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Letter to the Editor

Comparing Mortality of SARS-CoV-2 or Influenza Infected Ventilations Requires Inclusion of All Possibl Cofounding Factors

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Letter to the Editor

We were interested to read the article by Oud *et al*. on a retrospective, population-based cohort study on the short-term mortality among mechanically ventilated patients with COVID-19 compared to contemporaneous counterparts infected with influenza [1]. Altogether, 19659 of the ventilated hospitalizations had COVID-19 and 2,536 had influenza [1]. Short-term mortality among mechanically ventilated hospitalizations with COVID-19 and influenza was 49.1% vs. 20.7% respectively [1]. It was concluded that population-level short-term mortality among mechanically ventilated hospitalizations with COVID-19 was higher than that among those with influenza during the latter years of the pandemic [1]. The study is remarkable, but several points should be discussed.

The first point is that the study design was retrospective [1]. Retrospective designs have the disadvantage of limited control over population sampling and limited control over the type and quality of predictor variables. In addition, the relevant predictors may not have been recorded in the medical record, and it may be difficult or impossible to detect confounding variables and causality. In addition, some information may inevitably be missing, as the data are based on the review of medical records that were not originally intended for the collection of data for research purposes. Selection and recall errors also affect the results, which can lead to bias [2].

The second point is that the applied data set did not include information about the vaccination status of the included patients [1]. Since the outcome of both infections with SARS-CoV2 and with influenza may heavily depend on whether a patient was vaccinated against the agent that caused admission to the ICU, it would have been imperative to know how was vaccinated and who not. It is conceivable that those vaccinated against the causative agent had more likely a favourable outcome than those who were not vaccinated.

The third point is that through the use of the Deyo modification of the Charlston comorbidity index only a limited number of comorbidities were included in the assessment as risk-adjustment covariates. The Charlston comorbidity index does not consider chronic infectious or inflammatory disease, neurological disease other than stroke or tumour, why causes for mortality such as meningitis or encephalitis may have been missed. The Charlston index also does not include sepsis, electrolyte disorders, endocrine disorders other than diabetes, or acidosis/alkalosis as comorbidities.

The fourth point is that current medications were also not included in the analysis [1]. Since SARS-CoV-2 or influenza infection can change metabolisation or excretion of drugs metabolites, it is conceivable that overdosage or even intoxication with the current medication could have occurred that also significantly influence the outcome of the cohort.

The fifth point is that it has not been convincingly reported how it was ascertained that truly all included patients were tested for both SARS-CoV-2 and influenza. Were there cases that were not tested for SARS-CoV-2 or influenza because they were already positive for influenza or SARS-CoV-2?

To summarize, this review has some limitations that affect the reliability of data and their interpretation. Addressing these limitations may modify the conclusions and the message of the study. A population based study on the mortality of SARS-CoV-2 or influenza infected ventilated patients must include their vaccination status, the entire spectrum of their comorbidities and all co-medications.

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