Analysis on recent hospital case fatality and variant of concern VOC2020-01 using CO-CIN data (10th February 2021)

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This is a rapid report based on a snapshot of data extracted from CO-CIN. The data has not been source verified.

This report follows the SAGE report we published on the 20th January 2021, using an updated dataset. We explore the hypothesis that infection with the UK variant of concern VOC202012-01 (lineage B.1.1.7) is linked to a significant increment in hospital case fatality rate. A mixed-effects multivariable logistic regression model on a limited data sample does not suggest that the new variant is associated with a higher 28day fatality rate in patients admitted to hospital. Limitations of the analysis are described below.

VOC cases, determined by sequencing, were matched (1:1) by age, sex and admission date (+- 7 days) to non-VOC cases for the period 1st October to 12th January 2021 with 28 days follow-up. We accessed the whole CO-CIN dataset where matching to a VOC determination is possible. Matching by admission date was used to account for changes observed in hospital case fatality rate over time, but there was insufficient data to match by hospital to effectively account for local activity (busyness). The model adjusted for age and sex, and clustering by hospital was added using a random effect. The matched dataset included patients from 91 hospitals with 43 hospitals contributing VOC cases. All 91 hospitals were in England. We did not match for ethnicity, as non-white representation in the VOC group was too low to allow this variable to be robustly assessed.

Despite the significant caveats to this analysis, we are unable to find any evidence that VOC increases the hospital case fatality rate (Table 1). An additional analysis using a different matching strategy (1:3, n= 103 matchable VOC cases) resulted in a similar conclusion. We also ran a Cox proportional hazards survival regression model where VOC cases were matched to non-VOC cases (1:3; proportional hazard assumption was not rejected based on the data, p-value=0.66). The survival model adjusted for age, sex and hospital (as random effect). The results from the survival model (Table 2, Figure 1) do not change our current conclusion that in the period of observation there is no evidence of an increase in hospital case fatality rate linked to VOC202012-01, with low confidence.

Limitations:

- The analysis is based on a relative low number of VOC cases (202 VOC cases, of which 108 VOC cases had 28d mortality outcome). COG-UK sampling is not widespread and mostly sourced from the community (pillar one) and so does not at present overlap with CO-CIN sufficiently to give enough cases for a robust analysis, with significant potential for sampling bias.
- There is a high outcome missing rate, which increases over time and which correlates to the observed increase in VOC cases reported. Missingness affects the precision of the parameters' estimates and can be an unwanted source of bias (informative missingness).
- The wide 95% confidence interval of the VOC parameter is an indication of the high levels of uncertainty.
- Given the small sample size available, matching by hospital and appropriate model adjustment for additional risk factors associated to mortality (e.g., ethnicity, comorbidities) were not possible.
- Changes in case fatality rate in hospitals show a temporal lag behind pillar 2 testing data. This is due both to the natural history of COVID-19 in patients, but also to the delay between the outcome being reached (course of disease in hospital) and the data being entered into CO-CIN, a delay which may be expected to be greater in the busier hospitals, and thus may confound mortality.
- During the course of this analysis, we observed that some patients had more than one genotypic determination (VOC and non-VOC infection in the same patient). In this analysis we have classified any patient with VOC at any time point as being in the VOC group for the purpose of this analysis. We require more time to further explore the significance of this observation.

Additional considerations:

There was one VOC202012-02 case included in the survival model (censored observation). The effect of the busiest hospitals, under the most extreme pressures, entering data late is the most important caveat. We expect the resulting ascertainment bias to push current data availability away from the busiest hospitals, possibly underestimating mortality. However, the biological process underlying the difference between VOC and non-VOC case fatality rate should be the same at all hospitals, if the difference is truly due to the virus alone. Therefore, even if the current sample is unrepresentative, we may be studying VOC/non-VOC managed under relatively close to ideal conditions, leaving viral variance as the only variable.

Conclusion:

Our analysis does not provide evidence to suggest that the variant of concern is linked to a higher risk in hospital case fatality. The small numbers of patients that we have in this analysis, and the instability of this dynamic dataset, leads us to have low confidence in this result. Further analysis with an appropriate sample size is required

to confirm these results. Enriching COG sampling from pillar one (NHS) testing and targeting CO-CIN data collection to patients with sequence available in COG-UK would assist our understanding of impact of this and future VOCs on cases admitted to hospital.

	Alive	**Died**	**Odds Ratio**	**95% CI**	***P*-value**
VOC202012/01					
No	77	31	ref	-	-
Yes	86	22	0.67	0.32, 1.40	0.285
Age					
<70	95	11	ref	-	-
70-79	26	14	5.12	1.88, 13.95	0.001
≥80	42	28	6.98	2.92, 16.68	<0.001
Sex					
Female	77	19	ref	-	-
Male	86	34	1.90	0.90, 4.03	0.094

Table 1: Results from the logistic mixed effects regression model with 1:1 case matching.

	Alive/ Censored	**Died**	**Hazard Ratio**	**95% CI**	***P*-value**
VOC202012/01					
No	518	88	ref	-	-
Yes	180	22	0.81	0.50, 1.32	0.400
Age					
<70	368	36	ref	-	-
70-79	142	34	2.62	1.62, 4.23	<0.001
≥80	188	40	2.52	1.58, 4.00	<0.001
Sex					
Female	299	49	Ref	-	-
Male	399	61	1.16	0.79, 1.71	0.450

Table 2: Results from the mixed effects cox model with 1:3 case matching.

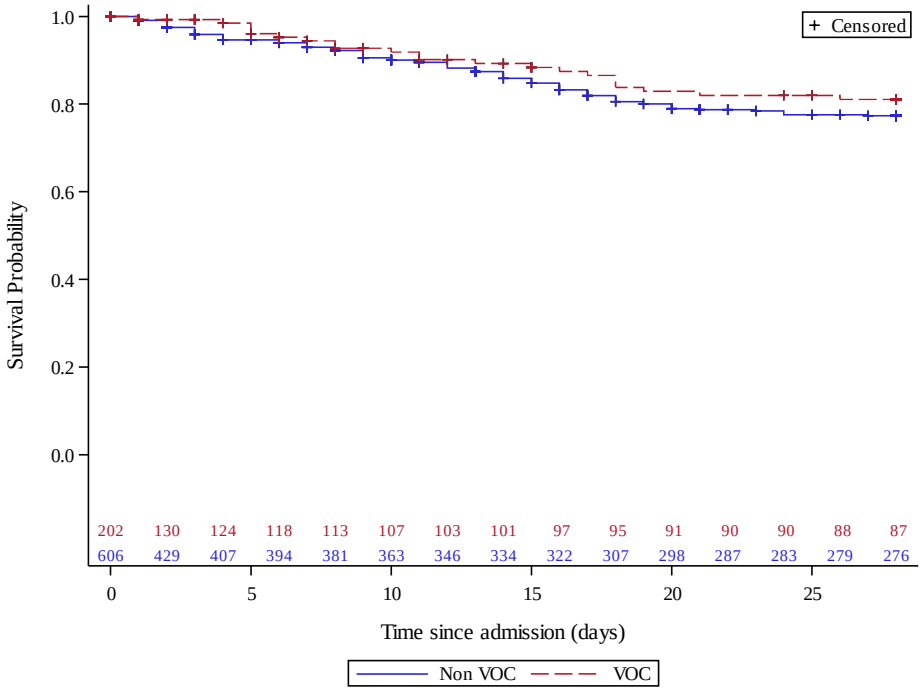

Figure 1: Kaplan-Meier plot of survival times for VOC and matched non-VOC patients (1:3), with numbers at risk