PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Stratification of the risk of developing severe or lethal Covid-19 by a new score from a large Italian population
AUTHORS	Corrao, Giovanni; Rea, Federico; Carle, Flavia; Scondotto, Salvatore; Allotta, Alessandra; Lepore, Vito; D'Ettorre, Antonio; Tanzarella, Cinzia; Vittori, Patrizia; Abena, Sabrina; Iommi, Marica; Spazzafumo, Liana; Ercolanoni, Michele; Blaco, Roberto; Carbone, Simona; Giordani, Cristina; Manfellotto, Dario; Galli, Massimo; Mancia, Giuseppe

VERSION 1 – REVIEW

REVIEWER	Craxi, Lucia University of Palermo
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	I wonder whether the improvement of knowledge on treatment options for COVID-19 may affect the performance of the score across time (first vs. second epidemic wave). The authors acknowledge as a limit the fact that education and socioeconomic information were not included because they were not present in administrative databases. This is a great limitation of the study, because it does not capture all those extra-clinical factors that can affect the outcome for COVID-19. Page 5 Line 26: replace "reside" with "resident" Page 8 Line 13: not only to make some patients preferential recipients, but also to exclude them if too severe to obtain any substantial benefit from the treatment Page 8 Line 26-27: no longer current, update information, or specify that the problem now arises only for low and middle income countries Page 9 Line 46: replace "coincident" with "coincide" Page 12 Line: specify the reason why you chose a different start date for the comparison for Lombardy and other regions. See previous comment about differences in treatment options across time Page 14 Lines 17-26: no longer current, update information Page 15 Line 24: replace "for to" with "to" Page 15 Lines 38-52: no longer current, update information Page 17 Line 13: Those who have diseases so debilitating or incapacitating to limit social contacts, need a caregiver , who could infect them. Therefore they cannot be counted as a low risk category.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

I wonder whether the improvement of knowledge on treatment options for COVID-19 may affect the performance of the score across time (first vs. second epidemic wave).

Reply: We agree with the Reviewer that knowledge on treatment options for COVID-19 improved across time. However, because the score (i) was built using the data from the first epidemic wave and (ii) performance was validated by applying the model to data from the second epidemic wave, our data suggest that improvement in COVID-19 treatment across time unlikely, or marginally, affected the performance of the score. Indeed, the discrimination performance was similar between periods, with superimposable values of AUC (0.89 vs 0.88 for the first and second epidemic wave, respectively).

In the new version of the manuscript, we specified that "*CVS performed similarly well during the second epidemic wave (i.e. after the summer 2020), in which knowledge on treatment options for Covid-19 improved*" (Page 15, Lines 14-18).

The authors acknowledge as a limit the fact that education and socioeconomic information were not included because they were not present in administrative databases. This is a great limitation of the study, because it does not capture all those extra-clinical factors that can affect the outcome for COVID-19.

Reply: We agree with the Reviewer on this limitation of the administrative databases. Although we acknowledged the lack of these data in the 'Strengths and limitations' section, we missed to declare this limitation in the previous version of the paper. In the new version of the manuscript, we reported this limit in the Discussion section (Page 15, Lines 23-25).

Page 5 Line 26: replace "reside" with "resident"

Reply: Done.

Page 8 Line 13: not only to make some patients preferential recipients, but also to exclude them if too severe to obtain any substantial benefit from the treatment

Reply: Although we agree with the logic moving the Reviewer's suggestion, excluding some patients from treatment according to a prognostic score entails ethical implications.

Page 8 Line 26-27: no longer current, update information, or specify that the problem now arises only for low and middle income countries

Reply: According to the Reviewer's suggestion, we revised the sentence as follow: "*The case of vaccination is particularly delicate because demand will outstrip supply for many months ahead in low- and middle-income countries.*"

Page 9 Line 46: replace "coincident" with "coincide"

Reply: The word “coincident” was replaced with “coinciding”.

Page 12 Line: specify the reason why you chose a different start date for the comparison for Lombardy and other regions. See previous comment about differences in treatment options across time

Reply: In the new version of the manuscript, we better specified the reason for the choice of different start dates, i.e., “*to validate the model across different temporal and geographic conditions (i.e., to assess the performance of CVS across different levels of treatment options, climatic characteristics, intensity of the epidemic spread, etc.)*” (Page 10, Lines 21-25). We believe that the superimposable discrimination performance of the score in the two epidemic waves strengths our findings.

Page 14 Lines 17-26: no longer current, update information

Reply: We updated the information. In particular, we refer the utility of our score to future vaccination programs (i.e., the third dose) or future treatment options (e.g., monoclonal antibodies) (Page 13, Lines 10-17).

Page 15 Line 24: replace "for to" with "to"

Reply: As requested, “for to” has been replaced with “to”. We thank the Reviewer for his/her advice.

Page 15 Lines 38-52: no longer current, update information

Reply: We revised the text to make clear the utility of our score to the third-dose vaccination campaign (Page 14, Lines 19-24).

Page 17 Line 13: Those who have diseases so debilitating or incapacitating to limit social contacts, need a caregiver, who could infect them. Therefore they cannot be counted as a low risk category.

Reply: We agree with the Reviewer. We revised the paragraph in order to make clear that patients who suffered from diseases that limit social contacts (regardless of the debilitating severity of the condition) should not be eligible to receive early protection (because they are not at greater risk of severe/fatal clinical manifestations of Covid-19) (Page 16, Lines 5-9). In addition, we specified that “*exclusion from the scoring system of diseases so debilitating or incapacitating to limit social contacts but requiring a caregiver is a major limitation of our study*”.