August 17, 2023,

Dr. Wang

Editor-in-Chief, World Journal of Critical Care Medicine

Re: "*New-Onset Atrial Fibrillation among COVID-19 Patients: A Narrative Review*"

Dear Dr. Wang,

We would like to thank the Editors and Reviewers for their insightful comments. Attached, please find below our detailed responses to the Editor's and Reviewers' comments and our revised manuscript to be considered for publication in WJCCM.

We appreciate your time and effort in reviewing our manuscript and would be happy to make further revisions that you feel might be needed. We hope our manuscript is now suitable for publication in the World Journal of Critical Care Medicine.

Thank you for your consideration. Please do not hesitate to contact me if you have any questions or comments.

Sincerely yours,

Salim Surani

Peer-review report

Reviewer #3: This review paper investigates the pathophysiology of new-onset atrial fibrillation (NOAF) after COVID-19 disease and compared it 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.

Comment 1. Apoptosis is a non-inflammatory way of programmed cell death essential for health and homeostasis. The human body has a daily cellular turnover of 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].

Comment 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 stimuli like the SARS-CoV-2 viral infection, and restore health. Only when a patient is under an ***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 overnutrition and lipotoxicity leading to a lot of medical conditions including NOAF.

Authors' response to Reviewer #3 Comments 1 and 2:

We thank the Reviewer for their valuable feedback. To differentiate apoptosis as a natural, healthy, non-inflammatory mechanism from those involved in prolonged injury, where

excessive activation of inflammatory responses leads to vicious remodeling, the following modifications have been made in the revised manuscript:

In the ***Hypoxemia*** section (Page 10, lines 160-166):

"***Gramley et al. previously observed a close association between prolonged hypoxic and increased angiogenic markers in the atrium with AF.***[46] *With the persistence of hypoxia, an endoglin called CD105 would up-regulate, which is a homolog to the type III receptor of transforming growth factor-β; leading to extracellular matrix formation. It was hypothesized that cardiac hypoxia could provoke AF through the hypoxia-inducible factor pathway and over-expression of connective tissue growth factor and angiogenic genes like vascular endothelial growth factor.*[46]"

In the ***Discussion*** section (Pages 17, Lines 323-331), we implemented reference #2 from the Reviewer:

''*In addition to AG II, sustained AF is also fostered by the release of proinflammatory cytokines and tissue injury mediators such as tumor necrosis factor-a, IL-6, and IL-8. While the initial purpose of this cascade is to facilitate a beneficial "self-destroy and rebuild" process,*[66] *its continuous activation is a widely recognized initiator of fibroblast-to-myofibroblast transformation leading to atrial remodeling.*[8] *Therefore, the prolonged presence of inflammatory cascades, and myocyte apoptosis whether through spike protein binding to cardiomyocyte, cytokine storm, prolonged hypoxemia or altered ANS could also potentially leads to ion channel dysfunction and excessive matrix production; likely generating electrical and structural remodeling and predisposing persistent AF.*"

Comment 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, TNFα) 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-1β and TNFα 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 of 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)

Authors' response to Reviewer #3 Comment 3:

We thank the Reviewer for bringing this critical point to our attention. The following changes have been made to reflect the author's understanding of the cited articles rather than the reproduction of the same content (Pages 8-9, Lines 106-128):

"***Endothelial dysfunction*** *The cardioprotective role of ACE2 was discussed, but it also plays beyond that and acts as a regulator of the Kallikrein-Bradykinin (KKB) system by hydrolyzing the potent ligand bradykinin 1 receptor (B1R), this exerts a crucial vasodilator effect, which counterbalances RAS vasopressor effect.*[52, 57] *Declined vascular levels of ACE2 in COVID-19 patients lead to overactivation of the KKB system and* ***increased permeability.***[57] ***The heightened permeability leads to the recruitment of diverse immune cells, inflammatory cytokines, and vasoactive molecules to the site. Consequently, the production of reactive oxygen species and other cytotoxic mediators by activated neutrophils synergizes with the release of vasoactive molecules, including thrombin, histamine, bradykinin, thromboxane A2, and vascular endothelial growth factor (VEGF). This, in turn, enhances the contractility of endothelial cells and the loosening of inter-endothelial junctions,***

ultimately leading to vascular leakage.[58] Also, IL-1β and TNFa, are recognized for their ability to promote fluid retention by increasing glycocalyx degradation and upregulating hyaluronic acid synthesis, the ultimate result of which is an increased deposition of hyaluronic acid in the compromised extracellular matrix, promoting fluid retention.[58] Both mechanisms ultimately converge on vascular impairment as an endpoint.

While the impact of AF on the vasculature has been better studied, recent discoveries indicate a bidirectional relationship between the two.[59, 60] Endothelial dysfunction would further increase oxidative stress, proinflammatory cytokines, and impaired nitric oxide-dependent vasorelaxation.[55] Excessive production of endothelial reactive oxygen species has been linked to atrial oxidative injury, resulting in structural and electrical remodeling, contributing to AF. Interestingly, there is evidence that patients with coronary endothelial dysfunction are at increased risk for developing persistent AF. [59, 60] Up to date, no similar human studies are available, and the current pandemic could present an opportunity to investigate this link."

Reviewer #2: Dear Author(s), Please correct the following deficiency:

Comment 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.

Authors' response to **Reviewer #2 Comment 1:**

We acknowledge the Reviewer's comments. To address them, the "background" and "NOAF during COVID-19" sections were combined to make the introduction clear, as

well as enhance references and retain only the essentials. The background was modified as follows (Pages 4-5; Lines 10-45):

"As atrial fibrillation (AF) incidence was approaching an epidemic proportion,[1] in January 2020, the world health organization announced the preliminary determination of a novel coronavirus in Wuhan, China. By March 2020, the novel virus was recognized as a global pandemic.[2, 3] AF was reported as the most common arrhythmia in a multicenter review of Coronavirus disease (COVID-19) cases in 76 countries, with a prevalence of 19% to 21% of all hospitalized cases.[4] The new onset of atrial fibrillation (NOAF) among COVID-19 patients (referred to as COVID-19-related NOAF) raises concerns for unfavorable outcomes, especially in critically ill patients, regarding in-hospital mortality, length of stay in the intensive care unit, and survival.[5, 6]

In individuals whose AF has progressed, it has previously been observed that various factors, such as oxidative stress, atrial dilatation, calcium overload, inflammation, and myofibroblast activation, interact in a way that significantly contributes to the remodeling of the atrial extracellular matrix (ECM) and electrical properties. This ultimately results in the continuous presence of AF. Nevertheless, the possibility of AF persisting following a COVID-19 infection has not undergone comprehensive investigation, and there is currently a dearth of prolonged studies that evaluate the consequences of COVID-19-related NOAF.[7, 8] Furthermore, maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks.[9] However, there is a paucity of the data regarding persistence of AF after COVID-19 infection. The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer, and a significant increase in peripheral thromboembolic events observed in NOAF patients calls for further investigation of the management of COVID-19-related NOAF.[10, 11]

Similar to the past pandemics in history, the COVID-19 pandemic presents a chance to broaden our knowledge, despite the challenges it poses.[3] Our objective was to explore the underlying mechanisms of NOAF in COVID-19 patients, with a particular emphasis on factors that could sustain the occurrence of this arrhythmia. To pursue this a comprehensive, structured literature search was conducted through EMBASE and MEDLINE for articles published between December 2019 and 20th May 2023 that reported the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management

of NOAF in COVID-19 were investigated. The search terms include each of the following terms individually and in combination: new-onset atrial fibrillation, NOAF, AF persistence, persistent atrial fibrillation, SARS-CoV-2, COVID-19, SARS, coronavirus as described in the supplementary table.[12] Two investigators (F.T. and A.B.) independently screened studies for eligibility. We focused primarily on published research articles, systematic reviews, and observational cohorts. The title, abstract, and keywords were checked for relevance initially. Studies were excluded if not written in English."

Comment 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.

Authors' response to **Reviewer #2 Comment 2**

We thank the Reviewer for their comment. To address this comment, the final paragraph of the discussion section was modified as follows (Page 18; Lines 343-351) :

"While the conclusions drawn from this review are limited due to its non-experimental nature, it is evident that among various factors contributing to the development of NOAF in COVID-19, some have the potential to perpetuate AF. These factors include modulation of myocardial ACE2 expression, spike protein binding, cytokine storm, endothelial dysfunction, increased permeability, and hypoxemia, which have the potential to induce atrial, extracellular matrix (ECM), or electrical remodeling, thereby perpetuating atrial fibrillation (AF). To gain a more comprehensive understanding, further fundamental studies are required to explore the interplay between these factors. Additionally, prospective long-term studies are necessary to investigate the outcomes of patients who develop NOAF after experiencing COVID-19 infection in the long run (Figure-2)."

Comment 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.

Authors' response to **reviewer #2 Comment 3**

We have taken the Reviewer's suggestion into consideration and we have summarized conclusion as follows (Page 18; lines 354-364):

"Among several mechanisms that contribute to COVID-19-related NOAF, those exerting oxidative stress, such as modulating of myocardial ACE2 expression, endothelial dysfunction, spike protein binding and cytokine storms have the potential to contribute to changes in atrial structure, extracellular matrix (ECM), and electrical characteristics, which are common factors perpetuating AF. The electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal as maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks. The long-term outcomes of NOAF, including the persistence of AF after COVID-19 infection, remain unknown. Long-term prospective studies are needed to follow up patients with COVID-19 related NOAF to address this knowledge gap."

Comment 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 references from 2023 and five years prior.

Authors' response to **reviewer #2 Comment 3**

We have taken note of the Reviewer's feedback and made the necessary adjustments to the text, eliminating any repetitive references as suggested. Notably, we have integrated

the "NOAF during COVID-19" segment into the "background" section for better coherence. Additionally, we have provided a more concise overview of the epidemiology section while excluding outdated references and instances of redundant information. As a result, the overall number of references in the manuscript has been reduced from 100 to 67.

Reviewer #1: I congratulate the authors for bringing together the literature on this very relevant and poorly studied topic. While the review focuses on an important issue, there are certain limitations that need to be set right.
General comments:

Comment 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.

Authors' response to **reviewer #1 Comment 1**

We would like to thank the Reviewer for their comment. As per the Reviewer's suggestion, we have incorporated the term "COVID-19-related NOAF" within the manuscript's content. Furthermore, we have restructured the initial Table 1 into the revised **Table 1**, leaving only **Figure 1** to exclusively focus on highlighting the shared pathophysiology of both COVID-19-related NOAF and persistent AF. Your insightful guidance has significantly contributed to these improvements.

	COVID-19-RELATED NOAF	PERSISTENT AF
Etiology and pathophysiology	• Diminished availability of ACE-2 receptors contributes to myocardial hypertrophy, vasoconstriction, ROS production, oxidative stress, tissue inflammation, and fibrosis, all of which play a role in the development of AF. • Endothelial dysfunction leads to increased vascular permeability and leakage culminating in an overproduction of ROS leading to structural and electrical remodeling predisposing to AF. • CD147- and myocyte's sialic acid-spike protein interaction upregulate the expression of several cytokines and ROS that induce extracellular matrix degradation, cardiac remodeling, and fibrosis. • Excessive release of proinflammatory cytokines in cytokine storm leads to ROS production,	Steady generation of ROS triggered by sustained high-electrical activity, followed by intracellular Ca2+ overload together with atrial dilatation, mitochondrial ROS and activation of inflammatory and pro-fibrotic pathways progressively alters gene expression clinically relevant sheep model of persistent AF, leading to myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling, all of which would occur relatively slowly but reach critical levels when AF becomes persistent at a median time of about 2 months: • Oxidative stress by ROS released either by NOX2/4 or mitochondria is the first consequence, the persistence of which leads to shortened APD and RF through reducing rapid L-type Ca2+ current (I Ca,L) and increasing inward rectifier

	progressive myocardial cell apoptosis or necrosis, which may lead to conduction disturbances leading to AF. • Impaired gas exchanges and intrathoracic pressure swings lead to cardiomyocyte injury and increased frequency of premature atrial beats and induce AF. • ANS alteration: SNS-mediated calcium influx increases the frequency of delayed afterdepolarization and triggers AP; PNS activation mediated by intrathoracic pressure swing leads to shortening of right atrial ERP, and APD both induce AF. • Sodium and water resorption increases blood pressure and excretion of potassium increase the resting membrane and enhances depolarization predisposing to AF.	K+ current (IK1) promoting the formation and stabilization of rotor that world in a vicious cycle to preserve sustained high electrical activity. • Inflammation leads to profibrotic signaling in response to cardiac injury by promoting fibroblast-to-myofibroblast trans-differentiation leading to either through increased expression of TRP channels or miR-21 resulting in structural remodeling by atrial dilation and fibrosis that maintains AF

Risk factors	• Older age, • A history of myocardial, infarction, • Renal dysfunction, • Raised D-dimer levels, • Hypertension	Risk factors for progression to more persistent forms of AF among patients with paroxysmal AF and varying degrees of CVD per HATCH score is:[62] • Heart failure, • Older age, • Previous transient ischemic attack or stroke, • Chronic obstructive pulmonary disease, • Hypertension.
Outcomes	Among patients hospitalized with COVID-19 infection, 5.4% could develop NOAF. All-cause mortality rates are 45.2% vs 11.9% and MACE is 23.8% vs 6.5% for patients with versus without new-onset AF.[67]	Among patients with persistent AF all-cause mortality rate is 4.41% and MACE is 5.09%.[67]
Treatment	• The initial approach is to enhance the treatment of underlying factors. Hemodynamic instability warrants immediate cardioversion, provided that the risk of embolism is low.	• Hemodynamic instability warrants immediate cardioversion provided that the risk of embolism is low.[15] • A similar efficacy of rate versus rhythm control in all-cause mortality and MACE had been noted. Thus,

	• Rate control therapy is preferred over rhythm control unless hemodynamic instability warrants the addition of rhythm control e.g., with Amiodarone. • Anticoagulation: Unfractionated heparin, LMWH is safe to use. Use DOACs with caution as they interact with some antiviral medications. VKAs induce a state of vitamin K deficiency that could potentially influence susceptibility to contracting COVID-19.	Current recommend an individualized decision taking into consideration that a rhythm control is most likely to fail in patients with long-term persistent AF (> 1 year), in whom atrial substrate alteration is greatest.[67] • The choice of anticoagulation should be individualized based on the patient's comorbidities, like other indications for anticoagulation and renal function.

Comment 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.

Authors' response to **Reviewer #1 Comment 2**

We acknowledge the Reviewer's comments. The manuscript was extensively revised to avoid repetitions, and the modifications are highlighted using red color for the text.

Comment 3. Avoid putting excessive details in the 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.

Authors' response to **Reviewer #1 Comment 3**

As per the Reviewer's comments, the background section was reduced to three paragraphs and the modifications are as follows (Pages 4-5; Lines 10-45):

"As atrial fibrillation (AF) incidence was approaching an epidemic proportion,[1] in January 2020, the world health organization announced the preliminary determination of a novel coronavirus in Wuhan, China. By March 2020, the novel virus was recognized as a global pandemic.[2, 3] AF was reported as the most common arrhythmia in a multicenter review of Coronavirus disease (COVID-19) cases in 76 countries, with a prevalence of 19% to 21% of all hospitalized cases.[4] The new onset of atrial fibrillation (NOAF) among COVID-19 patients (referred to as COVID-19-related NOAF) raises concerns for unfavorable outcomes, especially in critically ill patients, regarding in-hospital mortality, length of stay in the intensive care unit, and survival.[5, 6]

In individuals whose AF has progressed, it has previously been observed that various factors, such as oxidative stress, atrial dilatation, calcium overload, inflammation, and myofibroblast activation, interact in a way that significantly contributes to the remodeling of the atrial extracellular matrix (ECM) and electrical properties. This ultimately results in the continuous presence of AF. Nevertheless, the possibility of AF persisting following a COVID-19 infection has not undergone comprehensive investigation, and there is currently a dearth of prolonged studies that evaluate the consequences of COVID-19-related NOAF.[7, 8] Furthermore, maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks.[9] However, there is a paucity of the data regarding persistence of AF after COVID-19 infection. The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer, and a significant increase in peripheral thromboembolic events observed in NOAF patients calls for further investigation of the management of COVID-19-related NOAF.[10, 11]

Similar to the past pandemics in history, the COVID-19 pandemic presents a chance to broaden our knowledge, despite the challenges it poses.[3] Our objective was to explore the underlying mechanisms of NOAF in COVID-19 patients, with a particular emphasis on factors that could sustain the occurrence of this arrhythmia. To pursue this a comprehensive, structured literature search was conducted through EMBASE and MEDLINE for articles published between December 2019 and 20th May 2023 that reported the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. The search terms include each of the following terms individually and in combination: new-onset atrial fibrillation, NOAF, AF persistence, persistent atrial fibrillation, SARS-CoV-2, COVID-19, SARS, coronavirus as described in the supplementary table.[12] Two investigators (F.T. and A.B.) independently screened studies for eligibility. We focused primarily on published research articles, systematic reviews, and observational cohorts. The title, abstract, and keywords were checked for relevance initially. Studies were excluded if not written in English."

Comment 4. Reduce the discussion on pathophysiology and make it crisper and more straightforward.

Authors' response to **Reviewer #1 Comment 4**

The Reviewer's suggestions were addressed by combining the discussion on the pathophysiology of COVID-19-related-NOAF to those perpetuating AF as follows (Pages 15-17, Lines 293-331):

"COVID-19-related NOAF is still not well studied. Mechanisms involved in the development of NOAF after COVID-19 infection could potentially lead to atrial remodeling and fibrosis, which can further perpetuate AF, as shown in ***Figure 2****. Clinical studies suggested that the majority of the patients with AF remain paroxysmal, though the electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain*

paroxysmal.[62] *However, in this study a sizable overlap was noted in mechanism inducing COVID-19 associated NOAF and those persisting AF.*

The mechanism involved in the progression of AF is a constellation of oxidative stress, inflammation, atrial dilatation, calcium overload, and myofibroblast activation, all of which are likely to be involved in one way or another in AF-induced ECM and electrical remodeling.[7, 8] *Interestingly, many of these mechanisms seem to be mutual with suggestive models of COVID-19-related NOAF.* ***(Figure-1)*** *and looking back to the mutual mechanisms of persistent AF and COVID-19-related NOAF, could explain the possible risk of developing persistent AF after NOAF in COVID-19 patients.* ***(Table-1 and Figure-1)***

In the working model of AF perpetuation by Jalife et al. oxidative stress and ROS are the cornerstone of maintaining AF.[8] *In that model a putative mechanism of AF perpetuation involves AGII stimulation, which triggers the release of ROS from activates nicotinamide adenine dinucleotide phosphate oxidases (NOX)2/4. This process leads to a rapid reduction in L-type Ca2+ current ($I_{Ca,L}$) and an increase in inward rectifier K+ current (I_{K1}) within a short timeframe (i.e., hours or days). These alterations result in the shortening of the atrial action potential duration and refractory period promoting the formation and stabilization of rotors of AF persistent. Subsequently, intracellular Ca^{2+} overload ensues, promoting triggered activity and apoptosis.* [63, 64]

Nevertheless, Ca^{2+} overload, together with atrial dilatation, mitochondrial ROS and activation of inflammatory and pro-fibrotic pathways progressively alters gene expression. The eventual outcomes of these persistent alterations entail myocyte hypertrophy, interstitial fibrosis and ion channel remodeling. When these processes collectively escalate to a critical threshold, it could lead to the persistence of AF. In an animal study, after two months of tachypacing, the arrhythmia progressed to persistent AF.[65] *However, no study is available on the same time frame in COVID-19 patients.*

In addition to AG II, sustained AF is also fostered by the release of proinflammatory cytokines and tissue injury mediators such as tumor necrosis factor-a, IL-6, and IL-8. While the initial purpose of this cascade is to facilitate a beneficial "self-destroy and rebuild" process,[66] *its continuous activation is a widely recognized initiator of fibroblast-to-myofibroblast transformation leading to atrial remodeling.*[8] *Therefore, the prolonged presence of inflammatory cascades, and myocyte apoptosis whether through spike protein binding to cardiomyocyte, cytokine storm, prolonged hypoxemia or altered ANS could also potentially leads to ion channel*

dysfunction and excessive matrix production; likely generating electrical and structural remodeling and predisposing persistent AF."

Comment 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 have a lower risk of mortality in patients with AF compared to those without rate control". make it grammatically sound.

Authors' response to **Reviewer #1 Comment 5**

Based on the Reviewer's comments, the statement was omitted, as we have revised the management.

Comment 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 a 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 regard to CAD.

Authors' response to **Reviewer #1 Comment 6**

We thank the Reviewer for this comment. We have made the following addition regarding atrial fibrillation and coronary artery disease to the manuscript (Pages 11-12, Lines 194-214):

"***Association with Coronary Artery Disease***

Growing evidence highlights a strong link between CAD and AF and several observational studies have indicated that CAD and AF aggravate each other. Shared risk factors encompassing

hypertension, diabetes mellitus, and obesity substantiate this linkage. Notably, AF incidence has been found to be higher in people with CAD compared to age-matched adults without CAD.[52]

Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. CAD adversely affects AF by promoting progression via re-entry and increasing the excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF in turn accelerates atherosclerosis and together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout the cardiovascular system. Inflammation and endothelial dysfunction remain central to both disease processes.[53]

Patients with CAD associated with NOAF or persistent AF have significantly higher morbidity and mortality, predisposing to heart failure, life-threatening ventricular arrhythmias, and major adverse cardiovascular events.[53] *A recent comprehensive analysis supports heightened AF risk in CAD patients, yet a causal AF-to-CAD link remains unestablished.*[52] *Management of concurrent CAD and AF centers on anti-thrombotic strategies, balancing stroke prevention and stent thrombosis avoidance, while cautiously mitigating bleeding risk. Current guidelines recommend up to one year of combined oral anticoagulant (OAC) and antiplatelet therapy, preferably P2Y12 inhibitors, or OAC monotherapy. However, the limited quality of evidence in these guidelines and persistently high bleeding risk constrain their clinical applicability.*[54, 55]"

Comment 7. The differences in management and outcomes in NOAF vs persistent AF needs to be discussed. You have simply put here the management of paroxysmal/ persistent AF without any specificities on COVID-19-related NOAF.

Authors' response to **Reviewer #1 Comment 7**

Thanks for the point. The management section was entirely changed to a COVID-19-related NOAF focus discussion as follows (Pages 12-15; Lines 216-291):

*"**Management***

Recognition: *NOAF recognition in patients with COVID-19 can be done with electrocardiography, telemetry, or implantable device interrogation. Close observation of vital signs and regular electrocardiograms help monitor for dysrhythmias such as AF in patients with COVID-19.*[54]

Evaluation: *The initial evaluation of COVID-19-related NOAF parallels the standard management for AF. This involves conducting a routine two-dimensional transthoracic echocardiogram to assess for structural irregularities. However, if indications of heart failure, hemodynamic instability, unexplained clinical deterioration, or planned cardioversion are present, expedited evaluation is warranted.*[15]

Transesophageal echocardiography should be obviated by the early start of anticoagulation in NOAF to detect left atrium thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures.[55]

Treatment goals: *Treatment goals are regardless of the type, treatment goals encompass three primary objectives: managing heart rate during episodes of AF; and achieving the restoration, sustained maintenance of normal sinus rhythm (rhythm control), and mitigating the risk of systemic or cerebral embolism linked to the heightened embolic risk associated with AF all while minimizing the impact of drug interactions.*[15, 56]

Rate and rhythm control: *The contemporary therapy of AF with rate control vs rhythm control strategies is still disputed, there is a scarcity of data regarding the effectiveness of rhythm and rate control approaches for COVID-19-related AF. Current recommendations are based on acute management of AF in COVID-19 disease and long-term data is not available.*[55, 56] *Enhancing the treatment of underlying factors such as hypoxemia, inflammation, and potentially reversible triggers (like hypokalemia, hypomagnesemia, and acidosis) seems to form the empirical foundation for managing these cases. As with other settings, if NOAF is suspected to be a contributing factor to hemodynamic instability immediate cardioversion should be considered. Although, for the remaining patients who do not urgently require cardioversion, the decision to proceed should be weighed against the availability of necessary equipment and medical personnel, as well as the potential risk of virus transmission with intubation. In critically ill patients with compromised hemodynamics due to NOAF, intravenous amiodarone is the preferred antiarrhythmic medication for rhythm control.*[57]

Hospitalized patients who have developed COVID-19-related NOAF and are undergoing antiviral treatment while maintaining hemodynamic stability should give precedence to

discontinuing their anti-arrhythmic medications. Instead, the preferred approach involves initiating rate control therapy using beta-blockers or non-dihydropyridine calcium channel blockers, along with or without digoxin, unless contraindicated.[56] This approach ensures the safe administration of antiviral medication without the potential risk of QT prolongation.[55, 56]

Amidst a COVID-19 infection, the potential for QT interval-related risks could be heightened due to the simultaneous utilization of anti-arrhythmic medications with other QT-prolonging medications (such as hydroxychloroquine, azithromycin, lopinavir/ritonavir), along with factors like myocardial inflammation and electrolyte imbalances (like hypokalemia, hypomagnesemia, and/or hypocalcemia).[58] It's crucial to assess potential drug interactions, including those between antiviral and antiarrhythmic drugs, prior to initiating therapy.[55]

Unless dealing with highly symptomatic AF cases, such as individuals with AF-related heart failure or those experiencing medically refractory AF resulting in frequent emergency room visits, all AF ablation procedures ought to be delayed for a minimum of three months after recovering from a COVID-19 infection.[55]

Prevention of thromboembolic events: As a general guideline, for patients with a history of prior stroke, TIA, or a CHA2DS2-VASc score >2, who subsequently develop AF, oral anticoagulation is recommended.[15] Given that hospitalized COVID-19 patients are generally over the age of 65 and often have multiple underlying health conditions, a significant proportion of individuals with AF necessitate prolonged anticoagulation therapy.[11] Hemodynamically stable COVID-19 patients presenting with atrial AF during their hospitalization have treatment including unfractionated heparin, low molecular weight heparin (LMWH), or direct oral anticoagulants (DOACs). The specific choice among these options is influenced by factors like the suitability of oral administration, renal function, and additional clinical aspects. It's important to highlight that certain medications for COVID-19 treatment could potentially interact with DOACs. Lopinavir/ritonavir may create a potential interaction with DOACs through cytochrome P450 CYP3A4 interaction, and antimalarial drugs could influence DOACs via P-glycoprotein inhibition. If such interactions are pertinent, there may be an increased risk of bleeding, underscoring the need to avoid DOACs. Given this scenario, DOACs are favored over vitamin K antagonists (VKAs) due to their more favorable safety profile and standardized dosing schedule.[56]

VKAs are also considered for specific subsets of patients, including individuals with mechanical prosthetic valves or antiphospholipid syndrome. While VKAs typically induce a temporary deficiency of vitamin K, the observed lower levels of vitamin K in patients with COVID-

19 compared to healthy individuals suggest a need for additional investigation regarding the utilization of VKAs in COVID-19 patients.[59] The precise mechanisms driving this connection are yet to be fully understood.

The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer, and a significant increase in peripheral thromboembolic events observed in NOAF patients calls for further investigation of the management of COVID-19-related NOAF.[10, 11] Since heparins are unlikely to interact with drugs used in COVID-19 treatment, they represent a safe and attractive option for stroke prevention in AF patients who are hospitalized due to COVID-19. Remarkably, beyond their antithrombotic effects, heparins also possess anti-inflammatory properties that could be pertinent in this context.[55] Following recovery from COVID-19, continuation of long-term anticoagulation should be based on the CHA2DS2-VASc score."