

World Journal of Cardiology

Re: Heart Failure and Coronavirus 2019

ID: 75998

Dear Sir/Madam

Attached, please find the revised manuscript based on the recommendation from reviewers. We hope that revised manuscript is well received by your readership and may benefit from it. We like to take this opportunity to thank the reviewer and the editorial staff for their time and patience. Please let us know with any questions.

Regards

Salim Surani, MD

Response to reviewers questions

1) Considering the high incidence of RHF due to acute PE in COVID-19, it is worthwhile to go into more detail about this. The existing statement does not seem to suffice: "RHF due to acute pulmonary embolism has also been reported in 5-22% of cases by different authors [17,18].

Response: We appreciate the reviewers' comments. Acute right heart failure (RHF) in COVID-19 has been primarily thought to be due to acute respiratory distress syndrome (ARDS) and severe hypoxemia. RHF due to acute pulmonary embolism has also been reported in 5-22% of cases by different authors [17,18]. High clot burden was also found in patients with right heart strain from pulmonary embolism. Patients with COVID-19 are several times at higher risk of pulmonary embolism compared to non-COVID-19 patients and is also associated with higher mortality. Severe Acute Respiratory distress syndrome

may lead to pulmonary hypertension and cause right-sided heart failure. Myocardial injury and myocarditis can also weaken the right heart ventricle in COVID-19. Right heart failure in COVID-19 is associated with increased mortality. (several new references addressing these points have been added to the manuscript). Etiopathology of HF in COVID-19 has been summarized in inline diagrams in Figures 1 and 2.

2) It appears that a study that was cited many times in this review was [14]: Bader, Feras et al. "Heart failure and COVID-19." *Heart failure reviews* vol. 26,1 (2021): 1-10. doi:10.1007/s10741-020-10008-2. There are two issues with how this is done

i) It would be better to directly cite the studies they use, rather than the review itself ii) Heavy citing of [14] indicates that another review has already touched upon many of the pertinent points that your current review is aiming to address. Therefore, it will be worthwhile to better differentiate your findings from their review, and to diversify your sources in general.

Response: We appreciate the reviewers' comments. We have modified the manuscript and have used other alternate citations too.

3) The points regarding the link between cytokine storm and HF, as well as ARDs and HF, with acute exacerbations are very important, but only touched upon briefly. Will be worth putting more detail into this.

Response: Thanks for the feedback. Two types of mechanisms for myocardial injury have been described in prior literature. ie direct or specific and indirect effects (69).

SARS-CoV-2 directly attaches to the ACE2 on the myocardium and causes cell damage and death. It also decreases the protective and anti-inflammatory properties of ACE2 on the myocardium through its downregulation.

Sympathetic activity causing Tachycardia from underlying infection, prolonged immobility causing coagulopathy, hypoxemia are indirect effects worsening the cardiac status(69). Severe inflammatory response causing surge of cytokines like Interleukins, Tumor necrosis factor, interferons' play a major role in the pathogenesis of pulmonary and myocardial damage leading to ARDS and various cardiac complications (70). It can precipitate new cardiac failure and worsen the course in underlying failure patients (71). We appreciate the reviewer bring this up.

4) A table summarizing previous findings in the context of the value of i)NT-proBNP ii) EKG iii) echocardiogram iv) cMRI as investigation tools, and which includes the author's recommendations regarding screening/evaluating patient conditions, will be very useful.

Response: We agree with reviewers' comment and have created the table explain that issue.

5) You say "conflicting literature" in this sentence but do not cite. Please do so: "Conflicting literature states these medications are associated with upregulation of ACE2, worsening the COVID-19 infection, which was not proven in studies."

Response: We agree with the reviewer and have changed and removed "conflicting"

It was hypothesized that medications associated with upregulation of ACE2 receptors could worsen the COVID-19 infection, which was not proven in further studies.

6) This sentence is grammatically incorrect and poorly contextualized. Please revise: "Outcomes among heart failure patients were similar regardless of ACE or ARB use. (30)"

Response: Appreciate the feedback. We have revised: COVID-19 outcomes among heart failure patients were not worsened with ACE inhibitor or ARB use from prior studies(30).

7) Please discuss breakthrough infections, with epidemiological data in a bit more detail.

Response: We have added some of the info as suggested. One study described close to 12% of breakthrough infections after vaccination (65). In another study of 700 breakthrough cases close to 49% of the patients were symptomatic (66). Despite increased breakthrough infection in this patient population, they did not develop disease severe enough to require supplemental oxygen or ICU admission. (33, 65)

8) You touch upon shock only very briefly in the management section, but not in many other places in the paper. Please do so in more detail, with it being integrated in the early part, and complication section of the paper.

Response: We appreciate the reviewers' comments and have revised the manuscript and have added the info. One study evaluated that cardiogenic shock resulting from myocardial injury occurred in up to 10% of patients in shock and can result in worse prognosis compared to hypovolemic or distributive shock in COVID-19 patients (72). 48% of patients had normal Ejection fraction and low cardiac index shock from low end diastolic volumes which was due to use of Peak end expiratory pressures and mechanical ventilation causing decreased venous return. Cytokine storm detailed above can result in distributive shock (72). Pulmonary embolism from coagulopathy and pericardial tamponade can cause obstructive shock which are reported in COVID-19.

9) as stated above, differentiating the insights from this review, and prior reviews on HF and COVID-19 will be integral in highlighting the value of this review overall.

Response: We appreciate the reviewer comments. We have revised. Our study takes all the important considerations with evidence and presents a review of all the major topics related to heart failure and Covid-19 from epidemiology, diagnostic tools to the important management options, and post-recovery rehabilitation. It gives insights on breakthrough vaccination and cardiac complications post COVID-19. It attempts to touch on treatment options in various situations encountered while treating heart failure patients. Many prior reviews attempted on heart failure and COVID-19 have not touched upon topics like post recovery rehabilitation, breakthrough vaccination etc. This study also integrates the etio-pathogenesis and management sections in various cardiac complications encountered in COVID-19.

1) For this statement, should have appropriate citations: "Major putative factors in COVID-19 would be increased hemodynamic demands on a chronic HF, massive cytokine storm causing an inflammatory burden on cardiomyopathy, and a hypoxic insult to the myocardium.

Revised: removed and changed to

Revised: Two types of mechanisms for myocardial injury have been described in prior literature. ie direct or specific and indirect effects (69).

SARS-CoV-2 directly attaches to the ACE2 on the myocardium and causes cell damage and death. It also decreases the protective and anti-inflammatory properties of ACE2 on the myocardium through its downregulation.

Sympathetic activity causing Tachycardia from underlying infection, prolonged immobility causing coagulopathy, hypoxemia are indirect effects worsening the cardiac status(69). Severe inflammatory response causing surge of cytokines like Interleukins, Tumor necrosis factor, interferons' play a major role in the pathogenesis of pulmonary and myocardial damage leading to ARDS and various cardiac complications (70). It can precipitate new cardiac failure and worsen the course in underlying failure patients (71).

2) There seem to be numerous issues in the formatting of Figure 1. Please revise.

Response: Thanks for reviewer vigilance. We have reformatted the figure and created more simplified one

3) You say "tricky" in this sentence. Would be better to polish the language with a better terminology, such as "difficult." : "Overall, it can be tricky to accurately

distinguish most of the symptoms of HF from COVID-19 itself, so careful examination and use of diagnostic tools are imperative"

Response: Thanks for pointing this non-scientific term and we have revised to Overall, it can be difficult to accurately distinguish most of the symptoms of HF from COVID-19 itself, so careful examination and use of diagnostic tools are imperative.

4) You make the following statement: "Jugular venous distension, fine crackles at lung bases, wheezing, third heart sound, abdominal distension, ascites, and pitting pedal edema can be used as important clues at the bedside to determine new-onset or exacerbated HF." Can you elaborate a bit further? Will be useful for contextualizing this with COVID

Revised: Signs of fluid overload like weight gain, Jugular venous distension, fine crackles at lung bases, wheezing, third heart sound, abdominal distension, ascites, and pitting pedal edema can be used as important clues at the bedside to determine new-onset or exacerbation of HF in COVID-19 patients.

5) More should be discussed regarding the role of EKG in previous studies.

Revised: EKG changes commonly observed in COVID-19 patients were atrial fibrillation or flutter, Premature atrial (APCs) and ventricular contractions, Bundle branch block, interventricular conduction delay, and repolarization abnormalities. (54). Abnormal EKGs changes like APCs, Right BBB/Intraventricular block, Ischemic T wave inversions, and non-specific repolarization abnormalities were associated with an increased risk of adverse cardiac events or death in patients with underlying comorbidities like cardiovascular or renal diseases. (54, 55)

6) Fix "covid-19" to "COVID-19" in the following sentence: "Management of HF exacerbation during covid-19 should be based on the volume status, the previous history of heart failure, and vital signs"

Revised: Done

7) you cite a single guideline for diuretic [citation 40] use in management. Are there any other guidelines? If so, cite them and use them in the text.

Revised: Cited 63, 64 citations

8) In the following sentence, you should give an example of the specific antibiotics: "Nephrotoxic medications should be used carefully along with diuretics i.e., NSAIDs or nephrotoxic antibiotics. (40)"

Revised: Nephrotoxic medications should be used carefully along with diuretics i.e., NSAIDs, Remdesivir, or nephrotoxic antibiotics like vancomycin (40, 63) If there is diuretic resistance, then ultrafiltration can be considered to treat heart failure and AKI. (40)

9) remove extra bracket in this citation: “Carvedilol is the recommended beta-blocker in patients with heart failure and COVID-19 due to its anti-cytokine action. (36, 41))” 10) say “COVID-19” not “covid”: “Patients previously on beta-blockers can have inappropriate bradycardia with covid”

Revised: Done

11) in this sentence, give examples of specific antivirals: “Antiviral medications can influence the pharmacokinetics of cardiovascular medications, increasing the risk of toxicities and arrhythmias”

Revised: Antiviral medications like Remdesivir and Tocilizumab can influence the pharmacokinetics of cardiovascular medications, increasing the risk of toxicities and arrhythmias

12) fix grammar in this sentence to “If oral anticoagulants are”” If oral anticoagulants is needed in less sick patients, switching to direct oral anticoagulants is preferred over Vitamin K antagonists”

Revised: If oral anticoagulants are needed in mild to moderate COVID-19 patients, switching to direct oral anticoagulants is preferred over Vitamin K antagonists. Prophylactic Anticoagulation with LMWH can be considered in all inpatients if there is no hemorrhagic risk. (40)

13) Please discuss in more detail the high incidence of RHF caused by acute PE in COVID-19; link between cytokine storm and HF, as well as ARDs and HF, with acute exacerbations; and describe the new insights this manuscript provides compared to previous reviews on HF and COVID-19.

Revised:

Acute right heart failure (RHF) in COVID-19 has been primarily thought to be due to acute respiratory distress syndrome (ARDS) and severe hypoxemia. RHF due to acute pulmonary embolism has also been reported in 5-22% of cases by different authors [17,18]. High clot burden was also found in patients with right heart strain from pulmonary embolism (62). Patients with COVID-19 are several times at higher risk of pulmonary embolism compared to non-COVID-19 patients and is also associated with higher mortality (61). Severe Acute Respiratory distress syndrome may lead to pulmonary hypertension and cause right-sided

heart failure. Myocardial injury and myocarditis can also weaken the right heart ventricle in COVID-19. Right heart failure in COVID-19 is associated with increased mortality (59, 60) Etiopathology of HF in COVID-19 has been summarized in inline diagrams in Figures 1 and 2.

14) 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. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Revised: