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Research Article

Changes in CT manifestations and RT-PCR testings of the coronavirus disease 2019 until recovery in patients with afferent infection vs. second-generation infection outside the original city (Wuhan): An observational study

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Abstract

Objective: To investigate changes in CT manifestations and results of reverse transcription polymerase chain reaction (RT-PCR) testing between afferent and second-generation coronavirus disease 2019 (COVID-19) outside the original city (Wuhan) until recovery.
Methods: We collected 26 consecutive COVID-19 patients undergoing initial and follow-up CT scans together with RT-PCR until recovery from 2 hospitals outside the original city. Seventeen patients with afferent infection and 9 with second-generation infection were assigned to Group A and B, respectively. By observing CT manifestations, we scored COVID-19, and statistically analyzed numbers of patients with changes in CT scores and RT-PCR results between stages.
Results: The total score of COVID-19 on initial CT manifestations was higher in Group A than in Group B ($P < 0.05$). COVID-19 progressed more frequently from stage 1−2, and relieved from stage 3−4 in Group A ($P < 0.05$). The similar trend in Group A could not be found in Group B. Results of RT-PCR in most of patients in Group A turned negative at stage 4 while those in Group B turned negative at stage 3 ($P < 0.05$).
Conclusion: Changes in CT manifestation and RT-PCR result can be different between afferent and second-generation COVID-19 until recovery.

Keywords: Coronavirus; Pneumonia; Infection; Computed tomography; Polymerase chain reaction

1. Introduction

In December 2019, an outbreak of the coronavirus disease 2019 (COVID-19) occurred in Wuhan, Hubei Province, China [1,2]; this unprecedented coronavirus that caused COVID-19 was named SARS-CoV-2 (originally tentatively named 2019-nCoV) [3]. Having spread rapidly to all provinces within China and across the world, centering on Wuhan City (the original city of COVID-19), it has developed into a pandemic [4]. Current research shows that the source of infection was mainly patients with COVID-19, and the main route of transmission was transmission through respiratory tract and

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close contact [5,6]. Patients with COVID-19 usually have symptoms of pneumonia such as fever and a cough [7−9].

As a primary tool, computed tomography (CT) was used to screen and detect COVID-19, as well as to provide feedback on treatment. Recent literature shows a normal appearance on thoracic CT cannot exclude the diagnosis of COVID-19 [10]. A clear diagnosis of SARS-CoV-2 infection requires positive results of reverse transcription polymerase chain reaction (RT-PCR) testing [5]. The RT-PCR testing can accurately detect the RNA of the SARS-CoV-2 in patients' respiratory tract secretions sampled by bronchoalveolar lavage, endotracheal aspiration, nasopharyngeal swabs, oropharyngeal swabs, and sputum. However, some patients with COVID-19 may have false negative RT-PCR results [10], which can cause confusion to medical personnel who may make the wrong judgment on patients' conditions and efficacy evaluation. Therefore, thoracic CT examination and RT-PCR testing have certain advantages and limitations for the diagnosis and monitoring of COVID-19 after treatment until recovery.

In patients with COVID-19 outside the original city of this disease, the different origins of infection include an exposure history of the original city in short-term (i.e. afferent infection), and infection through close contact with infected individuals who have recent exposure to the original city (i.e. second-generation infection). To the best of our knowledge, there have been no reports focusing on the comparisons of efficacy evaluation of treatments of the patients with COVID-19 based on different origins of the infection. Therefore, our study aimed to investigate the changes of CT manifestations and RT-PCR testing results until recovery in patients with COVID-19 outside the original city between different origins of the infection.

2. Materials and methods

2.1. Patients

This respective study was approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (approval number: 2020ER007-1); informed consent was obtained from each participant before the study.

From January 23, 2020 to March 10, 2020, a total of 26 patients with laboratory-confirmed COVID-19 by initial positive RT-PCR testing were collected from 2 designated hospitals outside the original city of COVID-19. These patients were divided into 2 groups based on the infection routes as mentioned above: ① patients in Group A had afferent infection; ② the patients undergoing second-generation infection were allocated to Group B. According to the infection routes, 17 and 9 patients were enrolled into Groups A and B, respectively. In Group A, there were 9 males and 8 females with a mean age of 47.8 years (range, 24−77 years). In Group B, there were 6 males and 3 females with a mean age of 43.8 years (range, 10−60 years).

According to the guideline for the diagnosis and treatment of pneumonia caused by novel coronavirus (trial version 7) [5], patients with confirmed COVID-19 had been treated in isolation at hospitals and received corresponding treatments depending on the severity of the disease. The mean time course of COVID-19 from admission to recovery was 22.6 ± 6.6 days (range, 12−39 days) in Group A, and 16.5 ± 2.9 days (range, 11−20 days) in Group B. In addition, 2 patients in Group A were critically ill, and underwent extended hospital stays relative to the other patients. During treatment, all patients needed to undergo thoracic CT examinations and RT-PCR testing every 3−4 days to assess changes of COVID-19 so as to evaluate the efficacy of anti-viral therapy until recovery. All patients underwent their first CT examinations and RT-PCR testing on the day of hospitalization.

2.2. CT image acquisitions

In our cohort, 17 patients underwent thoracic CT examination with 16-row multidetector row CT (MDCT) system (uCT 510, United Imaging, Shanghai, China), and the remaining 9 patients underwent thoracic CT scans with a 128-row multidetector CT system (SOMATOM Definition Flash, Siemens Healthcare systems, Germany). Following the usual position for thoracic CT scan, each patient was placed in a supine position with arms raised and was asked to hold their breath during the CT examination. The coverage of thoracic CT scans was from the thoracic inlet to the middle of the kidney, and the overall scanning time was less than 2 s. The scanning parameters for the uCT 510 were as follows: peak voltage of 120 kV, tube current of 200 mA (using automatic exposure control), rotation time of 0.35 s, detector alignment of 0.625 mm, pitch of 1.5 mm, matrix of 512 × 512 mm, and slice thickness of 5 mm. The scanning parameters for SOMATOM Definition Flash scanner were similar to those for the uCT 510 except the tube current of 250 mA and detector collimation of 0.6 mm. Window settings included mediastinum window (window width of 350 HU, window level of 40 HU) and lung window (window width of 1000 HU, window level of 700 HU). After obtaining 5-mm this thick for the CT image, we reconstructed the thin layer CT image with a thickness of 1 mm to obtain more detailed useful information.

2.3. CT data analysis

The thoracic CT data were analyzed as follows. As reported [11−14], COVID-19 can be manifested as ground glass opacity (GGO), consolidation, and crazy-paving patterns (GGO with superimposed septal thickening). Two radiologists (readers 1 and 2, with 2 and 22 years of experience in body CT study respectively) interpreted the image data in consensus according to the above-mentioned CT manifestations. Because the time course of COVID-19 was divided into 4 stages, comprising stages 1, 2, 3 and 4 according to the relevant reported literature [15], we compared number of the patients with the changes in CT manifestations between 2 adjacent stages of the 4 stages in Group A and B, and patients at stage 1 were compared with patients at admission. In addition, stage 1 was the early stage (0−4 days after admission), stage 2 was

the progressive stage (5−8 days after admission), stage 3 was the peak stage (9−13 days after admission), and stage 4 was the absorption stage (≥14 days after admission).

Subsequently, the above-mentioned experienced radiologists (readers 1 and 2) scored the lesions of COVID-19 on the initial CT at the time of hospitalization based on the reported semi-quantitative scoring system [16]. According to the scoring system, the lesions in each lung lobe were scored from 0 to 5 based on the extent of each lobe involvement as follows: 0 was for no involvement; 1 was for the involvement of <5%; 2 was for 6%−25% involvement; 3 was for 26%−49% involvement; 4 was for 50%−75% involvement; and 5 was for >75% involvement. The total CT score, with the minimum of 0 and maximum of 25, was the sum of the individual lobe scores.

Similarly, we scored the lesions of COVID-19 on the follow-up CT after admission in both groups, and compared the number of patients with the changes in total CT scores between 2 adjacent stages of the 4 stages in Group A and B. Patients at stage 1 were compared with those at admission.

2.4. RT-PCR testing

In this cohort, all patients had initial positive RT-PCR results. After receiving corresponding treatments according to the guideline for the SARS-CoV-2 infection (Trial Version 7) [5], all patients received follow-up RT-PCR testing to detect whether the results of RT-PCR testing changed to negative results due to the treatments. In order to avoid the false negative results influencing our judgment, we analyzed patients with negative results for consecutive 2 RT-PCR examinations (at least 1 day apart). If results of the previous consecutive RT-PCR testing were negative, we considered the results of RT-PCR testing changed negative after treatment, and recorded the corresponding time course (stage) of COVID-19 in Groups A and B. By staging COVID-19, we further investigated the patients with the results of RT-PCR testing turning negative corresponding to the progressive or relieved disease based on the total CT scores after treatments in Groups A and B.

2.5. Statistics analysis

SPSS statistics software (version 22) was used to perform the statistical analysis of all data. Quantitative data were expressed as mean ± standard deviation (minimum−maximum) and compared by the independent sample student t-test. The qualitative data was described by percentages and analyzed by *Chi-Square* test. *P*-value of <0.05 implied statistical difference.

3. Results

3.1. Classification of COVID-19: afferent vs. second-generation infections

According to the guideline for the SARS-CoV-2 infection (Trial Version 7) [5], patients with COVID-19 in both groups were divided into 4 types: mild, moderate, severe and critical types. As for the 4 types of COVID-19 in our study, the numbers of patients in group A were 70.6% (12/17) cases of moderate type, 17.6% (3/17) of severe type, and 11.8% (2/17) of critical type, while in group B, the numbers of patients were 22.2% (2/9) cases of mild type, 66.7% (6/9) of moderate type, and 11.1% (1/9) of severe type. In both groups, statistics showed that the predominant type of COVID-19 could be the moderate type in patients with either afferent or second-generation infection, and there was no statistical difference in the number of different types of COVID-19 patients between groups A and B ($P = 0.171$).

3.2. CT characteristics of COVID-19: afferent vs. second-generation infections

The CT manifestations of COVID-19 in patients with afferent infection (Fig. 1) and second-generation infection

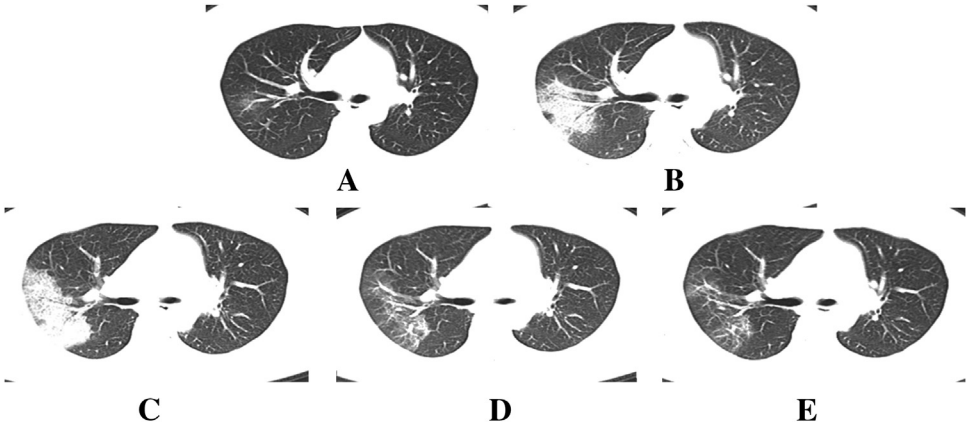

Fig. 1. Changes of the coronavirus disease 2019 as depicted on CT in a 46-year-old female with afferent infection. A, GGO is shown in right upper lobe at admission; B, on Day 3 after admission, the lesion of the right upper lobe has progressed and manifested as consolidate; C, on Day 6 after admission, the lesion of the right upper lobe expands and becomes more dense than before, and appears as crazy-paving pattern; D, on Day 12 after admission, the lesion of the right upper lobe has been absorbed greatly, and manifests as GGO; E, on Day 15 after admission, the lesion of the right upper lobe has been further absorbed, and the area of GGO reduces.

(Fig. 2) included subpleural GGO, consolidation, and crazy-paving pattern on initial and follow-up CT after admission during treatments. After the admission of COVID-19, CT manifestations of this disease changed from stages 1−4, and are recorded in Table 1. Based on the CT scores obtained on the initial CT data, the total score of COVID-19 was 10 (range, 7 to 21) in Group A, and 6 (range, 0−15) in Group B. Statistics showed that the total score of COVID-19 was significant higher in Group A than in Group B ($P = 0.038$).

Based on the comparisons of total score of COVID-19 obtained on follow-up CT scans during treatments between adjacent stages, the progressive and relieved patients in Group A and B are illustrated in Table 2. In Group A, statistics showed that COVID-19 progressed more frequently in patients with afferent infection from stage 1−2, and relieved more frequently from stage 3−4 ($P < 0.05$). The similar trend in Group A could not be found in Group B.

In addition, there were no statistical differences in gender and age of patients with COVID-19 between Group A and B after statistical analyses, while statistics showed that the time course in Group A was longer than in Group B ($P = 0.02$).

3.3. Corresponding relationship of changes in RT-PCR testing results with CT manifestations during follow-up after treatments

In both groups, the results of RT-PCR testing of all patients were positive at the time of admission, and did not turn negative at stage 1. At stages 2, 3 and 4, the results of RT-PCR

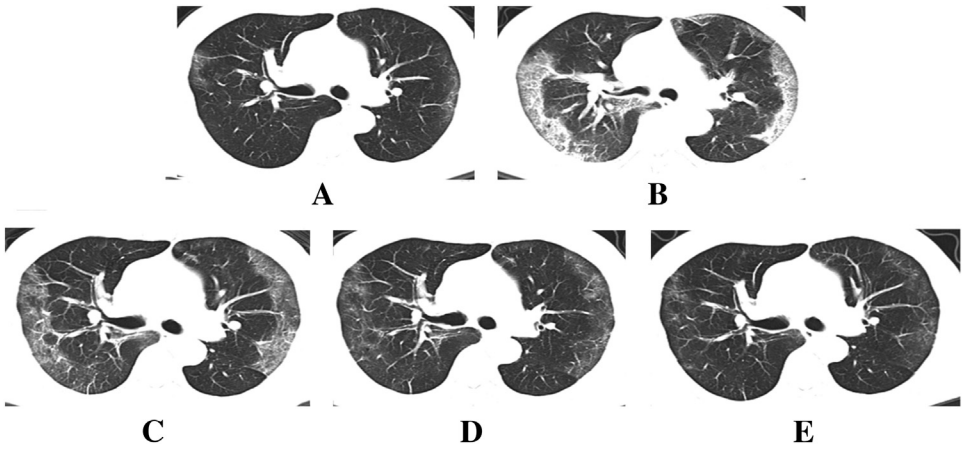

Fig. 2. Changes of the coronavirus disease 2019 as shown on CT in a 77-year-old female with second-generation infection. A, at admission, ground glass opacities (GGOs) are found in the subpleural areas of both lungs; B, on Day 4 after admission, areas of GGO have expanded and accompanied with superimposed inter- and intra-lobular septal thickening (crazy-paving pattern); C, on Day 7, the lesions have been absorbed slightly, and manifests as GGO; D, on Day 11 after admission, the areas of GGO in both lungs reduced, and the density of this disease has decreased greatly; E, on Day 15 after admission, only a small amount of GGO remains and the density of the lesions has further decreased.

Table 1
CT manifestations of coronavirus disease 2019 in groups of afferent infection (A) and second-generation infection (B) based on stages.

Group	CT manifestations	Stage			
		Stage 1	Stage 2	Stage 3	Stage 4
Group A ($n = 17$)	GGO	13 (76.4%)	14 (82.3%)	15 (88.2%)	14 (82.3%)
	Consolidation	7 (41.2%)	11 (64.7%)	8 (47.1%)	3 (17.6%)
	Crazy-paving pattern	9 (52.9%)	10 (58.8%)	10 (58.8%)	5 (29.4%)
Group B ($n = 9$)	GGO	5 (55.6%)	5 (55.6%)	6 (66.7%)	3 (33.3%)
	Consolidation	2 (22.2%)	4 (44.4%)	1 (11.1%)	0
	Crazy-paving pattern	2 (22.2%)	3 (33.3%)	1 (11.1%)	0

GGO, ground glass opacity.

Table 2
Comparisons of No. of patients with afferent infection (A) and second-generation infection (B) between adjacent stages.

Group	Changes in CT manifestations	Stage				*P*
		Stage 1	Stage 2	Stage 3	Stage 4	
Group A ($n = 17$)	Progressive cases	12 (70.6%)	11 (64.7%)	6 (35.3%)	2 (11.8%)	0.002
	Relieved cases	5 (29.4%)	6 (35.3%)	11 (64.7%)	15 (88.2%)	
Group B ($n = 9$)	Progressive cases	4 (44.4%)	2 (22.2%)	1 (11.1%)	0	0.102
	Relieved cases	5 (44.6%)	7 (77.8%)	8 (88.9%)	9 (100%)	

testing in both groups changed to negative results and remained negative until recovery in 5, 10 and 11 patients, respectively. Statistics showed that results of RT-PCR testing turned negative at stage 4 in a majority of patients in Group A while results of RT-PCR testing turned negative at stage 3 in most of the patients in Group B ($P = 0.048$). In detail, the corresponding relationship of RT-PCR testing results to turn negative with changes of CT manifestations during the follow-up after admission are shown in Table 3.

4. Discussion

To better understand the characteristics of COVID-19 based on different origins of infection for precise treatment outside the original city of this disease, we carried out this study to explore changes of CT manifestations and results of RT-PCR testing between patients with afferent infection vs. those with second-generation infection during follow-up after treatments until recovery.

Our study showed that the majority of patients with COVID-19 can be the moderate type in groups of afferent infection and second-generation infection. COVID-19 patients of critical type would be very few outside the original city (Wuhan). This can be explained by the virus load or the chance of being exposed to the virus in the environment of the districts outside the original city (Wuhan) being much lower than in the previous original city.

We found that the CT manifestations of COVID-19 in patients with afferent infection and second-generation infection can be subpleural GGO, consolidation, and crazy-paving pattern on initial and follow-up CT after admission during the follow-up after relevant treatments. Moreover, GGO can be the main manifestation at different stages of COVID-19, suggesting that this disease can have similar manifestations despite different routes of infection. Our findings are consistent with other published reports regarding CT appearances of pneumonia caused by virus [8−10]. We can presume that COVID-19 in patients with afferent infection and second-generation infection cannot be discriminated based on the CT manifestations alone, and we should combine the history of exposure to the original city of this disease or close contact with patients who have recently been exposed to the original city to make the differential diagnosis.

According to the reported semi-quantitative scoring system of COVID-19 based on the lung lobe involved [16], we scored the lesions of this disease on the initial CT after admission in patients with afferent infection and second-generation infection, and compared the scores of this disease between both routes of infection. Our study showed that COVID-19 could be more severe in patients with afferent infection than in those with second-generation infection at admission because the previous score of this disease was significantly higher in patients with afferent infection when compared with second-generation infection. The discrepancies in the scores between both routes of infection can be explained as follows: the RNA virus is characterized by error-prone viral replication and recombination, and usually generates progeny viruses with highly diverse genomes which might result in reduction of virulence and pathogenicity [17−19]. The SARS-nCoV-2, as a novel RNA virus meanwhile, might have the similar characteristics of reduction of virulence and pathogenicity resulted from the error-prone viral replication and recombination, leading to more serious condition of COVID-19 in patients with afferent infection than with second-generation infection. Because of the differences in severity of COVID-19 between both routes of infection, patients with afferent infection could have a longer hospital stay than with second-generation infection.

We used the total scores of COVID-19 based on the follow-up CT to explore the progress and outcome of this disease after treatment until recovery in patients with afferent infection and second-generation infection. Our study demonstrated that COVID-19 in patients with afferent infection aggravates from stage 1−2, and relieves from stage 3−4, but this trend could not be found in patients with second-generation infection. Our findings suggest that CT can be used to monitor the changes of COVID-19 after the treatments.

As shown in this study, RT-PCR testing can be the primary and critical tool for the diagnosis and monitoring recovery of COVID-19 in patients with afferent infection and second-generation infection. In cases with afferent infection and second-generation infection, results of RT-PCR testing may not turn negative at stage 1 of COVID-19 in all patients, but turn negative from stage 2 and maintain negative until recovery in some patients. However, the main improving phase can be different between patients with afferent infection and second-generation infection. In patients with afferent

Table 3
Number of patients with RT-PCR testings to turn negative: corresponding to CT changes during the follow-up after admission.

Group	Changes in CT manifestations	Results of RT-PCR testings to turn negative			
		Stage 1	Stage 2	Stage 3	Stage 4
A ($n = 17$)	Relieved cases	0	1 (5.8%)	2 (11.8%)	8 (47%)
	Progressive cases	0	2 (11.8%)	2 (11.8%)	2 (11.8%)
B ($n = 9$)	Relieved cases	0	1 (11.1%)	5 (55.6%)	1 (11.1%)
	Progressive cases	0	1 (11.1%)	1 (11.1%)	0

RT-PCR, reverse transcription polymerase chain reaction.

infection, the results of RT-PCR testing turn negative at stage 4 in a majority of cases. In contrast, the results of RT-PCR testing turned negative at stage 3 in most of patients with second-generation infection. Our findings suggest that the common stage for the results of RT-PCR testing to turn negative differs between patients with afferent infection and with second-generation infection. To ensure the accuracy of RT-PCR testing results, we performed 2 consecutive RT-PCR testing so as to avoid the possible false negative results caused by the absence of 2019-nCoV in the extracted samples or equipment errors to some extent [10].

Additionally, our research shows that the changes of CT manifestations cannot be completely corresponding to the changes of RT-PCR testing results in patients with afferent infections and second-generation infection. At stage 1, a small number of patients with afferent infection and approximately half patients with second-generation infection may be presented as relieved lesions as shown on CT, but the results of RT-PCR testing do not turn negative. At stage 2, the results of RT-PCR testing can turn negative, but the CT manifestations can be progressive or relived lesions in a small number of patients with afferent infection and second-generation infection. At stage 3, the corresponding relationship of negative results of RT-PCR testing with the changes of CT manifestations in patients with afferent infection can be similar with stage 2. As for patients with second-generation infection at stage 3, the CT manifestations can be relived lesions and the results of RT-PCR testing can turn negative in a large number of patients, but a very small number of patients might show negative results of RT-PCR testing and progressive lesions on CT. At stage 4, the results of RT-PCR testing can be negative, and the CT manifestations can be relived lesions in a large number of patients with afferent infection, but the critically ill patients can still show progressive lesions on CT. As for second-generation infection, a small number of patients can appear as negative results of RT-PCR testing and relieved lesions on CT.

There are some limitations to our study. On the one hand, our sample size is relatively small due to the effective prevention and control of COVID-19 outside the original city of this disease. On the other hand, the conditions of patients with COVID-19 in our study were mainly moderate, and the number of severe patients is relatively small because of the predominant type of the afferent and second-generation infections. Last but not the least, we simply recorded the results (T or F) of the RT-PCR in our study. Despite the limitations, our study revealed the changes in CT manifestations and RT-PCR testing of COVID-19 until recovery in COVID-19 patients with the afferent and second-generation infections.

In conclusion, our study shows that there are some discrepancies in changes of CT manifestations of COVID-19 and results of RT-PCR testing until recovery between patients with afferent and second-generation infections. The changes in CT manifestations of COVID-19 cannot be completely corresponding to the changes of RT-PCR testing results in patients with afferent infections and second-generation infection, suggesting that it is necessary and valuable to combine thoracic CT with RT-PCR testing to monitor COVID-19 after treatment. We hope that our findings can assist clinicians in formulating more accurate and effective treatment decision for COVID-19 patients with different origins of the infection outside the original city of this disease.

Ethic statement

This research was reviewed and approved by the Ethics Committee (seal) of Affiliated Hospital of North Sichuan Medical College.

Financial disclosure statement

None.

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Conflict of interest

There is no conflict of interest to declare in this study.

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