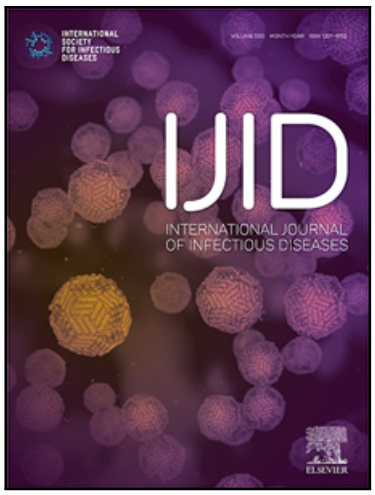
Cycle threshold values are inversely associated with poorer outcomes in hospitalised patients with Covid-19



Cycle threshold values are inversely associated with poorer outcomes in hospitalised patients with Covid-19: a prospective, observational cohort study conducted at a UK tertiary hospital.

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Title:

Cycle threshold values are inversely associated with poorer outcomes in hospitalised patients with Covid-19: a prospective, observational cohort study conducted at a UK tertiary hospital.

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Covid-19, Respiratory Infection, Viral Infection

Highlights

- Multivariable regression analysis of data for hospitalised COVID-19 patients.
- We studied the likelihood of death and admission Ct values.
- Known clinical risk factors for the disease were adjusted for.
- Lower Ct values were associated with poorer outcomes in hospitalised patients.

Unstructured abstract:

In this single centre observational study, we demonstrated that lower cycle threshold (Ct) values (indicating higher viral loads) on admission to hospital, were associated with poorer outcomes in unvaccinated, hospitalised patients with Covid-19. We prospectively collected demographic and outcome data on all adult patients who tested positively for SARS-CoV-2 on admission to the University Hospitals North Midlands (UHNM) NHS Trust between 1st February and 1st July 2020. Nasopharyngeal swab samples were obtained, and a valid Ct value determined for all patients using the Public Health England (PHE) validated Viasure© reverse transcription PCR assay on admission to hospital. Multivariable logistic regression results based on data from 618 individuals demonstrated a statistically significant inverse relationship between the odds of death and Ct values (adjusted odds ratio (aOR) 0.95, 95% CI 0.92 to 0.98, p-value 0.001). The association remained highly statistically significant after adjusting for known clinical risk factors for the disease.

Word count:

852 words (excluding title, abstract, table/figures and references).

Clinicians need to identify patients with a higher risk of poor outcome and mortality from Covid-19 at an early stage of hospital admission. We describe a prospective, observational cohort study conducted at a UK tertiary care hospital to determine the relationship between the likelihood of death and Ct values in an unvaccinated UK population with Covid-19 on admission to hospital. Statistical adjustment was made for other known risk factors associated with poor outcome. Cycle thresholds (Ct) are semi-quantitative values, which are inversely proportional to the viral load in a revere transcription polymerase chain reaction (PCR) test for SARS-CoV-2.

We prospectively collected demographic and outcome data on all adult patients who tested positively for SARS-CoV-2 on admission to the University Hospitals North Midlands (UHNM) NHS Trust between 1st February and 1st July 2020 using the ISARIC WHO Clinical Characterisation Protocol (Docherty et al., 2020). Nasopharyngeal swab samples were obtained, and a valid Ct value determined for all patients using the Public Health England (PHE) validated Viasure© reverse transcription PCR assay on admission to hospital. Ct

values below 38 were considered positive. Viasure© targets the *ORF1ab* (Target 1) and *N* genes (Target 2) of the SARS-CoV-2 viral genome (Public Health England, 2020). Target 1 was chosen as the primary exposure of interest as this is specific to SARS-CoV-2 viral genome. We combined Ct values with ISARIC data for statistical analysis.

Multivariable logistic regression was used to determine the association between Ct value and death within 28 days of a positive SARS-CoV-2 PCR test. We adjusted for age, gender, ethnicity, obesity and the presence of cardiovascular disease, chronic pulmonary disease, chronic kidney disease and diabetes. These covariates were selected apriori based on current understanding of the factors predicting poor outcomes in hospital cases of Covid-19 (Knight et al., 2020). Statistical significance was assessed at the 5% significance level and results presented as odds ratios and 95% confidence intervals. Analyses were conducted in R version 4.0.1.

A total of 803 SARS-CoV-2 positive adults (>18 years if age) with a valid Ct value determined on admission to hospital were eligible for inclusion in this study and were followed up for a period of up to 28 days [Figure 1]. The median age was 77 years (age range 19 to 100), 55% were male and 91% were of a white ethnicity. 35% had a history of cardiovascular disease, 18% chronic pulmonary disease, 19% had chronic kidney disease, 14% were asthmatic, 13% had either complicated and uncomplicated diabetes, and 7% were obese. The median cycle threshold value for target 1 was 25.8 (interquartile range 21.3 to 30.0). 285/803 patients (35.5%) died within 28 days of a positive SARS-CoV-2 PCR result.

Multivariable logistic regression results based on data from 618 (77.0%) individuals with complete covariate information are presented in Table 1. There was a statistically significant inverse relationship between the probability of death and Ct values (adjusted odds ratio [aOR 0.95(95% CI 0.92 to 0.98), p-value 0.001). The only other variables that were significantly associated with mortality were age [aOR 1.05 (95% CI: 1.03 to 1.06), p-value <0.001] and diabetes [aOR 1.73 (95%CI: 1.01 to 2.97), p-value 0.044]

Sensitivity analyses carried after imputing missing data produced results consistent with the complete case analysis for both outcomes. Similar results were obtained when target 2 was used in the analysis instead of target 1 (these data are available on request).

In this prospective, observational study carried out a tertiary UK hospital, lower Ct values (indicating higher viral loads) were associated with poorer outcomes in hospitalised patients with SARS-CoV-2 infection. This association remains highly statistically significant after adjusting for known clinical risk factors for the disease. High viral loads are associated with adverse outcomes in HIV and Ebola infections (Fitzpatrick et al., 2015; Li et al., 2015). There have been reports that higher viral loads are associated with adverse outcomes in Covid-19 patients in China, Taiwan and Brazil (Choudhuri et al., 2020; Faíco-Filho et al., 2020; Huang et al., 2020; Liu et al., 2020; Yu et al., 2020) but none from the UK.

The main strength of this study is that it uses a validated, generalisable dataset for analysis. Ct values were measured by validated methods. Robust statistical methods were used to account for interactions and missing data. Our study had several limitations. It was limited by its relatively small size. We therefore restricted our analysis to eight covariates known to be associated with poorer outcomes. Whilst this reduces the risk of confounding due to multiple

prospective, observational cohort study conducted at a UK tertiary hospital.

hypothesis testing it did not allow exploration of the data to determine whether other measurements, such as admission cardiovascular status, oxygen saturation and liver failure or need for mechanical ventilation were associated with death. However, a logistic regression model incorporating all of these did not show any statistically significant associations. Moreover, the data is limited to a single tertiary care centre in the UK and the population characteristics may vary in relation to other areas. It is also unclear if these associations will remain significant after accounting for therapeutic agents (e.g., dexamethasone, anti-IL-6 treatment) in Covid-19 management. Our findings suggest that Ct values may have the potential to help clinicians identify patients at high risk of mortality from COVID-19 at the point of admission to hospital. We suggest that the analysis be repeated using a larger, multicentre dataset across different time periods.

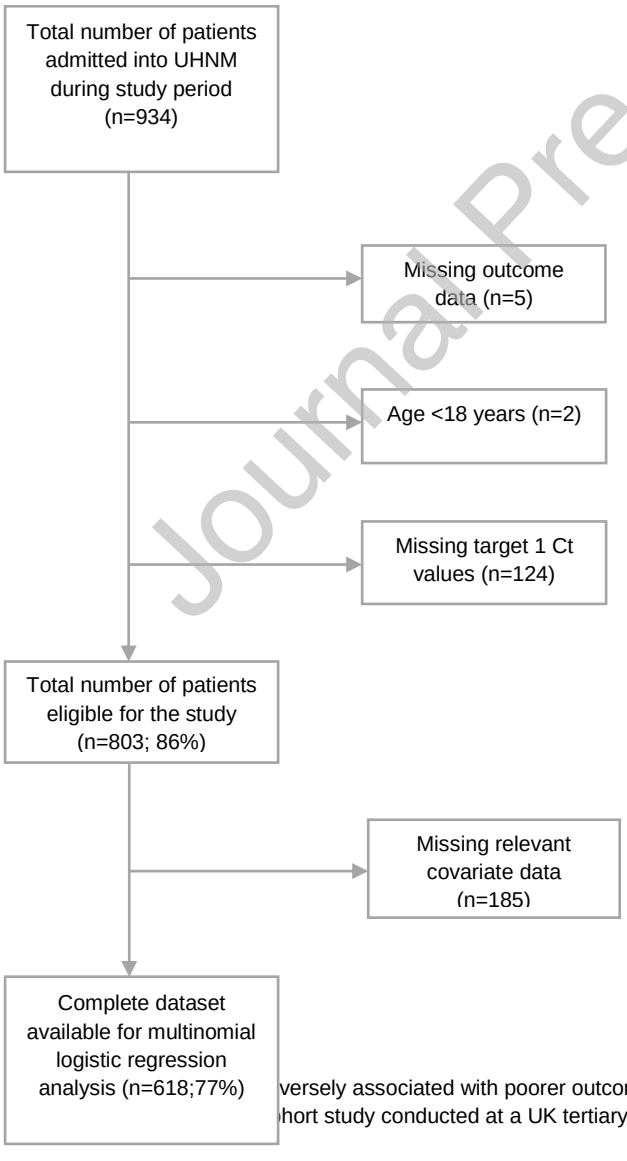

Figure 1: A flow diagram illustrating how the final study sample size was determined.

	Death		Death or continuous hospitalisation	
Variable	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age (years)	1.05 (1.03, 1.06)	<0.001	1.04 (1.02, 1.05)	<0.001
Male	1.43 (1.00, 2.07)	0.052	1.2 (0.85, 1.69)	0.308
Non-White	0.66 (0.15, 2.21)	0.539	0.77 (0.23, 2.27)	0.65
Cardiovascular disease	1.00 (0.68, 1.47)	0.992	0.95 (0.65, 1.39)	0.799

Chronic pulmonary disease	1.17 (0.75, 1.82)	0.475	1.17 (0.76, 1.82)	0.469
Chronic kidney disease	1.22 (0.78, 1.91)	0.382	1.51 (0.97, 2.36)	0.071
Diabetes	1.68 (1.03, 2.75)	0.037	1.35 (0.83, 2.22)	0.227
Obesity	1.33 (0.68, 2.53)	0.39	1.1 (0.59, 2.05)	0.764
Cycle threshold	0.95 (0.92, 0.98)	0.001	0.94 (0.91, 0.97)	<0.001
Constant	0.01 (0.00, 0.04)	<0.001	0.05 (0.02, 0.12)	<0.001

Table 1: Multivariable logistic regression results based on complete case analysis

Contributor statement:

TK and JW conceived this study and analysis. MGS, JKB and ISARIC4C investigators [https://isaric4c.net/about/authors/] conceived the ISARIC WHO CCP-UK study. TK, JW, LD, AA, WC and CT contributed to the study design. TK and JW obtained ethical approval for this study and analysis. AA, JW and ISARIC4C investigators collected data for the study. FA conducted the primary statistical analysis. All authors contributed to writing and editing the final manuscript.

HRA Ethical Approval:

Health Research Authority (HRA) approval for this study and analysis was issued by the London - Chelsea Research Ethics Committee (REC reference: 20/HRA/3967) on 10th November 2020. Ethical approval for data collection by ISARIC4C in England was given by the South Central-Oxford C Research Ethics Committee in England (reference 13/SC/0149). The ISARIC WHO CCP-UK study was registered at https://www.isrctn.com/ISRCTN66726260 and designated an Urgent Public Health Research Study by NIHR.

Sponsor Organisation:

University Hospitals of North Midlands NHS Trust

Clinicaltrials.gov Identifier:

NCT04651413

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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