Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Impact of the Alpha VOC on disease severity in SARS-CoV-2-positive adults in Sweden

Dear Editor,

Variants of concern (VOC) have rapidly become the dominating SARS-CoV-2 viruses worldwide.[1,2] Concerns have been raised that VOC may cause more severe disease than non-VOC.[3] Cevik and Mishra[3] concluded that Alpha VOC (lineage B.1.1.7) positivity was associated with increased risk for hospitalization in four of five, and for death in five of six community-based studies, but was not associated with increased mortality in 3 hospital-based studies. Two of these hospital-based studies[4,5] also evaluated disease severity and did not find an association with Alpha VOC. Accordingly, in this journal, Whittaker et al.[6] reported no difference between hospitalised patients infected with Alpha VOC and those infected with non-VOC, regarding length of stay in hospital, length of stay in the intensive care unit (ICU), and mortality.

The discrepancy between these community-based and hospital-based studies regarding the impact of the Alpha VOC on disease severity motivated us to conduct a Swedish study on disease severity in the population and among hospitalised individuals. Our primary analysis was a comparison between two national cohorts from a period prior to VOC introduction and a period of Alpha VOC dominance, respectively. Our secondary analysis included individuals diagnosed with Alpha VOC or non-VOC, respectively. The study was conducted by the Public Health Agency of Sweden and the National Board of Health and Welfare.

Three key considerations for studies on the association between specific SARS-CoV-2 lineages and disease severity have been pointed out,[3] these being: handling of confounding factors; avoidance of selection bias regarding population for inclusion; and comparative timing of inclusion to avoid influence from other factors such as change in hospital load. These key considerations were applied in this study. To handle confounding factors, we chose to include SARS-CoV-2 test-positive individuals 20–69 years old without comorbidity and without care dependency. To reduce the risk of selection bias regarding inclusion in the primary analysis, all individuals meeting the inclusion criteria in Sweden were included. To address timing of inclusion in the primary analysis, we designed a comparison analysis of two national cohorts of individuals fulfilling the inclusion criteria, with study periods containing similar numbers of positive cases per week in both cohorts – a non-VOC cohort (second national wave; weeks 45–51 2020; n = 186 313 [average 26 600/week]; median age 42 years, 53% females) and an Alpha VOC dominated cohort (third national wave; weeks 12–16 2021; n = 137 999 [average 27 600/week]; median age 41 years, 49% females). Among whole genome sequenced SARS-CoV-2-positive cases in Sweden, no case of Alpha VOC was identified during weeks 45–51 (the first case was identified in week 52),[7] but was identified in 87–95% of cases during weeks 12–16.[8] Until week 16, the vaccination against Covid-19 in Sweden had mainly covered persons with high age, care dependency, and/or comorbidity.

The secondary analysis was based on a nationwide typing project of individuals who were SARS-CoV-2 positive during weeks 5–12 (2021). Using targeted typing PCR, 12 321 individuals meeting the inclusion criteria were confirmed to be either Alpha VOC positive (n = 8273; median age 42 years, 55% females) or VOC negative (n = 4048; median age 41 years, 51% females).

Nationwide register data on demographic factors, country of birth, care dependency, comorbidity, hospitalization, ICU admission, mortality, discharge codes, SARS-CoV-2 positivity, and related variables were compiled, using the unique national personal identification number, as described previously.[9] Individuals who were admitted to hospital for any reason 5 days prior until 14 days after the first SARS-CoV-2 positive test were considered hospitalised due to COVID-19. Those who either received high-flow nasal oxygen (according to a specific national discharge code) or were admitted to an ICU during their hospital stay were considered to have severe illness due to COVID-19.

The results of the two analyses are displayed in Table 1. Compared to the non-VOC cohort, the Alpha VOC dominated cohort had significantly higher rates of hospitalisation, severe illness, and death overall, and a significantly higher rate of severe illness among hospitalised individuals. In the secondary analysis, Alpha VOC positive individuals had significantly higher rates of hospitalisation and severe illness than VOC negative individuals overall, but the numbers were too small to evaluate differences in severity rate among hospitalised individuals.

In conclusion, in this Swedish population of SARS-CoV-2-positive adult individuals, without risk factors, infection with the Alpha VOC was associated with greater disease severity in the overall population which is in agreement with most other community based studies[3]. However, among hospitalised individuals, we found a higher frequency of severe illness in the Alpha VOC dominated cohort than in the non-VOC cohort, indicating greater severity of Alpha VOC also in hospitalised individuals. This finding was in contrast to those of other hospital-based studies[4-6], and may be due to a greater number of individuals at risk in the present study. Continued surveillance of virus evolution and its influence on disease severity is crucial in the continued response to the pandemic. A model similar to that of the present study, in combination with vaccination data, could be used to assess the impact of Delta VOC on disease severity.

Ethics

The study was approved by the Swedish Ethics Review Authority, Uppsala (Dnr 2020–04,278).

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Table 1
Outcome frequencies and odds ratios (OR) for national cohort and variant of concern (VOC) status comparisons, among SARS-CoV-2 positive individuals 20–69 years old without comorbidity and without care dependency in Sweden.

Outcome	National cohort comparison			VOC status comparison		
	Non-VOC cohort No. with outcome/ No. at risk (%)	Alpha VOC dominated cohort No. with outcome/ No. at risk (%)	Alpha VOC dominated cohort *vs.* Non-VOC cohort OR[1] (95% CI)	VOC negative individuals No. with outcome/ No. at risk (%)	Alpha VOC positive individuals No. with outcome/ No. at risk (%)	Alpha VOC positive individuals *vs.* VOC negative individuals OR[2] (95% CI)
SARS-CoV-2 positive individuals (overall study population)						
Hospitalisation	3730/186,313 (2.0)	4420/137,999 (3.2)	1.71 (1.64–1.79)	49/4048 (1.2)	217/8273 (2.6)	2.38 (1.66–3.41)
Severe illness[3]	638/186,313 (0.34)	1001/137,999 (0.73)	2.09 (1.89–2.32)	6/4048 (0.15)	37/8273 (0.45)	2.85 (1.08–7.46)
Death[4]	87/186,313 (0.047)	98/137,999 (0.071)	1.54 (1.15–2.07)	2/4048 (0.049)	6/8273 (0.073)	NA[5]
Hospitalised SARS-CoV-2 positive individuals						
Severe illness[3]	638/3730 (17)	1001/4420 (23)	1.33 (1.18–1.50)	6/49 (12)	37/217 (17)	NA[5]
Death[6]	62/3730 (1.7)	80/4420 (1.8)	1.14 (0.80–1.61)	2/49 (4.1)	4/217 (1.8)	NA[5]

[1] From a logistic regression model adjusted for age, sex, country of birth, and healthcare region.
[2] From a logistic regression model adjusted for age, sex, country of birth, healthcare region, and week of positive test.
[3] High-flow nasal oxygen or admission to an intensive care unit during hospital stay.
[4] All-cause death within 45 days from the first SARS-CoV-2 positive test.
[5] NA, not analysed, due to low numbers of the outcome.
[6] All-cause death within 45 days from hospital admission.

Declaration of Competing Interest

The authors declare no competing interests.

CRediT authorship contribution statement

Kristoffer Strålin: Conceptualization, Visualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Daniel Bruce:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Erik Wahlström:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Sten Walther:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Moa Rehn, AnnaSara Carnahan:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Emmi Andersson:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Anna M Bennet Bark:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Håkan Hanberger:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing.

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Kristoffer Strålin
Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

Daniel Bruce, Erik Wahlström
National Board of Health and Welfare, Sweden

Sten Walther
Swedish Intensive Care Registry, Värmland County Council, Karlstad, Sweden
Department of Cardiothoracic and Vascular Surgery, Heart Centre, Linköping University Hospital, Linköping, Sweden
Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Moa Rehn, AnnaSara Carnahan, Emmi Andersson
The Public Health Agency of Sweden, Sweden

Anna M Bennet Bark
National Board of Health and Welfare, Sweden

Håkan Hanberger*
Division of Inflammation and Infection, Department of Biomedical and Clinical Sciences, Faculty of Medicine and Health Sciences, Linköping University, Linköping, Sweden
Department of Infectious Diseases, University Hospital Region Östergötland, Sweden

*Corresponding author at: Division of Inflammation and Infection, Department of Biomedical and Clinical Sciences, Faculty of Medicine and Health Sciences, Linköping University, Linköping, Sweden.
E-mail address: hakan.hanberger@liu.se (H. Hanberger)