

Radiologic evaluation of discharge quality in patients with COVID-19

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Abstract

Background Worldwide spread of the novel coronavirus disease 2019 (COVID-19) has made hundreds of thousands people sick and fortunately many of them have been treated and discharged. However, it remains unclear how well the discharged patients were recovering. Chest CT scan, with demonstrated high sensitivity to COVID-19, was used here to examine clinical manifestations in patients at discharge.

Methods This study registered retrospectively single-center case series of 180 discharged patients, all confirmed with COVID-19 at Wuhan Red Cross Hospital in Wuhan, China. Epidemiological, demographic, clinical, laboratory and treatment data were collected. CT imaging features of absorption vs progressive stage were compared and analyzed.

Results Five pulmonary lobes were affected in 54 (30%) of the 180 patients at the absorption stage, comparing to 66% of them at the progressive stage ($P=1.45\times 10^{-11}$). Forty five (25%) patients had pleural effusion on admission and 13 of them still carried hydrothorax when discharged as per standard discharge criteria

($P=4.48\times 10^{-6}$). Besides, compared with those at progressive stage, 97 (54%) discharged patients had interlobular thickening ($P=6.95\times 10^{-3}$) and 43% of them still presented adjacent pleura thickening ($P=5.58\times 10^{-5}$). The median total CT score of discharged patients at absorption stage was lower than progressive stage (3 vs 12.5). The median total CT score recovery rate was 67% (range, 0-100%) and 139 (77%) patients showed less than 90% improvement at discharge.

Conclusions A majority (77%) of the discharged patients had not recovered completely. The current discharge criteria may need to include 90% or higher CT score-based recovery rate.

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Authors Zhicheng Lin and Nian Xiong are joint last coauthors.

Introduction

Since the outbreak of novel coronavirus disease 2019 (COVID-19) in December 2019 Wuhan of China hundreds of thousands people have been diagnosed with this highly contagious pneumonia around the world [1]. Infection by its underlying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV) becomes a threat to global health [2]. With a period of symptomatic and supportive treatment, more than seventy eight thousand people in China had been reportedly cured of COVID-19 and discharged by April 15th, 2020 [3].

All the hospital discharges met four criteria: (1) normal temperature lasting for longer than three days, (2) resolved respiratory symptoms, (3) substantially improved acute exudative lesions on chest computed tomography (CT) images, and (4) two consecutively negative RT-PCR test results separated by at least

one day; which was a standard protocol of the Seven Revised Edition novel coronavirus pneumonia treatment guideline from the National Health Commission of China. However a recent study has indicated that positive RT-PCR test results can be found in recovered COVID–19 patients[4]. Moreover, another study has just indicated that RT-PCR results for pharyngeal swabs samples support only 32% of COVID–19 subjects [5], suggesting that many discharged patients may still carry this virus given the 68% false negative rate. Together, different discharged patients may carry various densities of the viral RNA, implying an elusive consequence. Therefore, whether or not a discharged patient has truly recovered becomes a *bona fide* concern at all levels.

At Wuhan Red Cross hospital (WRCH), Wuhan, Hubei, a general hospital which was turned into a healthcare system specialized for treating severe COVID–19 patients in January of 2020 and till March 15th, more than 1,100 COVID–19 patients had been discharged. We have found that among these patients, some had lung CT results back to normal whereas others had improved lungs but with obvious abnormality at discharge. Here we present for the first time clinical and radiological findings as a result of the analysis of 180 recovered and discharged patients with COVID–19, by comparing the imaging features of absorption stage with progressive stage.

Methods

Study Design and Participants

One hundred eighty discharged patients were registered at WRCH. WRCH, one mile away from Huanan Seafood Wholesale Market to which SARS-CoV-2 was tracked back, is a trusteeship hospital of Union Hospital and one of the first hospitals admitting COVID-19 patients only. All patients were diagnosed with COVID-19 according to the guideline of SARS-CoV-2 (Trial Version 5 to 7 of the Chinese Government). The data of included cases have been submitted to the Chinese Center for Disease Control and Prevention. We analyzed epidemiological, demographic, clinical and radiological features, and laboratory data. Outcomes including length of stay, discharges and fatality were followed up and recorded until March 6th, 2020. The study was approved by WRCH Ethics Committee and written informed consent obtained from each subject before enrolment, followed by retrospective data collection.

Data and Specimen Collection

Individuals confirmed to have COVID-19 by SARS-CoV-2 real-time reverse transcriptase–polymerase chain reaction (RT-PCR) were eligible for inclusion in this study. Data were collected at Wuhan Red Cross Hospital that provided care for these patients. Data from electronic health records were summarized using a standardized data collection form. Two researchers independently reviewed the data collection forms for accuracy.

Specimens (nasopharyngeal swabs) were collected at multiple time points in the first 2 weeks following study enrollment and tested by RT-PCR for the presence of SARS-CoV-2. After collection, the throat swabs were placed into a collection tube with 200 µL of virus preservation solution, and total RNA was extracted within 2 hours using the respiratory sample RNA isolation kit (Union hospital, Tongji Medical University, Huazhong university of Science and Technology and ADICON clinical laboratory). After standing at room temperature for 30 minutes, the collection tube was centrifugated at 8000 rpm/min for a few seconds. The suspension was used for RT-PCR assay of SARS-CoV-2. RT-PCR assay was performed under the following conditions: incubation at 50 °C for 15 minutes and 95 °C for 15 minutes, 45 cycles of denaturation at 94 °C for 15 seconds, and extending and collecting fluorescence signal at 55 °C for 45 seconds. RT-PCR cycle threshold values were collected. A cycle threshold value (Ct-value) less than 40 was defined as a positive test result. The cycle threshold value correlates with the number of copies of the virus in a biological sample, in an inversely proportional and exponential manner. Sequencing of PCR products of the RNA-dependent RNA polymerase (RdRp) gene were used to construct phylogenetic trees. (CoV-N-P: 5' FAM-TTGCCCCCAGCGCTTCA-BHQ1 3'; CoV-N-F: 5' TTGGGGACCAGGA ACTAAT 3'; CoV-N-R: 5' GAAGGTGTGACTTCCATGC 3'; ORF1ab-P: 5' HEX-TCCCACCCAAGAATAGCATAGATGC-BHQ1 3'; ORF1ab-F1: 5' TTTAGATATATGAATTCACAGGGA 3'; ORF1a-R1: 5' ACCAACACCCAACAATTTAAT 3'; RNP-F: AGATTTGGACCTGCGAG ; RNP-R: ACTGAATAGCCAAGGTGAG ; RNP-P: 5' Cy5-TCCACAAGTCCGCGCAGAG-BHQ2 3')

Clinical Management

Epidemiological information, clinical manifestations, laboratory results, radiological characteristics, treatments and outcomes were recorded during the hospital stays and then collected from the medical records. All data were checked by two trained physicians (J.L. and N.X.). Patients were asked about basic information, medical history, exposure history, symptoms and comorbidities. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [6]. As part of standard of care, complete blood cell count, tests of kidney and liver function, and measurement of C-reactive protein and lactate dehydrogenase levels were performed. Respiratory samples were tested for influenza and other respiratory viruses with a multiplex PCR assay. Treatment measures included symptomatic therapy, antiviral therapy, corticosteroid therapy and respiratory support. All patients received supportive therapy, including supplemental oxygen when saturations as measured by pulse oximeter dropped below 92%. Patients clinically suspected of having community-acquired pneumonia were administered empirically.

Informed consent for collection of clinical data from infected individuals was granted by the Wuhan Red Cross Hospital Committee. Written informed consent was obtained from study participants for collection of biological samples after review and approval of the study protocol by the institutional ethics committee.

Imaging analysis

All COVID-19 patients were from WRCH and were imaged with 1-mm slice thickness CT on a Siemens SOMATOM go.Top 64 scanner (Siemens Healthineers, Suzhou, China). Scanning field of view (FOV) 413×413mm, tube voltage 130kV, tube current 138mA, pitch 0.6, reconstruction layer thickness 1.5mm. Lung window reconstruction was performed using high-resolution algorithm. After inhaling, the patient held his breath to acquire images, and the scanning range was from the lung tip to the lung bottom. All CT images were reviewed by two fellowship-trained cardiothoracic radiologists with approximately five years of experience each (X.L, F.F, X.F.L, D.Z, Y.S, S.H) using a viewing console. Imaging was reviewed independently and final decisions reached by consensus are reported. No negative control cases were examined. For each patient, the chest CT scan was evaluated for the following characteristics: (1) presence of ground-glass opacities, (2) presence of consolidation, (3) laterality of ground-glass opacities and consolidation, (4) number of lobes affected where either ground-glass or consolidative opacities were present, (5) degree of involvement of each lung lobe in addition to overall extent of lung involvement measured by means of a “total severity score” as detailed below, (6) presence of nodules, (7) presence of a pleural effusion, (8) presence of thoracic lymphadenopathy (defined as lymph node size of ≥ 10 mm in short-axis dimension), (9) airways abnormalities (including airway wall thickening, bronchiectasis, and endoluminal secretions), (10) axial distribution of disease (categorized as no axial distribution of disease, central “peribronchovascular” predominant disease, or peripheral predominant disease), and (11) presence of underlying lung disease such as emphysema or fibrosis. Other abnormalities, including linear opacities, opacities with a rounded morphology, opacities with a “reverse halo” sign, opacities with a “crazy-paving” pattern, and opacities with intralesional cavitation, were noted. Ground-glass opacification was defined as hazy increased lung attenuation with preservation of bronchial and vascular margins, whereas consolidation was defined as opacification with obscuration of margins of vessels and airway walls. Each of the five lung lobes was assessed for degree of involvement and classified as none (0%), minimal (1 - 25%), mild (26 - 50%), moderate (51 - 75%), or severe (76 - 100%). No involvement corresponded to a lobe score of 0, minimal to a lobe score of 1, mild to a lobe score of 2, moderate to a lobe score of 3, and severe to a lobe score of 4. An overall lung “total severity score” was reached by summing the five lobe scores (range of possible scores, 0 - 20) [7]. The amount of time between the initial appearance of patient symptoms and the date of admission as well as the date of the initial chest CT examination was noted for each patient.

Statistical Analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described using median, minimum and maximum grades. SPSS (Statistical Package for the Social Sciences, version 25) was used for all analyses. $P < 0.05$ was considered as statistically significant. Continuous variables were expressed as median (range) and compared between independent groups by *Student's t* tests; categorical variables were expressed as number (%) and compared by χ^2 tests or Fisher's exact tests.

Results

Basic characteristics, Clinical symptoms, Complications and Treatment, Laboratory examinations

The study population had a group of 180 discharged patients all confirmed with COVID-19 and registered from January 21st to February 20th, 2020. The median age was 50 years (range, 21-87 years). Fifty seven (32%) of the 180 patients were over 60 years old. Females accounted for the majority of the infected patients (100 [56%]) in this study. Some patients had previous medical history underlying diseases, including common coexisting conditions like cardiovascular diseases (40[22%]) and endocrine system disease (20[11%]). A total of 158 (88%) patients had one or more followed symptoms for admission. The most common symptoms at onset of the illness were fever (141 [78%] of 180 patients), dry cough (126 [70%]), anorexia (92 [51%]), fatigue (77 [43%]). Patients with short of breath accounted for 36%. Only two discharged patients had complications including ARDS (1%) and three had acute respiratory injury (2%). Almost all patients received antiviral therapy and antibacterial therapy. Some were given systematic glucocorticoid therapy (47 [26%]) and intravenous immunoglobulin therapy (IVIG) (67 [37%]). 147 (82%) of the 180 patients received high-flow oxygen and only one received invasive ventilation (1 %) (Table 1).

The most results of laboratory examinations of these patients at admission were basically normal, except 37% with leucopenia (white blood cell count less than $4 \times 10^9 /L$), 13% with abnormal indexes such as high creatine kinase (CK) and lactate dehydrogenase (LDH) levels and 18% with increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. As noticed, the infection-related biomarker C-reactive protein (CRP) level did not drop to a normal range (Table 2).

CT image presentations

Multiple patchy ground glass opacities in bilateral multiple lobular with periphery distribution are chest tomographic features typical of the COVID-19 pneumonia [7]. We compared these features in discharged patients at absorption stage with those at progressive stage, as required by discharge criteria. Comparison of CT images between patients at progressive and absorption stages were showed in Figure 1.

In this cohort, 64% (115) patients presented bilateral pneumonia at absorption stage, compared with 84% (152) at absorption stage ($P=8.39 \times 10^{-6}$). At discharge, 40 (22%) patients had unifocal lobe involvement, comparing to only 10 (6%) at progressive stage ($P=4.83 \times 10^{-6}$), representing an improvement of the lung health.

Thirty percent of the 180 patients still had five involved pulmonary lobes at the absorption stage, comparing to 66% at the progressive stage ($P=1.45 \times 10^{-11}$). For all the patients at progressive stage, the lesion was in the left upper lobe in 145 cases (81%), left lower lobe in 152 (84%), right upper lobe in 139

(77%), right middle lobe in 130 (72%) and right lower lobe in 159 (88%). Lesions were inclined to distribute in the lower lobes. Multiple locations involved occasionally single or double lesions, independently of lobe or lung location. The results of absorption stage CT findings had improvements of all lobes (Table 3).

Of the 180 recovered patients at discharge, compared with images at their progressive stage, 61 (34%) of them still had mixed ground glass opacity and consolidation ($P=4.83\times 10^{-15}$), 53 (29%) still had consolidation ($P=1.58\times 10^{-13}$), and 29 (16%) patients still presented with crazy paving pattern ($P=8.90\times 10^{-9}$). Forty five (25%) patients showed pleural effusion on admission, and 13 (7%) of them had hydrothorax at discharge ($P=4.48\times 10^{-6}$). Besides, compared with the progressive stage, 97 (54%) patients still had interlobular thickening ($P=6.95\times 10^{-3}$) and 78 (43%) still presented adjacent pleura thickening ($P=5.58\times 10^{-5}$) at discharge. Out of 71 patients carrying air bronchogram sign at admission, 23 (13%) patients retained the sign at discharge ($P=8.43\times 10^{-9}$). Pericardial effusion, thoracic lymphadenopathy, and pulmonary emphysema were rare findings in these discharged patients (Table 3).

The median total CT score of discharged patients at absorption stage was lower than progressive stage (3 vs 12.5). According to the group CT scores, the average total CT score recovery rate was 63% ($63\% \pm 28\%$, range from 0-100%, and 100% for complete recovery). The group of patients whose total CT score ranged from 0 to 5, 5 to 10, 10 to 15, 15 to 20, and 20-25, their average total CT score recovery rate was $74\% \pm 33\%$, $65\% \pm 25\%$, $61\% \pm 19\%$, $57\% \pm 28\%$ and $56\% \pm 31\%$, respectively. Only 23% (41 in 180) patients showed a greater than 90% total CT score recovery rate at discharge[8-9] (Table 3). Figure 2 presented time course of chest CT scans of a 63-year-old female discharged patients with COVID-19.

Discussion

This report, to our knowledge, is the first CT evaluation of a large cohort of discharged patients with COVID-19. It presents the latest recovering status, at discharge, as revealed by chest CT imaging, the most consistently sensitive method for detecting COVID-19 progression. To our surprise, three quarters (77%) of the discharged patients carried unrecovered lungs, with common abnormalities including ground-glass opacities, pleural fluid and thickened adjacent pleura.

Still, these patients can be discharged according to the imaging criteria that most of the original inflammatory lesions are absorbed and no new lesions in the lung are found according to the Seventh Revised Edition Chinese guideline. A critical question here is whether any of the discharged patients are still carrying the virus. Consistently, some COVID-19 patients had reportedly showed re-fever and positive nucleic acid test results after discharged [4]. This might be due to the biological characteristics of SARS-CoV-2, the basic disease, clinical status, glucocorticoid using, sampling, processing, detecting, or related to viral re-infection [10]. Of course, another possibility is that the virus is still surviving in the partially recovered, although discharged, patients.

Because of that possibility, discharged patients with partially recovered lungs may become new source of infection. This possibility has not been verified in China yet because China's current polices require all

discharged patients to be under quarantine at a designated rehabilitation site for two weeks. Nevertheless, considering SARS-CoV-2's high contagiousity, we strongly suggest that more attention should be paid to CT results-based discharge of the patients, which may provide greater precaution about consequences of discharge. Repeated CT scanning is helpful for monitoring disease progression and implementing timely treatment. As an alternative detection method for assessing COVID-19, we suggest that viral serological (IgM, IgG) tests be performed when necessary [11], which have been added into the latest discharge criteria of the novel coronavirus pneumonia treatment guideline and may have a higher sensitivity compared with RT-PCR tests. Together, different measures may provide a better understanding of each discharge. Future studies are warranted to elucidate correlations between CT findings and clinical manifestations or viral viability, including individual variation and the underlying pathogenesis.

We are aware of limitations in this study. Our CT imaging had short-term follow-up only. Long-term follow-up CT data to observe prognosis of the disease should be collected. And CT data need to be correlated with clinical findings as well in order to further appreciate its clinical value.

Conclusion

A majority of patients (77%) did not recover completely at discharge. To better control the rapid spread of SARS-CoV-2 and consolidate clinical therapeutic efficacy of COVID-19 patients, current discharge criteria should consider total CT score recovery rate higher than 90%.

Declarations

Author Contributions: JL, XL, FF, XFL, DZ, YS, NL, QZ, XF, SH and NX collected epidemiological and clinical data and processed statistical data. JL, XL, FF and XFL drafted manuscript and share first authorship. NX and ZL finalized manuscript. NX is responsible for summarizing all epidemiological and clinical data.

Compliance with Ethical Standards

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Conflict of interests: The authors declare they have no conflict of interests.

Declaration of Helsinki: The research protocol have been submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. The Wuhan Red Cross

Hospital Ethics committee is transparent in its functioning, independent of the researcher, the sponsor and any other undue influence and is duly qualified. It has been taken into consideration the laws and FKERegulations of the country or countries in which the research is to be performed as well as applicable international norms and standards

Ethical approval: This study was approved by the Ethics Committee of the Wuhan Red Cross Hospital.

Informed consent: Obtained from all individual participants included in the study.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

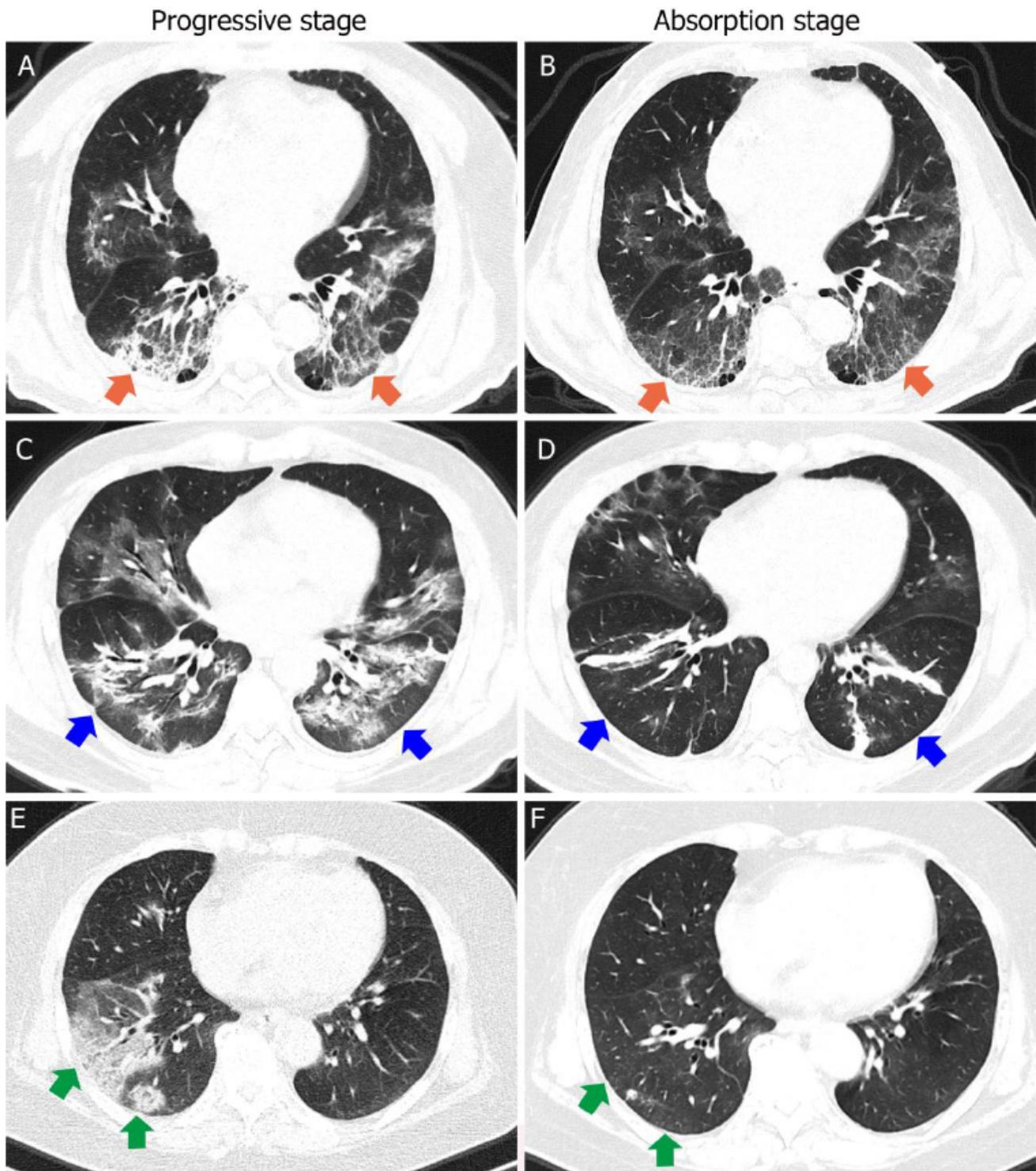


Figure 1

CT imaging of patients at progressive and absorption stages. (A-B, patients with a recovery rate less than 50%; C-D, patients with a recovery rate between 50%-90%; E-F, patients with a recovery rate over 90%)
From the CT findings of progressive stage images (A,C,E), sporadic multifocal spatchy bilateral ground-

glass opacities with adjacent pleura thickened were typical. At absorption stage (B,D,F), there was an obvious improvement of original lesions with lower density. The adjacent pleura was still thickened and fiber stripes appeared.

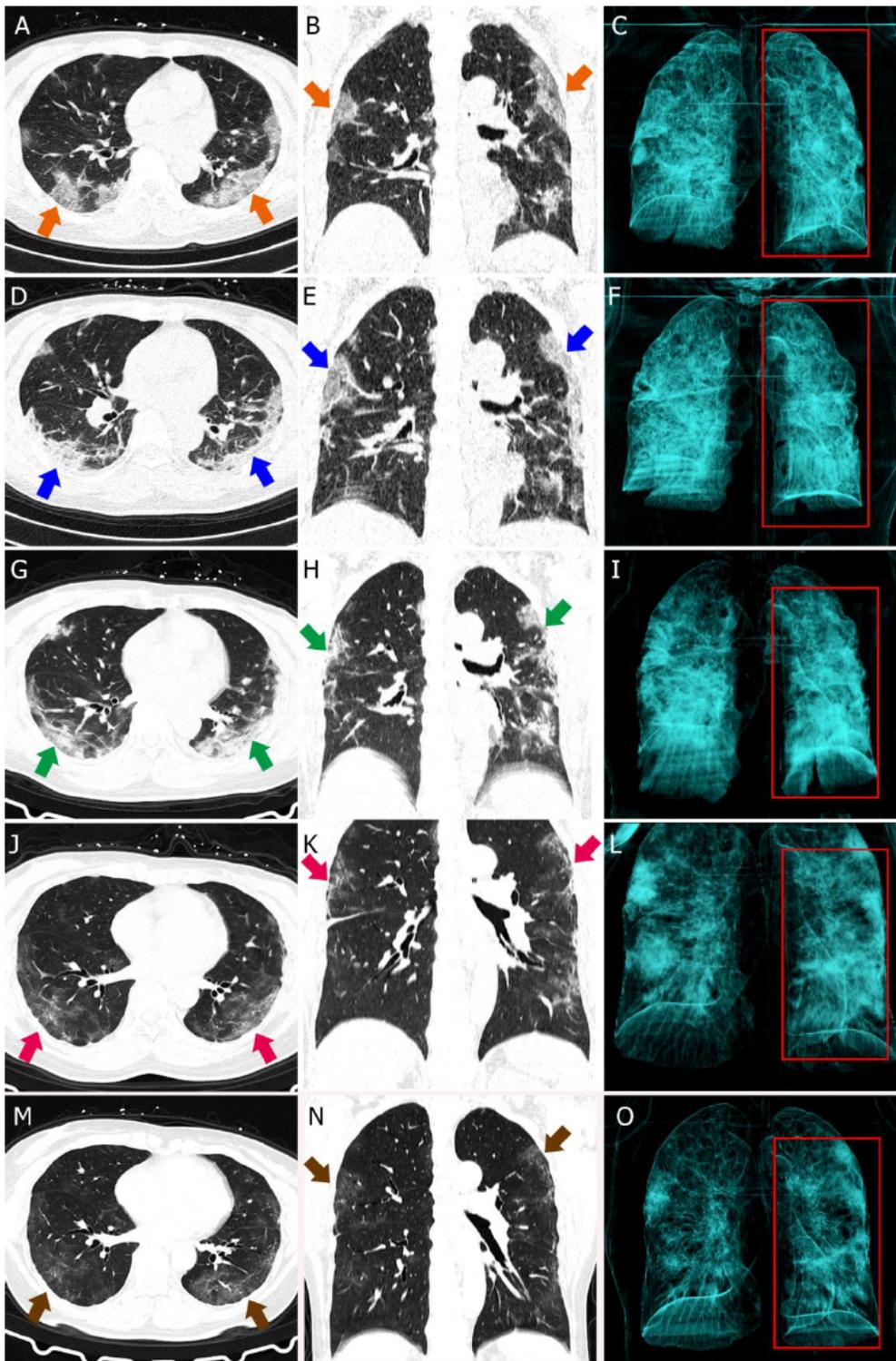


Figure 2

Time course of chest CT scan findings of a 63-year-old female discharged patients with COVID-19. (The first column, axis scans; the second column, coronal scans; the third column, three-dimensional

reconstruction) C) Illness day 9 CT image showed sporadic multifocal spatchy bilateral ground-glass opacities (marked by orange arrows) without pleural fluid, mainly in the subpleural area. (D-F) CT images on illness day 15 showed original lesions enlarged with a higher-density and fiber stripes appeared (marked by blue arrows). (G-I) Illness day 20 CT images showed an improvement of original lesions without pleural fluid (marked by green arrows). (J-L) CT images of illness day 27 showed further absorption of bilateral lesions (marked by red arrows), remaining some spatchy ground-glass opacities with small amount pleural effusion in the horizontal fissure of right lung. Meanwhile, the patient had two consecutive negative nucleic acid test for SARS-CoV-2 and met the criteria of discharge. (M-O) Eight days after discharge (illness day 35), follow-up CT reexamination images showed further absorption (marked by brown arrows) and fiber stripes. The adjacent pleura was also thickened. Red boxes denoted the disease progression of her left lung.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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