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Carlos J Pirola , Silvia Sookoian

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Age but not sex may explain the negative effect of arterial hypertension and diabetes on COVID-19 prognosis

Running Title: COVID-19 and comorbidities

Carlos J Pirola [1,2*], Silvia Sookoian [1,3*],

[1] University of Buenos Aires, School of Medicine, Institute of Medical Research A Lanari, Ciudad Autónoma de Buenos Aires, Argentina.

[2] National Scientific and Technical Research Council (CONICET)−University of Buenos Aires, Institute of Medical Research (IDIM), Department of Molecular Genetics and Biology of Complex Diseases, Ciudad Autónoma de Buenos Aires, Argentina.

[3] National Scientific and Technical Research Council (CONICET)−University of Buenos Aires, Institute of Medical Research (IDIM), Department of Clinical and Molecular Hepatology, Ciudad Autónoma de Buenos Aires, Argentina.

[*] Co-corresponding authorship

Correspondence: Co-Corresponding Authors

Carlos J. Pirola, Ph.D. and Silvia Sookoian, M.D., Ph.D.

Present/permanent address: Instituto de Investigaciones Médicas, IDIM-CONICET Combatientes de Malvinas 3150, CABA-1427, Argentina

E-mail: pirola.carlos@conicet.gov.ar and ssookoian@intramed.net

Phone: 54-11-52873905

SS and CJP should be considered joint senior authors

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Declaration of Competing Interest

We have no conflict of interest to declare.

Keywords: COVID-19; hypertension; diabetes; cardiovascular disease; prognosis

To the Editor,

We read with great interest the article of Zheng and colleagues who summarized current evidence regarding risk factors for severe clinical forms of COVID-19 (1). The authors concluded that patients who are males, aged over 65 and smoking might face a higher risk of developing into the critical or mortal condition by COVID-19 (1). Besides, the authors highlighted that comorbidities such as hypertension, diabetes, cardiovascular and/or pre-existing respiratory diseases could also significantly affect the prognosis of the COVID-19 (1). Collectively, the authors confirmed the negative effect of comorbidities on the natural course of COVID-19. Nevertheless, there are some aspects that need to be carefully assessed, including the influence of essential demographic confounding variables such as age and sex, which are also strongly associated with the above mentioned comorbidities but unfortunately were not thoroughly included in the analysis.

Hence, to answer the question of whether age and sex may influence the effect size/s of pre-existing comorbidities on COVID-19 severe prognosis, we used the data of the Zheng and coworkers (1) as input to perform a meta-regression analysis. Of note, we found that the negative effect of underlying arterial hypertension on COVID-19 critical illness significantly and positively correlated with the age difference between critical/mortal and non-critical patients (slope±SE: 0.0718±0.021, p=0.00066) but not with the difference in male sex proportion (slope:-0.010±0.023, p=0.66) (**Figure 1, A/B**). Likewise, the negative effect of type 2 diabetes on severe COVID-19 infection significantly and positively correlated with the age difference between the two groups (slope: 0.079±0.025, p=0.00185) but not with the difference in male proportion (slope: -0.040±0.027, p=0.133) (**Figure 1, C**).

On the contrary, by meta-regression analysis, we found that the negative effect of pre-existing respiratory disease on COVID-19 critical illness significantly and positively

correlated with the difference in male proportion (slope: 0.118±0.056, p= 0.034) but not with the age difference (slope: -0.030±0.048, p= 0.520).

Finally, we observed that the negative effect of pre-existing cardiovascular disease on severe COVID-19 clinical course is not influenced either by sex (slope: 0.0343±0.033, p= 0.300) or by age (slope: 0.048±0.033, p= 0.143).

In conclusion, there are three relevant messages to highlight. First, it is crucial to perform a meta-regression analysis to explain statistical heterogeneity in terms of study-level variables. Second, assessment of potential confounders, including essential demographic aspects, such as age and sex, are relevant to robustly demonstrate the putative association between variables, including assessment of disease risk and or severe prognosis. Most importantly, accurate assessment of confounding variables provides relevant information to stakeholders, including physicians and practitioners who need to take immediate action to reduce morbidity and mortality of COVID-19. Finally, assessment of the effect sizes of moderator variables on risk factors for severe COVID-19, including age and sex, may help to understand the biology of the disease in future larger studies.

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Figure

Meta-regression analysis between the difference in age (DifAGE) and male proportion between the critical/mortal and non-critical groups of COVID-19 patients and the effect of comorbidities on COVID-19 critical illness among the studies.

Meta-regression was used to examine the impact of moderator variables (age and sex) on effect sizes using regression-based techniques. To determine the slope, we used meta-regression (methods of moments). Each circle represents a study according to the meta-analysis of Zheng et al. (1).

Figure

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