Rebuttal Letter

REVIEWERS' COMMENTS

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Very comprehensive review, all the information is revealed in depth. Minor comments: 1. Please, provide permission for the figures if they are not carfted by the authors. 2. NETosis is one word.

Authors: We thank Reviewer 1 for the encouraging comments. Permissions for the figures have been obtained and uploaded and the word NETosis has been corrected (one word).

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: It has been demonstrated that COVID-19 causes acute myocardial injuries, as well as chronic damage to the cardiovascular system. Some reviews focusing on COVID-19 and cardiac injury, including clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up, have been published recently (J Hum Hypertens. 2021 Jan; 35(1): 4-11. Expert Rev Anti Infect Ther. 2021 Mar; 19(3): 345-357). This manuscript summarize the COVID-19 related cardiovascular complications (acute coronary syndromes, myocarditis, heart failure, arrhythmias), and discuss the underlying pathophysiological mechanisms. The manuscript Is well, some results are novel, but the manuscript will require minor revision before a decision can be made regarding its merit for potential publication.

Authors: We thank Reviewer 2 for the supportive comments. We are willing to address all of his/her concerns.

1) There are too many background descriptions in the abstract, the abstract does not summarize the main work described in the manuscript.

Authors: We agree with the Reviewer. Therefore, the abstract has been significantly revised:

"An outbreak of coronavirus disease 2019 (COVID-19) occurred in December 2019 due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a strain of SARS-CoV. Patients infected with the virus present a wide spectrum of manifestations ranging from mild flu-like symptoms, cough, fever and fatigue to severe lung injury, appearing as bilateral interstitial pneumonia or acute respiratory failure. Although SARS-COV-2 infection predominantly offends the respiratory system, it has been associated with several cardiovascular complications as well. For example, patients with COVID-19 may either develop type 2 myocardial infarction due to myocardial oxygen demand and supply imbalance or acute coronary syndrome resulting from excessive inflammatory response to the primary infection. The incidence of COVID-19 related myocarditis is estimated to be accountable for an average of 7% of all COVID-19 related fatal cases, whereas heart failure (HF) may develop due to infiltration of heart by inflammatory cells, destructive action of pro-inflammatory cytokines, micro-thrombosis and new onset or aggravated endothelial and respiratory failure. Lastly, SARS-COV-2 can engender arrhythmias through direct myocardial damage causing acute myocarditis or through HF decompensation or secondary, through respiratory failure or severe respiratory distress syndrome. In this comprehensive review we summarize the COVID-19 related cardiovascular complications (acute coronary syndromes, myocarditis, heart failure, arrhythmias), and discuss the main underlying pathophysiological mechanisms." **(Page 2)**

2) The sentence 'a novel single stranded RNA beta coronavirus, emerged in Wuhan, Hubei province, China' should be deleted.

Authors: Based on the Reviewer's suggestion the above sentence has been deleted.

3) In the Introduction, authors should adequately describe the present status and significance of this study, explain the main differences from the currently published reviews.

Authors: We thank the Reviewer for this important comment.

"In this comprehensive state of the art review we will attempt to summarize COVID-19 related cardiovascular complications, with a special concern in enlightening the subjacent mechanisms and pathophysiological traits below the main cardiovascular manifestations." (Page 3)

4) The English abbreviation appearing for the first time in the text shall be supplemented with the full English name, for example, TMPRSS2, CTSB and CTSL, in Page 5.

Authors: We agree with the Reviewer. Accordingly, the English abbreviation appearing for the first time in the text is supplemented with the full English name.

TMPRSS2 (Transmembrane Protease Serine 2), CTSB (Cathepsin B), CTSL (Cathepsin L)

5) Figures 1 and 3 cannot be the same as those in the original articles. Please pay attention to the copyright.

Authors: Thank you for the comment. Copyright permissions for figures 1 and 3 have been obtained and uploaded.

6) In conclusion, the pathogenesis should be summarized.

Authors: We agree with the Reviewer.

SARS-CoV-2, a single stranded RNA beta coronavirus, causes COVID-19 disease. The affinity of SAR-COV-2 infection to ACE-2 receptor has been proposed to be the core of the disease's pathophysiology. Although SARS-COV-2 infection predominantly offends the respiratory system, it is liable for various cardiovascular complications such as ACS, myocarditis, HF and arrhythmias. Several mechanisms have been implicated such as oxygen demand and supply imbalance, excessive inflammatory response to the primary infection, immunothrombosis, and myocardial injury. SARS-COV-2 infected patients with a history of cardiovascular disease have increased mortality.

7) Reference 67 lacks page number.

Authors: Sokolski M, et al: History of Heart Failure in Patients Hospitalized Due to COVID-19: Relevant Factor of In-Hospital Complications and All-Cause Mortality up to Six Months. J Clin Med 2022, 11(1):241. DOI: 10.3390/jcm11010241

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

The subject of this manuscript is of importance and effect many patients with COVID-19 disease. The manuscript is comprehensive, includes most of the relevant literature and discuss many of the underling pathophysiological processes in depth. After reviewing the paper, these are my comments:

Authors: We thank the Reviewer for the encouraging comments.

#1: Abstract and introduction – both mainly describe the COVID-19 pandemic in general while only the last 1-2 lines refer to the manuscript subject. Especially in the abstract, the reader should understand what the article is about and what are the main findings.

Authors: We agree with the Reviewer. The abstract has been revised (please also see answer to Reviewer 2).

"An outbreak of coronavirus disease 2019 (COVID-19) occurred in December 2019 due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a strain of SARS-CoV. Patients infected with the virus present a wide spectrum of manifestations ranging from mild flu-like symptoms, cough, fever and fatigue to severe lung injury, appearing as bilateral interstitial pneumonia or acute respiratory failure. Although SARS-COV-2 infection predominantly offends the respiratory system, it has been associated with several cardiovascular complications as well. For example, patients with COVID-19 may either develop type 2 myocardial infarction due to myocardial oxygen demand and supply imbalance or acute coronary syndrome resulting from excessive inflammatory response to the primary infection. The incidence of COVID-19 related myocarditis is estimated to be accountable for an average of 7% of all COVID-19 related fatal cases, whereas heart failure (HF) may develop due to infiltration of heart by inflammatory cells, destructive action of pro-inflammatory cytokines, micro-thrombosis and new onset or aggravated endothelial and respiratory failure. Lastly, SARS-COV-2 can engender arrhythmias through direct myocardial damage causing acute myocarditis or through HF decompensation or secondary, through respiratory failure or severe respiratory distress syndrome. In this comprehensive review we summarize the COVID-19 related cardiovascular complications (acute coronary

syndromes, myocarditis, heart failure, arrhythmias), and discuss the main underlying pathophysiological mechanisms."

In the **Introduction section** the following sentences have been added: "Although SARS-COV-2 infection predominantly offends the respiratory system, it is liable for various cardiovascular complications as well. In this comprehensive state of the art review, we will attempt to summarize COVID-19 related cardiovascular complications, with a special concern in enlightening the subjacent mechanisms and pathophysiological traits below the main cardiovascular manifestations." **(Page 3)**

#2: 3.1. COVID-19 and acute coronary syndromes –the subject of lower number of people addressing the ED with ACS is very interesting in my opinion. However, I believe the examples in this paragraph may be repetitive and can be summarized together. Maybe the authors can add more about possible explanations for this trend?

Authors: This is indeed an important comment.

"Despite the elevated incidence of myocardial infarction in COVID-19 patients, a substantial drop in the percentage of patients (up to 40%) addressing the emergency department due to acute coronary syndromes (ACS) has been observed in several countries, especially in the early stages of the pandemic (Braiteh N, et al. Decrease in acute coronary syndrome presentations during the COVID-19 pandemic in upstate New York. Am Heart J 2020, 226:147-151. / Mafham MM, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. Lancet 2020, 396(10248):381-389. / Vecchio S, et al. Impact of the COVID-19 pandemic on admissions for acute coronary syndrome: review of the literature and single-center experience]. G Ital Cardiol (Rome) 2020, 21(7):502-508.) In Greece, a country which implemented strict social measures, a reduction of approximately 30% in ACS hospitalizations during the COVID-19 outbreak was reported along with no excess in in-hospital mortality (Papafaklis MI, et al: "Missing" acute coronary syndrome hospitalizations during the COVID-19 era in Greece: Medical care avoidance combined with a true reduction in incidence? Clin Cardiol 2020, 43(10):1142-1149.) Several explanations for this trend have been proposed such as the reduction in participation in aerobic exercise, the reduced air pollution and changes in lifestyle and diet associated with the pandemic environment, or the fact that patients with less severe symptoms have avoided or delayed presenting to hospital. (Sutherland N, et al. Heart Lung Circ. 2022 Jan;31(1):69-76). **(Page 6)**

#3: 3.1. COVID-19 and acute coronary syndromes – Clinical data regarding patients with ACS and COVID-19 is lacking. For example, does ACS occur early or late in the disease sequela, possible correlations with the severity of pulmonary disease, change in the results of revascularizations compared to the general population?

Authors: We thank the Reviewer for the comment.

"Several studies have reported the substantial reduction in the total number of urgent and emergent coronary angiography performed in patients with ACS during the COVID-19 pandemic. COVID-19 patients with STEMI frequently did not receive guideline-recommended treatments, while the use of fibrinolysis over primary percutaneous coronary intervention (PCI) has been reported in a high number of cases (Esposito L, et al. Oxid Med Cell Longev. 2021 Aug 30;2021:4936571. \ Kwok CS, et al. Heart 2020, 106(23):1805-1811 \ Garcia S, et al. JACC 2020; 75(22):2871-2872. / Gluckman TJ, et al. JAMA Cardiology 2020; 5(12):1419–1424, 2020 / Mafham MM, et al. Lancet 2020: 396(10248):381–389, 2020.) However, an analysis from the Beijing Inpatient Database Study reported that the proportions of patients with ACS receiving PCI, the proportion of patients with STEMI receiving PCI within 24 h, and the proportion of patients with unstable angina receiving coronary artery bypass graft (CABG) were higher in the study period (December 1, 2019 to June 30, 2020,), compared to those in the control period (December 1, 2018 to June 30, 2019) (He L, et al. Lancet Reg Health West Pac. 2022 Feb;19:100335)." **(Page 6)**

"It is proposed that two different groups of COVID-19 patients with ACS exist. The first group includes patients with pre-existing atherosclerosis, a history of heart failure (HF) or multiple cardiovascular risk factors, who are prone to develop acute myocardial injury. Systemic hypoxia in patients with severe pneumonia or acute respiratory distress syndrome (ARDS) along with increased metabolic demands can precipitate imbalance between myocardial oxygen demand and supply, leading to type 2 myocardial infarction. Meanwhile, hypoxia-induced influx of calcium ions also leads to injury and apoptosis of cardiomyocytes. (Li B, et al. Clin Res Cardiol. 2020 May;109(5):531-538.) Therefore, not surprisingly hypoxemia (defined as pulse oximetry <96%) has been reported to be an independent risk factor of ACS development in COVID-19 patients (Alquézar-Arbé A, et al. J Emerg Med. 2022 Apr;62(4):443-454). Moreover, it is well recognized that sepsis increases the risk for cardiovascular events and the risk of myocardial injury is linearly associated to the severity of respiratory infectious diseases.

In the second group the excessive inflammatory response to the primary infection is the main mechanism. Patients may lack previous cardiovascular history or classic risk factors for coronary disease. Coronary occlusion occurs in the setting of procoagulant state and excessive autoimmune response. Such patients are usually sick for at least two

weeks with SARS-CoV-2, and ACS develops against the background of this infection (Shorikova DV, et al. COVID-19 and acute coronary syndrome: emphasis on ACS without atherothrombosis. e-Journal of Cardiology Practice 2021;21(5). https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-21/covid-19-and-acute-coronary-syndrome-emphasis-on-acs-without-atherothrombosis. Assessed 19/07/2022). A Swedish study which included 86 742 patients with COVID-19 and 348 481 matched control individuals reported an increased risk of myocardial infarction in COVID patients the first 2 weeks after the infection. (Katsoularis I, et al. Lancet. 2021 Aug 14;398(10300):599-607) **(Page 7)**

#4: 3.1.2 Immune response in acute myocardial infarction – This paragraph describes the inflammatory response after MI. While the connection to COVID-19 is explained in the last sentence, I believe the highly detailed inflammatory consequence is not needed and can be shortened.

Authors: Based on the Reviewer comment the paragraph has been shortened:

"Ischemic injury after acute myocardial infarction mobilizes a wide range of immune responses of innate and adaptive immunity. The progress commences with the release of preformed granules of resident mastic cells which induces the release of inflammatory cytokines and chemokines of the macrophages and endothelial cells. After that, neutrophils and macrophages mainly from the hematopoietic stem and progenitor cells (HSPCs) in the bone marrow, infiltrate the cardiac muscle in a biphasic response, sequencing the inflammatory cascade. Leukocytosis itself, although it starts initially as a compensatory mechanism for the preservation of cardiac muscle integrity, constitutes an independent cardiovascular risk factor. ~~At the early stages after a myocardial injury, the main functions of neutrophils and macrophages are to scavenge dead myocardial cells and DNA that is delivered in the extracellular space, as well as to release cytokines, mainly IL-1, IL-6, TNF-a, in order to further amplify the inflammation progress [37]. Moreover, neutrophils polarize the macrophages in a reparative phenotype via the release of gelatinase-associated lipocalin. After that they progressively decrease their number and are replaced by mainly Ly6Clow, macrophages [36]. During the reparative progress that continues to take place, macrophages produce molecules such as TGF-β and VEGF that promote inosis and neovascularization that pose a harmful long term impact in myocardial muscle [37].~~ The absolute balance of the immune response is crucial for the outcome of the disease, since an over-accumulation of immune cells in the early stages leads to thinning of the infarct tissue while an absence of a vigorous immune response can lead to an excess of

granulation tissue, making myocardial wall less stable and prone to rupture. Acute deregulation of the immune system in SARS-COV-2 infected patients can amplify immune response and precipitate multiple organ failure as well as acute myocardial infarction." **(Page 11)**

#5: 3.2.1. COVID-19 related myocarditis – This section is described well. The relationship between patients COVID-related myocarditis and other features of COVID-19 disease can be addressed. For example, severity of pneumonia in these patients, other extrapulmonary co-involvement, treatment, and prognosis. In addition, Authors might wish to hypothesize further mechanisms which might have led to the pathology described. I think the authors can discuss the issues I mentioned above in the context of the following paper, which presents a clinical and literature review on this topic. This review describes the inflammatory cardiac involvement and its prevalence, clinical features, possible underling mechanism and prognosis:

Concurrent myopathy and inflammatory cardiac disease in COVID-19 patients: a case series and literature review. Rheumatology International (2022). doi: 10.1007/s00296-022-05106-3

Authors:

Thank you for the comment.

"A retrospective cohort from 23 hospitals in the United States and Europe revealed chest pain and dyspnea as the most common symptoms at admission, whereas the majority of acute myocarditis occurred in the absence of pneumonia. Patients with concomitant myocarditis and pneumonia exhibited the worse prognosis at 120 days. (Ammirati E, et al. Circulation. 2022 Apr 12;145(15):1123-1139.)"

" Skeletal muscle myopathy is an extra-pulmonary manifestation of COVID-19, occurring in up to one-third of symptomatic patients and ranging from limited myalgia to myositis or rhabdomyolysis. A case series of patients with concurrent myopathy and inflammatory cardiac disease secondary to active COVID-19, revealed that most patients did not have a major respiratory complication and only two had critical COVID-19 pneumonia (Freund O, et al. Rheumatol Int. 2022 May;42(5):905-912.)"

"At present, treatment for viral myocarditis is largely supportive, including mechanical circulatory support for critical patients. When left ventricular systolic dysfunction occurs, heart failure therapy is recommenced (i.e. angiotensin-converting enzyme-inhibitors and b-blockers) in a patient with sufficient cardiac output and

haemodynamic stability. Several ongoing trials are exploring immunosuppressant therapy for the hyperinflammatory phase that may be beneficial for COVID-19-related myocarditis. (Castiello T, et al. Heart Fail Rev. 2022; 27(1): 251–261.)"

"Raised troponin levels in COVID-19 are associated with worse outcome, but the specific prognostic role of myocarditis is unknown. (Castiello T, et al. Heart Fail Rev. 2022; 27(1): 251–261.)"

"Intracellular SARS-CoV-2 might impair stress granule formation via its spike protein. Without the stress granules, the virus is allowed to replicate and damage the cell. Naïve T lymphocytes can be primed for viral antigens via antigen-presenting cells and the heart-produced hepatocyte growth factor. The primed CD8+ T lymphocytes migrate to the cardiomyocytes and cause myocardial inflammation through cell-mediated cytotoxicity (Siripanthong B, et al. Heart Rhythm. 2020 Sep; 17(9): 1463–1471). SARS-CoV-2 can also cause myocardial damage via the infection of endothelial cells in the heart. This theory is supported by the histological discovery of SARS-CoV-2 in endothelial cells of numerous organs, including the heart (Ali M, et al. Egypt Heart J. 2022 Apr 5;74(1):23)." **(Pages 13-15)**

#6: 3.3 HEART FAILURE AND COVID-19 – Any acute infectious disease can cause heart failure exacerbation in patients with preexisting heart disease. The authors might whish to further describe the higher burden of the disease specifically among COVID-19 patients. Other possible mechanisms might be cor-pulmonale secondary to ARDS or PE, both occur in high rates in COVID patients or the high use of steroids which can cause fluid overload.

The part discussing the diminished immunomodulatory response is not relevant to COVID-19 and might be off topic for the discussion.

Authors: We than the Reviewer for the comments.

"Infection is a usual trigger of HF hospitalization and it is related to increased mortality. Patients with COVID-19 are not the exception. The prevalence of HF as a comorbid condition ranged from 3.3 to 21% among SARS-CoV-2-infected patients, whereas during COVID-19 hospitalization, about one-third of patients with previous HF had an acute decompensation of HF (Italia L, et al. Front Cardiovasc Med. 2021 Aug 10;8:713560."

"SARS-COV-2 is accountable for viral inclusions in myocardium and the consequent infiltration by monocytes/macrophages, neutrophils, and lymphocytes. COVID-19 related myocarditis may progress to dilated cardiomyopathy and advanced HF with reduced ejection fraction. Other possible mechanisms include a) cor-pulmonale secondary to ARDS or pulmonary embolism, b) the use of steroids which can cause fluid overload, and c) the administration of cardiotoxic drugs (i.e. hydroxychloroquine or azithromycin) (Italia L, et al. Front Cardiovasc Med. 2021 Aug 10;8:713560.)" **(Pages 17-18)**

~~Immunomodulatory response is diminished in patients with moderate to severe HF [69]. The density and function of β-adrenergic receptors changes towards a predomination of beta-2 adrenergic receptors, while density of beta-1 is decreased [70]. Previous studies also evinced an impaired norepinephrine's ability to regulate cytokine production resulting in an increased production of TNF-α and reduced IL-10 in patients with HF compared to healthy subjects [71, 72]. These alterations imply an increased cardiac demand which is difficult to be achieved in patients with HF.~~

#7: 3.4.1. Supraventricular arrhythmias – "In hemodynamically unstable patients…" – this part in my opinion is a general description of the management of AF and is not related to COVID-19. I think the authors can address any change in treatment or special considerations in patients with COVID-19.

Authors: We than the Reviewer for the comment.

"Atrial fibrillation/atrial flutter occur in approximately 15-20% of patients hospitalized with COVID-19 (Eur Heart J. 2022 Mar 14;43(11):1059-1103)…

~~In hemodynamically unstable patients, synchronized direct cardioversion is indicated to restore sinus rhythm. In cases with no hemodynamic compromise, a rate control using a beta-blocker, a calcium channel blocker and/or digoxin, in absence of contraindications such as bronchospasm or acute HF, is a reasonable initial approach [92].~~ QTc interval should be measured to avoid a marked prolongation in cases of co-administration of other QT-prolonging drugs. Intravenous (IV) amiodarone is the choice for antiarrhythmic medication for rate and rhythm control. Its combination with hydroxychloroquine and/or azithromycin should be avoided in COVID-19 patients. COVID-19 is associated with increased risk of venous, arterial, and microvascular thrombotic and thromboembolic disease. Therefore, special attention should be given to anticoagulation therapy administration, taking in mind that CHA2DS2-VASc score may underestimate risk of stroke. (Eur Heart J. 2022 Mar 14;43(11):1059-1103). **(Page 20)**

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The article presents a comprehensive pathophysiological outlook of cardiac abnormalities in COVID-19. The literature review and methodology is robust and findings are of interest for the readership.

Authors: We are grateful to the Reviewer for the supportive comments.

Reviewer #5:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This review paper summarizes COVID-19 related cardiovascular complications, with particular concern in enlightening the subjacent mechanisms below the leading cardiovascular disease (CVD) manifestations. While pre-existing CVD is one of the risk factors for poorer results of patients with COVID-19, SARS-CoV-2 viral infection may cause myocardial injury, leading to CVD development in patients with COVID-19.

Authors: We thank the Reviewer for the comments.

*(Abstract) Please explain this abbreviation = CD209?

Authors: DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) also known as CD209 (Cluster of Differentiation 209) is a protein which in humans is encoded by the CD209 gene

*The introduction section should be more extensive. Please increase the narration of the COVID-19 in the introduction passage and the comparison with different acute respiratory syndromes and the usual management of COVID-19 briefly.

Authors: Thank you for the comment.

"Most of the patients with COVID-19 who become critically ill tend to have minor symptoms in the early stages of the disease. The condition of these patients suddenly deteriorates in the later stages of the disease or in the process of recovery, usually due to "cytokine storm" and acute lung injury (acute respiratory distress syndrome) (Triposkiadis F, et al. Heart Lung Circ. 2021 Jun;30(6):786-794). In general, acute respiratory syndromes can be divided in those stemming from direct lung injury factors (i.e. bacterial, viral or fungal pneumonia) and those from indirect lung-injury risk factors (i.e. sepsis, hemorrhagic shock or pancreatitis) (Thompson BT, et al. N Engl J Med. 2017 Aug 10;377(6):562-572.) The usual management of patients with COVID-19 includes self-isolation and supportive measures (antipyretics, rehydration) in mild cases (absence of signs of severe or critical disease), and hospitalization in severe (oxygen saturation < 90%on room air, signs of pneumonia, signs of respiratory distress) and critical cases (requires life sustaining treatment, acute respiratory distress syndrome, sepsis and septic shock) (Clinical management of COVID-19: Living guideline, 23 June 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2022-1 Assessed 19 July 2022). **(Pages 3-4)**

*Current research indicates that patients with COVID-19 comorbidities may be associated with incident myocardial damage on the second day in patients with normal troponin levels at admission. Please discuss this point. (Nuzzi, V., et al. (2021). The prognostic value of serial troponin measurements in patients admitted for COVID-19. ESC heart failure, 8(5), 3504–3511. https://doi.org/10.1002/ehf2.13462)

Authors: We thank the Reviewer for this important comment.

"The cardiac involvement of COVID-19 as demonstrated by increased troponin levels at hospital admission has been associated with adverse prognosis in several cohorts (Lombardi CM, et al. JAMA Cardiol 2020;5:1274–1280 / Guo T, et al. JAMA Cardiol 2020;5:811–818.) A recent study by Nuzzi et al. demonstrated the prognostic significance of troponin trajectories in hospitalized patients with COVID-19 (Nuzzi V, et al. ESC Heart Failure 2021; 8: 3504–3511). The authors reported that the strongest independent predictor of increased mortality was the presence of normal troponin at admission and elevated troponin (defined as values above the 99th percentile of normal values) on day 2 (hazard ratio 3.78, 95%confidence interval 1.10–13.09, P= 0.035). The aforementioned study suggests that COVID-19 patients deserve a serial troponin assessment, beyond baseline values, because it may have an additive prognostic role.

*Statement on Pg. 3 "Recent literature indicates that SARS-COV-2 infected patients with a history of cardiovascular disease display increased mortality. Patients with a history

of hypertension, diabetes, obesity are also considered frail [6]." Consider strengthening the statement with other supporting references. The following related reference may be included in this review to provide a complete picture of the topic (Pepera, G., et al. (2022). Epidemiology, risk factors and prognosis of cardiovascular disease in the Coronavirus Disease 2019 (COVID-19) pandemic era: a systematic review. Rev cardiovas med, 23(1), 28. https://doi.org/10.31083/j.rcm2301028)

Authors: We thank the Reviewer for the comment.

The suggested reference has been added.

*Figure 2 describes the mechanisms of acute myocardial injury in COVID-19 patients: is it the authors' work or derived from the papers included? explain this

Authors: Figure 2 is original. Based on the editor's comments the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022, has been added.

*The link between dyslipidemia and COVID 19 is of intense interest at present. Please, consider including this idea in light of one of the more extensive study focused on this topic, "Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. (e.g. Mitacchione, G (2021). Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. Journal of clinical lipidology, 15(1), 68–78. https://doi.org/10.1016/j.jacl.2020.12.008)

Authors: We thank the Reviewer for the important comment.

"**3.5. COVID-19 AND STATIN THERAPY**

The link between statin therapy and COVID-19 severity and outcomes is of intense interest at present. Several studies have demonstrated the association between statin therapy and reduced risk of pneumonia, milder disease, as well as reduced mortality (Kouhpeikar H, et al. Front Cardiovasc Med. 2022 Feb 24;9:820260 / Ganjali S, et al. Metabolism. 2020; 113:154375 / Vahedian-Azimi A, et al. BioMed Res Int. 2021; 2021:1772.) However, an Italian multicenter observational study, which enrolled 842 hospitalized patients with COVID-19, revealed no association between the use of statin and in-hospital mortality ($p = 0.185$). Interestingly, statin use was associated with a more severe disease (National Early Warning Score ≥5, $p = 0.025$), reflecting the presence of cardiovascular risk factors as dyslipidemia or coronary artery disease in

those patients. (Mitacchione G, et al. J Clin Lipidol. 2021 Jan-Feb;15(1):68-78.) **(Pages 23-24)**

Typos: Pg 11. sentence "Released from neutrophils in an inflammatory substrate, neutrophil extracellular traps constitute cell-free DNA structures, originating from decodensed chromatin, released to restrain pathogens." Revise the sentence to avoid a dangling modifier

Authors: Thank you for the comment.

"Another recently studied pathway of immunothrombosis in COVID-19 is associated with the formation of neutrophil extracellular traps (NETs). In response to certain stimuli, neutrophils enhance their antimicrobial activities by releasing NETs, composed of extracellular chromatin. Attached to these web-like DNA structures are histones and granule proteins such as myeloperoxidase (MPO), as well as cytosolic proteins. Activated neutrophils release nuclear DNA into the extracellular environment, where it can trap and neutralize pathogens. This process is termed NETosis (Thiam HR, et al. Annu Rev Cell Dev Biol. 2020 Oct 6; 36: 191–218)."

Pg 12. sentence "The formation of NETs in the vasculature results in platelet entrapment." This appears to be a sentence fragment; consider to revise

Authors: Thank you for the comment.

"It has been suggested that NETs provide the scaffold for fibrin deposition and platelet entrapment and subsequent activation." (Kambas K, et al. Front Immunol. 2012 Dec 18;3:385.)

Pg. 13. "In a cohort study of 1,914 patients presenting with ACS in the COVID-19 era; 7.75% was attributed to Takotsubo cardiomyopathy in contradiction to its former prevalence of 1.5-1.8% before the pandemic [50, 51]." Possibly too many words in the sentence; Consider to revise

Authors: Thank you for the comment.

"A recent study demonstrated a significant increase in the incidence of stress cardiomyopathy during the COVID-19 period (7.8%), compared with prepandemic timelines (1.5%-1.8%)".

Reviewer #6:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The article involved a lot of immunological mechanisms that are difficult to understand. Kindly simplify mechanisms by diagram.

Authors: We thank the Reviewer for the comment. Based on Reviewer suggestion, a new figure illustrating the main mechanisms discussed in the manuscript, has been added (Figure 4).

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. 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

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Authors: We are grateful to the Science Editor and Company Editor-in-Chief for their time and suggestions.