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Radiological Features on HRCT and RT-PCR Testing for the Diagnosis of Coronavirus Disease 2019 (COVID-19) in China: A Comparative Study of 78 Cases in Pregnant Women

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Research Article

Keywords: Novel coronavirus pneumonia, Covid-19, SARS-CoV-2, Computed tomography, Pregnant women with COVID-19 pneumonia, Reverse transcription-polymerase chain reaction (RT-PCR)

Posted Date: April 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-21005/v1

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Abstract

Objective: We aimed to evaluate the quantitative parameters of CT scans performed on pregnant women with COVID-19 who had different reverse transcription-polymerase chain reaction (RT-PCR) results.

Methods: Pregnant women with suspected cases of COVID-19 pneumonia (confirmed by next-generation sequencing or RT-PCR) who underwent high-resolution lung CT scans were retrospectively enrolled. Patients were grouped based on the results of the RT-PCR and the first CT scan: group 1 (double positive patients; positive RT-PCR and CT scan) and group 2 (negative RT-PCR and positive CT scan). The imaging features and their distributions were extracted and compared between the two groups.

Results: Seventy-eight patients were admitted to the hospital between Dec 20, 2019, and Feb 29, 2020. The mean age of the patients was 31.82 years (SD 4.1, ranged from 21 to 46 years). The cohort included 14 (17.95%) patients with a positive RT-PCR test and 64 (82.05%) with a negative RT-PCR test, there were 37 (47.44%) patients with a positive CT scan, and 41 (52.56%) patients with a negative CT scan. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CT-based diagnosis of COVID-19 were 85.71%, 60.94%, 32.40%, 95.12% and 65.38%, respectively. COVID-19 pneumonia mainly involved the right lower lobe of the lung. There were 53 semi-quantitative and 59 quantitative parameters, which were compared between the two groups. There were no significant differences in the quantitative parameters. However, the Hellinger distance was significantly different between the two groups, albeit with a limited diagnostic value (AUC=0.63).

Conclusions: Pregnant women with pneumonia usually present with typical abnormal signs on CT. Although multidimensional CT quantitative parameters are somewhat different between groups of patients with different RT-PCR results, it is still impossible to accurately predict whether the RT-PCR will be positive, which would allow for the earlier detection of SARS-CoV-2 infection.

Introduction

In late December 2019, a number of cases of “unknown viral pneumonia” were reported in China, and were later determined to be caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) with highly infectious (1, 2). In the past three months, SARS-CoV–2 has become a global health threat(3–5).

In the context of the coronavirus disease 2019 (COVID–19) epidemic, pneumonia is a critical disease that threatens the health of pregnant women and fetuses (6, 7). COVID–19 can cause severe pneumonia, leading to respiratory failure, septic shock, multi-organ dysfunction syndrome, and even maternal death in a short period (8–10). In addition, the intrauterine safety of the fetus should be supervised in depth in pregnant women with COVID–19, with the aim of establishing an early diagnosis(11).

High-resolution CT (HRCT) can show millimeter-scale ground-glass opacities (GGOs), and it can play a crucial role in the periodic evaluation of COVID–19(12). However, HRCT cannot be synchronized with the results of reverse transcription-polymerase chain reaction (RT-PCR). This is also a challenge for clinicians, who can neither fully grasp the optimal sampling time for RT-PCR nor make accurate diagnoses in a timely manner(13, 14).

In this study, we focused on quantifying the radiological imaging characteristics of lesions compared with associated structures of the normal lung based on COVID–19 status. We used a rigorous artificial intelligence (AI) system to find the optimal imaging characteristics in a large cohort using HRCT images from patient who had confirmed RT-PCR results(15, 16). We aimed to explore the value of the quantitative parameters of multidimensional CT for predicting positive RT-PCR results. In addition, we sought to identify the problems that radiologists are most likely to overlook to enable patients to benefit from CT diagnosis.

Methods

Study design and participants

The Ethics Commission of our hospital approved this study (NO.2020–0037). Written informed consent was waived due to the nature of the emergency and the need for infection prevention. This single-center study was performed at a hospital designated to treat pregnant women with COVID-19 in Wuhan. We retrospectively analyzed patients from Dec 20, 2019, to Feb 28, 2020, who had been screened by RT- PCR, viral detection and CT examination, according to the interim guidance from the WHO and China Food and Drug Administration (CDFA). The Department of Medical Laboratory of our hospital performed the laboratory confirmation of SARS-CoV-2 and influenza virus infections. For inpatients who underwent at least one chest CT scan, their real-time RT-PCR results were confirmed within two days before or after the CT examination. If the first result was negative, we obtained throat swab specimens every other day during the next few days of hospitalization to clarify the result.

Data collection and CT parameters

We collected data on age, maternal history, symptoms (fever, cough, and dyspnea) and epidemic influenza history. Our nurses monitored the patient's temperature every day and checked for any of these symptoms. To obtain missing information, we consulted with family members by phone during and after the patient’s hospital stay. When the pregnant women underwent lung CT examinations, we strictly protected other parts of the body and informed the patient of the radiation dose.

The CT instrument we used was one of two 64-slice spiral CT scanners: a GE Discovery 750HD scanner (GE Medical Systems, Milwaukee, WI) and a SOMATOM Definition (Siemens Healthineers, Forchheim, Germany). The patient was placed in a supine position in the middle of the examination bed, with arms raised and placed along the sides of the head. The CT scan was performed with a cross-sectional spiral scan ranging from the tip of the lung to the lower margin of the bilateral diaphragm.

The scanning field of view was 40 cm. The parameters of the CT scanner were as follows: detector collimation width 64 × 0·625 mm and tube voltage 120 kV (when the patient’s BMI was<25 kg/m2, the tube voltage was 100kV; when the patient’s BMI was ≥25 kg/m2, the tube voltage was 120 kV). The tube current (ranging from 100 to 350 mAs) was regulated by an automatic exposure control system (CARE Dose 4D, Siemens Healthineers) and slice automatic tube current modulation technique (GE Medical Systems). Images were reconstructed with a slice thickness of 1.25 mm and an interval of 1.0 mm. Lung window images (window width: 1500 Hounsfield unit [HU], window level: -700HU) and mediastinal window images (window width: 200 HU, window level: 40 HU) were reconstructed.

Image interpretation

Images from our hospital were randomly assigned to two experts to independently interpret all cases without access to any clinical information, including age or sex. The two confirming radiologists had different levels of experience (MLJ [a senior radiologist with 35 years of experience] and WDH [a radiology resident with 5 years of experience in interpreting chest CT images]). Any controversies were handled by discussion and consensus.

For the quantitative diagnosis of pneumonia, AI software (Hangzhou YITU Healthcare Technology Co., Ltd.) for COVID-19 pneumonia was employed as the CT image analysis tool. The system combines a convolutional neural network and thresholding methods for segmentation of the left and right lungs and the detection of patchy shadows. The distribution of CT values in the lungs was calculated to obtain a histogram, and subsequently, the quantitative parameters were computed, including the lung volume, the inflammatory volume, and the proportion of total volume accounted for by the inflammatory volume.

We also evaluated the Hellinger distance (closely related to, although different from, the Bhattacharyya distance), which quantified the similarity between two probability distributions. We also introduced the Jaccard coefficient to compare the similarity and diversity of sample sets, which is defined as the ratio between the size of intersection and the size of union of two sets. If group 1 and group 2 are all coincident, then Jaccard coefficient equal to one is defined (J range from 0 to 1)

Follow-up and additional cases

Patients with initially negative RT-PCR results underwent a second RT-PCR test within 2-14days. If the patient underwent CT reexamination (due to the severity of the COVID-19 outbreak, we performed low radiation dose CT in all patients.), we performed before-and-after comparisons based on the results of the RT-PCR tests, and the images were manually reviewed by the abovementioned radiologists. Thereafter, we assigned the CT results to two radiologists for verification to ensure that the quantitative parameters could be observed on the CT images included in this study. Finally, according to the RT-PCR results, the CT data were divided into a positive group (Group 1) and a negative group (Group 2).

Statistical analysis

Analyses were performed with SPSS software version 22.0. Normally distributed data are presented as the mean (SD), and standardized volume or CT value proportions are expressed as percentages (%). RT-PCR was used as the reference standard, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CT were calculated. Before comparison, we carried out a homogeneity test of variance (F-test) between grouped data. Thereafter, the differences between the two groups were analyzed by independent sample T tests (for 112 parameters extracted from CT images). The valuable parameters were analyzed using receiver operating characteristic (ROC) curves, and the areas under the curves (AUCs) were calculated.

Results

General information and pregnancy epidemiology

A total of 174 patients from the fever clinic and obstetrics department were included in this study. We excluded 84 outpatients and enrolled 90 pregnant women hospitalized for delivery. In addition, we excluded 12 patients with a history of pulmonary surgery, a history of infection, pleural effusion, and poor respiratory coordination. The final sample of 78 patients who had suspected cases of COVID-19 pneumonia were retrospectively enrolled in our study; the study selection process is shown in a flow chart (Figure 1).

Overall, the mean age was 31.82 years (SD 4.1; range 21–46 y), and the mean gestational age was 38 weeks (SD 1.29 w; range 36-41w). No significant difference in age (P=0.448) was observed between groups. The most common symptoms in group 1 were fever (9/12, [75%]) and dry cough (3/12, [25%]). The common symptoms in group 2 were fever (11/25, [44%]), dry cough (1/25, [4%]), and flu symptoms (4/25, [16%]). The clinical information of the patients is summarized (Table 1).

Epidemiologically, one patient was exposed to the hospital environment during her last perinatal examination. None of the patients had a history of exposure to the seafood market. In this study, we found that four patients had a history of human immunodeficiency virus (HIV) infection (Figure 2), one of them had an abnormal lung CT, and three patients did not undergo CT examinations. Another four patients had a recent history of influenza virus infection with negative RT-PCR results, and no pulmonary CT abnormalities were found on the CT images.

RT-PCR and CT results

The results showed that 14(17.95%) patients had positive RT-PCR results, and 37(47.44%) patients had positive CT results; 12(85.71%) patients had positive results for both RT-PCR and CT. In all, 41(52.56%) patients had negative CT and RT-PCR results. In addition, we found two (2/14) patients who had completely negative CT results but positive RT-PCR results (Table 1). According to the RT-PCR results, we calculated the diagnostic sensitivity, specificity, PPV, NPV and accuracy of CT, as shown in Table 2. Finally, we summarized the characteristics of the two groups. There were 12 patients with positive RT-PCR and CT (Group 1) and 25 with negative RT-PCR and positive CT (Group 2). No significant differences in CT images were found between four patients with symptomatic influenza virus infections.

The clinical characteristics of the patients with positive CT results are summarized in Table 1.

Table 1: Characteristics of the 78 enrolled cases

Characteristics	Results
Age（Years）	**Mean**
Overall age	31.82+4.1 rage of 21to 46
≤30	27.1 (21-30)
30-40	32.75 (31-38)
>40	41.5 (41-46)
RT-PCR results	**Number(percentage)**
Positive	14 (17.95%)
Negative	64 (82.05%)
CT results	
Positive (mild)	34 (43.59%)
Positive (severe)	3 (3.85%)
Negative	41 (52.56%)
Other virus	**Number(percentage)**
HIV	1 (1.28%)
Influenza virus	4 (5.13%)

Table 2: The performance of lung HRCT for COVID-19 according to the RT-PCR results

Groups	Total patients	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Overall	78	12	39	25	2	85.71	60.94	32.40	95.12	65.38
Age(years)										
≤30	35	6	15	14	0	100	51.72	30	100	60
>30	43	6	24	11	2	75	68.57	35.29	92.31	69.77

CT quantitative and semi quantitative parameters

The quantitative parameters included the volume (mm3) and CT value (HU) of the lesions, and there were no significant differences between the two groups (Table 3). Given the differences in lung volumes, we standardized the volumes of the lesions. Although the ratios of lesion volume to lung volume were calculated, no significant differences were found. The lesions were distributed in 5 lobes and 18 lung segments (bilateral distribution), and there were no significant differences in the volumes and proportions of lesions in each lung segment. However, there was an obvious trend towards larger volumes in the right lower lobe compared with the right upper lobe.

Table 3: Details of the inflammatory volume (IV) and proportion of the total lung volume accounted for by the inflammatory volume(POIV)

Parameters	Group1	Group2	*P* Value
Inflammatory volume (cm^3)			
Whole lung	79.1483±88.3214	60.2052±65.746	0.469
Right lung	40.5917±45.1150	30.5832±43.601	0.522
Left lung	38.5575±51.3670	29.6216±45.479	0.595
Right upper lobe	7.5683±15.0776	5.2164±12.022	0.611
Right middle lobe	0.6975±1.2360	1.9932±6.2432	0.484
Right lower lobe	32.3250±33.5777	23.3728±37.600	0.488
Left upper lobe	13.5217±18.2830	11.2168±23.712	0.769
Left lower lobe	25.0383±38.4856	18.4044±32.255	0.586
Proportion of the inflammatory volume (%)			
Whole lung	2.5650±3.5531	2.0488±2.431	0.607
Right lung	2.4183±3.0639	1.8952±2.792	0.608
Left lung	2.7567±4.5621	2.3616±4.329	0.799
Right upper lobe	1.2208±2.6214	0.8292±1.819	0.605
Right middle lobe	0.2408±0.4901	0.7688±2.384	0.298
Right lower lobe	4.6517±5.7531	3.3336±5.633	0.512
Left upper lobe	1.6083±2.2739	1.7068±4.1195	0.939
Left lower lobe	4.7000±9.4204	3.7224±8.6072	0.756

There were four main types of suspicious lesions distributed in the lung, which were accurately distinguished by quantitative CT values using histograms. The CT value ranges of GGOs, mesh-like(Figure 3), mixed and solid lesions were -700 to -600 HU, - 600 to -500 HU, -500 to -200 HU and -200 to 60 HU, respectively. Comparisons of the average, peak, and median CT values in the two groups showed no significant differences ($P > 0.05$). In addition, there were no significant differences in CT values among the pulmonary lobes and segments.

Using available big data regarding CT results for normal lungs as a reference, we found that the Hellinger distance (t=2.33, P=0.015) and Jaccard coefficient (t=2.28, $P = 0.029$) of the whole lung were significantly different between groups 1 and 2. The Hellinger distance (t=2.23, $P = 0.032$) and Jaccard coefficient (t=2.64, $P = 0.0124$) in the right lobe were significantly different between the two groups. However, the

Jaccard coefficient in the left lobe was not different between the two groups (t= 1.80, $P = 0.081$). As shown in Table 4.

Table 4: The Hellinger distance and Jaccard coefficient in the two groups

	Group1	Group2	P Value
Hellinger distance			
Whole lung	0.2117±0.0381	0.2568±0.0694	0.016
Left lung	0.2158±0.0406	0.2584±0.0754	0.032
Right lung	0.2100±0.0369	0.2580±0.0664	0.008
Jaccard coefficient			
Whole lung	0.7208±0.0730	0.6384±0.1472	0.029
Left lung	0.7042±0.0810	0.6340±0.1563	0.081
Right lung	0.7267± 0.0649	0.6376±0.1406	0.012

ROC analysis of effective parameters

The results of the ROC analysis showed that the Jaccard coefficient (AUC=0.63) had only limited diagnostic value, while the Hellinger distance (AUC=0.313) had no diagnostic value. All the calculated data are listed in Table 5.

Table 5: ROC analysis of the Hellinger distance and Jaccard coefficient

	AUC	P Value	95%CI	
			lower	upper
Hellinger distance				
Whole lung	0.277	0.03	0.103	0.45
Right lung	0.4	0.34	0.19	0.609
Left lung	0.313	0.069	0.131	0.495
Jaccard coefficient				
Whole lung	0.63	0.206	0.453	0.807
Rght lung	0.536	0.732	0.338	0.734
Left lung	0.588	0.39	0.409	0.768

Note: 95CI is 95% confidence interval.

Discussion

Early diagnosis of COVID-19 is crucial for disease treatment and control(17). At present, the clinical value of CT for assessing COVID-19 is widely accepted(18). In our study, RT-PCR was used as the reference standard; the sensitivity, specificity and accuracy of CT were 85.71%, 60.91% and 65.38%, respectively. The corresponding PPV and NPV were 32.43% and 95.12%, respectively. However, our results are quite different from those reported in the literature(17). Our sensitivity was significantly lower (85.71% vs 97%), while the specificity was higher (60.91% vs 25%) than that reported in the literature. By comparing our results with those in the literature, we found that the main reason was that the majority of our patients had mild pneumonia, and the average age was significantly lower than that of the RT-PCR-positive patients in the literature. In this study, the PPV of CT was 95.12%, which was also consistent with the explanations proffered above.In our study, there were still some patients with positive CT and negative RT-PCR results (19, 20). We also noticed that the rate of positivity on RT-PCR was not high; this may be related to our sampling time, specimen source, and different stages of pneumonia(21).

Our results show that almost all RT-PCR-positive patients (12/14) had the characteristic CT features in the early phase, which were described in recent studies (17, 22-24). Despite the high sensitivity of CT, especially in patients younger than 30 years old (sensitivity is 100%), there was still one patient with no symptoms and no abnormal manifestations on pulmonary CT (18). Even more surprisingly, a pregnant woman combined with HIV and COVID-19 (2).

Negative CT results cannot eliminate the possibility of infection with SARS-CoV-2, and CT manifestations suggesting infection with SARS-CoV-2 also do not immediately appear (25, 26); therefore, these patients may also simply be carriers. In addition, the inflammatory manifestations of COVID-19 on lung CT are very similar to those caused by HIV infection, which may lead to misdiagnosis and improper treatment. This indicates that a comprehensive and detailed history of viral infections can be very useful for the early detection of suspected cases.

As mentioned in previous studies, nearly 30% of patients infected by SARS-CoV-2 are women(27, 28). Among pregnant women, more than 90% had mild pneumonia, whose clinical histories were very similar. Therefore, whether qualitative CT parameters can accurately reflect the characteristics of pneumonia are become the key point. On the one hand, it is very difficult for radiologists to quantitatively measure lesions due to their different CT manifestations (14, 29). On the other hand, there may be overlap and subtle differences between pneumonia lesions that are difficult to identify accurately(12). Clinically, the volume, density and distribution of the manifestations are the most important parameters for clinicians (16). However, the results suggest our parameters were not significantly different between the groups with positive and negative RT-PCR results. This may be another indication of the diversity and complexity of COVID-19. In addition, the results suggested that pneumonia was more common in the dorsal segment of the lower lobe of the right lung, which was consistent with previous reports(22). The unexpected results suggested that the original belief that the larger the size of the lesions, the greater the number of lesions, and the wider the lung segment involved, the higher the probability was of positive RT-PCR detection was inaccurate. Other studies have suggested that a higher negative rate of throat swabs compared with sputum samples is a possible cause(19). In this study, samples were collected two or more times (2-8 times) from each patient to ensure the accuracy of the results as much as possible. These results still need to be confirmed by follow-up antibody testing for COVID-19.

In this study, we found two new valuable parameters, the Hellinger distance and Jaccard coefficient(30); Ernst Hellinger introduced the Hellinger distance in 1909(31). On the one hand, when we considered the whole lungs, we found that the Hellinger distance was similar between normal lungs and the lungs of patients with positive RT- PCR results, and the coincidence rate of Jaccard coefficient was relatively higher (72.67%). These results were significantly different from those in patients with negative RT-PCR results. Obviously, the histogram analysis of each lesion indicated that there were no differences in the mean, peak and median CT values between the two groups. These two seemingly contradictory results suggest that the findings are similar whether pneumonia manifests as solid or mixed density lesions. However, the Hellinger distance indicated that the GGOs and fibrosis foci distributed in different positions along the curve were significantly different. This is consistent with the literature regarding the radiological characteristics of SARS-CoV-2 infection, such as GGOs and reticular opacities (18). These quantitative results strongly suggest that the pulmonary manifestations in patients with positive RT-PCR results are relatively more likely to be associated with GGOs and reticular opacities(19, 32). However, imaging changes may lag behind changes in patients' clinical symptoms, causing clinicians to miss the optimal timing for the RT-PCR.

The diagnostic value was based on a single figure of merit with a test AUCs of 0.63 for the Jaccard coefficient, while the AUC for Hellinger distance was 0.313. Based on these results, we cannot independently diagnose COVID-19 by using only the Hellinger distance and Jaccard coefficient (29).

Our study had several limitations. First, there is a limited window of time within which to determine the COVID-19 status of pregnant women before they give birth, and the number of cases that could be included was quite limited. Second, due to the limitations on CT radiation doses, it is difficult to perform follow-up CT reexaminations within a short period. Third, although we performed strict image quality control, there were several patients with small pulmonary nodules, which can affect feature extraction from CT images. Finally, other potential causes of CT imaging errors, such as the CT partial volume effect, could not be estimated.

In conclusion, the possibility of influenza virus and HIV infection should be given close attention in pregnant women. Despite the high PPV of CT examination, the limited value of CT for patients with mild pneumonia and no lesion cases. The current results do not support the prediction of COVID-19 pneumonia based on the parameters extracted from CT. Therefore, we should spend much more time investigating the value of CT rather than replacing RT-PCR with CT.

Declarations

Acknowledgments: We thank all our colleagues who helped us during the current study. This study was supported by grant 81771819 from the National Natural Science Foundation of China and grant 2017YFC0108803 from the National Key Research and Development Plan of China.

Conflicts of interest statement and funding: We declare no competing interests.

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Figures

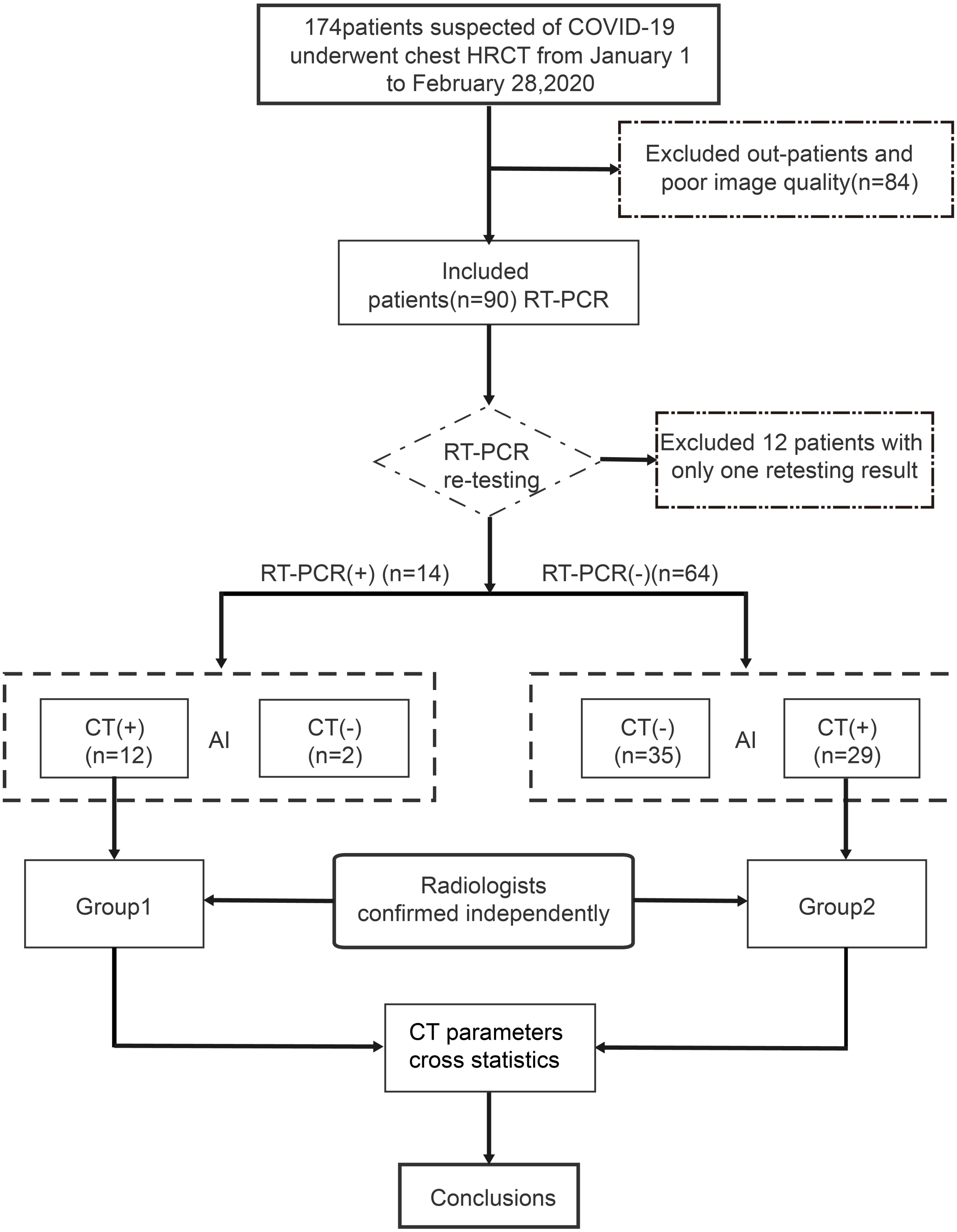

Figure 1

The flow chart of this study

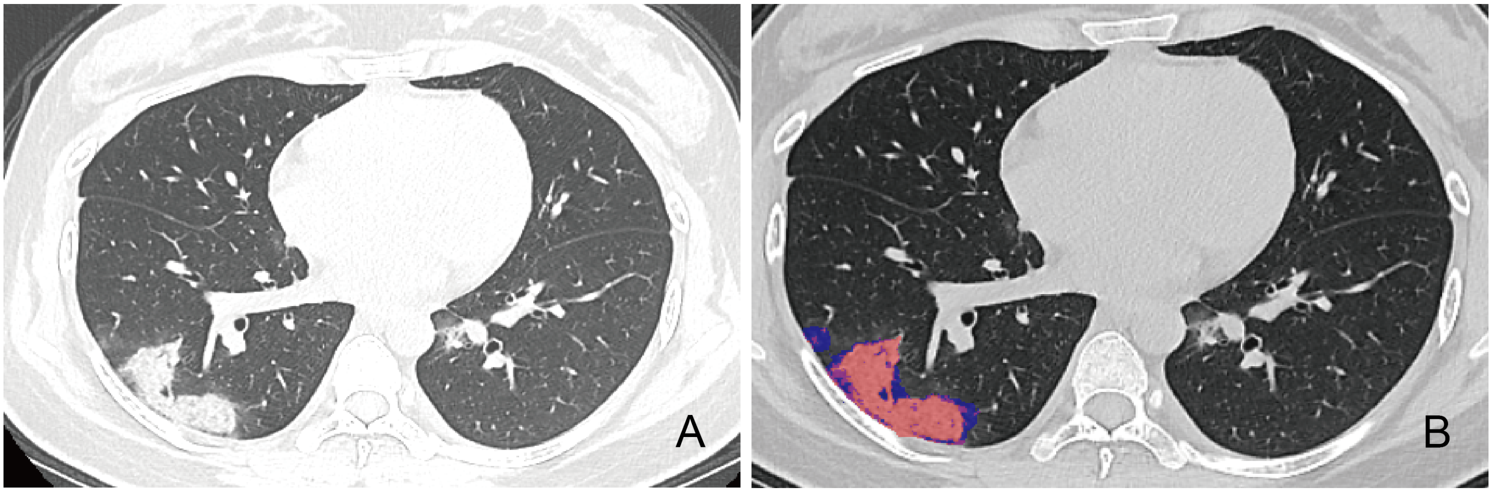

Figure 2

Chest CT images of a 27-year-old woman with fever for 2 days. The results of the RT-PCR assay for SARS-CoV-2 using a swab sample and the CT results were positive (A,B). The chest CT findings show the ground-glass opacities and patchy consolidation. The final diagnosis was confirmed as COVID-19 combined with HIV (A). The CT color map shows the pattern of mixed lesions extracted by AI software (B). The Hellinger distance and Jaccard coefficient were 0.18and 0.79, respectively.

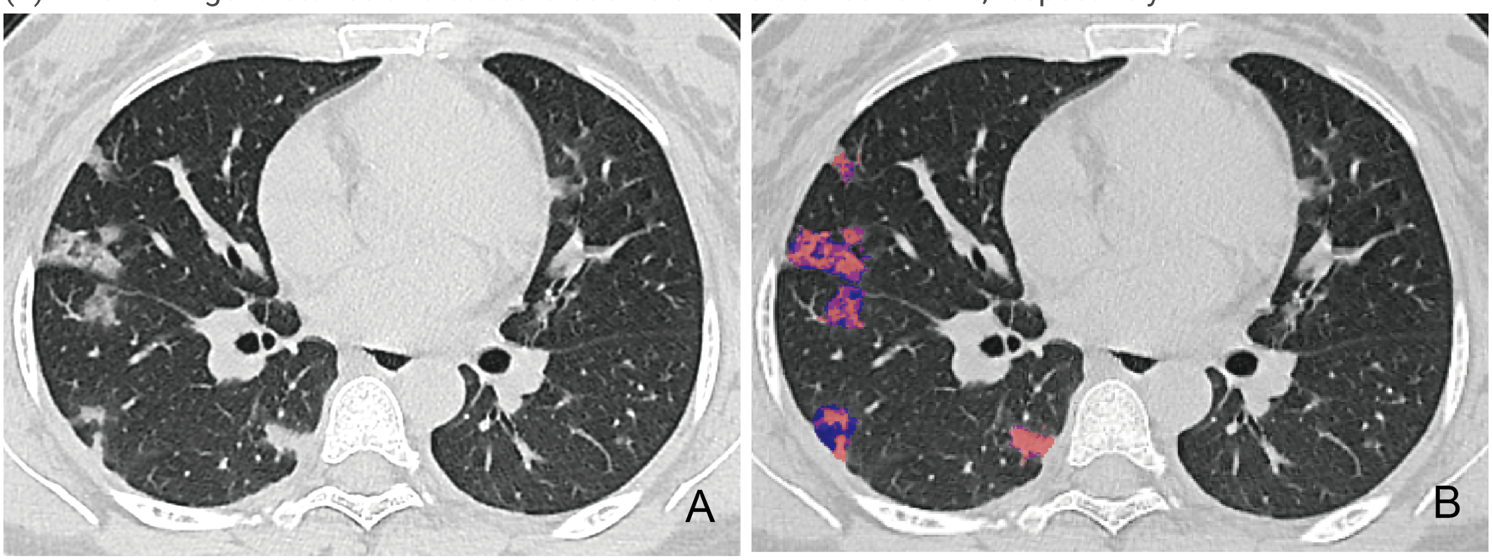

Figure 3

Chest CT images of a 26-year-old woman without any symptoms. A positive RT-PCR assay result for SARS-CoV-2 was obtained using a swab sample (A, B). Chest CT with an axial plane shows multiple manifestations with a focal ground-glass opacity (blue) and reticular opacities (brownish red) in the right lower lobe and middle lobe of right lung in the early stage of COVID-19 pneumonia (B). The Hellinger distance and Jaccard coefficient were 0.25 and 0.57, respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx