Wave comparisons of clinical characteristics and outcomes of COVID-19 admissions - Exploring the impact of treatment and strain dynamics

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Abstract

Objectives

Dexamethasone has now been incorporated into the standard of care for COVID-19 hospital patients. However, larger intensive care unit studies have failed to show discernible improvements in mortality in the most recent wave. We aimed to investigate the impacts of these factors on disease outcomes in a UK hospital study.

Methods

This retrospective observational study reports patient characteristics, interventions and outcomes in COVID-19 patients from a UK teaching hospital; cohort 1, pre 16th June-2020 (pre-dexamethasone); cohort 2, 17th June to 30th November-2020 (post-dexamethasone, pre-VOC 202012/01 as dominant strain); cohort 3, 1st December-2020 to 3rd March-2021 (during establishment of VOC202012/01 as dominant strain).

Results

Dexamethasone treatment was more common in cohorts 2 and 3 (42.7% and 51.6%) compared with cohort 1 (2.5%). After adjusting for risk, odds of death within 28 days were 2-fold lower in cohort 2 vs 1 (OR:0.47,[0.27,0.79],p=0.006). Mortality was higher cohort 3 vs 2 (20% vs 14%); but not significantly different to cohort 1 (OR: 0.86,[0.64, 1.15],p=0.308).

Conclusions

The real world finding of lower mortality following dexamethasone supports the published trial evidence and highlights ongoing need for research with introduction of new and ongoing concern of new COVID-19 variants.

Abstract word count: 193

Keywords: COVID-19 waves, dexamethasone, COVID-19 variants

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to a range of clinical outcomes from asymptomatic carriage to severe Coronavirus disease (COVID-19) (1, 2). During the first COVID-19 peak May-2020, large clinical trials, including ACCORD and RECOVERY, were initiated to rapidly test and identify new COVID-19 therapeutics (3-5). On 16th June-2020, the RECOVERY trial identified dexamethasone as effective at reducing deaths in patients receiving oxygen or invasive ventilation by a third, and was rapidly translated into standard of care for all COVID-19 patients with oxygen requirement (4, 6, 7). However, since then, the larger intensive care unit studies, such as the Intensive Care National Audit and Research Centre (ICNARC) report on COVID-19 in critical care, have failed to show discernible improvements in oxygen requirements and 28-day in-hospital mortality risk in the most recent wave (8).

A new SARS-CoV-2 virus lineage(B.1.1.7), known as Variant of Concern (VOC)202012/01, the "Kent" variant, was detected in England in September-2020 and reported to have increased transmissibility (9). A recent report highlighted infection with this lineage to associate with increased oxygen requirements and a 60% higher 28-day in-hospital mortality risk in intensive care unit (ITU) patients (10). By the peak of the third wave (end of December-2020), this new variant established itself as the most prevalent SARS-CoV-2 lineage in South East of England (Figure 1) (11).

Using data from the Research Evaluation Alongside Clinical Treatment in COVID-19 (REACT COVID-19) study, established to provide a real-time database of a broader cohort of well-characterised hosptial patients with COVID-19 (12, 13), we report COVID-19 patient clinical and

biochemical parameters, interventions and outcomes for each COVID-19 wave. Through comparison of the pre-dexamethasone first wave (cohort 1), the pre-VOC202012/01 post dexamethasone period (cohort 2) and the most recent VOC202012/01 wave (cohort 3), we aimed to gain insights around the impact of changing clinical practice and dexamethasone use and VOC202012/01 on clinical outcomes.

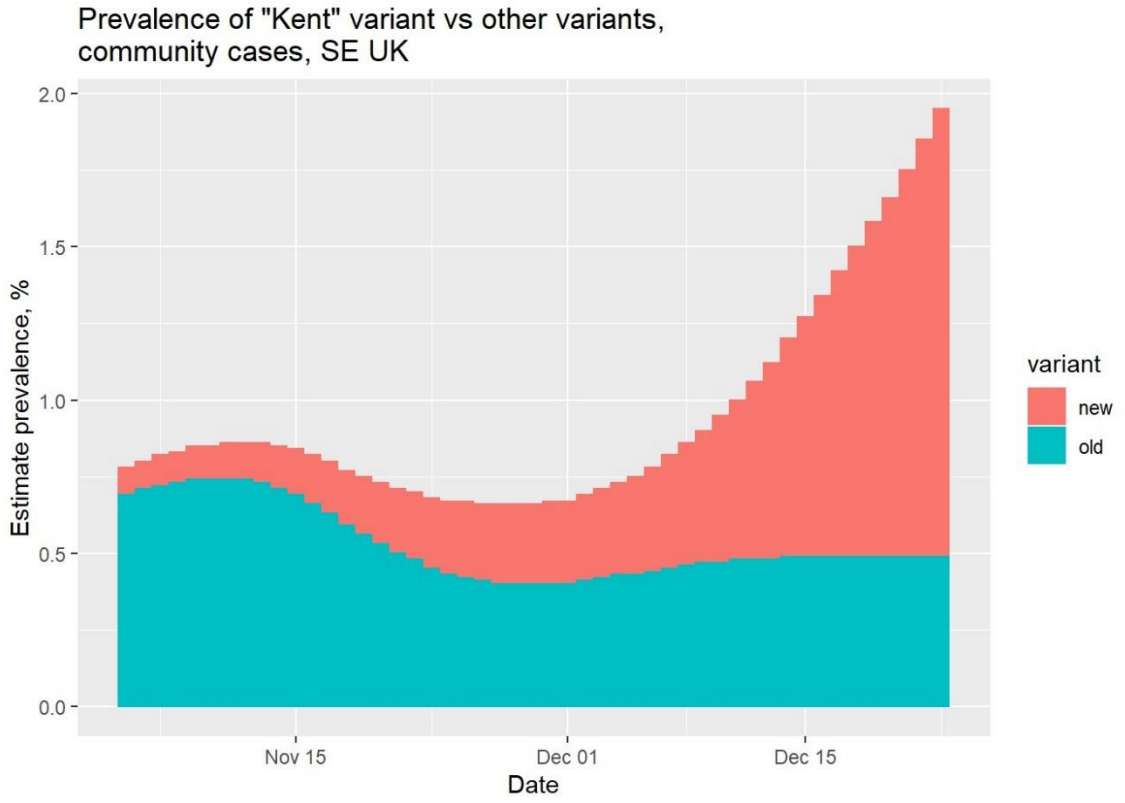


Figure 1: changes in prevalence of new COVID-19variant, SE England. Estimates from the ONS (11) suggest that the prevalence of the novel COVID-19variant (VOC202012/01) within the community in South East England started to become dominant from December 2020 onward.

Methods

Study design and setting

Data were collected as part of the REACT observational and biobanking study of COVID-19 on COVID-19 positive patients admitted to University Hospital Southampton 7th March-2020-3rd March-2021 (12). Ethical approval was obtained from HRA specific review board (REC 20/HRA/2986).

Participants

Patients were included in the study if admitted to hospital with a positive RT-PCR result from nasopharyngeal swab or bronchoalveolar lavage for SARS-CoV-2 and were split into 3 cohorts dependent on date of presentation (Table 1). Patients with a first positive test date fewer than 28 days before the data cut-off date were excluded.

Table 1: Cohorts of patients

Cohort 1	first positive test up to 16 June 2020 (pre-dexamethasone, original variant)
Cohort 2	first positive test 17 June to 30 November (post-dexamethasone, original variant)
Cohort 3	first positive test 1 December 2020 to 3 March 2021 (post-dexamethasone, B.1.1.7)

Variables

Patients' characteristics included demographics (age, sex, body mass index) and comorbidities (including asthma, COPD, cardiac disease and others). Patients defined as having a neurological disease included those recorded as having a diagnosis of epilepsy, a demyelinating condition (e.g. multiple sclerosis), an extra-pyramidal condition (e.g. Parkinson's disease), stroke, myasthenia gravis, Huntington's, spina bifida, motor neuron disease, cerebral palsy, a degenerative disease of the nervous system, spinal muscular atrophy, hydrocephalus, alcohol related neurological disease, vascular related neurological disease or Alzheimer's.

Data collected at admission and throughout hospitalization as part of routine clinical care were recorded (Table 3). Timing, dose and duration of treatments, including corticosteroids, anticoagulants, antibiotics, antivirals and antifungals were collected. Data up to and including 28 days after each patient's first positive test were included in the analysis.

Outcomes

The primary outcome was in-hospital mortality within 28 days of first positive test. For evaluation of changes in parameters, analysis was restricted to patients who were hospitalised for 2 or more days.

Data sources / measurement

Clinical data were captured longitudinally, with change over time treated as explicit. A detailed study protocol and overview of methodology has previously been published (12).

In order to adjust the analysis of mortality based on known COVID-19 risk factors, weighted risk scores were calculated for patients after the first positive SARS-CoV-2 test (first available value up to and including the day after test) using available variables and equivalent weightings as described previously for 4C mortality score. Briefly, the following weightings were applied: age (50-60 years score +2, 60-70 years score +4, 70-80 score years +6, >80 years score +7); sex (male score +1); number of relevant comorbidities (1 score +1, >1 score +2); respiration rate (20-30 score +1, >30 score +2); peripheral oxygen saturation (<92% score +2); urea (7-14 mmol/l score +1, >14 mmol/l score +3); CRP (50-100 mmol/l score +1, >100 mmol/l score +2). Glasgow Coma Scale values were not included in risk score calculation, as approximately 90% of patients did not have values available.

Statistical methods

Continuous data were summarised as median (interquartile range) and categorical as frequency (percentage). Cohorts were compared using Chi-squared or Kruskal-Wallis tests, respectively. Associations between cohorts and outcome were investigated using logistic regression adjusted for the first risk score. P-values were adjusted for multiple testing using Holm–Bonferroni method. Multivariable analysis of differences between cohorts upon presentation was performed using machine learning models including tree-based models and regularised regression models, combined with bootstrapping and recursive feature elimination. Given the study's real-world nature, there were a number of missing data points. as this paper is mainly descriptive, we have not performed any imputation for missing data but describe the data as they stand. For each model, the number of patients may vary due to missing values.

Results

Patient characteristics

To compare the clinical characteristics and outcomes of COVID-19 patients in each wave, we collected data for all patients admitted to a NHS teaching hospital. 1,763 patients were included in this analysis, 680 in Cohort 1, 213 in Cohort 2 and 870 in Cohort 3. After adjusting for multiple testing, there were no significant differences in age or sex between cohorts (Table 2). Pre-existing neurological disease was more common in cohort 1 (217/680, 31.9%) vs cohorts 2 (44/213, 20.7%) and 3 (218/870, 25.1%), adjusted p-value=0.017. However, no significant differences in other comorbidities at presentation were seen, including cardiovascular disease, obesity, COPD or diabetes (Table 2). Similarly, median (IQR) risk scores upon presentation were not significantly different, cohort 1 (10 [6,12] vs cohort 2 (9 [5,11] vs cohort 3 (9 [6,11]), (p=0.144).

Table 2. Patient demographics according to cohort

	Cohort 1 n = 680	Cohort 2 n = 213	Cohort 3 n = 1036	Overall N = 1763	P-value (adjusted)
Age, median (IQR)	72 (54,83)	68 (46,81)	69 (54,81)	70 (53,82)	0.210
Male, n (%)	387 (56.9%)	116 (54.5%)	449 (51.6%)	952 (54.0%)	1
Number comorbidities, median (IQR)	2 (1,3)	1 (0,2)	1 (1,3)	1 (1,3)	1
Cardiac disease, n (%)	215 (31.6%)	61 (28.6%)	268 (30.8%)	544 (30.9%)	1
COPD, n (%)	129 (19.0%)	33 (15.5%)	143 (16.4%)	305 (17.3%)	1
Diabetes, n (%)	190 (27.9%)	49 (23.0%)	227 (26.1%)	466 (26.4%)	1

	Cohort 1 n = 680	Cohort 2 n = 213	Cohort 3 n = 1036	Overall N = 1763	P-value (adjusted)
Dementia, n (%)	31 (4.6%)	9 (4.2%)	33 (3.8%)	73 (4.1%)	1
Human Immunodeficiency Virus (HIV), n (%)	4 (0.6%)	0 (0.0%)	4 (0.5%)	8 (0.5%)	1
Cancer, n (%)	38 (5.6%)	11 (5.2%)	35 (4.0%)	84 (4.8%)	1
Neurological disease, n (%)	**217 (31.9%)**	**44 (20.7%)**	**218 (25.1%)**	**479 (27.2%)**	**0.017**
Obesity, n (%)	191 (28.1%)	62 (29.1%)	301 (34.6%)	554 (31.4%)	0.238
Renal disease, n (%)	204 (30.0%)	56 (26.3%)	269 (30.9%)	529 (30.0%)	1
Thromboembolism, n (%)	4 (0.6%)	0 (0.0%)	1 (0.1%)	5 (0.3%)	1
Risk scores*					
Missing, n (%)	148 (22%)	52 (24%)	150 (17%)	350 (20%)	
First score, median (IQR)	10 (6,12)	9 (5,11)	9 (6,11)	9 (6,11)	0.144

*Based on first available values within 1 day after admission; Statistical significance tested using Kruskal-Wallis for continuous data and Chi-squared for categorical data, p-values adjusted using Bonferroni-Holm correction. Significant values ($p<0.05$) indicated in bold.

Patients defined as having a neurological disease included those recorded as having a diagnosis of epilepsy, a demyelinating condition (e.g. multiple sclerosis), an extra-pyramidal condition (e.g. Parkinson's disease), stroke, myasthenia gravis, Huntington's, spina bifida, motor neuron disease, cerebral palsy, a degenerative disease of the nervous system, spinal muscular atrophy, hydrocephalus, alcohol related neurological disease, vascular related neurological disease or Alzheimer's.

Biochemical characteristics

Biochemical parameters were compared between cohorts using first available measurements following positive SARS-CoV-2 test. Median (IQR) CRP was higher cohort 1 (91 (34, 153.5)) vs cohort 2 (68 (21, 113)) and cohort 3 (72 (23, 131)) (p=0.002), differences in ferritin, glucose and hemoglobin were also seen. However, no differences were seen for other biochemical parameters, including total white blood cells, lymphocytes, neutrophils, eosinophils, d-dimer, or creatinine (Table 3).

Due to cohort 3 including patients infected with both the original and VOC202012/01 variant (Figure 1), we further evaluated the distribution of each biochemical parameter according to month of first positive test to look for a bimodal distribution of values (potentially suggestive of strain-related differences). There was bimodal distribution in CRP values. However, this was seen in both cohorts 1 and 3, suggesting it unrelated to strain differences (data not shown). Similarly, using multivariable analysis and various machine-learning methods to classify patients into cohorts based on demographic and biochemical parameters upon presentation, prediction of an individual's cohort had no greater accuracy than 60%, suggesting no consistent differences in these features between cohorts (data not shown).

Table 3: Cohort biochemical characteristics from first available measurements

	Cohort 1 n = 582	**Cohort 2 n = 169**	**Cohort 3 n = 744**	**Overall N = 1495**	**P-value (adjusted)**
Alanine aminotransferase (ALT)	27 (16, 44)	28.5 (19, 41.25)	27 (16, 43)	27 (17,43)	1

	Cohort 1 n = 582	Cohort 2 n = 169	Cohort 3 n = 744	Overall N = 1495	P-value (adjusted)
Aspartate aminotransferase (AST)	44 (29, 72)	43 (26.5, 65.5)	40 (28, 57)	40 (27.25, 60)	1
BILIRUBIN	9.5 (7, 13)	9 (7, 13)	9 (7, 13)	9 (7, 13)	1
CREATININE	72 (52.25,103.75)	70 (56.25, 93)	78 (59, 105)	75 (57, 102.75)	0.067
CRP	**91** **(34, 153.5)**	**68** **(21, 113)**	**72** **(23, 131)**	**77** **(25, 138)**	**0.002**
D-DIMER	535 (363, 1029.5)	469.5 (319.250, 757.250)	467 (312, 896)	496 (325, 911)	0.502
EOSINOPHILS	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,1)	1
FERRITIN	**529** **(213.5, 1033)**	**355** **(186, 908.5)**	**364** **(159, 702)**	**403** **(175.5, 835.25)**	**0.015**
GLUCOSE	**6.5** **(5.7, 8.2)**	**6.85** **(5.7, 8.1)**	**7.3** **(6.1, 9.8)**	**6.9** **(5.8, 9.2)**	**<0.001**
HAEMOGLOBIN	**117** **(99.5, 133)**	**130.5** **(114.3, 142)**	**127** **(112, 141)**	**124** **(107, 138)**	**<0.001**
Lactate Dehydrogenase (LDH)	681 (506, 934)	603 (441, 799)	624.5 (455, 884.5)	640 (468.5, 891.3)	0.617
LYMPHOCYTES	0.9 (0.6, 1.2)	0.9 (0.63, 1.4)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	1
NEUTROPHILS	5.1 (3.6, 7.6)	4.9 (3.5, 7.2)	5.5 (3.5, 7.7)	5.3 (3.5, 7.6)	1
PLATELETS	226 (168.5, 298)	244.5 (169.5, 291.8)	222 (169, 297)	225 (169, 297)	1

	Cohort 1 n = 582	Cohort 2 n = 169	Cohort 3 n = 744	Overall N = 1495	P-value (adjusted)
POTASSIUM	4 (3.7, 4.4)	4 (3.8, 4.4)	4.1 (3.8, 4.4)	4.1 (3.8, 4.4)	1
SODIUM	137 (134, 139)	137 (134, 139)	137 (134, 139)	137 (134, 139)	1
TRIGLYCERIN	1.4 (1.1, 1.9)	1.4 (1, 1.9)	1.5 (1.1, 2)	1.4 (1.1, 2)	1
TROPONIN	13 (6, 33)	10 (5.5, 20.5)	13 (7, 31)	12.5 (6, 30.8)	0.963
UREA	6.2 (4.4, 9.4)	5.8 (4, 8.6)	6.5 (4.5, 9.5)	6.3 (4.5, 9.3)	0.502
WHITE BLOOD CELLS	6.9 (5, 9.5)	6.9 (4.9, 9.2)	7.2 (5, 9.8)	7 (5, 9.6)	1

Median (Q1, Q3) values reported. Statistical significance tested using Kruskal-Wallis. Significant values ($p<0.05$) indicated in bold.

Intervention use and outcomes between cohorts

We next looked at differences in treatments and outcomes between the cohorts. Dexamethasone treatment was more common in cohorts 2 and 3 (n=91, 42.7% and n=449, 51.6%, respectively) vs cohort 1 (n=17, 2.5%); similarly, tocilizumab treatment increased between cohorts from 2 patients in cohort 1 (0.2%), to 6 patients in cohort 2 (2.8%) and 42 patients (4.8%) in cohort 3 (Table 4). Remdesivir use was more common in cohort 2 (28, 13.1%) vs cohort 1 (10, 1.5%), but lower in cohort 3 (41, 4.7%) ($p<0.001$). Macrolide use decreased with later presentation, with 216 (31.8%), 23 (10.8%) and 66 (7.6%) receiving macrolide therapy in cohorts

1, 2 and 3, respectively. Tetracycline use increased from cohort 1 (63, 9.3%) to cohort 2 (56, 26.3%) and 3 (280, 32.2%) (p<0.001).

Respiratory support (including any supplemental oxygen through to invasive ventilation during 28 days after first positive test) was lower overall in cohort 2 (106, 49.8%) vs cohorts 1 (438, 64.4%) and 3 (551, 63.3%) (p=0.006) (Table 4). Specifically, lower levels of invasive ventilation were seen in cohort 2 (14, 8%) vs cohort 1 (62, 11%) and cohort 3 (108, 14%) (Table S1). However, high-flow nasal oxygen use was higher with later presentation, with 52 (9%), 33 (19%) and 184 (25%) receiving high-flow nasal oxygen, respectively. ITU admissions were similar between cohort 1 (86, 12.6%), 2 (25, 11.7%) and 3 (146, 16.8%) (p=0.432) (Table 4).

28-day mortality was substantially lower in cohort 2 vs cohort 1 (14% vs 27%, respectively) but was greater in cohort 3 vs cohort 2 (20% vs 14%, respectively) (p<0.001) (Table 4). Across all cohorts, 28-day mortality increased with risk score. However, mortality rates in cohort 2 for specific risk scores were lower vs cohorts 1 and 3 (Figure 2A). Moreover, after adjusting for risk score at positive test using a multivariable logistic regression model, odds of death were lower in cohort 2 vs cohort 1 (OR: 0.47; 95% CI: 0.27, 0.79; p=0.006) but not in cohort 3 (OR: 0.86; 95% CI: 0.64, 1.15; p=0.308; Figure 2A).

Table 4: Treatments, interventions and outcomes for each of the cohorts

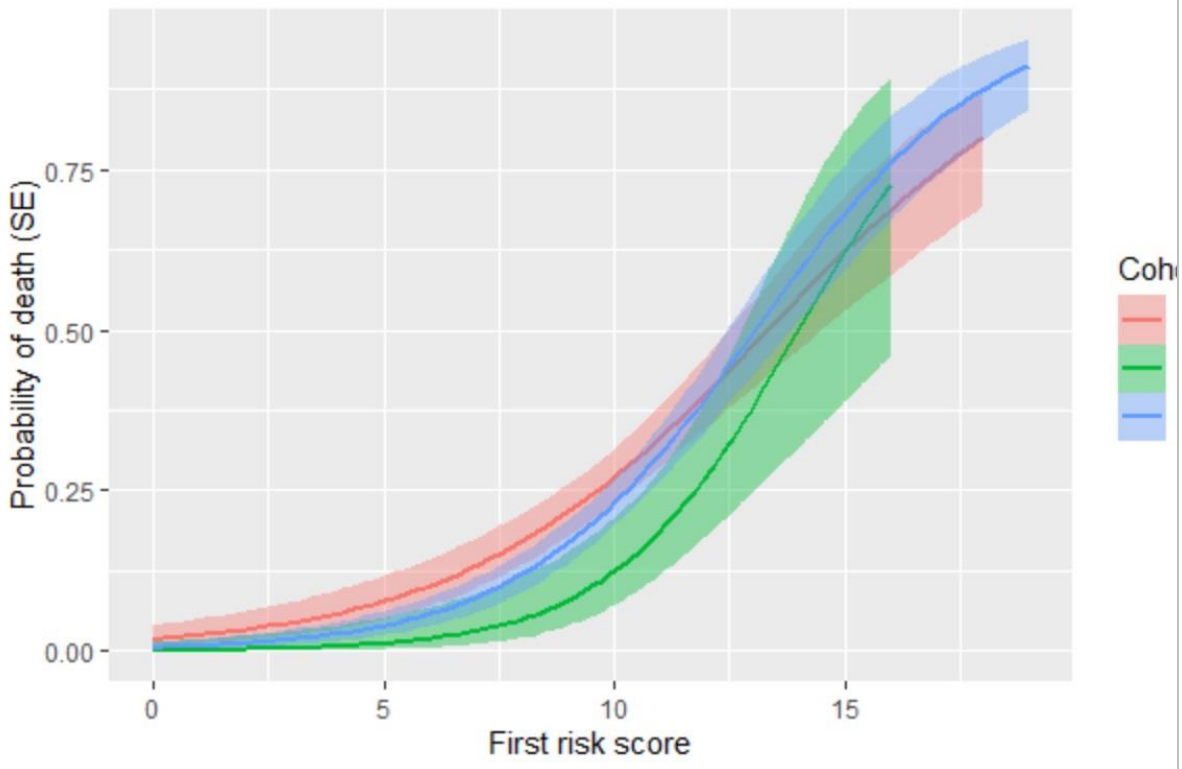
	Cohort 1 n = 680	Cohort 2 n = 213	Cohort 3 n = 1036	Overall N = 1763	P-value (adjusted)
Treatments, n (%)					
Dexamethasone	**17 (2.5%)**	**91 (42.7%)**	**449 (51.6%)**	**557 (31.6%)**	**<0.001**

Prednisolone	69 (10.1%)	16 (7.5%)	73 (8.4%)	158 (9.0%)	1
Remdesivir	**10 (1.5%)**	**28 (13.1%)**	**41 (4.7%)**	**79 (4.5%)**	**<0.001**
Tocilizumab	**2 (0.3%)**	**6 (2.8%)**	**42 (4.8%)**	**50 (2.8%)**	**<0.001**
Baricitinib	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Macrolides	**216 (31.8%)**	**23 (10.8%)**	**66 (7.6%)**	**305 (17.3%)**	**<0.001**
Tetracyclines	**63 (9.3%)**	**56 (26.3%)**	**280 (32.2%)**	**399 (22.6%)**	**<0.001**
Interventions, n (%)					
ITU admissions	86 (12.6%)	25 (11.7%)	146 (16.8%)	257 (14.6%)	0.432
Respiratory support	**438 (64.4%)**	**106 (49.8%)**	**551 (63.3%)**	**1095 (62.1%)**	**0.006**
Outcomes, n (%)					
Readmissions within 28 days	109 (16.0%)	37 (17.4%)	173 (19.9%)	319 (18.1%)	1
28-day mortality	**185 (27.2%)**	**30 (14.1%)**	**174 (20.0%)**	**389 (22.1%)**	**0.001**

Statistical significance tested using Kruskal-Wallis for continuous data and Chi-squared for categorical data, p-values adjusted using Bonferroni-Holm correction. Significant values ($p<0.05$) indicated in bold.

Respiratory support included treatment with any type of oxygen therapy including supplemental oxygen by nasal canula or facemask, non-invasive ventilation, invasive Ventilation and Optiflow / High-Flow.

A



B

Variable		N	Odds ratio	p
First risk score		1413	1.43 (1.36, 1.51)	<0.001
Cohort	1	532	Reference	
	2	161	0.47 (0.27, 0.79)	0.006
	3	720	0.86 (0.64, 1.15)	0.308

Figure 2: (A) 28-day mortality according to first risk score and cohort. Curves represent predicted probability of death within 28 days of first positive test according to cohort based on a binomial logistic regression model fitted to observed data. Shaded areas indicate 95% confidence interval. (B) Risk-adjusted mortality according to cohort. Odds of death within 28 days of first positive test based on a logistic regression model including first risk score and cohort.

Discussion

The REACT COVID-19 observational database is unique in data granularity and description of routine clinical management (12). We investigated changes in 28-day mortality associated with the widespread use of dexamethasone and emergence of VOC202012/01. We report lower mortality in cohort 2 (post-dexamethasone, pre VOC202012/01) vs cohort 1 after linear regression and adjustment for risk (14), supporting the RECOVERY dexamethasone arm results (4). The mortality rate in cohort 3 during VOC202012/01 emergence, however, was increased vs cohort 2, and risk-adjusted odds of death were no different cohort 3 vs cohort 1. This reflects UK wide data and highlights the need for continued evaluation of treatment outcomes with emergence of new SARS-CoV-2 variants (8, 10, 11).

Apart from the increase in dexamethasone treatment, other prescribing differences were also evident between cohorts and reflective of increased understanding and emergence of new treatments. Remdesivir was one of the first treatments to demonstrate survival benefit, and to be employed routinely in clinical practice (15, 16). However, with emergence of dexamethasone and tocilizumab and conflicting evidence around its efficacy, Remdesivir use fell (15-17). The

difference in tetracycline and macrolide use is also noteworthy and reflects the local antibiotic policy, since macrolides treatment excluded participation in some arms of RECOVERY and ACCORD (3, 4). Supportive care changed over the course of the first wave, with a shift towards greater use of non-invasive ventilation (18).

Recent reports have suggested that VOC202012/01 is associated with higher mortality, consistent with our finding that 28-day mortality rate was higher in cohort 3 vs cohort 2 (10). Despite higher use of dexamethasone and other effective therapies in cohort 3, risk-adjusted mortality was not significantly different vs cohort 1. These findings support the hypothesis that VOC202012/01 is associated with higher mortality than the original variant. The increase in high flow-nasal oxygen in later cohorts reflects what has been seen clinically, with various studies demonstrating its benefit in reducing ICU length of stay in specific patients (19, 20). Whilst dexamethasone has demonstrated efficacy in pre-B1.1.7 SARS-CoV-2 infection, its impact on VOC202012/01 hasn't been investigated in clinical studies.

It is important to note that, whilst we did see different levels of neurological disease between cohorts, this is unlikely to explain mortality rate variation. There were no statistically significant differences in rates of other comorbidities, age or sex, nor consistent variation in other patient characteristics or biochemical parameters at presentation that could explain the observed difference in mortality. Risk scores at presentation did not differ significantly between cohorts. Whilst several statistically significant differences in biochemical parameters between cohorts were reported (including CRP), the absolute differences were small, overall unlikely to be clinically significant, and did not reveal consistent differences between cohort 3 and cohorts 1

and 2 that could be suggestive of differing pathobiology between the varying lineages of SARS-CoV-2.

The data capture alongside clinical care is both a strength and limitation to the REACT COVID-19 Study. Whilst this design is more reflective of real-world clinical care, there is greater risk of bias, with sicker patients undergoing more sampling than those demonstrating improvements. The observational design allows only associations rather than causations to be determined, and other possible explanations for differences in mortality but not biochemical parameters must be considered.

First, it is noteworthy that cohort 2 required respiratory support levels and lower levels of invasive ventilation. Whilst our risk score adjusts for oxygen saturation and respiration rate at presentation, the lower requirement for respiratory support in cohort 2 suggests potential differences in disease severity between cohorts that are not fully accounted for by risk scores. Second, our data on strain prevalence are based on PHE local area data rather than direct patient-specific sequencing. Therefore, it was not possible to link outcome directly with lineage data at a patient level (11). Lineage data are available for greater numbers of patients in wave 3 through national sequencing programmes, but fewer tests were initially sequenced nationally and therefore a comparison was not possible. However, the PHE data reflect what we see in the increasingly available trust lineage data and we intend to investigate specific outcomes related to lineage data in the most recent cohort. Third, the choice of 28-day mortality outcome was made based on national mortality reporting. However, some patients have much longer hospitalisation, particularly those needing ventilation. Therefore, there may be differences in mortality beyond 28 days between cohorts not captured in this analysis that may explain some

of the differences described. Fourth, non-patient clinical factors have the potential to influence outcomes including trust COVID-19 pressure and ITU occupancy rates between cohorts. It is also important to bear in mind the initiation of vaccination in the middle of December. Whilst the number of patients vaccinated in the UK by the start of March was not substantial, these could have impacted disease outcomes in cohort 3. Moreover, although we provide an in-depth analysis of COVID-19 outcomes in the UK between June 2020-March 2021, the generalizability of these findings to the rapidly changing COVID-19 landscape around the rest of the world is less. Finally, symptom onset data were not available for all patients and therefore another consideration is the timing of testing relative to symptom onset that may differ between cohorts. However, in our initial analysis of wave 1, which did include symptom onset data, there did not appear to be an impact on outcome (21). With a rapidly changing COVID-19 international picture, future prospective studies are now essential to understand the impact of changing standard of care, vaccination coverage and variant dynamics on COVID-19 outcomes and complications such as mucormycosis, as well as how comorbidities impact these (22).

Conclusions

The REACT COVID-19 observational study provides a uniquely granular, longitudinal assessment of change in outcomes in SARS-CoV-2 over the course of this pandemic in a teaching hospital in England. Our data are reflective of larger, cross sectional studies in demonstrating an increase in mortality with the emergence of the VOC202012/01, that appears to cancel out any overall mortality benefit conferred by emerging treatments. The lack of variation in longitudinal clinical parameters suggests that the mechanism of disease remains similar. While it is hoped that

296 widespread vaccination will impact transmission and disease severity of COVID-19 globally, this
297 work highlights the need for ongoing research into treatments to mitigate the impact of future
298 mutations.

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Conflicts of interest statement

P.F. Reports that he is a previous employee of AstraZeneca and holds AstraZeneca shares. T.W. reports grants and personal fees from AstraZeneca; personal fees and other from MMH, grants

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