Dear Editor in Chief,

Thank you for the opportunity to revise our original article in *Acta Médica Portuguesa*. The suggestions offered by the reviewers have been helpful, and we also appreciate your insightful comments on revising the paper, which enabled us to improve its quality.

We have included the reviewers’ comments immediately after this letter and responded to all of each reviewers’ questions and concerns, also indicating how we addressed each one by describing the changes we have incorporated in the revised manuscript. The revised article is attached with this letter to the resubmission form.

We hope the revised manuscript will better suit the *Acta Médica Portuguesa*, but we are happy to consider further revisions, and we thank you for your continued interest in our research.

Please note, that given the concerns regarding the definition of risk by the reviewer, we suggest to change the article’s title to: POPULATION-BASED ESTIMATES FOR THE HIGHEST RISK OF SEVERE COVID-19 DISEASE DUE TO AGE AND UNDERLYING HEALTH CONDITIONS”.

We believe this title highlights the focus on the highest group and thereby better addresses the reviewer’s concerns.

Sincerely,

Pedro A. Laires & Carla Nunes

**Reviewer 1**

**Comment 1:** Adding a paragraph in the methodology justifying the proposed novel definition where they clearly state the potential underestimation of the proportion of the population at increased risk of severe illness.

**Response:** Manuscript changed accordingly.

**Comment 2:** Showing results from the same analysis but using the classical definition (maybe as supplementary material), so that the readers are better informed of the impact of the author choice.

**Response:** We attached a supplementary file with those results.

**Comment 3:** Adding a sentence to the discussion (both in the abstract and in the main text) highlighting their uncommon choice of high risk definition, such as: "Even considering a restrictive definition of high risk for severe illness, we estimated..."

**Response:** Manuscript changed accordingly.

**Comment 4:** Highlighting better which proportion of the population is being considered in the Introduction (in the abstract and in the main text). For example, something in the lines of: "We considered a restrictive definition of high risk to estimate (...) at the very high risk..."

**Response:** Manuscript changed accordingly.

**Comment 5:** Replacing the expressions "due to old age and ..." by "due to both old age and ..." a long the manuscript. This is specially important since, as the authors shown in their reply regarding the Canadian Health Authorities, without the proper phrasing these sentences out-of-context can be misleading. The same goes for the Resumo Portguês, where "os mais envelhecidos e expostos" should be replaced by "os mais envelhecidos que estão expostos a determinadas doenças crónicas", and "devido à idade e a determinadas condições crónicas pré-existentes" should be replaced by "considerando conjuntamente a idade e determinadas condições crónicas pré-existentes".

**Response:** Manuscript changed accordingly.

**Comment 6:** Replacing the expressions "due to old age and ..." by "due to both old age and ..." a long the manuscript. This is specially important since, as the authors shown in their reply regarding the Canadian Health Authorities, without the proper phrasing these sentences out-of-context can be misleading. The same goes for the Resumo Português, where "os mais envelhecidos e expostos" should be replaced by "os mais envelhecidos que estão expostos a determinadas doenças crónicas", and "devido à idade e a determinadas condições crónicas pré-existentes" should be replaced by "considerando conjuntamente a idade e determinadas condições crónicas pré-existentes".

**Response:** Manuscript changed accordingly.

**Comment 7:** Disclosing in the Methods which comorbidities are not being considered, namely chronic kidney diseases, chronic liver disease, hemoglobin disorder, immunocompromised, severe obesity (CDC Health Guidelines). The reasoning for choosing specific comorbidities from (Wang et al 2020 Aging) is fine, but the readers should be informed about which are being left behind.

**Response:** Manuscript changed accordingly.

**Comment 8:** The caveats of using epidemiological characterization of a population using data from 6 years ago should not be ignored. The authors make a good case for not overcomplicating the projection estimates, and simply using the 2014 sample as if it was from a population characterized by the 2018 demographic parameters. To be clear, this was not my suggestion. What I suggest is adding a paragraph in the discussion on the trends of the comorbidities within this 6 years gap by using Official data on Causes of Death in Deaths by Diabetes, Cardiovascular Diseases, Cerebrovascular Diseases and Chronic Obstructive Pulmonar Diseases. The expected differences between the "evolution" of prevalence and death can also be highlight to the readers, and is very relevant.

**Response:** We have changed the manuscript by adding to the Limitations section the following sentence, which highlights how likely the prevalence must have increased during this time gap:

“Thirdly, the INS included only noninstitutionalized adults and is from 2014, which likely leads to underestimation of results. Prevalence of the analyzed chronic diseases must have increased in the meanwhile (for instance, Laires PA et al. estimated a 3.1% growth in the projected prevalence of multimorbidity between 2014 and 2020 in Portugal).”

**Comment 9:** The comparison between the results of the study and studies from other countries is important and should be available to the readers. Even with different definitions of severe risk (or, actually, because of it), the authors should compare their findings with the cited (Adams et al 2020 Emerg Infect Dis), which found 45.5% at increased risk in US. They should also compare their results with (Kome et al 2020 KFF), cited by Adams. (Jordan and Chang 2020 KFF) and (Banerge et al 2020 Lancet) also estimated the proportion at severe risk in UK, and their results should be discussed. Other studies from important EU countries (e.g. Italy, Spain, France or Germany) may have been missed by the authors and should be looked into.

**Response:** Manuscript changed accordingly.

**Comment 10:** When authors state that regions have "highest/lowest risk", they should state "highest/lowest proportion of high-risk population". Both terms should not be confused. A specific person in the North region does not have a highest risk for severe illness, rather there is a higher chance of find an individual at highest risk for severe illness in the North region.

**Response:** We clarified this point and changed the manuscript accordingly.

**Comment 11:** Regarding the differences found between genders, I am happy with the changes. But I suggest citing (Sama et al 2020 Eur HeartJ) on the concentrations of ACE2 in men and women, because further research on gender is indeed available.

**Response:** We added this reference in the manuscript and changed the manuscript accordingly.

**Comment 12:** Statements regarding the start of the epidemic in the North should be avoided. On the 3rd March there were 2 cases in Norte, 1 in Centro and 1 in Lisboa e Vale do Tejo. Furthermore, many countries are finding evidences of covid-19 cases before early reports. Stating "larger initial outbreak in Norte" is more reasonable.

**Response:** Manuscript changed accordingly.

**Comment 13:** In the limitations section, the authors should consider referring the potentially outdated data on the comorbidities.

**Response:** We believe this is already covered, when highlighting the date from the INS (2014) and due limitation.

**Comment 14:** A section on the strengths of the study following the limitations section reads awkwardly. Perhaps, this could be stated in the last paragraph of the introduction or in the methodology. However, I discord with the statement saying that the comorbidities adopted are the ones where available evidence exists. The authors chose comorbidities from a meta-analysis using Chinese epidemiology, which is fine. But I challenge the fact that these are all the comorbidities with available evidence. In fact, the authors cite a study by CDC's Covid-19 Response Team which shows evidences for increased proportion of ICU admissions (compared to non-hospitalized) in "Immunocompromised condition", "Chronic renal disease" and "other chronic disease", "Neurologic disorder" and "Former smokers". Furthermore, other studies show evidences, for example, of "morbid obesity" as a comorbidity (Lighter et al 2020 Clin Infect Dis).

**Response:** Manuscript changed accordingly.

**Reviewer 2**

**Comment 1:** Bar/line chart can be improved for better understanding. For this kind of data lines are not advised.

**Response:** Manuscript changed accordingly.

**Comment 2:** Too many categories for a pie chart. Data is hard to be visualized for smaller categories.

**Response:** We respectfully disagree with the reviewer’s comment since we consider the pie chart to be appropriate (not too many categories and easy to understand), but we leave the final decision to the editor. We may change it to a bar type graph.

**Comment 2:** Regional and sex data could be standardized, allowing a better comparison between regions - which has a dimension bias, as authors mentioned.

**Response:** We understand the reviewer’s suggestion, but our approach required age- and sex-specific prevalence data in order to estimate the population at the highest risk. Therefore, we did not consider to be appropriate to use age and sex standardized prevalence estimates. Regarding comparisons across regions we actually explicitly wanted to compare the raw prevalence of underlying conditions and the population at highest risk.