Peer Review File

Reviewer A:

I am very glad the authors wrote this essay. It is needed information of the current status

of "data publication" from a certain perspective. This is my opinion piece.,

Major flaws:

Comment 1:

The results and statistical analysis are conflicting. The authors documented "The independent variables with a P-value of ≤0.1 on univariate analysis was tested in the multivariate model". In Table 6, the sinus tachycardia was not significantly associated with mortality with a p-value of 0.12 which is > 0.1. Can the authors clarify why the authors included sinus tachycardia on the multivariable analysis because sinus tachycardia is a significant predictor of mortality in multivariable analysis? Further, other variables with a p-value of more than 0.1 in the univariate analysis were included in the multivariable analysis (Table 6).

Reply 1:

We included variables in the multivariate analysis that were statistically significant on univariate analysis (P≤0.1) as well as clinically significant variables that did not reach statistical significance.

P-value is affected by sample size. If you work with a relatively small sample, some variables can have a substantive importance, although they may not be statistically significant. The decision which variables to include / exclude in the model should rely on some theoretical base. If the insignificant variable "has" to be in the model, according to the theory, you should enter it despite its insignificance. (https://www.researchgate.net/post/Is-it-right-to-include-variables-to-multivariate-analysis-by-a-logistic-regression-model-if-they-have-no-significance-in-univariate analysis/57cc8f44dc332d07ed6c8f6e/citation/download)

Sinus tachycardia has been shown to be a predictor of mortality in patients with COVID-19 (Cho JH, Namazi A, Shelton R, et al. Cardiac arrhythmias in hospitalized patients with COVID-19: A prospective observational study in the western United States. PloS one. 2020 Dec 28;15(12):e0244533) and therefore, due to its clinical relevance it was included in the multivariate analysis.

Changes in the text:

Under statistical analysis section, highlighted: Univariate and multivariate logistic regression analyses were used to identify possible independent determinants of mortality. The independent variables with a P-value of ≤0.1 on univariate analysis and

variables that had clinical significance were tested in the multivariate model.

Minor flaws:
Comment 1:

1) "Most of the patients were obese and had hypertension (69.5%)". The authors need to report the percentage for each co-morbidity.

"Most of the patients had more than one co-morbidity". The authors need to report the percentage.

"Majority of the patients were female with multiple co-morbidities and cardiac

abnormalities were common" The authors should clarify the percentage of multiple co-morbidities to avoid confusion. Because the authors write that being obese and having hypertension is 69.5%, therefore there is one predominant co-morbidity, not multiple co-morbidities.

Reply 1: This has now been clarified in the manuscript under results section. Table 1 provides detailed break down of each co-morbidity percentage. In order to maintain clarity, we have removed the statements "Most of the patients had more than one co-morbidity". "Majority of the patients were female with multiple co-morbidities and cardiac abnormalities were common". The first line of the conclusion under abstract has been modified.

Changes in the text:
Results (main manuscript)
The baseline characteristics of the study patients are summarized in Table 1. The mean age was 56.4±15.6 years and majority were African females. Most of the patients were obese (65.5%) and had hypertension (69.5%). Other co-morbidities included Pulmonary tuberculosis (9%), chronic kidney disease (10%), malignancy (3%) and chronic obstructive pulmonary disease (5%) and autoimmune disease (1%).

Abstract (conclusion section):
Majority of the patients were obese females with underlying hypertension. Echocardiography altered management in half the patients. Mortality amongst this cohort of patients was high and they were predominantly males.

Comment 2:
2) In ensuring that the accuracy or integrity of any part of the work is appropriately investigated and resolved" should be in the method, not in the statistical analysis.
Reply 2: This comment has been noted. The paragraph has now been moved to the methods section.
Changes in the text: Under methods section of the manuscript

Ethics approval for the study was obtained from the University of the Witwatersrand ethics committee (M200678). The authors are accountable for all aspects of the work in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Comment 3:

3) While the authors write "In our study only CRP was associated with increased risk of death in univariate and multivariate analysis", they write "Mortality amongst this select group of patients was high and those who died were predominantly males and had higher markers of myocardial injury and inflammation" in the conclusion. I think higher markers of myocardial injury should not be in the conclusion.

Reply 3:

This comment has been noted. The conclusion has now been amended and the section on myocardial injury has been removed.

Changes in the text: Under conclusion section of the manuscript

The South African patient with COVID-19 and cardiac disease are predominantly obese females with underlying hypertension. Hand-held echocardiography is a useful tool in the setting of COVID-19 disease and cardiac disease. Mortality amongst this select group of patients was high and they were predominantly males. Hypoxia and raised CRP were important predictors of mortality in this study, however, sinus tachycardia emerged as the most important independent predictor of in-hospital mortality.

Comment 4:

4) "Frequently documented electrocardiography finding was sinus tachycardia (63%) with atrial fibrillation noted in 7% of patients." The authors should not use the word "with". I think "and" is better to replace for the word "with".

Reply 4:

The comment has been noted and suggested amendment has been made under the results section of the abstract.

Changes in the text: Under results section of the abstract:

Dyspnoea on admission was noted in 88.5% of patients. Seventy nine percent of patients had abnormal Chest X-Ray. Frequently documented electrocardiography finding was sinus tachycardia (63%) and atrial fibrillation was noted in 7% of patients. Most common indication for echocardiography was heart failure (30%).

Comment 5:

5) "Echocardiography changed or modified management in 53% of cases. An inhospital mortality of 17.5% was noted". The authors should give more details of what result of echocardiography changing or modifying management.

Reply 5:

This section is from the results part of abstract and therefore was abbreviated in a sentence. The discussion section of the manuscript elaborates further on the

management. Once the diagnosis was confirmed after echocardiography each condition was managed as per standard guideline recommendations. For example, echocardiography aided in confirming infective endocarditis and this assessment allowed for focused management of infective endocarditis in the respective patient.

Changes in the text: Under discussion section of the manuscript.

Echocardiography accompanied with good multi-disciplinary clinical assessment allowed focused management of patient's diseases. These included conditions such as infective endocarditis, pericardial effusion with tamponade, pulmonary embolism, acute coronary syndromes and titration of heart failure therapy. Dweck et al reported a similar change in patients management in their study.

Comment 6:

6) "Majority of the patients were female with multiple co-morbidities and cardiac abnormalities were common." The authors should not write that "cardiac abnormalities were common" because cardiac abnormalities and covid-19 disease are100% in the research sample.

Reply 6:

This comment has been noted. The denoted section has been addressed in the conclusion section of the abstract.

Changes in the text: Under conclusion section of the abstract.

Conclusion

Majority of the patients were obese females with underlying hypertension. Echocardiography altered management in half the patients. Mortality amongst this cohort of patients was high and they were predominantly males.

Comment 7:

7) While the authors write "Majority of the patients were female with multiple co-morbidities and cardiac abnormalities were common", they write "mortality amongst patients hospitalised with cardiac disease and COVID-19 was high" in conclusion. All mortality patients are male, therefore female shoud not be written here and female (57.5%) should not be majority.

Reply 7:

The conclusion has been amended and rephrased both in the abstract section and in the main manuscript after discussion to avoid this confusion. To clarify not all patients that died were males. As represented in Table 5 of the 35 patients that died 16 were females and 19 were males.

Changes in the text: Under conclusion section of the abstract.

Majority of the patients were obese females with underlying hypertension. Echocardiography altered management in half the patients. Mortality amongst this cohort of patients was high and they were predominantly males.

Changes in the text: Under conclusion section of the manuscript.

The South African patient with COVID-19 and cardiac disease are predominantly obese

females with underlying hypertension. Hand-held echocardiography is a useful tool in the setting of COVID-19 disease and cardiac disease. Mortality amongst this select group of patients was high and they were predominantly males. Hypoxia and raised CRP were important predictors of mortality in this study , however, sinus tachycardia emerged as the most important independent predictor of in-hospital mortality.

Comment 8:
8) "In univariate analysis higher SaO2 was associated with lower risk of mortality (OR 1.02 (95% CI 1.00 – 1.05) p=0.046)". The authors should consider to include this in conclusion.
Reply 8:
The conclusion has been further amended in the manuscript to accommodate this suggestion.
Changes in the text: Under conclusion section of the manuscript.
The South African patient with COVID-19 and cardiac disease are predominantly obese females with underlying hypertension. Hand-held echocardiography is a useful tool in the setting of COVID-19 disease and cardiac disease. Mortality amongst this select group of patients was high and they were predominantly males. Hypoxia and raised CRP were   important predictors of mortality in this study , however, sinus tachycardia emerged as the most important independent predictor of in-hospital mortality.

Suggestions:

1) "The structure of the paper and language are not concise and clear" I would suggest that author re-organized the paper and the paper needs to be proofread by an English professional or a native speaker". For example, this paragraph "Ethics approval for the study was obtained from the University of the Witwatersrand ethics committee (M200678). The authors are accountable for all aspects of the work.

2) The result section is repetitive and redundant with tables. It would be better if authors can provide the result in a concise way, thus readers can easily follow the paper.

In summary, this is a study with a lot of bias. It should be improved by having more controls.

Comment/Reply:
The suggestions have been noted and improved where possible. The design of the study is retrospective descriptive study and was not intended to include controls. However, we think this is a good suggestion and hope to conduct a prospective study in the near future comparing patients with COVID-19 with and without cardiac disease.

Reviewer B:
Comment 1:

#1 There is increasing data to suggest that COVID-19 is associated with increased mortality and morbidity in patients with cardiovascular disease and this study aims to add to that increasing wealth of knowledge. The authors report on demographic, clinical and echocardiographic characteristics of patients with cardiac disease and COVID-19 in their centre in South Africa. Although there are an increasing number of studies regarding the impact of COVID-19 on patients with cardiovascular disease, Africa is under-represented in these and the authors have correctly identified that there is a need for this data and information to add to knowledge base and help guide medical staff in these communities. The author has highlighted that the South African patient with COVID-19 and cardiac disease may differ from other patients around the world. They have also highlighted the use of hand-held echocardiography for the COVID-19 patient and how its use can change our management. Finally, they remind us that mortality in this patient population is high and that biomarkers and ECG changes can help us predict mortality. Overall it is an interesting topic and adds important information to what we know about COVID 19 and cardiac disease.

Comment 2:
#2 One of the main limitations to this study is that the patients which were included had to have cardiac disease on echocardiogram. As there is no control or comparison group, this is a descriptive study. Did the authors consider including patients with normal echocardiogram results to allow for comparison between a group with COVID-19 and no evidence of cardiovascular disease?

Reply 2 Yes, this is a retrospective descriptive study and as such was largely reliant on information from hospital records. As patients without suspected cardiovascular disease were minority and did not have indications for clinical echocardiogram, they were not all routinely scanned. Therefore, this group could not be included in the study. However, we do plan to do a prospective study and will actively include such a group for comparison between patients with COVID-19 and cardiovascular disease and those without cardiovascular disease.

Comment 3:
#3 There is a small group of patients in this study group with pre-existing cardiac disease however there is no comment on whether they had previous echocardiograms and whether the echocardiograms in the setting of COVID-19 were similar or showed new changes to baseline. This would be an interesting topic to mention in terms of what pre-existing cardiac conditions these patients had and then whether they had new or stable echocardiographic findings when an echo was performed in the setting of COVID. Why do the authors think that only 26 patients had pre-existing cardiac disease, however 127 patients were on diuretics?

Reply 3: The 26 patients had previously documented cardiac disease in their hospital records. The old echocardiogram records of this group were not always accessible to allow for comparison with the echocardiogram done during the COVID-19 infection.

Main reason for diuretic prescription was for management of hypertension as majority of Africans have been noted to have salt sensitive hypertension. As hypertension was a common co-morbidity in this group it makes sense that use of diuretic was high for this indication. Majority of these patients had never undergone echocardiographic scan prior to the admission due to COVID-19 and there was no information on previously confirmed structural heart disease.

Comment 4:
#4 Hypertensive heart disease was an indication for an echocardiogram in 24.5% of patients. It is not clear in the paper why this is a clinical indication for an echocardiogram. Did these patients have ECG changes suggestive of significant left ventricular hypertrophy and therefore they had an echocardiogram, or did these patients have significant hypertension which was therefore an indication for an echocardiogram? Perhaps the authors should elaborate on this or change their terminology to patients with 'suspected' hypertensive heart disease.

Reply 4: This point has been noted and terminology has been changed in the text.

Changes in the text: Under results section in the manuscript
The main indications for echocardiographic scans comprised heart failure (30%), suspected hypertensive heart disease (24.5%), right heart failure (13%), abnormal electrocardiogram (10%), dysrythmias (7.5%), acute coronary syndrome (7%), suspicion of pulmonary embolism (4%) and infective endocarditis (4%). Echocardiography changed management in 53% of cases.

Comment 5:
#5 Figure 1a and Figure 1b add little to the paper. It is interesting to know the ECG findings in patients presenting with COVID-19 however the figures of the ECGs themselves are likely not required.

Reply 5: The point has been noted. We have now removed these figures from the manuscript.
Changes in the text: Results section in the manuscript
The main electrocardiographic findings are depicted in Table 3. Sinus tachycardia was noted in the majority (63%). Sinus bradycardia was noted in 10 (5%) patients who were all above age of 50 years. Atrial fibrillation was the most common tachy-arrythmia (7%).

Comment 6:
#6 The authors included figure 2 which discusses the location of where echos were performed, however this figure is not discussed or mentioned in the discussion section. What information do the authors feel this figure adds to the study, and if it is to be included it should be discussed in the main body of the text.
Reply 6: We have now removed this figure from the manuscript.

Changes in the text: Results section of the manuscript
The main indications for echocardiographic scans comprised heart failure (30%), suspected hypertensive heart disease (24.5%), right heart failure (13%), abnormal electrocardiogram (10%), dysrythmias (7.5%), acute coronary syndrome (7%), suspicion of pulmonary embolism (4%) and infective endocarditis (4%).

Comment 7:
#7 The results section is clear and easy to read. The second last paragraph in the results section finishes with a list of patient characteristics and odds ratios which takes away from the succinct nature of the result section. Would the authors consider including this in the appropriate table as opposed to listing these results in the result section?
Reply 7: This section has now been modified and more succinctly phrased in the manuscript. As none of these variables were significant in univariate or multivariate analysis we did not add an additional table or incorporate into an existing table.
Change in the text: Results section of the manuscript
In univariate analysis higher SaO2 was associated with lower risk of mortality (OR 1.02 (95% CI 1.00 – 1.05) p=0.046) (Table 6). Higher CRP was associated with increased risk of dying (OR 1.0 (95% CI 1.001-1.006) p=0.04). There were no statistically significant associations between mortality and the rest of the patient characteristics such as obesity, troponin, hypertension, diabetes mellitus, ACEI/ARB, ejection fraction, pulmonary hypertension and sinus bradycardia (P>0.05).

Comment 8:
8 One of the important things about this study is that it adds to a growing field of knowledge about patients with COVID-19 and cardiovascular disease, and particularly is one of the first studies to discuss patients in South Africa. Most of the discussion is about how the authors results compare to those already published and this is highly important and I commend the authors on this. If there is a discrepancy between the findings of this study and previously published data, the authors should ensure they comment on why this may be the case.
Reply 8: This point has been noted and we have made full attempt to compare our findings of our study with the rest from the available literature.

Comment 9:
9 The structure of some sentences are inadequate. Minor language revision is needed.
Reply 9: The point has been noted and sentence structure scrutinized and restructured where needed.