Dear Editor in Chief,

Thank you for the opportunity to revise our original article entitled “Population-Based Estimates of Chronic Conditions Potentially Affecting Risk for Complications from Coronavirus Disease In Portugal” for publication 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.

Sincerely,

Pedro A. Laires & Carla Nunes

**Comments from Reviewer A**

**Comment 1:** Estudo descritivo que poderia ser mais aprofundado, nomeadamente com
comparação mais detalhada entre sexos. Faria sentido considerar população imunossuprimida e sujeita a tratamento oncológico.

**Response:** We understand the reviewer´s comment, but we have to point out that we focused our analysis only on those risk factors from the metanalysis by Wang B et al., which did not include cancer treatment and immunosuppression. Furthermore, unfortunately such information is not available in the latest INS survey, which was our primary source of data. Thus, not only those risk factors were out of the scope of our analysis, but also if would not be feasible to include them. Given the *a priori* defined objectives of our research, we consider that the level of detail we provide is adequate (including those regarding gender).

**Comment 2:** Por vezes confunde-se um maior risco de contrair a infeção por coronavírus SARS-CoV-2 e um maior risco de manifestações grave de COVID-19.

**Response:** We understand the reviewer’s concern and we changed the manuscript in order to make it very clear that our scope is “risk for complications following COVID-19 infection”.

**Comment 3:** O maior risco de infeção acaba por também estar associado a contextos de clusters, que não são identificados no estudo.

**Response:** We believe that despite the relevance of this topic it goes beyond the scope and objectives of our work.

**Comments from Reviewer C**

**Comment 1:** The authors do not show why their proposed definition is better than the classical approach. They cite Health Authorities guidelines from Canada and New Zealand to support their proposal, but actually both of these guidelines consider comorbidites and old-age as separate risk factors. Moreover, the proposed definition, being more restrictive can lead to an underestimating of the real proportion of people at increased risk.

**Response:** We share the concerns of the reviewer regarding the definition of high risk. It actually triggered a lot of debate among the authors. While many doubts persist regarding risk factors, it is difficult to finalize a definition of high risk. A lot is still to be known about risk factors (for instance, hypertension), let alone the definition of high-risk population. In fact, Lipsitch M et al. in an article published in the NEJM urged the scientific community to focus their epidemiologic research on 4 key priorities, including one aiming for better knowledge on COVID-19 risk factors.[[1]](#endnote-1) This uncertainty led to several definitions of high risk across the globe (e.g. for instance the adopted list of morbidity risk factors varies). In fact, the reviewer himself/herself first claims that our definition is “less conservative” and then in another comment says it is “more restrictive”. Please note that if we were to use, for instance the definition used by Adams and colleagues (high risk = old age OR at least one chronic disease), then the projected high-risk PT population would sum up to approximately 3.8M, which is around half of the adult PT population, which intuitively seems way too much. Certainly, and more importantly, way too much to aid prioritization. Such approach would be sort of useless from a health policy standpoint, when it comes to prioritize measures on those more vulnerable. Thus, given the lack of a fixed and unified definition of high risk, we decided upfront to use a more restrictive definition (high risk = old age AND at least one chronic disease). That being said, we are not assuming that those who are above 65 year old AND no disease and those bellow 65 AND suffering from at least one chronic disease are risk-free. All we are assuming is that those under both conditions (i.e. above 65 AND suffering from at least one chronic disease) are at the greatest risk. During the abovementioned uncertainty, and while there is no fixed and final definition of high risk, it was our decision to choose such definition, obviously with an *a priori* and explicit reasoning (Methods section). We believe such approach would serve better our Authorities when to target vulnerability, namely by being more aware of risk linked with frailty (age and comorbidities) rather than simply age, for instance.

Since we share this concern with the reviewer and because depending on the adopted definition the estimates of population at risk change as well, we decided to highlight this issue in the revised manuscript.

*Further notes on the Health Authorities guidelines:*

* *Copy-paste from the Canadian Health Authorities website: “While diseases can make anyone sick, some Canadians are more at risk of developing severe complications from an illness due to underlying medical conditions and age”*
* *Copy-paste from the Neo Zealand Health Authorities website: “Older people, in particular those who have underlying health issues, including respiratory issues that make them more vulnerable to COVID-19”.*

**Comment 2:** Epidemiological characterization of a population using data from 6 years before should be considered carefully. The authors did use projections for 2018, but they do not mentioned how this was done. Did they recalibrated the samples using as margins demographic information from 2018? Also, this projection does not consider changes in the prevalence of comorbidities. The authors should have analysed trends of the comorbidities whitin this 6 years gap, for example by using Official data on Causes of Death in Deaths by Diabetes, Cardiovascular Diseases, Cerebrovascular Diseases and Chronic Obstructive Pulmonar Diseases.

**Response:** We share the concern regarding the 6 years gap on the information from INS 2014, but we respectfully disagree on the proposed methodology to update the prevalence estimates. It is true that we could use the demographic trends to update overall prevalence estimates based on the population dynamics (basically if the population is getting older, the oldest age-groups necessarily gain population share and, because typically prevalence of chronic diseases increases with age, then the overall prevalence grows as well). We have done it in the past with multimorbidity (Laires PA et al. estimated a 3.1% growth in the projected prevalence of multimorbidity between 2014 and 2020)[[2]](#endnote-2), but for this case this is an inadequate methodology because we are not working with the overall prevalence, but rather with age-specific prevalence, and therefore this methodology does not apply. On the other hand, using proxies such has causes of death, as suggested by the reviewer, is inadequate as well, not only due to the known notification errors associated with such records, but especially because we know that the evolution of mortality does not evolve in a similar way as the evolution of prevalence. For instance, CV death in Portugal versus prevalence of CV disease. Mortality evolution depends on many other factors besides prevalence (e.g. improvement on treatment and management of disease). We believe such proxy would deliver a higher error than the issue of the 6 years gap (more conservative approach). Until we do not have another INS or other recent nationwide prevalence study on these illnesses, we think it is better to stick with these available 2014 estimates. Thus, we do not find a valid way to properly update the prevalence of diabetes, hypertension, CV and COPD for all the analyzed age-groups (indeed we do not have a more recent valid and detailed nationwide data on age-specific prevalence for all these diseases, neither do we have proxies to be used in a valid way). We included this 6 years gap issue on the Limitation section of the revised manuscript.

**Comment 3:** The methodology for estimates of 95% CIs is also not clear. Did the authors used a Jackknife procedure similar to the one used in INS 2014?

**Response:** We changed the manuscript accordingly.

**Comment 4**: The comparison between increased risk for severe illness between Females
and Males is also problematic. In one hand the authors do not present error
measures, neither disclose which hypothesis is assumed for the p-value. In
the other hand, they take it very lightly that, globally, actual Covid-19
reported deaths is higher in Males. It has been shown that Males have higher
plasma ACE2  concentration. Given that ACE2 is the functional receptor for
coronaviruses, Sex can even be considered another risk factor.

**Response**: We agree that there is still a lot to be known regarding the gender effect on the risk for COVID-19 severe disease. Knowledge in this field is obviously changing rapidly, but as far as we know, gender is not established yet as a risk factor. Also, by checking the current guidelines there is no separation between males and females regarding risk, for instance: CDC (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html>). Nonetheless, the scope of our analysis for the definition of people at risk was age and morbidity, and within morbidity we decided to focus on only those diseases highlighted in the metanalysis by Wang B et al., as explained before. Therefore, the differences we found in the size of population at risk between females and males are only based on the demographic differences (i.e. nr of older females > older males) and the prevalence of the analyzed risk factors (71.8% vs. 67.6% in men, p=0.023. Where the H0: no differences in the prevalence between females and males, was the null hypothesis rejected at a significance level of 5%); and definitely not on the hypothetical gender risk *per se*. Therefore, we cannot further explore the gender issue because it would be out of the scope of this research and hence speculative. We actually highlighted in the manuscript the need for further research in this field. In order to make this point clearer we changed the manuscript in the Discussion section.

**Comment 4**: The comparison between the results of the study and studies from other countries is not thorough enough.

**Response:** We did not find results from other studies than those mentioned in the manuscript. In fact, this highlights the need to publish such sort of research.

**Comment 5**: Some statements regarding Covid-19 have yet to be confirmed, e.g. origin in Whuan (in fact, early cases reported in Guangdong province have the closest genetic similarities with bat coronavirus).

**Response:** We changed the manuscript accordingly.

**Comment 6**: The virus is no longer called "2019 novel coronavirus", now it is "severe acute respiratory syndrome coronavirus 2" or "SARS-CoV-2".

**Response:** We changed the manuscript accordingly.

**Comment 7**: Some claims in discussion should be backed by REFs, particularly the ones regarding the epidemiology in Portugal.

**Response:** We changed the manuscript accordingly.

**Comment 8**: Some technical terminology is used improperly, e.g. "cumulative" and "selective mortality" (This terminology have specific meanings in their own fields).

**Response:** We changed the manuscript accordingly.

**Comment 9**: references should be more carefully assembled: 1) reference for 2018 official demographic data should be (INE 2018) and not (INE/PORDATA 2018) and should include the web address:

[https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine\_indicadores&indOcorrCod=0008273](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ine.pt_xportal_xmain-3Fxpid-3DINE-26xpgid-3Dine-5Findicadores-26indOcorrCod-3D0008273&d=DwMGaQ&c=ZbgFmJjg4pdtrnL2HUJUDw&r=rtoDuxuZX8o9DHr5asnf5Somm7gyHx5j1SOWIe37RyU&m=jANhwIFGrX8TID2xVzn7MEv0q4V5fklHtsKbCAXJDyA&s=wQpnMSGzlQQnDq2x3-Kuvn4X2fPjuqni2R8O9wHmIRA&e=);

**Response:** We changed the manuscript accordingly.

**Comment 10**: Reference XXVI is the same as XXVII (!); 3) reference to INS 2014 should be given when mentioning the calibration of samples to match the population (if the authors used the weights provided, which is not clear); 4) last reference is in a very low case

**Response:** We changed the manuscript accordingly.

**Comment 11**: A few grammatical errors and incorrections, e.g. "have showed" should be
"has shown", "according with" should be "according to", "estimate the
population", "exposed to chronic disease" should be "suffering from chronic
disease", "proportion of patients may develop (...) death".

**Response:** We changed the manuscript accordingly.

**Comment 12**: The Resumo Portugues is not carefully written.

**Response:** We changed the manuscript accordingly.

1. Lipsitch M, Swerdlow DL, Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed N Engl J Med. 2020 Mar 26;382(13):1194-1196. doi: 10.1056/NEJMp2002125. Epub 2020 Feb 19. [↑](#endnote-ref-1)
2. Laires PA, Perelman J. The Current and Projected Burden of Multimorbidity: A Cross-Sectional Study in a Southern-Europe Population. Eur J Ageing. 2018 Sep 1;16(2):181-192. [↑](#endnote-ref-2)