Dear Editors and Reviewers of the *Acta Médica Portuguesa*

Thank you for your thorough review of our work. We have modified the text according to the suggestions made.

We thank you for your time and for your help in improving this review,

Warm regards,

Maria Trêpa

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Notas do editor:

- com o objectivo de optimizar a legibilidade do seu artigo e assim incrementar potencialmente as citações do mesmo, recomendamos que os conteúdos redigidos em inglês sejam revistos por um "native speaker", tradutor qualificado ou empresa especializada em serviços de "language polishing"

O conteúdo foi revisto por um native speaker.

- o resumo e o abstract deverão estruturar-se de forma semelhante ao do artigo, com um parágrafo independente para cada uma das secções;

O resumo foi restruturado em português e inglês.

Introduction: Cardiovascular complications associated with the COVID-19 pandemic are being reported increasingly.

Methods: Narrative review for relevant articles on the topic.

Risk factors: Classical cardiovascular risk factors, like age, obesity, diabetes, and hypertension are linked to adverse outcomes in COVID-19 patients.

Cardiovascular complications: Clinical presentation includes silent myocardial injury, acute coronary syndromes, thromboembolism, arrythmias and heart failure. There are multiple mechanisms of cardiac injury that are not mutually exclusive. Approach to diagnosis and management should be done according to usual practice while considering the particularities of COVID-19 infection.

Conclusion: The interaction between COVID-19 and the heart is complex and manifests in multiple ways. Regardless of the clinical presentation, cardiac complications convey a worst prognosis. They should be actively monitored and treated accordingly.

- na listagem final de referências deverão ser identificados os seis primeiros autores das obras consultadas, e só depois fazer-se uso da expressão "et al";

- na listagem final de referências, as ref.ªs nr 22 e 23, entre outras, estão incompletas, não indicando o volume nem o nr de páginas dos artigos consultados

A bibliografia foi revista e alterado o estilo de acordo com a recomendação. Foi utilizada uma formatação automática do programa endnote X7.

Alguns artigos são “e-pub ahead of print” pelo que ainda não tem disponível volume e número de paginas.

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Revisor C:

Trepa and colleagues provided a manuscript which is a narrative review about the cardiovascular complications of COVID-19 infections. The topic is interesting but I have some comments, most of them regarding accuracy and a few about content.

Major comments:

Due to the nature of the review (which should be explicitly mentioned at least in the abstract but also in the title), I see the methods section as inadequate and uninformative.

R: The title was changed to include the word review.

The methods were made clearer:

A narrative review using PubMed was conducted using the keywords“COVID-19” or “SARS-COV-2” together with “cardiovascular”, “cardiac”, “arrythmia”, “myocardial injury”, “myocardial infarction”, “ pulmonary embolism”, “out-of-hospital-cardiac-arrest” and “heart failure”. The authors included prospective studies, retrospective studies, reviews, meta-analysis, clinical guidelines and guidance documents and case reports. . Relevant articles published in English were screened and included only after critical review by the authors.

In the risk factors of COVID-19 infection the authors cite articles that support that CV risk factors are risk factors for severe disease and not for the infection as mentioned by the authors. In fact the cited landmark Danish cohort states that “In general, we only observed minor differences in age, sex, medical history and prior drug use between PCR-positive cases and test-negative individuals”. I am not sure if the subtitle “Risk factors for COVID-19 infection” fits as authors only accurately addressed risk factors for severe disease.

R: Thank you for your comment. This section was rewritten to be more accurate.

Subtitle: Risk factors for severe COVID-19 infection

First paragraph: Classic cardiovascular risk factors, namely, hypertension, diabetes and obesity, are frequent comorbidities in COVID-19 patients and convey an increased risk for adverse outcomes(5-9)

In heart failure subchapter: the authors missed pulmonary embolism as a cause of right-sided acute HF;

Pulmonary embolism was added.

it is not clear why hypervolemia can be a issue is these patients; most of the subchapter does not include any novelty and corresponds to usual (non-COVID 19) management of HF (since “Careful assessment…” until the end of the subchapter)

Hypervolemia is mentioned as it is a frequent cause of HF decompensation and is more likely to occur in patients where infection is the main focus. Fluid balance is harder, especially in patients in shock, and there is a tendency to treat hypotension with fluids, frequently overlooking the hemodynamic profile of the patient and the heart failure.

In the authors experience, hypervolemia frequently complicates the course of management in these patients and deserves mention.

The authors failed to identify the paper from Harrison, Stephanie L., et al.

"Atrial fibrillation and the risk of 30‐day incident thromboembolic events, and mortality in adults≥ 50 years with COVID‐19." Journal of Arrhythmia (2020) <https://emea01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1002%2Fjoa3.12458&amp;data=04%7C01%7C%7Cefd2f5345c3d418b6c4608d8d9aaeef0%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C637498675455894333%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&amp;sdata=%2FmU2EVfFd9jSErjq02wvFA3ioBNxCFyCqLzT6Z0%2Bba0%3D&amp;reserved=0>, which is currently the major paper evaluating the association of COVID-19, Afib and thromboembolic events.

Thank you for the suggestion, we added this article to our review: AF is one of the common chronic comorbidities found in patients deceased due to COVID-19 (43). In a large propensity score matched study of COVID-19 patients aged ≥50 years, AF significantly increased short-term mortality and thromboembolic events (44).

The explanation to why this article was not originally included relates to timing. This paper was first published in 11.12.2020. By this date our main research was concluded (this review was originally submitted to AMP in 22nd December 2020).

The authors missed to mention pericardial disease (including

myopericarditis) as a CV complication which might be one of the causes for the high rate of non-obstructive CAD in coronary angiography following STEMI suspicion.

A pericarditis subtitle was added:

## Pericarditis and pericardial effusion

Isolated pericarditis has been seldomly reported in relation to COVID-19 infection, however, pericardial effusion accompanying myocarditis has been reported in up to 50% of cases (20). In the available case reports (44, 45), the clue for the diagnosis was the typical chest pain, and the evolution was benign. Regarding treatment, experts recommend maintaining colchicine, while reserving ibuprofen for worsening pleuritic pain. For fever and other systemic symptoms, paracetamol should be preferred. Furthermore, corticosteroids and anakinra (a recombinant modified version of the interleukin 1 receptor antagonist protein) can be considered to treat both situations (46).

As for myocarditis the need for systematic exclusion of coronary disease was added in the myocarditis subtitle.

If the definition of cardiovascular includes pulmonary embolism, perhaps it should have also a subchapter about stroke.

Thank you for the suggestion. This topic was not included due to the word limit and since it could also be integrated in a “neurological complications” review.

Out-of-hospital cardiac arrest was shallowly approached in the arrhythmias subchapter but it deserves its own subchapter due to the growing evidence and interest about the topic

The authors agree that this is an interesting topic. The growing evidence and complexity of the topic makes it challenging to expand in this general review of cardiovascular complications and still respect the word limit. We separated OHCA creating a subtopic and added selected new information.

“Since the start of the COVID-19 pandemic an increase - of out-of-hospital-cardiac-arrest (OHCA) has been consistently reported worldwide (46-49) This rise was accompanied by a reduction in survival from resuscitation efforts. Reasons appointed include longer times of emergency services response, fewer shockable rhythms and less bystander initiated cardiopulmonary resuscitation. This concerning rise in OHCA is the more severe reflection of the indirect impacts of the pandemic. “

Minor comments:

“Pathophysiology mechanisms” is not correct. Should not it be:

Pathophysiological mechanisms?

Thank you. It was corrected.

Regarding myocarditis, the authors state that “Endomyocardial biopsy is the gold standard and a class I indication in persisting severe HFand fulminant myocarditis” without reference, but should they perform the recommended pathway as stated in Caforio’s paper (your reference 18) “All patients with clinically suspected myocarditis should be considered for selective coronary angiography and EMB”. ?

Thank you for the suggestion. We included the need to exclude coronary disease in the text.

“ Myocarditis diagnosis involves well defined criteria from four different categories: symptoms, EKG, troponin elevation and imaging (echocardiography and cardiac magnetic resonance [CMR]) (18). All patients with suspected myocarditis should have coronary disease excluded. Endomyocardial biopsy is the gold standard and a class I indication in persisting severe HF and fulminant myocarditis.”

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Revisor D:

O manuscrito em avaliação é uma revisão bibliográfica cujo objectivo foi o de reportar as complicações cardiovasculares da infecção por SARS-CoV2. Trata-se de um tema actual desenvolvido de forma completa mas simultaneamente simples o que facilita a sua leitura e consulta. O manuscrito encontra-se correctamente redigido apresentando-se estruturado de acordo a temática. Em primeiro lugar e após uma breve introdução são elencados os factores de risco apresentados pelo doente e relacionados com complicações e prognóstico, a fisiopatologia da infecção e finalmente as suas complicações cardiovasculares. O título e o resumo são adequados espelhando a intenção dos autores.

Analisando a frequência com que o tema tem sido abordado na literatura científica, foram encontrados na PubMed 1114 revisões publicadas no último ano. Os autores referenciam adequadamente algumas das publicações consideradas mais pertinentes nesta área.

Concluímos declarando que o manuscrito merece publicação na AMP e que pertinência do tema justifica a sua publicação a curto, médio prazo.

Trata-se de um tema atual e pertinente

R: Muito obrigado pelos comentários e revisão efetuada.

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Revisor E:

In this review article, Trêpa et al. provide a narrative review of the present knowledge on the cardiovascular manifestations of SARS-COV2 infection, spanning from arrhythmias to acute coronary syndromes, myocarditis, and acute heart failure. The authors certainly realize the challenge of writing a review article on a topic in constant evolution and where it’s difficult to keep up with the output of scientific data. The article is well written and concise, and the conclusions seem appropriate in light of the current knowledge, which is, of course, constantly evolving. I have a few comments and suggestions for improving the manuscript:

1)   I think that a little bit more emphasis should be put on what we don’t currently know about the cardiovascular manifestations of COVID-19.

A lot has been learned in a year, but the knowledge gaps are still enormous.

I think this should be more clearly stated in the manuscript;

Thank you, we added this in the introduction.

This clinical review focuson the most common cardiovascular complications associated to COVID-19 infection and their undelying mechanisms. Bearing in mind this topic is in constant evolution and that there are still significant uncertainties, we aim to provide a clinical update of the latest evidence

2)   Pericardial involvement seems to have been largely overlooked in this review. It should be noted that approximately 10% of cases of COVID-19-associated myocarditis have pericardial involvement with pericardial effusion, and that data from several case reports suggest that

COVID-19 pericardial effusions are usually sterile, suggesting a secondary inflammatory process, rather than pericardial infection;

Thank you for the comment. We added a focused pericarditis subchapter.

## Pericarditis and pericardial effusion

Isolated pericarditis has been seldomly reported in relation to COVID-19 infection, however, pericardial effusion accompanying myocarditis has been reported in up to 50% of cases(20). In the available case reports(44, 45), the clue for the diagnosis was the typical chest pain and the evolution was benign. Regarding treatment, experts recommend maintaining colchicine while reserving ibuprofen for worsening pleuritic pain. For fever and other systemic symptoms paracetamol should be preferred. Furthermore, corticosteroids and anakinra can be considered to treat both diseases(46).

3)   When discussing the potential cardiovascular adverse effects of pharmacological therapy to treat COVID-19, the authors mention hydroxicloroquine and azithromycin, which were used without evidence in the early stages of the pandemic. Although I find the reference appropriate, I absolutely think it should come with a warning that these drugs have since been proven ineffective against SARS-COV2 infection. A brief mention to the drugs that have in fact been shown to work also seems warranted in this review;

In a study assessing the QT interval in COVID-19 patients, the hydroxychloroquine-azithromycin combination regimen was not associated with arrhythmic fatalities and none of the dead had a QTc >500 ms (50). The National Institutes of Health COVID-19 treatment guidelines panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized and nonhospitalized patients. In fact, recent randomized clinical trials concluded that neither hydroxychloroquine alone nor hydroxychloroquine plus azithromycin improved clinical outcomes compared to usual standard of care (Peter Horby, Marion Mafham, Louise Linsell, Jennifer L Bell, Natalie Staplin, Jonathan R Emberson, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv 2020.07.15.20151852; doi: <https://doi.org/10.1101/2020.07.15.20151852>; Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med. 2020 Nov 19;383(21):2041-2052). In addition, data from observational studies did not consistently show evidence of a benefit for hydroxychloroquine, with or without azithromycin, in hospitalized patients with COVID-19 (Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Jun 18;382(25):2411-2418).

4)   I would also suggest taking a more cautious approach when it comes to the prevalence of several of these cardiovascular manifestations. We should acknowledge that many early reports were fraught with selection bias, and tended to overestimate the prevalence and severity of several complications.

For example, early reports on post-COVID myocarditis in athletes suggested a relatively high prevalence, but larger and more recent series show a much smaller figure, of 3% or less;

We added in the introduction that there are important knowledge gaps and that we have to base our review on the available evidence. We also updated this review with more recent (and robust) studies and eliminated early studies that probably overestimate the prevalence of some risk factors and complications.

5)   The impact of the COVID pandemic is briefly mentioned in terms of delays in seeking and delivering medical treatment. I would suggest adding a reference to its impact on the diagnosis of heart disease

(doi.org/10.1016/j.jacc.2020.10.054)

This reference was added in the ACS subchapter:

Importantly, the general ACS admission rate (non-COVID related) during the first wave of the pandemic, decreased up to 54% according to an international report(25). Likewise, a reduction in coronary angiography and other diagnostic tests was noted(26).

Minor issues:

English writing is generally good, but some occasional typos should be corrected. Here are some examples: “arrythmia” instead of “arrhythmia” (this one is recurrent in the manuscript); “quantitively”, “catherization”, etc.

Thank you. These typos were corrected and the manuscript was revised by a native English speaker.

“In one report the SARS-COV-2 particles outside the cardiomyocytes” – last sentence in the myocarditis section, seems like a fragment – please revise

It was revised as follows:

The timing of presentation is currently uncertain with reports of symptoms weeks after the COVID-19 infection(23). Furthermore, histological evidence of COVID-19 inside the cardiomyocyte is unavailable, however, one report found particles outside the cardiomyocytes (24).

Revisor F:

Cardiovascular complications of COVID-19 infection: a brief update

Comments to the author

Dear colleagues, I have read with great interest your manuscript regarding the cardiovascular complications of COVID.

I congratulate you on this relevant, comprehensive and well written review.

It is important to review this topic in a balanced and evidence-based manner given the importance of the disease in current times.

 I hope that my comments will help you improve the quality of the manuscript.

Abstract:

1. In the description of the methods I would suggest “narrative” review instead of “literature” review. This is to emphasize the non-systematic nature of the research methods.

Thank you. The methods sections was revised according to the suggestions.

A narrative review using PubMed was conducted using the keywords“COVID-19” or “SARS-COV-2” together with “cardiovascular”, “cardiac”, “arrythmia”, “myocardial injury”, “myocardial infarction”, “ pulmonary embolism”, “out-of-hospital-cardiac-arrest” and “heart failure”. The authors included prospective studies, retrospective studies, reviews, meta-analysis, clinical guidelines and guidance documents and case reports. . Relevant articles published in English were screened and included only after critical review by the authors.

2. It seems to me that it is inappropriate to have a “results” section in a non-systematic review of the literature.

The abstract was restructured:

Introduction: Cardiovascular complications associated with the COVID-19 pandemic are being reported increasingly.

Methods: Narrative review for relevant articles on the topic.

Risk factors: Classical cardiovascular risk factors, like age, obesity, diabetes, and hypertension are linked to adverse outcomes in COVID-19 patients.

Cardiovascular complications: Clinical presentation includes silent myocardial injury, acute coronary syndromes, thromboembolism, arrythmias and heart failure. There are multiple mechanisms of cardiac injury that are not mutually exclusive. Approach to diagnosis and management should be done according to usual practice while considering the particularities of COVID-19 infection.

Conclusion: The interaction between COVID-19 and the heart is complex and manifests in multiple ways. Regardless of the clinical presentation, cardiac complications convey a worst prognosis. They should be actively monitored and treated accordingly.

Introduction:

4. Death rate or case-fatality rate ?

Case fatality rate indeed. Thank you. The current global case fatality rate is 2.2% (1, 2)

5. The typical manifestation of COVID-19 infection in severe cases is viral pneumonia.

This was corrected. The typical manifestation of severe COVID-19 infection is viral pneumonia. However, the clinical picture varies widely from asymptomatic or mild flu-like symptoms, often accompanied by anosmia and ageusia, to an acute respiratory distress syndrome (ARDS), with or without cardiovascular manifestations

6. To cite early data from China is inappropriate when referring to the % of severe cases. In those days the case definition was different and many asymptomatic patients were not accounted for.

Thank you, this was corrected by using a recent meta-analysis and meta-regression.

In a recent meta-analysis the intensive care unit admission rate was 10.9%(4).

7. How do the cardiovascular complications differ from other pneumonias ?

 Interesting question. Comparative data is very scarce as no other viral disease had this impact and was this extensively studied regarding complications. Although theoretical considerations can be made, at this stage, it is difficult to support them with hard facts from well conducted studies. For viral myocarditis for instance, COVID-19 doesn’t appear to be particularly “cardiotropic”. For ACS, we learned from influenza the relation between viral mediated inflammation and the instabilization of coronary plaques.

But for thromboembolic complications there is some evidence that COVID-19 mechanisms of endothelial injury are particularly nefarious with higher reported rates of VTE than for H1N1.

For pneumonias in general is even harder to compare as they caused by multiple microorganisms or other agents precluding direct analysis.

However, the final pathway, namely the ongoing inflammation leading to endothelial injury and ARDS is probably similar in all severe pneumonias.

Do cardiovascular complications occur in severe cases, in all cases ?

Cardiovascular complications are more frequent in severe cases. However, in our experience , they also appear in patients with mild or otherwise asymptomatic disease. In other words, some patients seem to present with only CV complications. But clear data on the prevalence of CV complications as single/isolated manifestations of COVID-19 is lacking.

8. Only in the last sentence of introduction do the authors refer that the review is about the “mechanisms”. This should have been pointed out later.

Thank you for the suggestion. We changed the introduction.

Methods:

9. In a narrative review, such as this one, it is not common to have a methods section given the non-systematic nature of the work.

The methods sections was included in compliance with the AMP journal rules for publication.

Risk factors for COVID-19 and adverse outcomes

0. Is this about risk factors for COVID infection ? For COVID outcome ? Or for cardiovascular complications in COVID infection ? The title is misleading.

 Thank you, we corrected the title to: Risk factors for severe COVID-19 infection

11. “The presence of these comorbidities conveys an increased risk of developing severe forms of COVID-19 infection: in the study from China 5, 39% of the critically-ill had at least one comorbidity (vs. 24% of the patients with milder disease).” This sentence alone does not support and independent association between comorbidities and outcome. The subsequent studies cited seem to be more appropriate and for simplicity only the main results are described by the authors.

Thank you. That sentence was eliminated to avoid confusion. We agree that early studies are less informative.

The presence of these comorbidities conveys an increased risk of developing severe forms of COVID-19 infection:The New York study (9) highlighted obesity as a significant risk factor for mechanical ventilation. A meta-analysis(6) found that cardio or cerebrovascular disease increased 3 times the risk of developing severe manifestations of COVID-19. In a nationwide Danish study(8), risk factors for death included age (odds ratio [OR] 15 for 70-79 years, when compared with the 50-59 years age group), male sex, co-morbidities and chronic diseases. Likewise, the presence of ischemic heart disease and heart failure(HF) increased the risk of hospitalization (OR 1.4 and 2.6, respectively). In the Guo et al (10) study, mortality in patients with previous cardiovascular disease was 38% if they did not have troponin elevation during hospitalization, whereas rising to 69% in those with elevated troponin

12. The troponin cannot be viewed as a risk factor, since it is a biomarker for myocardial injury. This should in my view de reported in subsequent sections.

 Thank you. This was simplified and put in the myocardial injury section.

Pathophysiology

 13. I think it would be interesting to reflect on which of these pathophysiological mechanisms are unique to COVID. The mechanisms described by the authors are part of the concept of Systemic Inflammatory Response Syndrome, which is known to occur in response to severe infectious and non-infections insults to the organism, and was extensively used in the past to characterize septic syndromes. In the authors opinion, is COVID just another etiology of SIRS which is important today because of the pandemic, or does COVID has unique mechanisms to damage human cells and systems ?

 Thank you for your important question. In the authors opinion the COVID-19 probably does incite an unique immunological response from the host in the beginning of infection. However once it is widespread and severe we believe it enters the vicious cycle of SIRS and it has less to do with specific viral characteristics and more to do with the hosts response and perpetuation of (mal)adaptative mechanisms. Understanding the particularities of the initial interaction between COVID-19 and host will be critical to develop effective treatments. Although the authors would like to expand further on these considerations, we had to focus on a clinical and practical review of topics we are most comfortable with.

Cardia complications of COVID-19 infection

Myocardial injury

14. It should be clarified the type of troponin essays, if high-sensitive or not. “Zhou et al16 found troponin elevations in more than 50% of non-survivors that had exponential troponin values after the 10th day of illness.” This type of cross-sectional analysis is in my view not informative about the impact of troponin. One would have to compare non-survivors with survivors and adjusted for cofounders. The same sentence could probable be said about every disease admitted to intensive care.

Myocardial injury in infected patients can occur by the multiple mechanisms mentioned earlier. It is expressed quantitively by the release of troponin. Troponin elevation occurs in 17 to 22% of hospitalized patients with COVID-19 infection (15, 16). Myocardial injury is not a clinical diagnosis in itself, but troponin elevation is linked to adverse prognosis in early observational studies (10, 16). A subsequent study using cox regression found a ~4.2 (95% CI, 1.92-9.49) higher risk of death in patients with cardiac injury) (15). A review suggests monitoring troponin at baseline for all patients, and then every 48 hours in intermediate-high risk patients. While this might help risk stratification and provide clues to a potential cardiac complication, the document also reinforces the need for good clinical judgment when interpreting the results(17).

15. “An independent association between a higher risk of complications and death in patients with cardiac injury (hazard ratio 4.3 and 3.4,

respectively) was also reported.” It would be more informative to give confidence intervals of the hazard ratio. Was this adjusted for covariates ?

 Yes, it was done using a Cox regression model. The text was corrected.

A subsequent study using cox regression found a ~4.2 (95% CI, 1.92-9.49) higher risk of death in patients with cardiac injury)

Myocarditis

16. I would add only the fact that the treatments used have not been tested in randomized clinical trials and result from the treatment of severe COVID itself and from the treatment of other etiologies of myocarditis.

Thank you, the following sentence was added: However none of these treatments have been tested in specific trials.

17. The last sentence is not clear. Please review.

 Indeed it was missing words. It was reviewed has follows: In one report the SARS-COV-2 particles were found outside the cardiomyocytes

Heart failure

18. I would suggest adding a sentence or two referring summarizing the evidence and consensus regarding ACEi use in COVID patients with heart failure.

 This was added: Of note, despite initial controversies with the use of ACE-inhibitors, large cohort studies (37, 38) and a randomized trial (39) found no association between ACE inhibitors and adverse outcomes.

Arrhythmias

19. “hydroxycloroquine and/or azithromycine” these are exemples but are drugs can have similar effects.

 Thank you for your comment.

Pulmonary embolism

20. In my view, it would be interesting to our readers to refer to the % of thromboembolism events in patients admitted to the ICU with other etiologies of pneumonia and respiratory failure. This would help to put COVID numbers in perspective.

 This information was added using the comparative that we more sought best: the H1N1 influenza crisis.

Pulmonary embolism (PE) is one of the more severe thromboembolic manifestations. Recent studies report overall incidences of PE in COVID-19 patients between 1.1-3.4% (50, 51), but mounting up to 17-27% in critical patients(52, 53). In an autopsy study, PE was the direct cause of death in 33% of COVID-19 patients (54). These rates are higher than previous reports for other infections. For instance for H1N1 influenza the venous thromboembolism rate were ~6%(55).

21. Clinical trials regarding anticoagulation strategies in COVID patients are ongoing. In severe patients, adverse effects led to trial discontinuation on the possibility of harm. The contrary was observed in moderate patients. If the authors consider appropriate, I think it would be interesting to refer to these trials in the discussion, although the analysis is complex (REMAP-CAP, ACTIV-4, and ATTAC).

Thank you for the suggestion. It would be interesting to include but due to the word limit we had to opt to keep it focused.

Conclusion

It is very well written and balanced.

Thank you

Revisor G:

This is a well structured revision and well written manuscript of the potential cardiovascular complications of Covid 19 infection, and could be a good contribute for a quick update of this topic, so I think it should be published.

My only remark is on the chapter referring to Myocarditis, where the last sentence "In one report the SARS-COV-2 particles outside the cardiomyocytes." seems to be unfinished and should be rephrased.

Thank you for your comments. The sentence was rewritten: The timing of presentation is currently uncertain with reports of symptoms weeks after the COVID-19 infection(23). Furthermore, histological evidence of COVID-19 inside the cardiomyocyte is unavailable, however, one report found viral particles outside the cardiomyocytes (24).