTSS2). There was no performance report. Chung et al[5] scored each of the five lung lobes by the percentage of involvement from 0-4. CTSS was the sum of the five lobe scores, with a maximum of 20 (CTSS3). Li et al[6] implemented CTSS3 and reported an area under the curve (AUC) of 0.918 for receiver operator characteristic (ROC) curve to diagnose severe/critical disease; the CTSS cut-off of 7.5 had 82.6% sensitivity and 100% specificity. Other researchers used another CTSS. Each of the 5 lung lobes was visually scored from 0 to 5 as: 0, no involvement; 1, <5%; 2, 5-25%; 3, 26-49%; 4, 50%-75% and 5, >75% involvement. The maximum total score was 25 (CTSS4).[7,8] They reported no ROC curve or cut-off point. We propose another CTSS which is almost the same as CTSS4 but considers lingula as a separate lobe (CTSS5) with a maximum score of 30. Xiong et al[9] assessed each lobe for opacification and lesion size with a maximum sum of 20 (CTSS6). Yang et al[10] developed another CTSS in which the 18 segments of the lung were divided into 20 regions. The lung opacities in all the 20 lung regions were evaluated on chest CT using a system attributing score of 0, 1, or 2 according to absence or presence of 50% or more segmental opacification with a maximum of 40 (CTSS7). The area under the ROC curve for diagnosing patients in the severe/critical group was 0.892 (95% confidence interval: 0.814-0.944). The optimal CTSS threshold for identifying

Table 1. Seven proposed COVID-19 CT severity score systems

CTSSs	Segmentation	Severity Score for each segment	Maximum Score
CTSS1[3]	Three zones in each lung are divided by carina and lower pulmonary vein	1-4 according to percentage of involvement (<25, 25-49, 50-74, >75)	24
CTSS2[4]	The same zonal concept as CTSS1 with additional division of each zone into anterior and posterior regions divided by midpoint of diaphragm antero-posteriorly	1-4 according to percentage of involvement (<25, 25-49, 50-74, >75)	48
CTSS3[5,6]	Five anatomic lobes of the lungs	1-4 according to percentage of involvement (<25, 25-49, 50-74, >75)	20
CTSS4[7,8]	Five anatomic lobes of the lungs	1-5 according to percentage of involvement (<5, 5-25, 25-49, 50-74, >75)	25
CTSS5 [current authors]	Five anatomic lobes of the lungs with additional consideration of the lingula as a separate lobe	1-5 according to percentage of involvement (<5, 5-25, 25-49, 50-74, >75)	30
CTSS6[9]	Five anatomic lobes of the lungs	1-4 according to the diameter of the largest lesion in each lobe (<1cm, 1-3cm, >3cm up to 50% of the lobe, >50% of a lobe	20
CTSS7[10]	18 anatomic segments of the lung with an additional division of apico-posterior segment of the left upper lobe into apical and posterior divisions and anteromedial segment of the left lower lobe into anterior and medial segments	No involvement=0 <50% involvement=1 ≥50% involvement=2	40

Table 2. Clinical severity of COVID-19				
Measured Indicator of Severity [a]	**Mild**	**Moderate**	**Severe**	**Critical**
Respiratory Rate	≥24	≥30	-	-
SPO_2	≥93	$93>SPO_2≥90$	$89>SPO_2≥85$	<85 [b]
Respiratory Distress	None	None	Mild to moderate	Severe [c]
Blood Pressure	-	-	-	<90/60

a: presence of any of the severity indicators of the more severe group places the patient in the more severe group
b: despite high-flow O_2 administration
c: nasal flaring, dyspnea, intercostal retraction, subcostal retraction

severe/critical patients was 19.5, with 83.3% sensitivity and 94% specificity. To the best of our knowledge, we are the first group who evaluated the performances of different proposed CTSSs in triage and prognostication in different age groups of patients with COVID-19.

We aimed to determine the value of CTSS in making decisions about the intensity of the treatment of respiratory failure (triage) and predicting the risk of development of severe/critical disease in the course of COVID-19 in correlation with selected clinical parameters (prognostic value). We also evaluated the same CTSS values in patients aged 65 or more and younger patients separately. Additionally, we compared seven different CTSS systems pairwise.

Methods

Patients

Our institutional review board waived the requirement to obtain written informed consent for this retrospective test performance study, which evaluated de-identified data and involved no potential risk for patients. To avert any potential breach of confidentiality, no link between the patients and the researchers was made available.

We enrolled patients with COVID-19 referred to Firoozabadi Hospital (Tehran, Iran) from February 22 to July 24, 2020. The diagnosis was based on positive results of reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens at any time during hospitalization. Exclusion criteria were significant cardiopulmonary comorbidity, defined as cardiothoracic ratio >60% on CT topogram image[12] and diameter ratios of central branches of the pulmonary artery to corresponding bronchi >2;[13,14] and pre-existing pulmonary disease involving >30% of the lungs, diagnosed subjectively by visual assessment of the same CT images by the radiologist (AAN). Those patients that did not have any CT examination in our hospital were also excluded.

We retrospectively collected clinical and laboratory data from the hospital information system, including disease severity at presentation, severity in the most severe disease period, outcome (death or discharge), place of hospital admission (ward or intensive care unit [ICU]), state of intubation, and any comorbidity.

The severity of the disease was decided by the information derived from patients' records, as is presented in Table 2.[15] For less complexity, when the exact required data were not available, we regarded those who had undergone tracheal intubation or had died from the disease as critical. The patients were divided into two groups of moderate and severe/critical disease both at the time of admission (to evaluate CTSS for triage purposes) and at the most severe period of the disease (to evaluate CTSS for prognostic purposes).

Image Acquisition

Chest CT imaging was performed by a 16-detector-row CT scanner (Emotion; Siemens; Germany). All patients were

Table 3. Patients' demographic data and distribution of disease severity at presentation and peak disease severity				
	Number (Male/ Female)	**Age≥ 65 y (Male/ Female)**	**Age≤ 64 y (Male/ Female)**	**Mean age (y) ± SD**
Total	96 (57/39)	55 (34/21)	41 (23/18)	63.6±17.4
Moderate disease at presentation	41 (25/16)	17 (9/8)	17 (7/10)	57.3±18.9
Severe disease at presentation	53 (31/22)	36 (24/12)	24 (16/8)	68.2±14.9
Critical disease at presentation	2 (1/1)	2 (1/1)	0 (0/0)	71.5±6.4
Moderate disease at peak severity	22 (13/9)	8 (5/3)	14 (8/6)	52.5±20.1
Severe disease at peak severity	31 (17/14)	15 (9/6)	16 (8/8)	62±16.8
Critical disease at peak severity	43 (27/16)	32 (20/12)	11 (7/4)	70.4±12.9
Discharged	56 (32/24)	26 (16/10)	30 (16/14)	59±18.6

examined in a supine position. CT images were acquired during a single inspiratory breath-hold. The scanning range was from the apex of the lung to the costophrenic angle.

CT scan parameters: X-ray tube parameters, 110KVp, 45-60 effective mAs; rotation time, 0.6 seconds; collimation, 16x1.2; pitch, 1.5; section thickness, 5 mm; reconstruction interval, 5 mm with B70 sharp convolution kernel; additional reconstructions at slice thickness, and reconstruction interval of 1.5 mm with B70 and B31 convolution kernels were also made to generate lung and mediastinal windows, respectively. Lung window images were viewed at a width/level of 1200/-600 and mediastinal window images at 350/50 window settings.

Image Interpretation

Two radiologists, one with 17 years and one with 3 years of experience (AAN and RSh, respectively), who were blinded to clinical data, independently reviewed CT images of all the patients and scored each patient's images according to each of the 7 scoring systems mentioned in the introduction section (Table 2). They viewed images on hospital PACS (Marco PACS Version 2.0.0.0) and resorted to multiplanar reformation whenever needed. To determine lung involvement for scoring we took into account 7 imaging features defined in a previous article:[16] ground-glass opacities (GGO), consolidation (with or without air-bronchogram), mixed GGO and consolidation, crazy paving pattern, architectural distortion, tree-in-bud and bronchial wall thickening. Any other relevant pathological findings such as enlarged heart, other pulmonary parenchymal diseases such as cavities and emphysema, pleural effusion, pericardial effusion, enlarged intrapulmonary vessels and mediastinal lymph nodes were also recorded, although they did not change CTSS scores.

Statistical Analysis

All statistical analyses were done using SPSS 26.0 software (IBM, Armonk, NY), excluding comparison of ROC curves and AUCs and selection of cut-off points that were conducted by MedCalc statistical software version 19.9.4.0. A *P* value of <0.05 was considered statistically significant. Statistical analysis was performed by AAN. Quantitative data were expressed as mean ± standard deviation and/or median. Inter-rater reliability for each CTSS was evaluated first, using intraclass correlation coefficients (ICCs) for CTSSs. ICC estimates were calculated based on a two-way random model, single measurement form and, absolute agreement type ($ICC_{2,1}$ with absolute agreement).[17] ICCs were interpreted as follows: poor reliability <0.5; moderate reliability, 0.5-0.74; good reliability, 0.75-0.89; and excellent reliability, 0.9-1.0).[18] ROC curve analysis was performed on the averages of reported CTSSs by the two raters for each CTSS to calculate the AUC for diagnosing severe/critical COVID-19 at the time of hospital admission (for triage). Then AUCs were classified unsatisfactory if AUC<0.7, acceptable if 0.7≤AUC<0.8, excellent if 0.8≤AUC<0.9, and outstanding if AUC ≥0.9.[19] Threshold, specificity, and sensitivity for each CTSS were calculated. We chose the best thresholds according to the Youden index method, which is choosing the threshold producing the largest Youden Index (Sensitivity+Specificity-1).[20] The ROC curves were compared pairwise by z test. The same statistical procedure was applied to the CTSSs for predicting severe/critical disease groups at peak disease severity (for prognostication).

We applied the same type of analysis for the patients aged ≥40 years and again for each 5-year increment in patients' lower age limit up to ≥75 years, observing some progressive increase in AUCs with increasing lower age limit up to the ≥65 years group; above which no further increase in AUCs was observed. Therefore, we divided our cohort using this age limit into a group including 55 patients aged 65 years or older and a group of 41 patients aged 64 years or younger. Then we evaluated CTSS for each of the older and younger age groups separately.

Results

There were 145 confirmed cases. Of these patients, 110 have had at least one CT scan record in the hospital PACS. After reviewing the CT images, 14 patients with cardiopulmonary comorbidity were excluded, consisting of 13 patients with significant heart failure and one patient with significant centrilobular emphysema. There were 96 patients included in the study. In the study group, the mean age was 63.6 ± 17.4 years (range: 21-88 years, median: 67 years). There were 57 (59,4%) men and 39 (40.6%) women. Disease severity at the time of hospitalization was as follows: 41 (42.7%) moderate, 53 (55.2%) severe, and 2 (2.1%) critical. In the most severe period of their disease, 22 (22.9%) were moderate, 31 (32.3%) severe, and 43 (44.8%) critical; 40 (41.7%) patients died. Demographic and clinical data are summarized in Table 3.

All 96 patients underwent initial thoracic CT scan within the first 24 hours of admission, on average 4±3.4 days after the onset of symptoms (range 0-19 days, median 3 days). Inter-rater reliabilities between two raters for CTSSs 1-7 calculated as ICCs, as well as related inference, is presented in Table 4. All CTSSs showed good inter-rater reliability as ICC= 0.764-0.837. CTSS2 and CTSS7 showed the largest values (0.837 and 0.834, respectively).

Table 4. Inter-rater reliability between the two radiologists with confidence intervals and related inference

CT Severity Score	Intraclass Correlation	Confidence Interval	Inference about Inter-rater Reliability
CTSS1	0.783	0.451 - 0.891	good
CTSS2	0.837	0.722 - 0.900	good
CTSS3	0.764	0.313 - 0.896	good
CTSS4	0.778	0.448 - 0.892	good
CTSS5	0.784	0.431 - 0.898	good
CTSS6	0.773	0.678 - 0.843	good
CTSS7	0.834	0.748 - 0.890	good

Table 5. AUC, confidence interval, related inference, best threshold, and related sensitivity and specificity for ROC curves with respect to different CTSSs for the diagnosis of severe/critical group at presentation (upper set) and at peak disease severity (lower set) for all the patients in the cohort

	Average CTSS	AUC for ROC Curve	95% Confidence Interval	Inference about AUC	Best Threshold	Sens./ Spec. (%)	Sens.+ Spec. (%)
Diagnosis of severe/critical patients at presentation	CTSS1	0.697	0.591-0.803	unsatisfactory	11.0	60/70.73	130.73
	CTSS2	0.700	0.595-0.806	acceptable	15.0	78.18/53.66	131.84
	CTSS3	0.692	0.584-0.800	unsatisfactory	12.0	49.09/85.37	134.46
	CTSS4	0.696	0.589-0.803	unsatisfactory	14.5	56.36/75.61	131.97
	CTSS5	0.688	0.580-0.897	unsatisfactory	16.0	61.82/68.29	130.11
	CTSS6	0.678	0.569-0.787	unsatisfactory	13.5	67.27/60.98	128.25
	CTSS7	0.668	0.558-0.778	unsatisfactory	24.5	52.73/73.17	125.90
Diagnosis of severe/critical patients at peak disease severity	CTSS1	0.776	0.670-0.882	acceptable	7.5	81.08/59.09	140.17
	CTSS2	0.781	0.677-0.886	acceptable	13.0	86.49/59.09	145.58
	CTSS3	0.759	0.648-0.869	acceptable	9.5	55.41/86.36	141.77
	CTSS4	0.767	0.655-0.879	acceptable	10.0	83.78/59.09	142.87
	CTSS5	0.765	0.651-0.879	acceptable	11.5	85.14/59.09	144.23
	CTSS6	0.761	0.651-0.871	acceptable	16.0	48.65/90.91	139.56
	CTSS7	0.765	0.653-0.876	acceptable	15.5	87.84/54.55	142.39

Sens.= Sensitivity, Spec.=Specificity

Table 6. AUC, confidence interval, related inference, best threshold, and related sensitivity and specificity and their sum for ROC curves for different CTSSs with respect to the diagnosis of severe/critical group at presentation (upper set) and at peak disease severity (lower set) for patients aged ≥65 years.

	Average CTSS	AUC for ROC Curve	95% Confidence Interval	Inference about AUC	Best Threshold	Sens./ Spec. (%)	Sens.+ Spec. (%)
Diagnosis of severe/critical patients at presentation	CTSS1	0.808	0.679-0.902	excellent	11.0	65.79/94.12	159.91
	CTSS2	0.830	0.705-0.918	excellent	15.0	84.21/76.47	160.68
	CTSS3	0.804	0.675-0.899	excellent	10.5	60.53/94.12	154.64
	CTSS4	0.812	0.684-0.905	excellent	14.5	63.16/94.12	157.28
	CTSS5	0.821	0.694-0.911	excellent	15.5	68.42/94.12	162.54
	CTSS6	0.796	0.667-0.926	acceptable	15.0	60.53/94.12	154.65
	CTSS7	0.806	0.677-0.900	excellent	18.5	73.68/82.35	156.04
Diagnosis of severe/critical patients at peak disease severity	CTSS1	0.895	0.783-0.961	excellent	7.5	85.11/87.50	172.61
	CTSS2	0.919	0.813-0.975	outstanding	15.0	76.60/100.00	176.60
	CTSS3	0.860	0.740-0.939	excellent	6.5	76.60/87.50	164.10
	CTSS4	0.891	0.778-0.959	excellent	10.0	85.11/87.50	172.61
	CTSS5	0.904	0.794-0.967	outstanding	11.5	87.23/87.50	174.73
	CTSS6	0.859	0.739-0.938	excellent	10.0	85.11/75.00	160.11
	CTSS7	0.871	0.753-0.946	excellent	18.5	65.96/100.00	165.96

Sens.= Sensitivity, Spec.=Specificity

Table 7. AUC, confidence interval, related inference, best threshold, and related sensitivity and specificity and their sum for ROC curves for different CTSSs with respect to the diagnosis of severe/critical group at presentation (upper set) and at peak disease severity (lower set) for patients aged ≤ 64 years.

	Average CTSS	AUC for ROC Curve	95% Confidence Interval	Inference about AUC	Best Threshold	Sens./ Spec. (%0	Sens.+ Spec. (%)
Diagnosis of severe/critical patients at presentation	CTSS1	0.565	0.386-0.744	unsatisfactory	6	94.12/20.83	114.95
	CTSS2	0.539	0.356-0.722	unsatisfactory	28.5	29.41/87.50	116.91
	CTSS3	0.556	0.378-0.735	unsatisfactory	6.5	76.47/41.67	118.14
	CTSS4	0.550	0.371-0.729	unsatisfactory	9	94.12/25.00	119.12
	CTSS5	0.539	0.359-0.719	unsatisfactory	12	82.35/37.50	119.85
	CTSS6	0.549	0.371-0.728	unsatisfactory	10.5	94.12/25.00	119.12
	CTSS7	0.513	0.353-0.672	unsatisfactory	21.5	58.82/50.00	108.82
Diagnosis of severe/critical patients at peak disease severity	CTSS1	0.689	0.526-0.824	unsatisfactory	13	48.15/85.71	133.86
	CTSS2	0.681	0.517-0.818	unsatisfactory	21	51.85/78.57	130.42
	CTSS3	0.693	0.530-0.827	unsatisfactory	9.5	55.56/78.57	134.13
	CTSS4	0.680	0.516-0.817	unsatisfactory	9	92.59/35.71	128.31
	CTSS5	0.668	0.504-0.807	unsatisfactory	19	44.44/85.71	130.16
	CTSS6	0.700	0.537-0.833	acceptable	16.0	48.15/85.71	133.86
	CTSS7	0.694	0.531-0.828	unsatisfactory	14	96.3/42.86	139.15

Sens.= Sensitivity, Spec.=Specificity

For all the patients in the cohort, AUC for ROC curves for diagnosis of severe/critical disease at the time of admission as well as related inference, threshold, sensitivity, and specificity for each CTSS is presented in Table 5 (upper set). Only CTSS2 showed an acceptable AUC (0.700), and the sum of sensitivity and specificity for the best threshold value was 131.84%. Corresponding ROC curves are shown in Figure 1A (left image). Pairwise comparison of AUCs of these ROC curves showed that there was no significant difference between them. ROC curves AUCs for predicting severe/critical disease at the time of peak disease severity as well as related inference, threshold, sensitivity, and specificity for each CTSS are presented in Table 5 (lower set). All CTSSs showed acceptable AUCs (0.759-0.781). The sum of sensitivity and specificity for the best thresholds was 140.17-145.58% for different CTSSs. Corresponding ROC curves are shown in Figure 1A (right image). Pairwise comparison of AUCs of these ROC curves showed that there was no significant difference between them.

In patients aged 65 years or older (n=55), regarding AUCs of ROC curves for diagnosis of severe/critical disease at presentation, all the CTSSs were excellent (AUC=0.806-0.830, Sens.+Spec.= 155-162%), excluding CTSS6, which was acceptable (AUC=0.796, Sens.+Spec.= 154.65%) (Table 6, upper set). Corresponding ROC curves are shown in Figure 1B (left image). Pairwise comparison of AUCs of these ROC curves showed that there was no significant difference between them. Regarding AUCs for ROC curves for predicting severe/critical disease at peak disease severity CTSS2 and CTSS5 were outstanding (AUC=0.904-0.919, Sens.+Spec.= 174.73-176.6%) and the other CTSSs were excellent (AUC=0.86-0.89, Sens.+Spec.= 160-173%) (Table 6, lower set). Pairwise comparison of AUCs of these ROC curves showed that there was no significant difference between them, excluding CTSS2-CTSS7 pair (P=0.481). Corresponding ROC curves are shown in Figure 1B (right image).

In patients aged 64 years or younger (n=41), regarding AUCs of ROC curves for diagnosis of severe/critical disease at presentation, all the CTSSs were unsatisfactory for clinical implementation (AUC=0.487-0.565) (Table 7, upper set). Regarding AUCs for ROC curves for predicting severe/critical disease at peak disease severity, all the CTSSs were unsatisfactory for clinical implementation (AUC=0.668-0.694), excluding CTSS6 with a borderline acceptable AUC value (AUC=0.700, Sens.+Spec.= 133.86%) (Table 7, lower set). Corresponding ROC curves for patients aged 64 or less are shown in Figure 1C. Pairwise comparison of AUCs of these ROC curves showed that there was no significant difference between them in neither triage nor prognostication ROC curve groups.

Discussion

Many studies have used CTSS as a disease quantifying tool in COVID-19.[1-10] Some of them evaluated CTSS by ROC curve AUC, sensitivity, specificity, and other indices of test performance.[6,10] To the best of our knowledge, six types of CTSS have been proposed, and we propose another one

(CTSS5). We evaluated seven CTSS types for their performance in triage and prognostication.

Because RT-PCR was ordered rarely, if ever, in our institution for patients with mild symptoms due to lack of resources, our cohort comprised more severely affected patients compared with other studies,[3-10] and the mortality rate was much higher (42%). Like most of the other mentioned studies,[3-5,8-10] male patients were more frequent in our cohort than women (57 vs. 39). This may indicate that women are affected less, probably because of estrogen protective effect,[21] or possibly they less frequently seek medical assistance.

There are many comorbidities that may aggravate COVID-19, for example, hypertension, obesity, diabetes, active cancer, chemotherapy, solid organ transplant, chronic kidney disease and immunosuppressive therapy.[22] Most of these comorbidities including hypertension result in disturbances in immune system[22] that may present as more extensive inflammation leading to higher scores on CT images. Regarding CT severity quantification, two other comorbidities are of special importance: heart failure and preexisting lung disease, because they may lead to clinically more severe disease and higher mortality rate without increasing the extent of COVID-19 lung involvement on CT. Considering the whole patients population heart failure is a major risk factor for in-hospital mortality,[23,24] with odds ratio of 3.46 reported in a systematic review.[22] Preexisting respiratory disease has also a major impact on the COVID-19 mortality with a reported adjusted odds ratio of 1.36 in a study.[25] Consequently, it is a good practice to place patients with heart failure or preexisting significant pulmonary disease in the high-risk group without any judgment upon their CTSS. We regarded heart failure and significant preexisting respiratory disease as confounders, and those patient with evidence of these diseases were excluded from our study. A case of heart failure with mild lung involvement and moderate disease at hospital admission with rapid progression to severe disease and critical outcome is presented in Figure 2.

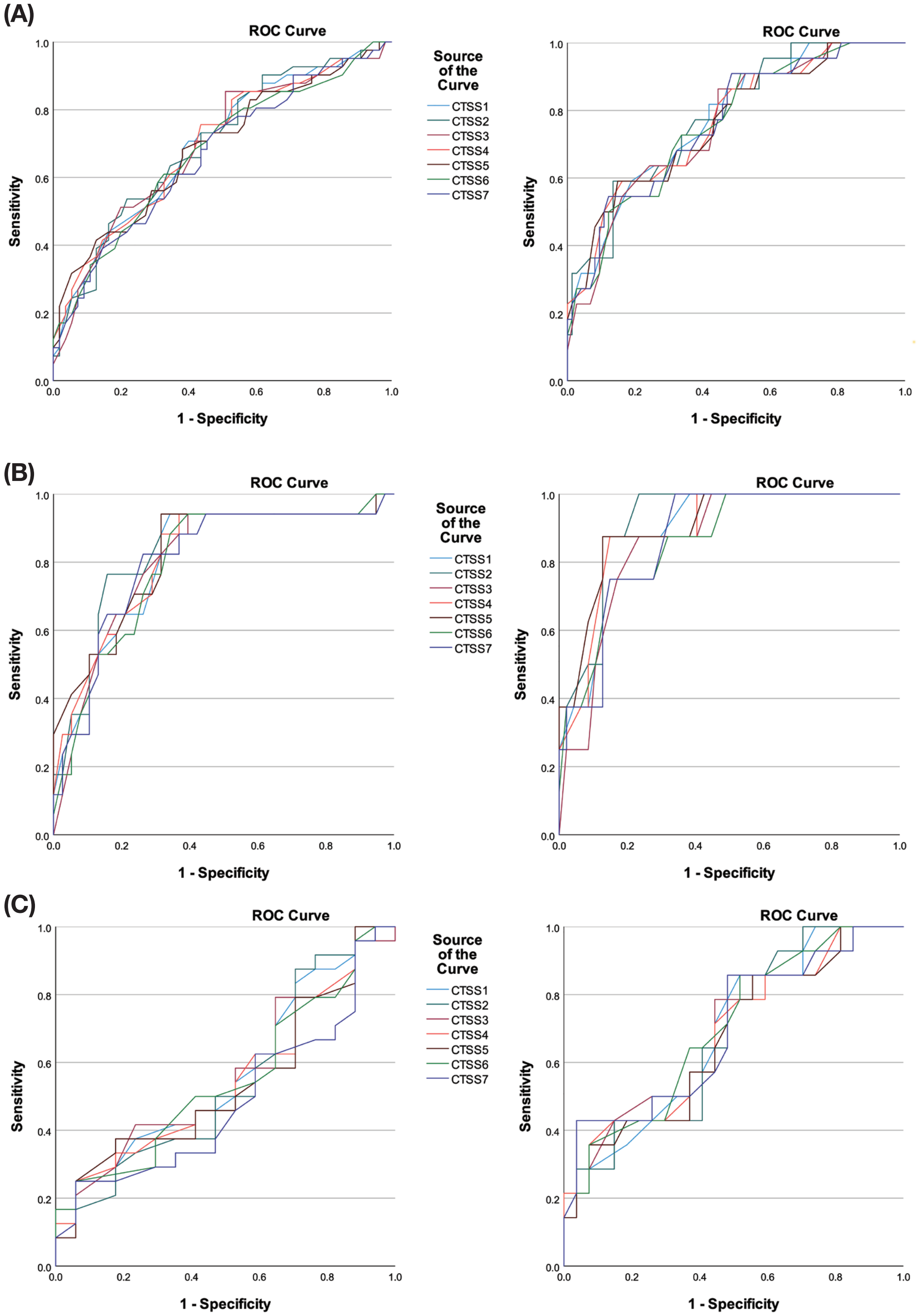

Figure 1. ROC curves plotted for different average CTSSs for diagnosing severe/critical disease at the time of hospital admission (left) and severe/critical disease at peak disease severity (right) for all patients in the cohort (A), for patients ≥65 years old (B) and for patients ≤64 years old (C).

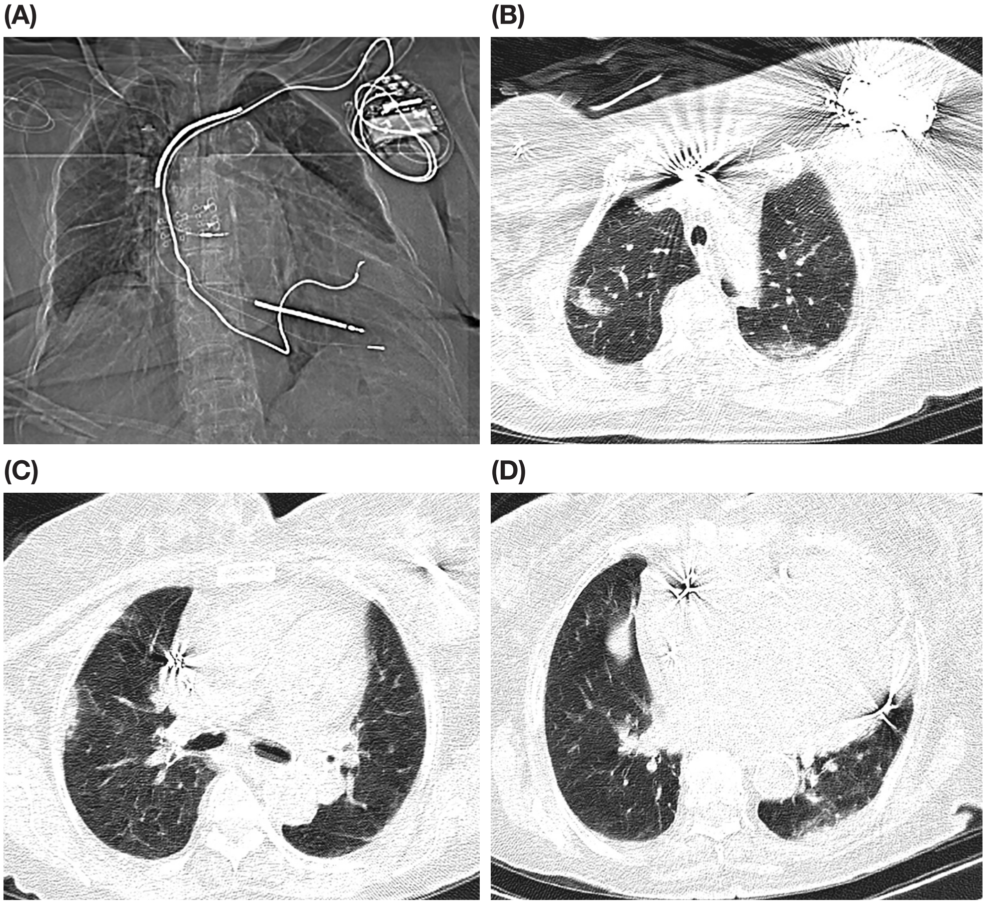

Figure 2. A 79-year-old, non-diabetic woman with heart failure, suggested by a large heart (CT ratio>60%) and cardiac resynchronization therapy leads in place on topogram image (A) and large intrapulmonary arteries (broncho-arterial ratio<0.5) (D), showed mild lung involvement in the form of small peripheral foci of mixed GGO and consolidation in her first-day in-hospital CT (B-C) with CTSS1= 6/24, CTSS2= 12/48, CTSS3= 5/20, CTSS4= 5/25, CTSS5=6/30, CTSS6= 5/20, CTSS7= 14/40. She presented with moderate disease which progressed to severe disease with ICU admission after 2 days and further progression to intubation (critical disease) after another day and died the next day (critical outcome).

In our study, all CTSSs showed good interrater reliability, and the best ICCs were for the CTSSs with more numerous segmentations (CTSS2 and CTSS7). The excellent ICCs reported in some previous studies (0.976 for CTSS3 and 0.936 for CTSS7)[4,10] were not reproduced in our study, probably because of the higher rate of severe/critical disease in our study, requiring a more complex scoring process.

We showed that the scoring systems with more numerous segmentations in the lung parenchyma has better interrater reliability. Therefore, it is wise to use CTSS2, CTSS7, or probably CTSS5 if a later follow-up by CT is contemplated or if the scores are going to be used in an analytical comparative study.

We evaluated the discriminatory performance of CTSSs between the two moderate and severe/critical groups at presentation as triage performance and at the most severe period of the disease as prognostic performance. We also assessed such discriminatory abilities in two separate age groups: patients aged 65 years or older, and younger patients.

In the whole cohort, only one CTSS, namely CTSS2, showed sufficient ROC curve AUC to justify clinical implementation in the triage of the patients, and it showed a borderline value with its performance far from ideal. These results are not compatible with previously reported values; as for CTSS3 the reported AUC for diagnosing severe-critical type was 0.918 (95% CI 0.962–0.985), and CTSS3 cut-off of 7.5 had 82.6% sensitivity and 100% specificity in diagnosing severe/critical group at presentation.[6] Our computed AUC value is 0.692, which is regarded as unsatisfactory. The same is true for CTSS7 with a reported AUC of 0.892 (95% CI 0.814, 0.944),[10] but our calculated AUC was 0.668 (CI 0.558-0.778), which was again unsatisfactory. This discrepancy in results is most probably related to the relatively low incidence of severe/critical disease in the mentioned studies as their cohort included only about 10% severe/critical disease patients in the CTSS3 study[6] and < 18% in the CTSS7 study,[10] but in our study, the corresponding percentage was 57%.

CTSSs performed better for prognostic purposes than triage with acceptable AUCs for all the CTSSs in discriminating moderate from severe/critical group at peak disease severity, as all the related AUCs were acceptable for clinical use with AUCs of 0.761-0.793. Recent reports are compatible with our results as Hajiahmadi et al[26] reported ROC curve AUC 0.764 for CTSS1 for predicting severe/critical disease in a cohort including 24% severe/critical disease patients while our calculated figure was 0.776. In addition, Aminzadeh et al.[27] used a CTSS method similar to our CTSS5 and reported ROC curve AUC of 0.65 for prognostic prediction of severe/critical patients[27] and our corresponding calculated value for CTSS5 was 0.765.

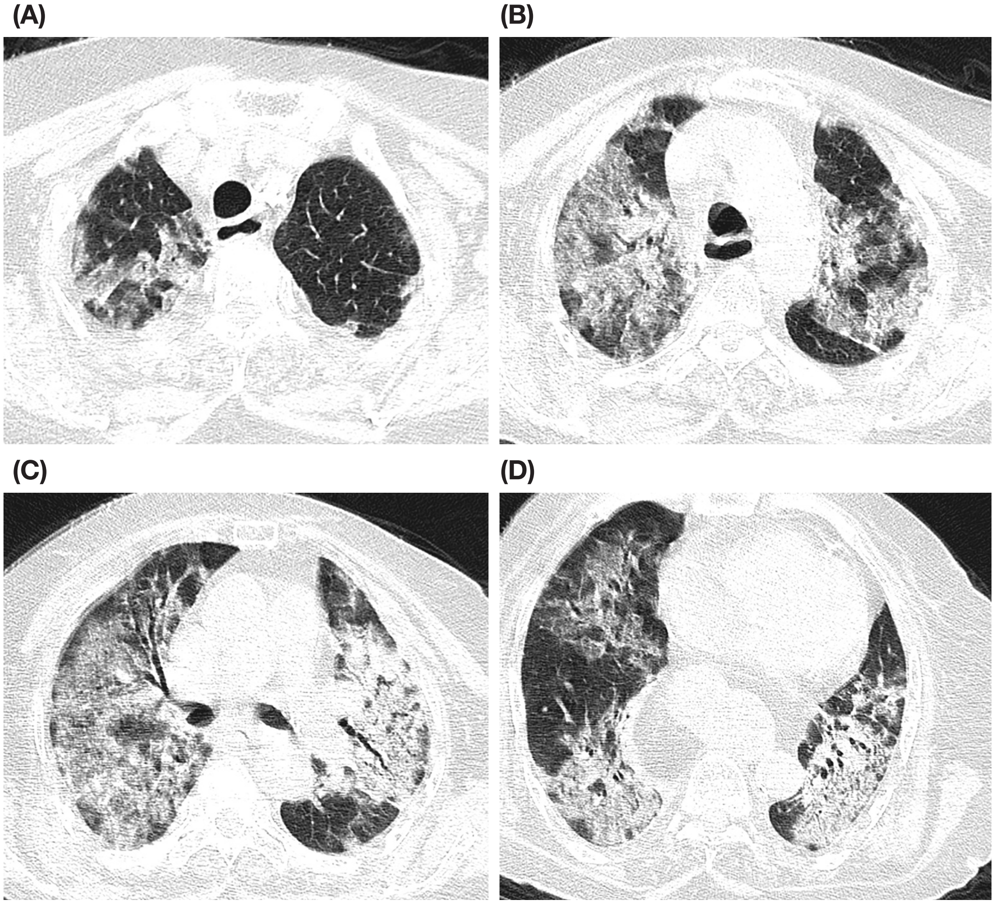

Figure 3. A 71-year-old, diabetic woman without heart failure, hospitalized with severe disease at presentation, shows extensive lung parenchymal involvement, mainly GGO with minimal consolidation in her first-day in-hospital CT scan (A-D): CTSS1=17/24, CTSS2= 33/48, CTSS3= 13/20, CTSS4= 18/25, CTSS5=21/30, CTSS6= 18/20, CTSS7= 33/40. She was admitted to ICU (severe disease at triage), got intubated after 2 days (critical disease) and died after 6 more days (critical outcome).

Therefore, we do not favor a very powerful role for CTSS in the triage of patients without consideration of their age, although some role still exists, more specifically for CTSS2, but it is acceptable to use CTSS for prognostic purposes irrespective of the patients' age. The CTSS cut-off point and corresponding sensitivity and specificity for differentiating moderate from severe/critical outcomes (differentiating uncomplicated recovery from ICU admission/intubation or death) are presented in Table 5 (lower set).

Older age has been shown to be a major risk factor of adverse outcome in COVID-19 patients.[28]-[31] Xu et al[29] presented threshold of 60 years old for adverse outcome. Two other studies by Khan et al[30] and Song et al[31] presented a threshold of 65 years. To the best of our knowledge, we are the first ones who assessed CTSS performance in triage and prognostic purposes in COVID-19 in different age groups. We divided the study population into two groups of ≥65 years old and younger according to our own objective data, which was explained earlier. In patients aged 65 years or older, all CTSSs showed excellent performance in the triage of severe/critical disease patients. CTSSs performed better in prognostication in this age group, and two CTSSs, namely CTSS2 and CTSS5, are outstanding in predicting severe/critical disease in the peak disease severity. All the other CTSSs were excellent in this regard. Chest CT scan of a patient aged 71 years with severe disease at presentation and progression to critical disease after 2 days, who died after an additional 6 days is shown in Figure 3.

In patients aged 64 years or younger, CTSSs were not suitable for patients' triage at all. They were not essentially applicable for predicting severe/critical disease either, excluding a borderline role for CTSS6. Chest CT scan of a 62-year-old patient with moderate disease at presentation, with almost the same CTSS values as the patient in Figure 3, and progression to severe disease after 5 days is shown in Figure 4. The patient recovered and was discharged after an additional 7 days.

Regarding the scarcity of resources in COVID-19 pandemic era in developing countries, careful triage of the patients is of utmost importance to make the best use of resource expenditure. In view of their excellent performance, we recommend using all CTSSs for triage of patients aged ≥65 years. This means that CTSS can be included in ICU admission criteria in patients aged ≥65 years. Corresponding cut-off points for each CTSS to differentiate moderate from severe/critical disease at presentation with corresponding sensitivity and specificity are presented in Table 6 (upper set). It is obvious that due to imperfect performance of CTSS, clinical correlation should also be included in a decision-making process as also was stated in previous studies.[32] Using CTSS for patients' triage is not recommended in patients aged ≤64 years and the physician had better to rely mainly on clinical findings for triage in this age group.

We also recommend using CTSS2 or CTSS5 for prognostic purposes in patients aged ≥65 years regarding their outstanding to relatively low power of our study to detect significant differences between CTSSs' performance in pairwise comparisons between them. Still other limitation is that our study is a single-center one and the effects of different treatment policies which may occur in different centers and probably different socioeconomic status of the patients on the course and final outcome of the disease are not included in our study. The other shortcoming was the absence of long-term follow-up after discharge to evaluate the relation of CTSSs to long-term sequelae produced by COVID-19.

Conclusion

- Quantification of lung disease in COVID-19 is a readily available and easy tool to be used in triage and prognostication, but its use is not encouraged in heart failure or chronic respiratory disease patients. These patients are at high risk of critical disease irrespective of CTSS.
- Best inter-rater reliabilities are for those CTSSs with more numerous segmentations.
- Considering all age groups, CTSS has little value in diagnosis of severe/critical disease but is acceptable as an indicator of prognosis.
- In patients ≥65 years, CT-severity score shows excellent performance in both triage and prognostic purposes.
- In patients aged ≤64 years, CT-severity score has almost no value in triage and determining prognosis.
- There is not much difference among performances of seven different proposed CT-severity scores.
- Multicenter studies in larger populations with inclusion of mildly diseased patients are needed.

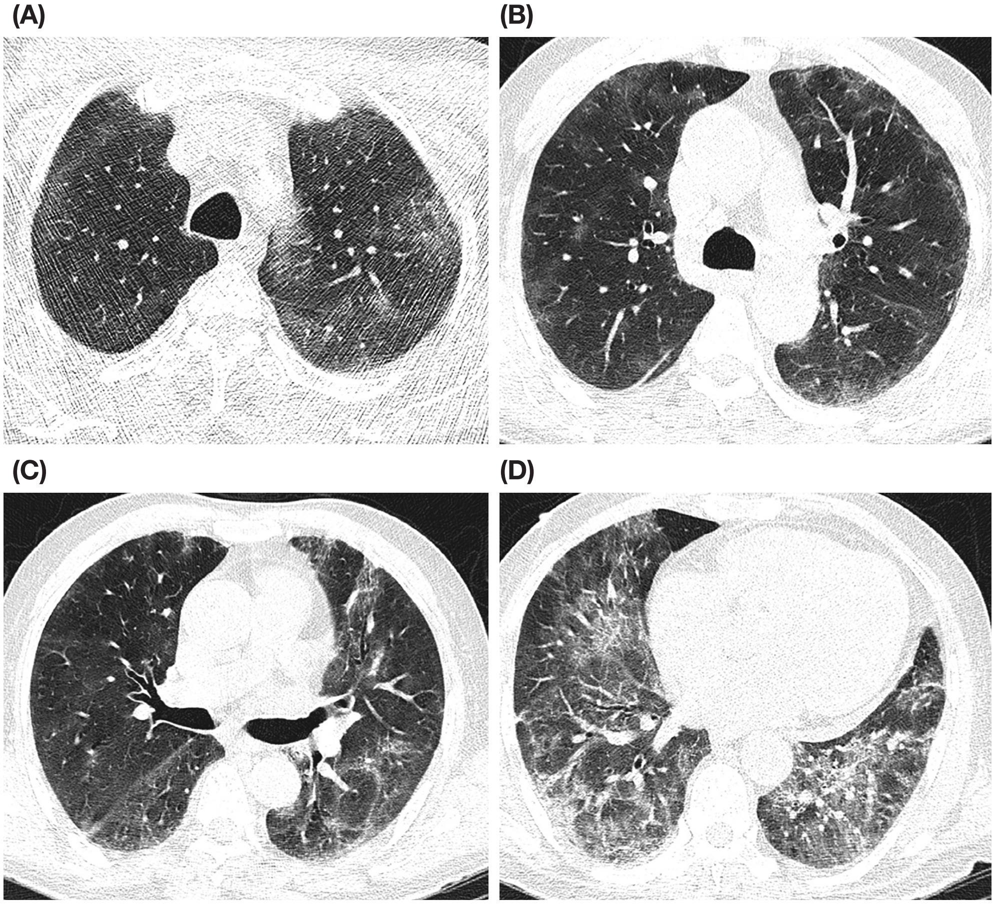

Figure 4. **A 62-year-old, non-diabetic man without heart failure, hospitalized with moderate disease at presentation, shows in his first-day in-hospital CT scan extensive lung parenchymal involvement, mainly GGO with minimal consolidation (A-D): CTSS1= 17/24, CTSS2= 32/48, CTSS3= 14/20, CTSS4= 19/25, CTSS5= 22/30, CTSS6= 18/20, CTSS7= 27/40. He was admitted to the ward (moderate disease at triage), admitted to ICU after 5days (severe outcome) and was discharged after 12 days in-hospital stay without intubation.**

performance, although the other CTSSs are also applicable with excellent performance. Corresponding thresholds for each CTSS to differentiate moderate from severe/critical outcome are presented in Table 6 (lower set). This way a physician can predict which patients are at greater risk of untoward outcome and provide more intense treatment options in advance. This application of CTSS is more suitable for more resourceful countries or non-pandemic situations in which there is not much limitation in resource allocation.

Several limitations in our study should be considered. One is the absence of mildly diseased patients in our cohort, because RT-PCR was not ordered routinely for patients with mild disease who were not hospitalized. Therefore, we could not evaluate performance of CTSS in differentiating mild from moderate/severe/critical disease. This would have an impact on decision-making to hospitalize patients. Another limitation is that our sample size is not very large; leading to wide confidence intervals for ROC curve AUCs and ICCs in addition

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