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Real-world effectiveness of steroids in severe COVID-19: longer courses associated with lower risk of death or ICU admission

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Abstract

Purpose

We aim to investigate the associations of steroid and length of steroid use with outcomes in severe COVID-19.

Methods

Severe cases of COVID-19, defined by hypoxia at presentation, and admitted to a multi-site healthcare institution in London were analysed between 02-Sep-2020 and 27-May-2021. The associations between duration of steroid treatment (prescription-days) and outcomes were explored using Cox proportional-hazards models adjusting for confounders. Length of steroid treatment was analysed as both a continuous variable and categorised into < 3, 3–10, and > 10 days. The primary outcome was in-hospital mortality and secondary outcome was in-hospital mortality or intensive care unit (ICU) level-3 admission.

Results

734 severe COVID-19 cases were included, with 137/734 (18.7%) treated with steroids for < 3 days, 497/734 (67.7%) for 3–10 days, and 100/734 (13.6%) for > 10 days. Cox modelling with continuous days showed increasing length of steroids decreased the hazard of in-hospital mortality by a factor of 0.98 [95% CI: 0.96-1.0] per additional day and in-hospital mortality or ICU admission by a factor of 0.91 [95% CI: 0.87–0.95] per additional day. Further, when taking 3–10 days steroid treatment group as the reference group, > 10 days steroid showed trends towards decreased hazards for death (HR 0.59 [95%CI: 0.30–1.14]) and was significantly protective for death/ICU outcome (HR 0.28 [95%CI: 0.11–0.68]).

Conclusion

The protective effect of steroid for severe COVID-19 reported in randomised clinical trials was replicated in this large real-world cohort. We found an association between longer steroid courses and lower risk of death or ICU admission that warrants further investigation.

Background

Currently, steroids are the main treatment for coronavirus disease 2019 (COVID-19) infection[1], which has infected over 200 million people and caused over 5 million deaths worldwide[2]. The RECOVERY trial[3,4] was the first randomised controlled trial to show that in patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support. Some

meta-analyses have shown a benefit of steroids at preventing mortality[5,6] and reducing need for mechanical ventilation[6]. However, other meta-anlysis from both observational studies and randomised controlled trials have shown conflicting results[7,8].

A guideline was issued by WHO on use of dexamethasone and other corticosteroids (hydrocortisone or prednisone) for treatment of severe and critically unwell COVID-19 patients in September 2020[9]. However, many uncertainties remain on the optimum choice, dose and duration of steroid therapy[10–13] and, to the best of our knowledge, no studies have investigated whether there is an association between duration of steroid treatment and outcome. Our objective was to determine whether the effect of steroids on outcomes for severe COVID-19 patients reported in randomised trials is replicated in a large real-world cohort spanning the duration of the pandemic thus far, and whether there is an association between duration of steroid treatment and outcomes in patients with severe COVID-19 disease.

Methods

Population of interest and setting

Guy's and St Thomas' NHS Foundation Trust (GSTT) is a multi-site inner-city healthcare institution in South London. Only COVID-19 cases admitted through the GSTT emergency department from the release of WHO steroid treatment guideline (2nd September 2020) to 27th May 2021 were included in this study. Patients dying or being discharged in the first 24 hours were considered most likely to have reached study endpoint independent of any steroid effect and were excluded from the primary analysis. When the endpoint includes ICU admission, patients admitted to ICU within 24 hours after admission were excluded for this endpoint for the same reason.

SARS-CoV-2 laboratory testing

GSTT has an on-site laboratory providing SARS-CoV-2 testing to all patients and hospital care workers. Assays used for the detection of SARS-CoV-2 RNA include PCR testing using Aus Diagnostics or by the Hologic Aptima SARS-CoV-2 Assay. Nucleic acid was first extracted using the QIAGEN QIAsymphony SP system and a QIAsymphony DSP Virus/Pathogen Mini Kit (catalogue No: 937036) with the off-board lysis protocol. Cases without laboratory confirmation of SARS-CoV-2 infection were excluded.

Definitions

Cases were identified by the first positive SARS-CoV-2 RNA test. Severe cases were defined by hypoxia at admission (oxygen saturations of < 94%, requiring supplemental oxygen, or if the fraction of inspired oxygen was greater than 0.21).

Determination of SARS-CoV-2 lineage

Whole genome sequencing of residual samples from SARS-CoV-2 cases was performed on GridION (Oxford Nanopore Technology), using version 3 of the ARTIC protocol[14] and bioinformatics pipeline[15].

Samples were selected for sequencing if the corrected CT value was 33 or below, or the Hologic Aptima assay was above 1000 RLU. Lineage determination was performed using updated versions of pangolin 2.0[16]. Samples were regarded as successfully sequenced if over 50% of the genome was recovered and if lineage assignment by pangolin was given with at least 50% confidence.

Data sources, extraction and integration

Clinical, laboratory and demographic data for all cases with a laboratory reported SARS-CoV-2 PCR RNA test on nose and throat swabs or lower respiratory tract specimens were extracted from hospital electronic health record (EHR) data sources using records closest to the test date. Data was linked to the Index of Multiple Deprivation (IMD), with 1 denoting the least deprived areas, and 5 the most deprived ones. Age and sex were extracted from EPR. Self-reported ethnicity of cases were stratified to be White, BAME (Black, Asian, and Minority Ethnic) according to the 18 ONS categories of White (British, Irish, Gypsy and White-Other), Black (African, Caribbean, and Black-Other), Asian (Bangladeshi, Chinese, Indian, Pakistan, and Asian-Other), and Mixed/Other.

Comorbidities, medication history, and medicine data were extracted from the EHR using structured queries with corresponding dictionaries. Comorbidities were extracted from any of the databases covering the pathway of the cases from arrival to hospital discharge or death. Cases were characterised as having/not having a past medical history of hypertension, cardiovascular disease (stroke, transient ischaemic attack, atrial fibrillation, congestive heart failure, ischaemic heart disease, peripheral artery disease or atherosclerotic disease), diabetes mellitus, chronic kidney disease, chronic respiratory disease (chronic obstructive pulmonary disease, asthma, bronchiectasis or pulmonary fibrosis), and neoplastic disease (solid tumours, haematological neoplasias or metastatic disease). If a comorbidity was not recorded we assume that it was not present. Additionally, checks on free text data were performed by a cardiovascular clinician to ensure the information was accurate.

Steroids

Steroid treatment was measured by number of prescription-days with dexamethasone, hydrocortisone, prednisolone or methylprednisolone. Hospital guidelines in GSTT recommend 10 days of treatment with oral dexamethasone 6mg once a day or intravenous hydrocortisone 50mg three times a day. Duration, formulation, or route of steroids could be increased on advice of the hospital's specialist lung inflammation service. Additionally, individuals may have been treated with steroids as therapeutic immunomodulation for co-existing medical conditions.

Duration of steroid treatment was calculated as cumulative days through hospital admission to discharge or death. Steroids used in wards only before ICU admission were used for the secondary outcome analysis. The lengths of steroid use in days were continuous, and were further categorised as < 3 days (0 < = steroid-days < 3), 3–10 days (3 < = steroid-days < = 10), and > 10 days (steroid-days > 10). The cut-offs for the steroid treatment days were chosen according to WHO guidelines (7–10 days) and the interquartile range (IQR) of steroid-days [3, 10] in RECOVERY trial. Both continuous and categorisations of steroid-days were analysed in separate multivariate models.

Outcomes

The primary outcome was all-cause in-hospital mortality (WHO-COVID-19 Outcomes Scale 8), with patients still hospitalised at the end of the cohort considered censored. Secondary outcome was all-cause in-hospital mortality or level-3 ICU admission (WHO-COVID-19 Outcomes Scale 7). Level-3 ICU admission was defined as requiring advanced respiratory support or multi-organ support.

Statistical analysis

The general statistics were summarised with mean and standard deviation (SD) for continuous variables if the distribution is normal and median and IQR if the distribution is non-normal. Count and percentages were used for categorical variables. For the comparisons of the cohort statistics with different lengths of steroid-days (< 3 days, 3–10 days, > 10 days), Kruskal-Walllis test was used for continuous variables and Chi-squared test for categorical variables. The reference significant level was set to be $p < 0.05$.

Cox proportional hazards models were used for time-to-event survival analysis in which the time was starting from hospital admission and events as the defined outcomes. Adjusted hazards ratios for the primary and secondary outcomes from the Cox models were presented. The adjusted variables used in the model were selected via literature review and clinical expertise (Supplementary Table I: literature review for risk factors). Age, sex, Body Mass Index (BMI) > 30 kg/m^2, hypertension, cardiovascular disease, diabetes, respiratory disease, chronic kidney disease, sequenced SARS-CoV-2 variant and medications including steroids and tocilizumab/sarilumab were used as pre-defined covariates to adjust in multivariable models.

Cox models with continuous steroid-days were used to evaluate the effect of increasing steroid treatment per additional day. For Cox models with categorical steroid-days, the < 3 days group was set to be the reference group to compare the effect of longer treatment (> 10 days and 3–10 days) with short treatment (< 3 days). To further compare the effects of > 10 days steroid treatment with 3–10 days treatment, another Cox model was performed with the 3–10 days group as the reference.

Missing values of the variant, BMI, and ethnicity were imputed as a new category and IMD were imputed with median value of all patients. There were no missing values in other adjusted variables.

Data management was performed using SQL databases, with analysis carried out on the secure King's Health Partners Rosalind high-performance computer infrastructure[18] running Jupyter Notebook 6.0.3, R 3.6.3 and Python 3.7.6.

Results

Description of population, steroid use and outcomes

746 patients were identified with hypoxia on admission of which 734 were included in the analysis after removal of 12 cases that stayed for less than 24 hours after admission. Among these patients, 15 missing IMD were imputed with median. Overall, the cohort had an in-hospital mortality rate of 10.5%, with 693/734 (94.4%) individuals were treated with steroids (> 0 days) and the median of steroid-days (including 0 days) was 5, IQR [3, 8]. Figure 1 showed the distribution of the steroid-days. Hospital mortality was 8.8% amongst 137 patients receiving steroids < 3 days, 8.0% for 497 patients receiving steroids for 3–10 days and 25.0% for 100 patients receiving steroids for > 10 days (Table 1).

Further when studying the composite outcome in-hospital mortality/ICU admission, 670 patients were left for the analysis after removing 64 patients admitted to ICU within 24 hours. 12 missing IMD were imputed with median. Overall, 116/670 (17.3%) patients either died or were admitted to a level-3 ICU with 49/173 (28.3%) death/ICU admission in < 3 days steroid treatment group, 61/455 (13.4%) in 3–10 days steroid treatment group, and 6/42 (14.3%) in > 10 days steroid treatment group (Supplementary Table II).

During the whole hospital stay, patients in the longer steroid treatment group were older than those in the shorter steroid treatment group (66.0 [57.0,75.2] for > 10 days group vs 63.0 [53.0,75.0] for 3–10 days group vs 59.0 [46.0,70.0] for < 3 days group, p = 0.008) (Table 1). There were no significant differences in sex, ethnicity, IMD, and BMI among patients in the three steroid course length groups. Some pre-admission comorbidities were more frequent in > 10 days group compared with both 3–10 days and < 3 days groups including hypertension (41.0% vs 36.0% vs 26.3%, respectively; p = 0.041), chronic respiratory disease (28.0% vs 15.3% vs 15.3%, respectively; p = 0.007), cancer (12.0% vs 3.4% vs 3.6%, respectively; p = 0.001), HIV infection (8.0% vs 1.8% vs 2.2%, respectively; p = 0.002), and transplantation (6.0% vs 2.2% vs 0.7%, respectively p = 0.029). Cardiovascular disease, diabetes, and kidney disease were not significantly different among the three treatment groups. Cohort statistics for steroids used before ICU admission were presented in Supplementary Table II.

Cox proportional hazard model for the outcomes of death and death or ICU

The Cox proportional hazard models showed significant protective effects of steroids for both outcomes using continuous steroids treatment days. For every increment in days of steroid treatment, the hazard decreases by a factor of 0.98 (95%CI: 0.96-1.0) for in-hospital mortality and a factor of 0.91 (95%CI: 0.87–0.95) for in-hospital mortality or ICU admission (Table 2). When the duration of steroids was categorised, longer treatment of steroids was associated with decreased in-hospital mortality (HR: 0.39 (95%CI: 0.19–0.79) for 3–10 days and 0.23 (95%CI: 0.10–0.55) for > 10 days) compared with < 3 days treatment. The composite endpoint of in-hospital mortality or ICU admission was also lower in patients treated for 3–10 days (HR: 0.27 (95%CI: 0.18–0.41)) and > 10 days (HR: 0.08 (95%CI: 0.03–0.19)) compared with < 3 days of steroid treatment (Table 2). Further when taking 3–10 days steroid treatment group as the reference in Cox model, > 10 days steroid treatment had no significant effect on death (HR 0.59 (95%CI: 0.30–1.14)) but was protective for death/ICU outcome (HR 0.28 (95%CI: 0.11–0.68)) (Table 2).

Other variables (Table 3) that had significant effects on both outcomes were age per year older (HR: 1.06 (95%CI: 1.04–1.09) for death and HR: 1.02 (95%CI: 1.0-1.03) for death/ICU), cardiovascular comorbidities (HR: 1.75 (95%CI: 1.03–2.95) for death and HR: 1.78 (95%CI: 1.15–2.75) for death/ICU), HIV infection (HR: 3.60 (95%CI: 1.34–9.67) for death and HR: 3.01 (95%CI: 1.28–7.08) for death/ICU), and transplantation (HR: 6.52 (95%CI: 1.89–22.49) for death and HR: 5.42 (95%CI: 2.02–13.58) for death/ICU). IMD quintiles (HR: 1.26 (95%CI: 1.0-1.60 for death) were significantly associated with death, but not the composite outcome of death/ICU. Chronic respiratory disease was significantly associated with death/ICU (HR 1.72 [95%CI: 1.11–2.68]) but not death. The remaining variables including sex, ethnicity, hypertension, diabetes, cancer, kidney disease, and infection with the alpha variant were not significantly associated with either outcome in the Cox model. The confidence levels for the variables were similar between the models used with continuous steroid-days and categorised steroid-days (Supplementary Table III and Table IV).

Table 1
Characteristics for patient groups receiving different steroid treatment-days during their hospital admission

	Overall	< 3 days	3–10 days	> 10 days	P-Value
n	734	137 (18.7%)	497 (67.7%)	100 (13.6%)	
Age, median [Q1,Q3]	63.0 [52.0,74.0]	59.0 [46.0,70.0]	63.0 [53.0,75.0]	66.0 [57.0,75.2]	0.008
Male, n (%)	411 (56.0)	75 (54.7)	273 (54.9)	63 (63.0)	0.315
Ethnicity, n (%)					0.777
White	297 (40.5)	50 (36.5)	203 (40.8)	44 (44.0)	
BAME	283 (38.6)	57 (41.6)	188 (37.8)	38 (38.0)	
Unknown	154 (21.0)	30 (21.9)	106 (21.3)	18 (18.0)	
BMI, n (%)					0.082
BMI < 30	345 (47.0)	63 (46.0)	226 (45.5)	56 (56.0)	
BMI > 30	270 (36.8)	46 (33.6)	188 (37.8)	36 (36.0)	
BMI Unknown	119 (16.2)	28 (20.4)	83 (16.7)	8 (8.0)	
Cardiovascular, n (%)	177 (24.1)	34 (24.8)	117 (23.5)	26 (26.0)	0.852
Hypertension, n (%)	256 (34.9)	36 (26.3)	179 (36.0)	41 (41.0)	0.041
Diabetes, n (%)	200 (27.2)	30 (21.9)	138 (27.8)	32 (32.0)	0.203
Chronic respiratory disease, n (%)	125 (17.0)	21 (15.3)	76 (15.3)	28 (28.0)	0.007
Cancer, n (%)	34 (4.6)	5 (3.6)	17 (3.4)	12 (12.0)	0.001
Kidney disease, n (%)	82 (11.2)	13 (9.5)	52 (10.5)	17 (17.0)	0.131
HIV infection, n (%)	20 (2.7)	3 (2.2)	9 (1.8)	8 (8.0)	0.002
Transplantation, n (%)	18 (2.5)	1 (0.7)	11 (2.2)	6 (6.0)	0.029
IMD Quintile, n (%)					0.167
1	183 (25.5)	28 (20.9)	123 (25.3)	32 (32.3)	
2	372 (51.7)	74 (55.2)	255 (52.5)	43 (43.4)	
3	97 (13.5)	16 (11.9)	69 (14.2)	12 (12.1)	
4	47 (6.5)	11 (8.2)	30 (6.2)	6 (6.1)	
5	20 (2.8)	5 (3.7)	9 (1.9)	6 (6.1)	

	Overall	< 3 days	3–10 days	> 10 days	P-Value
Tocilizumab or sarilumab use, n (%)	12 (1.6)		6 (1.2)	6 (6.0)	0.001
Variant, n (%)					0.095
Alpha	210 (28.6)	34 (24.8)	136 (27.4)	40 (40.0)	
non-Alpha	22 (3.0)	5 (3.6)	15 (3.0)	2 (2.0)	
nonSequenced	502 (68.4)	98 (71.5)	346 (69.6)	58 (58.0)	
Death, n (%)	77 (10.5)	12 (8.8)	40 (8.0)	25 (25.0)	< 0.001

Table 2
Hazard Ratios (HRs) of steroid variable for Cox models with death and death/ICU admission outcomes

Outcome	Death		Death/ICU	
	Events/n (%)	HR (95% CI)	Events/n (%)*	HR (95%CI)
Model: Steroid in days (continuous > = 0)				
Steroid-days		0.98 (0.96-1.0)		0.91 (0.87–0.95)
Model: Categorial steroid-days < 3 (reference) vs 3–10 vs > 10 days				
< 3 days (reference)	12/138 (8.8)	1	49/173 (28.3)	1
3–10 days	40/497 (8.0)	0.39 (0.19–0.79)	61/455 (13.4)	0.27 (0.18–0.41)
> 10 days	25/100 (25.0)	0.23 (0.10–0.55)	6/42 (14.3)	0.08 (0.03–0.19)
Model: Categorial steroid-days < 3 vs 3–10 (reference) vs > 10 days				
< 3 days	12/138 (8.8)	2.57 (1.26–5.24)	49/173 (28.3)	3.71 (2.46–5.61)
3–10 days (reference)	40/497 (8.0)	1	61/455 (13.4)	1
> 10 days	25/100 (25.0)	0.59 (0.30–1.14)	6/42 (14.3)	0.28 (0.11–0.68)

* Cohort statistics for patients used in the death/ICU model with stratified steroid-days were shown in Supplementary Table II.

Table 3
Hazard Ratios (HRs) for Cox models with continuous steroid-days

	Death		Death/ICU	
	HR	95% CI	HR	95% CI
Age	1.06	1.04–1.09	1.02	1.0-1.03
Female	0.84	0.51–1.40	0.72	0.49–1.08
Ethnicity BAME vs White	1.52	0.84–2.76	1.20	0.76–1.89
Ethnicity Unknown vs White	1.45	0.76–2.78	1.69	0.98–2.92
IMD Quintile	1.26	1.0-1.60	1.10	0.9–1.35
Cardiovascular	1.75	1.03–2.95	1.78	1.15–2.75
Hypertension	0.71	0.42–1.21	0.73	0.47–1.12
Diabetes	0.96	0.56–1.65	0.82	0.53–1.28
Chronic respiratory disease	0.95	0.52–1.75	1.72	1.11–2.68
Cancer	1.36	0.58–3.21	0.89	0.41–1.95
Kidney disease	0.79	0.42–1.51	1.09	0.65–1.82
HIV infection	3.60	1.34–9.67	3.01	1.28–7.08
Transplantation	6.52	1.89–22.49	5.42	2.02–13.58
Alpha vs non-Alpha	1.10	0.32–3.84	0.65	0.23–1.87
Non-Sequenced vs non-Alpha	1.44	0.42–4.96	0.67	0.24–1.86
BMI > 30 vs BMI < = 30	0.65	0.33–1.27	0.99	0.63–1.57
BMI Unknown vs BMI < = 30	2.56	1.46–4.48	1.13	0.67–1.91
tocilizumab or sarilumab[+]	3.17	0.92–10.85		
steroid-days	0.98	0.96-1.0	0.91	0.87–0.95

[*] Steroid-days used in the death model were cumulative days from admission to discharge or death and in the composite death or ICU-admission model were cumulative days from admission to ICU admission, death or discharge.

[+] tocilizumab and sarilumab were only used in ICU thus only used in the death model.

Discussion

This study provides evidence for real-world effectiveness of steroids in reducing either in-hospital mortality or a composite endpoint of in-hospital mortality/ICU admission amongst severe COVID-19 patients. The protective effect-size of treatment with steroids was similar to that reported in the RECOVERY clinical trial[3] for a comparable group of patients defined by receipt of oxygen therapy. This adds to the evidence base for a clinical benefit of steroid treatment in COVID-19.

Our study shows longer steroid treatment is associated with lower risk of in-hospital mortality or ICU admission. We found a significant decreased hazard of both death and death/ICU admission using the continuous steroid-days in the multivariate model. Further increasing confidence in this finding, hazards when associated with longer steroids (> 10 days) were lower than with treatment captured by categories of shorter duration: <3 days and 3–10 days. Whilst the group treated with longer durations of steroids had the highest overall crude mortality, suggesting the group treated with longer duration of steroids had more severe disease than others treated with shorter courses, steroids were protective once analysis adjusted for other factors affecting severity. This finding supports additional assessment of the association between duration of steroid treatment and severe outcomes, and to our knowledge is the first study to address this question.

Originally, we set out to confirm the RECOVERY trial in a real-world setting, also finding a surprising effect of longer duration of steroids. We adjusted for potential confounders (e.g. age, sex, ethnicity, comorbidities, BMI and IMD) with the effect of steroids remaining statistically significant and a clear trend towards lower hazard ratio with longer durations. To avoid the non-consistent treatment of COVID-19 patients before and after the steroid WHO treatment guideline, only patients after the guideline were included in the study to ensure as few confounders as possible. Undoubtedly, we are unable to adjust for all confounders, including other improvements introduced around the time of steroids e.g. thromboprophylaxis and proning. However, it is reassuring that steroid-days (which also includes no steroid treatment) as a continuous variable are significant, suggesting the associations found are robust.

It is notable the study was done in a centre that had good overall comparative NHS outcomes and an SMR of 0.5 in ICU and had guidelines and practice recommending longer courses of steroids for severe patients. Over 80% of the > 10 steroid-days group were treated deliberately with long steroids and the remaining were on long term steroids as therapeutic immunomodulation for other conditions. We hypothesise from the analysis that there is a sub-population of COVID-19 patients that have prolonged severe high-inflammatory disease that benefit from longer course of steroids treatment, that reduces their mortality. This hypothesis needs formal trial analysis to resolve. Causality between longer steroid treatment and improved outcomers should not be inferred before interventional trials are conducted.

Clinical trials will also need to assess whether longer duration of steroids increase the risk/rate of adverse events, which includes delayed viral clearance[19]. Some studies are identifying other potential adverse events associated with steroids such as invasive mould infections including aspergillosis and mucormycosis[20], with work ongoing to assess the effect of steroids on risk of bloodstream infection [21].

In this study we investigated the association of steroid duration with outcomes, however our analyses are agnostic to the dose of steroids used. There may be reasons why duration of steroid treatment mediate effects on outcomes independently of cumulative dose, for instance if a sustained period of immunosuppression is needed to prevent immune-mediated inflammation.

Many other studies on the real-world effectiveness of steroids have failed to reproduce the findings of clinical trials. Partly, this may be due to small sample size, heterogeneity of treatment and non-treatment groups, and incorrectly testing associations on individuals not expected to benefit, i.e. cases without evidence of hypoxia. Additionally our adjustment accounts for many baseline variables which have previously been associated with severe outcomes. The validity of our analyses is supported by the findings that variables previously associated with severity, such as age and cardiovascular comorbidity retain significance in our modelling.

Other studies have found the alpha variant of SARS-CoV-2 to be associated with severe disease, especially mortality[22–24] and hypoxia on admission[25]. However, another study in hospitalised patients did not find such an association[26]. To our knowledge, no studies on alpha variants adjusted for newly introduced therapeutics. Interestingly, the association of alpha variant with severe disease as measured by mortality and ICU admission was not found in this study. This is in contrast to our initial findings in the same dataset that the Alpha variant was associated with severity as measured by hypoxia on admission[25]. It may be that severity of the alpha variant is ameliorated by efficacious treatment of hospitalised patients. This may be especially true as during the second wave steroid treatment had been introduced and standardised as the alpha variant emerged. This would also explain the disparity between findings of other published studies, with the only study of variant status and death in hospitalised patients not finding an association.

Further limitations might include potential bias for patients who did not have a chance to receive steroids or received very short steroids because they were very severe and died, or went to ICU soon after admission. This is an issue that is intractable with retrospective study, and we attempt to address this by excluding those who died (or went to ICU for the secondary outcome) in the first 24 hours after admission.

Conclusions

The protective effect of steroids in severe COVID-19 seen in our cohort is similar to that seen in clinical trials, confirming the real-world effectiveness in clinical practice. Our results suggest longer courses of steroids may be associated with lower risk of death or ICU admission. Further work, probably clinical trials are required to formally assess the optimum duration of steroids, the population most likely to benefit and to measure adverse events associated with longer courses.

Abbreviations

ICU
Intensive Care Unit
COVID-19
Coronavirus Disease 2019
GSTT
Guy’s and St Thomas’ NHS Foundation Trust
EHR
Electronic Health Record
IMD
Index of Multiple Deprivation
SD
Standard Deviation
IQR
Interquartile Range
BMI
Body Mass Index
HIV
Human Immunodeficiency Virus
HR
Hazard Ratio

Declarations

Ethics approval and consent to participate

Ethical approval for data informatics was granted by The London Bromley Research Ethics Committee (reference (20/HRA/1871)) to the King's Health Partners Data Analytics and Modelling COVID-19 Group to collect clinically relevant data points from patient's electronic health records.

Whole genome sequencing of residual viral isolates was conducted under the COVID-19 Genomics UK (COG-UK) consortium study protocol, which was approved by the Public Health England Research Ethics and Governance Group (reference: R&D NR0195).

Patient consent was not required as approved by The London Bromley Research Ethics Committee (reference (20/HRA/1871))

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from Guy's and St Thomas' NHS Foundation Trust (GSTT) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of GSTT.

Competing interests

None

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Author’s contributions

WW and LBS contributed to conceptualisation, data curation, methodology, formal analysis, and writing – original draft and editing. DF performed data curation and visualisation. ALG, NMP, CH and SDW provided data interpretation and review&editing. VC performed supervision, funding acquision, project administration, and review&editing. JDE and YW performed conceptualisation, supervision, funding acquision, methodology, project administration, data interpretation, and review&editing. All authors have read and approved the manuscript.

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References

1. Sahin AR, Erdogan A, Agaoglu PM, et al. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. Eurasian J Med Oncol. 2020;4(1):1–7. doi:10.14744/ejmo.2020.12220.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533–4. doi:10.1016/S1473-3099(20)30120-1.
3. Dexamethasone in Hospitalized Patients with Covid. -19 — Preliminary Report. N Engl J Med Published online July. 2020;17:NEJMoa2021436. doi:10.1056/NEJMoa2021436.
4. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Lond Engl. 2021;397(10285):1637–45. doi:10.1016/S0140-6736(21)00676-0.
5. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330–41. doi:10.1001/jama.2020.17023.
6. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020;24(1):696. doi:10.1186/s13054-020-03400-9.
7. Sahilu T, Sheleme T, Melaku T. Severity and Mortality Associated with Steroid Use among Patients with COVID-19: A Systematic Review and Meta-Analysis. Interdiscip Perspect Infect Dis. 2021;2021:6650469. doi:10.1155/2021/6650469.
8. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020;81(1):e13–20. doi:10.1016/j.jinf.2020.03.062.
9. Corticosteroids for COVID-19. Accessed August 17. 2021. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Corticosteroids-2020.1.
10. Noreen S, Maqbool I, Madni A. Dexamethasone. Therapeutic potential, risks, and future projection during COVID-19 pandemic. Eur J Pharmacol. 2021;894:173854. doi:10.1016/j.ejphar.2021.173854.
11. Berton AM, Prencipe N, Giordano R, Ghigo E, Grottoli S. Systemic steroids in patients with COVID-19: pros and contras, an endocrinological point of view. J Endocrinol Invest. 2021;44(4):873–5. doi:10.1007/s40618-020-01325-2.
12. Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. Lancet Respir Med. 2021;9(1):e8. doi:10.1016/S2213-2600(20)30530-0.
13. Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. Crit Care Explor. 2020;2(4):e0111. doi:10.1097/CCE.0000000000000111.
14. Quick J. nCoV-2019 sequencing protocol. Published online January 22, 2020. doi:10.17504/protocols.io.bbmuik6w.

15. Artic Network. Accessed August 17. 2021. https://artic.network/ncov-2019/ncov2019-bioinformatics-sop.html.
16. Pangolin CoV-lineages. 2021. Accessed August 17, 2021. https://github.com/cov-lineages/pangolin.
17. Figliozzi S, Masci PG, Ahmadi N, et al. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. Eur J Clin Invest. 2020;50(10):e13362. doi:10.1111/eci.13362.
18. Acknowledging - Rosalind Research Computing Infrastructure. Accessed August 17. 2021. https://rosalind.kcl.ac.uk/acknowledging/.
19. Yu WC, Hui DSC, Chan-Yeung M. Antiviral agents and corticosteroids in the treatment of severe acute respiratory syndrome (SARS). Thorax. 2004;59(8):643–5. doi:10.1136/thx.2003.017665.
20. Fernandes M, Brábek J. COVID-19, corticosteroids and public health: a reappraisal. Public Health. 2021;197:48–55. doi:10.1016/j.puhe.2021.05.028.
21. Snell LB, Irwin J, Buckingham C, et al. *Increasing Rates of Intensive Care Unit Bloodstream Infections During the Second COVID-19 Pandemic Wave, Particularly Primary Endogenous* Enterococcus Faecium, *with High Crude Mortality and Associated with Introduction of Immunomodulatory Therapy*. Social Science Research Network; 2021. doi:10.2139/ssrn.3895049.
22. Patone M, Thomas K, Hatch R, et al. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. Lancet Infect Dis Published online June 23, 2021. doi:10.1016/S1473-3099(21)00318-2.
23. Patone M, Thomas K, Hatch R, et al. *Analysis of Severe Outcomes Associated with the SARS-CoV-2 Variant of Concern 202012/01 in England Using ICNARC Case Mix Programme and QResearch Databases*.; 2021:
2021.03.11.21253364
. doi:10.1101/2021.03.11.21253364.
24. Davies NG, Jarvis CI, Edmunds WJ, Jewell NP, Diaz-Ordaz K, Keogh RH. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021;593(7858):270–4. doi:10.1038/s41586-021-03426-1.
25. Snell LB, Wang W, Alcolea-Medina A, et al. *First and Second SARS-CoV-2 Waves in Inner London: A Comparison of Admission Characteristics and the Impact of the B.1.1.7 Variant*.; 2021:
2021.03.16.21253377
. doi:10.1101/2021.03.16.21253377.
26. Frampton D, Rampling T, Cross A, et al. Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study. Lancet Infect Dis Published online April 12, 2021. doi:10.1016/S1473-3099(21)00170-5.

Figures

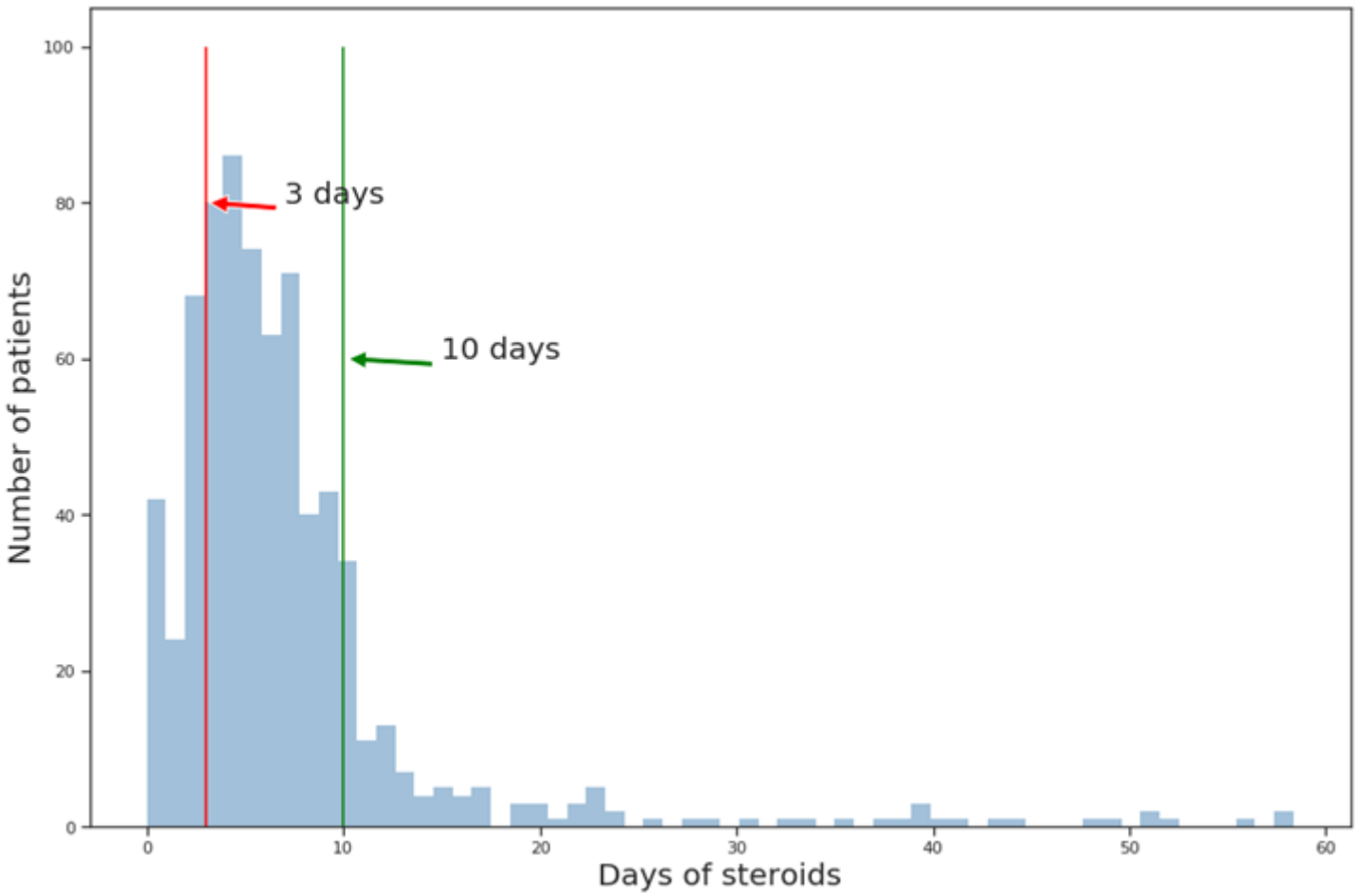

Figure 1

Frequency of steroid treatment-days for patients. Note: Steroid treatment days are recorded for the whole hospital stay and truncated at 60 days. Only 4 patients had treatment for >60 days during their admission

Supplementary Files

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- SupplementaryMaterial.pdf