

## Peer review file

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### Reviewer A

**Comment 1:** The introduction could be shortened as much of the information around the emergence of COVID-19 is well known/established. This would allow more opportunity to discuss the emerging evidence around radiological changes and where this study fits.

**Reply 1:** Thank you for your suggestion; the introduction has been shortened as suggested.

**Changes in the text:** The changes in the text are on lines 57-60, page 3 of the revised manuscript.

**Comment 2:** The results are clearly described, and the evolution of the disease in terms of progression and recovery is clearly demonstrated. The figures are extremely useful to support the conclusions and track the radiological changes. The supplementary table are useful to clinicians to correlate the radiological findings with the clinical course, especially in these mild cases. If allowable within the confines of the journal's editorial policy moving supplemental table 3 to the main body of the article would increase its quality for a clinical reader.

**Reply 2:** Thanks for your nice comments on our study. Supplemental Table 3 has been moved to the main body and has been renamed Table 4.

**Changes in the text:** The Table 4 is on page 23 of the revised manuscript.

**Comment 3:** Watch formatting throughout. There are a number of lines with additional spaces between words, or a lack of space before a bracket. This will need to be revised prior to acceptance.

**Reply:** Thank you for your suggested modifications in the format, which we have implemented.

**Changes in the text:** The suggested changes have been made throughout the manuscript.

### Reviewer B

**Comment 1:** Kong et al retrospectively investigated sequential changes of chest CT image during treatment of mild patients with COVID-19. Predominant image of mild cases with COVID-19 were similar to previously reported cases, such as bilaterally subpleural ground glass opacities (GGO) with or without lung consolidation. This study provides important sequential changes of chest CT images that are fundamental for the diagnosis of COVID-19 but little is known to date.

**Reply 2:** Thank you for your complimentary comments on our article.

**Changes in the text:** None.

**Comment 2:** This study enrolled 22 mild cases with COVID-19 who underwent at

least two chest CT examinations. It is surprising that 90.9% of mild patients with COVID-19 have undergone more than three chest CT examinations with a short interval time between each chest CT scan. It is understandable that chest CT scans will be examined if patients' condition changes rapidly, but it should be clarified why such frequent CT scans were needed for patients' treatment as practice.

**Reply 2:** COVID-19 is an emerging infectious disease. There is still no standard follow-up strategy due to limited cognition regarding COVID-19. Therefore, repeated chest CT was employed to assess the COVID-19 patient's condition accurately. For example, after admission, patients need to undergo a chest CT to screen and identify possible COVID-19 infection. According to the diagnosis and treatment protocols of COVID-19 pneumonia published by the National Health Commission of the People's Republic of China, the average incubation period of COVID-19 is 3-7 days. The specific IgM antibody of COVID-19 becomes positive mostly between 3 and 5 days after onset of the disease, therefore, we speculate that COVID-19 pneumonia may have a period of disease progression ranging between 3-7 days after the onset of the disease. Accordingly, repeated chest CT at this time is necessary. In addition, repeated chest CT examination may also be conducted based on the patient's symptoms and signs as well as laboratory tests during the clinical process. Finally, patients need to be re-examined by chest CT before discharge.

**Changes in the text:** None.

**Comment 3:** Were there any differences in laboratory data, symptoms, or days to resolution of shadows between cases with GGO dominant or consolidation dominant?

**Reply 3:** In the present study, no difference was observed in laboratory data, symptoms, or days to resolution of shadows between cases with GGO dominant or consolidation dominant.

**Changes in the text:** None.

**Comment 4:** What kinds of antibacterial drugs were used for treatment of patients with mild COVID-19?

**Reply 4 :** Three kinds of antibacterial drugs were used for the treatment of patients with mild COVID-19: levofloxacin(n=8), azithromycin(n=5), and ceftriaxone(n=1), which are shown in table 4.

**Changes in the text:** The changes in the text are shown in Table 4, which are on page 23 of the revised manuscript.

**Comment 5:** The dose and duration of corticosteroids used should be stated.

**Reply:** In the present study, methylprednisolone sodium succinate (40mg/qd) was used for the treatment of COVID-19 patients through an intravenous drip for three days.

**Changes in the text:** The changes in the text are shown in the section of prognosis (section 5), which are on lines 178-180, pages 8-9 of the revised manuscript.

**Comment 6:** They newly suggest that fibrosis-like stripes, which is not a primary

chest CT manifestation, is possibly showing atelectasis of sub-segmental lung tissue of COVID-19. I agreed with authors that subpleural fibrosis-like stripes in the lower lung lobes is possible atelectasis as I also encountered a similar patient with COVID-19. Did these patients with fibrosis-like stripes have higher incidence of productive cough?

**Reply 6:** In the present study, three out of eight patients with fibrosis-like stripes had a cough and/or sputum, while five out of 14 patients without fibrosis-like stripes had a cough and/or sputum; we did not observe that patients with fibrosis-like stripes had a higher incidence of productive cough compared with patients without fibrosis-like stripes (3/8 vs 5/14, P=1.000).

**Changes in the text:** None.

### **Reviewer C**

**Comment 1:** This study is a retrospective and a single-center study which reports on the evolution of chest CT features and clinical outcomes among 22 COVID-19 patients. The authors presented very detailed radiological findings in different stages of the disease, combined with clinical and laboratory data. The CT results showed a wide range of various pathological results, of which most reduced or disappeared in a relatively short period of time. Overall, it is a very interesting study, and as authors emphasize, a new one in terms of its longitudinal character. Especially nowadays, we need urgently such studies which are connected to the COVID-19 infection.

Below please find a few questions/comments to the authors:

**Reply 1:** Thanks for your nice comments on our study.

**Changes in the text:** None.

**Comment 2:** In my opinion, the percentage numbers of patient subgroups with distinct CT features are a little bit confusing. As not all patients received 3 or 4 CT's, you cannot divide the number of patients with distinct CT patterns on the third or fourth CT by the whole number of patients enrolled in the study. For example, you write in the section 3.3.1. that "the fourth CT examination revealed that the GGO lesions significantly decreased in number or disappeared in 9 patients (40.1%),...". As only 11 patients out of 22 obtained the fourth CT, the percentage number should be here 81.8%. When you write 40.1% you assume that 13 patients did not have these changes, but you do not know this for sure, because you did not prove it by a CT scan. I know that probably the most of the patients who did not get the third or fourth CT scan did not have these changes, because on the previous scan(s) the majority of the lung changes was significantly reduced or disappeared, however in cases of patients 17 and 20 they still had changes on the last CT's ("vascular thickening unchanged", "multiple GGO increased", respectively) and in spite of that did not receive the next CT scan (probably due to the fact that they were already clinically much better). So, you should correct the percentage numbers for all patients receiving the third and the fourth CT scan. For the clarity of the readers you may write a sentence, e.g. as the last sentence of section 3.1.: "All percentages in brackets in the sections 3.3.1-3.3.8. are a result of dividing the number of patients with distinct CT features by the number of

patients who received two, three, or four CT scans, respectively”.

**Reply 2:** We feel deeply indebted to you for your professional and hard review work on our article. One reviewer suggested that writing the percentage next to every number was superfluous. He also suggested that the results presented in the sections 3.3.1-3.3.8 lacked focus. We agree with these observations. Accordingly, we decided to remove the percentage next to every number and rewrite the evolution of important CT manifestations to make the results more concise. We hope this revision is acceptable.

**Changes in the text:** The changes in the text are shown in the section of evolution of main CT image manifestations (section 3.3), which are on lines 134-144, pages 6-7 of the revised manuscript.

**Comment 3:** Connected to this problem, there is a mistake in section 3.3.1., first sentence: “GGO lesions reduced in 10 patients (45.5%)”. As you mentioned in the section 3.1., there were only 9 patients who received the third CT, so you cannot have 10 patients with three CT scans. Please correct this and check again all the numbers and percentages throughout the whole manuscript.

**Reply 3:** We are very sorry for our inaccurate expression in section 3.1. In this section, the first sentence: " Of the 22 COVID-19 patients, 2 patients (9.1%) underwent two chest CT examinations during hospitalization, 9 patients (40.9%) underwent three chest CT examinations, and 11 patients (50%) underwent four chest CT examinations." This sentence is very likely to lead to ambiguity. The sentence "2 patients (9.1%) underwent two chest CT examinations during hospitalization" means the number of patients who only received the second CT is two. Similarly, 9 patients (40.9%) underwent three chest CT examinations, and 11 patients (50%) underwent four chest CT examinations." What we really want to say is, 9 patients received the third CT, and 11 patients received the fourth CT (these patients who received the fourth CT also underwent three previous CT scans), so the total number of patients with three CT scans is 20 (as shown in the supplemental Table 1). However, to avoid potential ambiguity, the sentence "Of the 22 COVID-19 patients, 2 patients (9.1%) underwent two chest CT examinations during hospitalization, 9 patients (40.9%) underwent three chest CT examinations, and 11 patients (50%) underwent four chest CT examinations." has been replaced with, " Of the 22 COVID-19 patients, 22 patients underwent two chest CT examinations during hospitalization, 20 patients underwent three chest CT examinations, and 11 patients underwent four chest CT examinations. ".

**Changes in the text:** The changes in the text are shown in the section of general information on imaging examination (section 3.1), which are on lines 115-117, page 6 of the revised manuscript.

**Comment 4:** In the Discussion you write that “the imaging stages may guide physicians in assessing disease progression and in adjusting treatment strategies, in a timely manner”. Have you already used this information to treat adequately your

patient population (e.g. cessation of antiviral/antibacterial therapy at stage III of recovery or later at stage IV of dissipation)?

**Reply 4:** There is still no consensus on the course of antiviral treatment for COVID-19. Our clinical experience found that the COVID-19 virus is very tenacious and hard to eliminate completely. Furthermore, the nucleic acid testing performed during the course of clinical treatment could become negative temporarily, and then become positive again. A possible reason may be that although the virus in sputum may be eliminated, however, the virus in the inflammation of the lungs may still persist. Therefore, all patients in the present study were treated with a full course of antiviral treatment. Nevertheless, for patients receiving antibacterial therapy, the majority of patients (13/14) discontinued antibacterial therapy at stage III of recovery and one patient discontinued antibacterial therapy at stage IV of dissipation.

**Changes in the text:** None.

**Comment5:** Have you found any correlations between clinical status and/or laboratory data (e.g. inflammation) with CT results?

**Reply 5:** In the present study, we found a correlation between patients' clinical status (fever and cough) and the CT results. However, correlations between laboratory data and the CT results were not observed. For 19 patients with fever as the initial symptom, the median duration of fever was 4 days (2-19 days). Of these patients, 14 experienced a disappearance of fever during the progressing stage (stage II), 4 patients experienced disappearance of fever during the recovery stage (stage III), and 1 patient experienced disappearance of fever during the dissipation stage (stage IV), which may indicate that image change has some lag when compared with fever change. For 6 patients with a cough as the initial symptom, the median duration of the cough was 13.5 days (10-20 days). All 6 patients experienced a disappearance of the cough at the dissipation stage (stage IV). The longer duration of the cough may be associated with the stimulation of residual inflammation. These findings indicate that the imaging stages based on the CT results correlate with clinical status and may aid in assessing disease progression.

**Changes in the text:** The changes in the text are shown in the section of correlations between clinical and radiological findings (section 4), which are on lines 164-174, page 8 of the revised manuscript.

**Comment 6:** Discussion, page 12, line 7, advantage 3 of the study: you write that fibrosis-like stripes may guide physicians to whether an early antifibrosis treatment is required. The problem is you do not know if it is a “real” fibrosis, actually you doubt it, because of a very quick disappearance of these CT changes, which may speak more for atelectases than fibrosis. And which antifibrotic therapy you mean? Glucocorticoid? Other therapy? Do your data support the fact that e.g. patients receiving glucocorticoid had less fibrotic-like stripes? Or they disappeared earlier than in those without such a therapy?

Generally, I would be careful with formulating such a sentence.

**Reply 6:** Thank you for your professional comments on our study. We agree with the

criticism. Patients in the present study did not receive specific anti-fibrotic therapy, therefore, formulating the sentence "fibrosis-like stripes may guide physicians to whether an early anti-fibrosis treatment is required" was ill-considered. Advantage 3 of the study "Fibrosis-like stripes are currently one of the important imaging signs of COVID-19 patients, and understanding its possible pathogenesis is of great significance to guide clinicians on whether early anti-fibrosis treatment is required. This study proposed a new hypothesis for the fibrosis-like stripes, and for the first time, identified key imaging evidence to support this hypothesis." has been replaced with, "In the present study, we propose a new hypothesis that fibrosis-like stripes are a sub-segmental atelectasis, rather than a fibrosis lesion, and for the first time, we identified key imaging evidence to support this hypothesis. We think this finding may contribute to a better understanding of the pathogenesis of COVID-19. "

**Changes in the text:** The changes in the text are shown in the advantage 3 of the discussion section, which are on lines 292-296, page 14 of the revised manuscript.

**Comment 7:** Please correct some spelling errors:- 3.3.: Dynamic evolution of first CT image manifestaiones◇ Dynamic evolution of first CT image manifestations

**Reply 7:** Thank you for your observation."Dynamic evolution of first CT image manifestaiones" has been replaced as "Evolution of main CT image manifestations ".

**Changes in the text:** The change in the text is shown in the section 3.3, which is on line 133, page 6 of the revised manuscript.

**Comment 8:** Discussion, page 11, line 6 from the bottom: We speculat◇ We speculate

**Reply 8:** " We speculat " has been corrected to " We speculate ".

**Changes in the text:** The change in the text is on line 280, page 13 of the revised manuscript.

**Comment 9:** Table 1: pharyngalgia◇Pharyngalgia

**Reply 9:**"pharyngalgia " has been changed to "Pharyngalgia" in Table 1 as you suggest.

**Changes in the text:** The change in the text is shown in Table 1, which is on page 18 of the revised manuscript.

**Comment 10:** Table 2: Please write number 9 in superscript to indicate neutrophil and lymphocyte count

**Reply 10:** The suggested change has been made in Table 2.

**Changes in the text:** The changes in the text are shown in Table 2, which are on page 19 of the revised manuscript.

**Comment 11:** Table 2: Maybe you should add to GGO also the word "number" throughout the table to distinguish GGO number from GGO density, because when you write only e.g. GGO increased and the GGO density increased, the readers might ask what increased in that first case.

**Reply 11:** We agree with your suggestion. The suggested change has been made in table 3.

**Changes in the text:** The changes in the text are shown in Table 3, which are on pages 20-22 of the revised manuscript.

**Comment 12:** Figure 3, last line under this figure description: “Local enlarged images shows bronchioles...”-> “Local enlarged images show bronchioles...”

**Reply 12:** "Local enlarged images shows bronchioles.." has been replaced with "Local enlarged images show bronchioles..." in the last line under figure3's description.

**Changes in the text:** The change in the text is shown in the figure description of Figure 3, which is on line 481, page 25 of the revised manuscript.

**Comment 13: Supplemental table 3: Glucocorticoids treatment** ⇄ **Glucocorticoid treatment**

**Reply 13:** The supplemental Table 3 has been moved to the main body and has been renamed Table 4. " Glucocorticoids treatment " has been replaced with " Glucocorticoid treatment " in Table 4.

**Changes in the text:** The change in the text is shown in Table 4, which is on page 23 of the revised manuscript.

#### **Reviewer D**

**Comment 1:** To begin with some general concerns/remarks regarding the whole of the paper.

- May I mention that throughout the manuscript there are some grammatical errors which in some cases even affect the meaning. i.e. lines 79 (fourteen-fold), 202 (negative) 246 (lesions), 254 (consolidated)

**Reply 1:** We agree with your observations. The introduction has been shortened based on your comments, and "fourteen-fold" in the introduction has been deleted. The evolution of CT manifestations has been rewritten, and "negative" has been deleted. In addition, "some lesions demonstrated single or multiple lung consolidation" has been replaced by "other common CT manifestation was single or multiple lung consolidation". Moreover, "consolidated" has been replaced as "consolidation".

**Changes in the text:** The sentence "other common CT manifestation was single or multiple lung consolidation" is on lines 201-202, page 10 of the revised manuscript. Moreover, "consolidated" is replaced as "consolidation", which is on line 209, page10 of the revised manuscript.

**Comment 2:** The continuous use of the word 'and' or comma (,) creates lengthy sentences which are difficult to follow. i.e. Lines 105-108, 231-235

**Reply 2:** Thanks for your suggestion. The paragraph, "The collected data included epidemiological history (history of Wuhan residence or exposure), demographic data, clinical symptoms, and physical signs at the time of clinic visit, complications, laboratory test indicators, dynamic evolving characteristics of chest CT, and clinical

outcomes." has been replaced with "The collected data included epidemiological history (history of Wuhan residence or exposure), clinical data (demographic data, clinical symptoms, physical signs, laboratory test indicators, complications, and clinical outcomes) and image data (dynamic evolving characteristics of chest CT)." It greatly endangers the public health security and human life. Early diagnosis and early quarantine and treatment are important methods to stop the spread of the epidemic. Clinically, some COVID-19 patients lack a clear history of epidemiological exposure, and clinical symptoms and signs and routine laboratory tests lack specificity for its clinical diagnosis." has been replaced with, "posing a significant threat to public health security. Early diagnosis and isolated treatment are important ways of controlling the epidemic. However, it is difficult to make a clinical diagnosis of COVID-19 because some infected patients lack a clear history of epidemiological exposure and clinical features as well as specific laboratory indicators."

**Changes in the text:** The revised paragraph "The collected data included epidemiological history (history of Wuhan residence or exposure), clinical data (demographic data, clinical symptoms, physical signs, laboratory test indicators, complications, and clinical outcomes) and image data (dynamic evolving characteristics of chest CT)," is shown in the section of clinical information collection, which is on lines 85-88, page 4 of the revised manuscript. In addition, the revised paragraph "posing a significant threat to public health security. Early diagnosis and isolated treatment are important ways of controlling the epidemic. However, it is difficult to make a clinical diagnosis of COVID-19 because some infected patients lack a clear history of epidemiological exposure and clinical features as well as specific laboratory indicators," is shown in the section of discussion, which is on lines 186-190, page 9 of the revised manuscript.

**Comment 3:** The abstract is slightly longer than allowed (360 words) as it should be less than 300

**Reply 3:** The number of words in the abstract has been reduced to less than 300, as you suggested.

**Changes in the text:** The revised abstract is on lines 29-53, pages 2-3 of the revised manuscript.

**Comment 4:** Although the inclusion criteria are clear, it is not clear, at least to me, how the 76 patients selected initially (line 96) were narrowed to 22 (line 117)

**Reply 4:** As of February 15, 2020, the majority of inpatients (51/76, 67.1%) diagnosed with COVID-19 at the Taizhou Enze Hospital came from Wenling city. Taizhou city includes four counties (Tiantai, Xianju, Sanmeng and Yuhuan) and two county-level cities (Wenling and Linhai). Wenling is an economically developed county-level city, and many people are engaged in business in Wuhan city; therefore, Wenling contributed to the majority of COVID-19 cases in Taizhou city. Taizhou Enze Hospital is a center for infectious-disease control and prevention in Taizhou city, and all COVID-19 patients in Taizhou city must be transferred to Taizhou Enze Hospital for further treatment. However, the initial chest CT examinations of these

COVID-19 cases transferred from Wenling were performed in the First People's Hospital of Wenling. These important imaging data could not be obtained in the present study, so these COVID-19 cases were excluded from the study. In addition, as of February 15, 2020, three other COVID-19 patients in Linhai city were excluded from the study because these three patients merely underwent the first CT examination due to a short hospital stay.

**Changes in the text:** None.

**Comment 5:** In the laboratory findings paragraph (128-133), the medical terminology (lymphopenia, thrombopenia etc.) could be used rather than describing the values.

**Reply 5:** Thank you for your suggestion. The paragraph, "Eleven patients had lymphocyte below the normal range, 4 patients had platelet below the normal range, and 3 patients had mildly decreased white blood cell counts and neutrophil counts. In addition, 12 patients had CRP values higher than normal, and 7 patients had ESR higher than normal; 8 patients had decreased albumin levels; and 8 patients had myoglobin levels below normal value (Table 2)," has been replaced with, "Eleven patients had lymphopenia, 4 patients had thrombopenia, and 3 patients had leukopenia and neutropenia. Besides, 8 patients had hypoalbuminemia, and 8 patients had myoglobinemia. In addition, 12 patients had CRP values higher than normal, and 7 patients had an ESR higher than normal (Table 2)."

**Changes in the text:** The changes in the text are shown in the section of laboratory information (section 2), which are on lines 108-111, page 5 of the revised manuscript.

**Comment 6:** Beginning in line 156 and until 203 all these subcategories (3.3, 3.3.1 etc.) are lost in the text and should be somehow highlighted/underlined. In this piece of text, explaining the evolution of the CT manifestations, it would better to concentrate on the important findings rather than listing every finding, which can be found in the tables.

**Reply 6:** We thank you for your professional comments on our study and agree with your suggestion. The evolution of important CT manifestations has been rewritten as you suggested. We hope the revision is acceptable.

**Changes in the text:** The changes in the text are shown in the section of evolution of main CT image manifestations (section 3.3), which are on lines 133-144, pages 6-7 of the revised manuscript.

**Comment 7:** Moreover, writing the percentage next to every number is superfluous as the same cohort of patients is used throughout the manuscript.

**Reply 7:** We agree with your suggestion and have removed the percentage next to every number.

**Changes in the text:** The percentage next to every number in the section of results has been removed (see pages 5-7 of the revised manuscript).

**Comment 8:** In the discussion section, the results are repeated (lines 266-270) unnecessarily

**Reply 8:** The sentence, "Further investigation revealed that the median time for the appearance of early imaging manifestations was 3 days (1–8 days) after onset, the median time of the progressing stage was 7 days (4–17 days) after onset, the median time of the recovery stage was 10 days (8–14 days) after onset, and the median time of dissipation period was 19.5 days (11–25 days) after onset," has been deleted as you suggested.

**Changes in the text:** The unnecessarily repeated sentence in the discussion section has been removed (see page 10 of the revised manuscript).

**Comment 9:** My last but for me the most important remark would be that I could not find any information about the correlation, if one exists, between the radiological and clinical findings of these 22 patients.

**Reply 9:** In the present study, we found a correlation between patients' clinical status (fever and cough) and the CT results. However, the correlations between laboratory data and the CT results were not observed. For 19 patients with fever as the initial symptom, the median duration of the fever was 4 days (2-19 days). Of these patients, 14 patients experienced a disappearance of fever during the progressing stage (stage II), 4 patients experienced a disappearance of fever during the recovery stage (stage III), and 1 patient experienced a disappearance of fever during the dissipation stage (stage IV), which may indicate that image change has some lag when compared with fever change. For 6 patients with a cough as the initial symptom, the median duration of the cough was 13.5 days (10-20 days). All 6 patients experienced a disappearance of the cough at the dissipation stage (stage IV). The longer duration of a cough may be associated with the stimulation of residual inflammation. These findings indicate that the imaging stages based on the CT results correlate with clinical status and may aid in assessing disease progression.

**Changes in the text:** We have added the suggested revisions regarding the correlations between clinical and radiological findings. The changes in the text are shown in the section of correlations between clinical and radiological findings (section 4), which are on lines 164-174, page 8 of the revised manuscript.