

PEER-REVIEW REPORT

Name of journal: *World Journal of Critical Care Medicine*

Manuscript NO: 86094

Title: New-onset atrial fibrillation among COVID-19 patients: A narrative review

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05824934

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Singapore

Author's Country/Territory: United States

Manuscript submission date: 2023-05-30

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-07-03 01:37

Reviewer performed review: 2023-07-09 06:53

Review time: 6 Days and 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This review paper investigates the pathophysiology of new-onset atrial fibrillation (NOAF) after COVID-19 disease and compared to that of persisting atrial fibrillation (AF). The topic is very interesting and should be published. Yet, the authors have misunderstandings about programmed cell death like apoptosis, and about inflammation and the release of proinflammatory cytokines by the immune system. The authors need to substantially revise the manuscript to properly address these misunderstandings before it can be accepted for publication. 1. Apoptosis is a non-inflammatory way of programmed cell death which is essential for health and homeostasis. The human body has a daily cellular turnover around 330 billion cells, and half of them are destroyed by apoptosis and cleared by efferocytosis [1]. Dysfunction of apoptosis and impaired clearance of apoptotic cells is the main cause of many diseases like autoimmunity, cardiovascular diseases and cancer [2]. 2. Localized transient acute inflammation is essential in resolving injurious stimuli and restoring health [3-6]. By using such a “self-destroy and rebuild” strategy, the immune system is able to eliminate most of the harmful stimulus like the SARS-CoV-2 viral infection, and restore health.

Only when a patient is under over-nutrition state with a lot of ectopic fats in the non-adipose tissues, lipotoxicity [7-9] becomes the dominant injurious stimulus for cell dysfunction and cell death, the harmful stimulus, lipotoxicity, cannot be eliminated by programmed cell death and inflammatory response, systemic and chronic inflammation will happen and persist, leading to all kind of diseases. In the event of viral infection, the degradation of infection damaged cells by macrophages creates more immunonutrition which worsens the overnutritiona and lipotoxisity leading to a lot of medical conditions including NOAF. 3. Unintentional plagiarism. From page 10, from line 169 to line 183, the paragraph "Synergism of activated neutrophils, producing reactive oxygen species ensuing structural and electrical remodeling, contributing to AF." is almost a word-to-word copy of "Activated neutrophils, recruited to endothelial cells, produce histotoxic mediators including reactive oxygen species [58]. Then immune cells, inflammatory cytokines (IL-6, IL-8, TNF α) and vasoactive molecules (thrombin, histamine, bradykinin, thromboxane A2, vascular endothelial growth factor) lead to enhanced endothelial cells contractility and the loosening of inter-endothelial junctions. [57], [58] The cytokines IL-1 β and TNF α activate glucuronidases that degrade the glycocalyx and upregulate hyaluronic acid synthase type-2, leading to increased deposition of hyaluronic acid in the extracellular matrix promoting fluid retention [58]. Together, these mechanisms lead to increased vascular permeability and vascular leakage. Finally, the virus can directly (via apoptosis and pyroptosis) impair endothelial cell function, because SARS-CoV-2-infected endothelial cells were detected in several organs of deceased patients [59]. Endothelial dysfunction increases oxidative stress, increases the formation proinflammatory cytokines and impairs nitric oxide-dependent vasorelaxation. Excessive production of reactive oxygen species is likely involved in the atrial oxidative injury, and the structural and electrical remodeling, contributing to AF [60]." (<https://doi.org/10.1016/j.ijcha.2020.100631>) References: 1. Sender R and Milo,

R. (2021) The distribution of cellular turnover in the human body. *Nat. Med.*, 2021, 27, 45-48. DOI: 10.1038/s41591-020-01182-9 2. Xu X, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Biosci Rep.* 2019 Jan 18;39(1):BSR20180992. DOI: 10.1042/BSR20180992. 3. Kuriakose T, Kanneganti TD. Pyroptosis in Antiviral Immunity. *Curr Top Microbiol Immunol.* 2019 Dec 25;10.1007/82_2019_189. DOI: 10.1007/82_2019_189. 4. Zhang, G., Wang, J., Zhao, Z. et al. Regulated necrosis, a proinflammatory cell death, potentially counteracts pathogenic infections. *Cell Death Dis* 13, 637 (2022). DOI: 10.1038/s41419-022-05066-3 5. Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell.* 2010; 140:771–776. DOI: 10.1016/j.cell.2010.03.006 6. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget.* 2017 Dec 14;9(6):7204-7218. DOI: 10.18632/oncotarget.23208 7. Schaffer JE. Lipotoxicity: Many Roads to Cell Dysfunction and Cell Death: Introduction to a Thematic Review Series. *J Lipid Res.* 2016 Aug;57(8):1327-8. DOI: 10.1194/jlr.E069880 8. Garbarino, J.; Sturley, S.L. Saturated with fat: new perspectives on lipotoxicity. *Curr. Opin. Clin. Nutr. Metab. Care*, 2009, 12, 110–116. DOI: 10.1097/MCO.0b013e32832182ee 9. van Niekerk, G.; du Toit, A.; Loos, B.; Engelbrecht, A.M. Nutrient excess and autophagic deficiency: explaining metabolic diseases in obesity. *Metabolism*, 2018, 82, 14-21. DOI: 10.1016/j.metabol.2017.12.007

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Manuscript NO: 86094

Title: New-onset atrial fibrillation among COVID-19 patients: A narrative review

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05213310

Position: Editorial Board

Academic degree: PhD

Professional title: Adjunct Professor, Full Professor

Reviewer's Country/Territory: Saudi Arabia

Author's Country/Territory: United States

Manuscript submission date: 2023-05-30

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-07-24 09:29

Reviewer performed review: 2023-07-24 09:54

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear Author(s), Please correct the following deficiency: 1. The study's introduction requires more organization. I trust that the author(s) will limit themselves to no more than three paragraphs. - The first paragraph should describe the significance of this study. - The second paragraph should describe the knowledge gap that the current paper intends to address. - The third and final paragraph should describe the research problem and how it will be addressed within the context of the study's purpose. 2. The final paragraph of the discussion section should be devoted to a review of the strengths and shortcomings of the current study, as well as a clarification of its future directions. I hope the author(s) will resolve this deficiency by adding a final paragraph that fulfills these requirements to the discussion section. 3. The conclusion of the study is very lengthy, and the primary query was not addressed: Was the research problem resolved, i.e., were the study's objectives met? I hope the author(s) will resolve this deficiency. 4. The number of references in this study is excessive and does not meet the requirements of this paper. Therefore, I expect the author(s) will reduce the number of references and retain only the essentials, as well as remove all non-recent references while relying on



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references from 2023 and five years prior. Good luck,

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Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06368927

Position: Editorial Board

Academic degree: Doctor, FACC, MD

Professional title: Assistant Professor, Senior Researcher

Reviewer's Country/Territory: India

Author's Country/Territory: United States

Manuscript submission date: 2023-05-30

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-07-25 04:27

Reviewer performed review: 2023-07-28 17:28

Review time: 3 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I congratulate the authors for brining together the literature on this very relevant and poorly studied topic. While the review focusses on an important issue, there are certain limitations which need to be set right. General comments: 1) The authors have discussed at length the details of NOAF in covid-19 and their pathophysiological mechanisms but in general the paper lacks clear structure and organization. I would rather like to see clear tables which underline the key differences in NOAF after Covid compared to persistent AF (in terms of pathophysiology, aetiologies, outcomes and management differences). This will help summarise your paper and make it easier for the readers to grasp. 2) Too much repetition of sentences. The authors keep making mention of the increased mortality and poorer outcomes in NOAF after covid time and again. Correct it. Specific comments: 3) Avoid putting excessive details in background about COVID-19. That is not the theme of this paper. So reduce the last 2-3 paragraph in background to a couple of sentences. 4) Reduce the discussion on pathophysiology and make it more crisp and straight forward. 5) Correct the statement in treatment (medications) section "In a study conducted by Tze-Fan Chao et al., it was observed that rate-controlling drugs



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have a lower risk of mortality in patients with AF compared to those without rate control". make it grammatically sound. 6) An important issue has not been discussed: the close association of coronary artery disease and atrial fibrillation. Many pathophysiological pathways you have discussed are common to CAD as well. I would suggest discussion of the association of these two closely linked disease processes. Add a paragraph and refer to recent integrative/narrative reviews linking the two diseases. I do not see in any of the literature you have shown, the discussion of CAD and NOAF. Was the rate of NOAF similar in those with or without underlying CAD. The same would have been discussed in the studies you have presented. Go through these studies and share details in regards to CAD. 7) The differences in management and outcomes in NOAF vs persistent AF needs to be discussed. You have simply put here management of paroxysmal/ persistent AF without any specificities on COVID-19 related NOAF.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Critical Care Medicine*

Manuscript NO: 86094

Title: New-onset atrial fibrillation among COVID-19 patients: A narrative review

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06368927

Position: Editorial Board

Academic degree: Doctor, FACC, MD

Professional title: Assistant Professor, Senior Researcher

Reviewer's Country/Territory: India

Author's Country/Territory: United States

Manuscript submission date: 2023-05-30

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2023-08-21 10:40

Reviewer performed review: 2023-08-21 14:19

Review time: 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors have adequately answered most of the concerns raised during the initial review. The addition of table differentiating between COVID related AF and de novo persistent AF is indeed relevant and improves the quality of manuscript. Other concerns too have been discussed by the authors at length.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Critical Care Medicine*

Manuscript NO: 86094

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Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05824934

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Singapore

Author's Country/Territory: United States

Manuscript submission date: 2023-05-30

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2023-08-21 03:02

Reviewer performed review: 2023-08-22 04:30

Review time: 1 Day and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

As the authors has properly addressed my previous review comments and revised the manuscript accordingly, the manuscript can now be accepted for publication in its current form.