Independent analysis on recent hospital case fatality and variant of concern VOC2020-01 using CO-CIN data (20th January 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.

Here we explore the hypothesis that infection with the UK variant of concern VOC2020-01 (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 indicate that the new variant is associated with a higher 28day fatality rate. Limitations of the analysis are described below.

VOC cases, determined by sequencing, were matched (1:5) by age, sex and admission date (+- 7 days) to non-VOC cases for period 1st October to 14th December 2020 with 28d follow-up. Matching by admission date was used to account for changes observed in hospital case fatality rate over time and local activity (business). The model adjusted for age, sex and hospital (as random effect) and took into account matching. 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). We ran several additional exploratory models, using different matching strategies. None of them changes our current conclusion that in the period of observation there is no evidence of an increase in hospital case fatality rate linked to VOC2020-01, with low confidence.

Limitations:

- The analysis is based on a very low number of VOC cases, only 60 (as recorded in the dataset at the time this analysis was conducted). 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 highly 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, appropriate model adjustment for additional risk factors associated to mortality (e.g., ethnicity, comorbidities) was 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.

Additional considerations:

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	228	72	ref	-	-
Yes	47	13	0.576	0.226, 1.336	0.220
Age					
<70	139	17	ref	-	-
70-79	61	29	4.218	1.965, 9.668	<0.001
≥80	75	39	5.649	2.684, 13.134	<0.001
Sex					
Female	144	30	ref	-	-
Male	131	55	1.964	1.075, 3.703	0.031

Table 1: Results from the logistic mixed effects regression model with 1:5 case matching.

Revised model (29th January 2021)

Following submission of this rapid report to SAGE we identified two errors in our R code which affected the matching process. We have corrected these, and the revised model is presented in Table 2. The rest of the report, including conclusion and key considerations, remains the same.

	Alive	Died	Odds Ratio	95% CI	*P*-value
VOC202012/01					
No	236	64	ref	-	-
Yes	47	13	0.865	0.378, 1.982	0.732
Age					
<70	148	8	ref	-	-
70-79	64	26	7.403	3.077, 17.813	<0.001
≥80	71	43	12.646	5.373, 29.762	<0.001
Sex					
Female	145	29	ref	-	-
Male	138	48	1.656	0.922, 2.974	0.091

Table 2: Results from the logistic mixed effects regression model with 1:5 case matching (revised model)