Identification of common and severe COVID-19: the value of CT texture analysis and correlation with clinical characteristics

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Abstract

Objective To explore the value of CT texture analysis (CTTA) for determining coronavirus disease 2019 (COVID-19) severity.

Methods The clinical and CT data of 81 patients with COVID-19 were retrospectively analyzed. The texture features were extracted using LK2.1. The two-sample *t* test or Mann–Whitney *U* test was used to find the significant features. Minimum redundancy and maximum relevance (MRMR) method was performed to find the features with maximum correlation and minimum redundancy. These features were then used to construct a radiomics texture model to discriminate the severe patients using multivariate logistic regression method. Besides, a clinical model was also built. ROC analyses were conducted to evaluate the performance of two models. The correlations of clinical features and textural features were analyzed using the Spearman correlation analysis.

Results Of the total cases included, 60 were common and 21 were severe. (1) For textural features, 20 radiomics features selected by MRMR showed good performance in discriminating the two groups (AUC > 70%). (2) For clinical features, chi-square tests or Mann–Whitney *U* tests identified 16 clinical features as significant, and 12 were discriminative ($p < 0.05$) between two groups analyzed by univariate logistic analysis. Of these, 10 had an AUC > 70%. (3) Prediction models for textural features and clinical features were established, and both showed high predictive accuracy. The AUC values of textural features and clinical features were 0.93 (0.86–1.00) and 0.95 (0.95–0.99), respectively. (4) The Spearman correlation analysis showed that most textural and clinical features had above-moderate correlations with disease severity (> 0.4).

Conclusion Texture analysis can provide reliable and objective information for differential diagnosis of COVID-19.

Key Points

- CT texture analysis can well differentiate common and severe COVID-19 patients.
- Some textural features showed above-moderate correlations with clinical factors.
- CT texture analysis can provide useful information to judge the severity of COVID-19.

Keywords Coronavirus · Disease · Tomography · X-rays

Abbreviations

COVID-19 Coronavirus disease 2019
CTTA CT texture analysis
GGO Ground-glass opacity
GLRLM Gray-level run length matrix

GLSZM Gray-level size zone matrix
LGOCV Leave-group-out cross-validation
MRMR Minimum redundancy and maximum relevance
VOI Volume of interest

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Introduction

In December 2019, coronavirus disease 2019 (COVID-19) was discovered in Wuhan, China, and then spread across the country [1–3]. According to Chinese guideline, COVID-19 is clinically divided into four types: mild, common, severe, and critically severe [4]. Compared with healthy individuals, mild COVID-19 shows no obvious CT abnormality, but the other three do. Yang et al [5] reported that the mortality of severe COVID-19 in Wuhan exceeded 60%. Therefore, early and correct evaluation of COVID-19 severity and timely treatment can improve patients' prognosis.

CT plays an important role in the evaluation of COVID-19. Clinical CT results are made by physicians through analyzing the size, shape, position, and internal density of CT images. However, this analysis fails to capture diagnostic/prognostic information about the lesion. Through, texture analysis, mathematical methods are used to extract meaningful characteristics of an image at different gray levels, so as to quantify the lesion's heterogeneity [6]. This retrospective study was performed to analyze the correlations among CT texture features, clinical features, and clinical subtypes of COVID-19 and to

explore the value of CT texture analysis in determining the severity of COVID-19.

Materials and methods

Patients and ethical approval

Our institutional review board (IRB) waived written informed consent for this retrospective study, which evaluated de-identified data and brought no potential risk to patients. To avert any potential breach of confidentiality, no link between the patients and the researchers was available.

The patients' data were collected from the First Affiliated Hospital of University of Science and Technology of China and the Affiliated Infectious Disease Hospital. During the period between January 20, 2020 and February 20, 2020, patients were included if they met the following criteria: (1) exhibiting positive results of 2019-nCoV nucleic acids and (2) having undergone chest CT examination during the initial diagnosis (within 3 days after admission). Excluded were those who had no obvious lung CT abnormalities or had

Fig. 1 A common case of COVID-19. A man aged 53 years presented with a 3-day history of fever, cough, and sputum. **a, b** On the third day after disease onset, CT imaging revealed pure ground-glass opacity

(GGO) and GGO with fine grid in the bilateral lobes. **c, d** The area of the lesions was delineated on the axial and reconstructed images. **e** Histogram map of the lesions

pneumonia caused by other common bacterial or viral pathogens. According to the clinical classification criteria, 81 patients were enrolled (60 common cases and 21 severe cases).

Scanning

CT was performed for all patients within 3 days after disease onset, with a 128-slice CT detector (NeuViz 128) without contrast agent. The scanning parameters were as follows: tube voltage, 120 kVp; tube current, 150 mA; rotation time, 0.8 s; slice thickness, 5 mm; slice interval, 5 mm; pitch, 1.2; matrix, 512×512 ; and breath-holding when fully aspirated.

Region-of-interest segmentation and feature extraction

All images were segmented on the LK2.1 software package (GE Healthcare). First, the images were resampled to voxel size $1 \times 1 \times 1 \text{ mm}^3$, and a Gaussian filter was applied for denoising. Then, the lung was automatically segmented into five lobes, three-dimensional volumes of interest (VOIs) were created for each lobe, and the CT score was calculated [7]. If the automatic segmentation failed to create favorable volumes, an experienced radiologist was assigned to manually delineate the VOIs, and another radiologist to check the

segmentation. Any difference in opinions was resolved through negotiation. Pyradiomics was performed to extract features. In total, 1042 features were extracted, including histogram features, gray-level co-occurrence matrix, gray-level size zone matrix (GLSZM), and gray-level run length matrix (GLRLM) features.

Statistical analysis of radiomics and clinical features

All statistical analyses were performed using R (version 3.5.1; www.R-project.org) software. First, for radiomics features and CT score, the independent *t* test or Wilcoxon test was used. For clinical features described as continuous variables, the Mann–Whitney *U* test was used for abnormal distributions and *t* test for normal distributions. For clinical features described as nominal variables, chi-square test or Fisher's exact test was used. Features with $p < 0.05$ were deemed statistically significant. Second, for radiomics features, univariate logistic analysis was performed to evaluate whether the features were discriminative in two groups ($p < 0.05$). Then, the minimum redundancy and maximum relevance (MRMR) algorithm was applied to further select the relevant and non-redundant features. For clinical factors, univariate logistic analysis was performed to find the discriminative features ($p < 0.05$). Third, for both radiomics features and clinical features, backward

Fig. 2 A severe case of COVID-19. A man aged 47 years presented with a 7-day history of fever, cough, and sputum. **a, b** On the third day after disease onset, CT imaging revealed diffuse pure GGO and GGO with fine

grid in the bilateral lobes. **c, d** The area of the lesions was delineated on the axial and reconstructed images. **e** Histogram map of the lesions

stepwise multivariate logistic regression selection was performed, and the likelihood ratio test was used to select the subset of the most predictive features and construct the predictive model. Finally, to verify the reliability of texture analysis, 100-fold leave-group-out cross-validation (LGOCV) was performed. Finally, Spearman correlation analyses were performed to evaluate the correlations between the predictive radiomics features and clinical factors.

Results

Eighty-one patients with a mean age of 51.35 ± 14.31 years diagnosed with COVID-19 were included. Of which, 21 (26%) had severe and 60 (74%) had common symptoms.

The CT characteristics included ground-glass opacity (GGO) or GGO combined with fine grid or consolidation. Patients with severe disease exhibited diffuse lesions; in four patients, initial CT images showed involvement in all the segments of both lungs. Most lesions were observed in the peripheral zone of the lung field, particularly the lower lobe. Figures 1 and 2 show representative images of common and severe COVID-19, respectively.

Of the 1042 radiomics features, 511 were statistically significant when assessed by independent *t* test or Mann–Whitney test ($p < 0.05$). Of these, 358 were selected by univariate logistic analysis ($p < 0.05$), then 20 were retained after MRMR analysis. The AUC values of these 20 radiomics features are shown in Fig. 3 a. All of them showed good predictive performance, with AUC values $> 70\%$. Of the clinical

Fig. 3 **a** Performance of 20 radiomics features. All showed good performance (AUC $> 70\%$). **b** AUC values of 12 clinical features. Both the radiomics signature and the clinical model showed favorable

predictive accuracy. **c** The radiomics signature had an AUC value of 0.93 (0.86–1.00). **d** The corresponding AUC value for the clinical model was 0.95 (0.95–0.99)

Table 1 Epidemiological history and clinical data of 81 confirmed patients

Variable	Sample	class 1	class 2	Statistics	p value
Gender					
male	47	32 (52.46%)	15 (75.00%)	3.142	0.076
female	34	29 (47.54%)	5 (25.00%)		
Epidemiology					
Epidemiology1	24	20 (32.79%)	4 (20.00%)	—	0.037
Epidemiology2	17	8 (13.11%)	9 (45.00%)		
Epidemiology3	16	14 (22.95%)	2 (10.00%)		
Epidemiology4	24	19 (31.15%)	5 (25.00%)		
Cough					
NO	18	13 (21.31%)	5 (25.00%)	0.001	0.973
yes	63	48 (78.69%)	15 (75.00%)		
expectoration					
NO	58	40 (65.57%)	18 (90.00%)	4.42	0.036
yes	23	21 (34.43%)	2 (10.00%)		
dyspnea					
no	80	61 (100.00%)	19 (95.00%)	—	0.247
yes	1	0 (0.00%)	1 (5.00%)		
Fatigue					
no	60	45 (73.77%)	15 (75.00%)	0.012	0.913
yes	21	16 (26.23%)	5 (25.00%)		
nausea and vomiting					
no	80	61 (100.00%)	19 (95.00%)	—	0.247
Yes	1	0 (0.00%)	1 (5.00%)		
diarrhea					
no	73	58 (95.08%)	15 (75.00%)	4.754	0.029
yes	8	3 (4.92%)	5 (25.00%)		
Tight chest					
no	62	52 (85.25%)	10 (50.00%)	8.551	0.003
yes	19	9 (14.75%)	10 (50.00%)		
thoracodynia					
no	78	58 (95.08%)	20 (100.00%)	0.0	0.571
yes	3	3 (4.92%)	0 (0.00%)		
shake					
no	74	57 (93.44%)	17 (85.00%)	0.501	0.479
yes	7	4 (6.56%)	3 (15.00%)		
PCT					
no	25	23 (37.70%)	2 (10.00%)	5.984	0.05
yes	56	38 (62.3%)	18 (90.00%)		
Age	81	43.00 (29.00, 51.00)	56.50 (44.45, 68.00)	−3.499	< 0.001
temperature	81	36.90 (36.50, 37.30)	36.70 (36.34, 37.39)	0.964	0.335
heartrate	81	85.00 (78.00, 90.60)	85.00 (82.00, 95.10)	−1.227	0.22
WBC	81	5.21 ± 1.81	5.50 ± 1.47	−0.651	0.517
NEU%	81	64.54 ± 13.70	79.52 ± 10.94	−4.442	< 0.001
LYM%	81	26.80 (17.72, 35.19)	12.45 (8.23, 18.90)	4.085	< 0.001
Mon%	81	7.50 (5.64, 8.36)	5.60 (4.59, 7.61)	1.922	0.055
NEU	81	3.15 (2.12, 4.20)	4.61 (3.42, 5.31)	−2.125	0.034
LYM	81	1.29 (0.87, 1.69)	0.74 (0.40, 1.07)	3.806	< 0.001
Mon	81	0.36 (0.27, 0.46)	0.33 (0.24, 0.51)	0.274	0.784
ESR	81	30.10 (25.85, 49.60)	30.10 (23.30, 63.21)	−0.027	0.978
MYT	81	30.00 (28.00, 34.90)	35.50 (29.45, 73.00)	−2.256	0.024
hsCRP	81	8.50 (1.56, 22.40)	55.35 (16.59, 98.27)	−4.37	< 0.001
ALT/AST	81	0.78 (0.63, 1.12)	0.95 (0.67, 1.34)	−1.035	0.301
CK	81	86.40 (54.41, 144.64)	106.90 (73.39, 192.00)	−1.04	0.298
DDimer	81	0.20 (0.09, 0.29)	0.28 (0.22, 0.57)	−2.826	0.005
CD4	81	513.00 (376.00, 828.20)	271.50 (123.70, 338.95)	3.926	< 0.001
CD8	81	350.00 (215.20, 638.48)	152.12 (103.07, 213.90)	4.315	< 0.001
CD3	81	927.00 (632.50, 1593.40)	449.00 (247.75, 594.10)	4.14	< 0.001
CD4_CD8	81	1.41 (1.22, 1.79)	1.51 (0.88, 2.06)	0.0	1.0
score	81	8.00 (3.00, 12.00)	16.00 (14.45, 18.55)	−5.076	< 0.001

Table 2 Multivariate logistic of the predictive radiomics features

VarName	OR(95%CI)	<i>p</i> value	AUC
(Intercept)	0.14(0.04–0.37)	0.00	
log_sigma_1_0_mm_3D_glszm_LargeAreaEmphasis	0.03(0.00–0.42)	0.03	0.86
log_sigma_5_0_mm_3D_glszm_SizeZoneNonUniformity	0.23(0.03–1.34)	0.12	0.80
CT_score	3.20(0.73–20.92)	0.17	0.87
wavelet_HHL_glrmlm_RunLengthNonUniformity	129.08(2.19–3637.51)	0.04	0.82
wavelet_HLL_glrmlm_RunLengthNonUniformity	0.00(0.00–0.40)	0.05	0.87
wavelet_HLH_glszm_LargeAreaHighGrayLevelEmphasis	41.03(2.95–1498.64)	0.03	0.86
log_sigma_5_0_mm_3D_glszm_LargeAreaHighGrayLevelEmphasis	14.23(0.70–809.09)	0.13	0.87
log_sigma_3_0_mm_3D_glszm_GrayLevelNonUniformity	60.43(1.82–7167.65)	0.04	0.83

factors, 16 features were statistically significant when assessed by the chi-square or Mann–Whitney *U* test (Table 1), and 12 clinical features were retained after univariate logistic regression ($p < 0.05$). These 12 features' AUC values are shown in Fig. 3 b. After backward stepwise multivariate logistic regression and selection with the likelihood ratio test, eight radiomics features (Table 2) and four clinical features (Table 3) were finally retained, and predictive models were constructed. Both the radiomics signature and the clinical model showed favorable predictive accuracy, with AUC values of 0.93 (0.86–1.0) and 0.95 (0.95–0.99), respectively (Fig. 3c, d).

The sensitivity, specificity, and accuracy were calculated based on the Youden index (Table 4). Both the clinical model and radiomics signature showed good performance in discriminating patients with common and severe COVID-19. In the clinical model, the accuracy, sensitivity, and specificity values were 0.91, 0.81, and 0.95, respectively; in the radiomics signature, these values were 0.90, 0.90, and 0.90, respectively.

The mean accuracy, sensitivity, and specificity values of the 100-fold LGOCV are shown in (Table 5). Both the clinical and radiomics models showed good stability, indicating that the texture analysis was valuable for discriminating common and severe COVID-19 patients, and that the results were not due to overfitting.

The correlations between the predictive radiomics and clinical features are shown in Fig. 4. The association was defined as strong ($r = 0.7–1$), moderate ($r = 0.4–0.69$), or low ($r = 0.1–0.39$). The prediction score showed strong correlations with wavelet_LLL_glrmlm_RunLength NonUniformity ($r = 0.80$, $p < 0.0001$),

log_sigma_5_0_mm_3D_glszm_SizeZoneNonUniformity ($r = 0.71$, $p < 0.0001$), wavelet_HHL_glrmlm_RunLength NonUniformity ($r = 0.75$, $p < 0.0001$), and wavelet_HLL_glrmlm_RunLengthNonUniformity ($r = 0.79$, $p < 0.001$). Most other clinical features and radiomics features showed moderate correlations (Fig. 4).

Discussion

Chest CT can be used to make rapid diagnosis and assess the severity of COVID-19 patients [8]. On CT images, COVID-19 may be manifested with GGO, GGO combined with grid, and/or consolidation, all changing rapidly [9]. We can judge the severity of the disease by the lesion range on the CT image, the results of which may be subjective and inaccurate.

In CT texture analysis, image features of different gray levels can be filtered out. An image's pixel and spatial parameters are used to quantitatively extract pathophysiological features of the lesions that cannot be recognized by naked eyes and to reveal the internal heterogeneity between tissues [10–12]. Texture analysis is objective in that it evaluates lesion with gray level on the image [13].

COVID-19 is an acute and highly infectious disease [12]. Early prediction and timely treatment can improve patients' prognosis. The clinical stages of COVID-19 have been rarely classified by texture analysis based on CT images. In this study, a radiomics texture model and a clinical model were established for 81 patients to early predict the clinical stages of COVID-19, and a correlational study was conducted to reveal the associations between CT and clinical variables in common

Table 3 Multivariate logistic of the predictive clinical features

VarName	OR(95%CI)	<i>p</i> value	AUC
(Intercept)	0.05(0.001–0.20)	0.00	
score	2.45(0.99–7.59)	0.08	0.88
CD8	0.06(0.001–0.51)	0.03	0.82
hsCRP	3.77(1.48–12.73)	0.01	0.83
Tight chest	2.52(1.15–6.19)	0.03	0.68

Table 4 The sensitivity, specificity, accuracy of clinical model and radiomics signature

	threshold	Accuracy	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value
Clinical model	−0.77	0.90	0.9	0.90	0.75	0.96
Radiomics signature	0.04	0.91	0.81	0.95	0.85	0.93

and severe patients. Both radiomics and clinical models showed favorable predictive accuracy, with an AUC of 0.93 (0.86–1.0) and 0.95 (0.95–0.99), respectively. The prediction model based on CT text features achieved a sensitivity of 0.80 and a specificity of 0.95, which means that CT texture analysis can early accurately assess disease severity.

It has been reported that coronavirus acts mainly on lymphocytes, especially T lymphocytes, as SARS-CoV does. Therefore, a decrease in lymphocytes can be used as a reference index for clinical diagnosis of new coronavirus infection [14–17]. CD3 represents the total count of T lymphocytes, and CD4 or CD8 represents that of their subsets. Among the clinical features measured in this research, the percentage and absolute count of lymphocytes and the counts of CD3, CD4, and CD8 in the severe group decreased significantly and showed high diagnostic value to differentiate patients of different COVID-19 severity levels (all AUC > 70%). These results suggest that the lymphocyte count in the severe group was much lower than that in the common group. Feng et al [18] used a semi-quantitative scoring system to quantitatively estimate the pulmonary involvement of lung lesions. The inflammation score was correlated with the severity. Our results showed that the inflammation score was also effective in the differential diagnosis between the two groups (AUC = 88%).

We used LGOCV to verify the reliability of the multivariate logistic regression model, and the results showed that both the imaging and clinical models had good stability. In the training and validation sets, the average accuracy, sensitivity, and specificity values resulting from 100-fold cross-validation were above 0.8, indicating that the results of the model were not caused by overfitting. The results of 100-fold cross-validation in the imaging model showed that the logarithmic transformation characteristics of `log_sigma_3_0_mm_3D_glszm_GrayLevelNonUniformity` and `log_sigma_1_0_mm_3D_glszm_LargeAreaEmphasis` appeared more than 50 times during the 100 times cross-validations (Supplementary Materials). The

`glszm_GrayLevelNonUniformity` variable was used to measure the variability of gray-level intensity values in the image, with lower values indicating higher homogeneity of intensity values. Further, `glszm_LargeAreaEmphasis` was used to measure the distribution of large-sized area zones, with greater values indicating more large-sized area zones and more coarse textures. And the wavelet characteristics include `wavelet_HHL_glrIm_RunLengthNonUniformity` and `wavelet_HLH_glszm_LargeAreaHighGrayLevelEmphasis`, of which `wavelet_glrIm_RunLengthNonUniformity` measures the similarity of run lengths throughout the image, with a lower value indicating more homogeneity among run lengths in the image, and `wavelet_HLH_glszm_LargeAreaHighGrayLevelEmphasis` measures the proportion in the image of the joint distribution of larger-sized zones with higher gray level. Besides, the CT score also showed more than 50 times, which means these features had high stability and diagnostic values of the severity of the patients. In the clinical model, inflammation score, hsCRP, CD3, PCT, and other factors showed more than 50 times during the 100 times cross-validation (Supplementary Materials), indicating that these parameters were highly correlated with the severity of COVID-19. In addition, the Spearman correlation analysis was performed to evaluate the correlation between significant imaging and clinical features. The results showed that most of the clinical features (e.g., lymphocyte ratio; absolute value; CD3, CD4, and CD8 counts; CRP; and D dimer) had moderate correlations with the imaging features (> 0.4). The strong correlation was found between inflammatory score and partial wavelet transform features and region size matrix GLSZM features (> 0.7), indicating that these image features are closely related to disease severity and can be used for clinical type classification of the COVID-19 patients.

This study has some limitations. Firstly, this study is retrospective, and the sample size is small, especially in the severe group, with only 21 cases. Secondly, some cases have small ground-glass lesions that may be missed when

Table 5 Cross validation of clinical model and radiomics signature

	Group	Accuracy	Sensitivity	Specificity
Clinical model	Training	0.97	0.98	0.97
	Test	0.90	0.93	0.81
Radiomics signature	Training	0.95	0.96	0.91
	test	0.89	0.92	0.80

the ROI is automatically delineated. In future studies, it is necessary to increase the number and type of samples. Thirdly, in clinical practice, COVID-19 should be differentiated from other pulmonary diseases or other pneumonias. But, we did not apply CTTA to differentially diagnose COVID-19 in this study. Finally, our results may have had some bias. In this study, we did not consider the effect of patient's underlying disease, such as chronic respiratory disease (emphysema or interstitial pneumonia, etc.), on the severity judgment. We will establish a multicenter study to explore the value of CT texture analysis in the differential diagnosis of COVID-19.

Statistics and biometry Yaqiong Ge kindly provided statistical advice for this manuscript, and no complex statistical methods were necessary for this paper.

Ethical approval Institutional review board approval was obtained.

- retrospective
- diagnostic or prognostic study
- performed at one institution

Compliance with ethical standards

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