Japanese Journal of Radiology (2021) 39:956–965
https://doi.org/10.1007/s11604-021-01134-4

ORIGINAL ARTICLE

Quantitative evaluation of COVID-19 pneumonia severity by CT pneumonia analysis algorithm using deep learning technology and blood test results

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Received: 12 March 2021 / Accepted: 5 May 2021 / Published online: 14 May 2021

Abstract

Purpose To evaluate whether early chest computed tomography (CT) lesions quantified by an artificial intelligence (AI)-based commercial software and blood test values at the initial presentation can differentiate the severity of COVID-19 pneumonia.

Materials and methods This retrospective study included 100 SARS-CoV-2-positive patients with mild (n = 23), moderate (n = 37) or severe (n = 40) pneumonia classified according to the Japanese guidelines. Univariate Kruskal–Wallis and multivariate ordinal logistic analyses were used to examine whether CT parameters (opacity score, volume of opacity, % opacity, volume of high opacity, % high opacity and mean HU total on CT) as well as blood test parameters [procalcitonin, estimated glomerular filtration rate (eGFR), C-reactive protein, % lymphocyte, ferritin, aspartate aminotransferase, lactate dehydrogenase, alanine aminotransferase, creatine kinase, hemoglobin A1c, prothrombin time, activated partial prothrombin time (APTT), white blood cell count and creatinine] differed by disease severity.

Results All CT parameters and all blood test parameters except procalcitonin and APPT were significantly different among mild, moderate and severe groups. By multivariate analysis, mean HU total and eGFR were two independent factors associated with severity ($p < 0.0001$). Cutoff values for mean HU total and eGFR were, respectively, − 801 HU and 77 ml/min/1.73 m^2 between mild and moderate pneumonia and − 704 HU and 53 ml/min/1.73 m^2 between moderate and severe pneumonia.

Conclusion The mean HU total of the whole lung, determined by the AI algorithm, and eGFR reflect the severity of COVID-19 pneumonia.

Keywords COVID-19 · Chest CT · Deep learning · Quantitative analysis

Introduction

First detected in Wuhan, China in December 2019, the novel coronavirus SARS-CoV-2 infection (COVID-19) has spread rapidly around the world causing a global pandemic [1]. In Japan, more than 400,000 people were infected by February 2021. COVID-19 causes non-specific respiratory symptoms of varying severity ranging from asymptomatic pneumonia to acute respiratory distress requiring mechanical ventilation. Reported clinical risk factors and predictors for severe illness include age, gender, C-reactive protein (CRP), lactate dehydrogenase (LDH), lymphocyte count, ferritin, d-dimer and comorbidities such as diabetes, chronic obstructive pulmonary disease, hypertension, heart disease, hyperlipidemia and hyperuricemia [2].

The general role of diagnostic imaging is to complement clinical evaluation and laboratory tests in the management of patients already diagnosed with COVID-19 [3]. However, COVID-19 pneumonia can be suspected based on ground-glass opacity (GGO) with or without consolidation on chest computed tomography (CT) even before the results of reverse transcription-polymerase chain reaction (RT-PCR) are available [4, 5]. The positive

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rate for CT imaging for the diagnosis of suspected COVID-19 patients was 88% vs. 59% by RT-PCR, and the sensitivity of CT increased to 97% based on positive RT-PCR results, confirming the role of CT as a primary tool for diagnosis [6]. Several studies have shown the ability of visual quantitative evaluation of CT images to predict mortality and severity with high consistency [7–10], and these scoring techniques are now applied to the risk prediction and severity evaluation of COVID-19 pneumonia using artificial intelligence (AI) [11–14]. In these AI-based approaches, the use of routine blood test results is still limited to a few studies. CRP, IL-6, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR) and d-dimer were shown to be correlated with the quantification results of CT images [15, 16], while a multivariable regression analysis of clinical and CT parameters showed that the consolidation burden and GGO attenuation were better independent predictors of clinical deterioration and death than CRP and history of heart failure and chronic lung disease [17]. Given the importance of early detection and severity assessment of COVID-19 pneumonia for timely intervention and optimization of outcomes, an AI-based approach combining quantitative CT image evaluation and blood test results would provide an indispensable tool.

The purpose of the present study was to evaluate whether early CT lesions quantified by an AI-based commercial software and blood test values at the initial presentation can differentiate the severity of COVID-19 pneumonia.

Materials and methods

Patients and data

This retrospective observational study was approved by the institutional review board at our center (No. 2010108). The patient privacy was maintained by anonymization of patient data. Medical records of 107 patients who were suspected of having COVID-19 pneumonia, underwent CT and tested positive for SARS-CoV-2 by RT-PCR at our center between January and November 2020 were included in the study. Seven patients were excluded because of incomplete breath-hold during CT, and a total of 100 patients [77 men and 23 women; median age, 64 years (interquartile range, IQR, 25)] were included in the further analysis (Fig. 1). The clinical severity was determined according to the guideline of the Ministry of Health, Labour and Welfare of Japan [18] and classified as mild (SpO_2 of ≥ 96%; coughing only without shortness of breath), moderate (SpO_2 of 93–96%; shortness of breath with radiologic evidence of pneumonia or requirement for oxygen therapy) and severe (requiring admission to an intensive care unit or artificial ventilation). The highest severity during the disease course was employed for analysis. Blood test parameters that were determined at the time of initial hospital visit, i.e., procalcitonin, estimated glomerular filtration rate (eGFR), CRP, lymphocyte percentage (% LYM), ferritin, aspartate aminotransferase (AST), LDH, alanine aminotransferase (ALT), creatine kinase (CK), hemoglobin A1c (HbA1c), prothrombin time (PT), activated partial prothrombin time (APPT), white blood cell count (WBC) and creatinine, were included in the analysis.

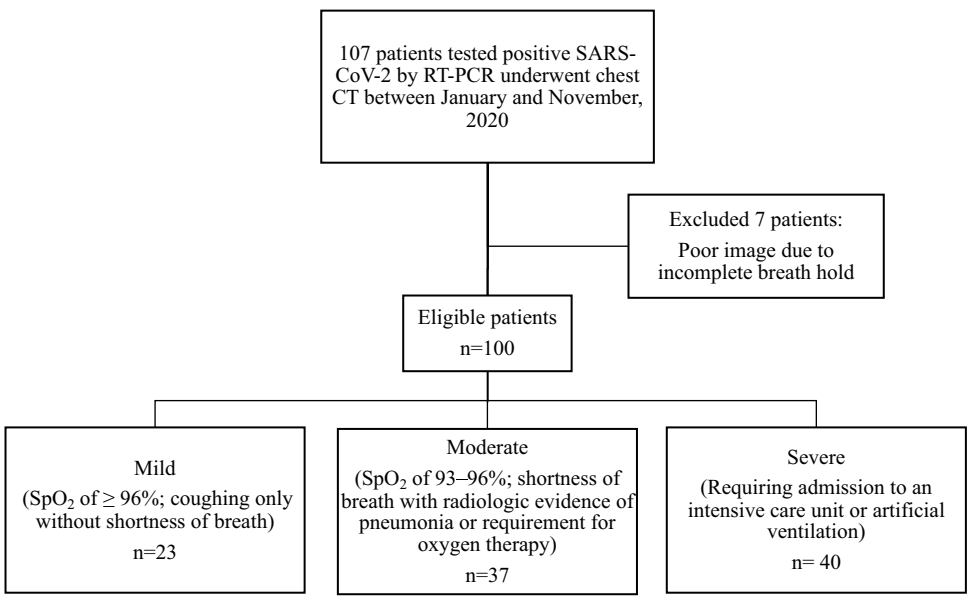


Fig. 1 Flow chart of this study

Chest CT protocol

The first non-contrast CT images taken after the onset of symptoms were included in the study. The median time from PCR diagnosis to CT was 6 days (IQR, 5). Chest CT scans were acquired using a multidetector scanner with 80 detector rows (Aquilion PRIME, Canon Medical Systems, Tochigi, Japan) with the following parameters: 120 kVp; automatic tube current modulation; pitch, 0.625 mm; matrix, 512 × 512; reconstructed slice thickness, 3 mm; and field of view, 36 cm. CT image data sets were reconstructed with a standard algorithm. The CT dose index volume (CTDI vol; in mGy), a standardized measure of the output radiation dose of a CT scanner, was examined.

AI analysis

CT Pneumonia Analysis (Siemens Healthineers, Erlangen, Germany) was used for the quantitation of chest CT lesions. This AI-based software automatically detects and quantifies GGO and consolidation using the algorithm that has been trained by deep learning. Using non-contrasted chest CT data as input, the algorithm automatically detects GGO and consolidation, performs 3D segmentation of lesions, lungs and lobes and quantifies the extent of overall abnormalities as well as the presence of high opacity abnormalities. The quantitative results included in the present analysis were: the opacity score, which was calculated for each lobe by estimating % of opacity within a given region (< 1%, score = 0; 1–25%, score = 1; 25–50%, score = 2; 50–75%, score = 3; and > 75%, score = 4), total opacity score (the sum of opacity scores of all lobes), volume of opacity as the absolute value of lung parenchyma affected by infection (mL), % of opacity within a given lung region, the volume of high opacity as an absolute value (mL), % of high opacity within a given lung region, the mean Hounsfield unit (HU) total of all parenchyma within a given lung region and the mean HU of opacity within a given lung region. A high opacity region is defined as a region of ≥ − 200 HU. Figures 2 and 3 show representative CT features and image by this software.

Statistical analysis

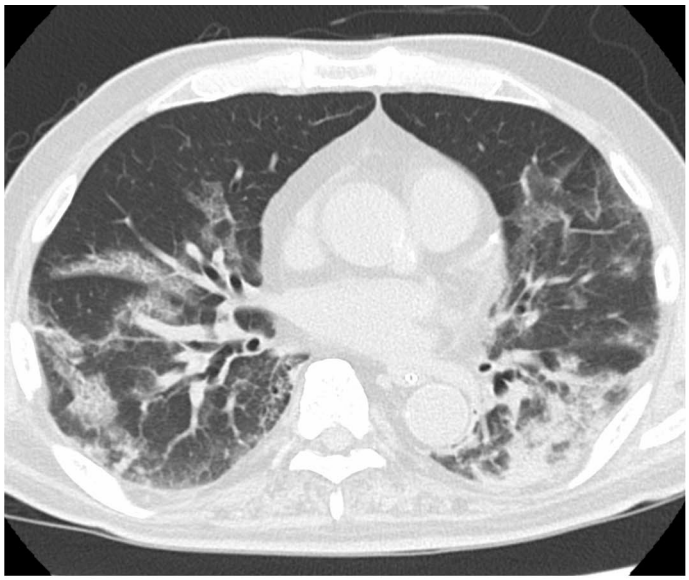
Data were expressed as median and IQR. Univariate analysis by the Kruskal–Wallis test was performed for comparison of age as well as quantitative chest CT and blood test variables among three severity groups (mild, moderate and severe). All variables were also checked for multicollinearity, and those with high correlation were excluded from the multivariate analysis that followed. Significant variables based on the univariate analysis were entered into backward stepwise regression analysis to select the 7 most significant variables. The ordinal logistic analysis was used for multivariate analysis since the response variables were ordinal. In addition to stepwise selection, combinations of CT variables (opacity score, % opacity, % high opacity, mean HU total and mean HU opacity) and age, eGFR and were analyzed by a multivariate analysis model. Finally, cutoff values for mild, moderate and severe pneumonia were estimated by receiver operating curve (ROC) analysis and Youden's index. All statistical analyses were performed using JMP version 14.2 (SAS Institute, Cary, NC, USA) and PRISM version 8.4 (GraphPad Software, La Jolla, CA, USA). p values less than 0.05 were considered statistically significant.

Results

Data of 100 patients diagnosed with COVID-19 pneumonia and results of univariate analysis are summarized in Table 1. Pneumonia was mild in 23, moderate in 37 and severe in 40 patients. The median CT dose index volume for patients was 16.2 mGy (IQR,7). By the Kruskal–Wallis test, all of the quantitative CT parameters were found to be significant factors ($p < 0.05$). Age as well as eGFR, CRP, % LYM, ferritin, AST, LDH, CK, HbA1c, PT, WBC and creatinine were also significant ($p < 0.05$). Multiple linear regression analysis showed high correlations between % opacity and volume of opacity (r = 0.84) and between % high opacity and volume of high opacity (r = 0.91). Volumes of opacity and high opacity were excluded from the multivariate analysis. No other significant correlations were found.

After stepwise regression analysis, % opacity, mean HU total, eGFR, WBC, % LYM, LDH and CK were found to be significant. By multivariate analysis, significant variables were the mean HU total [$p = 0.038$; likelihood ratio $\chi^2 = 4.30$; 95% confidence interval (CI), − 0.0258 to − 0.001] and eGFR ($p = 0.008$; likelihood ratio $\chi^2 = 7.07$; 95% CI, 0.0068 to 0.044) (Table 2). Multivariate analysis of combinations also identified the mean HU total ($p = 0.0425$) and eGFR ($p = 0.0335$) as independent factors.

The ROC analysis for all CT quantitative analysis values and blood test results in each binary group are shown in Table 3. For the two factors that were significant in the multivariate analysis, the cutoff values of the mean HU total were -801 HU for mild vs. moderate (AUC = 0.75; Youden's index = 0.47; sensitivity, 0.82; specificity, 0.65; $p = 0.002$, 95% confidence interval (CI), 0.61 to 0.88) and -704 HU for moderate vs. severe (AUC = 0.71; Youden's index = 0.46; sensitivity, 0.59; specificity, 0.86; $p = 0.002$, 95% CI, 0.59 to 0.83). The cutoff values of eGFR were 77 for mild vs. moderate (AUC = 0.61; Youden's index = 0.33; sensitivity, 0.61; specificity, 0.71; $p = 0.16$, 95% CI, 0.45 to 0.77) and 53 for moderate vs. severe (AUC = 0.64; Youden's index = 0.4; sensitivity, 0.54; specificity, 0.86; $p = 0.036$, 95% CI, 0.51 to 0.79).



Results

Pulmonary Density

AI-Rad Companion

LUNG OPACITY	Both Lungs	Right Lung	Left Lung
Opacity Score	11	5	6
Total Volume [ml]	3097.96	1778.24	1319.72
Opacity Volume [ml]	1444.90	704.92	739.98
Opacity Percentage [%]	46.64	39.64	56.07
High Opacity Volume [ml]	227.64	104.02	123.62
High Opacity Percentage [%]	7.35	5.85	9.37
Mean HU Total [HU]	-667.37	-692.08	-634.08
Mean HU of Opacity [HU]	-521.85	-525.90	-517.98
Standard Deviation Total [HU]	282.27	277.19	285.61
Standard Deviation of Opacity [HU]	271.26	268.00	274.28

Not for diagnosis *

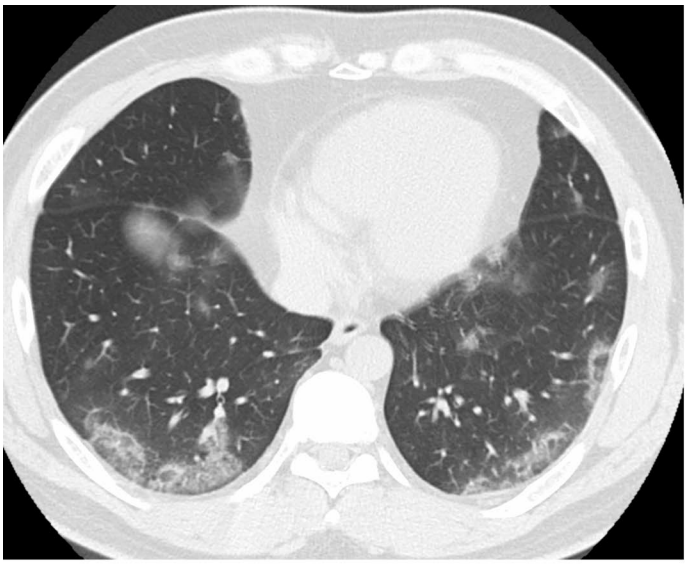
LUNG LOBE OPACITY	Right Upper	Right Middle	Right Lower	Left Upper	Left Lower
Opacity Score	2	1	2	3	3
Total Volume [ml]	730.59	394.73	652.92	918.17	401.54
Opacity Volume [ml]	339.31	71.60	294.01	493.27	246.70
Opacity Percentage [%]	46.44	18.14	45.03	53.72	61.44
High Opacity Volume [ml]	50.10	6.01	47.91	32.39	91.23
High Opacity Percentage [%]	6.86	1.52	7.34	3.53	22.72
Mean HU Total [HU]	-692.14	-815.90	-617.14	-700.01	-483.32
Mean HU of Opacity [HU]	-533.71	-607.65	-496.99	-600.37	-353.24
Standard Deviation Total [HU]	284.98	212.86	275.88	240.56	321.12
Standard Deviation of Opacity [HU]	273.60	250.98	260.65	225.21	289.01

* Colors are based on institutional settings.
They are not an indication or recommendation for treatment.
To interpret the results, please refer to the user documentation.

Fig. 2 Chest CT of a 70 old-male diagnosed severe COVID-19 pneumonia shows consolidation and ground-glass opacity with a crazy-paving appearance in the bilateral lobe. CT pneumonia analysis displays various quantitative values

Discussion

By multivariate analysis of chest CT values quantified by a deep learning algorithm and clinical laboratory values, we found that the mean HU total and eGFR are independent factors that reflect the severity of COVID-19 pneumonia ($p < 0.0001$). Early risk identification using these factors is expected to facilitate severity assessment and determine optimal treatment strategies at earlier stages.



Results

Pulmonary Density

AI-Rad Companion

LUNG OPACITY	Both Lungs	Right Lung	Left Lung
Opacity Score	5	3	2
Total Volume [ml]	4782.77	2787.07	1995.71
Opacity Volume [ml]	679.86	313.46	366.40
Opacity Percentage [%]	14.21	11.25	18.36
High Opacity Volume [ml]	74.75	36.78	37.97
High Opacity Percentage [%]	1.56	1.32	1.90
Mean HU Total [HU]	-759.74	-785.45	-723.82
Mean HU of Opacity [HU]	-515.26	-520.15	-511.09
Standard Deviation Total [HU]	230.10	220.13	238.75
Standard Deviation of Opacity [HU]	229.95	239.89	221.01

Not for diagnosis *

LUNG LOBE OPACITY	Right Upper	Right Middle	Right Lower	Left Upper	Left Lower
Opacity Score	1	1	1	1	1
Total Volume [ml]	1005.21	607.01	1174.84	1109.53	886.18
Opacity Volume [ml]	75.64	18.17	219.64	192.69	173.72
Opacity Percentage [%]	7.53	2.99	18.70	17.37	19.60
High Opacity Volume [ml]	5.83	0.34	30.61	17.33	20.64
High Opacity Percentage [%]	0.58	0.06	2.61	1.56	2.33
Mean HU Total [HU]	-815.04	-850.53	-726.52	-753.26	-686.95
Mean HU of Opacity [HU]	-601.88	-640.71	-482.02	-536.79	-482.58
Standard Deviation Total [HU]	202.16	165.62	243.73	231.33	242.75
Standard Deviation of Opacity [HU]	236.39	180.87	234.99	224.07	213.98

* Colors are based on institutional settings.
They are not an indication or recommendation for treatment.
To interpret the results, please refer to the user documentation.

Fig. 3 Chest CT of a 38 old-male diagnosed with moderate COVID-19 pneumonia shows peripheral ground-glass opacities predominantly in the lower lungs. CT pneumonia analysis displays various quantitative values

Reported imaging parameters that can predict clinical deterioration include quantitative bilateral consolidation on CT [odds ratio (OR), 4.84] [17] and chest radiographic abnormality (OR, 3.39) [19], and the number of affected lobes is also correlated with prognosis [21]. Yuan et al. reported that the CT score determined by experienced pulmonologists was higher in the mortality group compared to the survival group and concluded that a simple scoring method could predict mortality [7]. Li et al. also reported that visual quantitative evaluation of CT images reflected the

Table 1 Patient data, CT and blood parameters and *p* values for group comparisons by Kruskal–Wallis test

	Total (n = 100)	Mild (n = 23)	Moderate (n = 37)	Severe (n = 40)	*p*
Sex					
Male	77	13	32	32	
Female	23	10	5	8	
Age	64 ± 27 (22–85)	52 ± 23 (22–77)	65 ± 27 (31–85)	70 ± 16 (29–85)	0.0017
CT values					
Opacity score	5 ± 6 (0–17)	2 ± 3 (0–12)	5 ± 6 (1–12)	8 ± 7 (0–17)	< 0.0001
Lung volume (ml)	3738.31 ± 1438.43 (2268.16–7048.26)	4253.33. ± 1543.22 (2504.1–6387.95)	3858.72 ± 1351.79 (2541.07–5984.29)	3482.93 ± 886.05 (2268.16–7048.26)	0.033
Volume of opacity (ml)	349.29 ± 867.25 (0.56–2157.76)	153.74 ± 229.81 (0.56–1743.37)	481.83 ± 835.03 (27.13–1395.03)	819.21 ± 1138.95 (0.98–2157.76)	< 0.0001
% of opacity	8.21 ± 25.82 (0.011–64.19)	4.11 ± 5.90 (0.01–51.58)	10.18 ± 19.40 (0.52–39.84)	25.52 ± 38.01 (0.035–64.19)	< 0.0001
Volume of high opacity (ml)	38.92 ± 134.29 (0.014–471.05)	17.50. ± 27.01 (0.014–303.40)	38.45 ± 80.96 (1.29–420.07)	125.61 ± 227.05 (0.11–471.05)	< 0.0001
% of high opacity	1.22 ± 3.83 (0.00026–24.24)	0.45 ± 0.689 (0.00026–8.71)	1.25 ± 1.61 (0.027–14.55)	3.78 ± 6.88 (0.0039–24.24)	< 0.0001
Mean HU total (HU)	− 770.95 ± 112.43 (− 903.06–630.1)	− 814.76 ± 50.99 (− 903.06–630.1)	− 773.25 ± 51.34 (− 845.62–585.5)	− 692.88 ± 137.78 (− 822.68–501.67)	< 0.0001
Mean HU of opacity (HU)	− 544.11 ± 129.55 (− 751.3–318.09)	− 588.18 ± 166.53 (− 751.3–361.8)	− 551.04 ± 102.76 (− 675.99–318.09)	− 505.35 ± 151.93 (− 664.4–338.69)	0.039
Blood test values					
Procalcitonin (ng/ml)	0.09 ± 0.10 (0.02–29)	0.06 ± 0.085 (0.02–29)	0.08 ± 0.07 (0.02–0.43)	0.13 ± 0.16 (0.03–2.3)	0.28
eGFR (ml/min/1.73 m^2)	69.5 ± 38.25 (6–145)	78.15 ± 21.58 (31–145)	70.28 ± 22.3 (6–120)	50.00. ± 44.75 (8.− 110)	0.008
C-reactive protein (mg/dl)	4.89 ± 7.22 (0.07–24.25)	1.79 ± 3.15 (0.07–10.83)	5.21 ± 6.11 (0.31–24.25)	6.76 ± 6.80 (0.31–22.15)	< 0.0001
% Lymphocyte	18.15 ± 16.48 (0.8–54.7)	23.05 ± 12.63 (9–54.7)	16.7 ± 17.15 (0.8–36)	14.9 ± 14.25 (4–53.6)	0.0075
Ferritin (ng/ml)	827.5 ± 895.75 (4–6667)	546 ± 523.25 (4–886)	1003 ± 1073 (31–6667)	868.66 ± 834 (222–6000)	0.0041
AST (IU/l)	38 ± 29.75 (14–151)	27 ± 21.75 (14–121)	38 ± 23 (22–79)	43 ± 40.5 (16–151)	0.0038
LDH (U/l)	327.83 ± 184 (75–1173)	263.23 ± 100.25 (75–1173)	309.95 ± 150 (144–535)	392.86 ± 243.25 (80–1112)	0.0006
ALT (IU/l)	30 ± 22.5 (10–391)	24.5 ± 23 (10–258)	33 ± 23 (10–391)	31 ± 21.75 (12–168)	0.39
CK (U/l)	85 ± 126 (0.79–3008)	62 ± 38 (28–583)	74.5 ± 139.25 (0.79–2133)	126 ± 238 (29–3008)	0.0022
HbA1c (%)	6.1 ± 1.3 (5–13.4)	5.85 ± 1.3 (5–11.4)	5.9 ± 1.1 (5–10.8)	6.4 ± 1.08 (5.4–13.4)	0.013
PT (sec)	11 ± 1.05 (9.5–99.3)	10.9 ± 0.45 (9.6–12.3)	10.8 ± 1.15 (9.5–99.3)	11.4 ± 1.85 (10.2–95)	0.022
APTT (sec)	33.1 ± 7 (24.4–73.8)	33.1 ± 5.15 (25.2–46.9)	32.55 ± 6.95 (27.4–73.8)	35.25 ± 8.08 (24.4–64.1)	0.36
WBC ($\times 10^9$/l)	5.6 ± 3.05 (1.88–33.3)	4.3 ± 2.59 (2.81–33.3)	5.26 ± .2.61 (1.88–13.65)	6.35 ± 3.66 (2.65–12.59)	0.007
Creatinine (mg/dl)	0.86 ± 0.45(0.43–5396)	0.76 ± 0.34(0.52–1.91)	0.85 ± 0.18(0.43–5396)	1.07 ± 0.63(0.55–5.91)	0.013

Data are expressed as median ± IQR (range), and *p* values less than 0.05 were considered significant

eGFR estimated glomerular filtration rate, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase, *ALT* alanine aminotransferase, *CK* creatine kinase, *HbA1c* hemoglobin A1c, *PT* prothrombin time, *APTT* activated partial prothrombin time, *WBC* white blood cell count

severity of COVID-19 [8]. In a study by Zhou et al., the total CT score was one of the independent risk factors for poor prognosis, and temporal changes of CT findings and severity scores were important factors for the early identification of severe cases, which would help to minimize the mortality rate [9]. We did not perform a qualitative, visual assessment of CT images and instead used an AI-based quantitative analysis which is increasingly employed for accurate severity stratification of COVID-19 patients. In a study by Mergen et al. [15], % opacity and % high opacity were significantly higher in patients requiring In a study by Mergen et al. [15], % opacity and % high opacity were significantly higher in patients requiring mechanical ventilation and moderately correlated with CRP (r = 0.49–0.60, both $p < 0.001$) and WBC (r = 0.30–0.40, both $p = 0.05$). The % opacity was also negatively correlated with SpO_2. In a study using the same CT Pneumonia Analysis software, the opacity score, % opacity, volume of opacity, volume of high opacity, % high

Table 2 Chi-square and *p* values and 95% confidence interval (CI) for multivariate analysis

	Chi-square	*p*	Lower 95% CI	Upper 95% CI
Percentage of opacity	0.00	0.980	− 0.057	0.054
Mean HU total*	4.30	0.038	− 0.026	− 0.001
eGFR*	7.07	0.008	0.0068	0.044
White blood cell count	1.38	0.240	− 0.061	0.206
% Lymphocyte	1.99	0.159	− 0.012	0.074
LDH	1.38	0.239	− 0.0053	0.001
CK	2.68	0.102	− 0.007	0.000

eGFR estimated glomerular filtration rate, *WBC* white blood cell count, *LDH* lactate dehydrogenase, *CK* creatine kinase, *HbA1c* hemoglobin A1c

*$p > 0.05$

opacity and mean HU total were significantly higher in the moderate and severe groups compared to the mild group, while the total lung volume was significantly lower in the severe group compared to the mild group [14]. The results of our study also showed significant differences in % opacity and % of high opacity in univariate analysis, which is consistent with their results. In our study, however, the mean HU of opacity was not significantly different between moderate and severe patients. This is probably because different clinical criteria were used for moderate and severe classification. Nonetheless, results in their study and ours suggest that AI-based quantitative CT assessment is a valuable early tool with high sensitivity and specificity for severity assessment. It is expected to play an important role in early COVID-19 management.

The results of the multivariate analysis in our study showed that a higher mean HU total, i.e., higher density in both lungs, is more likely to be associated with severe disease. GGO in the dorsal aspect of the lower lobe accompanied by reduced lung volume is a characteristic CT finding in COVID-19 pneumonia, and consolidation is more frequently found in severer cases [22]. In one study, which also used AI for the quantification of CT findings, multivariate analysis showed that % GGO, semi-consolidation volume and consolidation volume were significantly better predictors of severity than NLR or d-dimer [16]. Another AI-based CT study evaluated the CT severity score, GGO volume, % GGO volume, consolidation volume and % consolidation volume and found that the consolidation volume was a strong predictor for unfavorable outcome by multivariate regression analysis (hazard ratio, 1.053; $p = 0.006$) [13]. Although different parameters are available in the AI analysis software we used, the mean HU total was associated with severity. Collectively, these findings strongly indicate the usefulness of quantitative CT lesion assessment in COVID-19 pneumonia.

Reported cutoff values for the mean HU total to differentiate mild from moderate and severe cases were − 637.7 (AUC, 0.876; 81.8% sensitivity and 81.9% specificity) [14] and − 816 (AUC, 0.87; 91% sensitivity and 90% specificity) [23]. In these studies, mild pneumonia included patients with respiratory symptoms and evidence of pneumonia on CT. In our study, the cutoff value was − 801 HU for differentiation of mild (SpO_2 of ≥ 96%; coughing only with no shortness of breath) from moderate pneumonia (SpO_2 of 93–96%; shortness of breath with radiographic evidence of pneumonia or requirement for oxygen therapy). These results indicate that cutoff values for the mean HU total are likely able to differentiate mild, moderate and severe diseases early in the disease course. The ability to predict clinical deterioration based on the earliest CT images should assist early identification of and early intervention for patients who are likely to develop severer pneumonia.

Factors associated with severer COVID-19 have been extensively studied and reviewed. These include age, comorbidities such as chronic obstructive pulmonary disease, diabetes, hypertension, chronic kidney disease and malignancy, sequential organ failure assessment score and history of cancer. Among blood test parameters, NLR, LDH, direct bilirubin, albumin, creatinine, d-dimer, LDH, AST, ALT, BUN, creatinine, procalcitonin, IL-6, KL-6 and ferritin have been associated with severity [24–26]. Although we did not include comorbidities in our analysis, we found that eGFR, CRP, % LYM, ferritin, AST, LDH, CK, HbA1c and PT were significantly associated with disease severity. By multivariate analysis, we found that eGFR was the most significant factor among them. One study reported that a high percentage of COVID-19 patients had renal abnormalities and that although the majority of proteinuria, hematuria and acute kidney injury resolved within 3 weeks of the onset of symptoms, renal involvement was associated with higher mortality [27]. Thus, renal function impairment in the early stage of COVID-19 is likely associated with the disease severity. The role of early severity assessment based on initial blood test results s and CT values quantified by a deep learning algorithm are significant, as physicians would be better prepared for early intervention before clinical deterioration occurs and able to provide appropriate treatment at the time of deterioration with watchful waiting. If the usefulness of

Table 3 Cutoff values for CT and blood test to differentiate mild from moderate and severe cases

Mild vs moderate	Cut off	AUC	Sensitivity	Specificity	Youden's index	Lower 95% CI	Upper 95% CI	*p*
CT values								
Opacity Score*	3.00	0.76	0.84	0.54	0.38	0.64	0.88	0.000
Volume of opacity*	473.3	0.73	0.54	0.92	0.46	0.60	0.86	0.002
Percentage of opacity*	9.48	0.72	0.54	0.88	0.43	0.59	0.85	0.003
Volume of high opacity*	32.25	0.70	0.59	0.77	0.36	0.57	0.84	0.006
Percentage of high opacity*	0.94	0.69	0.57	0.77	0.34	0.56	0.83	0.010
Mean HU total*	-801	0.75	0.82	0.65	0.46	0.62	0.88	0.002
Mean HU of opacity	-612	0.61	0.84	0.46	0.24	0.46	0.76	0.150
Blood test values								
Procalcitonin	0.43	0.42	1.00	0.18	0.18	0.39	0.77	0.367
eGFR	77	0.61	0.61	0.71	0.33	0.46	0.77	0.164
C-reactive protein*	3.73	0.80	0.78	0.69	0.53	0.69	0.91	< 0.0001
Percentage of Lymphocyte*	13.50	0.67	0.47	0.88	0.36	0.54	0.81	0.020
Ferritin*	932	0.75	0.55	1.00	0.55	0.61	0.88	0.004
AST*	29	0.68	0.81	0.54	0.35	0.55	0.83	0.011
LDH*	301	0.71	0.54	0.85	0.39	0.44	0.74	0.004
ALT	28	0.59	0.65	0.62	0.26	0.44	0.74	0.238
CK	170	0.61	0.30	0.96	0.26	0.47	0.75	0.151
HbA1c	9.8	0.48	0.97	0.17	0.14	0.34	0.69	0.848
PT	11.30	0.48	0.34	0.84	0.19	0.35	0.68	0.856
APTT	27.40	0.50	1.00	0.16	0.16	0.34	0.67	0.979
WBC count	2.62	0.43	0.08	1.00	0.08	0.43	0.72	0.335
Creatinine	0.79	0.60	0.75	0.58	0.33	0.44	0.75	0.192
Moderate vs severe	Cut off	AUC	Sensitivity	Specificity	Youden's index	Lower 95% CI	Upper 95% CI	*p* value
CT values								
Opacity Score*	11	0.67	0.38	0.95	0.32	0.55	0.80	0.011
Volume of opacity	1405.55	0.64	0.32	100.00	0.32	0.49	0.75	0.078
Percentage of opacity*	37.84	0.68	0.43	0.95	0.38	0.56	0.80	0.008
Volume of high opacity*	101.05	0.66	0.62	0.81	0.43	0.53	0.79	0.020
Percentage of high opacity*	2.11	0.68	0.65	0.78	0.43	0.55	0.81	0.008
Mean HU total*	-704	0.71	0.59	0.86	0.46	0.59	0.83	0.002
Mean HU of opacity	-482	0.60	0.43	0.76	0.24	0.47	0.73	0.134
Blood test values								
Procalcitonin*	95	0.33	0.97	0.03	0.03	0.57	0.82	0.047
eGFR*	53	0.64	0.85	0.54	0.40	0.51	0.79	0.036
C-reactive protein	6.67	0.65	0.67	0.57	0.26	0.50	0.76	0.064
Percentage of Lymphocyte	25.7	0.54	0.86	0.28	0.14	0.39	0.66	0.706
Ferritin	293	0.50	0.97	0.15	0.12	0.36	0.64	0.980
AST	61	0.61	0.43	0.84	0.27	0.49	0.76	0.064
LDH*	422	0.62	0.44	0.77	0.28	0.52	0.77	0.031
ALT	34	0.51	0.64	0.46	0.10	0.38	0.65	0.817
CK*	113	0.64	0.64	0.68	0.31	0.54	0.79	0.015
HbA1c*	6.1	0.69	0.77	0.65	0.38	0.54	0.81	0.017
PT*	0.13	0.66	0.52	0.79	0.30	0.51	0.80	0.005
APTT*	37.3	0.61	0.42	0.75	0.23	0.51	0.77	0.048
WBC count	5.6	0.65	0.69	0.59	0.29	0.50	0.76	0.058
Creatinine*	1.13	0.65	0.51	0.85	0.37	0.52	0.79	0.028

AUC area under the curve, *eGFR* estimated glomerular filtration rate, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase, *ALT* alanine aminotransferase, *CK* creatine kinase, *HbA1c* hemoglobin A1c, *PT* prothrombin time, *APTT* activated partial prothrombin time, WBC white blood cell count

*$p > 0.05$

these results in clinical practice is demonstrated by further studies, it will allow us to evaluate the severity of COVID-19 patients, determine whether they should be hospitalized or stay at home and allocate available medical resources.

The present study has some limitations. First, it is a single-center study involving a relatively small number of patients. Second, our center primarily accepts severe COVID-19 patients, and therefore the study results may be biased toward severe cases. Third, the patients in this study were classified according to the greatest severity they experienced during the course of the disease, while only the earliest CT data were used for AI analysis. CT data later in the disease course were not included. In some patients, the condition may deteriorate quite rapidly with acutely progressive GGO, even though GGO was minimal on initial CT assessment. Fourth, the small number of samples did not allow simultaneous multivariate analysis of all variables. Although stepwise regression has both advantages and disadvantages, multivariate analysis of combinations of CT data and inflammatory markers also demonstrated that the mean HU total and eGFR were the independent predictors. Therefore, it was considered a meaningful approach as part of the sensitivity analysis even with a limited number of cases.

Conclusion

We found that the mean density of the whole lung, as determined by the deep learning algorithm, and eGFR were significant predictors of the severity of COVID-19 pneumonia.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This work was approved by the local institutional review board. No. 2010108.

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