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Open Access Journal | Volume: 3.2

Journal of Emerging and Rare Diseases

ISSN 2517-7397

Ultra-High-Resolution Computed Tomography Follow-Up for Coronavirus Disease 2019: A Deep-Learning Approach

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Abstract

Background and Objective: The pandemic of coronavirus disease 2019 (COVID-19) has spread globally and become a major threat to public health. The application of computed tomography (CT) contribute to the identification and evaluation for patients with COVID-19. Thus, we aim to investigate the ultra-high-resolution CT (UHR-CT) findings of COVID-19 pneumonia from the initial diagnosis to early-phase follow-up.

Design and Methods: This retrospective study included confirmed cases with COVID-19 pneumonia. Initial and follow-up UHR-CT scans (within 5 days) were reviewed for characterizing the radiological findings. The normalized total volumes of ground-glass opacities (GGOs) and consolidations were calculated and compared during the radiological follow-up by deep-learning-based methods.

Results: Eleven patients (3 males and 8 females, aged 32-74 years) with confirmed COVID-19 were evaluated. Subpleural GGOs with inter/intralobular septal thickening were typical imaging findings. Other diagnostic CT features included distinct margins (8/11, 73%), pleural retraction or thickening (7/11, 64%), intralesional vasodilatation (6/11, 55%). Normalized volumes of pulmonary GGOs (p=0.003) and consolidations (p=0.003) significantly increased with various radiologic signs during the follow-up.

Conclusions: GGOs with peripleural distribution, consolidated areas, septal thickening, pleural involvement and intralesional vasodilatation could be clearly visualized on UHR-CT for the diagnosis of COVID-19. During the early-phase follow-up, COVID-19 cases could manifest significantly progressed GGOs and consolidations with various patterns.

Keywords: Coronavirus; COVID-19; Pneumonia; Ultra-high-resolution CT

Introduction

An outbreak of mystery pneumonia with the ability of inter-human transmission has been reported in Wuhan, China since December 2019 [1]. The novel infectious disease, currently known as coronavirus disease 2019 (COVID-19), has spread rapidly and become a global pandemic [1,2]. Severe acute respiratory syndrome (SARS) was the first emerging infectious disease of the 21st century caused by coronavirus with a tremendous threat and a high case-fatality rate of approximately 10% [3]. As another respiratory tract contagious disease caused by SARS-coronavirus-2 (SARS-COV-2), COVID-19 may also lead to progressive respiratory failure and varied ground-glass opacity (GGO) pattern on chest computed tomography (CT) as previously reported [3-7].

Positive CT findings could be found earlier than available results of real-time reverse-transcription-polymerase-chain-reaction (rRT-PCR) for patients with COVID-19 [8,9]. A considerable number of cases with early-stage COVID-19 demonstrated mild nonspecific symptoms (such as fever, fatigue and dry cough). COVID-19 patients with mild symptoms may represent considerably infectivity and develop rapidly in a short period of time, which may lead to delay of medical treatment and expansion of epidemic situation [2,10]. Although rRT-PCR testing is essential for diagnosis, the application of CT examination is still helpful for the timely identification, evaluation and follow-up for patients with high suspicion of COVID-19 [9].

The conventional CT features of COVID-19 pneumonia have been widely described in preliminary studies. However, the ultra-high-resolution CT (UHR-CT, with a large matrix size of 1024×1024) features of the disease remain ambiguous. Thus, we aim to determine the characteristics of early-stage COVID-19 on thin-section UHR-CT images, and to evaluate the development of pulmonary lesions during a short-term CT follow-up.

Article Information

DOI:	10.31021/jer.20203125
Article Type:	Research Article
Journal Type:	Open Access
Volume:	3 **Issue:** 2
Manuscript ID:	JER-3-125
Publisher:	Boffin Access Limited
Received Date:	15 July 2020
Accepted Date:	23 July 2020
Published Date:	25 July 2020

Funding:

This study was funded by the scientific and technological plan project of Xiamen (3502Z20174081).

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Citation: Lin Y, Lv S, Wang J, Kang J, Zhang Y, et al. Ultra-High-Resolution Computed Tomography Follow-Up for Coronavirus Disease 2019: A Deep-Learning Approach. J Emerg Rare Dis. 2020 July;3(2):125.

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Design and Methods

Patients

This study was approved by our institutional review board; informed consent was waived for the retrospective nature of our investigation. Records for patients with highly suspected COVID-19 from 20 January 2020 to 15 February 2020 in our hospital were reviewed. Our inclusion criteria were: (1) positive detection of COVID-19 by rRT-PCR; (2) necessary clinical and laboratory information; (3) available base-line UHR-CT scan; (4) initial UHR-CT scan with evidence of pneumonia (could be a base-line CT scan or a subsequent repeated CT scan); (5) follow-up UHR-CT scan within 5 days. Patients with other causes of pneumonia (common bacterial and viral pathogens) were excluded.

CT imaging

UHR-CT scans were uniformly performed using a multi-detector spiral CT scanner (Ingenuity, Philips Medical Systems, the Netherlands) with a breath-hold after full inspiration. The CT protocols were as follows: tube voltage: 120 kV; automatic tube current; collimation: 64×0.625 mm; pitch: 1.2; matrix: 512×512 (for routine workup) or 1024×1024 (for further analysis); reconstruction technique: hybrid iterative algorithm (iDose4); thickness: 1 mm; increment: 1 mm. Multiplanar reconstruction, minimum intensity projection, and volume rendering were conducted on a professional workstation.

Data processing

Two radiologists (with 20 and 6 years of experience of cardiothoracic radiology, respectively) reviewed all the UHR-CT images independently. The senior radiologist made the final decision when there was a discrepancy.

UHR-CT images of all cases were assessed for the following abnormalities (1) affected lobes; (2) distribution (peribronchovascular, peripleural and scattered/diffuse); (3) margin (sharp or indistinct); (4) specific signs (air bronchogram, intralobular interstitial thickening and/or interlobular septal thickening, intralesional vasodilatation, pleural retraction/thickening, and pleural effusion).

Quantitative analyses were automatically performed in all cases using a deep-learning-based image analysis system (Intelligent Evaluation System of Chest CT, Yitu Healthcare, China, https://www.yitutech.com/en). Pulmonary inflammatory lesions of the initial and followed-up UHR-CT images were intelligently recognized based on morphological features and segmented based on the attenuation differences (areas of GGO and consolidation with a cut-off value of -250Hu, Figure 1).

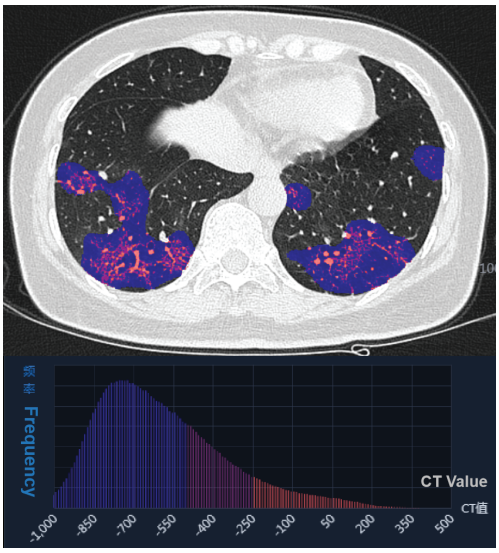

Figure 1: The heat-map of pulmonary inflammatory lesions on CT scan in the deep-learning-based quantitative analyses. Red areas represent consolidation; blue and purple areas represent ground-glass opacity.

Parameter		Number (%)
Gender (male/female)		3 (27%) / 8 (73%)
Age (year old)		53 (32-74)
Exposure history		
	Recent epicenter contact	8 (73%)
	Exposure to infected case	3 (27%)
Initial symptoms		
	Fever	9 (82%)
	Cough	6 (55%)
	Fatigue	4 (36%)
	Stuffy and runny nose	2 (18%)
	Headache and dizziness	1 (9%)
	Muscle soreness	1 (9%)
Comorbidity		3 (27%)
Laboratory findings		
	Reduced leukocyte count	3 (27%)
	Reduced neutrophil count	1 (9%)
	Reduced lymphocyte count	8 (73%)
	Elevated C-reactive protein	6 (55%)

Table 1: Demographic and clinical features of patients with COVID-19 (n=11)

The estimated total volumes of different components of lesions (GGO and consolidation) were calculated automatically. Normalized volume (nV) was obtained by normalizing to the estimated total lung volume based on the following formula: nV= volume of GGO or consolidation / volume of lung × 100%.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (IBM Inc., USA). All quantitative data were presented as mean ± standard deviation or median (range). The comparisons of paired quantitative data during the CT follow-up were evaluated by the Wilcoxon test. A p-value of < 0.05 was defined as statistical significance.

Results

Clinical features

A total of 11 patients (3 males and 8 females, median age 53 years, range 32-74 years) with rRT-PCR confirmed COVID-19 were enrolled in the study (Table 1). All patients have a history of epidemiological exposure (8 cases had lived in or traveled to Wuhan, 3 cases had contact with confirmed cases from Wuhan). The patients received clinical intervention including supportive care, symptomatic treatment, antiviral therapy and traditional Chinese medicine treatment during hospitalization.

The most common symptoms were fever (9/11, 82%) in our case series. Mild to moderate symptoms of cough (6/11, 55%) and fatigue (4/11, 36%) were found in COVID-19 patients. Decreased lymphocyte count (8/11, 73%) and elevated C-reactive protein level (6/11, 55%) were major abnormal laboratory findings. Only three (27%) patients had comorbidities (diabetes, hyperuricemia, tuberculosis and cardiac disease). In our cohort, no severe cases (respiratory rate >30 breaths/min and/or requirement for mechanical ventilation) with COVID-19 were found during the follow-up.

Findings		Patients
No. of Affected lobe(s)		
	1	2 (18%)
	2	2 (18%)
	3 - 5	7 (64%)
Distribution		
	Peripleural	10 (91%)
	Peribronchovascular	7 (64%)
	Scattered or diffuse	3 (27%)
Sharp margin		8 (73%)
Radiologic feature		
	Air bronchogram	11 (100%)
	Inter/intralobular septal thickening	11 (100%)
	Pleural retraction or thickening	7 (64%)
	Vasodilatation	6 (55%)
	Pleural effusion	1 (9%)

Table 2: Initial ultra-high-resolution CT findings of COVID-19 cases (n=11)

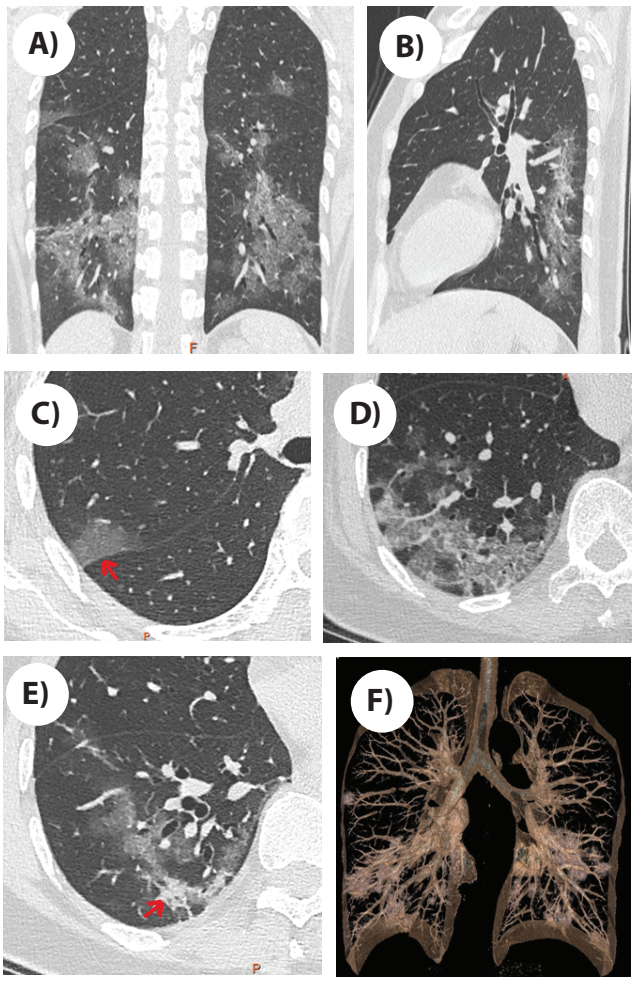

Figure 2: Initial coronal (a) and sagittal (b) CT images of a 53-year-old female with COVID-19 show multiple well-defined pulmonary lesions with subpleural and peribronchovascular distribution. The lesions show ground-glass opacity (GGO) with pleural retraction and thickening (arrow) (c), GGO with interlobular septal thickening and vasodilatation (arrow) (d), and GGO with patchy consolidation (arrow) and pleural retraction (e). Volume rendering image (f) vividly illustrates the lesion characteristics.

The base-line CT scan [obtained 3 (0.5-6) days after onset of clinical symptoms] showed positive results of pneumonia in 8 (73%) cases with COVID-19. In 3 cases, the initial positive result of pneumonia was found in the second or third CT examination (3-6 days from symptoms onset) after hospitalization. Interestingly, all cases except one showed signs of pneumonia on CT images before achieving positive rRT-PCR results.

Initial CT findings

All of the eleven patients underwent at least two chest CT scans (median interval: 3 days, range: 2-5 days). Data from initial and follow-up chest CT imaging with positive findings (n=11) in patients with COVID-19 were presented in Tables 2 and 3, and Figure 2 and 3. There were 10 (91%) patients with peripleural distribution, 7 (64%) patients with peribronchovascular distribution, 9 (82%) patients with bilateral involvement, 9 (82%) patients with affected lower lobes, and 7 (64%) patients with multiple (≥ 3) involved lobes.

Air bronchogram sign (as a typical exhibition of pneumonia), and interlobular or intralobular septal thickening were widely observed in all cases of our study. Other common findings included roughly distinct margin (8/11, 73%), pleural retraction and thickening (7/11, 64%) with subpleural radiolucent area, intralesional vasodilatation (6/11, 55%), and a small amount of pleural effusion (1/11, 9%).

CT follow-up

During the early-phase CT follow-up, the abnormal pulmonary findings show progressions in different forms in all patients. Gradually increased GGOs and consolidations with “fried egg sign” (peripheral GGO halo with central solid component) or “reversed halo sign” (peripheral solid halo with central GGO component) were main findings on the follow-up CT scans. In the quantitative analysis, significantly increased nV of GGO ($p = 0.003$) and consolidation ($p = 0.003$) were discovered between initial and follow-up UHR-CT (Table 3). However, the early-phase progression of each GGO lesion in our study was diverse and overlapping (including increased, enlarged, consolidated, merged, blurred and partially absorbed lesions). All patients in our study eventually recovered and discharged after continuous treatment. Pulmonary inflammation on CT was absorbed with various degrees of fibrosis at discharge in all patients.

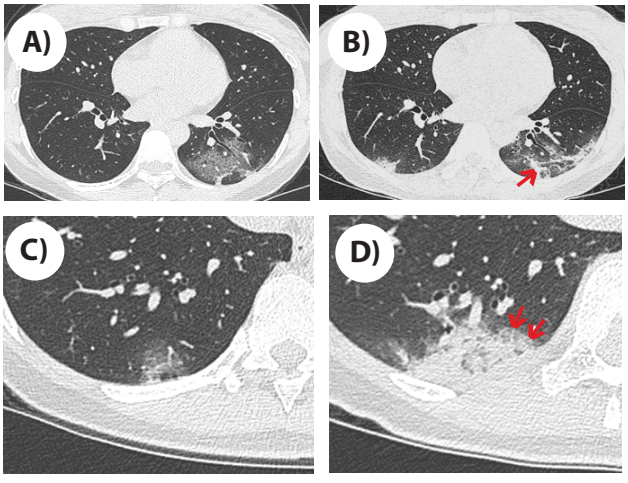

Figure 3: Initial CT images (a) of a 33-year-old female with COVID-19 show subpleural patchy areas of ground-glass opacity (GGO) with inter/intralobular septal thickening and air bronchogram. Follow-up CT images (b) after 5 days depict a prominent progression of GGO and consolidation with “reversed halo sign” (arrow). Initial (c) and follow-up (d) CT images indicate an increased volume and density of the inflammatory lesion of the right inferior lobe. Follow-up CT image also suggests the lesion with a “fried egg sign” (arrow).

nV	Initial CT	Follow-up CT	*p* value
GGO (%)	1.85 ± 3.27	3.55 ± 4.29	0.003
Consolidation (%)	0.25 ± 0.38	1.03 ± 1.34	0.003

Table 3: Comparison of normalized volume (nV) of ground-glass opacity (GGO) and consolidation during the CT follow-up (n=11)

Discussion

Viruses in the same family may share a similar genetic structure, pathogenesis pattern and radiological characteristics. SARS-CoV-2 is a new sub-type of subfamily *Coronavirinae* with genetic similarity to bat-like SARS coronavirus [11]. Currently, no effective treatment or reliable vaccine is available for the emerging infectious disease.

Previous reports of COVID-19 advocated the application of chest CT (with a sensitivity of 98%) for patients with epidemiologic suspicions but negative rRT-PCR results [9]. UHR-CT with maximum matrix size improved the spatial resolution and image quality of CT scans, which was more suitable for the assessment of GGO, intralobular reticulation, and intralesional vessels than conventional chest CT [12]. In this study, UHR-CT provided visualized details about the radiological pattern of COVID-19 pneumonia.

Bilateral multifocal subpleural distributed GGOs with clear margins were common imaging features of COVID-19 in our cohort. GGOs with interlobular or intralobular septal thickening, also regarded as "crazy paving sign", was another typical chest CT finding (Figure 2). "Crazy paving sign" could be clearly displayed on UHR-CT since such modality enabled precise visualisation of the tiny pulmonary structures. Characterization of "crazy paving sign" may be pathologically attributable to partial alveolar filling or collapse, and thickening of interstitial tissues with increased capillary volume [13]. Chung et al. revealed a typical manifestation of COVID-19 of subpleural ground-glass lesions with consolidation [4,5,14], which is consistent with our research.

To the best of our knowledge, adjacent pleural retraction, local pleural thickening, and intralesional vasodilatation on UHR-CT were firstly reported in our study, and might help the timely diagnosis of COVID-19. We assumed histological finding of focal cellular fibromyxoid exudates, alveolar collapse and granulation tissue formation might lead to the above radiological signs, which require further radiologic-histopathologic analysis [13,15].

On the early-phase follow-up CT images, significantly increased volume of both GGO and consolidation could be frequently observed with the infection rapidly progressed. Our findings seemed to be consistent with previous preliminary reports that follow-up CT images displayed rapid progression of pulmonary lesions with increasing number and density of GGOs and consolidations [5,6]. A recent study also demonstrated predominantly GGO abnormality in the early course of COVID-19, then greater consolidated areas, developed "crazy paving sign" and increased total lung involvement in the later course [7]. Notably, our study suggested that patients with mild symptoms (as the majority of COVID-19 cases) might manifest rapid short-term progression of lung lesions even after immediate treatment, which deserved close observation and follow-up by clinicians.

The majority of pulmonary GGOs in our study exhibited overlaps of imaging features and evolution modes. "GGO migrans" (enlarged and absorbed lesions at the same time) could be found in some cases based on the UHR-CT images comparison (Figure 3), corroborating previous studies [6]. Moreover, we reported the characteristic "fried egg sign" or "reversed halo sign" on follow-up CT images (Figure 3), which may help to indicate the complex evolution patterns of pneumonia. Analogously, another study of COVID-19 revealed that both GGOs and consolidation developed with a variety of patterns during the CT follow-up with four-day intervals [14]. More sensitive recognition and more accurate segmentation of pulmonary lesions by applying deep learning technology should be further investigated in the dynamic quantitative assessment of COVID-19.

Our study has several limitations. Firstly, our study was based on a short-term follow-up and a small sample from a single center. Furthermore, most COVID-19 cases in our study were imported from the remote endemic center, and lack pediatric population and severe infection. In addition, some patients may receive early medical intervention before the base-line CT scans. Finally, some fibrous lesions, incidental nodules (not related to viral inflammation), motion artifact and intralesional vessels might become confounding factors in the artificial intelligence-based analysis.

In summary, UHR-CT imaging patterns of peripleural GGO with interlobular and intralobular septal thickening, pleural retraction and thickening, and intralesional vasodilatation indicate the preliminary diagnosis of COVID-19. The COVID-19 cases manifest marked increased volume of both GGOs and consolidations with varied pattern during the early-phase follow-up. UHR-CT provides visualized details of the radiological signs and evolution pattern of COVID-19 pneumonia. The application of UHR-CT with deep-learning-based methodology should be further explored in the COVID-19 pandemic.

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