Clinical manifestations, CT features and outcome of 39 patients with COVID-19: retrospective case analysis

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Abstract

1. Background

To explore the manifestations and evolution of the pulmonary CT in COVID-19, and to analyze the causes and countermeasures of “Recurrent positive” in discharged patients.

2. Methods

Data of 39 patients with COVID-19 were collected. RT-PCR was positive at admission. From onset to discharge, pulmonary CT was performed regularly. During the treatment, Blood-RT, CRP and D-dimer were detected.

3. Result

From the onset to 14 days, the lesions in pulmonary CT increased significantly. After treatment, pulmonary CT before discharge showed that some patients' lesions were completely absorbed, and some residual strip like lesions or ground glass opacity with reduced density. Two weeks after discharge, there were 2 patients with new ground glass opacity. There were 20 patients with D-dimer increased.

4. Conclusion

In the early stage of COVID-19, the pulmonary CT has the characteristic manifestations, which is helpful for early diagnosis. In the middle stage, pulmonary lesions changed rapidly. In the recovery stage, some of the patients remained strip like lesions. It is necessary to pay attention to the possibility of pulmonary fibrosis after recovery. The discharge standard of COVID-19 needs to be more strict to avoid “Recurrent positive”, the discharged patients should continue to be observed. D-dimer was increased in some patients, it is safe to use heparin in anticoagulation without contraindications.

1. Background

Since December 2019, there have been many cases of “unidentified viral pneumonia” related to the local seafood wholesale market in Wuhan, Hubei Province, China[1]. The pathogen is novel coronavirus, which is suspected to be originated from bat. Chinese scientists have rapidly separated the virus and completed the virus sequencing[2]. The novel coronavirus was named by the World Health Organization (WHO) in January 12, 2020. The virus was named as the new coronavirus 2019 (2019-nCoV). On January 30, 2020, WHO announced the 2019-nCoV epidemic as a public health emergency of international concern. On February 11, 2020, WHO named the disease caused by 2019-nCoV as COVID-19. Since December 2019, the virus has spread from Wuhan to the whole country and even the world. As of 09:00 on March 26, 2020, there are 81,960 confirmed cases and 3,293 deaths in China, 382,148 confirmed cases and 17,734 deaths in other countries. COVID-19 has a long incubation period with strong infectious[3]. Clinical symptoms are hidden, and some patients have no clinical symptoms. If they can not be detected early, it is possible to cause wide spread, and threat to people's life and health. Some patients
have “Recurrent positive” after treatment and discharge, we must attach importance to it, which can reduce the occurrence of “Recurrent positive” and eliminate the adverse effects of “Recurrent positive” on the critical moment of epidemic control. The clinical data of 39 patients diagnosed with COVID-19 were analyzed retrospectively, in order to provide reference for the diagnosis, treatment, discharge criteria and management of discharged patients in the future.

2. Methods

The medical ethics committee of our college (Union Hospital, Tongji Medical College, Huazhong University of science and technology, Wuhan, Hubei Province) approved the retrospective study and gave up the written informed consent. From January 27, 2020 to February 13, 2020, 39 patients with COVID-19, 22 males and 17 females, aged 27.0-69.0 years (mean 47.1 ± 6.3 years), were diagnosed in the Union Hospital, Tongji Medical College, Huazhong University of science and technology. There were 5 cases with hypertension and 3 cases with diabetes. According to the novel coronavirus pneumonia diagnosis and treatment guide issued by the National Health Commission, all patients were examined for pulmonary CT and nucleic acid RT-PCR, and nucleic acid RT-PCR test was positive. Time from onset to hospital visit: 14 cases were less than 1 day, 23 cases were 1-3 days, 2 cases were more than 3 days. All 39 patients were admitted to the isolation ward. After admission, Blood routine examination, CRP and clotting time were completed, antiviral and symptomatic treatment were carried out, and all patients were discharged successfully. Discharge standard[5]: (1) The patient’s temperature returned to normal for more than 3 days; (2) The respiratory symptoms improved significantly; (3) The pulmonary CT showed that the acute exudative lesions absorbed significantly; (4) RT-PCR was negative in respiratory tract samples such as nasopharynx swabs for two consecutive times (the sampling interval was at least 24 hours). The novel coronavirus specific antibodies were detected in all patients at discharge. The duration of hospitalization was 15-32 days, 22.7 days on average.

CT scan: Siemens SOMATOM perspective, SOMATOM spirit, SOMATOM Definition AS+ were used. Scanning parameters: detector collimation width 64 × 0.6mm or 128 × 0.6mm, tube voltage 120kV, adaptive tube current (CARE Dose 4D), high resolution algorithm reconstruction, reconstruction layer thickness 1.5mm, layer interval 1.5mm. CT images were reviewed by two radiologists (1 chief physician and 1 senior physician). The location, range, distribution and morphology of the lesions were observed, and to compare the evolution of CT manifestations in different stages of the disease.

RT-PCR detection of nucleic acid: RT-PCR kit of Shanghai biomedical Biotechnology Co. Ltd. approved by China Food and Drug Administration (CFDA) was used for the detection of nasopharyngeal swab.

During the period of hospitalization, CT was performed every other week. Two weeks after discharge, pulmonary CT and nucleic acid were examined.

Statistical analysis: Using IBM SPSS statistical software (Version 24; IBM, New York, USA). Quantitative data are expressed as mean ± standard deviation (minimum and maximum). Unless otherwise specified, count data is expressed as a percentage of the total.
3. Results

3.1 Epidemiological history

39 patients lived in Wuhan, 21 of them had close contact history (53.8%), 6 had been to the area where people gathered, 12 had no special epidemiological history. The main symptoms of the patients were fever: 34 cases (87.2%, less than 38.5 degrees 26 cases, > 38.5 degrees 8 cases), cough in 27 cases (69.2%, dry cough in 15 cases, cough in foam like sputum 12 cases), chest tightness 26 cases (66.7%), fatigue 36 cases (92.3%), sore throat 30 cases (76.9%), diarrhoea 5 cases (12.8%), muscle soreness 11 cases (28.2%).

3.2 CT manifestations

The patients were examined every week after the onset of the disease: < 7 days, 7-14 days, 14 days - discharge, and 2 weeks after discharge.

(1) Range of lesion involvement

< 7 days: the lesions were located in bilateral lungs in 12 cases, unilateral lung in 27 cases (left lung in 11 cases, right lung in 16 cases);

7-14 days: the lesions were located in bilateral lungs in 26 cases, unilateral lung in 13 cases (left lung in 5 cases, right lung in 8 cases);

14 days - discharge: the lesions were located in bilateral lungs in 25 cases, unilateral lung in 11 cases (left lung in 4 cases, right lung in 7 cases); 3 cases without lesions in lung;

Two weeks after discharge: the lesions were located in bilateral lungs in 13 cases, unilateral lung in 6 cases (left lung in 2 cases, right lung in 4 cases); 20 cases without lesions in lung;

(2) Distribution and morphological characteristics of lesions: Calculate the number of lung segments with lesions.

There are three types of lesions: ground glass opacity lesions (including ground glass nodule and flake ground glass shadow), solid lesions (including solid nodule and flake shadow), and strip like lesions. The types of lesions in the involved lung segments were counted. If multiple lesions existed at the one segment, they were calculated separately.

< 7 days: 86 lung segments were involved. There were 79 ground glass opacity lesions (Fig.1), 26 solid lesions and 17 strip like lesions.

7-14 days: 214 lung segments were involved. There were 195 ground glass opacity lesions (Fig.2), 141 solid lesions and 108 strip like lesions.
14 days - discharge: 113 lung segments were involved. There were 64 ground glass opacity lesions, 47 solid lesions and 93 strip like lesions (Fig.3). The density of most ground glass lesions decreased significantly.

Two weeks after discharge: 39 lung segments were involved (2 patients had new lesions in 3 lung segments). There were 79 ground glass opacity lesions (3 new lesions), 26 solid lesions and 17 strip like lesions (Fig.4).

3.3 Laboratory examination

Blood routine examination on admission: Lymphocyte was normal in 11 cases, Lymphocyte decreased in 28 cases.

C-reactive protein on admission: Increased significantly in 32 cases, no increase in 7 cases. The reference value of our hospital is < 8mg/L.

During 7-14 days of onset, D-dimer was normal in 19 cases, increased in 12 cases (< 10 times of reference value), and significantly increased in 8 cases (> 10 times of reference value). Note: the reference value of our hospital is < 0.5mg/L.

3.4 Detection of nucleic acid in nasopharynx swab by RT-PCR

Contains nCovORF lab and 2019nCov-N. Note: the reference value of our hospital is < 10Au/ml. RT-PCR results of 39 patients at admission: 26 cases were positive for both nCovORF lab and 2019nCov-N, 5 cases were positive only for nCovORF lab, 8 cases were positive only for 2019nCov-N.

RT-PCR was negative at the time of discharge, and the interval between the two tests was at least one day.

Two weeks after discharge, RT-PCR was positive in 2 patients with new CT lesions. One case was nCovORF lab(+) and 2019nCov-N(+). One case was nCovORF lab(-) and 2019nCov-N(+). The second patient experienced RT-PCR tests two times, the first time was negative, the second time was positive, the interval was 3 days.

3.5 Detection of virus antibody

At the time of discharge, the patients were tested for virus antibody, including 2019N Cov antibody IgM and 2019N Cov antibody IgG. Among them, 15 cases were IgM (+) IgG (+), 21 cases were IgM (-) IgG (+), 3 cases were IgM (-) IgG (-).

Reexamination 2 weeks after discharge, two patients with positive nucleic acid test, the antibody test results of these two patients at discharge: one case was IgM (+) IgG(+), the other case was IgM (-) IgG(+).

4. Discussion
SARS-CoV-2 is a coronavirus, belonging to β-coronavirus cluster. COVID-19 is the third known zoonotic coronavirus after SARS and MERS. SARS-CoV and MERS-CoV are also β-coronavirus clusters. Huang et al. [1] showed that of the 41 SARS-CoV-2 patients they studied, 73% were male, 32% had basic diseases, the median age was 49 years old, in this study the age of onset is similar to our study. Guan et al. [4] reported 1099 cases of 2019-nCoV infection, they found that fever (87.9%) and cough (67.7%) were the most common symptoms, and diarrhea (3.7%) and vomiting (5.0%) were rare.

At present, the real-time reverse transcription polymerase chain reaction (RT-PCR) detection technology of COVID-19 has been developed and applied in clinic. Although RT-PCR is still the reference standard for the diagnosis of COVID-19, due to its high false negative rate [3] and lack of RT-PCR detection in the early stage of the outbreak, the timely diagnosis of infected patients is limited. Radiology, especially thin-layer pulmonary CT, plays an important role in the fight against this infectious disease[6]. Pulmonary CT has been recommended as the main basis of clinical diagnosis in Hubei Province. COVID-19 has a variety of CT manifestations, typical CT manifestations include ground glass opacity, spot like solid lesions, strip like lesions, with prominent subpleural distribution, and the most common posterior or inferior lobe involvement [7-9]. CT image of this group in the first time, all segments of the left and right lobes were involved, especially the lower lobes of bilateral lungs. The lower lobes of the right lung were more common, which was consistent with the previous research results of H7N9 avian influenza[10], which may be related to the relatively short and straight main bronchus in the right lower lobe of the lung.

In this group, in the early stage (< 7 days), the lesions in the lung are mainly ground glass opacity lesions, most of which are mainly distributed under the pleura or along the bronchovascular bundle, which is consistent with the pathological characteristics of viral pneumonia[11]. In the 7-14 days of the disease, the pulmonary lesions changed obviously and progressed rapidly, the density of some ground glass opacity lesions increased, and the solid lesions increased significantly. Pan et al.[12] reviewed 21 patients who were diagnosed and recovered. They had CT examination every 4 days and summarized four stages of the disease: early stage, progressive stage, peak stage and absorption stage. They found that ground glass opacity lesions would grow rapidly with the development of the disease. After treatment (>14 days), the lesions entered the absorption stage, the solid lesions decreased, the density of ground glass opacity lesions decreased, and the cord like lesions increased significantly. Two weeks after discharge, 20 patients (51.3%) had complete absorption of pulmonary lesions. Some of the patients had residual strip like lesions in the lung. Sheng et al.[13] found that viral infection can increase the risk of pulmonary fibrosis. Therefore, pulmonary fibrosis may be one of the serious complications after convalescence of COVID-19.

In this group, two patients found new ground glass opacity lesions in the lung two weeks after discharge, at the same time, the patients were positive in RT-PCR test. There were reports of “Recurrent positive” after discharge[14]. Zhou research reported[15], and the proportion of “Recurrent positive” was even as high as 14%. At present, the most commonly used specimen for RT-PCR detection is nasopharynx swab, the sampling site is in the upper respiratory tract of patients, but the main infection site of COVID-19 is in the lower respiratory tract and lungs, and a certain amount of virus is needed to detect the nucleic acid
positive. When the throat swab is taken from the upper respiratory tract, false negative results may occur. If the sputum can be discharged through the alveolar lavage fluid and induction, the detection rate can be improved. At the same time, we can combine other detection methods, such as virus antibody detection. Through comprehensive analysis, to improve the accuracy of diagnosis. Li Reported[16] virus antibody detection combined with RT-PCR detection can improve the detection rate of patients. It is also possible that after antiviral treatment during hospitalization, the level of virus replication is reduced, and the positive rate of RT-PCR of nasopharynx swab is low, resulting in false negative results after discharge. The antiviral treatment was stopped after discharged. The virus in the patient's body was duplicated again, the titer was increased, the pathogenicity was enhanced, and new active lesions appeared in the lung. At the same time, RT-PCR was positive. Liu et al.[17] found that 58% of patients with COVID-19 were given systemic glucocorticoids during hospitalization, and the more serious the disease was, the more glucocorticoids they used. It was also found that the time of poisoning was prolonged after hormone treatment, and the condition fluctuated after hormone discontinuation, which may even lead to “Recurrent positive” of nucleic acid detection. At the same time, the basic research on the virus is not thorough at present, the immune reaction process of the body is complex, whether there is a similar situation with HBV in the treatment process of COVID-19, some patients can not produce antibodies and completely eliminate the virus in the body, high-intensity anti-virus treatment only temporarily let the virus enter the dormancy period, which needs further research confirmation. The occurrence of “Recurrent positive” also reminds us to pay attention to discharge standards and management of patients after discharge. The virus detection method with higher sensitivity and specificity can ensure that the virus turns negative when the patient leaves the hospital. Before more effective detection methods appear, the discharged patients can be considered to continue isolation observation for a period of time. Discharged patients need regular reexamination. Because of the regular reexamination of this group, the aggravation of “Recurrent positive” patients can be prevented, so as to avoid their spread to the surrounding population and bring great pressure to the epidemic control.

In this group, 51.3% of the patients showed D-dimer elevation during the treatment, which was also reported in other studies [1,18]. Zhong[4] summarized the clinical characteristics of 1099 Chinese patients with COVID-19, showing that the increase of D-dimer accounted for 46.4%. The rise of D-dimer may be related to the formation of microthrombosis in the process of disease. It has been found in previous studies of SARS-COV that there is diffuse microthrombosis in the lung tissue of patients[19]. Because the disease of COVID-19 may have chest distress, dyspnea and decrease of blood oxygen, when the patient's condition changes, it is necessary to consider whether there is the possibility of pulmonary embolism. If necessary, CTA can be used to eliminate it. At the same time, according to the treatment experience of this group, in the absence of obvious anticoagulation contraindication, patients with D-dimer elevation are treated with low molecular weight heparin. There was no definite event of pulmonary embolism in this group, and there was no complication caused by anticoagulation.

5. Conclusion
Pulmonary CT has characteristic manifestations in the early stage. Combined with RT-PCR detection and virus antibody detection, it can be used for early diagnosis and reduce the risk of epidemic spread. In the middle stage of COVID-19, the pulmonary lesions changed rapidly with various CT manifestations. In the convalescent stage, some of the lesions in the lung were absorbed without residual. But some patients remained the strip like lesions in the lung. It is necessary to pay attention to the possibility of pulmonary fibrosis in the convalescent stage of COVID-19.

The discharge standard of patients with COVID-19 needs to be stricter, so as to avoid the “Recurrent positive” of patients with “false negative” after discharge, and to look forward to more sensitive tests in the future. It is suggested that the discharged patients should continue to observe in isolation and reexamine to understand the prognosis of the disease, which is conducive to early detection and early treatment. The D-dimer of some patients with COVID-19 increased during the treatment. To exclude the possibility of pulmonary embolism, low molecular weight heparin can be used for anticoagulation without anticoagulation contraindications.

There are several limitations in this study. First, the sample size of this study is small, lack of a large number of cases to support the CT manifestations and the cause of “Recurrent positive”, which needs further summary of large sample data in the later stage. Second, the follow-up time of this group of patients is not long enough, and the final change of the lesions in the lung of the patients is not observed, so we need to follow up for a longer time.

**Abbreviations**

World Health Organization (WHO); new coronavirus 2019 (2019-nCoV); Reverse Transcription-Polymerase Chain Reaction (RT-PCR); Coronavirus Disease 2019 (COVID-19);

**Declarations**

**Ethics approval and consent to participate**

The medical ethics committee of our college (Union Hospital, Tongji Medical College, Huazhong University of science and technology, Wuhan, Hubei Province) approved the retrospective study and gave up the written informed consent. The study obtained informed consent from all participants. The consent obtained was verbal, because they think this is a retrospective study, which is the collection and analysis of the data of the patients in the past. This study did not change the diagnosis and treatment process of patients, did not affect the prognosis of patients, and did not increase any risk of them. During follow-up, we informed patients about the study and they agreed to use their data. And the ethics committee approved this procedure.

**Consent to publish**
All participants’ information, images and inspection results are agreed to be published and have obtained written consent. The details, images will be freely available on the internet and may be seen by the general public. The consent form is available if requested. These patients have not been reported in any other submission by anyone.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and company that could be construed as influencing the position presented in this manuscript.

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No funding is provided in this study.

Authors' Contributions

All authors have read and approved the manuscript, and all the authors agree to send the article to your journal. HL have made substantial contributions to the conception and design of the work, and the acquisition, analysis of data. CZ have made contributions to the design of the work. QT have made contributions to the acquisition, analysis of data. JT have made contributions to analysis, interpretation of data, and write the article. All authors have agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. HL is corresponding author, and responsible for ensuring that all listed authors have approved the manuscript before submission.

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References


Tables

Table 1: Characteristics of the patient cohort

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>47.1±6.3(27.0-69.0)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td><strong>Initial symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>34(87.2%)</td>
</tr>
<tr>
<td>Low grade fever(≤38.5°)</td>
<td>26(66.7%)</td>
</tr>
<tr>
<td>High grade fever(&gt;38.5°)</td>
<td>8(20.5%)</td>
</tr>
<tr>
<td>Cough</td>
<td>27(69.2%)</td>
</tr>
<tr>
<td>Dry cough</td>
<td>15(38.5%)</td>
</tr>
<tr>
<td>Cough phlegm like sputum</td>
<td>12(30.8%)</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>26(66.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36(92.3%)</td>
</tr>
<tr>
<td>Throat pain</td>
<td>30(76.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5(12.8%)</td>
</tr>
<tr>
<td>Muscle soreness</td>
<td>11(28.2%)</td>
</tr>
</tbody>
</table>

Table 2: The CT feature of the pulmonary involvement in four stages
### Stage-1 7d

<table>
<thead>
<tr>
<th>Stage-2 7~14d</th>
<th>Stage-3 14~Discharge time</th>
<th>Stage-4 Two weeks after discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left and right lung</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Left lung</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Right lung</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>No lesion in lung</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Number of involved segments</td>
<td>86</td>
<td>214</td>
</tr>
<tr>
<td>Ground glass opacity (GGO)</td>
<td>79</td>
<td>195</td>
</tr>
<tr>
<td>Consolidation</td>
<td>26</td>
<td>141</td>
</tr>
<tr>
<td>Fibrotic streaks</td>
<td>17</td>
<td>108</td>
</tr>
</tbody>
</table>

### Table 3: Laboratory examination

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Decrease</th>
<th>Increase</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count</td>
<td>11(28.2%)</td>
<td>28(71.8%)</td>
<td></td>
<td>7(17.9%)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td></td>
<td></td>
<td>32(82.1%)</td>
<td></td>
</tr>
<tr>
<td>D-dimer</td>
<td>Normal</td>
<td>Increase (&lt;10 times reference value)</td>
<td>12(30.8%)</td>
<td>Increase (&gt;10 times reference value)</td>
</tr>
</tbody>
</table>

### Table 4: RT-PCR on admission and Virus Antibody at discharge

<table>
<thead>
<tr>
<th>RT-PCR</th>
<th>nCoVORF lab</th>
<th>2019nCov-N</th>
</tr>
</thead>
<tbody>
<tr>
<td>nCoVORF lab</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2019nCov-N</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Number of cases</td>
<td>26(66.7%)</td>
<td>5(12.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Virus Antibody</th>
<th>2019n cov antibody IgM</th>
<th>2019n cov antibody IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019n cov antibody IgM</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2019n cov antibody IgG</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Number of cases</td>
<td>15(38.5%)</td>
<td>21(53.8%)</td>
</tr>
</tbody>
</table>

Note: Quantitative data were presented as mean ± standard deviation (minimum-maximum), while the counting data were presented as count (percentage of the total).

**Figures**
Figure 1 showed ground glass opacity in the right lower lobe within 7 days from onset.

Figure 2 showed that there were ground glass opacity and solid lesions in the lower lobes of bilateral lungs at 7-14 days, and air bronchogram sign was seen.
Figure 3

showed that the strip like lesions and some solid lesions in bilateral lungs before discharge.

Figure 4

showed that lesions of bilateral lungs were well absorbed, and only a few strip like lesions remained at two weeks after discharge.