



LETTER

A Response to: Letter to the Editor Regarding “Influence of Baseline Physical Activity as a Modifying Factor on COVID-19 Mortality: A Single-Center, Retrospective Study”

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Received: November 10, 2021 / Accepted: January 21, 2022 / Published online: February 2, 2022
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Dear Editor,

We appreciate Dr. Lucena Alves and colleagues' interest in our article about the influence of baseline physical activity on the prognosis of COVID-19 [1]. We will take this opportunity to clarify all the issues that were perhaps not be clear in the original manuscript.

Dr. Lucena Alves in his letter emphasizes the general limitations of retrospective observational studies whose usefulness is only exploratory and to generate hypotheses—a concept with which readers are probably familiar without further clarification. We believe that our article is clear in this regard from the first moment in the title and in the methodology description. The conclusions presented are those that the authors draw from the data, and in the limitations section it is made clear that these conclusions must be confirmed through a prospective study.

It is also pointed out that the main variable, baseline physical activity level, was obtained through a self-assessment questionnaire. We agree that this is not the ideal way to obtain this information, but it is important to know the

period in which this work was designed and carried out. The study includes patients admitted to our center from February 15, 2020 to April 15, 2020. This time corresponds to the first wave of COVID-19 in our country, at the peak of the incidence of infection and mortality. The national health system was saturated and the government had decreed complete confinement, whereby the population could leave their homes only in exceptional situations [2]. Therefore, the only way to contact patients was through telephone consultation and the only method to estimate the level of training was through self-assessment. In addition, the main variable was the level of physical activity before infection, parameters that are not empirically measurable with a posteriori test. To facilitate the understanding of the questionnaire by patients of any age and sociocultural context, we selected the Rapid Assessment of Physical Activity Scale (RAPA) questionnaire, which has been proven useful for self-assessment of baseline physical training status [3]. The questionnaire includes two scales: the first (RAPA 1) refers to the frequency and intensity of physical training, which is the main variable of the study; the second (RAPA 2) focuses on the characteristics of muscle training (strength and flexibility), which was of less interest for the analysis and which did not match with some aerobic sports such as walking, dancing, etc. The information that RAPA 2 provided was

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considered to be spurious and confusing for the study objective and was therefore not included. The criteria for defining the level of sport intensity (mild, moderate, and intense) are included in the RAPA questionnaire itself with a brief explanation to unify criteria. If the exercise produces some tachycardia but allows speaking and singing, it is considered mild effort; if the tachycardia is greater but it is possible to speak but not to sing, it is classified as moderate effort; and intense effort would be that with maximum tachycardia that allows speaking but with intermittent pauses for deep breathing. In addition, the questionnaire provides a series of examples of mild, moderate, and intense exercises. If readers are interested they can download it for free at <https://depts.washington.edu/hprc/programs-tools/tools-guides/rapa/>.

As Dr. Lucena Alves and colleagues rightly point out that an inherent limitation in observational studies such as ours is that it is not possible to control the different confounding factors, as occurs in experimental studies. Therefore, in our sample, group 1 or sedentary group more frequently presented comorbidities that could directly influence their prognosis during SARS-CoV-2 infection. For this reason, the statistical analysis was not limited to analyzing the different variables independently but was subjected to a multivariate statistical analysis through a two-way stepwise Cox regression, including all variables that had been previously studied in the univariate analysis, and finally only four of them were shown to have an independent impact on mortality: age, renal failure, smoking habit, and sedentary lifestyle. It is not true, as is commented in the letter, that male sex, hypertension, pulmonary disease, heart disease, cerebrovascular disease, and liver disease were not included. They were included, but the statistical analysis discarded them because they were not relevant in the mathematical model for predicting mortality.

As for the sample size, Lucena Alves and colleagues questioned whether it was optimal for the results obtained. The patients included were 93.5% of all patients admitted to our center with a confirmed diagnosis of COVID-19. In order to increase the number of patients, it would have been necessary to extend the study

period and this would have been the case if we had not obtained conclusive results in the pre-analysis. Increasing the number of patients may be interesting to demonstrate differences that would have been at the limit of statistical significance, but it is unlikely to change the result in terms of the relationship found between sedentary lifestyle and mortality, which already achieved statistical significance with a p value of less than 0.05 with our sample. Nevertheless, we agree that the limited number of patients does not allow us to establish a more approximate value of the hazard ratio of the sedentary lifestyle variable, requiring a confidence interval that is too wide. This is a problem of precision in the estimation of the results but not a methodological problem as stated in the letter.

Finally, we thank the journal and the authors of the letter for the opportunity to share and contrast our study and to allow us to clarify all the doubts raised.

ACKNOWLEDGEMENTS

We thank Stuart J. Pocock for his statistical advice and his useful suggestions. We also thank the participants of the study.

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ricardo Salgado-Aranda. The first draft of the manuscript was written by Ricardo Salgado-Aranda and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. Ricardo Salgado-Aranda has nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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