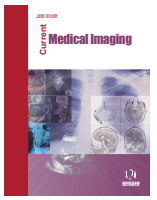
Current Medical Imaging, 2021, *17*, 1142-1150

RESEARCH ARTICLE

Visual and Quantitative Assessment of COVID-19 Pneumonia on Chest CT: The Relationship with Disease Severity and Clinical Findings



Furkan Kaya[1,*], Petek Şarlak Konya[2], Emin Demirel[1], Neşe Demirtürk[2], Semiha Orhan[3] and Furkan Ufuk[4]

[1]*Department of Radiology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey;* [2]*Department of Infectious Disease, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey;* [3]*Department of Intensive Care, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey;* [4]*Department of Radiology, University of Pamukkale, Denizli, Turkey*

Abstract: ***Background*:** Lungs are the primary organ involved in COVID-19, and the severity of pneumonia in COVID-19 patients is an important cause of morbidity and mortality.

***Aim*:** We aimed to evaluate the pneumonia severity through the visual and quantitative assessment on chest computed tomography (CT) in patients with coronavirus disease 2019 (COVID-19) and compare the CT findings with clinical and laboratory findings.

***Methods*:** We retrospectively evaluated adult COVID-19 patients who underwent chest CT along with theirclinical scores, laboratory findings, and length of hospital stay. Two independent radiologists visually evaluated the pneumonia severity on chest CT (VSQS). Quantitative CT (QCT) assessment was performed using a free DICOM viewer, and the percentage of the well-aerated lung (%WAL), high-attenuation areas (%HAA) at different threshold values, and mean lung attenuation (MLA) values were calculated. The relationship between CT scores and the clinical, laboratory data, and the length of hospital stay were evaluated in this cross-sectional study. The student's t-test and chi-square test were used to analyze the differences between the variables. The Pearson correlation test analyzed the correlation between the variables. The diagnostic performance of the variables was assessed using the receiver operating characteristic (ROC) analysis.

***Results*:** The VSQS and QCT scores were significantly correlated with procalcitonin, d-dimer, ferritin, and C-reactive protein levels. Both VSQ and QCT scores were significantly correlated with the disease severity ($p < 0.001$). Among the QCT parameters, the %HAA-600 value showed the best correlation with the VSQS ($r = 730$, $p < 0.001$). VSQS and QCT scores had high sensitivity and specificity in distinguishing disease severity and predicting prolonged hospitalization.

***Conclusion*:** The VSQS and QCT scores can help manage the COVID-19 and predict the duration of the hospitalization.

ARTICLE HISTORY

Received: October 27, 2020
Revised: January 21, 2021
Accepted: January 25, 2021

DOI:
10.2174/1573405617666210215142528

Keywords: COVID-19, pneumonia, quantitative CT, visual CT, disease severity score, CURB-65.

1. INTRODUCTION

A cluster of viral (coronavirus) pneumonia cases were reported in China in late 2019, after which the virus causing this disease was named coronavirus disease-2019 (COVID-19) [1, 2]. Although most patients have mild symptoms, COVID-19 can cause serious complications, such as respiratory failure, acute respiratory distress syndrome, disseminated intravascular coagulation, pulmonary thromboembolism, pulmonary air leak syndromes, multiple organ failure, systemic inflammatory response syndrome, sepsis, and death [3-6]. Lungs are the primary organ involved in COVID-19, and the extensive alveolar damage and the exudation secondary to inflammation, has been reported as the underlying possible pathological mechanism [7].

Bilateral, multifocal ground-glass opacity (GGO) and consolidation areas are the most common imaging findings used for the COVID-19 patients with pneumonia [8, 9]. Computed Tomography (CT) of the chest plays a complementary role in the diagnosis of viral pneumonia and it can also provide valuable information about the pneumonia severity and prognosis of the patients. Pneumonia severity on chest CT is a prognostic determinator and can be assessed visually (semi-quantitative assessment) or using soft-

*Address correspondence to this author at the Department of Radiology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey;
Tel: +905305692966; Fax: +90 272 228 14 29;
E-mail: furkaya157@hotmail.com

1875-6603/21 $65.00+.00

ware-based algorithms (quantitative assessment) [10-12]. Although many studies have focused on the Visual Semi-Quantitative (VSQ) CT assessment to evaluate the pneumonia severity in COVID-19 patients, VSQS is a subjective method [4, 10, 12]. Quantitative Computed Tomography (QCT) assessment is an objective tool and not dependent on the observers' experience. Moreover, QCT has an increasing role in the diagnosis, prognosis, and management of patients with diffuse lung diseases and different QCT methods have been defined for assessing the pneumonia severity [13].

There are a limited number of studies examining the relationship between QCT scores and disease severity or prognosis in COVID-19 patients, and more data are needed on this topic [11]. Therefore, the aim of this study is to evaluate the visual and quantitative pneumonia severity on chest computed tomography (CT) in patients with COVID-19 and compare the CT findings with clinical disease severity, laboratory findings, and hospital stay length. The present study also aimed to investigate the different QCT methods in assessing pneumonia severity and explore the most successful quantitative CT parameters. We suggest that this study's findings will be useful in the management of patients with COVID-19 pneumonia and will guide future research.

2. MATERIALS AND METHODS

2.1. Study Population

The adult COVID-19 patients who underwent chest CT from March 15, 2020, to June 10, 2020, were retrospectively evaluated. Exclusion criteria included the presence of lung tumor (previously known or unknown), apparent sequelae of pulmonary tuberculosis or other pulmonary infections, pulmonary edema, known interstitial lung disease, history of lung surgery or radiotherapy, and the presence of significant motion artifacts on chest CT. Besides, patients younger than 18 and patients who underwent contrast-enhanced CT examination were also excluded from the study.

2.2. Computed Tomography Imaging

Chest CT images were obtained from the apex to the basis of the lungs using a multislice CT scanner (Toshiba Aquilion Prime, Japan) at full inspiration in the supine position. Chest CT parameters were: 1 mm slice thickness, 120 kV tube voltage, 0.5 x 80 mm collimation, 370 mm field of view, 512 x 512 matrix, 0.35s rotation speed, 15 mm/s table speed, and 0.813 pitch factor. Contrast medium was not used, and the scan time was 2 - 4 seconds. Axial, coronal, and sagittal image reconstructions were performed using a soft tissue algorithm.

2.3. Computed Tomography Analysis of the Visual Semi-Quantitative Score

Chest CT images were independently evaluated by two observers with six and eight years of experience in thoracic imaging for the visual semi-quantitative score (VSQS). Observers were unaware of the patient's data (clinical and laboratory findings). In the event of disagreement between observers, a final decision was made with a third observer with ten years of experience in thoracic imaging. Semi-quantitative pneumonia severity score was calculated as the percentage of involvement in each lung lobe, as previously described in a simple method [4]. Each of the five lung lobes was evaluated for the percentage of lobar involvement. In this evaluation, the percentage of involvement of each lobe was calculatedas no pulmonary involvement: 0 point, 1% to 25% pulmonary involvement: 1 point, 26% to 50% pulmonary involvement: 2 points, 51% to 75% pulmonary involvement: 3 points, and 76% to 100% pulmonary involvement: 4 points. The VSQ score was found by summing the scores in five lobes (between 0 - 20 points) [4].

2.4. Quantitative Computed Tomography Image Analysis

Chest CT images were transferred to the Chest Imaging Platform (CIP) of 3D Slicer (freely available at http://www.slicer.org version: 4.10.2) software for quantitative CT assessment. Large airways, main vascular structures, mediastinum, and ribs were automatically excluded from voxel analysis. In the pulmonary densitometric evaluation, both lungs were analyzed separately using two different methods: % HAA (percentage of high attenuation area) and mean lung attenuation (MLA).

[a] In the % HAA method, the voxels in the relevant region were measured using the density masking method, and the ratio of voxels below a certain threshold Hounsfield Unit (HU) values to total voxels was calculated as a percentage (%). Five different values were used as threshold HU values: -700 HU, -600 HU, -500 HU, -250 HU, and lung attenuation values between -600 HU and -250 HU. Moreover, the percentage of the well-aerated lung (%WAL) was calculated between -950 and -700 HU values (Fig. **1**) [11, 13].

[b] In the mean lung attenuation (MLA) method, total lung volume was automatically calculated, and the histogram analysis was performed. In the histogram analysis, skewness, and kurtosis values were calculated (Fig. **1**).

2.5. Clinical classifications

Two different methods were used to determine the severity of the disease in clinical classification.

[1] *CURB-65 scoring system:* Pneumonia severity was classified using the following parameters (one point for each parameter): new onset of confusion, blood urea level > 7 mmol/L, respiratory rate ≥ 30/min, systolic blood pressure ≤ 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and > 65 years of age. In this classification, the lowest score was 0, while the highest score was 5. According to the CURB-65 score, the patients were divided into two groups, mild pneumonia (scores with 0 and 1) and severe pneumonia (scores ≥ 2) [14, 15].

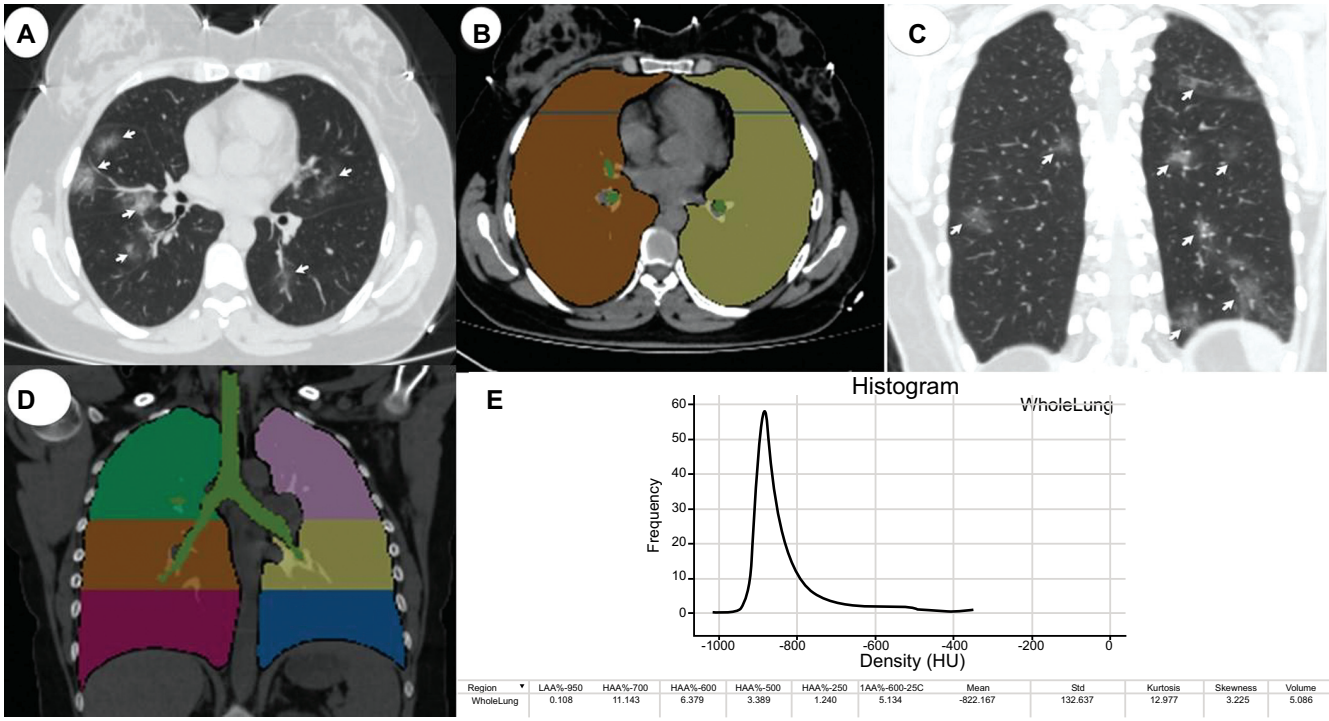


Fig. (1). Chest CT images and quantitative CT assessment in a 53-year-old female patient with coronavirus disease 2019 (COVID-19) pneumonia; **A**: Axial and **C**: coronal unenhanced chest CT images show multi-lobar and peripheral ground-glass opacities (arrows) with the visual semi-quantitative score of pneumonia of 5. **B, D**: The same images as in A and B, which highlights the fully automatic segmentation of lung parenchyma using 3D Slicer software (version 4.10.2, https://www.slicer.org). **E**: The quantitative CT assessment results with different values. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[2] *Disease severity score (DSS):* All patients with COVID-19 were divided into four groups based on the clinical, radiological, and laboratory findings, which was defined by the Chinese National Health Commission as follows [16]:

- [A] Mild disease: COVID-19 patients without pneumonia on imaging (chest CT).
- [B] Common disease: COVID-19 patients with pneumonia on chest CT, who do not need supplemental oxygen therapy and no respiratory failure.
- [C] Severe disease group: COVID-19 patients with pneumonia and severe respiratory failure and/or increased respiratory rate (equal or more than breaths/min) and/or decreased oxygen saturation (SpO2 ≤ 93%) on room air, and/or PaO2/FiO2 ratio equal or less than 300 mmHG.
- [D] Critical disease group: COVID-19 patients with pneumonia and severe respiratory failure requiring mechanical ventilation, and/or COVID-19 patients with septic shock and organ failure requiring intensive care unit (ICU) stay.

Due to the low number of cases in the present study, the patients were divided into two groups as non-severe (disease groups A and B) and severe disease (disease groups C and D) groups.

2.6. Laboratory Findings and Hospitalization Period of the Patients

Laboratory test results (white blood cell count [WBC], lymphocyte, the neutrophil-to-lymphocyte ratio [NLR], C-reactive protein [CRP], ferritin, D-dimer, procalcitonin) were recorded, obtained on the same day as that of thechest CT. The length of hospital stay was calculated from the archive. Patients who died during hospitalization were not included in the analysis of hospital stay length.

2.7. Statistical Analysis

Statistical analyzes were performed using SPSS version 20.0 (IBM corp. Armonk, NY). Continuous variables were presented as mean value and standard deviation, and categorical variables were presented as frequency and percentages. The student's t-test and chi-square test were used to analyze the differences between the variables. The correlation between VSQ, QCT scores, and laboratory test results were analyzed by the Pearson correlation test. To assess the differential performance of the VSQ and QCT scores in the evaluation of disease severity, receiver operating characteristic (ROC) analysis was used. A p-value < 0.05 was considered statistically significant.

Table 1. Clinical characteristics of patients.

-	Total (n = 58)	Non-Severe Disease (n = 42)	Severe Disease (n = 16)	p - value
Age (years)	53.1	49.19	63.19	0.002
Sex (female/male)	29/29	27/15	2/14	< 0.001
Smoking history, n (%)	17 (29.3)	9 (24.4)	8 (50)	0.033
Comorbidities, n (%)	-	-	-	-
Hypertension	11 (19)	5 (11.9)	6 (37.5)	0.026
Diabetes mellitus	5 (8.6)	3 (7.1)	2 (12.5)	0.516
Cardiovascular disease	7 (12.1)	2 (4.8)	5 (31.3)	0.006
Cerebrovascular disease	2 (3.4)	1 (2.4)	1 (6.3)	0.470
COPD	5 (8.6)	1 (2.4)	4 (25)	0.006
Malignancy	5 (8.6)	2 (4.8)	3 (18.8)	0.09
Chronic kidney disease	7 (12.1)	2 (4.8)	5 (31.3)	0.006
Chronic liver disease	2 (3.4)	1 (2.4)	1 (6.3)	0.470
Symptoms, n (%)	-	-	-	-
Fever (> 37.3)	34 (58.6)	24 (57.1)	10 (62.5)	0.711
Cough	40 (69)	28 (66.7)	12 (75)	0.540
Sputum	5 (8.6)	3 (7.1)	2 (12.5)	0.516
Myalgia or fatigue	29 (50)	22 (52.4)	7 (43.8)	0.557
Headache	8 (13.8)	5 (11.9)	3 (18.8)	0.499
Sore throat	18 (31)	15 (35.7)	3 (18.8)	0.212
Nausea and vomiting	16 (27.6)	12 (28.6)	4 (25)	0.786
Anosmia	6 (10.3)	4 (9.5)	2 (12.5)	0.739
Diarrhea	13 (22.4)	11 (26.2)	2 (12.5)	0.264
Dyspnea	11 (19)	3 (7.1)	8 (50)	< 0.001
Length of hospital stay (days ± SD)	8.51 ± 5.75	6.42 ± 4.8	14 ± 4.25	< 0.001
Exitus, n (%)	5 (8.6)	0	5 (31.2)	< 0.001

COPD: chronic obstructive pulmonary disease, SD: standard deviation.

3. RESULTS

3.1. Study Population

Among 88 patients diagnosed with COVID-19 who underwent chest CT, nine patients with a history of lung surgery, malignancy, or radiotherapy, nine patients with intense motion artifacts on CT, five patients with unsuccessful CT segmentation for quantitative analysis, five patients with contrast-enhanced CT examination, and a patient with severe pulmonary fibrosis due to tuberculosis were excluded from the study. A total of 58 patients (29 male, 50%) were included in the study, and the mean age of patients was 53.07 $\pm$ 15.62 years. Fever (58.6%), cough (69%), and myalgia or fatigue (50%) were the most common clinical symptoms of the patients (Table **1**).

3.2. Clinical Classifications

When the COVID-19 patients were classified according to the disease severity score (DSS) (16), there were 11 patients (25.86%) in group A, 31 patients (53.45%) in B, 11 patients (25.86%) in C, and five patients (8.62%) in D. In total, 42 patients (72.41%) had non-severe, and 16 patients (27.59%) had severe disease.

When the patients were classified into two groups according to the CURB-65 score for the severity of pneumonia (14, 15), 40 patients (68.97%) had mild pneumonia, and 18 patients (21.03%) had severe pneumonia. In both classifications, a significant difference was found between the groups in terms of age; elderly patients had more severe pneumonia (DSS; $p = 0.002$, CURB-65, $p < 0.001$) (Table **1**). An excellent agreement was found between both classification scores (DSS classification and CURB-65 score) in COVID-19 patients with a kappa (K) value of 0.751 (%95 confidence interval: 0.560 - 0.935).

3.3. The relationship between laboratory findings and visual (semi-quantitative) score and quantitative CT analysis

The VSQ and QCT (%WAL, %HAA, MLA, skewness, and kurtosis) scores were significantly correlated with procalcitonin, d-dimer, ferritin, and CRP values (Table **2**). The

Table 2. The correlation of visual semi-quantitative CT and quantitative CT scores with laboratory findings.

-	-	WBC (× 10^9/L) N = 58	NLR N = 58	Lymphocyte (× $10^\wedge$9/L) N = 58	CRP (mg/dL) N = 58	D-Dimer (µg/L) N = 58	Ferritin (µg/L) N = 58	Procalcitonin (ng/mL) N = 58
VSQS	*r-value*	0.379	0.321	-0.087	0.714	0.537	0.638	0.543
	p-value	0.003	0.014	0.518	< 0.001	< 0.001	< 0.001	< 0.001
%WAL	*r-value*	-0.236	-0.199	0.122	-0.575	-0.465	-0.582	-0.319
	p-value	0.074	0.135	0.365	< 0.001	< 0.001	< 0.001	0.017
%HAA-700	*r-value*	0.235	0.192	-0.116	0.569	0.476	0.581	0.307
	p-value	0.075	0.148	0.384	< 0.001	< 0.001	< 0.001	0.021
% HAA-600	*r-value*	0.242	0.195	-0.118	0.574	0.475	0.602	0.333
	p-value	0.068	0.143	0.376	< 0.001	< 0.001	< 0.001	0.012
%HAA-500	*r-value*	0.25	0.188	-0.129	0.566	0.544	0.597	0.325
	p-value	0.058	0.157	0.333	< 0.001	0.001	< 0.001	0.015
%HAA-250	*r-value*	0.243	0.085	-0.037	0.468	0.429	0.577	0.283
	p-value	0.066	0.578	0.781	< 0.001	0.001	< 0.001	0.035
%HAA-(600-250)	*r-value*	0.234	0.198	-0.118	0.572	0.482	0.595	0.328
	p-value	0.077	0.137	0.377	< 0.001	< 0.001	< 0.001	0.013
MLA	*r-value*	0.212	0.154	-0.114	0.502	0.468	0.472	0.200
	p-value	0.111	0.249	0.396	< 0.001	< 0.001	< 0.001	0.140
Skewness	*r-value*	-0.24	-0.218	0.129	-0.617	-0.455	-0.640	-0.359
	p-value	0.069	0.1	0.333	< 0.001	< 0.001	< 0.001	0.007
Kurtosis	*r-value*	-0.235	-0.194	-0.11	-0.607	-0.404	-0.644	-0.366
	p-value	0.076	0.145	0.409	< 0.001	0.001	< 0.001	0.006

VSQS: Visual semi-quantitative score; %HAA: Percentage of the highly attenuated area at threshold value; MLA: Mean lung attenuation; WAL: Well-aerated lung, NLR: Neutrophil to lymphocyte ratio, CRP: c-reactive protein.

neutrophil-to-lymphocyte ratio (NLR) and white blood cell count (WBC) showed a low correlation with VSQS but did not significantly correlate with QCT parameters. Lymphocyte count did not show a significant correlation with both VSQS and QCT. The correlation of laboratory findings with the visual semi-quantitative score (VSQS) and quantitative CT (QCT) analysis is presented in Table **2**.

3.4. The Relationship of the Visual Semi-Quantitative Score and Quantitative CT Analysis with Clinical Classification

The non-severe and severe disease groups showed a significant difference, according to VSQ scores and QCT values ($p < 0.001$) (Table **3**). In addition, there was a statistically significant difference for the VSQS and QCT values between the groups in the mild (score of 0 - 1) and severe pneumonia (score ≥ 2), according to the CURB-65 score ($p < 0.001$) (Table **3**).

3.5. Correlation Between Visual Semi-Quantitative Score and Quantitative CT Analysis Results

Among the QCT parameters, HAA-600% value showed the best correlation with the VSQ score (VSQS) ($r = 730$, $p < 0.001$). The %HAA-700, %HAA-500, %HAA-(600, 250), and %WAL values showed a good correlation with VSQS, while %HAA-500 and MLD values were moderately correlated with VSQS. Moreover, skewness and kurtosis values showed a significant negative correlation with VSQS ($p < 0.001$ for both) (Table **4**).

3.6. The Performance of VSQ and QCT Scores in the Detection of Pneumonia Severity

The cut-off value of VSQ score in distinguishing between non-severe and severe pneumonia was ≥ 7 with a sensitivity of 87.5% and specificity of 85.7%, having an area under the curve (AUC) of 0.946 (95% CI, 0.88 - 1). In quantitative CT analysis, when the 12.94 value was accepted as a cut-off value for the distinction of mild from severe pneumonia, the %HAA-600 parameter had 81.3% sensitivity and 89% specificity with an AUC of 0.916 (95% CI, 0.837 - 0.995). In addition, the %HAA-250 parameter showed 81.3% sensitivity and 85.7% specificity for the 2.39 cut-off value with an AUC of 0.929 (95% CI, 0.823 - 0.994). In addition, the %WAL cut-off value of 75.55 showed 81% sensitivity and 81.2% specificity with AUC of 0.907 (95% CI, 0.821 - 0.993) (Table **5** and Fig. **2**).

3.7. The Relationship of Patients' Length of Hospital Stay with VSQ and QCT Scores

The mean hospitalization length of the patients was 8.51 ± 5.75 days. According to the DSS, the length of stay in the non-severe group was 6.42 ± 4.8 days and 14 ± 4.25 days in

the severe group. There was a significant difference in hospitalization duration in the severe and non-severe groups ($p < 0.001$). While no patient died in the non-severe disease group, five (31.2%) patients died in the severe disease group ($p < 0.001$) (Table **1**).

When the hospitalization length of 10 days or more was considered as a "long hospital stay," the most successful QCT parameter for the detection of "long hospital stay" was HAA-500%, and a 5.9% cut-off value of HAA-500% had 82% sensitivity and 81% specificity with an AUC of 0.854 (95% CI, 0.728 - 0.980). In the VSQ assessment, for a score of 6 and above, the sensitivity was calculated as 77% and specificity as 83% with an AUC of 0.882 (95% CI, 0.792-0.972).

Table 3. The correlation of visual semi-quantitative score and quantitative CT analysis with clinical classification.

-	Non-Severe Group (n = 44)	Severe Group (n = 14)	CURB-65 score (0 - 1) (n = 40)	CURB-65 score (≥ 2) (n = 18)	p-value
VSQS	3.57 (2.76)	11.06 (3.51)	3.63 (3.01)	10.11 (3.98)	< 0.001
%WAL	84.55 (8.29)	63.45 (13.53)	85.01 (8.42)	64.75 (12.98)	< 0.001
%HAA-700	15.29 (8.23)	36.14 (13.49)	14.83 (8.46)	34.85 (12.94)	< 0.001
% HAA-600	8.55 (4.17)	22.72 (9.95)	8.46 (4.729)	21.36 (9.66)	< 0.001
%HAA-500	4.66 (2.18)	13.12 (6.39)	4.69 (2.64)	12.12 (6.31)	< 0.001
%HAA-250	1.68 (0.58)	3.32 (1.46)	1.69 (0.59)	3.10 (1.51)	< 0.001
%HAA-(600-250)	6.86 (3.73)	19.38 (8.82)	6.75 (4.28)	18.23 (8.41)	< 0.001
MLA (HU)	-793.6 (48.5)	-711.2 (55.3)	-796.2 (48.2)	-714.7 (53.3)	< 0.001
Skewness	3.16 (0.78)	1.64 (0.65)	3.21 (0.79)	1.70 (0.58)	< 0.001
Kurtosis	13.03 (6.01)	3.53 (3.12)	13.38 (6.01)	3.81 (2.67)	< 0.001

VSQS: Visual semi-quantitative score; %HAA: Percentage of the highly attenuated area at threshold value; MLA: Mean lung attenuation; WAL: Well-aerated lung; HU: Hounsfield unit; *All values were reported as mean ± (standard deviation).

Table 4. The correlation of visual semi-quantitative score and quantitative CT analysis results.

-	-	%WAL	%HAA -700	%HAA -600	%HAA -500	%HAA -250	%HAA-(600-250)	MLA	Skewness	Kurtosis
VSQS	*r*	-0.709	0.707	0.730	0.723	0.690	0.729	0.621	-0.770	-0.770
	p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

VSQS: Visual semi-quantitative score; %HAA: Percentage of the highly attenuated area at threshold value; MLA: Mean lung attenuation; WAL: Well-aerated lung.

Table 5. The diagnostic performances of visual semi-quantitative CT assessment and quantitative parameters according to receiver operating characteristic curve in distinguishing the clinically severe from non-severe COVID-19.

-	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Cut-Off
VSQS	94.6 (88 - 100)	87.5	85.7	≥ 7
%WAL	90.7 (82.1 - 99.3)	81	81.2	< 75.55
%HAA-700	90.3 (81.6 - 98.9)	81.3	83.3	25.13
% HAA-600	91.6 (83.7 - 99.5)	81	89	12.94
%HAA-500	91.7 (84 - 99.5)	81.3	76.2	6.28
%HAA-250	92.9 (82.3 - 99.4)	81.3	85.7	2.39
%HAA-(600-250)	90.8 (82.3 - 99.4)	81.3	78.6	10.97
MLA (HU)	84.7 (73.9 - 95.6)	75	78.6	-751.07

VSQS: Visual semi-quantitative score; %HAA: Percentage of the highly attenuated area at threshold value; MLA: Mean lung attenuation; WAL: Well-aerated lung; HU: Hounsfield unit; AUC: Area under the curve.

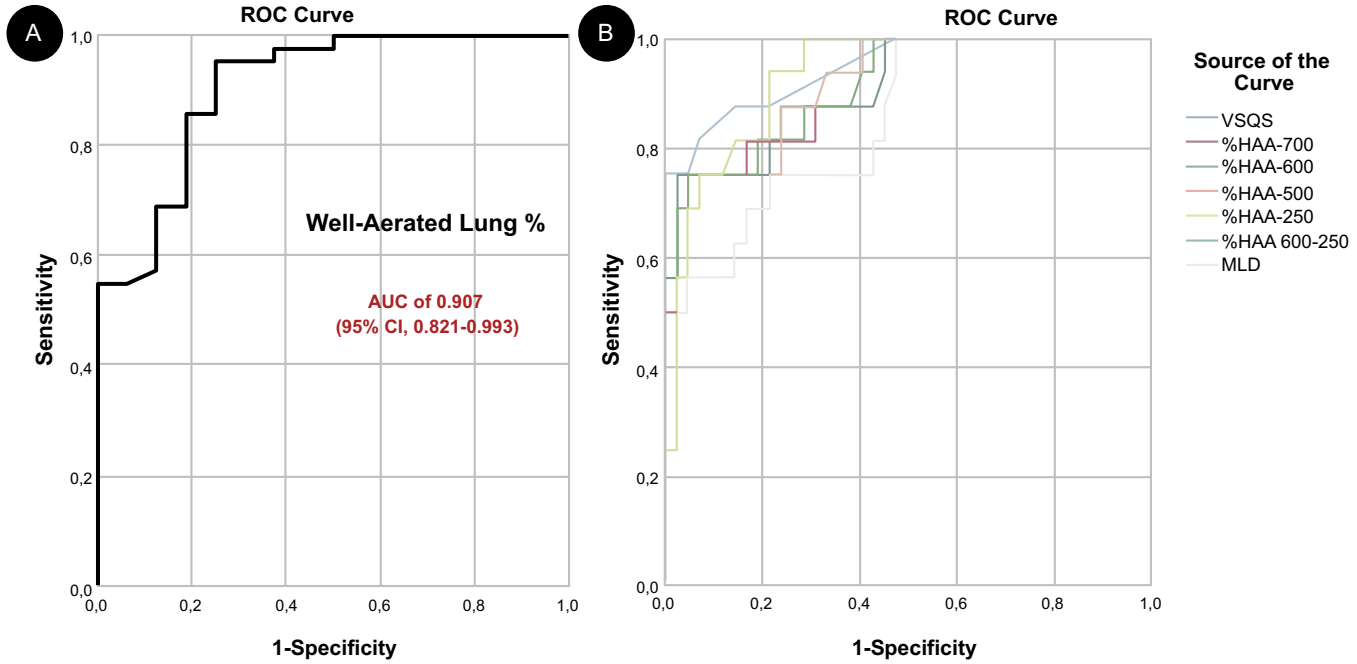


Fig. (2 A and B). Graphs show the diagnostic performance of predicting severe disease for patients with coronavirus disease 2019 (COVID-19) based on baseline unenhanced chest CT at hospital admission. Receiver operator characteristic (ROC) curves of the models based on the percentage of the well-aerated lung (%WAL, solid black line) in **A**. Visual semi-quantitative score (VSQS, blue line), percentage of high attenuation area (%HAA) with different cut-off values, and mean lung attenuation (MLD) values in **B**. The area under the ROC curve (AUC) for VSQS was 94.6 (95% confidence interval [CI]: 88 - 100), %WAL was 90.7 (CI: 82.1 - 99.3), %HAA-700 was 90.3 (CI: 81.6 - 98.9), % HAA-600 was 91.6 (CI: 83.7 - 99.5), %HAA-500 was 91.7 (CI: 84 - 99.5), %HAA-250 was 92.9 (CI: 82.3 - 99.4), %HAA-(600 - 250) was 90.8 (CI: 82.3 - 99.4), and MLA was 84.7 (CI: 73.9 - 95.6). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. DISCUSSION

Our results revealed that both VSQ and QCT scores were significantly correlated with disease severity. QCT can provide valuable and objective information regarding lung involvement as a part of COVID-19 disease. VSQ and QCT scores can predict the prolonged hospital stay with high sensitivity and specificity. Early evaluation of the disease severity in COVID-19 patients can guide therapy options and reduce complications.

In a recent study by Huang *et al.*, significant differences were found in the percentage of lung opacification measured by the deep learning algorithm among COVID-19 patients with different clinical severities [12]. Sun *et al.* showed that ground-glass opacities and consolidation areas on chest CT of patients with COVID-19 pneumonia were significantly correlated with disease severity [17]. The cut-off value for the lung opacities of 8.2% had 91.3% sensitivity and 91.8% specificity for distinguishing severe and non-severe disease in that study. In the present study, the aim was to investigate the success of different QCT parameters in COVID-19 patients and to assess the optimal QCT parameters to estimate disease severity. Similar to Sun *et al.*, the %HAA-600 parameter with a cut-off value of 12.94 has 81.3% sensitivity and 89% specificity with an AUC of 0.916 (95% CI, 0.837-0.995) was found in the present study [17]. Moreover, the diagnostic performance of VSCT and different QCT parameters was also demonstrated in the present study.

Attenuation values below -950 HU in QCT studies indicate areas with emphysema [13]. Therefore, it has been stated that attenuation values between -700 HU and -950 HU may indicate healthy lung parenchyma in COVID-19 pneumonia [11, 18]. Calculating the percentage of healthy lung volume prevents both inadequate extractions of vessels with a density similar to lung opacities and the potential detrimental effects of underlying lung abnormalities, such as emphysema or pulmonary fibrosis in COVID-19 patients. A recent study found that less than 71% of well-aerated lung volume, based on a software-based assessment, can predict intensive care unit (ICU) admission or death in COVID-19 patients [11]. In another study, the percentage of healthy aerated lung parenchyma below 81.1% had asensitivity of 86.5% and a specificity of 86.7% to predict ICU admission [19]. In the same study, it was stated that when QCT evaluated the percentage of the healthy lung parenchyma, a threshold value lower than 82.45% could indicate severe pneumonia with 83.1% sensitivity and 84.2% specificity [19]. Similarly, in the present study, the WAL% value with a cut-off value of <7 5.55% had a sensitivity of 81% and a specificity of 81.2% for distinguishing severe and non-severe disease. The present study also reveals the performance of different QCT

parameters, VSQS, and laboratory analysis to evaluate disease severity.

Typical CT findings of COVID-19 are well-defined in the literature [4]. Based on chest CT features of COVID-19 pneumonia, Yuan *et al.* defined a scoring method to screen patients based on admission CT scans [20]. Li *et al.* proposed a visual semi-quantitative analysis associated with the total severity score and the clinical severity score, depending on the parenchymal infiltration degree [10]. However, the fact that visual pneumonia severity assessment is subjective appears to be a disadvantage. Moreover, a recent article revealed that quantitative CT assessment is superior to VSQS in assessing the pneumonia severity in COVID-19 patients [21]. In the present study, the QCT method provided a rapid and standardized, and consistently reproducible assessment for parenchymal disorders. The used program in the present study had advantages, such as being free and open-source software that is not connected to any workstation, having a low learning curve, and being easily usable during the coronavirus pandemic process with internet support.

Consistent with previous studies' findings, the mean age of the patients in the severe group was higher than the age of the non-severe group [6, 22]. Although the number of males and females were similar to that in the recent studies, COVID-19 was more severe in males than in females [23, 24]. The most common symptoms in the study of Chen *et al.* were fever, cough, and fatigue, and they found that the shortness of breath was more frequent in severe cases compared to moderate cases [25]. In the present study, the results were similar to the findings ofChen *et al.*, he probable reason of which was that shortness of breath primarily indicates pulmonary involvement.

In the present study, the acute phase reactants that showed the highest correlation with VSQS and QCT parameters were CRP and ferritin, and they were observed to be similar to the recent studies [19]. According to those recent studies, it has been reported that both VSQS and QCT analyzes show a significant correlation with length of hospital stay, as well as prediction of the admission in the ICU and severe pneumonia [19, 26]. Similarly, in our study, a significant difference was found between the severe and non-severe groups in hospital stay length. Patients in the severe group had a more extended hospital stay. Although it has been stated that more urgent and widely used lung ultrasound in COVID patients can predict the severity of the disease, it has many disadvantages, especially being observer-dependent [27]. The quantitative CT assessment largely eliminates these disadvantages.

There were some limitations in our study. Firstly, the sample size of the study is small and larger samples are needed to clarify the findings further. Secondly, some patients' images showed inappropriate segmentation and were excluded from the study. Therefore, the applicability of QCT is limited in low-quality CT images. Finally, the patients' other prognostic information (intubation, mechanical ventilation, and intensive care admission) was not directly investigated, however, previous studies have shown that the disease severity score is very important for the prognosis of COVID-19 [10, 11, 20, 28].

CONCLUSION

The VSQ and QCT scores were significantly correlated with disease severity. Moreover, VSQ and QCT scores can predict prolonged hospital stays with high sensitivity and specificity. Among the QCT parameters, the HAA-600% value showed the best correlation with the VSQS. Therefore, VSQ and QCT scores, especially HAA-600% value, can help manage the disease since they are significantly correlated with disease severity.

LIST OF ABBREVIATIONS

CT	=	Computed Tomography
COVID-19	=	Coronavirus Disease 2019
VSQS	=	Visual Semi-Quantitative Score
QCT	=	Quantitative Computed Tomography
%WAL	=	Well-Aerated Lung
HAA	=	High-Attenuation Areas
MLA	=	Mean Lung Attenuation
GGO	=	Ground-Glass Opacity
DSS	=	Disease Severity Score

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol of this study was approved by the Clinical Research Ethics Committee of Afyonkarahisar University of Health Sciences, Turkey (Reference number: 2020/357).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The reported experiments on humans were in accordance with the ethical standards of the committee, responsible for human experimentation (national institutions) and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/).

CONSENT FOR PUBLICATION

Written informed consent was waived because of its retrospective observational nature.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author [F.K] upon request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506. http://dx.doi.org/10.1016/S0140-6736(20)30183-5 PMID: 31986264

[2] Zhu N, Zhang D, Wang W, *et al.* China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in china, 2019. N Engl J Med 2020; 382(8): 727-33. http://dx.doi.org/10.1056/NEJMoa2001017 PMID: 31978945

[3] Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical coronavirus disease 2019 (COVID-19) pneumonia: Relationship to negative RT-PCR testing. Radiology 2020; 296(2): E41-5. http://dx.doi.org/10.1148/radiol.2020200343 PMID: 32049601

[4] Chung M, Bernheim A, Mei X, *et al.* CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology 2020; 295(1): 202-7. http://dx.doi.org/10.1148/radiol.2020200230 PMID: 32017661

[5] Shi H, Han X, Jiang N, *et al.* Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; 20(4): 425-34. http://dx.doi.org/10.1016/S1473-3099(20)30086-4 PMID: 32105637

[6] Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061-9. http://dx.doi.org/10.1001/jama.2020.1585 PMID: 32031570

[7] Xu Z, Shi L, Wang Y, *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8(4): 420-2. http://dx.doi.org/10.1016/S2213-2600(20)30076-X PMID: 32085846

[8] Song F, Shi N, Shan F, *et al.* Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology 2020; 295(1): 210-7. http://dx.doi.org/10.1148/radiol.2020200274 PMID: 32027573

[9] Ufuk F. Three-dimensional CT of COVID-19 Pneumonia. Radiology 2020; 296(3): E180. http://dx.doi.org/10.1148/radiol.2020201183 PMID: 32228362

[10] Li K, Fang Y, Li W, *et al.* CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol 2020; 30(8): 4407-16. http://dx.doi.org/10.1007/s00330-020-06817-6 PMID: 32215691

[11] Colombi D, Bodini FC, Petrini M, *et al.* Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology 2020; 296(2): E86-96. http://dx.doi.org/10.1148/radiol.2020201433 PMID: 32301647

[12] Huang L, Han R, Ai T, *et al.* Serial quantitative chest ct assessment of covid-19: Deep-learning approach. Radiol Cardiothorac Imaging 2020; 2(2): e200075. http://dx.doi.org/10.1148/ryct.2020200075

[13] Chen A, Karwoski RA, Gierada DS, Bartholmai BJ, Koo CW. Quantitative CT analysis of diffuse lung disease. Radiographics 2020; 40(1): 28-43. http://dx.doi.org/10.1148/rg.2020190099 PMID: 31782933

[14] Lim WS, van der Eerden MM, Laing R, *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58(5): 377-82. http://dx.doi.org/10.1136/thorax.58.5.377 PMID: 12728155

[15] Park B, Park J, Lim JK, *et al.* Prognostic implication of volumetric quantitative CT analysis in patients with COVID-19: A multicenter study in daegu, korea. Korean J Radiol 2020; 21(11): 1256-64. http://dx.doi.org/10.3348/kjr.2020.0567 PMID: 32767868

[16] National health commission & state administration of traditional chinese medicine on diagnosis and treatment protocol for novel-Coronavirus pneumonia(Trial Version 7). 2020. http://en.nhc.gov.cn/2020-03/29/c_78469.htm Jun 23, 2020

[17] Sun D, Li X, Guo D, *et al.* CT quantitative analysis and Its relationship with clinical features for assessing the severity of patients with COVID-19. Korean J Radiol 2020; 21(7): 859-68. http://dx.doi.org/10.3348/kjr.2020.0293 PMID: 32524786

[18] Ohkubo H, Kanemitsu Y, Uemura T, *et al.* Correction: normal lung quantification in usual interstitial pneumonia pattern: The impact of threshold-based volumetric CT analysis for the staging of idiopathic pulmonary fibrosis. PLoS One 2016; 11(8): e0160231. http://dx.doi.org/10.1371/journal.pone.0160231 PMID: 27490799

[19] Durhan G, Ardalı Düzgün S, Başaran Demirkazık F, *et al.* Visual and software-based quantitative chest CT assessment of COVID-19: correlation with clinical findings. Diagn Interv Radiol 2020; 26(6): 557-64. http://dx.doi.org/10.5152/dir.2020.20407 PMID: 32876569

[20] Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PLoS One 2020; 15(3): e0230548. http://dx.doi.org/10.1371/journal.pone.0230548 PMID: 32191764

[21] Ufuk F, Demirci M, Uğurlu E, Çetin N, Yiğit N, Sarı T. Evaluation of disease severity with quantitative chest CT in COVID-19 patients. Diagn Interv Radiol 2021; 27(2): 164-71. http://dx.doi.org/10.5152/dir.2020.20281 PMID: 33044173

[22] Guan WJ, Ni ZY, Hu Y, *et al.* China medical treatment expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in china. N Engl J Med 2020; 382(18): 1708-20. http://dx.doi.org/10.1056/NEJMoa2002032 PMID: 32109013

[23] Li X, Xu S, Yu M, *et al.* Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; 146(1): 110-8. http://dx.doi.org/10.1016/j.jaci.2020.04.006 PMID: 32294485

[24] Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care 2020; 24(1): 108. http://dx.doi.org/10.1186/s13054-020-2833-7 PMID: 32188484

[25] Chen G, Wu D, Guo W, *et al.* Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130(5): 2620-9. http://dx.doi.org/10.1172/JCI137244 PMID: 32217835

[26] Liu Z, Jin C, Wu CC, *et al.* Association between initial chest CT or clinical features and clinical course in patients with coronavirus disease 2019 pneumonia. Korean J Radiol 2020; 21(6): 736-45. http://dx.doi.org/10.3348/kjr.2020.0171 PMID: 32410412

[27] Leonard-Lorant I, Severac F, Bilbault P, *et al.* Normal chest CT in 1091 symptomatic patients with confirmed Covid-19: frequency, characteristics and outcome. Eur Radiol 2021; 31(7): 5172-7. PMID: 33439316

[28] Ufuk F, Demirci M, Sagtas E, Akbudak IH, Ugurlu E, Sari T. The prognostic value of pneumonia severity score and pectoralis muscle Area on chest CT in adult COVID-19 patients. Eur J Radiol 2020; 131: 109271. http://dx.doi.org/10.1016/j.ejrad.2020.109271 PMID: 32942198