A Novel Machine Learning-derived Radiomic Signature of the Whole Lung Differentiates Stable From Progressive COVID-19 Infection

A Retrospective Cohort Study

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Objective: This study aimed to use the radiomics signatures of a machine learning-based tool to evaluate the prognosis of patients with coronavirus disease 2019 (COVID-19) infection.

Methods: The clinical and imaging data of 64 patients with confirmed diagnoses of COVID-19 were retrospectively selected and divided into a stable group and a progressive group according to the data obtained from the ongoing treatment process. Imaging features from whole-lung images from baseline computed tomography (CT) scans were extracted and dimensionality reduction was performed. Support vector machines were used to construct radiomics signatures and to compare differences between the 2 groups. We also compared the differences of signature scores in the clinical, laboratory, and CT image feature subgroups and finally analyzed the correlation between the radiomics features of the constructed signature and the other features including clinical, laboratory, and CT imaging features.

Results: The signature has a good classification effect for the stable group and the progressive group, with area under curve, sensitivity, and specificity of 0.833, 80.95%, and 74.42%, respectively. Signature score differences in laboratory and CT imaging features between subgroups were not statistically significant (P > 0.05); cough was negatively correlated with GLCM Entropy_angle_90_offset4 SD (r = -0.578), but was positively correlated with ShortRunEmphasis_AllDirect_offset4 SD (r = 0.454); C-reactive protein was positively correlated with Cluster Prominence_AllDirect_offset4 SD (r = 0.47).

Conclusion: The radiomics signature of the whole lung based on machine learning may reveal the changes of lung microstructure in the early stage and help to indicate the progression of the disease.

Key Words: radiomics, coronavirus disease, lung infection, machine learning
in COVID-19 infection and disease development prediction becomes crucial and thus worth exploring. Furthermore, the appearance of pneumonia on CT is different from boundary-clear solid tumors, and the boundary of inflammation is sometimes unclear. This is often compounded by the limited grayscale spectrum visible to the human eye when CT images are viewed during pulmonary windowing. It is, therefore, possible that there may be some potential lesion areas in the adjacent areas of the consolidation that cannot be observed by the unaided eye. It is crucial to improve visual resolution in the early COVID-19 pneumonia imaging that often has no abnormal findings. On top of this, a comprehensive evaluation of the condition of the whole lung is very crucial because the disease also involves both pulmonary interstitial and parenchymal inflammation. Consequently, it becomes imperative that patients with COVID-19 pneumonia undergo whole-lung evaluation to further clarify the severity of the disease and its evolution.

Machine learning, as an important part of imaging data analysis, can use specific data-feature algorithms to extract a large amount of quantitative information from imaging data, thus identifying clinically valuable imaging patterns that human readers cannot recognize. Therefore, we hypothesized that radiomics based on machine learning can carry out heterogeneous analyses of the whole lung to facilitate the quantitative assessment of disease severity and predict disease progression trends. This may reveal the relationship between early microstructural changes in the lung and disease course, providing new biological insights into disease mechanisms.

METHODS

Data Sources and the Study Population

This study was approved by the relevant institutional review board and the local ethics committees. All investigations were conducted in accordance with the Helsinki Declaration. Because of the retrospective nature of the study, the local ethics committee did not require written informed consent. The researchers retrospectively obtained the imaging and clinical data of 64 patients diagnosed with COVID-19 infection from January 21 to February 19, 2020. Inclusion criteria were as follows: (1) nucleic acid test positivity and (2) 2 or more CT scans done. On the basis of the results of 2 serial CT scans, these patients were divided into stable groups (n = 21) and progressive groups (n = 43), shown in Figures 1 and 2. Six negative patients were included in the stable groups.

CT Scanning Parameters

A Siemens SOMATOM Perspective 16-row helix or China Lianying UCT 550 helix scanner was utilized for CT imaging using a single inspiratory phase for chest CT scans. To reduce motion-related artifacts, each patient received breath-holding guidance; the CT images were obtained during one breath-holding period. For CT acquisition, the tube voltage was set at 110 or 100 kVp automatic tube current regulation technology.

CT Imaging Grade Assessment

On the basis of current clinical practice and a previous study’s findings on the scope and presentation of the lesions, it has been recommended that the CT manifestations of COVID-19 infection be divided into 3 stages, namely, early, advanced, and severe, and the details of CT images in 3 stages can be found in supplementary materials, Supplemental Digital Content 1 (http://links.lww.com/JTI/A174). In this study, we defined the progressive group as follows: (1) increased ground-glass opacity (GGO) lesions and (2) newly occurring lesions exceeded the potential cumulative range. All images were evaluated independently by 2 experienced radiologists; where there were differences of opinion, the final opinion was reached after consultations between them (Dr Li has 11 y of experience in the interpretation of CT images, whereas Dr Gong has 26 y of experience).

Segmentation and Preprocessing of the Whole Lung

Each lung window image of the first CT scan of all cases was imported into the LK software (Lunk Intelligence Kit, version 2.0, GE Healthcare) in DICOM format for automatic full-lung cutting. The 3-dimensional (3D) lung images were manually modified by 2 experienced neuroradiologists (radiologist A and radiologist B, with 5 and 15 y of chest-imaging experience, respectively) who were blinded to the clinical data using the ITK-SNAP software (http://www.itksnap.org). This was accomplished by the following steps: (1) removal of the miscut trachea and vascular shadows; (2) correction of the cutting error at the junction of the heart and lung; and (3) correction of the incomplete cut area caused by pulmonary fibrosis or consolidation, resulting in a full 3D image of the lung. The 3D, full lung images are...
imported into the QAK software (Quantitative Analysis Kit, version 1.2, GE Healthcare) for image preprocessing. First, all images were resampled to a resolution of 1×1×1 mm by linear interpolation to eliminate the anisotropy effect on the features. The Gaussian filter was then applied to reduce noise, which also helps to minimize external interference factors. Finally, intensity standardization was performed to limit the grayscale of all images to 0 to 32 so that they can be compared without bias.15

The process of segmentation for the whole lung is shown in Figure 3.

**Radiomics Feature Selection**

Preprocessed images use QAK software to extract radiomics features, including histograms, shape factors, gray-scale symbiosis matrix (GLCM), run-time matrix (RLM), and gray-scale region matrix features (GLZSM), which are features of cancer heterogeneity and may reflect...
changes in image structure.\textsuperscript{16} We used the features that were most robust against the manual correction among different radiologists (19) to ensure the robustness and repeatability of radiomics features. The Spearman rank correlation test was used to calculate the correlation coefficient (CC) for each feature, between features set-A (from radiologist A) and feature set-B (from radiologist B). Features with CC > 0.8 were considered robust features. Also, because of the existence of a “curse of dimensionality”, often makes data reduction or feature selection necessary to obtain meaningful results from the pattern recognition analysis.\textsuperscript{17}

Therefore, this study first uses the minimum redundancy maximum correlation (mRMR) algorithm to screen the extracted features.\textsuperscript{18} The maximum correlation program aims to select the features that are most relevant to the actual pneumonia progression. Meanwhile, the minimum redundancy process ensures that the selected features have minimal redundancy in other features. Therefore, an optimal feature set with high correlation and low redundancy was obtained using the mRMR method. Finally, the least absolute shrinkage and selection operator (LASSO) algorithm was used to select the selected features to construct the radiomics signature. We used the bootstrapping method for feature selection for mRMR and LASSO algorithms throughout the dimension reduction process.

**Radiomics Signature Establishment and Evaluation**

Machine learning involves building data-derived signatures and methods to improve signature accuracy, performance, or predictive power, which is an important component of radiomics.\textsuperscript{19,20} Therefore, in this study, support vector machines (SVM) were used to construct radiomics signature. We used K(K-1)/2 binary SVM models using the one-versus-one coding design, where K is the number of unique class labels (levels) from MATLAB. We applied the oneleave-out cross-validation method for differentiation between training and test data because of the limited number of available patients. For example, we assigned one case as the test case and used the remaining 63 cases as the training data for the SVM classifier. The SVM model was used to calculate the radiomics score (rad-score) to reflect the progression of new coronavirus pneumonia. Finally, the receiver operating characteristic (ROC) curve was used to evaluate the accuracy of the radiomics signature. A 2-class rad-score analysis of CT typical manifestations, clinical typical manifestations, and laboratory examination of all cases was carried out to assess whether it was associated with disease progression. At the same time, the correlation analysis of the detection characteristic and radiomics features was carried out to further evaluate the ability of the signature to identify disease progression.

**Statistical Analysis**

The Statistical Package for Social Sciences (SPSS) version 22.0 and GraphPad Prism6 software packages were used for statistical analysis. The Kolmogorov-Smirnov test was used for the normality testing of the measurement data. The normally distributed data were evaluated using the independent-sample $t$ test, whereas the non-normal distribution data were evaluated using the Mann-Whitney $U$ test. The differences between categorical variables were tested using the $\chi^2$ test. All analyses were controlled for age and sex. Results $P < 0.05$ were considered significant.

**RESULTS**

**Clinical Data**

The baseline data of the patients in the stable and the progressive groups included descriptive statistics, typical clinical manifestations, laboratory test results, and CT imaging findings (Table 1). The number of lesions in the stable group and the progressive group was statistically different ($P < 0.05$).

**Establishment and Evaluation of Imaging Labels**

By mRMR and LASSO algorithms, seven best features were finally left, including 3 features of GLCM, 2 features of RLM, and 1 feature of the form factor and 1 texture feature (Table 2). The specific dimensionality-reduction process and feature introduction are included in the supplementary materials, Supplementary Digital Content 1 (http://links.lww.com/JTI/A174). On the basis of the ROC curve, the results demonstrate that using the SVM classifier shows that area under curve, sensitivity, and specificity were 0.833, 80.95%, and 74.42%, respectively. The rad-score of the signature calculated according to the SVM formula was significantly different between the stable group and the progression group ($P < 0.05$) (Fig. 4).

**Detection Index Stratification Analysis and Correlation with Radiomics Features**

There was a significant difference in rad scores among the C-reactive protein subgroups. The differences between other test features including laboratory and CT imaging indicators were not statistically significant ($P > 0.05$) (Table 3). A correlation analysis of the radiomics features of constructing signature with the detection index showed a negative correlation between cough and GLCM Entropy_angle90_offset4 ($r = -0.578$), positive correlation with ShortRunEmphasis_AllDirection_offset4_SD ($r = 0.454$), and positive correlation with C-reactive protein (CRP) with ClusterProminence_AllDirection_offset4_SD ($r = 0.47$) (Fig. 5).

**DISCUSSION**

This study showed that machine learning-based radiomics signatures from the whole lung could distinguish between stable and progressive patients in the early stage, who usually showed fever or respiratory symptoms (eg, cough, myalgia, fatigue). In addition, these results suggest that the microstructure of the lungs may have changed before the point at which they can be visually detected on the CT images, including among those patients who may have shown normal lung imaging. Besides, cough and CRP abnormalities may be 2 extrinsic hallmarks of this microstructural change in the lungs. The cough and CRP abnormalities may help to better identify and to direct focus on the risk of potential progression in the patient population.

This was especially significant when the disease was in the progressive stage, whereby the lung infection becomes rapidly aggravated and develops into the bilateral opacities distribution.\textsuperscript{21} The changes during the progressive stage could lead to the variabilities of different stages of the disease between the groups; thus, we should try our best to find out the cause of this change. Age is a related factor in lung structural changes.\textsuperscript{22} Also, in this outbreak, age is considered to be one of the key elements of disease occurrence and progression. Death from COVID-19 occurs commonly among the elderly, in whom the disease may develop or
TABLE 1. Clinical Characteristics of Patients in the Stable and Progressive Groups

| Variables                              | Stable Group (n = 43), n (%) | Progressive Group (n = 21), n (%) | P     |
|----------------------------------------|-----------------------------|----------------------------------|-------|
| Descriptive statistics                 |                             |                                   |       |
| Age (y)                                | 46 ± 13                     | 47 ± 14                           | 0.83  |
| BMI (kg/m²)                            | 23.7 ± 3                    | 24.9 ± 3.4                        | 0.189 |
| Sex                                    |                             |                                   |       |
| Male                                   | 19 (44.2)                   | 10 (47.6)                         | 0.796 |
| Female                                 | 24 (55.8)                   | 11 (52.4)                         |       |
| The period between the onset of initial symptoms and the first scan (d) | 4.2 ± 2                      | 3.4 ± 1.4                         | 0.065 |
| The period between 2 CT scans (d)      | 5.9 ± 2.4                   | 4.8 ± 2.0                         | 0.054 |
| Hospitalization time (d)               | 13.2 ± 4.3                  | 14.1 ± 5.7                        | 0.466 |
| Initial symptoms                       |                             |                                   |       |
| Fever                                  | None                        | 7 (16.3)                          | 0.133 |
| Low (37.3-38°C)                        | 21 (48.8)                   | 14 (66.7)                         |       |
| Moderate (38.1-39°C)                   | 9 (20.9)                    | 6 (28.6)                          |       |
| High (≥ 39.1°C)                        | 6 (14)                      | 0 (0)                             |       |
| Cough                                  | None                        | 19 (38.5)                         | 0.407 |
| Yes                                    | 24 (56.5)                   | 14 (66.7)                         |       |
| Chest pain                             | None                        | 41 (95.3)                         | 0.315 |
| Yes                                    | 2 (4.7)                     | 0 (0)                             |       |
| Diarrhea                               | None                        | 35 (81.4)                         | 0.667 |
| Yes                                    | 8 (18.6)                    | 3 (14.3)                          |       |
| Laboratory test data                  |                             |                                   |       |
| White blood cell count                 | Normal                      | 29 (67.4)                         | 0.951 |
| Abnormal                               | 14 (32.6)                   | 7 (33.3)                          |       |
| Lymphocyte count                       | Normal                      | 33 (76.7)                         | 0.391 |
| Abnormal                               | 10 (23.3)                   | 7 (33.3)                          |       |
| C-reactive protein                     | Normal                      | 13 (30.2)                         | 0.891 |
| Abnormal                               | 30 (69.8)                   | 15 (71.4)                         |       |
| Liver function                         | Normal                      | 37 (86)                           | 0.971 |
| Abnormal                               | 6 (14)                      | 3 (14.3)                          |       |
| Myocardial enzymes                    | Normal                      | 41 (95.3)                         | 0.984 |
| Abnormal                               | 2 (4.7)                     | 1 (4.8)                           |       |
| Chest CT imaging data                  |                             |                                   |       |
| Number of lesions                      | Negative                    | 6 (14)                            | 0.042*|  
| Abnormal                               | 4 (9.3)                     | 6 (28.6)                          |       |
| Multiple                               | 33 (76.7)                   | 15 (71.4)                         |       |
| Location of lesions (n)                | Pleura                      | 9 (20.9)                          | 0.256 |
| Others                                 | 34 (79.1)                   | 19 (90.5)                         |       |
| Ground-glass opacity (n)               | None                        | 8 (18.6)                          | 0.135 |
| Yes                                    | 35 (81.4)                   | 20 (95.2)                         |       |
| Minor mesh change (n)                  | None                        | 33 (76.7)                         | 0.645 |
| Yes                                    | 10 (23.3)                   | 6 (28.6)                          |       |
| Thick and large shadow                 | None                        | 26 (60.5)                         | 0.63  |
| Yes                                    | 17 (39.5)                   | 7 (33.3)                          |       |

*Mean P < 0.05.
BMI indicates body mass index.

TABLE 2. Classification and Weight Value of the Features

| Category | Feature | Weight Value |
|----------|---------|--------------|
| GLCM     | InverseDifferenceMoment_AllDirection_offset4_SD | −0.3071 |
|          | GLCMEntropy_angle90_offset4 | 0.7943 |
|          | Correlation_angle0_offset7 | −1.1446 |
| RLM      | LongRunLowGreyLevelEmphasis_AllDirection_offset4_SD | 2.4542 |
|          | ShortRunEmphasis_AllDirection_offset4_SD | −0.5895 |
| Texture  | Parameter | ClusterProminence_AllDirection_offset4_SD | −1.182 |
| Form factor | parameter | Maximum3DDiameter | 0.5136 |

progress faster. However, it could also be caused by underlying diseases. It has been reported that middle-aged and elderly patients with underlying diseases such as hypertension or diabetes are more prone to respiratory failure and have a poor prognosis, which may also point to the effects of underlying diseases or comorbidities on the whole lung. In the current study, age has not been shown to be a key factor in disease progression. Further analysis found an interesting phenomenon, whereby the age of our study cohort was generally younger than the age of typical patients with COVID-19. This was probably because most of our cases were not in the epidemic center region (Wuhan) and were dominated by input-type individual cases that were mostly younger people working in Hubei or Wuhan. As a result, age (advanced) did not become a key factor in predicting disease progression in our study.

We carried out a 2-class analysis of all the features of the whole-lung imaging scores, and the results showed that there were no statistically significant differences, suggesting that the current disease manifestations as detected by clinical, laboratory tests, and imaging examinations did not indicate early disease progression. However, the radiomics analysis of the whole lung can distinguish between the stable group and the progressive group of COVID-19 pneumonia patients, which further suggested that pulmonary heterogeneity was different between the 2 groups. According to the latest research, patients with COVID-19 pneumonia mainly showed pulmonary infiltrative lesions on CT imaging. Similar observations were also found in asymptomatic patients and those with false-negative nucleic acid test results. Therefore, on the basis of radiomics technology, CT is a sensitive tool for screening and assessing the severity of the disease among patients with COVID-19.

In patients with COVID-19 pneumonia, cough often manifests as an early clinical symptom. Coughing is a natural reflexive defense action of the human body that removes secretions and foreign bodies from the respiratory tract. Histologic examination of the lung tissue from the COVID-19 pneumonia patients revealed that COVID-19 caused diffuse alveolar injury and mucoid exudation. These findings suggest that the patient’s cough may have emerged as a result of infection with the COVID-19. In this study, we noted that there are 2 radiomics features associated with cough, the entropy in the GLCM category. In a previous oncological study, this characteristic often indicated the heterogeneity of the tumor, a feature also confirmed for the whole lung in this study. The ShortRun Emphasis in the other RLM category mainly reflects the roughness and

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directionality of the texture. The directional texture will normally have a longer course at some angle. In the medical field, it represents the loss of regular structure after tissue injury.\textsuperscript{30} The lung imaging findings in patients with COVID-19 infection typically include multifocal bilateral GGO with patchy consolidations that are prominently distributed to the sub pleura periphery and to the posterior parts or lower lobes. The consolidations, often accompanied by pulmonary fibrosis, are commonly caused by the thickening of the GGO within the interlobular and intralobular septum during disease progression.\textsuperscript{31} Therefore, this characteristic of ShortRunEmphasis appears to suggest that such changes occur early. In addition, this study showed that CRP is also associated with specific imaging features. CRP is a sensitive marker and an indicator of inflammation in the body, especially in viral pneumonia.\textsuperscript{32} In COVID-19 pneumonia, mononuclear inflammatory infiltration composed of lymphocytes is mainly interstitial.\textsuperscript{33} The upregulation of CRP is a relevant indicator of changes in the whole-lung microstructure. It directly correlates with the extent of pulmonary inflammatory infiltration and thus may be responsible for the association of CRP with imaging features.

The study has several limitations. We used a smaller sample size based on the number of patients available to us and also fulfilling the inclusion criteria. The use of machine learning in CT scan reading and disease staging may require a larger sample size in the future to validate the present results. Also, this is a single-center study and, in particular, the collection of cases was not from the epicenter of the epidemic. However, it is important to note that all patients had a traceable positive history of exposure to the epicenter in Wuhan city. In addition, the disease progression period of the study used only short-term follow-up data. Usually, short-term imaging performance is consistent with the severity of COVID-19.\textsuperscript{34} Finally, feature selection was performed before 10-fold cross validation, and this may introduce bias, and prevent the area under curve reported here from being a reliable measure of generalization accuracy of the model. A larger validation on an independent testing dataset is necessary.

Our study provides an early way to identify the progression of COVID-19 pneumonia disease. Conclusions drawn from the data of this study may enable the clinicians to rationally identify those COVID-19 patients with potential risk for disease progression. Besides, these preliminary results are beneficial toward future integration of AI in the diagnosis and evaluation of COVID-19 pneumonia and providing a new biological perspective.

TABLE 3. Statistical Analysis of Radiomics Scores in the Clinical Features Subgroup

| Check Features                  | Characteristic Subgroup | P      |
|--------------------------------|-------------------------|--------|
| White blood cell count         | Normal                  | Abnormal | 0.295 |
|                                | 0.43 ± 1.24             | 0.78 ± 1.2 | 0.16  |
| Lymphocyte count               | Normal                  | Abnormal | 0.034* |
|                                | 0.68 ± 1.24             | 0.18 ± 1.15 | 0.768 |
| C-reactive protein             | Normal                  | Abnormal | 0.034* |
|                                | 1.05 ± 1.32             | 0.33 ± 1.14 | 0.768 |
| Liver function                 | Normal                  | Abnormal | 0.034* |
|                                | 0.56 ± 1.19             | 0.43 ± 1.52 | 0.86  |
| Myocardial enzymes             | Normal                  | Abnormal | 0.034* |
|                                | 0.49 ± 1.22             | 1.74 ± 0.49 | 0.631 |
| Number of lesions              | Negative                | Solitary  | Multiple | 0.465 |
|                                | 0.53 ± 1.44             | 0.15 ± 2.49 | 0.13 ± 3.2 |
| Location of lesions            | None                    | Pleura    | Others    | 0.288 |
|                                | −0.04 ± 1.36            | 0.58 ± 1.39 | 0.61 ± 1.18 |
| Ground-glass opacity           | None                    | Yes       | 0.488    |
|                                | 0.18 ± 1.44             | 0.62 ± 1.18 | 0.782 |
| Minor mesh change              | None                    | Yes       | 0.488    |
|                                | 0.28 ± 1.19             | 0.59 ± 1.24 | 0.947 |
| Thick and large shadow         | None                    | Yes       | 0.488    |
|                                | 0.52 ± 1.2              | 0.62 ± 1.34 | 0.947 |
| Consolidation                  | None                    | Yes       | 0.947    |
|                                | 0.55 ± 1.24             | 0.53 ± 1.24 | 0.947 |

*Mean P < 0.05.

FIGURE 4. Diagnostic performance of radiomics signature. A, Diagnostic accuracy of the fractional values calculated by the SVM classifier in the study queue. B, Violin distribution of the scores calculated by the SVM classifier in the stable and progression groups. AUC indicates area under curve.
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