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Letter to the Editor

Trajectories of hospitalisation for patients infected with SARS-CoV-2 variant B.1.1.7 in Norway, December 2020 – April 2021

Dear Editor,

The COVID-19 pandemic has put unprecedented strain on health systems around the world, and the emergence of variants of concern (VOC) remains an area of substantial concern as we continue to battle the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This includes lineage B.1.1.7 (alpha variant), first detected in south-east England in September 2020.[1] In Norway (population 5.4 million), the first infection with B.1.1.7 was sampled in week 48 2020, and B.1.1.7 became the predominant circulating variant nationally in week 5 2021. In addition to increased transmissibility,[1] B.1.1.7 infection has been associated with increased risk of hospitalisation compared to non-VOC in Norway,[2] as well as other European countries.[3,4] Evidence on differences in patient trajectories and outcomes among hospitalised patients infected with B.1.1.7 compared to other lineages is thus essential to support ongoing capacity planning in the health system.

In this journal, a study from Garvey and colleagues analysed a cohort of 152 patients from the UK's largest hospital trust infected with the VOC B.1.1.7 (and one B.1.351) compared to other variants.[5] They reported no statistically significant difference in the mean length of stay (LoS) in hospital or ICU, proportion of patients admitted to ICU, nor proportion of patients who died.[5] In Norway we have conducted a similar study on a representative cohort of 1103 SARS-CoV-2 positive patients using linked, patient-level data from national registries.

A full description of the data sources and methods is available here.[6] Briefly, the data come from the national emergency preparedness registry, which comprises data from a variety of central health registries, national clinical registries and other national administrative registries. We included notified cases of COVID-19 who were hospitalised not more than two days before and less than 28 days after a positive SARS-CoV-2 test in Norway between 21 December 2020 and 25 April 2021, who had available variant data after whole genome sequencing (WGS) or PCR screening, and who had not been vaccinated with a COVID-19 vaccine before sampling or hospitalisation. We extracted and linked data on 2 June 2021, ensuring a minimum of 36 days follow-up since last date of hospitalisation. Although elective surgeries in some regions were postponed during a surge in hospitalisations among COVID-19 cases in mid-March, hospitals in Norway functioned within capacity during the study period, while there were no major changes in treatment guidelines for SARS-CoV-2 patients in hospital or ICU. Variants were identified based on WGS using Illumina or Nanopore technology, partial sequencing by Sanger sequencing or PCR screening for selected targets. Of 2354 unvaccinated patients in the study period, 1186 (50%) had known virus variant, and few differences were observed between patients who had known virus variant and those who did not.[6] We used survival analysis (Kaplan Meier curves, adjusting for right censuring) to examine the association between B.1.1.7 and time from symptom onset to hospitalisation, and LoS in hospital and in ICU, compared to non-VOC. We used logistic regression to examine the association between B.1.1.7 and mortality up to 30 days post discharge compared to non-VOC. For the analysis of mortality, we analysed a subset of the dataset, including patients who had been discharged by 30 April 2021, in order to ensure at least 30 days of follow-up post discharge for all patients. We built multivariable models by forward model selection and AIC comparison. Explanatory variables included in the multivariable models are detailed in Table 2. Statistical modelling was performed using R version 3.6.

Of the 1186 patients, 946 (81%) were B.1.1.7 and 157 (13%) were non-VOC, while 27 (2%) were another VOC (B.1.351, P.1 or B.1.617.2) and 53 (4%) could not clearly be distinguished as VOC or non-VOC. Characteristics of the 1103 patients infected with B.1.1.7 or a non-VOC are presented in Table 1. The proportion of B.1.1.7 increased throughout the study period from 0% in week 52, 2020 to 41% in week 5, 2021 and 88% in week 7, 2021. From week 11, 2021 onwards, 99% of patients were B.1.1.7. In both the univariable and multivariable models, we did not observe a statistically significant difference in the time from symptom onset to hospitalisation, LoS in hospital nor LoS in ICU for B.1.1.7 patients compared to non-VOC patients (Table 2). Of the 1103 patients, 1037 (94%) were discharged by 30 April 2021; 880 B.1.1.7 and 157 non-VOC. For B.1.1.7, 50 patients died in hospital (6%), one died less than seven days post discharge (0.1%), and three died 7–30 days post discharge (0.3%). For non-VOC, 10 patients died in hospital (6%), two died less than seven days post discharge (1.3%), and two died 7–30 days post discharge (1.3%). In both the univariable and multivariable models, we did not observe a statistically significant difference in the odds of death for B.1.1.7 patients compared to non-VOC patients (Table 2).

Our findings indicate no difference in the time from symptom onset to hospitalisation, LoS in hospital and ICU, nor odds of mortality up to 30 days post discharge for persons infected with B.1.1.7 compared to non-VOC in Norway. These findings are in line with Garvey et al.[5], and other published studies from the UK.[7–9] This suggests that, while B.1.1.7 seems to increase the risk of hospitalisation,[2–4] other patient characteristics determine patient trajectories and healthcare required among those hospitalised with COVID-19. These findings, along with the success of vaccination programmes, are encouraging for ongoing capacity planning in the

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Table 1
Characteristics of hospitalised SARS-CoV-2 positive patients infected with B.1.1.7 or a non-VOC, Norway, 21 December 2020 – 25 April 2021.

Characteristics		Variant type Non-VOC (n = 157)	B.1.1.7 (n = 946)
Method used to determine variant	WGS	120 (76%)	451 (48%)
	PCR-screening	37 (34%)	495 (52%)
Sex	Female	69 (44%)	392 (42%)
	Male	88 (56%)	554 (59%)
Age group	0–24 years	9 (6%)	52 (6%)
	25–44 years	20 (13%)	236 (25%)
	45–64 years	65 (41%)	431 (46%)
	≥ 65 years	63 (40%)	227 (24%)
Born in Norway	Yes	97 (62%)	440 (47%)
	No	53 (34%)	475 (50%)
	Unknown	7 (4%)	31 (3%)
Risk factors	Asthma	18 (11%)	105 (11%)
	Diabetes	34 (22%)	169 (18%)
	Cancer	5 (3%)	42 (4%)
	Chronic lung disease, except asthma	19 (12%)	60 (6%)
	Chronic neurological or neuromuscular disease	5 (6%)	40 (4%)
	Heart disease including hypertension	70 (45%)	302 (32%)
	Immunocompromised, including HIV	9 (6%)	31 (3%)
	Kidney disease	16 (10%)	28 (3%)
	Liver disease	2 (1%)	6 (1%)
	Obesity (BMI≥ 30)*	22 (31%)	225 (43%)
	Pregnant	3 (2%)	25 (3%)
	Current smoker	9 (6%)	43 (5%)
At least one stay where COVID-19 was the reported main cause of admission	Yes	127 (81%)	815 (86%)
	No	28 (18%)	126 (13%)
	Unknown	2 (1%)	5 (1%)
Admission to ICU	Yes	25 (16%)	175 (18%)
	No	132 (84%)	771 (82%)
Mortality	Died in hospital	10 (6%)	52 (6%)
	< 7 days post discharge	2 (1%)	1 (0%)
	7–30 days post discharge	2 (1%)	4 (0%)
	Alive > 30 days after hospital discharge	143 (91%)	889 (94%)
Number of patients still in hospital at end of study period	In ICU	0 (0%)	8 (1%)
	In hospital, not in ICU	0 (0%)	8 (1%)
	Discharged from hospital	157 (100%)	930 (98%)

VOC: Variant of concern; WGS: Whole genome sequencing; ICU: Intensive care unit; BMI: Body mass index.
* In our dataset, 85 (54%) non-VOC and 424 (45%) B.1.1.7 patients had unknown information on height and weight, and thus unknown data on BMI.

hospital sector, particularly as societies ease lockdowns. Timely analysis on the association between current and future VOC, such as B.1.617.2 (which overlook B.1.1.7 as the predominant circulating variant in Norway in week 27, 2021), and the risk of severe disease and impact on patient trajectories remains essential to ensure health systems are best prepared and able to appropriately respond to this evolving public health threat. These analyses need to come from a variety of settings, considering local epidemiological characteristics.

CRediT authorship contribution statement

Robert Whittaker: Conceptualization, Writing – original draft, Data curation, Validation, Investigation, Formal analysis, Writing – review & editing. **Anja Bråthen Kristofferson:** Data curation, Validation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Elina Seppälä:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Beatriz Valcarcel Salamanca:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Lamprini Veneti:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Margrethe Larsdatter Storm:** Funding acquisition, Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Håkon Bøås:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Umaer Naseer:** Funding acquisition, Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Karoline Bragstad:** Funding acquisition, Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Reidar Kvåle:** Funding acquisition, Data curation, Writing – original draft, Writing – review & editing. **Karan Golestani:** Writing – original draft, Writing – review & editing. **Siri Feruglio:** Writing – original draft, Writing – review & editing. **Line Vold:** Writing – original draft, Writing – review & editing. **Karin Nygård:** Writing – original draft, Writing – review & editing. **Eirik Alnes Buanes:** Conceptualization, Funding acquisition, Data curation, Writing – original draft, Writing – review & editing.

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Table 2
Crude and adjusted hazard ratios from survival analysis for time from symptom onset to hospitalisation, and length of stay in hospital and intensive care, and crude and adjusted odds ratios from logistic regression for death in-hospital or up to 30 days post discharge, among hospitalised SARS-CoV-2 positive patients infected with B.1.1.7 compared to a non-VOC, Norway, 21 December 2020 – 25 April 2021.

Outcome	Variant type Non-VOC Number of patients	Median (IQR)	B.1.1.7 Number of patients	Median (IQR)	Crude hazard ratio for B.1.1.7 compared to non-VOC (95%CI)	Adjusted^ hazard ratio for B.1.1.7 compared to non-VOC (95%CI)
Days from symptom onset to hospitalisation*	93	8(4–11)	445	8(5– 10)	1.22 (0.97 – 1.52)	1.21 (0.94 – 1.55)
Days in hospital for patients not admitted to ICU	132	4.1 (2.1 – 7.5)	771	4.0 (2.1 – 6.8)	1.08 (0.90 – 1.31)	0.96 (0.79 – 1.17)
Days in hospital before admission to ICU	25	2.1 (0.1 – 4.7)	175	1.2 (0.2 – 3.7)	1.28 (0.83 – 1.96)	1.03 (0.67 – 1.59)
Days in ICU	25	11.0 (7.2 – 16.4)	175	10.6 (5.4 – 19.6)	0.97 (0.61 – 1.56)	0.83 (0.51 – 1.34)
Days in hospital after discharge from ICU**	20	7.2 (3.5 – 11.3)	141	5.9 (3.2 – 9.8)	1.06 (0.65 – 1.71)	1.00 (0.61 – 1.63)
	Non-VOC No (%)	Yes (%)	B.1.1.7 No (%)	Yes (%)	Crude odds ratio for B.1.1.7 compared to non-VOC (95%CI)	Adjusted^^ odds ratio for B.1.1.7 compared to non-VOC (95%CI)
Death in-hospital or up to 30 days post discharge***	143 (91%)	14 (9%)	826 (94%)	54 (6%)	0.67 (0.36 – 1.23)	1.39 (0.68 – 3.01)

VOC: Variant of concern; ICU: Intensive care unit; IQR: Interquartile range; 95%CI: 95% confidence interval.
^ Adjusted for age (continuous variable either linearly or with a spline), sex, county of residence, regional health authority, week of admission, country of birth (Norway, overseas and unknown), main cause of hospitalisation (COVID-19, other, unknown) and underlying risk factors. The variables included in the final multivariable model were obtained by forward model selection and AIC comparison.[6]
^^ age (continuous variable either linearly or with a spline), sex, county of residence, regional health authority, week of admission, country of birth (Norway, overseas and unknown), main cause of hospitalisation (COVID-19, other, unknown), underlying risk factors and admission to ICU. The variables included in the final multivariable model were obtained by forward model selection and AIC comparison.[6]
* Number of patients with known date of symptom onset: non-VOC 93/157 (60%); B.1.1.7 445/946 (47%).
** Excludes eight B.1.1.7 patients who were still admitted to ICU at the end of the study period, and five non-VOC and 26 B1.1.7 who passed away in ICU.
*** Death in-hospital or up to 30 days post discharge is limited to patients who had been discharged by 30 April 2021 (157 non-VOC, 880 B1.1.7), in order to ensure at least 30 days of follow-up post discharge for all patients.

of timely and complete data to the Norwegian Intensive Care and Pandemic Registry, as well as colleagues at the register itself. We would also like to thank Anja Elsrud Schou Lindman, project director for the national preparedness registry, and all those who have enabled data transfer to this registry, especially Gutorm Høgåsen at the NIPH, who has been in charge of the establishment and administration of the registry. We would like to acknowledge Jacob Berild and Camilla Mauroy, who coordinate the surveillance of COVID-19 related deaths at the NIPH. We would like to thank Trude Marie Lyngstad, Anders Skyrud Danielsen, Nora Dotterud and Evy Dvergsdal at the NIPH for their assistance in cleaning the data from different registries.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Role of funding sources

The authors received no specific funding for this work.

Ethics

Ethical approval for this study was granted by Regional Committees for Medical Research Ethics - South East Norway, reference number 249509.

Data availability statement

The datasets analysed during the current study come from the national emergency preparedness registry for COVID-19, housed at the Norwegian Institute of Public Health. The preparedness registry is temporary and comprises data from a variety of central health registries, national clinical registries and other national administrative registries. Further information on the preparedness registry, including access to data from each individual data source, is available at https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

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