The role of Continuous Positive Airway Pressure (CPAP) in Delaying or Avoiding Mechanical Ventilation in COVID-19 Respiratory Failure: A Retrospective Cohort Study

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Abstract

Background - During the winter of 2020-2021, the second wave of the COVID19 pandemic in the United Kingdom caused increased demand for intensive care unit (ICU) beds, and in particular, for invasive mechanical ventilation (IMV). To alleviate some of this pressure, some centres offered non-invasive continuous positive airway pressure (CPAP), delivered on specialised COVID high dependency units (cHDUs). However, this practice was based largely on anecdotal reports, and it is not clear from the literature how effective CPAP is at delaying or preventing IMV.

Methods - This was a retrospective observational cohort study of consecutive patients admitted to a specialised cHDU at Glasgow Royal Infirmary between November 2020 and February 2021. Each patient had a continuous record of the level of respiratory support required, and was followed up to hospital discharge or death. We examined patient outcomes according to age, sex and maximum level of respiratory support, using logistic regression and time-to-event analysis. The number of patients who could not be oxygenated by standard oxygen facemask but could be oxygenated by CPAP was counted and compared to the number of patients admitted to ICU for IMV over the same period.

Results - There were 152 admissions to cHDU over the study period. Of these, 125 received CPAP treatment. Of the patients who received support in cHDU, the overall mortality rate was 37.9% (95% CI 30.3% - 46.1%). Odds of mortality were closely correlated with increasing age and oxygen requirement. Of the 152 patients, 44 patients (28.8%, 95% CI 22.0 – 36.9%) went on to require IMV in ICU. This represents 77.2% of the 57 COVID-19 admissions to ICU during the same period. However, there were also 41 patients who received levels of respiratory support on cHDU which would normally necessitate ICU admission but who never went to ICU, potentially reducing ICU admissions by 41.8% (95% CI 32.1 – 52.2%).

Conclusion - Providing respiratory support in cHDU reduced the number of potential ICU admissions by 41.8%, as well as delaying IMV for over 75% of ICU admissions. This represents a significant sparing of ICU capacity at a time when IMV beds were in high demand.

Introduction

The SARS-Cov-2 pandemic has caused significant morbidity and mortality worldwide, being responsible for more than 3 million deaths globally as of May 2021 ^[1]. Despite the recent development of therapies shown to reduce mortality and the rollout of vaccination programmes against COVID-19, global case numbers, hospitalisations and deaths remain high ^[1-3].

The large number of patients with COVID-19 has put pressure on many health services, and in particular a high demand for critical care beds; at the peak of the second COVID-19 wave in the UK in January 2021, there were over 4,000 patients on invasive mechanical ventilation (IMV) for COVID-19 across the country ^[4].

Beginning in March 2020, some National Health Service (NHS) resources were diverted to help support intensive care units (ICUs) in preparation for the anticipated demand. In several centres, this included the development of respiratory support units (RSUs) and COVID-19 high dependency units (cHDUs), as areas where patients could receive non-invasive respiratory support such as continuous positive airway pressure (CPAP) and high flow nasal oxygen (HFNO). Both of these modalities are considered aerosol-generating procedures (AGPs), and hence must be provided in specific facilities with stringent infection control procedures and specialized staff. CPAP and HFNO are used for a variety of reasons in COVID-19, but one rationale is to reduce the number of patients requiring IMV at any one time ^[5–7].

CPAP has been used previously in pneumonitis caused by other coronaviruses, playing a role in the treatment of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) ^[8, 9]. Its utilization in COVID-19 was also described in hospitals in China and Italy at the start of the pandemic ^[10]. This led the British Thoracic Society to recommend CPAP as first-line respiratory support in patients with COVID-19 pneumonitis who fail to oxygenate adequately on standard oxygen therapy ^[11].

CPAP typically uses less oxygen than high-flow nasal oxygen therapy, and thus places less of a burden on a hospital's oxygen supply when the hospital has a high COVID-19 workload. Due to it being a non-invasive modality, CPAP has the potential to act as both a bridge to delay or avoid IMV, and as a ceiling of care for those unsuitable for IMV.

To our knowledge, the extent to which a dedicated CPAP unit can relieve the demand for ICU beds has not been well described in the literature.

Objectives

The aim of this study is to describe the outcomes of a cohort of patients with COVID-19 pneumonitis treated in a dedicated COVID-19 high dependency unit. In particular, we examine whether use of CPAP or HFNO therapy could delay or avoid IMV.

Methods

Study Design

This was a retrospective cohort study of consecutive patients admitted to the cHCU at Glasgow Royal Infirmary over a three-month period coinciding with the second wave of Coronavirus in the UK between November 2020 and February 2021.

Setting

The Glasgow Royal infirmary (GRI) is a large 950-bedded city teaching hospital serving a population of around 320,000 people. The city as a whole had a high prevalence of COVID-19 during the study period with a peak 7-day rate of cases per 100,000 population of 402 at the beginning of January 2021 ^[12].

During the first wave of the pandemic in March 2020, a 14-bedded COVID-19 high dependency unit (cHDU) was established at GRI. By the time this was reestablished for the second wave of COVID-19 in Autumn 2020, staff had already developed considerable experience in managing COVID-19 with CPAP and HFNO, and there were agreed referral and treatment pathways already in place. Dexamethasone had been introduced as an evidence-based treatment, and there was emerging evidence for the use of other therapeutics such as Remdesevir and Tocilizumab.

The unit’s facilities included a 2:1 patient-to-nurse ratio; the ability to provide continuous invasive monitoring when indicated; 24-hour senior-level medical presence, and appropriate physical barriers around the ward so that aerosol generating procedures (AGPs) could take place in a sealed environment. Staff wore full personal protective equipment including FFP3 respirator masks to minimise exposure.

CPAP was provided via face mask using ResMed Stellar™ machines with supplemental oxygen administered via a wall-mounted flow valve capable of 30L/min delivery. We used a standard PEEP of 10 cmH₂O for all patients on CPAP, and all patients treated with CPAP were given 5mg midazolam and 5mg morphine over 24 hours by subcutaneous infusion to improve mask tolerance unless specifically contra-indicated.

In-house testing of the FiO₂ achieved at various oxygen flow rates was undertaken by our Respiratory Physiology Colleagues, this is summarised in Table 1.

Table 1
Measured FiO₂
achieved with various
oxygen flow rates on
CPAP device

Oxygen	FiO ₂ .
10 l/min	40–45%
15 l/min	50%
20 l/min	60–70%
25 l/min	80%
30 l/min	75–90%

NHFO was provided by the Fisher and Paykel AIRVO 2™, which on maximum settings provided 60 L/min of warmed, humidified gas with an FiO₂ of 95%.

Oxygenation was assessed by pulse oximetry, and the oxygenation target was 90–94% unless the patient was known to have chronic hypoxia from a pre-existing condition, in which case the target was 88–92%.

Patients

We examined records for all consecutive adult patients admitted to the cHDU at Glasgow Royal Infirmary between 15th November 2020 and 14th February 2021 inclusive. Admission to the unit was the sole eligibility criterion. The start date was chosen for convenience, as this was when daily electronic recording of observations began on the unit, and the end date was chosen because the number of new admissions had fallen to low levels.

Variables

The data extracted from electronic records included each patient's age, sex and NCoV-19 PCR status. We recorded dates and times of admission to hospital, admission to cHDU, and where appropriate, admission to ICU. Each patient's date of discharge from hospital (or date of death) was also obtained. For each patient, a daily record of various parameters measured during their time in cHDU was obtained. This included respiratory rate and SpO₂, type of respiratory support, FiO₂ and PEEP.

Our main outcome variables were the binary outcomes of ICU admission and of death. The explanatory variables were type of respiratory support, amount of supplemental oxygen, and duration of respiratory support. Age and sex were considered as important confounding variables.

Data sources

Patients were identified and cross-checked using the WardWatcher and TrakCare™ patient information systems, which also provided dates and times of admissions, discharges and deaths. The patient observations and respiratory settings were extracted from the TURAS COVID-19 application, which allowed electronic recording of each patient's parameters throughout their cHDU stay. Each TURAS daily review (and initial TURAS assessment, where available) was obtained in Portable Document Format (PDF) from Orion Software's Clinical Portal™ and the relevant data extracted from the PDF file using the pdftools package in R ^[13]. Missing data was rectified by review of electronic scans of written clinical notes available as PDFs on Clinical Portal.

Bias

Since this was an observational study, there will be unmeasured confounding variables. The most important are likely to be patient-level variables such as co-morbidities and frailty, which would affect the decision to admit to ICU, and make adverse outcomes more likely. However, there may also be a time-dependent patient selection bias, as bed availability dropped during the peak of the wave in January, meaning that patients admitted during this time may well have been more unwell as the threshold for admission to cHDU increased. For the same reason, there may have been a time-dependent changing of the threshold for admission to ICU. There is no straightforward way to measure or correct for these potential biases, and they simply need to be borne in mind when interpreting the results.

Study size

Our study size was determined by the demand for and capacity of the unit during the study period. This allowed us to capture the majority of patients treated in the second wave of the coronavirus pandemic.

Quantitative variables

The daily data for each patient was summarized to give a duration of time spent on respiratory support, and a *maximum* FiO₂ or oxygen flow rate during their stay. To help give a more complete summary of the respiratory support on a per-patient basis, we also recorded the number of days spent on a high level of non-invasive respiratory support. This was defined as being on greater than 15L/min of oxygen whilst on CPAP or being on HFNO with an FiO₂ of ≥ 0.9 . These numbers were chosen because by consensus they represented levels of support beyond that which could be achieved by standard oxygen therapy.

Statistical methods

Data was manually tidied and verified before being converted to comma separated variable format and imported into R version 4.1.0 ^[14]. Simple summary statistics including means, medians, ranges and histogram plots were produced using base R functions. Confidence intervals for simple proportions were calculated using binomial confidence intervals^[15]. Comparison of proportions in two groups was done using Fisher's exact test. Comparisons of medians between two groups was performed using the Mann-Whitney U test. Age density plots were created using normal kernel density estimates. The effect of binary outcomes according to continuous variables such as age or peak supplemental oxygen was carried out by logistic regression analysis. Kaplan-Meier curves were also constructed to perform survival analysis between men and women.

There was no missing data, as we were able to reconstruct missing data points from the written clinical notes.

To ensure reproducibility and transparency of the results, the statistical analysis code and methods section of this paper were written in R Markdown prior to the final data set becoming available.

Results

Participants

There were 1045 observations found for 153 episodes in 152 unique patients. The episodes comprised 71 admissions of women and 82 admissions of men.

The median age was 60, with a range of 24–87, and an interquartile range of 53–68. The age distribution is shown more completely in the histogram in Fig. 1.

A total of 58 episodes ended in death, giving a crude mortality rate of 37.9% (95% confidence interval 30.3% – 46.1%) per admission.

The median length of stay in hospital was 11.8 days, with a range of 0.2–115 days and interquartile range of 8–18.5 days.

The mean age of those who survived was 55.7, whereas those who died had a mean age of 65.1 ($p < 0.001$ by Mann-Whitney). Survivors were therefore around 10 years younger than non-survivors on average. The relative age distribution of survivors and non-survivors is depicted in Fig. 2.

Association between age and mortality

Age had a significant association with mortality. Logistic regression (Fig. 3) showed that the odds of death approximately doubled for every extra 8.0 years of age, with the survival odds being 1 (i.e. 50% probability of survival) at an age of 66.5 years.

Association between sex and mortality

31 out of the 71 women died (43.7%) versus 27 of the 82 men (32.9%). This difference was non-significant by Chi Square test ($p = 0.231$).

A comparison of the Kaplan Meier survival curves for men and women is shown in Fig. 4, and does appear to show a difference, with the hazard ratio for men being 0.606, but the effect size just misses statistical significance (CI 0.352–1.044, $p = 0.071$). This effect does not appear to be attributable to age, as there was less than 3 months' difference between the mean age of men and women in the cohort.

ICU admission and mortality

Of the patients who died after admission to cHDU, 27 of these died in ICU. The other 31 died either in cHDU or in a step down ward.

Use of CPAP and HFNO

142 patients had either continuous positive airway pressure (CPAP) applied via a facemask, or had high flow nasal oxygen (HFNO) for at least part of their time in cHDU.

The predominant modality was CPAP, with 95 (62.1%) patients receiving CPAP only as their main modality. Only 17 (11.1%) patients had HFNO only, with 30 (19.6%) switching between modalities for various reasons, and 11 (7.2%) not receiving either.

Of the 11 patients who did not receive an AGP, four patients were Covid positive with complex HDU needs other than respiratory support. Four patients had been stepped down from ICU, two were thought to require an AGP but stabilized quickly on admission and never required one. There was also one patient who turned out not to have Covid at all.

These findings are summarised in Table 2.

Table 2
Modes of respiratory support used

CPAP only (+/- HFNO for breaks)	HFNO only	Switched between CPAP and HFNO as primary device	Had neither HFNO nor CPAP
95	17	30	11

Association between level of respiratory support and survival

Of the 125 patients who received CPAP at some point during their stay, there was a strong correlation between the need for maximum supplemental oxygen (30 litres per minute) and subsequent mortality. Only six out of 41 patients who required 30 litres per minute of supplemental oxygen with CPAP survived, a survival rate of 14.6%. Of those who survived after reaching 30 litres, there were two patients who did not receive treatment in ICU. These both reached 30 litres for relatively short periods.

Conversely, patients who required less than 30 litres per minute had an overall survival rate of 81.0%, though only nine patients reached a peak of between 20 and 30 litres per minute and only five (55.6%) of them survived. The distribution of peak oxygen requirements, and their associated outcomes, is shown in Fig. 5.

This can be shown in percentage terms to get a better feel for the survival rate according to peak oxygen requirement (Fig. 6).

Again, we can perform a regression of peak supplemental oxygen with survival to show this correlation. The result is shown in Fig. 7.

We can see that a peak oxygen requirement of above 21 litres per minute makes death the most likely outcome. The log odds of death increase by 0.16 per litre of oxygen required, amounting to a doubling of the odds of death for every extra 4.2 litres of oxygen required per minute ($p < 0.001$).

A similar pattern was seen with patients on HFNO. Those with a peak FiO_2 below 0.9 had a survival rate of 72.7%, whereas above 0.9 the survival rate fell to 41.7% (Fig. 8).

If we consider high respiratory support as being an FiO_2 of 0.9 or more or CPAP with more than 15 litres of supplemental oxygen, then we can further examine the outcomes based on the number of days that a patient spent on high respiratory support (Fig. 9), where we can see that those with the greatest time on high respiratory support had the worst outcomes.

ICU transfers and outcomes

44 patients (28.8%, CI 21.9% – 36.7%) went to ICU. Of these, 17 (38.6%) survived.

Of these 17 ICU survivors, in two cases, the Covid swab was negative and the final diagnosis was not Covid pneumonitis. A further three patients had radiological evidence of bacterial pneumonia in addition to Covid at the time of their admission to ICU.

This means that 12 patients out of the 39 (30.8%) patients with uncomplicated severe Covid pneumonitis survived their ICU admission. Even among this group, there is significant residual morbidity. One patient went home on domiciliary oxygen; another with a Zimmer frame for mobility. One patient has since been readmitted with right heart failure due to post-Covid pulmonary fibrosis. Most have community rehab needs and some require ongoing community mental health input.

Total ICU admissions during the study period and ICU avoidance

There were 57 admissions in total to our ICU during the study period. These comprised 53 new admissions and four re-admissions. Our ICU were heavily pressured during the majority of this period, with full occupancy plus expansion beds opened elsewhere in the hospital. During this time, there were 41 patients treated in cHDU with levels of respiratory support exceeding the threshold that would normally mandate a transfer to ICU for IMV - that is, being on CPAP plus more than 15 litres per minute of oxygen, or being on HFNO with greater than 90% FiO₂. These are patients who typically could not be oxygenated on a ward without NIV or IMV. Although some of these patients may not have been deemed appropriate for IMV in ICU, this sets an upper limit of a 42% reduction in ICU admissions during the study period as a result of the facilities available in cHDU.

Although these patients are likely to have had a shorter length of stay in ICU than those who were actually taken for IMV, this still represents a large reduction in the burden placed on ICU resources.

ICU admissions and maximal CPAP

None of the 22 patients who were on the maximal 30 litres per minute of oxygen for more than 24 hours survived without going to ICU. Of the 14 patients on maximum CPAP for more than 24 hours who *were* taken to ICU, none who were on maximum CPAP for more than 3 days survived. There is likely an element of selection bias here, and the numbers are small, but in our cohort it seems that if a patient was on maximum CPAP for more than 24 hours, the prognosis was grim.

Complications

Six of the patients treated with CPAP (5%) developed a pneumomediastinum, and one of these cases was associated with a small pneumothorax. Although two of these patients subsequently died, the pneumomediastinum was not thought to be a contributory cause. However, when pneumomediastinum or pneumothorax was identified in any of these patients, CPAP was discontinued and HNFO was used as an alternative. The increased incidence of pneumomediastinum in mechanically ventilated patients has already been discussed in the literature, and there are case reports of patients with COVID-19 pneumonitis

developing pneumomediastinum even without IMV or NIV, so it is not clear that CPAP was the direct cause of these complications^[16, 17].

Discussion

Key results

Admissions to cHDU in this cohort were almost all appropriate candidates, meaning that the majority required some form of respiratory support beyond standard oxygen therapy. Predominantly these patients were brought for CPAP to treat COVID pneumonitis. Out of 153 patients, only two did not have a diagnosis of COVID pneumonitis.

Over 80% of patients received CPAP during their time in cHDU and less than 10% did not require an AGP. Only seven patients brought for respiratory support did not require an AGP. Four other patients were brought appropriately for complex care needs and did not receive an AGP. This suggests an appropriate use of the facility during the second wave of the pandemic.

The strongest clinical predictor of death was age, with the odds of a patient dying approximately doubling for every eight years of age. There was also a non-significant trend for women to have worse outcomes than men in our cohort.

The overall mortality rate appeared to be high, at 37.9%. This was despite the introduction of evidence-based therapeutics such as Dexamethasone, Tocilizumab and Remdesivir. A possible explanation for this is that we had a high threshold for admission during the second wave.

There were 41 patients who did not go to ICU despite being on levels of respiratory support that would normally mandate an ICU admission. If one posits that the main value of CPAP is in preventing intubation and protecting ICU capacity, then cHDU has been successful in achieving this goal during wave two, reducing ICU admissions by up to 42%.

High levels of respiratory support, particularly patients receiving the maximum of 30 litres of supplemental oxygen with CPAP, was found to be a very poor prognostic marker. Indeed after 24 hours of such treatment, the only survivors in this group were those who went to ICU. Even of those that went on to invasive ventilation the survivor numbers were still small.

Interpretation

There is currently no evidence of a survival benefit from CPAP or HFNO in the context of Covid pneumonitis. However, it is thought that non-invasive CPAP may prevent the need for intubation and ventilation in cases where the patient cannot be adequately oxygenated by simple supplemental oxygen.

In our experience, patients with Covid pneumonitis whose gas exchange is sufficiently impaired to require CPAP plus 15 litres of oxygen per minute could not be adequately oxygenated with a standard oxygen

mask. In some other units, patients reaching this level of support would be considered for ICU admission.

In contrast, our practice has been to provide up to 30 litres of oxygen with CPAP and up to 0.95 FiO₂ with HFNO. In fact, of our 153 admissions, close to half of our patients (73 or 47.7%) were treated with high levels of respiratory support at some point during their stay in cHDU. Of these, 32 ended up going to ICU anyway, but 41 did not. Of the 41 who did not go to ICU, we had only 14 survivors (34.1%), though the patients who were this unwell and *were* taken to ICU had similar mortality rates. This certainly suggests a role for high-level respiratory support in an HDU setting as an alternative to invasive ventilation in ICU for some patients.

Limitations

We need to be cautious in interpreting these findings, since it is likely that there are clinical differences between the ICU and non-ICU groups that are not apparent in the data. It may be that the cohort taken to ICU were at the more severely unwell end of this range, or had level 3 care needs other than respiratory support. However, there does not seem to have been a clear disadvantage in terms of mortality to the cohort treated within cHDU as opposed to ICU, and this suggests that CPAP with high levels of supplemental oxygen may be a reasonable alternative to invasive ventilation in selected patients with Covid pneumonitis.

Although our 153 patients allow us to make some very clear inferences about outcomes based on age and level of respiratory support, this is observational data and there will certainly be confounding variables and selection biases that are not recorded in the data. We should therefore be careful not to over-interpret apparent patterns in the data.

Finally, the design of this study does not allow any definite conclusions to be drawn about the optimal mode of respiratory support in patients with Covid-19 pneumonitis.

Generalisability

Our results suggest that for patients with severe COVID-19 pneumonitis, CPAP with up to 30 litres per minute of supplemental oxygen is a reasonable alternative to IMV and can protect ICU capacity. For patients who fail to oxygenate at 30 litres per minute, the prognosis is very poor whether they are intubated or not, but at this level we would consider that a trial of CPAP has failed. There is no reason to suspect that these findings would be substantially different in other populations.

Conclusion

Our data suggests CPAP has a clear role in preventing or delaying ICU admission in patients with severe respiratory failure due to COVID-19. It can be safely delivered with up to 30 litres per minute of supplemental oxygen in a non-ICU setting. Prognosis is poor for those who require high levels of supplemental oxygen with CPAP for a prolonged period of time, with or without subsequent IMV. CPAP should be considered a key tool in alleviating pressure on IMV beds due to COVID-19.

Abbreviations

CPAP Continuous Positive Airway Pressure

ICU Intensive Care Unit

IMV Invasive Mechanical Ventilation

cHDU COVID High Dependency Unit

NHS National Health Service

RSU Respiratory Support Unit

HFNO High Flow Nasal Oxygen

AGP Aerosol Generating Procedure

GRI Glasgow Royal Infirmary

Declarations

Ethics Approval

This study was approved by the chair of our Regional Ethics Committee (Ref GSH/21/ME/001), and the use of anonymised patient data was granted by the local Caldicott Guardian.

Consent for Publication

Not applicable.

Availability of Data and Materials

Datasets used and analysed during this study are available from the corresponding author on request.

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There was no external funding used.

Competing Interests

None of the authors have any competing interests to declare.

Author Contributions

AC collected and analysed the data, and wrote the methods and results sections. SF and LK researched the existing literature and wrote the introduction and discussion sections. PG helped with study design

and interpretation of results, as well as having editorial input to writing the paper. The authors followed the STROBE checklist for reporting cohort studies when writing this paper.

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Figures

Figure 1

Age Distribution

Figure 2

Age density of survivors and non-survivors

Figure 3

Logistic regression model of association between age and survival with 95% confidence interval

Figure 4
Kaplan-Meier survival curves for men and women

Figure 5
Survival according to maximum supplemental oxygen required with CPAP (absolute numbers)

Figure 6

Survival according to maximum supplemental oxygen required with CPAP (as proportion)

Figure 7

Logistic regression of survival on maximum supplemental oxygen required with CPAP, including 95% confidence interval

Figure 8

Survival according to maximum FiO2 required with HFNO

Figure 9

Survival according to duration on high respiratory support