



In reply: Sex-specific outcomes in COVID-19: missing pieces of the puzzle

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To the Editor,

We thank Drs Magoon and Choudhary for their interest¹ in our study and the raised issues regarding thrombotic complications in COVID-19 and their potential impact on mortality.

When we planned and initiated the international COVIP study in March 2020 at the beginning of the pandemic,

The COVIP study group (<https://www.vipstudy.org>; covip@med.uni-duesseldorf.de) is part of the Very Old Intensive Care Patients (VIP) project by the European Society of Intensive Care Medicine (ESICM).

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there was little knowledge on the prothrombotic risk of COVID-19. As is evident from our paper² and many other analyses (e.g., Jung *et al.*³) we published from the database, we considered an abundance of parameters in the design regarding disease severity, frailty, quality of life and—unlike many other observational studies—treatment limitations. Nevertheless, we did not include information on thrombotic complications and were thus unable to evaluate sex-specific thrombotic events.

Overall, our present analysis aimed at analyzing sex-specific mortality with adjustment for a variety of confounders of disease severity, treatment intensity, and treatment limitations. Sex-specific thrombotic events would have increased a potential gap in mortality

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between men and women; however, after multivariate adjustment, we were unable to find such a gap.

Because of a lack of data, we can only speculate whether thrombotic events may have occurred with sex-specific differences in the COVIP cohort: the referenced study by Wilcox *et al.*⁴ found no significant differences in thrombotic events in patients > 75 yr of age with COVID-19. Additionally, there is still no evidence of benefit from therapeutic anticoagulation as a reaction to prothrombotic risk in COVID-19 in critically ill patients, as data from the REMAP-CAP, ACTIV-4a, and ATTACC trials⁵ as well as the HEP-COVID trial⁶ were negative in patients treated in intensive care. This might hint toward lower differential risk between sexes both in older age groups and with higher disease severity.

We thus do not think the differential sex-specific thrombotic risk in our particular cohort of older critically ill patients was significant and may have resulted in differential mortality impact. We look forward to further elucidating risk factors in critically ill old patients in the future—a cohort that has been neglected by other studies to date.

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