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The impact of chronic cardiovascular disease on COVID-19 clinical course

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Ref.: Ms. No. JCTRes-D-22-00032
The impact of chronic cardiovascular disease on COVID-19 clinical course
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Dear Miss Kajimoto Magalhães,

A top expert in the field has now commented on your paper. You will see that the reviewer raised some critical points, that led to a rejection verdict. However, since the CAPACITY/LEOSS study that the reviewer alludes to excluded a Brazilian cohort, the editorial board wishes to give you a chance at considerably revising the paper in line with the reviewer's commentary. Please note that the points raised must be sufficiently addressed if we are to reconsider the manuscript for re-review. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jun 02, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #2: The authors report a retrospective, single centre, case-control study of 2675 patients to assess whether pre-existing cardiovascular disease (CVD) is an independent risk factor for death in patients hospitalised with COVID-19.

Points for consideration

1) Aim and rationale
The research question is appropriate and of scientific interest and the general approach is appropriate. The authors make a statement that no other studies have employed multivariate analysis to explore the relationship between CVD and COVID-related mortality, however a recent publication in the European Heart Journal from the CAPACITY-COVID and LEOSS groups (https://doi.org/10.1093/eurheartj/ehab656) has done just this and in a larger population.

2) Classification of cardiovascular disease.
a. The authors include arterial hypertension as a diagnosis of CVD. While this is entirely appropriate, all of the other CVD diagnoses relate purely to cardiac, not cardiovascular, disease. Moreover, other similar studies have categorised arterial hypertension as a risk factor, rather than cardiovascular disease. If arterial hypertension is included, should not other arterial diseases such as peripheral vascular disease, or cerebrovascular disease be included as well? In the studied population, over 90% of the CVD group had arterial hypertension. Given that other studies have shown CVD risk factors (including arterial hypertension) to not be associated with mortality in COVID-19, it is possible that the categorisation of arterial hypertension has included many patients who have cardiovascular disease in the broad sense, but no cardiac disease. It would be prudent to perform further analysis excluding patients with arterial hypertension as a sole CVD diagnosis, although I suspect this would leave much smaller number with true cardiac diagnoses.
b. A further inclusion criterion for cardiovascular disease in this study is the use of antiplatelet agents. Although I am not aware of common practice in Brazil, in the UK it is still common to see patients on antiplatelet therapy for primary prevention of CVD, or indeed for secondary prevention of non-cardiac disease (e.g. stroke). Although Figure 2 suggests the number of patients included on the basis of use of antiplatelet is extremely small (it is not included at all on Figure 2), this is a curiously broad inclusion criterion.
c. In contrast to the broad inclusion criteria discussed in points a and b, it is striking to note that there is no classification for "heart failure"/"left ventricular dysfunction". Indeed, in the CAPACITY-COVID/LEOSS study mentioned above, NYHA III-IV HF was the only

classification of CVD that remained significantly associated with mortality following multivariate adjustment.
In summary, the classification of CVD used to include cases should be justified as it appears to severely limit the work.
3. Results.
In general the results are presented appropriately, however paragraphs 2 and 3 of the results are perhaps discursive enough to belong in the discussion

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Authors' response

Dear Editor,

It is a pleasure to resubmit for publication the revised version of JCTRes-D-22-00032: "The impact of chronic cardiovascular diseases on COVID-19 clinical course". We would like to thank you and the reviewers for the time dedicated evaluating the article.

The most substantial revision concerns to classification of chronic cardiovascular disease. Following the reviewer's advice, we deepened the assessment of chronic CVD as an independent risk factor in patients hospitalized with COVID-19 and the manuscript's writing was improved.

We tried to address all the reviewer's concerns, and, after careful revisions, we hope our manuscript approaches all the points raised. If necessary, the authors will be happy to readjust the article to enhance the study's quality.

Below are the point-by-point responses. All modifications in the manuscript were highlighted in red.

Best regards,

Bianca Kajimoto Magalhães.

Adjustments based on the reviewer's comments:

Reviewer #2: The authors report a retrospective, single center, case-control study of 2675 patients to assess whether pre-existing cardiovascular disease (CVD) is an independent risk factor for death in patients hospitalized with COVID-19.

Points for consideration

1) **Aim and rationale**

The research question is appropriate and of scientific interest and the general approach is appropriate. The authors make a statement that no other studies have employed multivariate analysis to explore the relationship between CVD and COVID-related mortality, however a recent publication in the European Heart Journal from the CAPACITY-COVID and LEOSS groups (https://doi.org/10.1093/eurheartj/ehab656) has done just this and in a larger population.

Response:

Thank you for pointing this out.

Unfortunately, we did not make clear our recognition of studies addressing the relationship between chronic cardiovascular diseases and COVID-19. It is our understanding that there are still few studies in the area. Concerned about this, we added the highlighted sentence to the abstract to endorse it:

*"**Background**. According to previous univariate analyses, chronic cardiovascular disease (CVD) has been associated with worse prognoses in severe cases of Coronavirus disease 2019 (COVID-19). However, in the presence of a complex system, such as a human organism, the use of multivariate analyses is more appropriate and there are still few studies with this approach."*

We appreciate the contribution. CAPACITY/LEOSS study was incorporated into our discussion and, consequently, in the manuscript references.

2) **Classification of cardiovascular disease.**

a. The authors include arterial hypertension as a diagnosis of CVD. While this is entirely appropriate, all the other CVD diagnoses relate purely to cardiac, not cardiovascular, disease. Moreover, other similar studies have categorized arterial hypertension as a risk factor, rather than cardiovascular disease. If arterial hypertension is included, should not other arterial diseases such as peripheral vascular disease, or cerebrovascular disease be included as well? In the studied population, over 90% of the CVD group had arterial hypertension. Given that other studies have shown CVD risk factors (including arterial hypertension) to not be associated with mortality in COVID-19, it is possible that the categorization of arterial hypertension has included many patients who have cardiovascular disease in the broad sense, but no cardiac disease. It would be prudent to perform further analysis excluding patients with arterial hypertension as a sole CVD diagnosis, although I suspect this would leave much smaller number with true cardiac diagnoses.

Response:

We acknowledge the importance of this point and agree with the stated need regarding the analysis excluding arterial hypertension as a sole diagnosis of CVD.

Although we had already performed an analysis separating cardiovascular disease into the subcomponents studied, removing isolated arterial hypertension from the total group of patients with chronic cardiovascular disease contributes to resolve the doubt in relation to the possibility that other CVD are being "overshadowed" by the high percentage of arterial hypertension.

In supplementary material (Supplementary Table 3), complete multivariate logistic regression analysis was added separating isolated arterial hypertension from the cardiovascular disease group. Other adjustments relevant to this topic were carried out in methods and results.

Supplementary Material

Supplementary table 3 - Complete multivariate analysis excluding arterial hypertension as a sole CVD diagnose (n=2675)

Model	Variables	Coefficient	ODDS Ratio 95%CI	P
3.1	Age	0.056	1.058 (1.049 - 1.066)	<0.0001
	Male sex	0.372	1.451 (1.186 - 1.775)	=0.0003
	Diabetes	0.470	1.601 (1.296 – 1.976)	<0.0001
	Chronic cardiovascular disease (without isolated arterial hypertension)	0.276	1.317 (0.959 – 1.810)	=0.0891
	Isolated arterial hypertension	0.045	1.046 (0.829 – 1.321)	=0.7028
	Chronic neurological disease	0.914	2.495 (1.819 – 3.423)	<0.0001
	Chronic kidney disease	0.527	1.693 (1.095– 2.618)	=0.0178
	Chronic lung disease	0.576	1.779 (1.241 - 2.550)	=0.0017
	Obesity	0.357	1.428 (1.136 - 1.796)	=0.0023
	Immunosuppression	1.044	2.842 (1.904 – 4.242)	<0.0001
	Asthma	0.692	1.997 (1.157 – 3.448)	=0.013
	Down Syndrome	3.914	50.117 (9.025 – 278.307)	<0.0001
3.2	Age	0.057	1.058 (1.050 - 1.067)	<0.0001
	Male sex	0.369	1.446 (1.183 – 1.768)	=0.0003
	Diabetes	0.480	1.617 (1.318 – 1.983)	<0.0001
	Chronic cardiovascular disease (without isolated arterial hypertension)	0.246	1.279 (0.967 – 1.692)	=0.0843
	Chronic neurological disease	0.914	2.495 (1.819 – 3.423)	<0.0001

	Chronic kidney disease	0.532	1.702 (1.102– 2.631)	=0.0166
	Chronic lung disease	0.576	1.780 (1.241 - 2.551)	=0.0017
	Obesity	0.362	1.436 (1.143 – 1.803)	=0.0018
	Immunosuppression	1.044	2.842 (1.904 – 4.241)	<0.0001
	Asthma	0.691	1.996 (1.156 – 3.445)	=0.0131
	Down Syndrome	3.918	50.306 (9.038 – 280.008)	<0.0001
3.3	Age	0.058	1.059 (1.051 - 1.067)	<0.0001
	Male sex	0.386	1.471 (1.205 - 1.797)	=0.0002
	Diabetes	0.484	1.626 (1.325 – 1.994)	<0.0001
	Chronic neurological disease	0.922	2.515 (1.833 – 3.540)	<0.0001
	Chronic kidney disease	0.582	1.789 (1.162– 2.753)	=0.0082
	Chronic lung disease	0.590	1.803 (1.259 - 2.583)	=0.0013
	Obesity	0.359	1.432 (1.141 - 1.798)	=0.0019
	Immunosuppression	1.055	2.871 (1.925 – 4.282)	<0.0001
	Asthma	0.690	1.995 (1.158 – 3.437)	=0.0129
	Down Syndrome	4.007	54.980 (9.703 -311.528)	<0.0001

CI: confidence interval

Methods *(2.1.1 Model development; fourth paragraph):*

"In the third, the objective was to evaluate the predictive potential of chronic cardiovascular diseases excluding arterial hypertension as their only diagnosis. With this, we intend to study CVD in a less broad sense, at the level of heart disease. The other components of the multivariate logistic regression design used in the previous models were kept."

Results *(3.1 Global analysis; fifth paragraph):*

"These same results were confirmed in the third multivariate logistic regression (Supplementary Table 3): the preexistence of chronic cardiovascular disease (excluding arterial hypertension as a sole CVD diagnosis) was not independently associated with death (OR 1.317; 95% Confidence Interval [CI] 0.959 – 1.810; p=0.0891), as well as isolated arterial hypertension itself (OR 1.046; 95% Confidence Interval [CI] 0.829 – 1.321*; p=0.7028). "*

b. A further inclusion criterion for cardiovascular disease in this study is the use of antiplatelet agents. Although I am not aware of common practice in Brazil, in the UK it is still common to see patients on antiplatelet therapy for primary prevention of CVD, or indeed for secondary prevention of non-cardiac disease (e.g. stroke). Although Figure 2 suggests the number of patients included on the basis of use of antiplatelet is extremely small (it is not included at all on Figure 2), this is a curiously broad inclusion criterion.

Response:

We appreciate the observation made.

Unfortunately, this point was not clear in our original article.

The use of antiplatelet agents was not an exclusive inclusion criterion in none of patients; all of them had another cardiovascular disease simultaneously (e.g. previous cardiac surgery and/or acute myocardial infarction, coronary artery disease, valvopathy/biological or metallic valve prothesis). Accordingly with the importance of make the correction, the highlighted sentence was altered (second paragraph in methods):

"With the aim of evaluating the impact of chronic CVD on the course of COVID-19 disease, the following diagnoses were considered prior to a SARS-CoV-2 infection diagnosis: ischemic heart disease with exercise tests and myocardial scintigraphy positive for ST segment alteration; obstructive coronary artery disease, demonstrated on cardiac catheterization; congenital heart disease; valvopathy characterized by significant stenosis or insufficiency; myocardial hypertrophy, demonstrated on echocardiography; enlargement of the cardiac area (on chest X-ray), continuous use of anticoagulants and/or antiplatelet agents accompanied by other chronic CVD; Chagas disease; use of pacemakers; previous cardiac surgery and/or angioplasty; continuous use of antiarrhythmics; and arterial hypertension, associated with the use of antihypertensives or diuretics; and/or other heart diseases recorded in electronic medical records."

c. In contrast to the broad inclusion criteria discussed in points a and b, it is striking to note that there is no classification for "heart failure"/"left ventricular dysfunction". Indeed, in the CAPACITY-COVID/LEOSS study mentioned above, NYHA III-IV HF was the only classification of CVD that remained significantly associated with mortality following multivariate adjustment. In summary, the classification of CVD used to include cases should be justified as it appears to severely limit the work.

Response:

We recognize the value of the observation made, given that the patients with heart failure (HF) at stages NYHA III-IV or ACC/AHA C-D are serious carriers of heart diseases.

However, since HF is a clinical syndrome, we do not consider appropriate to include it as an isolated diagnosis of chronic cardiovascular disease, seeing that, by definition, heart failure already accompanies the confirmed cases of CVD. The fact that the group with heart disease

(without considering arterial hypertension as a sole diagnosis) is entirely made up of cases with the presence of structural alterations (valvar, coronary, or myocardial) already covers HF in stages B-D (Hunt, SA, et al ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2001). Additionally, based on ACC/AHA, we understand that patients in initial stage of heart failure were also included in this study when the carriers of arterial hypertension were.

Endorsing these points, the analysis of cardiovascular disease as a unique group ("any history of cardiac disease") in the CAPACITY-COVID/LEOSS study was not independently associated with death. Suggesting that, even though we have not made a specific classification for heart failure, our work had contemplated these patients.

Even so, we appreciate the commentary made and comprehend the importance of mention it as a limitation (4.1 Study limitations):

"In this single-center, retrospective study, multiple inferential and exploratory analyses were performed. Due to the review of electronic medical records of all those hospitalized patients during the study period, no sample calculation was performed for the priori statistical hypotheses. Furthermore, due to the lack of data on clinical and laboratory variables analyzed as predictive factors, the study restricted to patients with chronic CVD included a small number of participants. Moreover, we did not conduct a specific analysis for cumulative cardiovascular disease as happens in heart failure, considering that the different stages of the syndrome had already been covered by the confirmed cases of heart diseases."

3. Results

In general the results are presented appropriately, however paragraphs 2 and 3 of the results are perhaps discursive enough to belong in the discussion

Response:

We ratify that point. Thank you.

In order to adapt the paragraphs indicated (2 and 3) to the results, we carry out the following changes:

Second paragraph

*"Population characteristics are presented in **Table 1**. The median age was 60.40 years (interquartile range [IR] 47.73 and 72.38), with 55.33% of participants being male. In our univariate analysis, chronic heart disease was associated with death ($p<0.0001$); similarly, advanced age (median of 70.3 years [IR 61,4 and 81]), male sex, and other explored morbidities, except for chronic liver and hematological diseases, were too associated with death."*

Given its fully discursive character, we considered removing the excerpt below, which appeared in the second paragraph of results. It was not added to discussion as there is already a similar one (first paragraph of discussion: "The high prevalence of chronic heart disease (55.89%) among the total number of patients is consistent with univariate analyses that showed that it may cause greater severity in clinical condition with COVID-19."

Removed excerpt: "In previous univariate analyses that compared deaths with hospital discharges to understand whether they were related to greater severity in COVID-19 cases, chronic heart disease was associated with death (p<0.0001)."

Third paragraph

However, notably, chronic CVD considered as a unique group (OR 1.199; 95% Confidence interval [CI] 0.956–1.504; p=0.1169), using multivariate regression analyses, did not appear to explain the deaths in the cases studied. The statistically significant variables are listed in ***Table 2****.*

The expression present in the third paragraph (results) – "had not been analyzed as an independent predictor of death from COVID-19 using multivariate regression analyses. In the present study, multivariate logistic regressions were used and" – was transferred to discussion (first paragraph) as follows: " However, reiterating conclusions by Vudathaneni et al. [23] and other authors [8,12.14,15,17,22] the results of the present study indicate that chronic CVD can not be considered as an independent predictor of death from COVID-19, when using multivariate regression analyses, endorsing the importance of other variables in explaining the clinical outcome analyzed."

2nd Editorial decision
17-May-2022

Ref.: Ms. No. JCTRes-D-22-00032R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: