Temporal changes of quantitative CT findings from 102 patients with COVID-19 in Wuhan, China: A longitudinal study

Xiaohui Chen[a,1], Wenbo Sun[a,1], Dan Xu[b], Jiaojiao Ma[a], Feng Xiao[a] and Haibo Xu[a,*]

[a]*Department of Radiology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China*
[b]*Medical Imaging Laboratory, Wuhan University, Wuhan, Hubei 430071, China*

Abstract.
BACKGROUND: Computed tomography (CT) imaging combined with artificial intelligence is important in the diagnosis and prognosis of lung diseases.
OBJECTIVE: This study aimed to investigate temporal changes of quantitative CT findings in patients with COVID-19 in three clinic types, including moderate, severe, and non-survivors, and to predict severe cases in the early stage from the results.
METHODS: One hundred and two patients with confirmed COVID-19 were included in this study. Based on the time interval between onset of symptoms and the CT scan, four stages were defined in this study: Stage-1 (0 $\sim$7 days); Stage-2 (8 $\sim$ 14 days); Stage-3 (15 $\sim$ 21days); Stage-4 ($>$ 21 days). Eight parameters, the infection volume and percentage of the whole lung in four different Hounsfield (HU) ranges, (($-$, -750), [-750, -300), [-300, 50) and [50, $+$)), were calculated and compared between different groups.
RESULTS: The infection volume and percentage of four HU ranges peaked in Stage-2. The highest proportion of HU [-750, 50) was found in the infected regions in non-survivors among three groups.
CONCLUSIONS: The findings indicate rapid deterioration in the first week since the onset of symptoms in non-survivors. Higher proportion of HU [-750, 50) in the lesion area might be a potential bio-marker for poor prognosis in patients with COVID-19.

Keywords: COVID-19, quantitative CT parameters, temporal changes, early detection

1. Introduction

Since December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (COVID-19), was reported [1,2] and has rapidly spread to most countries in the world. By July 24 2020, the number of confirmed COVID-19 cases worldwide had risen above 15 million, and the death toll from COVID-19 passed 619,150 worldwide, equivalent to a mortality rate of around 4.13% [3].

COVID-19 has a high mortality rate, and it progresses rapidly without obvious signs. In previous studies, the times between onset of symptoms and the emergence of ARDS could be as short as 9 days [4]. Despite real-time reverse transcription polymerase chain reaction (RT-PCR) is used as one of the main tool for diagnosing COVID-19 [5], chest computed tomography (CT) imaging, as an auxiliary mean

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[1]These two authors contributed equally to the article.
[*]Corresponding author: Haibo Xu, Department of Radiology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China. Tel.: +86 2767812533; Fax: +86 2767812533; E-mail: xuhaibo1120@hotmail.com.

of examination, is fast and can produce fast diagnosis for suspected patients with COVID-19. Because of its high efficiency and sensitivity, CT imaging diagnosis report was once as one of the COVID-19 clinical diagnostic criterion in the Hubei Province by the Chinese Center for Disease Control and Prevention [6]. However, there are individual differences in observing the infection regions among radiologists. Therefore, a combination of artificial intelligence (AI) and CT imaging could be helpful in the diagnosis and prognosis of COVID-19 [7,8].

However, at present, there is no research on how to evaluate the severity from temporal changes of the quantitative CT findings in detail at the early stage [9,10]. In this study, we extracted the quantitative parameters associated with lesions from CT images and investigated temporal changes of 8 quantitative parameters in patients with COVID-19, and compared the quantitative parameters across the disease course between three clinic types patients (moderate\severe\non-survivors), aimed to screen severe cases and predict the outcome in the early stage.

2. Materials and methods

2.1. Patients

This retrospective study included 102 adult inpatients at Zhongnan Hospital of Wuhan University (Wuhan, China), who died or were discharged between Jan 1, 2020 and Mar 1, 2020. The requirement for informed consent was waived by the ethics commission for this retrospective study. The median age of the 102 patients was 56.0 years (IQR 41.0–68.0), ranging from 25 years to 96 years.

2.2. Inclusion and exclusion criterions

All patients diagnosed with COVID-19, confirmed by real-time RT-PCR analysis of throat swab specimens, with obvious lesions in their CT images were included. The patients whose RT-PCR results were positive but CT results normal were exclude.

2.3. Typing

Following the guideline of COVID-2019 (trial version 7) issued by the China National Health Commission, the severity includes four types: mild, common, severe, and critical [11]. In order to distinguish patients discharged or not, we categorized patients to three groups based on the severity: moderate (patients with mild symptoms, including mild and common), severe (survivors with severe symptoms, including severe and critical) and non-survivors. Mild symptoms were defined as not meeting the following three criteria and severe symptoms were defined as meeting one of the following criteria during the disease course: 1) severe respiratory distress (respiratory rate > 30 breaths/min); 2) Requirement for oxygen treatment support; 3) SpO2 $< 93\%$ in the resting state. Survivors with severe symptoms were discharged of severe symptoms and non-survivors were people who were died of severe symptoms. Patients were assigned to three groups: 43 (42%) patients had mild symptoms (the moderate group), 39 (38%) patients were discharged of severe symptoms (the severe group) and the remaining 20 (20%) died (the non-survivors group).

2.4. Stages

Based on the time interval between onset of symptoms and the CT scan, we designated four stages in

our study: Stage-1 (CT scans done $\leqslant$7 days after symptoms onset); Stage-2 (8 days $\leqslant$ CT scans done $\leqslant$ 14 days after symptoms onset); Stage-3 (15 days $\leqslant$ CT scans done $\leqslant$ 21 days after symptoms onset); Stage-4 (CT scans done $>$ 21 days after symptoms onset). Quality control of CT images was checked by two radiologists with several years of experience.

3. CT image analyses

3.1. Image acquisition

All CT scans were obtained with patients in the supine position, using GE discover CT750 (GE Healthcare, USA). Patients were scanned from the lever of the upper thoracic inlet to the inferior lever of the costophrenic angle. For CT acquisition, the tube voltage was 120 kVp and the tube current was modulated by automatic exposure control system. Images were reconstructed with a slice thickness of 1 mm from the raw data, respectively. The reconstructed images were transmitted to the workstation and picture archiving and communication systems (PACS) for post-processing.

3.2. Lesion segmentation

An artificial intelligence (AI) software, uAI-Discover-PNA (pneumonia) [12], developed by United Imaging Intelligence Co., Ltd, was used in the image analysis. The segmentation algorithm in the software is based on a modified 3-D convolutional neural network called VB-net [12]. The VB-net adopted the bottle-neck blocks during the down-sampling and up-sampling operations inside the V-shaped network (V-net) [12]. The bottle-neck blocks use a stacked 3-layer structure ($1 \times 1 \times 1$, $3 \times 3 \times 3$ and $1 \times 1 \times 1$ convolution kernels), which could help reduce and combine feature map channels, and makes the VB-net faster than the V-net in dealing with large 3D volumetric data [12]. Besides, a human-in-the-loop strategy was applied to iteratively update the VB-net segmentation network via a human-machine interaction manner [12]. The segmentation results produced by the VB-net would be corrected by the radiologist, and then the corrected segmentation results were fed into the model as new training data, which could improve the performance of the deep learning model after 3 iterations [12]. The VB-net could simultaneously segment five lung lobes, 18 lung segments and lung lesions, and yields a Dices index of 0.916 [13] between automatic and manual segmentations when validated on 300 COVID-19 subjects [12].

3.3. Image parameters extraction

According to the segmentation results, 8 parameters, which were potentially related to COVID-19, the infection volume and percentage of HU $(-, -750)$, HU $[-750, -300)$, HU $[-300, 50)$, HU $[50, +)$ in all lung were calculated. The infection volume and percentage of the whole lung, each lung lobe and segments were calculated in four HU ranges as following:

$$\text{Infection volume}(x) = V(x\_infection) \tag{1}$$

$$\text{Infection percentage} = \frac{V(x\_infection)}{V(x)} \tag{2}$$

Where V(.) represents the volume of the region of interest, x represents different lung lobes or segments, and x_infection represents the infection region in x [13].
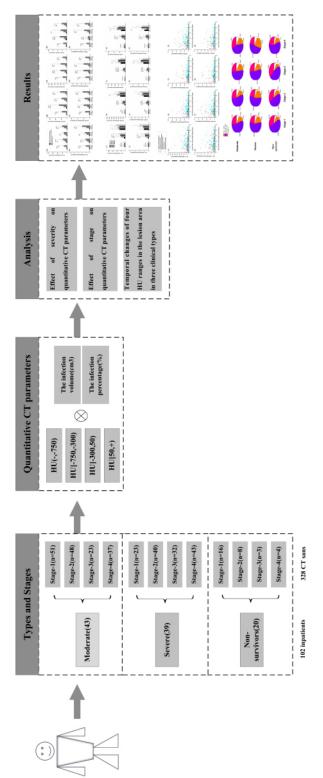
Table 1
Baseline characteristics

Characteristics	All patients ($n = 102$)	Patients with mild symptoms ($n = 43$)	Survivors with severe symptoms ($n = 39$)	Non-survivors ($n = 20$)	p
Age (years)	55.3 ± 17.5	45.2 ± 16.0	57.6 ± 12.8	72.5 ± 13.6	< 0.0001
Sex					0.023
Female	41 (40%)	24 (56%)	15 (38%)	5 (25%)	..
Male	61 (60%)	19 (44%)	27 (62%)	15 (75%)	..
Chronic diseases					
Hypertension	26 (25.5%)	3 (7%)	12 (30.8%)	11 (55%)	< 0.0001
Diabetes	10 (9.8%)	1 (2.3%)	7 (17.9%)	2 (10%)	0.047
Cardiovascular diseases	13 (12.7%)	1 (2.3%)	6 (15.4%)	6 (30%)	0.005
Chronic obstructive pulmonary disease (COPD)	4 (3.9%)	2 (4.7%)	5 (7.8%)	1 (2.6%)	1.000
Malignancy	7 (6.9%)	0 (0%)	3 (7.7%)	4 (20%)	0.008
Main signs and symptoms					
Fever	87 (85.3%)	41 (95.3%)	37 (94.9%)	19 (95%)	0.016
Highest temperature (°C)					
< 37.3	15 (14.7%)	12 (27.9%)	2 (5.1%)	1 (5%)	..
37.3 to 38.0	14 (13.7%)	7 (16.3%)	6 (15.4%)	1 (5%)	..
38.0 to 39.0	45 (44.1%)	20 (46.5%)	19 (48.7%)	6 (30%)	..
$\geqslant 39.0$	28 (27.5%)	4 (9.3%)	12 (30.8%)	12 (60%)	..
Cough	55 (53.9%)	22 (51.2%)	21 (53.8%)	12 (60%)	0.812
Myalgia or fatigue	60 (58.8%)	22 (51.2%)	25 (64.1%)	13 (65%)	0.425
Headache	10 (9.8%)	5 (11.6%)	3 (7.7%)	2 (10%)	0.909
Diarrhea	14 (13.7%)	4 (9.3%)	4 (10.3%)	6 (30%)	0.093
Dyspnea	19 (18.6%)	3 (7%)	8 (20.5%)	8 (40%)	0.006
Respiratory percentage (bpm)	20.5 ± 4.2	19.6 ± 1.4	20.3 ± 4.6	23.1 ± 6.2	0.023
Laboratory findings					
Leukopenia ($< 3.5 \times 10^9$/L)	29 (28.4%)	17 (39.5%)	12 (30.8%)	0 (0%)	0.001
Lymphocyte count ($< 1.1 \times 10^9$/L)	65 (63.7%)	23 (53.5%)	28 (71.8%)	14 (70%)	0.192

Data are mean $\pm$ SD or n (%). COPD = Chronic obstructive pulmonary disease, bpm = breaths per min; respiratory percentage represented the initial respiratory percentage on admission or on the day when visiting doctor.

The typical pattern of CT values in the range of HU $(-, -750)$ was intralesional cavitation, CT values in the range of HU $[-750, -300)$ was ground glass opacity (GGO) mainly, CT values in the range of HU $[-300, 50)$ was consolidation mainly, and CT values in the range of HU $[50, +)$ was microvascular enlargement [14] or fibrosis. Reticular pattern, crazy paving pattern, air bronchogram and pleural thickening might contribute to more than one range [15].

4. Statistical analysis

Statistical analyses were performed using Statistical Package for Social Science (SPSS version 19; IBM, New York, USA). Distribution normality was assessed using the Shapiro-Walk test. Continuous variables and categorical variables were presented as mean (SD) and frequency (%), respectively. We used the Mann-Whitney U test, the Kruskal-Wallis test, Fisher's exact test (for categorical data) or one-way ANOVA (for continuous data) to compare differences between patients with mild symptoms, survivors with severe symptoms and non-survivors where appropriate. We used the non-parametric test to compare differences between Stage-1, Stage-2, Stage-3 and Stage-4. A p-value of < 0.05 was defined as *, a p-value of < 0.01 was defined as **, a p-value of < 0.001 was defined as ***. A three-order polynomial estimation model was also conducted to investigate the slope and baseline in above parameters across different stages in the same group.

Fig. 1. System flowchart. The data flowchart can be divided into three parts: (1) 102 patients were assigned to three groups and t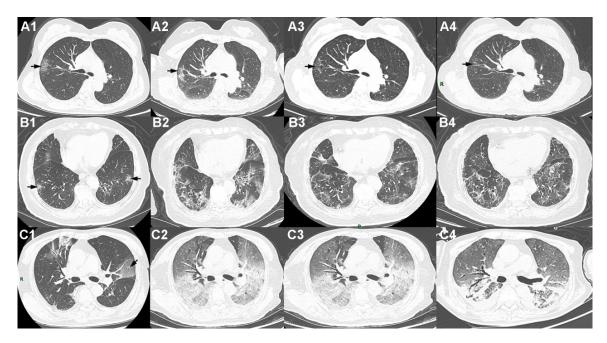hen four stages were designated based on the time interval between the onset of symptoms and the CT scans and the CT scans in each group; (2) eight quantitative parameters were calculated according to the segmentation results from 328 CT scans, and (3) statistical analysis was performed from the three perspectives.

Fig. 2. The CT images of three clinic types of patients at four stages. Shown in A1–A4 (Stage 1–Stage 4) are corresponding slices of a patient with mild symptoms (58 years, male). Shown in B1–B4 (Stage 1–Stage 4) are corresponding slices of a survivor with severe symptoms (82 years, female). Shown in C1–C4 (Stage 1–Stage 4) are corresponding slices of a non-survivor (70 years, male). The infection volume was obviously increasing in Stage-2 (8–15 days since symptom onset) in the three patients.

5. Results

As shown in Table 1, patients were divided into three clinic types based on severity: 43 (42%) patients with mild symptoms, 39 (38%) patients with severe symptoms and the remaining 20 (20%) were non-survivors. There were significant differences in age ($p < 0.0001$), sex distribution ($p = 0.023$), hypertension ($p < 0.0001$), cardiovascular disease ($p = 0.005$), diabetes ($p = 0.047$), malignancy ($p = 0.008$), dyspnea ($p = 0.006$) and Leukopenia ($< 3.5 \times 109/L$, $p = 0.001$) in three clinic types patients (Table 1).

In Stage-1, there were no differences between patients with mild symptoms and survivors with severe symptoms in the infection volume and percentage in four HU ranges. In Stage-2, there were no differences between survivors with severe symptoms and non-survivors in the infection volume and percentage of HU $(-, -750)$ and HU $[-750, -300)$ infection percentage. In Stage-3, there were significant differences between patients with mild symptoms and survivors with severe symptoms in the infection volume and percentage in four HU ranges, meanwhile there were no differences between survivors with severe symptoms and non-survivors in the infection volume and percentage in four HU ranges. In Stage-4, there were no differences between survivors with severe symptoms and non-survivors in the infection volume and percentage in four HU ranges (Fig. 3).

For moderate, there were significant differences in the infection volume and percentage of HU $(-, -750)$, HU $[-750, -300)$, HU $[-300, 50)$, HU $[50, +)$ between Stage-2 and Stage-1, Stage-4, and there were no differences in the infection volume and percentage of HU $(-, -750)$, HU $[-750, -300)$, HU $[-300, 50)$, HU $[50, +)$ between Stage-4 and Stage-1, Stage-3, and there were significant differences in the infection volume and percentage of HU $[-750, -300)$ between Stage-2 and Stage-3. For severe, there were significant differences in the infection volume and percentage of HU $(-, -750)$, HU $[-750,$
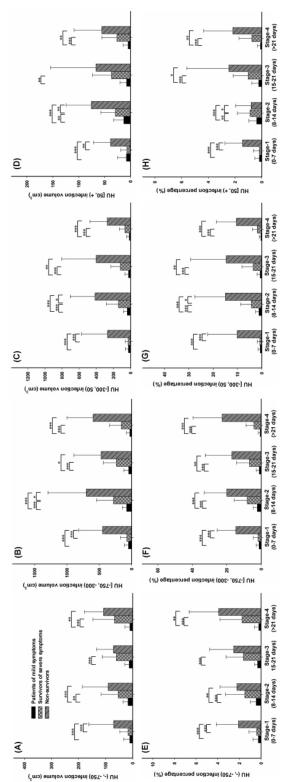
Fig. 3. Temporal changes in 8 parameters of CT images since symptom onset in three groups and the differences in 8 quantitative parameters of CT images between different groups in the same stage. The figure shows temporal changes in HU (−, −750) infection volume of three types patients (A), HU [−750, −300) infection volume (B), HU [−300, 50) infection volume (C), HU [50, +) infection volume (D), HU (−, −750) infection percentage (E), HU [−750, −300) infection percentage (F), HU [−300, 50) infection percentage (G), HU [50, +) infection percentage (H), and the differences between moderate, survivors with severe symptoms and non-survivors. A p-value of < 0.05 was defined as *, a p-value of < 0.01 was defined as **, a p-value of < 0.001 was defined as ***.
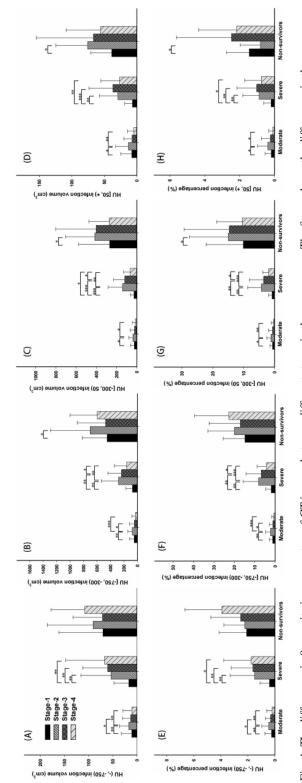
Fig. 4. The differences in 8 quantitative parameters of CT images between different stages in the same group. The figure shows the differences between four stages in HU ($-$, -750) infection volume (A), HU [-750, -300) infection volume (B), HU [-300, 50) infection volume (C), HU [50, $+$) infection volume (D), HU ($-$, -750) infection percentage (E), HU [-750, -300) infection percentage (F), HU [-300, 50) infection percentage (G), HU [50, $+$) infection percentage (H), and the differences in the same group between the four stages. A p-value of < 0.05 was defined as $*$, a p-value of < 0.01 was defined as $**$, a p-value of < 0.001 was defined as $***$.
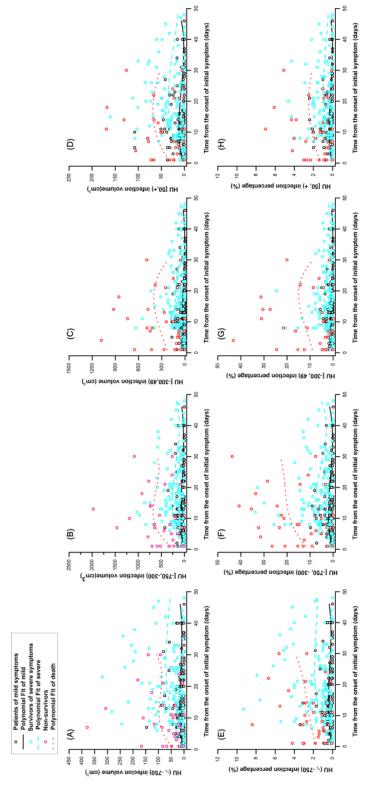
Fig. 5. The total volume and the percentage of the 8 parameters of CT images were fitted with a three-order polynomial estimation model from illness onset in three clinic types of patients with COVID-19. The figure shows temporal changes in HU $(-, -750)$ infection volume of three types patients (A), HU $[-750, -300)$ infection volume (B), HU $[-300, 50)$ infection volume (C), HU $[50, +)$ infection volume (D), HU $(-, -750)$ infection percentage (E), HU $[-750, -300)$ infection percentage (F), HU $[-300, 50)$ infection percentage (G), HU $[50, +)$ infection percentage (H).
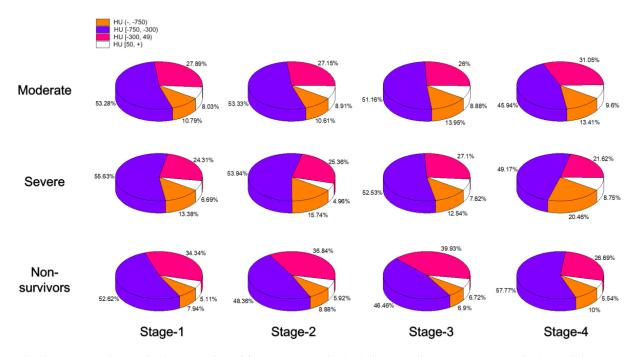
Fig. 6. Temporal changes in the proportion of four HU ranges in the lesion area since symptom onset in three clinic types, moderate (patients with mild symptoms), severe (survivors with severe symptoms) and non-survivors with COVID-19. The 3D color pie chart shows different patterns in proportion in the three groups in four stages.

−300), HU [−300, 50), HU [50, +) between Stage-1 and Stage-2, Stage-3, and there were significant differences in the infection volume and percentage of HU (−, −750), HU [50, +), the infection volume of HU [−750, −300) between Stage-1 and Stage-4, and there were significant differences in the infection volume and percentage of HU [−750, −300), HU [−300, 50) between Stage-4 and Stage-2, Stage-3. For non-survivors, there were significant differences in the infection volume and percentage of HU [−300, 50), HU [50, +), the infection volume of HU [−750, −300) between Stage-1 and Stage-2 (Fig. 4).

Figures 3 and 4 show that the infection volume and percentage in four HU ranges were significantly different between the three groups' patients in four stages. The infection volume and percentage of HU (−, −750), HU [−750, −300), HU [−300, 50) and HU [50, +) were small in Stage-1 (0–7 days from illness onset) and increased significantly in Stage-2 (8–15 days from illness onset) for moderate and severe, and the infection volume and percentage of HU (−, −750), HU [−750, −300), HU [−300, 50), HU [50, +) were decreasing in Stage-3 and Stage-4 for moderate while the 8 parameters had a larger value in four stages for non-survivors. The three-order polynomial estimation model results showed different change trend in three groups (ranked as: moderate < severe < non-survivors) (Fig. 5). The 3D color pie chart shows the highest proportion of HU [−300, 50) in non-survivors among three groups in Stage-1, Stage-2 and Stage-3 (Fig. 6).

6. Discussion

This study investigated temporal changes of quantitative CT findings in COVID-19 confirmed patients with different clinic types, including moderate, severe, and non-survivors. The infection volume and percentage of HU (−, −750), HU [−750, −300), HU [−300, 50), HU [50, +) in the total lung were

extracted from the CT image using artificial intelligence (AI) software. In this study, we investigated the correlation between the 8 quantitative CT parameters in four stages among three clinic patients confirmed with COVID-19 and revealed the cause of deterioration of the COVID-19 patients (Fig. 1).

6.1. Effect of severity on quantitative CT parameters

For HU [−750, −300), HU [−300, 50) and HU [50, +), a significant difference was found in infection volume and percentage between non-survivors and patients with mild symptoms in all four stages. Besides, a significant difference was found in the infection volume and percentage of four HU ranges between severe and moderate in Stage-2 and Stage-3. These findings might suggest more involvement in total lung infection in severe than moderate. For HU (−, −750), a significant difference was also found in infection volume and percentage between non-survivors and moderate in Stage-1, Stage-2 and Stage-4. A significant difference was also found in infection volume and percentage between severe and moderate in Stage-2, Stage-3 and Stage-4. These findings indicated more air content in severe group than that in moderate group, which might due to pulmonary edema and hyaline membrane formation [16]. For four HU ranges, a significantly higher infection volume and percentage was found between non-survivors and severe, and between non-survivors and moderate in Stage-1. However, significant differences in these parameters between severe and moderate were only found in Stage-2 and Stage-3. These findings indicate a faster deterioration in non-survivors in Stage-2 and Stage-3 than in the severe and moderate group.

6.2. Effect of stage on quantitative CT parameters

For the moderate and severe group, the infection volume and percentage of HU (−, −750), HU [−750, −300), HU [−300, 50), HU [50, +) in the total lung reached the maximum value in Stage-2, which indicated that their disease progressed since Stage-2. This finding was consistent with previous studies based on severity scores for each lung or lobes [12,17], which suggested that scores peaked at 6–11 days in CT abnormalities [18] and 10–12 days in chest X-ray abnormalities after symptom onset [18,19]. Another study on CT features in 62 patients showed a significantly increased mixed pattern, including GGO, reticular pattern, vacuolar sign, fibrotic streaks, a subpleural line, a subpleural transparent line, air bronchogram, bronchus distortion, and pleural effusion appeared in 8–14 days [19], which is also consistent with our finding (Fig. 2). For severe, the 8 parameters kept at a large valve in Stage-3 and Stage-4, which suggested that a mixed pattern sustained for a period. This might be due to that aggravation and repair might be coexisted at Stage-3, and indicate an irreversible impaired lung function.

6.3. Temporal changes of four HU ranges in the lesion area in three clinical types

For moderate, the three-order polynomial estimation model results showed that all 8 parameters had a stable change during course of disease, which was consistent with their good outcome. For severe, the three-order polynomial estimation model results showed that all 8 parameters increased at Stage-1 and Stage-2 and decreased since Stage-3 during course of disease, which implied the rehabilitation. For non-survivors, the three-order polynomial estimation model results that all 8 parameters increased even at Stage-3, which indicated a continuous progression during course of disease. The highest proportion of HU [−750, 50) (HU [−750, −300) + HU [−300, 50) > 80%) in the lesion area in non-survivors among three groups indicated that more GGO and consolidation might indicate a poorer prognosis, and quantitative CT parameter of HU [−750, 50) might help us screen severe cases at an early stage.

6.4. Limitations

The sample size of non-survivors is limited and the follow up CT scans of non-survivors were hard to be obtained because of the disease progress, especially in Stage-3 and Stage-4. Besides, without considering the clinic treatment options might lead to a bias in this study and prospective experimental design could eliminate the effect and is a better choice for such research. However, this is unrealistic for the outbreak of COVID-19. In order to make our research conclusion more credible, we will expand the sample size and refine our experimental design according to the preliminary research results in the future.

6.5. Conclusion

This study aimed to investigate temporal changes of quantitative CT findings in confirmed COVID-19 patients with different clinic types, including moderate, severe, and non-survivors. CT findings of quantitative parameters tend to manifest in different CT features in different stages from illness onset among different clinic type patients, and the infection volume of four HU ranges were rapidly increased in Stage-1 (the first week) in non-survivors, and peaked in Stage-2 (the second week) in three groups, which indicated that early and timely intervention is very important. Higher proportion of HU $[-750, 50)$ in the lesion area (HU $[-750, -300)$ + HU $[-300, 50) > 80\%$) might be a bio-marker for poor prognosis in patients with COVID-19.

Acknowledgments

Conflict of interest

The authors declared that they have no conflicts of interest to this work.

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