Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Myocarditis from direct viral injury or related to angiotensin-converting enzyme 2 (ACE2) downregulation with subsequent hyperactivity of the renin-angiotensin-aldosterone (RAAS) system plays an essential role in troponin elevation in COVID-19 patients. However, the effect of antiviral medications and steroids used to treat viral myocarditis has not been well-studied in patients with elevated troponins. This 1788 samples multicenter retrospective study aims to evaluate the effect of Dexamethasone, remdesivir, and ACEI on mortality in COVID-19 patients with elevated troponin. And found no significant difference in survival rates in COVID-19 patients with elevated troponin that received remdesivir, Dexamethasone, or ACEI versus those that did not. The implication for practice is that treatment with various medications that could be beneficial in viral myocarditis did not show any mortality benefit in this study for COVID-19 patients with troponin elevation. The content of this manuscript is interesting. We believe this manuscript is valuable for all the researchers who are interested in viral myocarditis in COVID-19 patients. This study focuses on current research hot spots and frontiers, which is very important for subsequent research. The article also puts forward the current problems and future research directions. But some sample sizes are in doubt, for example, in Table 2 Remdesivir, no 853, yes 883, total 1736 not 1788; CKD, no 1355, yes 427, total 1782 not 1788; in Table 4 Use of Remdesivir, total 1715 not 1788…Please check. Therefore, I recommend accepting and publishing this manuscript after being revised. Some sample sizes are in doubt, for example, in Table 2 Remdesivir, no 853, yes 883, total 1736 not 1788; CKD, no 1355, yes 427, total 1782 not 1788; in Table 4 Use of Remdesivir, total 1715 not 1788…Please check.

Authors response: Thank you so much for the feedback. We had some missing data in some variables, which was why some did not add up to 1788. We agree that our study provides directions for future research on myocarditis in COVID-19 patients.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Reviewer comments: The MAIN issue with the current study is that it is unclear what Elevated Troponin represents, in general, and in the present study?

Authors response: We added the definition of elevated troponin in our study in the methods section as below.

Elevated cardiac troponin (cTn) diagnostic of myocardial infarction is when the levels exceed the 99th percentile of a normal, healthy reference population [upper reference limit (URL)]. This value is determined for each specific troponin assay with appropriate quality control in each laboratory. Based on our laboratory assay, a troponin I (cTnI) level above 0.4 ng/ml was considered elevated for our study.

Reviewer comments: The present study relies on an inferred diagnosis of myocarditis, or CHF or increased myocardial load, manifesting as elevated troponin and looks at the effect of Dexamethasone, remdesivir, and ACEI on the mortality of those patients, a very dissimilar group. You suggest that viral load could result in Troponin increase. I wonder if it is the same type of shedding as elevated serum-ACE2 observed in COVID-19. I wonder if you looked into any association with CK-MB, LDH, ASAT, and troponin, not as a group as you do in Table 3, but on the same patient basis? How many of the 205 patients with elevated troponin had a concurrent elevation in LDH, CPK? I see 148 had LDH and 116 had CPK elevations; how many of those were concurrent, meaning: how many had cTn+LDH+ CPK, cTn+LDH, or cTn+CPK (do not see ASAT measurements). Patients with myocarditis should have elevations in all 3, as would any other patients with a real cardiac muscle involvement. On the other side, I see HTN, CKD, Bradycardia, and remdesivir use had almost 50% elevated troponin. The CKD group (and HTN) tells me that this could be a troponin renal clearance issue? Those are questions to be resolved before having any meaningful discussion on mortality and troponin.

Authors response: Thank you for your feedback. We added in the results section that we did a Kaplan Meier analysis in the subset of patients with elevated concomitant troponin, CPK, and LDH. Studies have shown that these enzymes are all elevated in patients with significant myocarditis. However, similar to our analysis in those with elevated troponin, we still found no difference in mortality between those that received Dexamethasone (0.88), ACEI (0.83), or remdesivir (p=0.93) and those that did not in this subset of patients.

Reviewer comments: Finally, you mention that “Troponin elevation (HR 1.25, p=0.1) was not independently associated with mortality after adjusting for age, comorbidities like CHF, ICU admission,

and inflammatory markers". How do you reconcile this with an inferred myocarditis diagnosis? I feel that the current results are not strong enough to recommend using Dexamethasone, remdesivir or ACEI on an inferred diagnosis of myocardial involvement.

Authors response: Thank you so much for your comments. We already mentioned in the discussion section that there was increased mortality in patients with troponin elevation (HR 1.25, p=0.1), although this was not statistically significant at a p-value of 0.05. The lack of statistical significance could be related to the fact that our study was underpowered to detect a difference. It could also be that patients in our study differ from those in previous studies.

However, we want to clarify that we are not recommending using Dexamethasone, remdesivir, or ACEI in those with elevated troponin. This study did not find any difference in mortality outcomes in COVID-19 patients with elevated troponin, including the sub-set with concomitant elevated CPK and LDH, who received Dexamethasone, remdesivir, and ACEI and those that did not.

Reviewer comment: Moreover, were Dexamethasone, remdesivir or ACEI initiated due to elevated cTn? Did cTn have any impact in deciding the treatment that was given or ICU admission, or was it just a part of a general algorithm deciding treatment options? Those are some of my thoughts and questions.

Authors response: Elevated troponin was not a criterion in deciding who got Dexamethasone, remdesivir, or ACEI in the COVID-19 patients. We had a multi-disciplinary team, including hospitalists, pulmonary and critical care physicians, and pharmacists in the different hospitals, who determined the treatment patients got based on the FDA recommendations and standards of care at that time. This study is just a retrospective study to determine if any associations were seen between the use of these medications and mortality outcomes in patients with elevated troponins based on hospital clinical data. Like any study of this type, we agree there are limitations to the data because they were not collected initially for research purposes.