Peer Review File

Review Comments:

Reviewer A:

This paper proposed an interesting insight into the relationship between COVID-19 and cardiac injury in the context of a hospital in Zhuhai, China, in a region not so badly hit by SARS-CoV-2. The paper is quite well structured and concise. However, some minor revisions could be useful in order to improve the manuscript.

Comment 1: To increase readability, dividing paragraphs using the indentation may be useful, and full English revision is needed.

Reply 1: We have divided paragraphs using the indentation and rechecked the wordings of our manuscript as advised.

Changes in the text: The format of each paragraph and full English revision of the main text, figures and tables.

Comment 2: In the introduction, it could be useful and interesting adding insights on the epidemiological background in Zhuhai, China, in the period of the study, in order to assess the hospital context and patients' origin.

Reply 2: Thank you so much for your advice. We have added epidemiological background information of our city in the period of the study in the introduction.

Changes in the text: In the introduction, we have added "Zhuhai city, as one of the special economic zones in China, is located in south-central Guangdong province. As the only designated hospital of COVID-19 in Zhuhai, we started receiving COVID-19 patients on January 17th. As of March 10th, all the patients were cured except for one old male patient died from COVID-19 though extracorporeal membrane oxygenation (ECMO) treatment had been used. Patients were all imported cases from Hubei Province, China, or cases who had close contact with them." **(see Page 5, line 86-91)**

Comment 3: In the results, it should be specified how many patients undergo electrocardiogram or echocardiography. It could also be useful to make some considerations on the sample size and to give some more details on the logistic model in supplementary materials (analysis on residuals, outliers, etc.).

Reply 3: In order to reduce the risk of nosocomial infection, we performed electrocardiogram and electrocardiography only for patients who were suspected to experience cardiac injury based on clinical manifestation. A total of 20(21.5%) patients had received transthoracic echocardiography and 27(29.0%) had received electrocardiogram.

We examined pearson residuals against each predictor. Both predictors are showing linear trend with Pearson residuals.
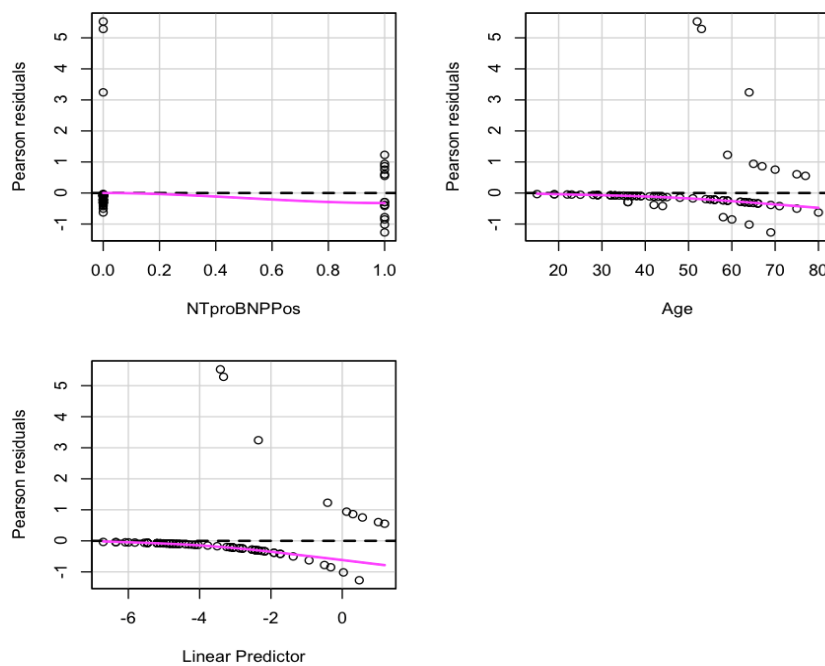
Cook's distance is used to evaluate the influence of each sample. Sample number 27 and 65 are suspicious outliers.

Diagnostic Plots
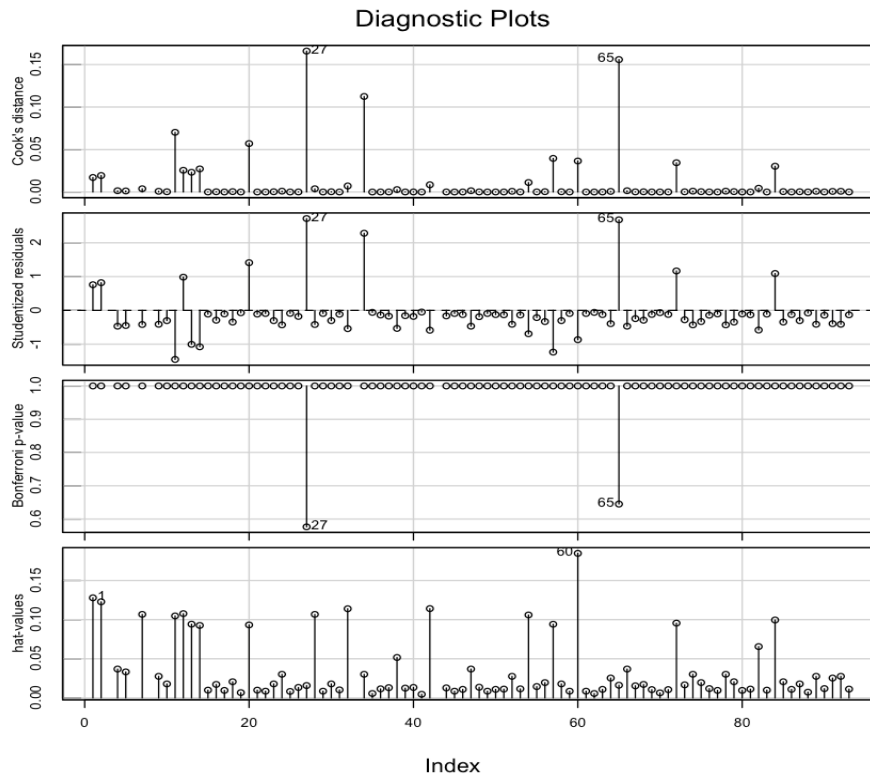
OutlierTest showed no significant outliers among all samples

 > outlierTest(m3)

No Studentized residuals with Bonferroni p < 0.05

Largest |rstudent|:

   rstudent unadjusted p-value Bonferroni p

27 2.718802   0.0065519   0.57657

After deleting sample No. 27, there was no significant difference when compared with the original model.

> m3m27<-update(m3,subset=c(-27))

> compareCoefs(m3,m3m27)

Calls:

1: glm(formula = CardiacInjury ~ NTproBNPPos + Age, family = binomial, data
   = testData)

2: glm(formula = CardiacInjury ~ NTproBNPPos + Age, family = binomial, data
   = testData, subset = c(-27))

                Model 1 Model 2

(Intercept)   -8.04   -8.00

SE   2.52   2.51

NTproBNPPos   2.387   2.370

SE   0.862   0.862

Age   0.0888   0.0884

SE   0.0398   0.0396

After deleting sample No. 65, there was no significant difference when compared with the original model.

> m3m65<-update(m3,subset=c(-65))

> compareCoefs(m3,m3m65)

Calls:

1: glm(formula = CardiacInjury ~ NTproBNPPos + Age, family = binomial, data = testData)

2: glm(formula = CardiacInjury ~ NTproBNPPos + Age, family = binomial, data = testData, subset = c(-65))

             Model 1 Model 2

(Intercept)   -8.04   -8.03

SE   2.52   2.53

NTproBNPPos   2.387   2.386

SE   0.862   0.862

Age   0.0888   0.0887

SE   0.0398   0.0398

Changes in the text: We have added "A total of 20(21.5%) patients had received transthoracic echocardiography and 27(29.0%) had received electrocardiogram." **on Page 7, Line135-137.**

Comment 4: More sound bibliographical sources may be needed, especially in the discussion: it could be interesting making comparisons with other similar studies conducted and recently published in different countries, especially on the risk factors, radiological results, and major cardiac comorbidities in COVID-19 patients.

Reply 4: Thank you so much for your advice. We have added the relevant bibliographical sources in the discussion, making comparisons with other similar studies conducted and recently published in different countries.

Changes in the text: In the discussion, we have added "The present study showed that acute cardiac injury was seen in the minority of patients presenting with COVID-19, occurring in 9.7%. Evidence for acute myocardial injury was less frequent in our patients compared to that reported from New York City including nearly 3,000 patients with a prevalence of 36%, and that reported from Wuhan, China (ranging from 12% to 27.8%)(3, 7, 13, 14). However, a study from Shenzhen, Guangdong Province, a city near Zhuhai, reported the prevalence of acute cardiac injury was 8.4%, which was quite close to our finding. Similar to these reports, we also demonstrated that patients with cardiac injury tended to be older and were more likely to combine with hypertension, more likely to be categorized as severe-critical cases. The reason why acute cardiac injury was less frequent in our patients than Wuhan and New York might be related to reality that our patients was not that sick as patients in New York or Wuhan, since our minimal, common, severe, and critical cases accounted for 18.3%, 58.1%, 17.2% and 6.5% respectively and the median TSS, a semi-quantitative score based on CT image to quantitatively estimate the severity the pulmonary involvement resulted from viral pneumonia, of our patients was 3. It is quite frankly probable that in a sicker population with more lung involvement and more hypoxemia that elevated hs-cTnI would be more prevalent. Besides, as Wuhan had an over 100-fold greater number of COVID-19 cases than Guangdong Province and the number of patients in New York was even larger, the

regional health care systems of both Wuhan and New York were faced with much more challenge, which might have potentially increased risk of cardiac injury due to delayed hospital admission. Another finding of our study was that elevation of cardiac injury markers of in our cohort was often mild. This finding was in keeping with the report from New York City". **(see Page 10-11, line 203-226)**

Reviewer B:

This manuscript was well written and focused on the very important topic in this pandemic situation by COVID-19.

The purpose of the present study was to evaluate the prevalence and predictors of cardiac injury in patients with COVID-19.

The current study demonstrated that cardiac injury was found in 9.7% of patients with COVID-19. As a retrospective study, they did frequent troponin tests (the median number of times was 13 in group with cardiac injury and 5 in the patients without cardiac injury), which meant that slight increases in troponin were less likely to be missed. This result may largely reflect the true incidence of myocardial injury in these COVID-19 patients.

In this article, these patients had only a slight increase in troponin levels, and echocardiography was performed under limited conditions in patients suspected of myocardial injury (about 20%), showing no significant difference in LVEF.

The authors further investigated the cause of the increase in troponin using CMR. It is regrettable that CMR was performed in only 3 patients. Nevertheless, in these patients with highest troponin demonstrate underlying heart disease.

However, there are some issues which should be addressed.

Comment 1: A growing number of studies have shown that COVID-19 causes vascular endothelial damage. Endothelium injury of the coronary arteries may lead to myocardial injury, which should be discussed in the DISCUSSION section.

Reply 1: Thank you so much for your advice. That endothelium injury of the coronary arteries may also lead to myocardial injury has been discussed in the DISCUSSION

section as advised.

Changes in the text: In the discussion, we have added "emerging evidence indicates that endothelium cell dysfunction is a central feature of COVID-19. As the vascular endothelium forms a critical interface between the circulatory system and is the key driver of cytokine dysregulation in ARDS as well as multiple cardiovascular pathologies, endothelium injury of the coronary arteries may play a critical role in COVID-19 related cardiac injury" **(see Page13, line 268-272)**

Comment 2: Have these patients with myocardial injury been tested for D-dimers? Is it higher than patients without myocardial injury?

Reply 2: It was a pity that we did not routinely test D-dimers in our patients. As it was a retrospective observational study, we felt really sorry that we could not further analyze the difference of D-dimers between the two groups.

Changes in the text: Not applicable.

Reviewer C:

In this study, the authors retrospectively analyzed demographic, clinical, laboratory and cardiovascular imaging data of COVID-19 patients.

It shows us the clinical data of the risk of acute cardiac injury in COVID-19 patients.

There are two suggestions:

Comment 1: The first sentence of Results in ABSTRACT should tell the readers how many patients were included in this study?

Reply 1: We have added data of the number of patients included in our study as advised **(see Page xx, line xx)**

Changes in the text: "A total of 93 patients were included in the study." has been added as the first sentence of Results in ABSTRACT.

Comment 2: This is a retrospective study. The correlation of increased NT-proBNP and cardiac injury is uncertain, which cannot be drawn as a conclusion. Therefore, the

CONCLUSIONS should be " Acute cardiac injury was seen in the minority of patients presenting with COVID-19. Older age was associated with cardiac injury in hospitalized Chinese COVID-19 patients outside Wuhan."

Reply 2: Thank you so much for your advice. But in our multivariable logistic regression analysis, increased NT-proBNP (HR:10.979, 95% CI: 2.024-59.555) were risk factor for cardiac injury (Table 4), which suggests that increased NT-proBNP were associated with acute cardiac injury. We did not intend to conclude that increased NT-proBNP will cause acute cardiac injury, but just simply tell that these two indices are relevant. Therefore, we have retained our original conclusion. Looking forward to your further comments.

Changes in the text: We have retained our original conclusion.