Dynamic Changes of Chest CT Follow-up In Coronavirus Disease-19 (COVID-19)

Pneumonia: Relationship To Clinical Typing

Abstract

Objectives To investigate the CT changes of different clinical types of COVID-19 pneumonia.

Methods This retrospective study included 50 confirmed patients with COVID-19 from 16 January 2020 to 25 February 2020. We analyzed the clinical and CT characteristics of the patients between the moderate group and the severe and critical group, and the dynamic changes of severity with the CT follow-up time.

Results There were no differences in the occurrence rate of CT characteristics between the moderate group (n=34) and the severe and critical group (n=16) in the initial CT (all p >0.05). There were differences in the CT score of right lung and total CT score at the initial CT between the two groups (all p <0.05). There was a quadratic relationship between total CT score and CT follow-up time in the severe and critical group (r²=0.137, p=0.008), the total CT severity score peaked at the second follow-up CT. There was no correlation between total CT score and CT follow-up time in the moderate group (p >0.05). The total CT score of the severe and critical group was different between the initial and first follow-up, the second and third follow-ups, the third and fourth follow-ups, and the fourth and fifth follow-ups CT (all p<0.05). The total CT score of the moderate group was different between the second and third follow-ups CT (p<0.05).

Conclusions COVID-19 pneumonia with the severe and critical types progressed rapidly with the greatest severity at the second follow-up CT, and the moderate type was relatively stable.
Keywords Coronavirus infections; Pneumonia; Tomography, X-Ray Computed; Follow-up Studies

Key Points

• Chest Computed Tomography follow-up is helpful to evaluate the disease severity of the COVID-19 pneumonia.

• There were differences in the dynamic changes of COVID-19 pneumonia with CT follow-up time in the moderate group and the severe and critical group.

• The interval time and frequency of follow-up CT should be selected reasonably according to the clinical type.

Abbreviations

COVID-19 Coronavirus Disease 2019
GGO Ground glass opacity
Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) pneumonia in Wuhan, Hubei Province of China in December 2019, the number of cases is increasing rapidly around the world, which is a major threat to public health[1,2]. With the joint efforts of public health officials, clinical physicians, and scientific communities, professional consensus, guidelines, and standards have been steadily established to prevent transmission and promote diagnosis and treatment[3-5].

Chest CT is currently one of the main methods for screening and diagnosis of COVID-19 pneumonia, and it is of great significance in early diagnosis and evaluation of the disease. Especially when an individual is suspected with COVID-19 infection but reverse transcription polymerase chain reaction (RT-PCR) screening is negative, the CT examination may be helpful for early diagnosis[6-8]. The initial CT findings of COVID-19 pneumonia had certain specificity and regularity[3,4,9-11], which provided an important basis for diagnosis and treatment. However, it is not clear whether there are differences in chest initial and follow-up CT findings of different clinical types. In the present, the National Health Commission of the People’s Republic of China[12] has taken the obvious absorption of lung inflammation by chest CT as one of the discharge criteria. Chest CT follow-up is of great value for the illness condition assessment and efficacy evaluation in COVID-19 pneumonia[13-15]. Dynamic CT observation is helpful to judge the evolution and prognosis of COVID-19 pneumonia. However, there is no uniform standard for the follow-up time window and the number of follow-up of chest CT. Therefore, the reasonable selection of CT follow-up time according to different clinical types will help to understand the disease condition in time and reduce the
radiation dose.

In this study, we retrospectively characterize the initial and follow-up CT findings in COVID-19 pneumonia with different clinical types and compared the chest CT follow-up time and the corresponding CT severity score to analyze the CT changes of different clinical types from initial diagnosis until patient recovery. This will help clinicians and radiologists to improve the understanding of CT changes with the evolution of COVID-19 pneumonia of different clinical types, so as to choose a reasonable CT follow-up time.

Materials and Methods

Our institutional review board waived the requirement to obtain written informed consent for this retrospective study.

Patients and CT image data acquisition

Fifty-three patients, who were admitted, from 16 January 2020 to 25 February 2020, to two cites in Sichuan province in China with confirmed COVID-19 and underwent chest CT followed ups, were enrolled in our study. Patient selection was consecutive and the exclusion criteria were COVID-19 patients without abnormal manifestations on CT. Finally, three patients were excluded because of no abnormal manifestations on CT and 50 patients were included. The clinical history, laboratory, epidemic characteristics, and chest CT images were collected. The date of both the first positive RT-PCR test and the initial chest CT examination was noted for each patient. All patients underwent CT scanning and laboratory tests on the same day when the initial mouth swab test was performed. All patients underwent follow-up chest CT without intravenous contrast material during the study time window. All patients were imaged with 0.6 mm to 1.25 mm thick slices in commercial multi-detector CT scanners.
(SOMATOM Definition AS and STRATON MX, Siemens Healthineers, Erlangen, Germany; Philips Ingenuity Core128, Philips Medical Systems, Best, the Netherlands; UCT 760 scanner, United Imaging, Shanghai, China; and BrightSpeed scanner, GE Medical Systems, Milwaukee, Wis). The mean CTIdvol was 6.6 ± 2.3 mGy (range: 4.1-10.3 mGy).

Clinical evaluation

All patients were at least two positive results by real-time RT-PCR assay for COVID-19 at laboratory testing of respiratory secretions obtained by means of the nasopharyngeal swab, oropharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage[3]. According to the guideline of COVID-19 (Trial Version 6) from the National Health Commission of the People’s Republic of China[12], the patients were typed into two groups. The moderate group was defined as: the patient had a fever, respiratory symptoms, and abnormal imaging findings of pneumonia. The severe and critical group was defined as meeting any of the following: 1. Severe respiratory distress (respiratory rate > 30 breaths/min); 2. Oxygen saturation (SpO2) ≤ 93% at rest; 3. Partial arterial oxygen pressure (PaO2)/ Fraction of inspired oxygen (FiO2) ≤ 300 mmHg (1 mmHg = 0.133kPa); 4. Respiratory failure and requirement for mechanical ventilation; 5. Shock and 6. Combined with multi-organ failure and requirement for intensive care unit (ICU).

The patients with confirmed COVID-19 pneumonia were hospitalized and isolated for treatment. Discharge standards[3,12] are as follow: 1. The body temperature returned to normal for more than 3 days; 2. Respiratory symptoms improved significantly; 3. Pulmonary imaging showed obvious signs of absorption in acute exudation inflammation of the lungs; and 4. Respiratory nucleic acid was negative for two consecutive times (one-day sampling
time interval at least). The patient who meets the four conditions simultaneously can be released from isolation.

**Chest CT evaluation**

The initial and follow-up chest CT images were evaluated for the following ten characteristics using internationally standard nomenclature defined by the Fleischner Society Glossary[16,17] and peer-reviewed literature on viral pneumonia[9,13]. The presence or absence of ten image characteristics was recorded: ground glass opacity (GGO), crazy-paving pattern, consolidation, pleural thickening or adhesion, fibrosis, discrete nodules, cavitation, lymph node enlargement, pleural effusion, and bronchiectasis. A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities on the basis of the area involved[9]. The area of abnormal pulmonary involvement was scored for each of the five lung lobes as follow: 0 score (no involvement), 1 score (1%-25% involvement), 2 scores (26%-49% involvement), 3 scores (50%-75% involvement), and 4 scores (76%-100% involvement). Finally, the total CT severity score was 20 by summing the five lobe scores ranging from 0 (no involvement) to 20 (maximum involvement). The interval time between initial chest CT and first follow-up CT scan was defined as Interval-1, and the interval between initial and second follow-up CT was defined as Interval-2, and so on.

Image analysis was performed by two radiologists with more than 8 years of experience (N.L. and XH.H.) by using a DICOM Viewer software (Medixant. RadiAnt DICOM Viewer [Software]. URL: https://www.radiantviewer.com). Images were reviewed independently, and final scores were reached by consensus.

**Statistical analysis**
All statistical analyses were performed by using SPSS (version 22.0, U.S.A.). Quantitative data was presented as mean±standard deviation (minimum-maximum) and the counting data were presented as the percentage of the total. The comparisons of non-paired and paired quantitative data were evaluated using the Mann-Whitney U test and Wilcoxon test, and Shapiro-Wilk test was used for the normal distribution. The categorical variables were evaluated by Chi-squared test or Fisher’s exact test, and continuous variables were evaluated by independent sample t test. SPSS curve estimation module was used to quantitatively evaluate the total CT severity score of pulmonary as a function of CT follow-up time. A p <0.05 was defined as statistical significance.

Results

Patient characteristics

The clinical characteristics and the numbers of CT scans of patients are listed in Table 1. There were 34 cases of moderate group (mean age, 44±12 years; age range, 21-69 years) and 16 cases of severe and critical group (mean age, 50±14 years; age range, 33-74 years). There was no significant difference in age, gender and symptoms with fever and cough between the moderate group and the severe and critical group (all p >0.05). There was significant difference in exposure history of recently travelling to Wuhan between the moderate group and the severe and critical group (16/34 vs. 16/16, p <0.001). The hospitalized period and numbers of scan in the severe and critical group were higher than that in the moderate group (28±7 vs. 20±8, p=0.002; 6±1 vs. 4±1, p <0.001, respectively). There was no significant difference in the consistency of PCR and CT results at the initial presentation between the two groups.
Different findings of initial CT images in two clinical groups

Among 50 patients, the top five CT characteristics were GGO (88%), pleural thickening or adhesion (52%), crazy-paving pattern (50%), consolidation (48%), and fibrosis (32%) (Table 2). The mean total CT severity score for the 50 patients was 5.6±4.4 (range 0 to 20).

The CT characteristics, distribution of lesions, and CT severity scores of initial CT were compared between the moderate group and the severe and critical group (Table 2). In the initial CT, the total CT severity score and the CT scores of right upper, middle and lower lobe in the severe and critical group was higher than that in the moderate group (all p <0.05). There were no statistical differences in the CT scores of left upper and lower lobe between the two groups (all p >0.05). There was no significant difference in the incidence of all CT characteristics and the number of involved lobes between two groups (all p >0.05).

The changes of CT severity scores with CT follow-up time in the two groups

The total CT severity score and CT follow-up time were compared between the moderate group and the severe and critical group (Table 3). There were no statistical differences in the interval time of Interval-1, Interval-2, Interval-3, and Interval-4 between the two groups (all p >0.05, table 3). The total CT severity score of the severe and critical group in the first, second, third, and fourth follow-up CT was significantly higher than that of the moderate group (all p<0.05, table 3).

In the severe and critical group, the total CT severity score peaked at the second follow-up CT (12.1±5.5, range 7 to 20) with a mean interval of 8±3 days after the initial CT scan, and then gradually decreased. The relationship between the total CT severity score and CT follow-up times was quadratic curve by the SPSS curve estimation module (r²=0.137, p=0.008, figure 1).
The total CT severity scores were significantly different between the initial CT and the first follow-up, the second and third follow-ups, the third and fourth follow-ups, and the fourth and fifth follow-ups (8.7±5.8 vs. 11.3±5.5, p=0.003; 12.1±5.5 vs. 11.7±5.4, p=0.034; 11.7±5.4 vs. 10.6±5.4, p=0.016; 10.6±5.4 vs. 8.7±5.5, p=0.024, respectively) (Figure 1). But the total CT severity scores were no difference between the first and second follow-ups, the fifth and sixth follow-ups, and the sixth and seventh follow-ups (11.3±5.5 vs. 12.1±5.5, p=0.085; 8.7±5.5 vs.4.7±0.6, p=0.102; 4.7±0.6 vs. 4.0±0.0, p=0.317, respectively).

In the moderate group, there was no correlation between the total CT severity score and CT follow-up times by the SPSS curve estimation module (p >0.05, figure 1). The total CT severity scores were significantly different between the second and third follow-up CT (5.0±2.7 vs. 4.9±2.5, p=0.007). But the total CT severity scores were no difference between the initial CT and the first follow-up, the first and second follow-ups, the third and fourth follow-ups (4.1±2.3 vs. 4.8±2.4, p=0.053; 4.8±2.4 vs. 5.0±2.7, p=0.589; 4.9±2.5 vs. 4.0±1.6, p=0.066, respectively).

**The changes of CT characteristics with CT follow-up time in the two clinical groups**

In the severe and critical group, the proportions of GGO, crazy-paving pattern, consolidation, pleural thickening or adhesion, and fibrosis changed dynamically with the CT follow-up time, as shown in Figure 2 and Figure 3. The GGO and pleural thickening or adhesion could be found in every CT follow-up and were the main signs in the last two CT follow-up. The proportions of patients with the crazy-paving pattern (75%) and consolidation (81%) peaked at the second follow-up CT, and then gradually decreased. The occurrence rate of fibrosis (73%) peaked at the fourth follow-up CT, and then gradually decreased. In the sixth and
seventh follow-up CT, the GGO, pleural thickening or adhesion, and fibrosis were the main demonstration without any crazy-paving pattern and consolidation.

The dynamic changes of CT characteristics in the moderate group with the follow-up time are shown in Figure 4 and Figure 5. In the initial CT, the GGO [32/34 (94%) of patients], pleural thickening or adhesion (50%), crazy-paving pattern (50%) and consolidation (41%) could be mostly found. In the first follow-up CT, the consolidation [20/34 (59%) of patients] and pleural thickening or adhesion (65%) extended to more pulmonary lobes with less crazy-paving pattern (44%) and GGO (91%). In the second follow-up CT, the GGO [23/28 (82%) of patients], consolidation (79%) and pleural thickening or adhesion (79%) were the main demonstration, and fibrosis (54%) extended to more pulmonary lobes with less crazy-paving pattern (39%). Both in the third and fourth follow-up CT, the GGO and pleural thickening or adhesion the main demonstration with the obviously absorption of consolidation and crazy-paving pattern, and fibrosis was still present.

**Discussion**

In our study, we analyzed the different characteristics and involvement severity of CT in the two clinical groups at initial diagnosis and follow-up. Our study found that the lesion's involvement of the severe and critical group was more extensive in the right lung and the whole lung than those of the moderate group in the initial CT. The dynamic changes of severity as CT follow-up time were different between the two groups. These findings can help clinicians to conduct the clinical typing of COVID-19 in the early stage, so as to achieve the purpose of early and accurate treatment.

The study showed that the most common initial CT characteristics of COVID-19 pneumonia
of the two groups are ground glass opacity, crazy-paving pattern, consolidation pleural thickening or adhesion, and mainly distributed in a subpleural area. These findings were consistent with previous studies[9,10,18-20]. However, we did not find differences in the incidence of above CT characteristics between the two groups in the initial CT, which was consistent with the previous study[21]. Only a recent study of 25 severe/critical cases[22] reported that the occurrence rates of consolidation and crazy-paving pattern in severe/critical patients were significantly higher than those of the moderate patients. The difference may be related to the sample size. Therefore, whether the clinical types can be distinguished by CT characteristics still requires a large sample study, while the dynamic changes of different clinical types can be demonstrated by CT characteristics.

Another interesting finding was that the patients with severe and critical type progressed rapidly with the greatest severity at the second follow-up CT, and then gradually recovered. The moderate type is relatively stable, though the total CT severity scores also peaked at the second follow-up CT. There was no difference in the interval time of each chest CT follow-up between the two groups, which indicated that the follow-up time window of the two groups was basically consistent. By comparing the total CT severity score of adjacent intervals, there was no significant difference in the changes of lesion involvement in late follow-up of the severe and critical group, as well as in the early follow-up of the moderate group. The findings indicated that we may take the interval with therapeutic changes as the time window of CT follow-up, and prolong the time window of follow-up with no therapeutic changes. Although the radiation dose has been reduced by low dose technology, iterative algorithm, care dose, and reduction of tube voltage[23,24], appropriate CT follow-up interval can help
reduce the radiation dose. Therefore, the frequency of CT follow-up should be decreased by prolonging the interval time in the late stage of severe and critical type and the early stage of moderate type.

This study has several limitations. Firstly, the sample size was relatively small, especially in the severe and critical group. Further studies with more patients are warranted to obtain a definitive answer. Secondly, the number and interval of CT follow-up per patient were different, though the interval time of each follow-up chest CT was of no difference between the two groups. These factors need to be considered when interpreting our findings. Finally, the quantitative and semi-quantitative measurements of the pulmonary lesions may have certain subjectivity, and can only partly reflect the severity. Accurate quantitative analyses should be made to identify the changes in clinical and imaging characteristics in future studies.

In conclusion, the results of this study confirmed the dynamic changes of chest follow-up CT in different clinical classifications of covid-19 pneumonia and the great significance of chest CT follow-up for the diagnosis and differentiation of moderate type and severe and critical type. COVID-19 pneumonia with severe and critical type progressed rapidly with the greatest severity at the second follow-up CT, and the moderate type is stable. The frequency of CT follow-up should be decreased by prolonging the interval time in the late follow-up of severe and critical type and the early follow-up of moderate type. Therefore, the interval and frequency of follow-up CT should be carefully considered and reasonably selected according to the clinical type in order to reduce the cumulative radiation dose.
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| Table 1: Patient Characteristics |
|----------------------------------|
|                                  | All patients (n=50) | Moderate type (n=34) | Severe and critical type (n=16) | t or \( \chi^2 \) P-value |
| **Age (years)**                  | 46±13 (21-74)       | 44±12 (21-69)        | 50±14 (33-74)                   | 0.080                        |
| **Gender**                       |                     |                      |                                 | 0.952                        |
| Man                              | 29                  | 20                   | 9                               |                              |
| Woman                            | 22                  | 15                   | 7                               |                              |
| **Exposure history**             |                     |                      |                                 | <0.001***                    |
| Recent travel to Wuhan           | 32 (64%)            | 16 (47%)             | 16 (100%)                       |                              |
| Exposure to infected patient     | 18 (36%)            | 18 (53%)             | 0 (0%)                          |                              |
| **Symptoms**                     |                     |                      |                                 |                              |
| Fever                            | 31 (62%)            | 20 (61%)             | 11 (69%)                        | 0.500                        |
| Cough                            | 29 (58%)            | 17 (50%)             | 12 (75%)                        | 0.095                        |
| **Initial RT-PCR test and CT**   |                     |                      |                                 | 1.000                        |
| Both RT-PCR and CT positive     | 46 (92%)            | 31 (91%)             | 15 (94%)                        |                              |
| RT-PCR negative and CT positive | 4 (8%)              | 3 (9%)               | 1 (6%)                          |                              |
| **The hospitalized period (d)**  | 23±8 (10-43)        | 20±8 (10-40)         | 28±7 (19-43)                    | 0.002**                      |
| **Mean number of scans**         | 4±2 (2-8)           | 3±1 (2-5)            | 6±1 (3-8)                       | <0.001***                    |
| The interval between the adjacent scans (d) | 5±3 (2-10) | 5±2 (2-13) | 5±2 (1-10) | NA |

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

NA, not applicable; ** p<0.01; *** p<0.001.
Table 2. Different findings of initial CT images between two clinical groups

| CT characteristics                              | All patients (n=50) | Moderate type (n=34) | Severe and critical type (n=16) | Mann-Whitney U or χ² | P-value |
|--------------------------------------------------|---------------------|----------------------|--------------------------------|----------------------|---------|
| ground glass opacity                             | 44 (88%)            | 32 (94%)             | 12 (75%)                       | 0.074                |         |
| consolidation                                    | 24 (48%)            | 14 (41%)             | 10 (63%)                       | 0.227                |         |
| crazy-paving pattern                             | 25 (50%)            | 17 (50%)             | 8 (50%)                        | 1.000                |         |
| pleural thickening or adhesion                   | 26 (52%)            | 17 (50%)             | 9 (56%)                        | 0.767                |         |
| fibrosis                                         | 16 (32%)            | 10 (29%)             | 6 (38%)                        | 0.746                |         |
| discrete nodules                                 | 4 (8%)              | 3 (9%)               | 1 (6%)                         | 1.000                |         |
| bronchiectasis                                   | 3 (6%)              | 2 (6%)               | 1 (6%)                         | 1.000                |         |
| thoracic lymphadenopathy                         | 2 (4%)              | 1 (3%)               | 1 (6%)                         | 0.542                |         |
| pleural effusion                                 | 2 (4%)              | 0 (0%)               | 2 (13%)                        | 0.098                |         |
| cavitation                                       | 1 (2%)              | 1 (3%)               | 0 (0%)                         | 1.000                |         |
| **Number of involved lobes**                     |                     |                      |                                |                      |         |
| Right upper lobe                                 | 34 (68%)            | 21 (62%)             | 13 (81%)                       | 0.208                |         |
| Right middle lobe                                | 24 (48%)            | 13 (38%)             | 11 (69%)                       | 0.069                |         |
| Right lower lobe                                 | 46 (92%)            | 31 (91%)             | 15 (94%)                       | 1.000                |         |
| Left upper lobe                                  | 34 (68%)            | 22 (74%)             | 12 (75%)                       | 0.533                |         |
| Left lower lobe                                  | 39 (78%)            | 24 (71%)             | 15 (94%)                       | 0.080                |         |
| **CT score in each lobe**                        |                     |                      |                                |                      |         |
| Right upper lobe                                 | 1.0±1.0 (0-4)       | 0.7±0.5 (0-1)        | 1.7±1.4 (0-4)                  | 0.017*               |         |
| Right middle lobe                                | 0.7±1.0 (0-4)       | 0.4±0.5 (0-1)        | 1.3±1.3 (0-4)                  | 0.007**              |         |
| Right lower lobe                                 | 1.5±1.0 (0-4)       | 1.2±0.7 (0-4)        | 1.9±1.2 (0-4)                  | 0.047*               |         |
| Left upper lobe                                  | 1.0±1.1 (0-4)       | 0.7±0.6 (0-2)        | 1.6±1.5 (0-4)                  | 0.057                |         |
| Left lower lobe                                  | 1.3±1.1 (0-4)       | 1.1±0.8 (0-3)        | 1.8±1.4 (0-4)                  | 0.123                |         |
| **The total CT severity scores**                 | 5.6±4.4 (0-20)      | 4.1±2.3 (0-11)       | 8.7±5.8 (1-20)                 | 0.008**              |         |

Note: Quantitative data were presented as mean ± standard deviation (minimum-maximum), while the counting data were presented as count (percentage of the total). *p<0.05; **p<0.01.
Table 3. The difference of CT severity scores and CT follow-up time between two groups

|                      | Moderate type (number of patients) | Severe and critical type (number of patients) | P-value by Mann-Whitney U test |
|----------------------|-----------------------------------|-----------------------------------------------|---------------------------------|
| Initial CT           | 4.1±2.3 (0-11) (n=34)             | 8.7±5.8 (1-20) (n=16)                        | 0.008**                         |
| First follow-up CT   | 4.8±2.4 (1-10) (n=34)             | 11.3±5.5 (5-19) (n=16)                       | <0.001***                      |
| Second follow-up CT  | 5.0±2.7 (1-10) (n=28)             | 12.1±5.5 (7-20) (n=16)                       | <0.001***                      |
| Third follow-up CT   | 4.9±2.5 (0-9) (n=15)              | 11.7±5.4 (6-20) (n=15)                       | 0.001**                         |
| Fourth follow-up CT  | 4.0±1.6 (0-8) (n=8)               | 10.6±5.4 (4-20) (n=14)                       | 0.002**                         |
| Fifth follow-up CT   | NA                                | 8.7±5.5 (4-20) (n=8)                         | NA                             |
| Sixth follow-up CT   | NA                                | 4.7±0.6 (4-5) (n=4)                          | NA                             |
| Seventh follow-up CT | NA                                | 4.0±0.0 (3-4) (n=2)                          | NA                             |
| Interval-1 (d)       | 4±2 (2-10)                        | 4±2 (1-8)                                     | 0.518                           |
| Interval-2 (d)       | 9±3 (5-13)                        | 8±3 (4-13)                                    | 0.102                           |
| Interval-3 (d)       | 14±4 (9-23)                       | 12±3 (8-18)                                   | 0.251                           |
| Interval-4 (d)       | 17±2 (14-19)                      | 17±4 (12-26)                                  | 0.743                           |
| Interval-5 (d)       | NA                                | 21±3 (19-26)                                  | NA                             |
| Interval-6 (d)       | NA                                | 25±7 (18-36)                                  | NA                             |
| Interval-7 (d)       | NA                                | 29±4 (24-32)                                  | NA                             |

Note: Quantitative data were presented as mean ± standard deviation (minimum-maximum), Interval-1, the interval between initial CT and first follow-up CT; Interval-2, the interval between initial CT and second follow-up CT, and so on. NA, not applicable; d, day.

** p<0.01; *** p<0.001.