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LETTER TO THE EDITOR

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

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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 ± 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

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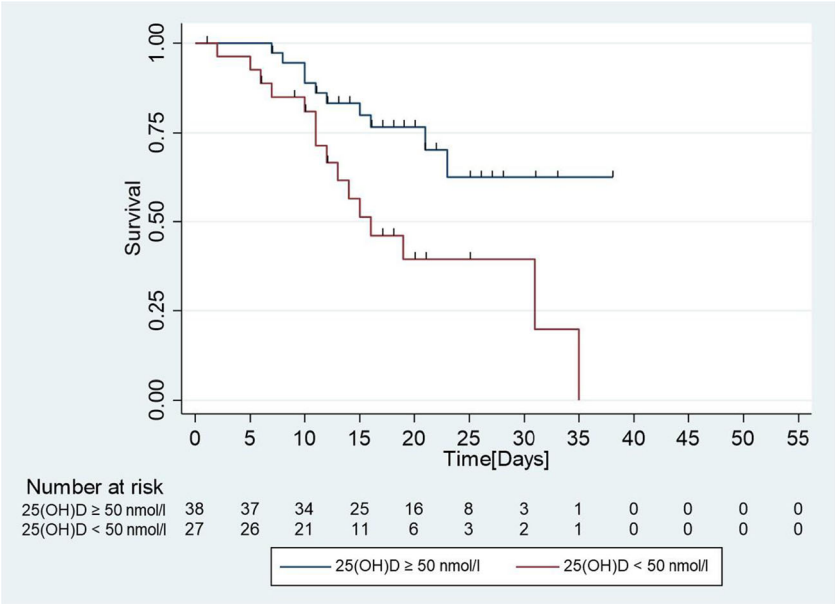

Fig. 1 Kaplan–Meier survival analysis according to 25-hydroxyvitamin D [25(OH)D] levels in men with COVID-19. Vitamin D deficiency [25(OH)D level < 50 nmol/L] was associated with reduced survival (log rank $p = 0.008$)

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.

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