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Reviewer A

The work entitled "Secondary infection in severe and critical COVID-19 patients in China: a multicenter retrospective study" presents important results about risk factors for secondary infections and the role of it in clinical outcomes. I believe that this work is going to contribute to the current understanding of COVID-19 in severe and critical cases after minor revisions.

We would like to thank the Reviewer for the valuable comments and suggestions. Please find the point-by-point responses below.

Comment 1: In lines 119-122: This information does not need to be described here, only "were extracted... in each hospital". Authors informations must be moved and adapted to "authors contributions" section.

Reply 1: Thanks for the advice. We totally agree with your opinion.

We deleted the sentences "Ling Sang and Bin Song in Jinyintan Hospital; Yin Xi and Ying Pan in Union West Hospital; Zhimin Lin and Chang-an Li in The First Affiliated Hospital of Guangzhou Medical University cross-checked for data accuracy" as you suggested.

And we modify the text as: The clinical data, including patient demographics, comorbidities, laboratory findings, treatment, pathogen culture results, and clinical outcomes were extracted from the electronic records in each hospital, subsequently cross-checked for data accuracy by two independent intensivists (see page 6, line 125-128 in the revise version of our manuscript).

Comment 2: In line 151: Please, make it clearer here why these 190 patients were included in this study, which criteria they accomplished.

Reply 2: Thank you for the comment. The inclusion criteria have been described in detail in the “Method” section. According to the suggestion of the Reviewer, we have modified our text as advised: " During the study period, a total of 190 patients infected with SARS-CoV-2 who met the severe or critical criteria defined by the Chinese guidelines (11) were enrolled."(see page8, line 155-156 in the revised version of our manuscript).

Comment 3: In lines 157-159: Please, describe briefly how all of these samples are distributed among only 190 patients. How many samples for patient on average?

Reply 3: Thank you for the comment. To avoid redundant description, instead of text, we used tables to enumerate the samples data. The distribution of the specimens was described in detail in table 2. According to the suggestion of the Reviewer, we have modified our text as " Among the 190 patients, 1929 specimens were collected (10.2 specimens per patient on average), and 1104 positive cultures (57.2%) were obtained." (see page8, line 162-163 in the revised version of our manuscript).

Comment 4: In discussion: A phragraph talking about microbial co-infections with SARS-CoV-2 in the respiratory tract must be added, mentioning other works that detected co-infections with it and making a comparison with their findings.

Reply 4: Thanks for the advice. According to the suggestion of the Reviewer, we added a paragraph talking about microbial co-infections with SARS-CoV-2 in the respiratory tract.

We added the following text: The coinfection of the SARS-CoV-2 with other microorganisms, which make the diagnosis and treatment more difficult and contribute to the poor prognosis in COVID-19 patients, is crucial in the management of COVID-19 patients (12). However, the true prevalence of coinfection in such patients remained largely unclear. Kirstine K.et al. observed a high frequency of secondary infections among hospitalized SARS-CoV-2-positive patients. Among 162 SARS-CoV-2-positive hospitalized patients, 31 secondary infections were diagnosed including five viral co-infections, 24 bacterial infections, and three fungal infections, and antibiotic or antifungal treatment was administered in 71 (43.8%) patients. They also found that hospital-acquired bacterial and fungal infections were more frequent among ICU patients than other patients (36.6% vs. 1.7%). (13). However, the prevalence of pulmonary microbial co-infections is modest among COVID-19 patients upon admission to ICU in Region Zealand in Denmark(14). (see page 12, line 226 in the revised version of our manuscript).

Comment 5: In conclusion: This study have more important results that must be also mentioned here beside these, as well as they meaning.

Reply 5: Thanks for the advice. According to the suggestion of the Reviewer, we have modified our text as advised:

In a retrospective cohort of severe and critical COVID-19 patients admitted to ICUs at the early stage the COVID-19 in China, the prevalence of secondary infection was high, particularly CRE and MDR bacteria, resulting in poor clinical outcomes.

Prevalence of secondary infection in COVID-19 patients may vary across different regions, which reveal matching of demand and supply of healthcare resources affect the prevalence of secondary infection.
(see page 15, line 300 in the revised version of our manuscript).

Reviewer B

A fluently written article on an interesting, contemporary issue. This entails an observational study (retrospective cohort) from 3 ICUs (at Guangzhou and Wuhan hospitals).
We would like to thank the Reviewer for the valuable comments and suggestions. Please find the point-by-point responses below.

Comments which should be taken into consideration before final manuscript acceptance:

Comment 1: line 115: criteria for severe/ critical COVID-19 according to Chinese guidelines, briefly to be clarified
Reply 1: Thanks for the advice. We will add the description of the criteria for severe/ critical COVID-19 according to Chinese guidelines as follow: “The disease is defined as severe type if the patient met one of the following conditions: respiratory distress, respiratory rate ≧30bpm or SPO2 ≦93% on room air or PaO2/FiO2 ≦300mmHg. The disease in defined as critical type if the patient met one of the following conditions: respiratory failure occurs and requires mechanical ventilation, shock, other organ dysfunction needing intensive care unit monitoring and treatment. The above two types of patients will be included in the analysis”(see page 6, line 117 in the revised version of our manuscript).

Comment 2: line 127: decision for microbiological cultivation by attending physician: did this also include possible routine screening for colonization or was that only confined to sampling on suspicion of infection ? Were all diagnoses relying on routine microbiological culture or were other detection methods also allowed (e.g. PCR)?
Reply 2: Thank you for the comment. In view of the COVID19 pandemic, at that time the decision to collect specimens for microbiologcal culture were based on the needs of clinical diagnosis and treatment of coinfection, rather than routine screening for colonization. The diagnosis of co-infection is relied on the routine microbial culture. PCR and other pathogenic microorganism detection methods were not included in this study.

Comment 3: line 131: limitation of the stated definition of infection is that microbiological results do not relate to clinical criteria: there is no mentioning of clinical suspicion or worsening biomarkers, or deteriorating clinical status (e.g septic shock) and thus definition is not specific to discriminate true infection from colonization; e.g tracheal aspirates with Candida albicans as pathogen or finding as fungal colonizer in these ICU patients?; Likewise how were positive blood cultures with coagulase negative Stapylococcus rated; what were the criteria to designate these as infectious episodes rather than skin colonizers recovered from blood culture ?. This is a limitation for the interpretation of frequencies of "secondary infection" and thus the "precision" reporting of the findings. This may impact on how sentences need phrasing throughout in the manuscript and should be discussed in the text as a limitation of the study design.

Reply 3: Thank you for your careful reading and valuable comments. We totally agree with the reviewer and discuss this as a limitation in our revised manuscirpt. We added a paragraph as follow: “

Our study has some limitations. Firstly, this is a retrospective study. Selection bias may affect the results, further prospective studies are needed to assess the true incidence of secondary infection in COVID-19 patients. Secondly, the definition of secondary infection is based on the microbiological culture results. The clinical data may not be sufficient to differentiae between infection and colonization in a retrospective study, which may influence the interpretation of frequencies of "secondary infection". However, the results of this study is still reasonably ‘representative’ and reflected the real situation during the early stage of the COVID-19.

”(see page 15, line 292 in the revised version of our manuscript).

Comment 4: 153: "severe" infection from "critical" infection. What were the definitions for categorization ?

Reply 4: Thank you for the comment. The classification of severe and critical type is based on the Diagnosis and Treatment of COVID-19 guidelines published by the National Health Commission of China. We added a brief description in the "Method" section. You can see the illustration in Reply 1.

Comment 5: 206: " ...the first study to describe the epidemiology of secondary infections in severe, critical COVID-19 patients ?" Is this phrase meant in the local context ? Reference is made to likewise surveys in other regions e.g. Baskaran et al; The current literature also states studies from China. Please countercheck and clarify.

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Reply 5: Thank you for the comment. We deleted the sentences you mentioned and modified the sentence as follow: "In this work we evaluate the epidemiology of secondary infections in severe and critical COVID-19 patients"(see page 11, line 211 in the revised version of our manuscript).

Other remarks

Comment 6: Were the isolated organisms and associated resistance pattern representative of the local hospital/ ICU ward microbiological ecology, as also encountered in non-COVID 19 patients ?

Reply 6: Thank you for the comment. The critical COVID-19 patients were treated in the designated hospitals and independent wards in China. No other critical patients were admitted to the ICUs of these 3 hospitals in our study at the same time.

Comment 7: The weakness, limitations of the retrospective study design (potential biases) should be mentioned in the discussion section.

Reply 7: Thanks for the advice. We added a paragraph to discuss limitations. You can see the illustration in Reply 3.