Clinical and Deep-Learning Based Quantitative Serial Chest CT Features of The COVID-19 Disease: Association with Clinical Subtypes and A Follow-Up Study

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Abstract

Background: To explore the clinical features and deep-learning (DL) based quantitative CT finding's applications and evolution as well as the correlations in COVID-19.

Methods: 273 chest CT scans (median interval, 6 days) from 75 COVID-19 RT-PCT positive patients (53 moderate and 22 severe) were included. Quantification parameters, such as CT value distribution, lesion (abnormal), GGO, consolidation rates, Hellinger distance and IOU, were automatically extracted from CT images by a combination of traditional image process algorithm and DL network. Clinical characteristics were also collected and analysed.

Results: The hypertension and diabetes were more common in severity. The CRP, ESP, LDH and D-dimer were higher while LYM and LYM% lower in severity ($P < 0.05$). The DL network was detected the lesions to obtain quantitatively CT indicators, with fast to process a chest CT images (average time, 2.2s) and high overlap with radiologist. The hellinger, abnormal, GGO, consolidation rates and HU values were higher and the IOU lower in severity than moderate patients ($P < 0.05$). The largest AUC was 0.943, using the cutoff value of 10.5% for abnormal rate. The CT score have positive correlations with CRP, D-dimer and ESR ($P < 0.05$). The increased levels of ESR and D-dimer were positively correlated with abnormal, consolidation and GGO rates ($P < 0.05$). Investigation for quantitative CT changes were performed in three periods: 1) 1-2 weeks, CT score and abnormal rate were increased. The GGO converted to consolidation in severity; 2) 2-5 weeks, CT scores stable trend, while abnormal and GGO rates had upward trend in severity; 3) > 5weeks, CT score and abnormal rate have decreased.

Conclusions: There were three phases of two patterns' evolutionary trends in quantitative CT findings with differences in two groups, and have correlations with laboratory markers, which helpful for evaluating severity and prognosis in COVID-19 patients.

1. Introduction

The high infectivity of Coronavirus disease 2019 (COVID-19) leads to a rapid increase in new cases and an outbreak worldwide [1, 2]. Chest CT has been reported as a reliable and rapid approach for screening of COVID-19 [3, 4]. From the recently literature, the typically radiologic findings in COVID-19 pneumonia included ground-glass opacification (GGO), consolidation, peripheral and diffuse distribution [3, 5]. But it is cumbersome for radiologists to analyze large number of the thin-slice chest CT images, which will lead to low precision after long time for vision work.

Recently, artificial intelligence has demonstrated a great success in medical imaging [6], with the advantage of the high efficiency and not be affected by the clinicians with different seniority and experiences. It could reduce the medical care burdens and release the difficulties of the epidemic prevention and shortages of medical staff. However, up to now, the quantification and progress evaluation of the pulmonary CT imaging in COVID-19 through the disease course had been rare. Meanwhile, the relationship between quantitative CT findings with clinical characteristics is not well investigated. The timely detection of severe infected patients and rapidly early interventions is conducive to shorten the course of disease, prevent progresses and decrease mortality. Therefore, in this study, we compared the clinical characteristics, serological investigation, and quantitative CT indicators between the moderate and severe patients to explore the related factors of severe patients. And we also aimed to clarify the evolution of the CT indicators and its correlation with clinical severity.

2. Materials And Methods

The retrospective study was approved by the ethics committee of our hospital. Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

2.1 Patients and Data collection

The patients diagnosed with COVID-19 pneumonia were retrospectively retrieved for the period from 15 January 2020 to 15 March 2020 with CT follow-up. The inclusion criteria were as followed: 1) having an epidemiological history; 2) real-time reverse-transcriptase polymerase-chain-reaction detection of SARS-CoV-2 nucleic acid positive; 3) having thin-section CT with abnormal manifestations. Based on the guidelines for diagnosis and treatment protocols from the National Health Commission of the People's Republic of China [7], the moderate patients present with fever, respiratory symptoms, and radiographic features, and the severe/critical (hereinafter, severe) patients meet one of the following criteria: 1) dyspnea, respiratory rate >30 breaths /min, 2) standard oxygen saturation $< 93\%$, 3) $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg, 4) respiratory failure, 5) septic shock, 6) multiple organ failure.

Patients' demographic, epidemiological, clinical characteristics and laboratory findings were collected, including a complete blood count, coagulation profile and serum biochemical test (renal and liver function, electrolytes sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, ferritin-1 (FER-1), Interleukin (IL) and etc.). Two researchers independently reviewed the data collection to double check the data collected.

2.2 Pulmonary CT Scans

CT scans were performed using 64-row multi-detector scanners (Siemens Definition AS+, Siemens Healthcare) with the following parameters: 120kVp; effective mAs, 155mAs; Collimator, 0.6*128; pitch, 1.2; Rotation Time, 0.5s; kernel, B60f; Matrix, 512*512; Slice Thickness, 1.0mm.

2.3 Deep Learning Model

Quantification parameters were extracted from chest CT images by a combination of the traditional image process algorithm and deep learning (DL) network.

The deep learning network was developed for lung lesion detection and segmentation, which was designed as a combination of U-net and Fully convolutional network [8, 9] (Supplementary Fig.1). Like the U-net structure, this DL network has a contracting path (Supplementary Fig.1) and an expansive path (downside in Supplementary Fig.1). This DL network consists of three different components: 1) convolutional segment, which includes convolutional layer, batch normalization layer and an activation layer; 2) max pooling layer; 3) transpose convolutional layer. The feature map was first extracted from input CT images and passed through convolutional segments. Max-pooling layer and transpose convolutional layer were used for up-sampling and down-sampling. In addition, concatenation operations were performed between convolutional segments as bridges of contracting and expansive paths.

CT images from 730 COVID-19 positive patients and 1013 chest normal patients were retrospectively collected as the training dataset with totally over 200000 CT slices. The test dataset included images from 212 COVID-19 patients and 327 chest normal subjects. The ground truth region of interest (GT-ROI) for lung lesion was first drawn by an experienced radiologist (~5-year experience) and then reviewed by a senior radiologist (~10-year experience), who was responsible to modify ROIs if not accepted. After training, the Dice coefficient was used to evaluate the performance of this in-house built network.

The Dice accuracy was defined as:

$$2 * \frac{\text{overlap area of PR-ROI and GT-ROI}}{\text{area of PR-ROI} + \text{area of GT-ROI}}$$

PR-ROI is the predicted ROI by DL network and the GT-ROI is the ROI drawn by radiologists.

2.4 Image Quantification

After lung lesions were detected by the DL network and confirmed or adjusted by two radiologists, quantification parameters related with lung lesion could be calculated, including lesion, GGO and consolidation volume. The separation of GGO and consolidation within lesion was determined by a CT value threshold [10]. Furthermore, the whole lesion rate (that is, abnormal rate) and GGO, consolidation rates were defined as: corresponding volume / whole lung volume *100%. The total CT score was the sum of the lung involvements (5 lobes, score 0-4 for each lobe, ranges, 0-20) .

The lung was also segmented by the adaptive thresholding and morphological operation, and the CT value distributions of the whole lung could be calculated based on the segmentation as well as the mean, median and peak values of the CT distribution[11]. Hellinger distance (hereinafter, hellinger) and intersection over union (IOU) of lung CT distribution were calculated between chest CT images of pneumonia patients and normal people[12, 13].

2.5 Statistical Analysis

Statistical analyses were performed using the GraphPad Prism 8.0 (GraphPad software) and IBM SPSS statistical software version 22 (IBM corp.). Categorical variables and counting data were summarized as frequencies and proportions, and their differences were analysed by the Chi-square test. Quantitative normally distributed data were presented as mean ± standard deviation, while the non-normally distributed data were expressed as the median and quartiles unless specified. The independent-samples t-test or Wilcoxon rank tests were used to compare the differences in groups. Receiver operating characteristic (ROC) analyses were used to evaluate the

diagnostic efficiency. The Spearman rank correlation or Pearson tests were used to detect the correlations between the laboratory findings and CT parameters in non-normally or normally distributed data, respectively. $P < 0.05$ was considered statistically significant.

3. Result

3.1 Model Performance

The average processing time for a whole lung CT slices was around 2.2 seconds on a workstation with NVIDIA GPU (GeForce GTX 1080 Ti). 100 training epochs was performed for networking training. And the Dice coefficient was 85% for the training set and 82.08% for the test set.

3.2 Clinical characteristics

A total of 75 patients (45 males and 33 females) were included, with 53 moderate cases and 22 severe cases. There were no significant differences in ages and in genders between the moderate and severe patients (Table 1). The initial clinical symptoms mainly presented as fever (80.0%), cough (64.0%) and fatigue (49.3%). Cough in the moderate patients was more common, while chest tightness in severe patients was more common ($P < 0.05$). The comorbidities mainly included hypertension (25.3%), diabetes (13.3%) and cardiovascular disease (10.7%). The hypertension and diabetes were more common in the severe than moderate patients ($P < 0.05$). The details were summarized in Table 1.

3.3 Laboratory findings

From the laboratory investigations, the ESR, alanine aminotransferase (ALT), LDH, FER-1 and IL-6 were increased in both the moderate and severe patients. The CRP, aspartate aminotransferase (AST) and D-dimer were significantly increased in the severe patients. The CRP, ESP, LDH and D-dimer were significantly higher while the LYM and LYM percentage were lower in the severe than moderate patients (all $P < 0.05$). The details were provided in Supplementary Table 1.

3.4 Pulmonary CT Evaluation

These patients underwent a total of 273 chest CT scans. The first CT scan was performed during an average of 14 ± 6 days after the onset of initial symptoms, and there was no significant difference between the moderate and severe patients ($P = 0.467$). Each patient underwent a median of 4 (IQR: 3-4) times of chest CT scans with a median interval of 6 (IQR: 5-8) days. The initial total lung severity score was 5 (IQR: 3-7) in these patients, and there was significant difference in the severe patients than moderate patients, as shown in Table 1.

3.5 Quantitative initial CT analysis

From the qualitative initial CT analysis, the Helling (0.16 ± 0.08 ; reference value, 0) was elevated, while IOU (0.66 ± 0.15 ; reference value, 1) was decreased in these patients. The total abnormal ($8.3 \pm 8.1\%$), GGO ($6.0 \pm 5.7\%$) and consolidation rates ($2.3 \pm 3.0\%$) were also elevated. The hellinge, abnormal, GGO, consolidation rates and HU values were significantly higher in the severe than moderate patients ($P < 0.001$, fig.1). And the IOU was significantly lower in the severe patients ($P < 0.001$, fig.1). ROC curve showed that the largest areas under the curve (0.943) was the abnormal rate, with the sensitivity, specificity and cut-off value were 86.4%, 94.3% and 10.5%, respectively (fig 2).

3.6 Correlation between Laboratory findings and initial quantitative CT

Elevated CRP levels were found to be associated with an increased CT score ($r's = 0.302$, $P = 0.010$). IL-6 levels were positively associated with HU peak values ($r's = 0.297$, $P < 0.05$). The D-dimer and ESR levels both had positive correlations with the CT score, the consolidation, GGO and abnormal rates ($r's$ range: 0.249-0.441, all $P < 0.05$; fig 3). And there was a positive correlation between the D-dimer and Helling ($r's = 0.368$, $P = 0.005$).

3.7 Dynamic quantitative CT analysis

Based on the interval between the adjacent CT scans, the patients were divided to seven groups for the further analysis, and the interval duration was one week. The representative changes of chest CT are presented for the moderate and severe patients with COVID-19 in Figure 4. The evolutionary trends of clinical types in quantitative parameters during the period between the onset of initial symptoms and follow-up CT scans were shown in Figure 5.

In the most of the periods of time, the CT scores and the abnormal, GGO, consolidation rates were significant higher in the severe than moderate patients ($P < 0.05$, fig.5). The CT scores of the severity tended to relatively higher stable in the first 5 weeks, while the moderate patient's involvement increased during the 1-2th week after the initial symptom onset, and then decreased gradually after a plateau phase in the 5-7th weeks for the both types (fig. 5A). The consolidation rate of the severe patients exhibited a relatively rapid rise to peak during the 1-2th weeks, and the GGO rate showed the corresponding decrease (fig.5C, D). During the 3-5th weeks, the consolidation rate of the severe patients tended to decreasing, and the GGO rate corresponding relatively increased, with a peak at 5th week in both the GGO and total abnormal rates. After this period, the abnormal, GGO and consolidation rates of the severe patients decreased gradually during the 5-7th weeks (fig 5B-D). For the moderate patients, the increases of the CT score and total abnormal rate were mainly due to an increased GGO ingredient (fig 5).

4. Discussion

In this study, a DL network was detected the lesions and component analysis to obtain quantitatively CT indicators in COVID-19 pneumonia. The ROC curves revealed that the optimal CT index was the total lesion rate for judging severity, and indicated the patients that over 10.5% were in a severe condition. Moreover, we compared the clinical characteristics, serological examination and quantitative CT findings between the moderate and severe groups, and revealed a degree of correlations between quantitative CT indicators and laboratory markers. Most patients have underwent a series of pulmonary CT examinations, so we also analysed the evolution of the quantitative radiological changes with reference to the time of onset of symptoms.

In COVID-19 patients, fever, cough and fatigue were most common symptoms, and a few patients had upper respiratory tract symptoms such as sore throat, which was consistent with recent report [14]. In our cohort, similarities of incidence about the gastrointestinal symptoms (eg. diarrhea) between COVID-19 and MERS-CoV or SARS-CoV infection about 20–25% of patients has been noted [15]. It has been reported that the age, male and comorbidities could be risk factors [16]. In addition, the comorbidities (hypertension and diabetes) of severe patients were higher than that of moderate patients, which indicated that as high-risk factors for COVID-19 patients.

In laboratory findings, most of patients had lymphopenia, increased serum ESR, LDH and ALT levels. Furthermore, severe patients had lower levels of LYM and LYM%, and higher levels of LDH, ESR, CRP and D-dimer than moderate patients. The decrease of lymphocytes may be critical in the disease progression [17]. In previous studies, LDH could be used as inflammatory predictor [18]. Researches have indicated that the critical condition of infected patients is not only induced directly by coronavirus, but also may be related to inflammatory response leading to a cytokine storm [17, 19]. Moreover, abnormally high levels of IL-6 and FER-1 were observed, that IL-6 is served as an indicator for severity and outcomes in cytokine storm, and the latter is an acute phase reactive protein. D-dimer level raised in severe cases, even persistently elevated in the nonsurvivors [20]. That indicated that the above laboratory indexes are beneficial in judging the condition of disease and guiding therapy.

Thus, it is important to explore the related factors between clinical features and radiologic findings for deepening the understanding of the COVID-19 mechanism and facilitating better patient management. Our results showed that CT score had positive correlations with CRP, D-dimer and ESR. And the increased levels of ESR and D-dimer in serum were positively correlated with quantitative CT indexes, including abnormal, consolidation and GGO rates. It is suggested that quantitative CT indexes could serve an effective way for monitoring disease severity and predicting prognosis in clinical practice.

We have collected previously a large number of images from multiple hospitals, included 730 COVID-19 and 1013 normal subjects CT examination. The DL-based analysis is very fast to process a whole chest CT images with the 2.2 seconds of the average time, and have high overlap with outlined lesions volume by radiologist. In our study, these quantitatively CT indicators indicated that severe patients had more extensive infected pulmonary tissues and far away from the normal reference. Although, the total CT score could evaluate the severity of the pneumonia and general dynamic changes. The different proportions of the lesions investigated through the quantitative CT in detail with more efficiency and objectivity, so that changes of conditions could be better provided. Furthermore, the abnormal rate was still maintained about 10% even after 7 weeks in severity. From this finding, it suggested that the severe lesion is not absorbed well, and the COVID-19 pneumonia is refractory; thus, the periods of treatments and isolation may should be extended.

From the dynamic analysis of quantitative CT indicators, three phases of COVID-19 can be summarized on weekly, as follows: 1. Rapidly progressive phase (1–2 weeks); In this stage, total CT score and abnormal rate elevated with an upward trend. The GGO would be relatively rapidly converted to consolidated ingredient in severe patients, while the increase of total lesion was mainly composed by GGO ingredient in moderate patients. 2. Stalemate phase (2–5 weeks); In this stage, the infected pulmonary underwent a complicated evolution. The CT scores trend was relatively stable, while a curve of total abnormal and GGO rates presented an upward trend in severity,

that indicating the process of converting consolidation into GGO. 3. Absorption phase (> 5weeks); In this stage, total CT score and abnormal rate decreased gradually, and the rate of absorption accelerated in severity, which means that the infection was under control to some extent. In moderate patients, the progressive of the infected condition was restricted after about 2 weeks.

There are some limitations in this study. First, possible selection bias may have impact on the results in a retrospective study at a single center, and it needs to be prospectively validated. Second, the P value provided in this study should be interpreted with caution, and the negative significance does not necessarily rule out the difference between severe and moderate patients. In addition, heatmaps were used to visualize lesions in images, and further confirmed or made the adjustments by two radiologists, resulting that the transparency is still lack for the all DL methods.

5. Conclusion

This work provides an early investigation for DL-based quantitative chest CT indicators, with significant difference and three phases of two patterns evolutionary trends in two groups, and had positively correlations with laboratory indices, which could be used for infectious monitoring and prognostic judgement of the COVID-19 pneumonia.

Declarations

Availability of data and material: All data generated or analysed during this study are included in this published article.

Consent for publication: Written informed consent for publication was obtained from all participants.

Conflicts of Interest: No conflict of interest exists in the submission of this manuscript.

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Ethics Approval: The retrospective study was approved by the ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

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Authors' contributions: C Zheng, J Wang and X Su contributed to the conception of the study; H Mei, Y Jia, Q Zhu, J contributed significantly to analysis and manuscript preparation; X Su, J Wang, C Zheng performed the data analyses and wrote the manuscript; B Liu and H Zhang helped perform the analysis with constructive discussions.

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Tables

Table 1
clinical characteristics and CT manifestation¹

		Total (n = 75)	Moderate (n = 53)	Severe (n = 22)	P value
Age (y)		58.1 ± 14	55.4 ± 14	64.6 ± 12	.082
Gender	Male	45 (60.0)	33 (62.3)	12 (54.6)	.534
	Female	30 (40.0)	20 (37.7)	10 (45.5)	
Symptoms	Fever	60 (80.0)	43 (81.1)	17 (77.3)	.704
	Cough	48 (64.0)	38 (71.7)	10 (45.5)	.031*
	Fatigue	37 (49.3)	27 (50.9)	10 (45.5)	.665
	Myalgia	22 (29.3)	18 (34.0)	4 (18.2)	.172
	Anhelation	20 (26.7)	11 (20.8)	9 (41.0)	.072
	Diarrhea	19 (25.3)	14 (26.4)	5 (22.7)	.738
	chest tightness	18 (24.0)	7 (13.2)	11 (50.0)	< .001***
	Expectoration	15 (20.0)	13 (24.5)	2 (9.1)	.128
	Headache	11 (14.7)	10 (18.9)	1 (4.5)	.110
	Sore throat	9 (12.0)	7 (13.2)	2 (9.0)	.617
	Loss of appetite	8 (10.7)	7 (13.2)	1 (5.0)	.269
	Dizziness	7 (9.3)	5 (9.4)	2 (9.0)	.963
	Nausea and vomiting	3 (4.0)	2 (3.8)	1 (5.0)	.877
Comorbidities	Hypertension	19 (25.3)	9 (17.0)	10 (45.5)	.010**
	Diabetes	10 (13.3)	4 (7.6)	6 (27.3)	.022
	Cardiovascular disease	8 (10.7)	7 (13.2)	1 (4.5)	.269
	Cerebral infarction	2 (2.7)	1 (1.9)	1 (4.5)	.515
	Chronic respiratory disease	2 (2.7)	1 (1.9)	1 (4.5)	.515
Pulmonary CT cans	The period ^a (d)	14.4 ± 6.5	14.1 ± 6.1	15.3 ± 7.6	.467
	Numbers CT scans	4 (3, 4)	3.5 (3, 4)	4 (3.75, 5)	.019
	The interval ^b (d)	6 (5, 8)	6 (5, 8)	7 (6, 7)	.264
	Initial total lung severity score (0 to 20)	5 (3, 7)	4 (3, 5)	8 (7, 12)	< .001***
¹ Note. Except where indicated, data are numbers of patients, with percentages in parentheses.					
^a The period between the onset of initial symptoms and the first pulmonary CT scan (d);					
^b The interval between the adjacent pulmonary CT scans (d); * < 0.05, ** < 0.01, *** < 0.001.					

Figures

Figure 1

The hellinge distance (A) and abnormal, GGO, consolidation rates (C) were both higher in severe patients than in moderate patients. The IOU (B) was significant lower in severe patients. The mean, median and peak of HU values (D) were higher in severe patients. Dotted lines present normal baselines; IOU, intersection over union; GGO, ground-glass opacification; M, moderate patients; S, severe patients; * <0.05 , ** <0.01 , *** <0.001 .

Figure 2

Receiver operating characteristic curve plots revealing the largest areas under the curve (AUC) was 0.943, using cutoff value of 10.5% for the abnormal rate in multi-parameters CT indexes. The numbers in parentheses indicate the respective AUC values. IOU, intersection over union; GGO, ground-glass opacification.

Figure 3

Spearman rank analysis shows the light to moderate positive correlations among laboratory findings and qualitative CT parameters in the heatmap. CRP, C-reactive protein; IL, interleukin; ESR, electrolytes sedimentation rate; IOU, intersection over union; GGO, ground-glass opacification; * <0.05 , ** <0.01 , *** <0.001 .

Figure 4

The follow-up chest CT scans shows the evolutions over time in moderate (A) and severe (B) patients with COVID-19. The chest CT with color-coded shows the lesion detection and lung segmentation based on a deep-learning model, included ground-glass opacification and consolidation in order to calculating quantitative CT indicators. The numbers in the upper left of the frame means the period based on the onset of initial symptoms. W, week.

Figure 5

The follow-up CT scans revealed that the trends of CT score (A), total abnormal (B), GGO (C) and consolidation (D) rates in the moderate and severe patients during the period between the onset of initial symptoms and CT scans. Dotted lines present normal baselines. GGO, ground-glass opacification; * <0.05 , ** <0.01 , *** <0.001 .

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