Assessment of mortality and hospital admissions associated with confirmed infection with SARS-CoV-2 Variant of Concern VOC-202012/01 (B.1.1.7) a matched cohort and time-to-event analysis

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Key points:

We observed a significantly increased risk in hospitalisation in variant cases compared to non-variant cases, but no difference was observed in 28-day mortality.

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Abstract: (250 words)

Background: The emergence of VOC202012/01 in England, known as B.1.1.7 or informally as the 'UK variant', has coincided with rapid increases in the number of PCR-confirmed positive cases in areas where the variant has been concentrated.

Methods: To assess whether infection with SARS-CoV-2 variant VOC202012/01 is associated with more severe clinical outcomes compared to wild-type infection, genomically sequenced and confirmed variant and wild-type cases were linked to routine healthcare and surveillance datasets. Two statistical analyses were conducted to compare the risk of hospital admission and death within 28 days of test between variant and wild-type cases: a case-control study and an adjusted Cox proportional hazards model. Differences in severity of disease were assessed by comparing hospital admission and mortality, including length of hospitalisation and time to death.

Results: Of 63,609 genomically sequenced COVID-19 cases tested in England between October and December 2020 6,038 were variant cases. In the matched cohort analysis 2,821 variant cases were matched to 2,821 to wild-type cases. In the time to event analysis we observed a 34% increased risk in hospitalisation associated with the variant compared to wild-type cases, however, no significant difference in the risk of mortality was observed.

Conclusion: We found evidence of increased risk of hospitalisation after adjusting for key confounders, suggesting increased infection severity associated with this variant. Follow-up studies are needed to assess potential longer-term differences in the clinical outcomes of people infected with the VOC-202012/01 variant.

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Background

Following detection of the first SARS-CoV-2 cases in England in January 2020 (1), by February 2021, the total number of confirmed COVID-19 cases in England now exceeds 4 million with over 114,000 people dying within 28 days of a positive test. Following the first wave of COVID-19 infections in England, a second wave was experienced in October and November 2020, with a transient decline in late November following a national lockdown. However, an acceleration in transmission was observed in December 2020, coinciding with the emergence of a new SARS-CoV-2 variant initially concentrated in the South East, East of England and London regions.

This new variant is defined by 23 mutations: 13-non synonymous mutations (including spike protein), 4 deletions and 6 synonymous mutations (5 in ORF1ab (C913T, C5986T, C14676T, C15279T, C16176T), and one in the M gene (T26801C) (2). Consideration of these mutations including the spike protein mutation raised the possibility of changes to transmissibility. A national risk assessment considered evidence which indicated that this variant had greater transmissibility compared to wild-type variants in England(3,4). Accordingly, variant of concern (VOC) 202012/01 was assigned as per standardised nomenclature(3). This new variant is also known as the “UK variant”, 20I/501Y.V1, or B.1.1.7 but is herein referred to as the “variant”.

Mathematical modelling indicated this variant was associated with an increased reproduction number(5). However, a broader public health risk assessment requires information on health outcomes. To gain insights into the pathogenicity of the new UK variant compared to the globally circulating wild-type, we assessed the outcomes associated with this variant in terms of hospital admission and mortality of people infected with genomically confirmed VOC-202012/01.

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Methods

Selection of genomically sequenced SARS-CoV-2 cases and data linkage

Wild type and VOC-202012/01 variant cases were identified from sequencing information nationally co-ordinated by the COG-UK consortium and uploaded to the CLIMB database (6). PCR confirmed cases are sampled for whole genome sequencing (WGS) with approximately 6% of laboratory confirmed cases in England sequenced to date. Confirmed VOC-202012/01 cases were defined as sequenced PCR positive cases which met the sequence definition for a confirmed VOC-202012/01 (7) with a specimen date between 01 October and 31 December 2020. Confirmed wild-type cases' sequence information was classified as distinct to the VOC-202012/01.

Variant and wild-type cases were linked to laboratory data from the Second-Generation Surveillance System (SGSS), the national microbiology data repository at Public Health England which includes statutory notifiable diseases such as COVID-19. Demographic and clinical information was extracted, such as age, sex, ethnicity, residential address , and symptom status at the time of test request. Address matching against national reference databases (Ordnance Survey AddressBase Premium) was undertaken to validate addresses, assign a Unique Property Reference Number (UPRN) and identify property type category: residential dwelling, care/nursing home and other property classifications (including prisons, residential institutions, and homeless).

To assess hospitalisation among the variant and wild-type cases the sequenced cases were linked to NHS hospital admission data from the NHS Digital Secondary Uses Service (SUS) (8) and hospitals admissions following emergency care attendance data from the Emergency Care Data Set (ECDS). SUS data was analysed based on data available at 31 January 2021. To assess severity of disease, hospitalisation was defined as an admission to hospital within 14 days following a positive COVID-19 test.

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Admissions data were grouped into periods of continuous inpatient spells (CIP) based on the start and end dates of care episodes. Cases were matched to the nearest CIP within 14 days after the sample specimen date, those tested on the same day as or after were not considered a hospital admission. The end of a hospital stay was considered the date of discharge or date of death during hospitalisation.

To assess mortality, both variant and wild-type cases were linked to the PHE COVID-19 mortality dataset(9) to determine if cases had died as of 5pm on 8 January 2020. These data record deaths in persons within 28 days following a laboratory confirmed SARS-CoV-2 infection in England and are identified by matching confirmed COVID-19 cases to deaths reports from four sources: i) hospital deaths reported by NHS England ii) deaths recorded on the NHS Spine (national electronic health record database) identified through Demographic Batch Service tracing iii) death registrations from the Office for National Statistics (ONS) and iv) deaths reported by local Health Protection Teams related to local public health enquiries.

Statistical analysis

Two statistical analyses were conducted to compare the risk of hospital admission within 14 days, and risk death within 28 days of a positive COVID-19 test between variant and wild-type cases: a matched cohort study and an adjusted Cox proportional hazards model.

In the matched cohort study, variant cases were frequency matched to wild-type cases using a one-to-one ratio on: age group (ten-year age bands), sex, specimen date (grouped into 2-week periods), and geographic region of residence, upper tier local authority (UTLA). These factors were selected to control for confounding to account for known associations between age and sex and poor clinical outcomes. and Matching on time and county-level geography minimises potential for confounding related to regional variation in the rapid ride in case rates and resulting system pressures in the National Health Service (NHS).

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In the matched cohort study, chi squared tests for trend were used to assess differences between the variant and wild-type cases in term of sex, age, ethnicity, NHS region of residence and residential property classification. The number and proportion of variant and wild-type cases hospitalised within 14 days of a positive test and died within 28 days were calculated. The median Length of hospital stay and time to death was assessed u and a Kruskal-Wallis test conducted to assess differences. Logistic regression models were used to estimate the difference in the odds of hospitalisation and death among variant cases compared to wild-type cases.

Due to limited number of potential control cases as the variant became endemic in England, the number of cases included in the matched cohort analysis were limited and thus variant cases were excluded from this analysis. Therefore, a time-to-event analysis was conducted using the entire sequenced dataset to assess outcomes in terms of hospitalisation and death. Two Cox proportional hazards models were performed: a) risk of hospitalisation within 14 days of a positive test and b) death within 28 days of a positive test. In each analysis a single variable model was run for potential confounders including: sex, age, ethnicity, NHS region of residence, residential property classification, week of specimen date. Testing pillar was also included as a potential confounder, Pillar 1 includes testing in PHE labs and NHS hospitals for those with a clinical need, and health and care workers, whereas, Pillar 2 includes swab testing available to the wider population, such as community testing sites and postal tests.

Multivariable proportional cox regressions were built using the backward step wise approach and each potential confounder was considered using likelihood ratio tests. Age, sex, ethnicity and time (week of specimen) were included in the model as a priori variables.

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Results

Of 63,609 sequenced confirmed COVID-19 cases, 6,038 VOC-202012/01 confirmed variant cases were identified. The cohort analysis included 2,821 variant cases matched to 2,821 to wild-type cases. 3,217 variant cases were excluded from the matched cohort analysis due to lack of a wild-type cases. These excluded variant cases differed from those included in the analysis in terms of age, geography and symptomatic status: excluded cases were more likely to be under 20 and over 60 years old (Chi-squared test overall, (X2 133.9, p=0.00), life in London, (X2 115.4 p=0.00) and report symptoms (X2 26.9, p=0.00).

Within the matched cohort study, the median age of variant cases was 37 years and 51.4% were female (Table 1) and predominantly from London (35.2%), the South East (29.2%), and East of England (20.4%). Comparator matching successfully selected a similar profile of wild-type cases (Table 1).

Variant cases were predominately of White ethnicity (74.3%) followed by Asian (11.7%) and Black (5.2%). The ethnic profile of wild-type cases was broadly similar however, included fewer people of White ethnicity and more of Asian ethnicity (X^2 13.9 p=0.02).

The majority of variant cases were resident at private residential dwellings (95.0% of variant cases and 94.7% of wild-type cases) and there was no difference between residential classification (X^2 2.9, p=0.89).

Four in 5 variant cases (79.8%) and wild-type cases (78.8%) self-reported symptoms at the time of test (X^2 8.3, p=0.02).

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Assessment of hospitalisation

Of the 5,642 cases included in the matched cohort study, 131 individuals had a record of hospital admission within 14 days of the date of specimen: 76 (2.7%) variant cases and 55 (1.9%) wild-type cases (X2 3.46 p=0.006). The median age of the hospitalised variant cases was 56 years (IQR 47-65.5; range 20-97) and of hospitalised wild-type comparators was 55 years (IQR 45-66; range 0-85). A higher proportion of hospitalised people were male for both the variant (55.3%) and wild-type (56.4%). (Table 2).

We found weak evidence of an association between infection with the variant and hospitalisation within 14 days of positive COVID-19 specimen date (Odds Ratio (OR): 1.39, 95%CI 0.98-1.98, p=0.07). The length of hospital stay was similar between patients in the variant and wild-type groups (median length of stay 5 days (IQR 3-10, range 0-37) vs 8 days (IQR 4-13.5 days, range 0-31), respectively). There was weak evidence of a difference in distribution of length of hospital stay between variant and wild-type cases (Kruskal Wallis p=0.07).

In the time-to-event analysis, of 63,609 sequenced confirmed cases, 60,510 (95.1%) cases had hospitalisation data and had complete demographic information and were included in analysis. Of these, 1,147 cases were hospitalised, 120 (2.02%) variant cases and 1,027 (1.88%) wild type cases (Table 4). The 60,510 contributed a total of 838,211 days of follow up time. In univariable analysis, there was no evidence of an association between infection with the variant and risk of hospitalisation within 14 days (HR: 1.07, 95%CI:0.89-1.29, p=0.48). However, after adjusting for potential confounders (sex, age, ethnicity, residential property classification and week of specimen date) we found a statistically significant association with the risk of hospitalisation in variant cases compared to wild type cases (HR 1.34, 95% CI:1.07-1.66, p=0.01). Overall, hospitalisation was significantly associated with

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being male, older age, of non-white ethnicity, living in a care or nursing home or other non-residential property type and the week of specimen date (Table 4). In stratified analysis, there was no differential effect of testing pillar on risk of hospitalisation (not shown).

Assessment of case fatality

Of the 5,642 cases included in the matched cohort study, a total of 76 individuals died within 28 days of a positive test; 36 (1.3%) variant cases died and 40 (1.4%) wild-type cases. (Table 3). The median age of variant cases who died was 86 years (IQR 82-891; range 49-99) compared to 79 years in wild-type cases (IQR 68-85; range 48-97). 41.7% of variant deaths were in females compared to 32.5% of wild-type deaths. In matched cohort analysis there was no evidence of an association between the variant and wild-type groups and death within 28 days of COVID-19 specimen date (OR: 0.90, 95%CI 0.57-1.41, p=0.64).

Among variant cases, the median time between positive specimen date and date of death was 8 days (IQR 4-15 days; range 2-26 days) compared with 9 days (IQR 5-12 days; range 2-26 days) among wild-type cases. There was no difference in distribution of time to death between variant and wild-type cases (Kruskal Wallis p=0.79).

In the time-to-event analysis, of 63,609 genomically sequenced cases, 1,262 died within 28 days of their specimen date, 69 (1.15%) variant cases and 1,189 (2.18%) wild type cases (Table 5). Of the 63,609, 60,656 cases were eligible for the time-to-event analysis and contributed 1,677,228 total days of follow up. Before adjusting for potential confounders, we observed a negative association between risk of death and infection with the variant (HR: 0.54, 95%CI:0.42-0.69, p=0.00). However, after adjusting for sex, age, ethnicity, residential property classification, week of specimen date and testing Pillar this association was no longer observed, and there was no difference in risk of death among variant cases compared to wild-type (HR: 1.06, 95%CI:0.82-1.38, p=0.65). Overall, death was significantly associated with being male, older age, being of Asian ethnicity; living in a care or nursing home or other non-residential property type and being tested in Pillar 1 (Table 5).

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Discussion

Following initial identification in England, the variant VOC-202012/01 has been a focus of international interest, with cases with and without epidemiological links to the United Kingdom now identified in more than 85 countries worldwide (10). England still has the highest number of genomically confirmed cases of this variant internationally.

Risk assessments of VOC-202012/01 by public health agencies and independent scientific groups suggest increased transmissibility based on mathematical modelling and the rapid increases in cases where the variant has been concentrated (11,12). In January 2021, further reports suggested the variant may be associated with an increased risk of mortality (13).

This study demonstrated an increased hospitalisation risk (HR 1.34, 95% CI:1.07-1.66) for variant cases confirmed on sequencing; it is the first to individually link hospitalisation records nationally to variant cases in England providing an improved level of evidence for public health decision making. Previous analysis of hospitalisation risk in England have either been ecological (for sequence confirmed variant cases without individual-level record linkage) (13) or reliant on the use of a proxy measure of S gene target failure (SGTF), whereby diagnostic PCR tests can detect the variant through failed PCR amplifications of the spike gene target but preserved detection of other targets. Although we studied a period where a high proportion of SGTF cases were verified VOC-202012/01, use of varying SGTF case definitions globally and misclassification during other time periods mean that sequence confirmation remains the gold standard for these analyses.

An additional advantage of this analysis is that while many previous SGTF analyses in England are sampled exclusively from mass testing in the community (“Pillar2”) where individuals are likely to be less unwell compared to those tested in hospital settings (“Pillar1”), our analysis includes cases detected through both routes. Therefore, cases

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included also represent the majority of patients at risk of severe COVID-19 presentations, including the elderly and those with co-morbidities.

Notably, most of the sequenced cases were initially identified through mass population testing and both variant and wild-type groups had similar proportions of asymptomatic infection at time of testing, suggesting initial presentations are similar for both groups.

We were unable to demonstrate an increased risk of death through either the Cox proportional hazard model or the matched cohort design whereas this has been observed via SGTF-based analysis elsewhere. This may be explained by the difference in scale with SGTF-based analyses being far larger in case numbers compared to sequence-confirmed cases, and therefore the former will have greater power to detect smaller differences.

These analyses were made possible by the large-scale, rapid identification of VOC-202012/01 variant and wild-type cases via the national COG-UK collaboration which has conducted large-scale whole genome sequencing of SARS-CoV-2 throughout the pandemic.

Due to the urgent need for a risk assessment of the variant, these analyses were limited by short follow-up time to event and relatively small numbers of events. This was managed by standardising the follow-up time after positive specimen date to within 14-days for hospitalisations and within 28-days for case fatality.

The use of routine admissions data designed for administrative purposes poses potential delays in identifying and reporting such signals, and these numbers are likely to represent a minimum estimate.

Variants of concern (VOCs) pose additional complexity to the pandemic response, with attention on VOC202012/01) extending to other lineages such as B.1.351 first detected in South Africa (VOC20212/02) and B.1.1.28 first detected in Japan in travellers from Brazil(10,15); rapid and systematic assessments of severe outcomes associated with emerging variants as described here, will need to become an essential part of the pandemic response going forward.

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Table 1: Demographic characteristics of variant and wild-type cases included in the Matched cohort study

	Variant cases		Wild-type cases			
	Count	**Percent**	**Count**	**Percent**	**χ2**	**p value**
Total	**2821**		**2821**			
Sex						
Female	1,492	52.9	1,492	52.9	0.00	1.00
Male	1,329	47.1	1,329	47.1		
Age						
<10	98	3.5	98	3.5	0.00	1.00
10-19	362	12.8	362	12.8		
20-29	551	19.5	551	19.5		
30-39	571	20.2	571	20.2		
40-49	536	19.0	536	19.0		
50-59	440	15.6	440	15.6		
60-69	155	5.5	155	5.5		
70-79	47	1.7	47	1.7		
80+	61	2.2	61	2.2		
Ethnicity						
Asian	330	11.7	410	14.5	13.9	0.02
Black	148	5.2	125	4.4		
Mixed	58	2.1	57	2.0		
Other	128	4.5	144	5.1		
Unknown	60	2.1	70	2.5		
White	2,097	74.3	2,015	71.4		
NHSE Region						
East of England	575	20.4	574	20.3	0.00	1.00
London	993	35.2	993	35.2		
Midlands	175	6.2	174	6.2		
North East and Yorkshire	111	3.9	112	4.0		
North West	105	3.7	106	3.8		
South East	825	29.2	826	29.3		
South West	37	1.3	36	1.3		
Residential category						
Care/Nursing home	29	1	28	1	2.9	0.89
House in multiple occupancy (HMO)	17	0.6	13	0.5		

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Medical facilities (including hospitals and hospices, and mental health)	2	0.1	3	0.1		
Other property classifications	21	0.7	25	0.9		
Prisons, detention centres, secure units	8	0.3	13	0.5		
Residential dwelling (including houses, flats, sheltered accommodation)	2,679	95.0	2,672	94.7		
Residential institution (including residential education)	6	0.2	9	0.3		
Undetermined	59	2.1	58	2.1		
Presence of Symptoms						
No	325	11.5	294	10.4	8.3	0.02
Yes	2,252	79.8	2,223	78.8		
Unknown	244	8.6	304	10.8		

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Table 2: Demographic characteristics of variant and wild-type cases included in the matched cohort study who were hospitalised within 14 days of specimen date

	Variant cases		Wild-type cases			
	Count	**%**	**Count**	**%**	**χ2**	**p value**
Hospitalised						
Yes	76	2.7	55	1.9	3.45	0.06
No	2,745	97.3	2,766	98.1		
Total	**2,821**		**2,821**			
Sex						
Female	34	44.7	24	43.6	0.02	0.90
Male	42	55.3	31	56.4		
Age						
<10	0	0.0	2	3.6	8.67	0.28
10-19	0	0.0	0	0.0		
20-29	4	5.3	0	0.0		
30-39	7	9.2	5	9.1		
40-49	12	15.8	11	20.0		
50-59	28	36.8	16	29.1		
60-69	9	11.8	10	18.2		
70-79	4	5.3	5	9.1		
80+	12	15.8	6	10.9		
Ethnicity						
Asian	6	7.9	5	9.1	1.96	0.74
Black	3	3.9	2	3.6		
Mixed	0	0.0	1	1.8		
Other	5	6.6	2	3.6%		
Unknown	0	0.0	0	0.0		
White	62	81.6	45	81.8		
NHSE Region						
East of England	19	25.0	15	27.3	6.57	0.36
London	20	26.3	22	40.0		
Midlands	3	3.9	1	1.8		
North East and Yorkshire	4	5.3	5	9.1		
North West	4	5.3	2	3.6		
South East	25	32.9	10	18.2		
Residential category						
Care/Nursing home	8	10.5	5	9.1	0.07	0.79
House in multiple occupancy (HMO)	0	0.0	0	0.0		
Medical facilities (including hospitals and hospices, and mental health)	0	0.0	0	0.0		

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Other property classifications	0	0.0	0	0.0		
Prisons, detention centres, secure units	0	0.0	0	0.0		
Residential dwelling (including houses, flats, sheltered accommodation)	68	89.5	50	90.9		
Residential institution (including residential education)	0	0.0	0	0.0		
Undetermined	0	0.0	0	0.0		
Presence of Symptoms						
No	8	10.5	5	9.1	2.49	0.29
Yes	57	75.0	36	65.5		
Unknown	11	14.5	14	25.5		

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Table 3: Demographic characteristics of variant and wild-type cases included in the matched cohort study who died within 18 days of specimen date

	Variant cases		Wild-type comparator cases			
	Count	**%**	**Count**	**%**	**χ2**	**p value**
Died						
Yes	36	1.3	40	1.4	0.21	0.64
No	2,785	98.7	2,781	98.6		
Total	**36**		**40**			
Sex						
Female	15	41.7	13	32.5	0.68	0.41
Male	21	58.3	27	67.5		
Age						
30-39	0	0.0	1	2.8	10.68	0.06
40-49	1	0.0	1	2.8		
50-59	1	2.8	4	11.1		
60-69	3	2.8	10	27.8		
70-79	3	8.3	7	19.0		
80+	28	77.8	17	47.2		
Ethnicity						
Asian	2	5.6	3	7.5	0.12	0.94
Black	0	0.0	0	0.0		
Mixed	0	0.0	0	0.0		
Other	1	2.8	1	2.5		
Unknown	0	0.0	0	0.0		
White	33	91.7	36	90.0		
NHSE Region						
East of England	14	38.9	18	45.0	4.71	0.32
London	7	19.4	6	1.0		
Midlands	3	8.3	0	0.0		
North East and Yorkshire	2	5.6	1	2.5		
North West	0	0.0	0	0.0		
South East	10	27.8	15	37.		
South West	0	0.0	0	0.0		
Residential category						
Care/Nursing home	7	19.4	5	12.5	3.28	0.51
House in multiple occupancy (HMO)	0	0.0	1	2.		

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Medical facilities (including hospitals and hospices, and mental health)	0	0.0	1	2.5		
Other property classifications	0	0.0	0	0.0		
Prisons, detention centres, secure units	0	0.0	0	0.0		
Residential dwelling (including houses, flats, sheltered accommodation)	29	80.6	32	80.0		
Residential institution (including residential education)	0	0.	0	0.0		
Undetermined	0	0.0	1	2.5		
Presence of Symptoms						
No	5	13.9	1	2.5	3.38	0.19
Yes	4	11.1	5	12.5		
Unknown	27	75.0	34	85.0		

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Table 4: Cox proportional hazards model to test hospitalisation within 14 days specimen date among all sequenced cases

						Univariate				Multivariate			
		Number of cases	**% of cases**	**Number of cases hospitalised**	**% of cases hospitalised**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**	**Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Variant	No	54,557	90.2	1,027	1.9	1	(base)			1	(base)		
	Yes	5,953	9.8	120	2.0	1.07	0.89	1.29	0.48	1.34	1.07	1.66	0.01
Sex	Female	31850	52.6	507	1.6	1	(base)			1	(base)		
	Male	28660	47.4	640	2.2	1.41	1.25	1.58	0.00	1.39	1.24	1.57	0.00
Age	<40	32,706	54.1	199	0.6	0.42	0.34	0.52	0.00	0.44	0.35	0.54	0.00
	40-49	9,239	15.3	133	1.4	1	(base)			1	(base)		
	50-59	8,875	14.7	254	2.9	2	1.62	2.47	0.00	2.12	1.72	2.62	0.00
	60-69	4,658	7.7	204	4.4	3.09	2.48	3.85	0.00	3.23	2.59	4.02	0.00
	70-79	2,520	4.2	200	7.9	5.69	4.57	7.09	0.00	5.98	4.78	7.47	0.00
	80+	2,512	4.2	157	6.3	4.46	3.54	5.62	0.00	4.64	3.63	5.94	0.00
Ethnicity	Asian	8,104	13.4	180	2.2	1.19	1.01	1.4	0.03	1.75	1.48	2.06	0.00
	Black	1,950	3.2	43	2.2	1.18	0.87	1.61	0.29	1.68	1.23	2.28	0.00
	Mixed	1,068	1.8	16	1.5	0.8	0.49	1.31	0.38	1.64	1	2.69	0.05
	Other	2,323	3.8	51	2.2	1.18	0.89	1.56	0.26	1.73	1.3	2.3	0.00
	Unknown	1,502	2.5	5	0.3	0.18	0.07	0.43	0.00	0.28	0.12	0.67	0.00
	White	45,563	75.3	852	1.9	1	(base)			1	(base)		
NHS Region	East of England	6,307	10.4	108	1.7	0.97	0.76	1.23	0.79				
	London	11,184	18.5	209	1.9	1.06	0.86	1.3	0.60				
	Midlands	9,264	15.3	164	1.8	1	(base)						

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	North East and Yorkshire	13,144	21.7	280	2.1	1.21	0.99	1.46	0.06				
	North West	12,123	20.0	225	1.9	1.05	0.86	1.28	0.65				
	South East	6,498	10.7	118	1.8	1.03	0.81	1.3	0.83				
	South West	1,990	3.3	43	2.2	1.22	0.87	1.71	0.24				
Residential property classification	Care/Nursing home	1,010	1.7	69	6.8	3.61	2.83	4.61	0.00	1.34	1.02	1.75	0.03
	Residential	54,380	89.9	1,055	1.9	1	(base)			1	(base)		
	Other property	5,120	8.5	23	0.5	0.23	0.15	0.35	0.00	0.31	0.2	0.47	0.00
Week	40	1,938	3.2	21	1.1	1	(base)			1	(base)		
	41	4,873	8.1	77	1.6	1.46	0.9	2.37	0.12	1.34	0.83	2.17	0.23
	42	5,566	9.2	107	1.9	1.78	1.12	2.84	0.02	1.52	0.95	2.43	0.08
	43	6,998	11.6	135	1.9	1.79	1.13	2.83	0.01	1.47	0.93	2.33	0.10
	44	4,207	7.0	100	2.4	2.21	1.38	3.54	0.00	1.51	0.94	2.42	0.09
	45	8,294	13.7	158	1.9	1.76	1.12	2.78	0.02	1.25	0.79	1.97	0.35
	46	9,891	16.4	166	1.7	1.55	0.99	2.44	0.06	1.09	0.69	1.72	0.70
	47	5,056	8.4	97	1.9	1.78	1.11	2.85	0.02	1.18	0.73	1.89	0.50
	48	2,902	4.8	60	2.1	1.92	1.17	3.15	0.01	1.2	0.73	1.98	0.47
	49	1,740	2.9	58	3.3	3.11	1.89	5.12	0.00	1.84	1.11	3.04	0.02
	50	4,378	7.2	86	2.0	1.82	1.13	2.93	0.01	1.25	0.77	2.03	0.37
	51	3,754	6.2	62	1.7	1.53	0.93	2.51	0.09	1.01	0.61	1.69	0.96
	52	903	1.5	18	2.0	1.85	0.99	3.47	0.06	1.1	0.58	2.08	0.77
	53	10	0.0	2	20.0	20.61	4.83	87.91	0.00	7.21	1.69	30.84	0.01

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Table 5: Cox proportional hazards model to test death within 18 days specimen date among all sequenced cases

						Univariate				Multivariate			
		Number of cases	**% of cases**	**Number of cases who died**	**% of cases who died**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**	**Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Variant	No	55067	90.2	1198	2.2	1	(base)			1	(base)		
	Yes	5984	9.8	69	1.2	0.54	0.42	0.69	0.00	1.06	0.82	1.38	0.65
Sex	Female	32096	52.6	551	1.7	1	(base)			1	(base)		
	Male	28955	47.4	716	2.5	1.46	1.31	1.63	0.00	1.69	1.5	1.89	0.00
Age	<40	32762	53.7	6	0.0	0.11	0.04	0.29	0.00	0.13	0.05	0.33	0.00
	40-49	9286	15.2	15	0.2	1	(base)			1	(base)		
	50-59	8971	14.7	62	0.7	4.09	2.32	7.21	0.00	4.04	2.29	7.12	0.00
	60-69	4767	7.8	141	3.0	18.06	10.6	30.79	0.00	14.03	8.22	23.94	0.00
	70-79	2610	4.3	316	12.1	80.79	48.12	135.64	0.00	39.25	23.23	66.32	0.00
	80+	2655	4.4	727	27.4	212.24	127.27	353.93	0.00	70.79	41.97	119.39	0.00
Ethnicity	Asian	8168	13.4	90	1.1	0.46	0.37	0.57	0.00	1.5	1.2	1.87	0.00
	Black	1968	3.2	17	0.9	0.34	0.21	0.56	0.00	0.75	0.46	1.23	0.26
	Mixed	1074	1.8	8	0.7	0.31	0.16	0.63	0.00	1.27	0.63	2.55	0.5
	Other	2343	3.8	31	1.3	0.56	0.39	0.8	0.00	1.19	0.83	1.7	0.34
	Unknown	1517	2.5	22	1.5	0.53	0.34	0.84	0.01	0.61	0.38	0.97	0.04
	White	45981	75.3	1099	2.4	1	(base)			1	(base)		
NHS Region	East of England	6393	10.5	215	3.4	1.57	1.29	1.9	0.00				
	London	11312	18.5	226	2.0	0.95	0.78	1.15	0.57				
	Midlands	9304	15.2	204	2.2	1	(base)						

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	North East and Yorkshire	13263	21.7	198	1.5	0.7	0.57	0.85	0.00				
	North West	12239	20.1	310	2.5	1.18	0.99	1.41	0.07				
	South East	6548	10.7	100	1.5	0.71	0.56	0.91	0.01				
	South West	1992	3.3	14	0.7	0.33	0.19	0.57	0.00				
Residential property classification	Care/Nursing home	1086	1.8	249	22.9	15.12	13.15	17.39	0.00	1.44	1.25	1.67	0.00
	Residential	54828	89.8	1003	1.8	1	(base)			1	(base)		
	Other property	5137	8.4	15	0.3	0.16	0.1	0.27	0.00	0.37	0.22	0.62	0.00
Week	40	1943	3.2	19	1.0	1	(base)			1	(base)		
	41	4893	8.0	67	1.4	1.38	0.83	2.31	0.21	0.88	0.53	1.47	0.64
	42	5595	9.2	87	1.6	1.58	0.96	2.6	0.07	1.08	0.66	1.78	0.75
	43	7042	11.5	107	1.5	1.49	0.91	2.42	0.11	0.86	0.53	1.41	0.56
	44	4230	6.9	121	2.9	2.91	1.8	4.73	0.00	1.07	0.66	1.74	0.78
	45	8344	13.7	140	1.7	1.7	1.05	2.75	0.03	0.85	0.53	1.38	0.51
	46	9978	16.3	187	1.9	1.88	1.17	3.01	0.01	0.85	0.53	1.36	0.49
	47	5128	8.4	123	2.4	2.39	1.47	3.88	0.00	0.85	0.52	1.39	0.52
	48	2979	4.9	110	3.7	3.72	2.28	6.07	0.00	0.85	0.52	1.39	0.51
	49	1779	2.9	80	4.5	4.65	2.82	7.68	0.00	1	0.6	1.65	0.99
	50	4411	7.2	93	2.1	2.11	1.28	3.45	0.00	0.9	0.54	1.47	0.67
	51	3796	6.2	74	2.0	1.98	1.19	3.28	0.01	0.9	0.54	1.5	0.69
	52	922	1.5	57	6.2	6.51	3.87	10.94	0.00	1.42	0.84	2.39	0.19

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	53	11	0.0	2	18.18	20.25	4.72	86.92	0.00	1.54	0.36	6.6	0.57
Pillar	1	7078	11.6	1001	14.14	31.43	27.44	36	0.00	5.57	4.77	6.49	0.00
	2	53973	88.4	266	0.49	1	(base)			1	(base)		

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