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LETTER

Sex versus gender-related characteristics: which predicts clinical outcomes of acute COVID-19?

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Dear Editor,

Clinical outcomes of coronavirus disease 2019 (COVID-19) differ substantially between women and men, with men facing an increased risk of critical illness and death. Besides differences in age and prevalence of comorbidities, biological (sex) differences in immune responses, expression levels of virus entry receptors, endocrinological mechanisms as well as gender-related factors have been suggested to account for the differential outcomes in women and men [1, 2]. However, recent research has questioned the major impact of biological sex differences on COVID-19 outcomes [3, 4], and it has been hypothesized that non-biological aspects of being male or female (e.g. social roles and personality traits), the so-called "gender" dimension, may provide a better explanation for the observed sex dysbalance in COVID-19 outcomes. Gender, measured by a set of prespecified variables, modifies the outcome in acute coronary syndromes [5], but its role in COVID-19 outcomes has been widely ignored.

We estimated associations between gender (sociocultural factors, Supplementary Materials) and sex (biological factors) with disease severity of acute severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection in a prospective, observational cohort study of 3005 (1357 [45.2%] women, mean age 44.8 ± 17.5 years) mildly to critically ill patients in Switzerland (Supplementary Table 1–4/Supplementary Fig. 1) who were recruited for this study at four Swiss study sites. Gender-related characteristics were assessed using the short version of a validated questionnaire (Supplementary Materials) [5], while clinical data were gathered from electronic medical records. Multiple logistic regression models with the backward selection method were applied to assess potential predictors of severe illness (a detailed description of the statistical approach is provided in Supplementary Materials).

In the overall study cohort, male sex (odds ratio (OR) 2.27 [1.39–3.70], $p<0.001$) was independently associated with the composite endpoint of intensive care unit (ICU) admission, invasive ventilation, and/or death in logistic regression models. However, once patients were hospitalized, male sex was no longer prognostic for the combined endpoint (OR 1.15 [0.56–2.33], $p=0.707$, Fig. 1). Gender did not predict disease severity following multivariable adjustment (OR 0.61 [0.28–1.33], $p=0.211$), independent of admission status. Clinical-biological variables including the presence of cardiovascular risk factors (OR 1.42 [1.21–1.67, $p<0.001$), dyspnoea (OR 5.76 [4.10–8.09], $p<0.001$) or neurological symptoms (OR 2.32 [1.15–4.69], $p=0.02$) at presentation, an increased respiratory rate (OR 1.08 [1.021–1.41], $p=0.007$) or elevated white blood cells (OR 1.07 [1.02–1.12], $p=0.006$) were all independently associated with severe illness, while anosmia (OR 0.48 [0.34–0.67], $p<0.001$) or higher testosterone:estradiol ratio (OR 0.88 [0.80–0.98], $p=0.02$) were associated with a mild

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The members of the COGEN study group are mentioned in the Acknowledgments section.

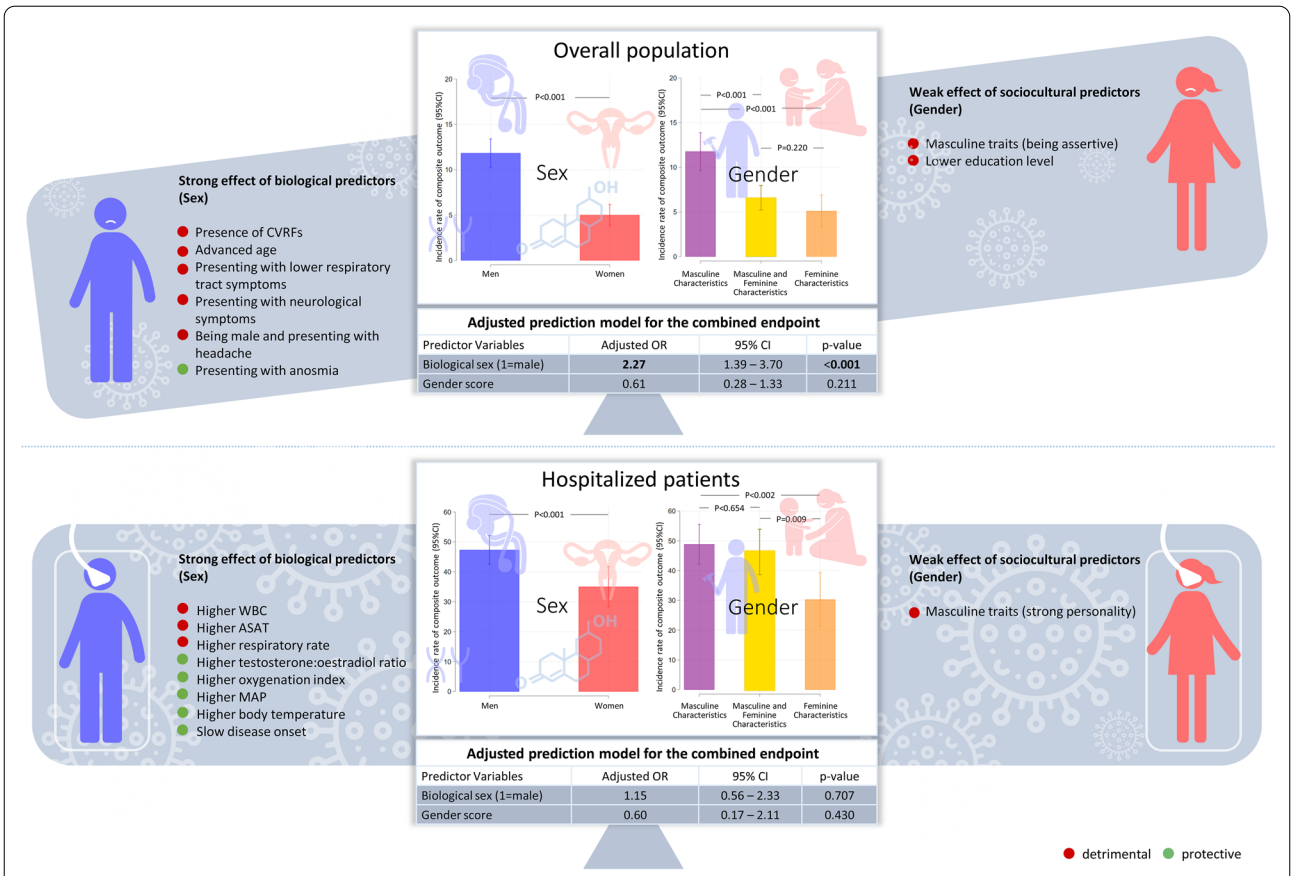

Fig. 1 Incidence of the combined endpoint (composite of death, admission to ICU/IMC, and/or invasive ventilation) in the overall populations (upper panel) and in hospitalized patients (lower panel) stratified by sex (left) or tertiles of gender (right). Data (bar graphs) are presented as incidence rates of the composite outcome and 95% confidence interval (CI). For each population, the prognostic value of biological sex and gender (as competing co-variates) for the combined endpoint are depicted. Models (tables) were adjusted for patient baseline characteristics including symptoms at presentation, pre-existing conditions, medications, anthropometric data, clinical and laboratory data and presented as odds ratio (OR) and 95% confidence interval (CI). Clinical biological predictors (left side) and sociocultural predictors (right side) of the combined endpoint selected by our multivariable models are also depicted. *CVRFs* cardiovascular risk factors, *WBC* white blood cells, *ASAT* aspartate aminotransferase, *MAP* mean arterial pressure, *ICU* intensive care unit, *IMC* intermediate care unit

disease course (Fig. 1). Assertiveness (OR 1.25 [1.09–1.42], $p=0.001$), having a strong personality (OR 1.22[1.04–1.43, $p=0.016$), and lower education (OR 2.88 [1.57–5.26], $p=0.001$) were the only gender-related parameters predicting disease severity in our cohort (Fig. 1). Lower education level is a well-known predictor of adverse health outcomes. The fact that hospitalized women had the lowest educational qualification in our cohort ($p<0.001$ vs hospitalized men) might point to important health disparities in this group.

Taken together, we demonstrate that male sex, but not gender, is independently associated with ICU admission, invasive ventilation, and/or death in COVID-19. Our data suggest that the male propensity towards a more severe disease course of COVID-19 can largely be explained by clinical-biological differences between men and women. However, the biological "advantage" of women disappears once they are hospitalized, indicating that during disease progression, currently unknown factors might adjust survival in both sexes. The risk predictors identified in our study might provide guidance in the current discussion about mask mandates and requirements for booster vaccination in high-risk demographic groups. Our data also emphasize that more research is needed to understand the complex impact of gender on health outcomes. Finally, the question why the survival advantage of women is reduced after hospitalization requires further study.

Supplementary Information

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Author contributions
CG, CEG, and VRZ conceptualized and designed the Swiss COGEN study. CEG, NH, and SB coordinated the study. CEG, PG, and SB prepared the study data. PG, CEG, SB, AT, and CG have verified the underlying data, performed the statistical analysis, and prepared tables and figures. CG, BG, CEG, and NH wrote the first manuscript draft. VRZ, KPB, RAS, ASZ, CA, SDB, DP, BW, JHB, AF, RT, GMK, HP, ST, JCS, TS, PDW, DAH, TS, HM, and MS contributed samples or data, participated in the interpretation of the results and critical revision of the manuscript. SB, KPB, CEG, CG, SDB, CA, DP, and BW implemented and coordinated the recruitment of study patients and biobank samples. All authors approved the final manuscript. CG is the guarantor for the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability
Based on the Business Administration System for Ethics Committees (BASEC) ethics approval, the non-anonymized raw data cannot be shared publicly. However, anonymised data that underlie the results reported in this article will become available to interested parties for non-commercial reasons, after the publication upon reasonable requests made to the corresponding author. Data requestors will need to sign a data access agreement.

Declarations

Conflicts of interest
Authors: CG has received research grants or speaker's fees from from the Novartis Foundation, Sanofi Genzyme, Switzerland, and Bayer Pharmaceuticals outside of the submitted work. The University Hospital Zurich (CG) holds a research contract with GE Healthcare outside of the submitted work. Study group: JCS and TS reports (full departmental disclosure) grants from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestle, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, Pan Gas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, Glaxo Smith Kline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Astellas, Astra Zeneca, CSL Behring, Novartis, Covidien, Nycomed, and Phagenesis, outside of the submitted work. The money went into departmental funds, no personal financial gain applies. All other authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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