Can J Anesth/J Can Anesth (2023) 70:1110–1112
https://doi.org/10.1007/s12630-023-02470-x

CORRESPONDENCE

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

Georg Wolff, MD · Bernhard Wernly, MD, PhD · Hans Flaatten, MD, PhD · Jesper Fjølner, MD · Raphael Romano Bruno, MD · Antonio Artigas, MD, PhD · Bernardo Bollen Pinto, MD · Joerg C. Schefold, MD · Malte Kelm, MD · Stephan Binneboessel, MD · Philipp Baldia, MD · Michael Beil, MD · Sigal Sivri, MD · Peter Vernon van Heerden, MD · Wojciech Szczeklik, MD, PhD · Muhammed Elhadi, MD · Michael Joannidis, MD · Sandra Oeyen, MD · Maria Flamm, MD, PhD · Brian Marsh, MD · Finn H. Andersen, MD · Rui Moreno, MD, PhD · Ariane Boumendil, PhD · Dylan W. De Lange, MD, PhD · Bertrand Guidet, MD, PhD · Susannah Leaver, MD · Christian Jung, MD, PhD · the COVIP study group

Received: 23 January 2023 / Revised: 23 January 2023 / Accepted: 24 January 2023 / Published online: 10 May 2023

Keywords COVID-19 · SARS-CoV-2 · sex-specific outcomes · thrombotic complications

To the Editor,

We thank Drs Magoon and Choudhary for their interest[1] 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, there was little knowledge on the prothrombotic risk of COVID-19. As is evident from our paper[2] 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

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).

G. Wolff, MD · R. R. Bruno, MD · M. Kelm, MD · S. Binneboessel, MD · P. Baldia, MD · C. Jung, MD, PhD (✉)
Department of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
e-mail: christian.jung@med.uni-duesseldorf.de

B. Wernly, MD, PhD
Department of Anaesthesiology, Perioperative Medicine and Intensive Care Medicine, Paracelsus Medical University, Salzburg, Austria

H. Flaatten, MD, PhD
Department of Clinical Medicine, Department of Anaesthesia and Intensive Care, Haukeland University Hospital, University of Bergen, Bergen, Norway

J. Fjølner, MD
Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark

A. Artigas, MD, PhD
Department of Intensive Care Medicine, CIBER Enfermedades Respiratorias, Corporacion Sanitaria Universitaria Parc Tauli, Autonomous University of Barcelona, Sabadell, Spain

B. B. Pinto, MD
Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland

J. C. Schefold, MD
Department of Intensive Care Medicine, Inselspital, Universitätsspital, University of Bern, Bern, Switzerland

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 trials[5] as well as the HEP-COVID trial[6] 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.

Disclosures The authors state that there is nothing to disclose in addition to disclosures in the original article.

Funding statement Please refer to the funding statement in the original article. Open Access funding enabled and organized by Projekt DEAL.

Editorial responsibility This submission was handled by Dr. Stephan K. W. Schwarz, Editor-in-Chief, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*.

M. Beil, MDS. Sivri, MD
Department of Medical Intensive Care, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

P. V. van Heerden, MD
Department of Anesthesia, Intensive Care and Pain Medicine, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

W. Szczeklik, MD, PhD
Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland

M. Elhadi, MD
Faculty of Medicine, University of Tripoli, Tripoli, Libya

M. Joannidis, MD
Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria

S. Oeyen, MD
Department of Intensive Care 1K12IC, Ghent University Hospital, Ghent, Belgium

M. Flamm, MD, PhD
Institute of General Practice, Family Medicine and Preventive Medicine, Paracelsus Medical University, Salzburg, Austria

B. Marsh, MD
Mater Misericordiae University Hospital, Dublin, Ireland

F. H. Andersen, MD
Department of Anesthesia and Intensive Care, Ålesund Hospital, Ålesund, Norway

Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

R. Moreno, MD, PhD
Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Faculdade de Ciências Médicas de Lisboa, Nova Médical School, Unidade de Cuidados Intensivos Neurocríticos e Trauma, Lisbon, Portugal

A. Boumendil, PhDB. Guidet, MD, PhD
UPMC Univ Paris, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe: épidémiologie hospitalière qualité et organisation des soins, Sorbonne Universités, Paris, France

Assistance Publique - Hôpitaux de Paris, service de réanimation médicale, Hôpital Saint-Antoine, Paris, France

D. W. De Lange, MD, PhD
Department of Intensive Care Medicine, University Medical Center, University Utrecht, Utrecht, The Netherlands

S. Leaver, MD
General Intensive Care, St George´s University Hospitals NHS Foundation Trust, London, UK

References

1. *Magoon R, Choudhary N.* Sex-specific outcomes in COVID-19: missing pieces of the puzzle. Can J Anesth 2023; https://doi.org/10.1007/s12630-023-02469-4
2. *Wolff G, Wernly B, Flaatten H, et al.* Sex-specific treatment characteristics and 30-day mortality outcomes of critically ill COVID-19 patients over 70 years of age-results from the prospective COVIP study. Can J Anesth 2022; 69: 1390–8. https://doi.org/10.1007/s12630-022-02304-2
3. *Jung C, Flaatten H, Fjølner J, et al.* The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study. Crit Care 2021; 25: 149. https://doi.org/10.1186/s13054-021-03551-3
4. *Wilcox T, Smilowitz NR, Seda B, Xia Y, Hochman J, Berger JS.* Sex differences in thrombosis and mortality in patients hospitalized for COVID-19. Am J Cardiol 2022; 170: 112–7. https://doi.org/10.1016/j.amjcard.2022.01.024
5. *REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al.* Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021; 385: 777–89. https://doi.org/10.1056/nejmoa2103417
6. *Spyropoulos AC, Goldin M, Giannis D, et al.* Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Intern Med 2021; 181: 1612–20. https://doi.org/10.1001/jamainternmed.2021.6203