



## Sex-specific association between vitamin D deficiency and COVID-19 mortality in older patients

M. Hars<sup>1,2</sup> · A. Mendes<sup>2</sup> · C. Serratrice<sup>3</sup> · F.R. Herrmann<sup>2</sup> · G. Gold<sup>2</sup> · C. Graf<sup>4</sup> · D. Zekry<sup>3</sup> · A. Trombetti<sup>1,2</sup> 

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Dear Editor,

We would like to call attention to a possible sex-specific association between vitamin D deficiency and COVID-19 mortality in the older population, and thus potential implications for the vitamin D research pipeline.

The COVID-19 disease pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to wreak havoc across the globe with a still uncertain outcome. At the time of writing, over 972,220 confirmed COVID-19-related deaths have been reported worldwide, the bulk of those deaths coming from older people, especially those over 80 years [1].

Emerging global data show sex disparities in COVID-19 mortality, infected men facing a higher risk to die of SARS-CoV-2 infection than women. This has led to a call to an in-depth analysis of sex-disaggregated data [2] and emphasized the need to understand the precise drivers and mechanisms of sex disparity in COVID-19 fatality which still remains poorly understood, especially in the understudied very old-aged population.

In the research efforts to identify drivers/risk factors for COVID-19 mortality, the role of vitamin D has received attracted interest, especially given its potent modulatory action

on the immune system and on the renin–angiotensin system (RAS), particularly the angiotensin-converting enzyme2 (ACE2), the main host cell receptor of SARS-CoV-2 [3, 4]. However, studies failed to explicitly address the effect of sex on the associations between vitamin D and COVID-19 outcomes.

With this in view, we assessed the sex-specific association between vitamin D deficiency and in-hospital mortality in an extension of the COVIDage study, a retrospective cohort conducted among Caucasian older COVID-19 patients hospitalized in our geriatric wards between March and April 2020 [5]. A total of 160 older inpatients (mean age  $85.9 \pm 6.6$  years; 95 women/65 men) with COVID-19 (i.e., positive SARS-CoV-2 swab or clinical/radiological diagnosis of COVID-19) and available serum level of 25-hydroxyvitamin D (25[OH]D) during acute disease were included in our analysis. Among them, 34% (32/95) of women and 42% (27/65) of men had vitamin D deficiency (i.e.,  $25[OH]D < 50$  nmol/L), without significant sex difference ( $p = 0.312$ ). Forty patients (25%; 25/65 men and 15/95 women) died during hospitalization. The in-hospital mortality risk was significantly higher in men than women (odds ratio: 3.10; 95% confidence interval (CI) 1.81–5.29;  $p < 0.001$ ). In sex-stratified Cox's proportional hazard models for survival analysis, severe vitamin D deficiency was independently associated with in-hospital mortality risk in men, in the univariate (crude hazard ratio (HR): 2.80; 95%CI 1.25–6.28;  $p = 0.012$ ) (Fig. 1) and multivariate models (adjusted HR for model with age, comorbidities, C-reactive protein level, and frailty status: 2.47; 95%CI 1.02–5.97;  $p = 0.044$ ). No association was found in women in either the univariate or the multivariate models (all  $p$  values  $> 0.521$ ).

These findings suggest that vitamin D research pipeline should integrate appropriate sex-specific analyses, from fundamental to clinical research. Especially they should inform

✉ A. Trombetti  
andrea.trombetti@hcuge.ch; andrea.trombetti@unige.ch

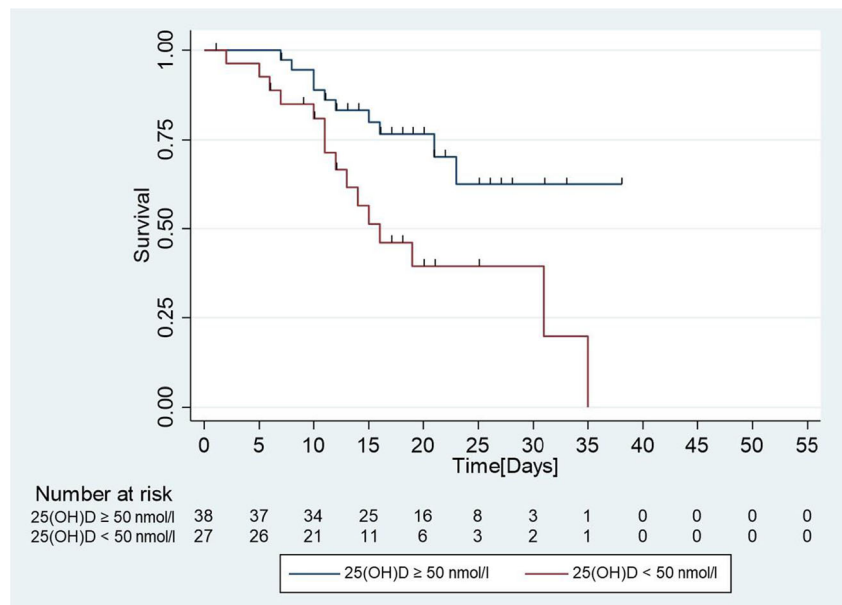
<sup>1</sup> Department of Medicine, Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, CH-1205 Geneva, Switzerland

<sup>2</sup> Department of Rehabilitation and Geriatrics, Division of Geriatrics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

<sup>3</sup> Department of Rehabilitation and Geriatrics, Division of Internal Medicine for the Aged, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

<sup>4</sup> Department of Rehabilitation and Geriatrics, Division of Rehabilitation and Internal Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

**Fig. 1** Kaplan–Meier survival analysis according to 25-hydroxyvitamin D [25(OH)D] levels in men with COVID-19. Vitamin D deficiency [25(OH)D level < 50 nmol/L] was associated with reduced survival (log rank  $p = 0.008$ )



the design and interpretation of awaited interventional trials evaluating the therapeutic potential of vitamin D supplementation in older COVID-19 patients. The mechanisms behind the sex-differential association, such as the implication of vitamin D deficiency on the X-chromosome linked RAS activity, remain to be fully elucidated [4].

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**Data availability** Selected data are available from the corresponding author on reasonable request.

### Compliance with ethical standards

**Conflicts of interest** None.

**Ethical approval** The COVIDage study was approved by the State of Geneva's Ethics Committee (protocol 2019–01288).

**Informed consent** Informed consent was not required for this retrospective study and all details that might disclose the identity of the subjects under study was omitted or anonymized.

### References

1. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19)-Situation Report-97 2020. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. Accessed 24 Sept 2020
2. Womersley K, Ripullone K, Peters SA, Woodward M (2020) Covid-19: male disadvantage highlights the importance of sex disaggregated data. *BMJ*. 370:m2870
3. Mitchell F (2020) Vitamin-D and COVID-19: do deficient risk a poorer outcome? *Lancet Diabetes Endocrinol* 8(7):570
4. Benskin LL (2020) A basic review of the preliminary evidence that COVID-19 risk and severity is increased in vitamin D deficiency. *Front Public Health*. <https://doi.org/10.3389/fpubh.2020.00513>
5. Mendes A, Serratrice C, Herrmann F et al (2020) Predictors of in-hospital mortality in older patients with COVID-19: the COVIDAge study. *J Am Med Dir Assoc*. <https://doi.org/10.1016/j.jamda.2020.09.014>

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