

Dear editors,

*We have revised the paper as your requested. The details are as follows:*

*Words in blue color are your requests. And words in black color are my answers.*

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Dear Authors, Thank you for your contribution. I personally enjoyed reading this study. Authors have compared a preCOVID era and COIVD era changes. This is an observation and difficult to have conclude any concrete results. But this is the challenge we all are facing due patients staying in home and delaying in seeking care. This is applicable in various emergency conditions like MI, acute leukemia, dialysis dependent ESRD. I have few suggestions which is based on my individual experience and the few of the recent publications which could improve the quality of this paper and improve the standards for our readers if considered for acceptance. Please make the changes pointwise so that I could review them for the edits. Also, considering adding the references quoted as many papers came up recently so discussion needs to be little modified based on this suggestions. Looking forward to see your review soon.

1.Pediatric case series: all patient presented with delay in diagnosis: [Ref: Snapiri O, Rosenberg Danziger C, Krause I, et al. Delayed diagnosis of paediatric appendicitis during the COVID-19 pandemic [published online ahead of print, 2020 May 27]. Acta Paediatr. 2020;10.1111/apa.15376. doi:10.1111/apa.15376]

*A: Thank you for the recommendation. We have noticed that reports about pediatric appendicitis. We rechecked pediatric cases from our hospital and added data at table 2(new version). Our hospital has relatively few pediatric surgery patients because some patients are inclined to children's hospitals at Hangzhou or Shanghai. As mentioned in the introduction section, Jiaxing locates in the center of Hangzhou and Shanghai. It's only an hour's drive to these cities. Our results about pediatric appendicitis may be influenced due to a small sample size and selection bias. We wonder which one is better, new version or old version? Anyway, we added discussion about pediatric appendicitis in the discussion section. ( added words are in red color)*

#### New version

*Results Appendectomies patient characteristics comparison between 2019 and 2020*

There was no significant difference in age or regional distribution of patients or **pediatric perforated appendicitis ratio** between 2019 and 2020.

Table 2 The characteristics comparison of appendectomies patients between 2019 and 2020

Period	2019	2020	$\chi^2/ t$	P
Age	37.7±19.8	40.9±19.9	1.13	0.26
Male/female	63/58	54/27	4.244	0.039
<b>Children/adults</b>	<b>19/102</b>	<b>12/69</b>	<b>0.029</b>	<b>0.864</b>
Local/nonlocal	116/5	79/2	0.058	0.81
Suppurative appendicitis(male/female)	58/53	40/26	1.169	0.28

<b>Perforated appendicitis(male/female)</b>	5/5	14/1	6.343	0.012
<b>Suppurative/perforated pediatric appendicitis</b>	18/1	10/2	1.063	0.302
<b>Suppurative/perforated appendicitis</b>	111/10	66/15	4.704	0.03

*Old version*

Table 2. The characteristics comparison of appendectomies patients between 2019 and 2020

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*Discussion (1<sup>st</sup> paragraph)*

In the early stage of the COVID-19 pandemic, acute appendicitis was more common in men, and the proportion of perforated appendicitis was higher in our research. Men were reported more often with perforated appendicitis [5], which is consistent with the conclusion of our study. Chinese people are used to returning to their hometown during the Spring Festival holiday, so appendicitis patients in this area are mainly local residents during February and March. **Holiday and traffic restrictions may be reasons for the declined number of appendicitis patients. The significant decrease in the number of appendicitis patients was also found in other cities such as Jerusalem, Israel [6], where there is no holiday or traffic restriction. Patients' willingness to go out and see a doctor was also affected by the pandemic [7]. And it could be a main reason for declined number of appendicitis cases since the incidence of acute appendicitis itself should not be affected by an outbreak of respiratory disease.** Some patients with mild symptoms may have achieved relief by taking pills themselves. However, most patients should be treated under physician supervision, as delayed medical treatment can aggravate appendicitis progression [8]. Our research shows that the chief complaint duration for perforated appendicitis patients was longer, accompanied by a higher WBC count and neutrophil ratio. **It has been noted that delayed diagnosis and higher complication rates in pediatric appendicitis cases during the COVID-19 outbreak [9]. Our results show no significant differences of pediatric perforated appendicitis ratio between 2019 and 2020. One of the main reasons is that local parents tend to go to children's hospitals for surgery. Anyway, we should pay more attention to patients, especially children and males with prolonged symptoms during the COVID-19 pandemic, since delay in diagnosis and treatment may become a big threat as COVID-19 itself.**

*Old version (1<sup>st</sup> paragraph)*

In the early stage of the COVID-19 pandemic, acute appendicitis was more common in men, and the proportion of perforated appendicitis was higher in our research. Chinese people are used to returning to their hometown during the Spring Festival holiday, so appendicitis patients in this area are mainly local residents during

February and March. ~~During the initial outbreak of COVID-19, the local government took strict measures to reduce crowding, thus reducing the chance of human to human transmission.~~ Due to the holiday and restrictions, the number of appendicitis patients was reduced. Patients' willingness to go out and see a doctor was also affected by the pandemic[5]. Some patients with mild symptoms may have achieved relief by taking pills themselves. However, most patients should be treated under physician supervision, as delayed medical treatment can aggravate appendicitis progression[6]. Our research shows that the chief complaint duration for perforated appendicitis patients was longer, accompanied by a higher WBC count and neutrophil ratio. We should pay more attention to patients with prolonged symptoms during the COVID-19 pandemic. (Men were reported more often with perforated appendicitis[7], which is consistent with the conclusion of our study).

2. Please consider adding a panel of figures showing imaging findings or operative findings, clinical images.

A: We have added figures and “Clinical images from simple group and complex group (Fig.6)” in results section

Added:

*Clinical images from simple group and complex group (Fig.6)*

Figure 6 (A1, A2, A3) was selected from a 20 years old male with chief complaint of abdominal pain for 4 hours in February 2020. He was arranged to simple group and postoperative diagnosis was suppurative appendicitis. Figure 6 (B1, B2, B3) was selected from a 38 years old male with chief complaint of abdominal pain for 72 hours in March 2020. He was arranged to complex group and postoperative diagnosis was perforated appendicitis.

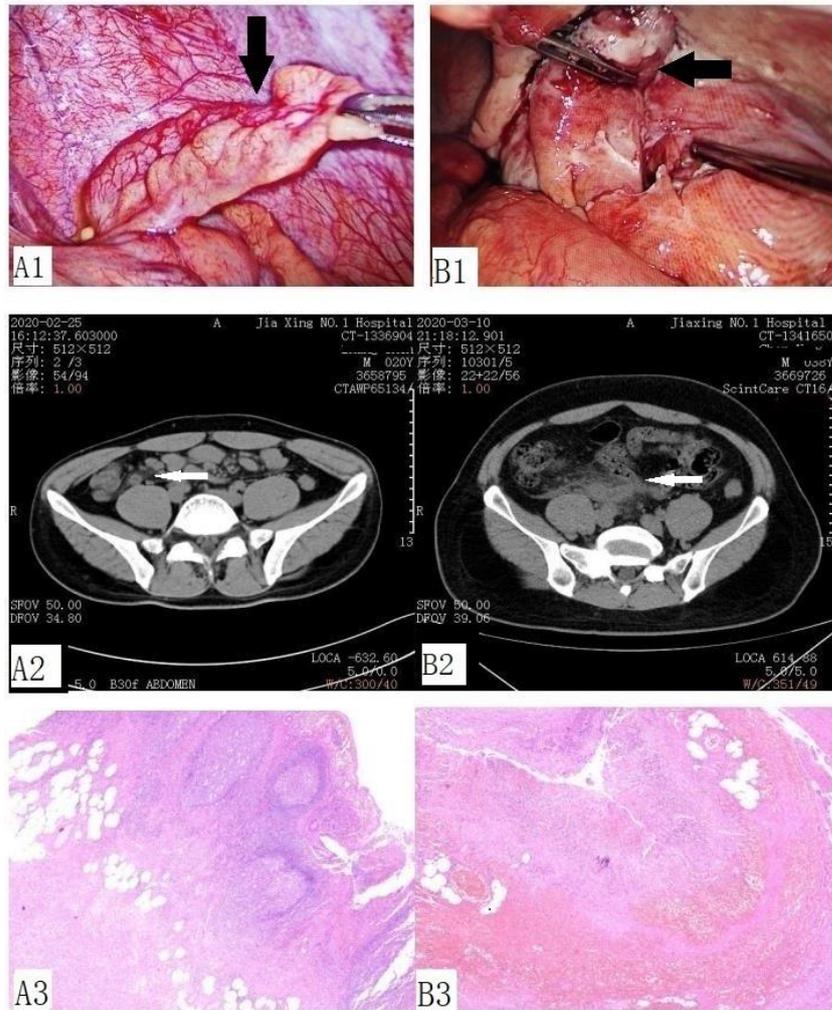


Fig.6 Clinical images from simple group and complex group

A. Simple group; B. Complex group. Operative photo: A1. Thickened appendix (black arrow) with slightly swollen mesentery. B1. Thickened and congestive appendix (black arrow) with exudation. The distal end of appendix is necrosis with purplish black color. Abdominal CT scan: A2. Slightly thickened appendix (white arrow) with exudation B2. Appendix is remarkably thickened and the boundary is obscure. Pathological section( $\times 40$ ): A3. Structure of appendix remains. The whole layer of appendix indicates obvious infiltration of neutrophils. B3 Structure of appendix disappears. The whole layer of appendix shows hemorrhage and necrosis with infiltration of neutrophils.

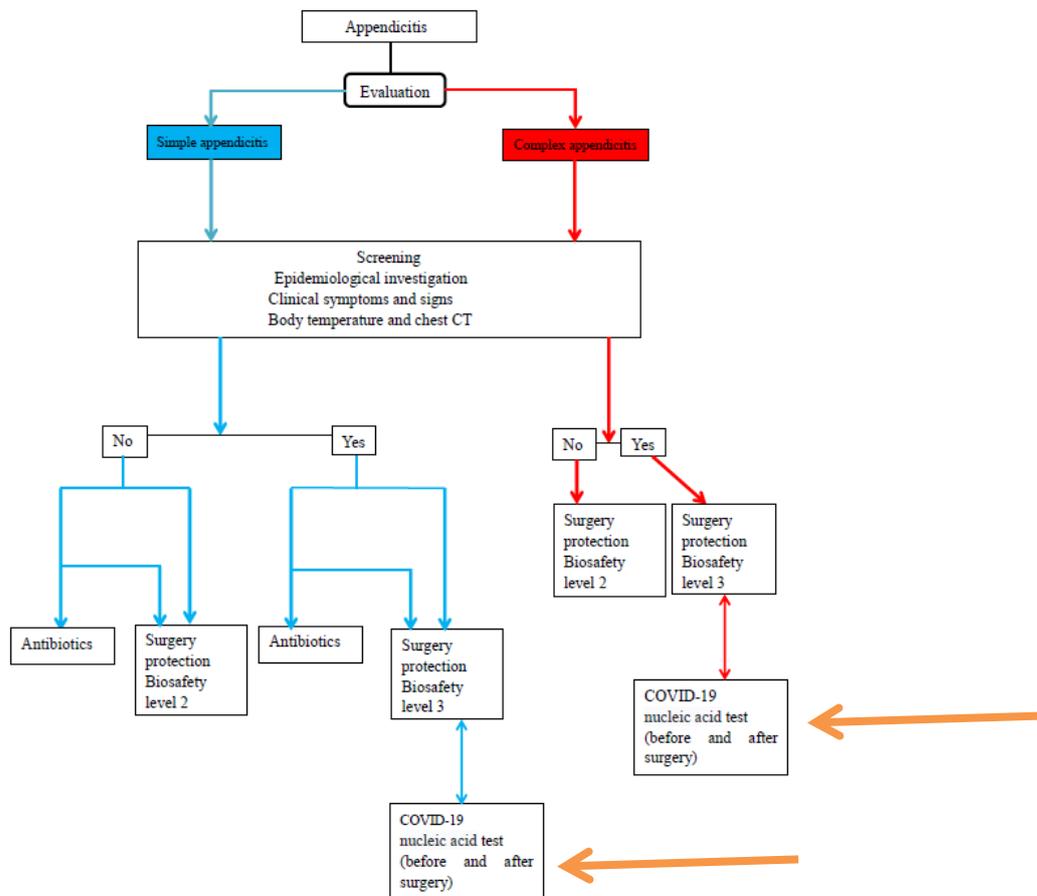
3.Result section: After screening, 6 patients were identified as unqualified and the nucleic acid tests were negative. [ I couldnot understand, why these patient were excluded, please can you rewrite this sentence for my better understanding]

A: Revised: After screening, 6 patients were identified as unqualified due to fever and then referred to the COVID-19 expert group. The results of the nucleic acid test were negative.

4. So, all 90 patients were COVID=19 negative, just wondering if I missed somewhere in the draft. Did we check for COVID-19, just need a clarification in the methodology? ( Some places did COVID-19 rapid test before taking patients for surgery 9 personal experience, what is the protocol at author's center)

A: The supply of nucleic acid detection kits was in shortage at the early stage of pandemic. Instead of nucleic acid detection for all cases, we only tested nucleic acid for these 6 cases. All 90 patients were conducted COVID-19 screening including epidemiological history, clinical signs and symptoms of respiratory tract infection, body temperature, chest CT, et al. If any of these results is abnormal, COVID-19 nucleic acid test was performed.

Our center routinely performs preoperative nucleic acid testing at present. The screening was conducted in a very period where supply of nucleic acid kits is in shortage. It could be better understanding after reading our flowchart (yellow arrow ).



5. There is a small interesting survey which authors should consider mentioning at some place just a brief 3-4 lines. This is about change in practice attitude of the surgeons [Please see Refer: Kelly ME, Murphy E, Bolger JC, Cahill RA. COVID-19 and the treatment of acute appendicitis in Ireland: a new era or short-term pivot? *Colorectal Dis.* 2020; 22(6):648-649. doi:10.1111/codi.15141]

A: We have cited the reference in the 2nd paragraph of discussion section. This part mainly discussed about pandemic influence on the accuracy of a surgeon's judgment. Your recommended literature is helpful and reminds us conservative treatment may result in different consequence. Thank you. We partially agree with authors'

*conclusion: “As our infection curves flatten and international professional societies update guidance to support the re-introduction of normal surgery (with the added protection of personal protection equipment and use of antiviral filters), we will be resuming our prior practice”. We resume that: “As the epidemic is becoming normalized, more specific measures for conservative treatment is required for better recovery and timely re-evaluation is necessary for patients under conservative treatment”.*

Discussion(2<sup>nd</sup> paragraph )

The accuracy of a surgeon’s judgment regarding the surgical indications of appendicitis may be influenced by the COVID-19 pandemic. When major supplies and personnel were diverted to departments such as the intensive care unit (ICU), infection prevention, and pulmonology for COVID-19 treatment, the other hospital departments inevitably faced difficulties such as a shortage of protective equipment, a lack of isolation wards, and a shortage of available medical staff [10]. Sometimes, it is difficult to differentiate between the inflamed and perforated appendix based on abdominal palpation, while it has been proven that US and CT imaging are very useful in the early and accurate diagnosis of perforated appendicitis [11]. The postoperative diagnosis was most often consistent with the preoperative assessment in our complex group, and only one case of perforated appendicitis occurred in the simple group. **Besides, surgeons are inclined to select conservative approach during pandemic [12].** We agree with Collard et al [13] that the non-surgical treatment as the preferred alternative for adults with simple acute appendicitis during the initial stage of the COVID-19 pandemic. **However, a survey in Ireland [12] shows that 54% acute appendicitis patients in the conservative care group had on-going discomfort on follow-up post-discharge. 63% would choose up-front appendicectomy if they could decide again. As the epidemic is becoming normalized, more specific measures for conservative treatment is required for better recovery and timely re-evaluation is necessary for patients under conservative treatment.**

Old version (2<sup>nd</sup> paragraph )

The accuracy of a surgeon’s judgment regarding the surgical indications of appendicitis may be influenced by the COVID-19 pandemic. When major supplies and personnel were diverted to departments such as the intensive care unit (ICU), infection prevention, and pulmonology for COVID-19 treatment, the other hospital departments inevitably faced difficulties such as a shortage of protective equipment, a lack of isolation wards, and a shortage of available medical staff [8]. ~~Our emergency preoperative management process was useful for doctors by standardizing emergency screening and assessing the operative indications of acute appendicitis so that patients in need of surgery could be treated within an appropriate timeframe.~~ Sometimes, it is difficult to differentiate between the inflamed and perforated appendix based on abdominal palpation, while it has been proven that US and CT imaging are very useful in the early and accurate diagnosis of perforated appendicitis [9]. The postoperative diagnosis was most often consistent with the preoperative assessment in

our complex group, and only one case of perforated appendicitis occurred in the simple group. We agree with Collard et al.[10] that the non-surgical treatment as the preferred alternative for adults with simple acute appendicitis during the initial stage of the COVID-19 pandemic. ~~Nine patients were successfully cured with medication therapy in our research. Besides, the shunt used in both the simple and complex groups reduced the pressure for emergency surgery preparation. Although the preoperative assessment time was longer in 2020 than in 2019, the surgical outcomes such as operating time and complications had no change between 2019 and 2020.~~

6. There is interesting study by Tankel et al who actually found that medical management at home reduced subsequent admissions. Authors might discuss this as well considering the fact that delaying the care by being in home may lead to more complication in appendicitis at east in certain proportion of patient.[Ref: Tankel J, Keinan A, Blich O, et al. The Decreasing Incidence of Acute Appendicitis During COVID-19: A Retrospective Multi-centre Study [published online ahead of print, 2020 May 26]. World J Surg. 2020;1-6. doi:10.1007/s00268-020-05599-8]

A: Thank you. We revised “Due to the holiday and restrictions, the number of appendicitis patients was reduced” to “Holiday and traffic restrictions may be reasons for the declined number of appendicitis patients. The significant decrease in the number of appendicitis patients was also found in other cities such as Jerusalem, Israel [6], where there is no holiday or traffic restriction.” (*1<sup>st</sup> paragraph*)

7. In discussion, please add the delay in care and challenges which other health care specialties are suffering [Please Ref to following suggested papers\*\* Sahu KK, Siddiqui AD, Cerny J. COVID-19 pandemic and impact on hematopoietic stem cell transplantation [published online ahead of print, 2020 May 4]. Bone Marrow Transplant. 2020;1-3.\*\* Jindal V, Sahu KK, Gaikazian S, Siddiqui AD, Jaiyesimi I. Cancer treatment during COVID-19 pandemic. Med Oncol. 2020;37(7):58. Published 2020 May 29

A: Thank you. We added the references and revised the last paragraph. We also added a reference about dialysis dependent ESRD.

[20] Shen Q , Wang M , Che R , et al. Consensus recommendations for the care of children receiving chronic dialysis in association with the COVID-19 epidemic. Pediatric Nephrology. Pediatr Nephrol. 2020 Apr 24 : 1–7. [PMID: 3233285 doi: 10.1007/s00467-020-04555-x]

#### Discussion (last paragraph )

Our management of acute appendicitis was a coping strategy in the early stages of the pandemic when little was known about COVID-19. In addition, our effective perioperative management was based on the strict control of relevant populations of COVID-19 patients by local disease control and prevention centers<sup>[18]</sup>. **The delay in care and challenges we all are facing not only in emergency surgeries, but also in other health care specialties like cancer<sup>[19]</sup>, dialysis dependent end-stage renal disease<sup>[20]</sup>, hematopoietic stem cell transplantation<sup>[21]</sup> et al.** We should make our clinical management compatible with the challenges and threats of this pandemic while trying to achieve the optimal therapeutic effect.

Old version (last paragraph)

~~Our management of acute appendicitis was a coping strategy in the early stages of the pandemic when little was known about COVID-19. Our research shows no nosocomial infection detected through screening and treatment, and no delay in treatment was observed. All patients received effective treatment, with no increase in hospital stay length or hospital expenses. In addition, our effective perioperative management was based on the strict control of relevant populations of COVID-19 patients by local disease control and prevention centers<sup>[21]</sup>. Effective prevention and control during a pandemic require the full attention of public health officials, local governments, the private sector, and all citizens<sup>[22]</sup>. The pandemic in Jiaying is gradually stabilizing, but clusters of outbreaks and nosocomial infections have reemerged in some Chinese cities such as Beijing, Haerbing and Jiling. The favorable geographical position of Jiaying not only results in developed transportation and economy, but also a much higher risk of COVID-19 recurrence. With a further understanding of COVID-19, we should make our clinical management compatible with the challenges and threats of this pandemic while trying to achieve the optimal therapeutic effect.~~

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors described their experiences during the COVID-19 pandemic in 90 acute appendicitis cases. When I searched the literature, I found that pediatric acute appendicitis cases were mostly presented during the COVID-19 outbreak. The authors wrote the discussion section too long. The authors should reduce the discussion section by at least 30%.

A: *The paper was rechecked by a native speaker in order to improve language quality.*

*Thank you for the recommendation. We have noticed that reports about pediatric appendicitis. We rechecked pediatric cases from our hospital and added data at table 2(new version). Our hospital has relatively few pediatric surgery patients because some patients are inclined to children's hospitals at Hangzhou or Shanghai. As mentioned in the introduction section, Jiaying locates in the center of Hangzhou and Shanghai. It's only an hour's drive to these cities. Our results about pediatric appendicitis may be influenced due to a small sample size and selection bias. We wonder which one is better, new version or old version? Anyway, we added discussion about pediatric appendicitis in the discussion section. ( added words are in red color)*

*We have reduced word counts from 1153 to 893in discussion section.*

New version

*Results Appendectomies patient characteristics comparison between 2019 and 2020*

*There was no significant difference in age or regional distribution of patients or **pediatric perforated appendicitis ratio** between 2019 and 2020.*

*Table 2 The characteristics comparison of appendectomies patients between 2019 and 2020*

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### Discussion (1<sup>st</sup> paragraph)

Our research shows that the chief complaint duration for perforated appendicitis patients was longer, accompanied by a higher WBC count and neutrophil ratio. **It has been noted that delayed diagnosis and higher complication rates in pediatric appendicitis cases during the COVID-19 outbreak [9]. Our results show no significant differences of pediatric perforated appendicitis ratio between 2019 and 2020. One of the main reasons is that local parents tend to go to children's hospitals for surgery. Anyway, we should pay more attention to patients, especially children and males with prolonged symptoms during the COVID-19 pandemic, since delay in diagnosis and treatment may become a big threat as COVID-19 itself.**

### **Editorial Office's comments**

Science Editor:

*Issues raised:*

(1) The "Author Contributions" section is missing. Please provide the author contributions;

A: *We added in title page: "Author contributions: Yuan Zhou and Lusha Cen contributes equally to this manuscript. Yuan Zhou participated in study design, drafted the manuscript, was involved in data collection, and assisted with data analysis; Lusha Cen participated in design, was involved in data collection, and supervision of the study; all authors read and approved the final version of the manuscript."*

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

A: *We have uploaded approval document.*

(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

A: *We have uploaded figures(1-6) using PowerPoint.*

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

A: *We have added the section at the end of text.*

**Editorial Office Director:** I have checked the comments written by the science editor. The authors described their experiences during the COVID-19 pandemic in 90 acute

appendicitis cases. Please don't include any \*, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as a<sup>P</sup> < 0.05, b<sup>P</sup> < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, c<sup>P</sup> < 0.05 and d<sup>P</sup> < 0.01 are used, and a third series of P values is expressed as e<sup>P</sup> < 0.05 and f<sup>P</sup> < 0.01.

A: We have deleted "P > 0.05". We have replaced "\*" with superscript letters in Fig.2-5 and results section.

*At last, I would like to appreciate your guidance and say thank you for all your recommendations. You are so nice that have such patience to guide me how to revise my paper. Since time is limited, especially for clinicians during the epidemic. I wonder if my revised version could meet your requirements. Please feel free to let me know if any further changes required. I am looking forward to seeing you your reply.*