BMJ Open Respiratory Research

Improved COVID-19 outcomes in a large non-invasive respiratory support cohort despite emergence of the alpha variant

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To cite: Turnbull CD, Porter BML, Evans SB, *et al*. Improved COVID-19 outcomes in a large non-invasive respiratory support cohort despite emergence of the alpha variant. *BMJ Open Resp Res* 2021;**8**:e001044. doi:10.1136/bmjresp-2021-001044

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Received 12 July 2021
Accepted 2 November 2021

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ABSTRACT

Introduction Respiratory high-dependency units (rHDUs) are used to manage respiratory failure in COVID-19 outside of the intensive care unit (ICU). The alpha variant of COVID-19 has been linked to increased rates of mortality and admission to ICU; however, its impact on a rHDU population is not known. We aimed to compare rHDU outcomes between the two main UK waves of COVID-19 infection and evaluate the impact of the alpha variant on second wave outcomes.

Methods We conducted a single-centre, retrospective analysis of all patients with a diagnosis of COVID-19 admitted to the rHDU of our teaching hospital for respiratory support during the first and second main UK waves.

Results In total, 348 patients were admitted to rHDU. In the second wave, mortality (26.7% s vs 50.7% first wave, χ^2=14.7, df=1, p=0.0001) and intubation rates in those eligible (24.3% s vs 58.8% first wave, χ^2=17.3, df=2, p=0.0002) were improved compared with the first wave. In the second wave, the alpha variant had no effect on mortality (OR 1.18, 95% CI 0.60 to 2.32, p=0.64). Continuous positive airway pressure (CPAP) (89.5%) and awake proning (85.6%) were used in most patients in the second wave.

Discussion Our single-centre experience shows that rHDU mortality and intubation rates have improved over time in spite of the emergence of the alpha variant. Our data support the use of CPAP and awake proning, although improvements in outcome are likely to be multifactorial.

Key messages

What is the key question?

- Were there differences in respiratory high-dependency unit (HDU) outcomes for patients with COVID-19 and respiratory failure between the two main UK waves and what was the effect of the alpha variant on second wave outcomes?

What is the bottom line?

- Our single-centre respiratory HDU experience shows that mortality and intubation rates have improved over time in spite of the emergence of the alpha variant, with most patients using continuous positive airway pressure and awake proning in the second wave.

Why read on?

- Respiratory HDU management is widely used and we report a large UK respiratory HDU cohort investigating outcomes in the first and second main UK COVID-19 waves.

INTRODUCTION

Respiratory high-dependency units (rHDUs) can feasibly manage respiratory failure in COVID-19, outside of the intensive care unit (ICU) for patients not requiring intubation.[1] We have reported our early experience of rHDU management including continuous positive airway pressure (CPAP) and awake proning during the first UK COVID-19 wave.[2] However, the impact of new treatments adopted as usual care[3] and the emergence of the alpha severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant in the second wave on rHDU outcomes have not yet been established.

METHODS

We conducted a single-centre, retrospective analysis of all patients with a diagnosis of COVID-19 admitted to the rHDU of our teaching hospital for respiratory support, aiming to (1) compare our clinical practice and rHDU outcomes between the first two main UK waves of COVID-19 infection and (2) identify factors that influence outcomes in the second wave.

Data analyses

Statistical analyses were performed using SPSS V26.0. Summary statistics were used to define the population. First and second wave characteristics and outcomes were compared using independent sample t-tests and χ^2 as appropriate. Oxygenation before and after awake proning was compared using paired t-tests, including in those who attempted awake proning after CPAP was established. Logistic regression analysis was used to evaluate factors associated with risk mortality and intubation in the second, and where significant these were adjusted for for age, frailty and symptom duration.

Patient and public involvement

Given the severe nature of the disease, the rapidity of the set-up of the respiratory HDU and the high mortality rate, patient and public involvement was not deemed suitable for the design, conduct and reporting of this retrospective study.

RESULTS

In total, 348 patients were admitted to rHDU; 71 (20.4%) during the first wave from 23 March to 4 June 2020, and 277 (79.6%) in the second wave between 10 October 2020 until 31 January 2021 when our evaluation ended. rHDU admissions accounted for similar proportions of total hospital admissions in the first (77 of 565 (12.6%)) and second waves (277 of 2028 (13.7%)).

Patient characteristics are shown in table 1. In the second wave, rHDU patients were less frail and a greater proportion were deemed candidates for potential intubation. Treatments with dexamethasone and remdesivir were more common. A greater patient proportion were managed with awake proning combined with CPAP, which was used for a longer duration, compared with the first wave.

Physiological effects of CPAP and awake proning

The oxyhaemoglobin saturation (SaO_2) to inspired oxygen fraction (FiO_2) ratio was used as a marker of lung injury severity. Where oxygen delivery was uncontrolled, the FiO_2 was estimated (0.2+0.04 × flow (L/min)). Physiotherapy, comprising both CPAP optimisation and semi or full-prone positioning, significantly improved the SaO_2:FiO_2 by +54.0 (95% CI +46.7 to+61.4, p<0.0001, n=229), indicating improved lung injury severity. In a subgroup of 15 patients already established on CPAP, additional semi-prone or full-prone positioning significantly improved the SaO_2:FiO_2 by +60.3 (95% CI +37.1 to +83.5, p≤0.0001), suggesting the effects of CPAP and proning are additive.

First and second wave outcomes

Table 2 shows patient outcomes. Overall rHDU mortality was lower in the second wave. While there was a greater proportion of patients who were not eligible for intubation in the first wave, mortality was still lower in the second wave in those not eligible for intubation. In patients eligible for intubation, mortality was comparable, but intubation rates were significantly lower in the second wave. Having identified these differences, factors associated with risk of death or intubation in the second wave were explored.

Factors affecting outcome in the second wave

Where available, the impact of the alpha variant on outcome was evaluated. There was no significant effect of the alpha variant on the unadjusted overall odds of mortality or odds of intubation among patients eligible for intubation; 45 (31.5%) patients with the alpha variant versus 16 (28.1%) with wild-type died (OR 1.18, 95% CI 0.60 to 2.32, p=0.64); 31 (29.8%) alpha variant versus 12 (28.6%) wild-type were intubated (OR 1.06, 95% CI 0.48 to 2.34, p=0.88).

To investigate the impact of CPAP prior to intubation, the effect of CPAP duration on mortality was explored in the subgroup eligible for intubation. Median CPAP duration prior to intubation was 4 days. Unadjusted odds of mortality were significantly increased in those intubated after 3 days of respiratory support (18 died (62.1%)), compared with those intubated within 3 days (six died (27.3%); OR 4.38, 95% CI 1.21 to 15.81, p=0.02), and this remained significant following adjustments for age, frailty and symptom duration (OR 4.36, 95% CI 1.17 to 16.26, p=0.03).

DISCUSSION

Our single-centre experience shows that mortality and intubation rates on rHDU have improved over time. Our cohort is novel in reporting rHDU outcomes following the routine use of medical therapies and following the emergence of the alpha variant, which were not present in previous reports.[1 4 5] Our results are comparable with the preliminary findings of a recent adaptive randomised controlled trial, which showed that CPAP reduced a combined outcome of intubation and mortality in comparison with standard oxygen therapy.[6]

Improvements in outcome are likely to be multifactorial. Patients were less frail and had milder serological and radiological evidence of COVID-19 severity in the second wave. However, selection differences are unlikely as a similar proportion of patients received rHDU care in the first and second waves. Pharmacological treatments of proven benefit were routinely available in the second but not the first wave.[3] CPAP and awake proning were more commonly used in the second wave which might have improved outcomes,[4] and we found a significant effect of combining CPAP with awake proning on reducing hypoxaemia.

Patients with the alpha variant of COVID-19 did not have worse outcomes in rHDU. This contrasts with community-based patients where the alpha variant increased mortality.[7] However, our findings are consistent

Table 1 Comparison of first and second wave characteristics and treatment data

	First wave	Second wave	Mean difference (95% CI)	X^2 (df)	P value
Baseline characteristics					
Age (years)	69.0 (52.0–80.0)	62.0 (52.0–71.0)	−3.4 (−7.8 to +1.1)	–	0.14
Sex ▶ Male ▶ Female	49 (69.0%) 22 (31.0%)	180 (65.0%) 97 (35.0%)	–	0.4 (1)	0.52
Ethnicity ▶ Asian ▶ Black ▶ White ▶ Other/unknown	7 (9.9%) 5 (7.0%) 59 (83.1%) 0 (0.0%)	27 (9.7%) 7 (2.5%) 165 (59.6%) 78 (28.2%)	–	28.2 (3)	<0.0001
BMI (kg/m^2)*	28.5 (24.9–33.6)	29.6 (24.8–34.9)	+0.6 (−1.7 to +2.9)	–	0.63
Comorbidities, frailty and level of care					
Hypertension	31 (43.7%)	125 (45.1%)	–	0.05 (1)	0.83
Diabetes mellitus	21 (29.6%)	81 (29.2%)	–	0.003 (1)	0.96
Cardiovascular disease	13 (18.3%)	77 (27.8%)	–	2.7 (1)	0.10
Asthma	8 (11.3%)	49 (17.7%)	–	1.7 (1)	0.19
COPD	10 (14.1%)	25 (9.0%)	–	1.6 (1)	0.21
No of comorbidities: ▶ None ▶ 1 ▶ 2 ▶ 3 ▶ 4 or more	15 (21.1%) 14 (19.7%) 14 (19.7%) 13 (18.3%) 15 (21.1%)	56 (20.2%) 71 (25.6%) 48 (17.3%) 49 (17.7%) 53 (19.1%)	–	1.1 (1)	0.89
Clinical Frailty Score: ▶ 1 to 2 (fit) ▶ 3 (managing well) ▶ 4 (very mild frailty) ▶ 5 (mild frailty) ▶ 6 (moderate frailty) ▶ 7+ (severe frailty)	18 (25.4%) 23 (32.4%) 13 (18.3%) 6 (8.5%) 7 (9.9%) 4 (5.6%)	132 (47.7%) 71 (25.6%) 30 (10.8%) 23 (8.3%) 9 (3.2%) 12 (4.3%)	–	15.6 (5)	0.008
Not eligible for intubation	37 (52.1%)	67 (24.2%)	–	21.0 (1)	<0.0001
Symptoms and severity markers					
Symptom duration	8 (5–11)	8 (6–11)	+0.2 (−1.0 to +1.3)	–	0.76
≥60% oxygen on HDU admission	52 (73.2%)	214 (77.3%)	–	0.51 (1)	0.48
CTPA performed	35 (49.3%)	251 (90.6%)	–	65.9 (1)	<0.0001

Continued

Table 1 Continued

	First wave	Second wave	Mean difference (95% CI)	X^2 (df)	P value
CT severity score	0 (0%)	5 (2.0%)	–	16.0 (3)	0.0012
▶ Mild	11 (29.7%)	131 (52.2%)			
▶ Moderate/severe	23 (62.2%)	113 (45.0%)			
▶ Severe	3 (8.1%)	2 (0.8%)			
▶ Atypical					
Pulmonary embolism present	10 (14.1%)	22 (7.9%)	–	12.1 (1)	0.0005
Lymphocytes on rHDU admission ($\times 10^9$/L)	0.8 (0.5–1.1)	0.8 (0.5–1.1)	–0.4 (–1.4 to +0.5)	–	0.35
CRP prior to rHDU admission (mg/L)	180.6 (118.0–210.0)	124.1 (78.1–175.6)	–44.1 (–66.9 to –21.3)	–	0.0002
D-dimer prior to rHDU admission (µg/L)	1252 (767–2528)	892 (603–1466)	–644 (–3530 to +2242)	–	0.66
Nasal pharyngeal PCR swab results					
Result	56 (78.9%)	274 (98.9%)	–	46.3 (1)	<0.0001
▶ Positive	15 (21.1%)	3 (1.1%)			
▶ Negative (clinical diagnosis)					
Spike gene testing†		143 (67.1%)	–	–	–
▶ Alpha variant	-	57 (26.8%)			
▶ Wild-type	-	13 (6.1%)			
▶ Ambiguous	-				
Treatments					
Dexamethasone	3 (4.2%)	266 (96.0%)	–	271.4 (1)	<0.0001
Remdesivir	4 (5.6%)	198 (71.5%)	–	100.6 (1)	<0.0001
Respiratory support duration	2 (1–4)	5 (3–8)	3.0 (1.8 to 4.2)	–	<0.0001
CPAP as primary respiratory support	32 (45.1%)	248 (89.5%)	–	71.1 (1)	<0.0001
Able to adopt semi-prone or full-prone position	42 (59.2%)	237 (85.6%)	–	24.8 (1)	<0.0001

Continuous variables are expressed as median (first quartile, third quartile) or mean±SD and categorical variables are expressed as number (percentage). Differences between the first and second waves were compared via t-tests for continuous variables and χ^2 tests for categorical variables.
*Missing for 11 (15.5%) patients in the first wave and 58 (20.9%) patients in the second wave.
†From December 2020, routine nasal pharyngeal swabs, tested by PCR, reported the presence or absence of the spike gene (S-gene), following the emergence of the alpha variant in the UK, suggested by absence of the spike gene.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, c reactive protein; CT, computed tomography; CTPA, CT pulmonary angiogram; HDU, high-dependency unit; PCR, polymerase chain reaction; rHDU, respiratory high-dependency unit.

Table 2 Outcome data compared by wave by ceiling of care

	Total	First wave	Second wave	X^2 (df)	P value
Overall (n=348)					
Admission outcome*	110 (31.6%)	36 (50.7%)	74 (26.7%)	14.7 (1)	0.0001
▶ Died	236 (67.8%)	35 (49.3%)	201 (72.5%)		
▶ Discharged					
Patients eligible for intubation (n=244)					
Admission outcome*	36 (14.8%)	5 (14.7%)	31 (14.8%)	0.001 (1)	0.97
▶ Died	206 (84.4%)	29 (85.3%)	177 (84.3%)		
▶ Discharged					
Respiratory HDU outcome	7 (2.9%)	0 (0.0%)	7 (3.3%)	17.3 (2)	0.0002
▶ Died	166 (68.0%)	14 (41.2%)	152 (72.4%)		
▶ Off respiratory support	71 (29.1%)	20 (58.8%)	51 (24.3%)		
▶ Intubated					
ICU outcome (*n*=71)*	29 (40.8%)	5 (25.0%)	24 (47.1%)	3.35 (1)	0.067
▶ Died	40 (56.3%)	15 (75.0%)	25 (49.0%)		
▶ Off respiratory support					
Patients not eligible for intubation (n=104)					
Respiratory HDU outcome	74 (71.2%)	31 (83.8%)	43 (64.2%)	4.5 (1)	0.035
▶ Died	30 (28.8%)	6 (16.2%)	24 (35.8%)		
▶ Discharged					

*Two second wave patients who were intubated were receiving ongoing hospital care at time of censor.
HDU, high-dependency unit; ICU, intensive care unit.

with an ICU population which showed no increase in ICU mortality even though alpha variant infection doubled the risk of ICU admission.[8]

Intubated patients had higher mortality in the second wave. However, a smaller proportion of eligible patients were intubated in the second wave. We found an increased risk of death in those intubated after 3 days of CPAP therapy in the second wave, similar to other reports suggesting that prolonged CPAP and delaying intubation may be harmful.[9] However, these data do not demonstrate causality. In the second wave, only 24.3% of patients deemed eligible were intubated. CPAP was used for a median duration 5 days in eligible patients who were not intubated, and longer durations of CPAP therapy lead to favourable outcomes in most patients.

Intolerance of CPAP is a common reason for early intubation, and late CPAP failure may reflect disease severity rather than tolerance, as is the case in other diseases.[10 11] Therefore, it is possible that those requiring early intubation simply represent a group who do not tolerate CPAP, and those who go on to require intubation later have more severe disease.

There are limitations to our data. This was a moderate size single-centre study with evolving management of patients due to evidence-based changes in standard care, meaning that our data are not definitive. Nevertheless, we have shown improved rHDU outcomes over time and have not found worse outcomes in those with the alpha variant. Our data highlight uncertainties in the rHDU management in need of focused clinical trials, particularly in those intubated following longer durations of CPAP therapy.

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Contributors The study was conceived by CDT, BMLP, SBE, RH, NPT, MB, NMR and NP. PJDE, CDT, MB, NP and NMR. Clinical care of the patients was conducted by all authors. Data collection was conducted by BMLP, PJDE, SBE, RL and OS. Data and statistical analysis was conducted by CDT. CDT and BMLP performed the literature search, and initial manuscript preparation. All authors reviewed and approved the final manuscript. CDT acts as guarantor for the manuscript accepting full responsibility for the work and the conduct of the evaluation, had access to the data, and controlled the decision to publish.

Funding This paper was not directly funded by any grant or funding body. RJH and CDT are Academic Clinical Lecturers in Respiratory Medicine funded by the National Institute for Health Research (NIHR). NMR, IDP and NP are funded by the NIHR Oxford Biomedical Research Centre.

Competing interests CDT reports personal fees from Bayer, outside the submitted work. NMR reports personal fees from LungTherapeutics and grants from BD, outside the submitted work. There are no other relevant competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was discussed and approved by the local lead for ethics, and considered to be an audit of clinical practice.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data can be made available on request at the discretion of the corresponding and senior authors.

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