

RETROSPECTIVE ANALYSIS OF CPAP USE IN THOSE ADMITTED TO ICU WITH COVID-19

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ABSTRACT:

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Background: Initial guidance on managing COVID-19 respiratory sequelae suggested early intubation be used to treat deteriorating patients, however at James Cook University Hospital (JCUH) (centre name) a trial of CPAP (Continuous positive airway pressure) was used when patients required more than 15 litres of oxygen.

Patients And Methods: We conducted a retrospective cohort study to see if this use of CPAP had protective properties against COVID-19 in Intensive Care Unit (ICU) patients. Patients included were admitted to JCUH ICU on or after 01/02/2020, and discharged before or on 31/05/2020, with their primary reason for admission to ICU being 'Pandemic Influenza'. Patients were excluded if they were intubated before admission to JCUH, invasively ventilated before they had CPAP, or received CPAP via a tracheostomy.

Results: 86 patients met the inclusion criteria ($n=86$). 6 did not receive CPAP or invasive ventilation, 67 had CPAP, of whom 23 were subsequently invasively ventilated, and 13 patients were invasively ventilated without prior CPAP. Patients escalated from CPAP to invasive ventilation had the highest mortality rate (95.65%), and the difference in outcome between patients who had CPAP and those who did not, was not statistically significant ($p=0.885$). There was a weak correlation ($+0.25$, $p=0.042$) between an increased number of days of CPAP and patients being discharged alive.

Conclusion: Having CPAP was not associated with an improvement in patient mortality, however patients who received CPAP for a greater number of days were more likely to survive. Disease severity (PaO_2/FiO_2 ratio) was the most strongly correlated factor with patient outcome.

Key Messages:

- Our centres' analysis suggests that patient selection and timing of intubation in COVID-19 patients is critical. Patients who received only CPAP had the lowest mortality, however, those who were subsequently intubated had a higher mortality than those who were intubated earlier in their disease progression (without receiving CPAP first).
- A higher number of days of CPAP received was significantly associated with a positive outcome whereas hours per day of CPAP was not.

Keywords: Continuous Positive Airway Pressure; COVID-19; Critical Care; Intubation; Hypoxia.

INTRODUCTION:

In December 2019, a cluster of cases of pneumonia of unknown origin was reported from Wuhan in China^[1]. Within a short period, this outbreak was identified to be caused by a novel coronavirus now known as COVID – 19^[2]. The World Health Organization (WHO) declared the outbreak of COVID-19 a pandemic on the 11th of March 2020^[3].

Early advice from China advocated the use of early intubation at a Spo₂ of less than 93% in room air and a Pao₂ to Fio₂ ratio of less than 300 mmHg. Their justification for such criteria being that unprepared emergent intubation carried more risks, including cross-infection. Additionally, they also described a degree of silent hypoxia, i.e. severe hypoxia without overt breathlessness, among some patients with this novel virus^[4, 5]. Early guidance drawn up by WHO and National Health Service England also supported ‘early’ intubation before the patient developed severe deterioration^[6-8].

Intubation is a lifesaving therapy in the management of severe respiratory failure, giving clinicians control over an unstable airway and maintaining safe oxygen levels^[9]. However, Italian experiences noted that high incidence of intubation also caused a decrease in critical care capacity, staff, and equipment as well as potentially prolonged critical care stay and that whether early intubation was associated with improved mortality was unknown^[10]. Additionally, intubation is associated with inherent complications with increased incidence over time, especially in ventilator-associated pneumonia and complications of decreased mobility^[11]. Patients who have survived mechanical ventilation in ICU after COVID-19 also have a reduced quality of life in multiple domains^[12].

With new research and guidance emerging during the pandemic, we decided to

adopt a clinical strategy involving a trial of CPAP for patients requiring more than 15 liters of oxygen via a high flow non-rebreathing face mask, which we adapted from the strategy recommended by the University College London to escalate treatment for inpatients affected with COVID (Appendix A). This was in order to prevent as many unnecessary intubations as possible and was often possible in patients in whom the hypoxia was asymptomatic^[13].

Anecdotally we felt that CPAP was providing better patient outcomes and even more patients were treated with CPAP rather than ventilation. Additionally, other units were reporting the use of CPAP in the management of ARDS in COVID-19^[14-18].

We therefore, conducted a service evaluation to analyze the impact of CPAP on patient outcome at our center, to determine if its use could be protective, preventing the need for intubation and decreasing mortality, or whether it merely served to delay intubation and had no difference in long term outcome.

PATIENTS AND METHODS:

We conducted a retrospective cohort analysis of method of respiratory support, CPAP vs ventilation, and hospital discharge of patients admitted to James Cook University Hospital Intensive Care Unit due to SARS-CoV-2 infection. This was registered with the Trust as a Service Evaluation.

Inclusion criteria:

Patients included in this study were all admitted to James Cook University Hospital (JCUH) Intensive Care Units (ICU) on or after 01/02/2020 and discharged from hospital on or before 31/05/2020. This period of time covered the peak of the SARS-CoV-2 first wave pandemic in the United Kingdom. All patients had SARS-CoV-2

infection as their primary reason for admission to ICU.

Exclusion criteria:

From this study, we excluded all patients who were invasively ventilated before they were admitted to JCUH, either being intubated at the scene of an incident or in another hospital. We further excluded data collected on patients after they received CPAP via a tracheostomy, or if they received CPAP after they were invasively ventilated.

Data collection:

Data was collected retrospectively using a number of sources, including Ward Watcher, patient ICU and ward hospital notes, Symphony, and e-Camis. The dataset collected included general patient demographics (gender, age, BMI, ethnicity), comorbidities, intensive care severity scores (APACHE 2 Score, APACHE 2 Mortality Prediction, ICNARC Score and ICNARC Probability), details of respiratory support received whilst in ICU (totals days and average hours per day on CPAP, if CPAP was given through mask or hood, if there were any pressure sores due to CPAP, and if patients were invasively ventilated), if escalation to invasive ventilation was appropriate as recorded on the patients' STEPs form, PaO₂/FiO₂ ratios on admission to ICU and before starting CPAP and/or before intubation as a measure of disease severity, and measures of patient outcomes (outcome on ultimate hospital discharge and days in ICU). For patients with a missing BMI, if they had 'high BMI' listed as a co-morbidity, they were included in the 'BMI over 30' category.

All the collected data was compiled into a spreadsheet and was then pseudo-anonymized by the removal of hospital, NHS, and ICNARC numbers, to protect patient identity. Once the dataset was complete, the spreadsheet was coded and analyzed using PSPP.

Data analysis:

Patients were divided into the following four groups based on the respiratory support they received:

- Patients who did not receive invasive ventilation or CPAP (Group 1)
- Patients who received CPAP and were not escalated to invasive ventilation (Group 2)
- Patients who received CPAP and were escalated to invasive ventilation (Group 3)
- Patients who were invasively ventilated without prior CPAP (Group 4)

We used descriptive analysis to compare patient demographics, comorbidities, ICU severity scores, PaO₂/FiO₂ ratios, details of respiratory support and pressure sores, and outcomes between the four groups. For this analysis, comorbidities were grouped into the following four groups; Respiratory, Cardiovascular, Diabetes Mellitus, and other, sorted by the primary physiological system the disease affects, or if the comorbidity was a type of Diabetes Mellitus. Continuous variables were expressed as the mean value for each group, and dichotomous and nominal data points were expressed as frequencies, and percentages where appropriate for each group.

We fully acknowledged there were other factors impacting a patient's outcome besides the differing aspects of their management, including age, comorbidities, the severity of a patient's condition and their respiratory function. It is for this reason we collected and compared the intensive care severity scores of patients as a measure of the severity of their condition, as well as the PaO₂/FiO₂ ratios of patients on admission to ICU and prior to starting CPAP and/or being intubated as a measure of their respiratory function and disease severity.

In the group of patients who received CPAP and were not escalated to invasive ventilation, mortality was compared between patients who were limited to non-invasive ventilation (NIV), which we took to suggest they had associated comorbidities preventing escalation to invasive ventilation, and those who were appropriate for escalation to invasive ventilation, according to their STEPs form. This comparison gave us further insight into how the disease process and severity may impact patient outcomes more than the specifics of the management they received.

Outcomes:

The principal outcome was an evaluation of the impact of managing SARS-CoV-2 ICU patients with CPAP on hospital discharge. To analyze further the differing aspects of patient management with CPAP, we looked at the relationship between the total number of days a patient spent on CPAP and the average number of hours per day a patient spent on CPAP, with patient outcome at hospital discharge.

Statistical analysis:

The significance of the difference in patient outcome at hospital discharge between the four groups was calculated using Pearson Chi-Squared analysis. Pearson bivariate correlation analysis was used to evaluate the relationship between specific details of patient management, intensive care

severity scores, and PaO₂/FiO₂ ratios on ICU admission, respectively, with patient outcome on hospital discharge.

RESULTS:

The cohort consisted of n = 86 patients who were admitted to JCUH ICU with their primary reason of admission including “Pandemic Influenza” between the dates of 01/02/2020 - 31/05/2020. A flow diagram of the cohort including excluded patients can be seen in *figure 1*. The cohort demographics can be seen in *Table 1*. 11 patients were limited to level 2 care, meaning they were not for escalation of treatment to invasive ventilation. In one patient, it was not recorded if they were limited to level 2 care. This cohort of patients was made up of a significantly lower proportion of non-white patients compared to the ICNARC average [19]. Additionally, there was a higher percentage of patients in the >30 BMI category compared to the ICNARC data in this category. Demographics of each patient group are shown in *table 2*. Cardiac comorbidities were more prevalent than respiratory comorbidities in all patient groups. Patients in Group 1 had the highest average BMI. The study is missing BMI data for 28 patients as height and weight were not always recorded in the patient notes. (Tables 1, 2 and Figure 1)

CPAP use and outcomes in COVID patients

Table 1. Demographics of patients admitted to JCUH ICU in the observational period

Demographic	N of Patients
N	86
Mean age	60.66
N of genders	58m, 28f
Ethnicity	78 white british, 4 asian - pakistani, 3 asian - other, 1 white - other
Mean BMI	33.31 (n = 28 missing)
N with a BMI > 30	30 (n = 26 missing)
N with a respiratory condition	26
N with a cardiac condition	45
N with diabetes mellitus	28
N with other medical conditions	60
N treated with CPAP	67
N treated with IV	36

BMI: body mass index; CPAP: continuous positive airway pressure; IV: invasive ventilation

Table 2. Demographics of patients admitted to JCUH ICU in the observational period split by therapy group

Variable	No CPAP or IV (Group 1)	CPAP Only (Group 2)	CPAP -> IV (Group 3)	IV Only (Group 4)
Average number of days of CPAP received	n/a	3.7	2.91	n/a
Average hours of CPAP received per day	n/a	10.99	11.24 (N = 2 missing)	n/a
N treated with CPAP hood/mask/both	n/a	32 mask, 4 hood, 8 both	16 mask, 3 hood, 4 both	n/a
N with CPAP complications	n/a	3 complications, (N = 5 missing)	3 complications (N = 2 missing)	n/a
Mean apache II score	13.25 (N = 2 missing)	14.41 (N = 3 missing)	15.87	17.23
Mean apache II mortality prediction score	18.68 (N = 2 missing)	23.6 (N = 3 missing)	26.52	31.89
Mean ICNARC score	18.67	15.59	19	25
Mean ICNARC probability	17.53	19.26	27.47	36.98
Mean PaO ₂ /FiO ₂ ratio on admission to ICU (mmHg)	309.52	194.34 (N = 3 missing)	137.11	202.14
Mean PaO ₂ /FiO ₂ ratio before commencing CPAP (mmHg)	n/a	147.76 (N = 12 missing)	104.41 (N = 5 missing)	n/a
Mean PaO ₂ /FiO ₂ ratio before commencing IV (mmHg)	n/a	n/a	94.21 (N = 2 missing)	109.36 (N = 3 missing)

BMI: body mass index; CPAP: continuous positive airway pressure; IV: invasive ventilation

Table 3. Details of respiratory management and illness severity scores on ICU admission by intervention group

	No CPAP or IV (Group 1)	CPAP Only (Group 2)	CPAP -> IV (Group 3)	IV Only (Group 4)
N	6	44	23	13
Mean age	47.5	59.98	67.48	57
N of genders	3m, 3f	27m, 17f	19m, 4f	9m, 4f
Ethnicity	5 white british, 1 asian - other	39 white british, 3 asian - pakistani, 2 asian - other	22 white british, 1 asian - pakistani	12 white british, 1 white - other
Mean BMI	45.23 (N = 1 missing)	31.39 (N = 15 missing)	32.95 (N = 5 missing)	33.68 (N = 7 missing)
N of BMI > 30		3 (N = 1 missing)	14 (N = 15 missing)	10 (N = 4 missing)
N with a respiratory condition		0	13	8
N with a cardiac condition	1	23	14	7
N with diabetes mellitus	3	13	7	5
N with other medical conditions	5		37	13
				5

CPAP: continuous positive airway pressure; IV: invasive ventilation; ICNARC: intensive care national audit & research centre; ICU: intensive care unit

Table 4. Outcomes of each intervention group

Correlation	All Patients (Significance)
Correlation of PaO2/FiO2 ratio on ICU admission and mortality	0.46 (0.000)
Correlation of a ICNARC score on ICU admission and mortality	-0.39 (0.000)
Chi-Squared significance of difference in mortality between CPAP and non-CPAP patients	(0.885)
Correlation between average hours of CPAP per day and outcome	-0.04 (0.766)
Correlation between number of days on CPAP and outcome	0.25 (0.042)

Table 5. Correlation of respiratory variables and ICNARC score with outcome

Outcome Measurement	No CPAP or IV (Group 1)	CPAP Only (Group 2)	CPAP -> IV (Group 3)	IV Only (Group 4)
Days in ICU	3.66	5.48	13.66	9.92
N lived	6	32 (1 patient limited to level 2 care)	1	3
N died	0	12 (9 patients limited to level 2 care)	22	10
Mortality (%)	0	27.27	95.65	76.92

CPAP: continuous positive airway pressure; IV: invasive ventilation; ICU: intensive care unit

CPAP use and outcomes in COVID patients

Detail of respiratory management and severity scores can be seen in *table 3*. 12 patients in the cohort were managed on both CPAP hood and mask; 7 patients were managed solely with CPAP hood, and 48 patients were managed solely using a mask in their CPAP management. Mean PaO₂/FiO₂ ratio on admission was lowest in Group 3 at 137.11mmhg in contrast to Group 4, in which the admitting PaO₂/FiO₂ average was 202.14mmhg. Patients in Group 4 had the highest average APACHE and ICNARC scores on admission. This is as expected as patients with a higher severity of disease

would have been escalated to invasive ventilation more rapidly.

Patients who were escalated to IV received 1 day less of CPAP on average compared to patients who received only CPAP however received a similar number of hours of CPAP per day. There were 6 patients in total who received a grade 1, 2 or 3 facial pressure sore complication from CPAP. (Table 3) Values are presented as

ICU: intensive care unit; ICNARC: intensive care national audit & research centre; CPAP: continuous positive airway pressure

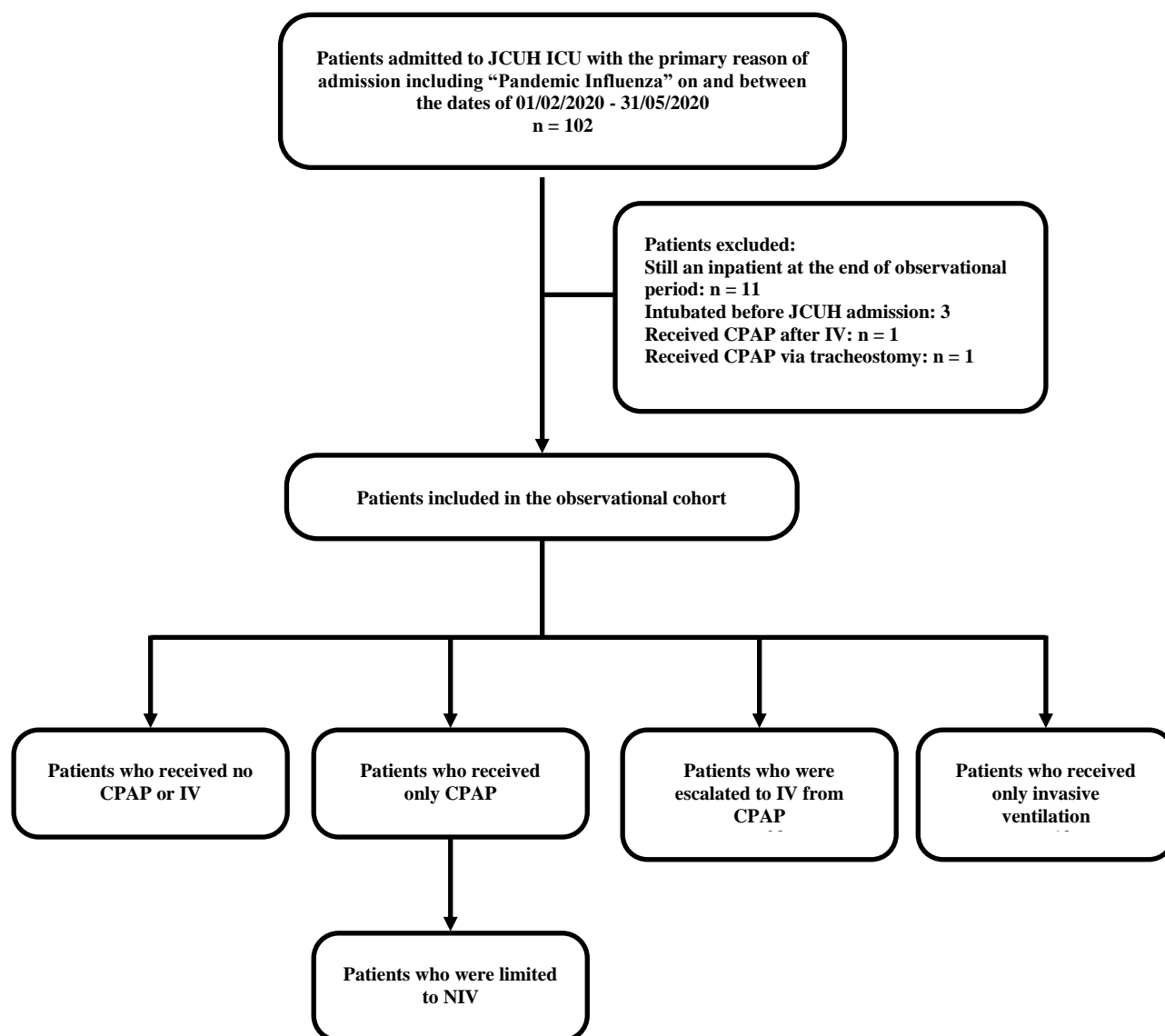


Figure 1. Cohort flowchart including exclusion criteria

The outcomes of each patient group can be seen in *table 4*. 36 patients in total were intubated. Patients who were initially on CPAP and then escalated to invasive ventilation had the highest mortality rate at 95.65%. Patients who were intubated without any prior respiratory support had a lower mortality rate at 76.92%. Patients who had CPAP solely had the lowest mortality rate at 27.27% ($P = 0.000$). 9 out of 12 patients in group 2 who died were limited to level 2 care. (Table 4)

The relationship between PaO₂/FiO₂ ratio, ICNARC score on admission and CPAP variables on patient outcome can be seen in *table 5*. It is seen that the higher the PaO₂/FiO₂ ratio on admission is, the more likely the patient was to survive their hospital stay ($P = 0$). Patients with a higher ICNARC score on admission to ICU with COVID-19 had a lower probability of survival ($P=0$). The difference in outcome between those who received CPAP and those who did not was not statistically significant ($P = 0.885$). There was no significant correlation between the average hours of CPAP received per day and outcome ($P = 0.734$). The correlation between receiving more days of CPAP treatment and surviving the hospital stay was statistically significant ($P = 0.042$). (Table 5)

DISCUSSION:

This cohort analysis supports evidence that suggests CPAP has a significant role in the management of Covid-19. Mortality was significantly lower in those patients who were treated with prolonged CPAP rather than IV, but then worse in the subgroup who were subsequently ventilated, having failed CPAP. The “CPAP only” group had the lowest mortality at 27.27%. An increase in the number of days of CPAP was associated with a reduction in mortality; however, the delivery and number of hours of CPAP was not associated with any such reduction. Notably, the length of stay of the CPAP group

was significantly lower at 5.5 days than the IV group, which was 13.6 days. Patients escalated from CPAP to IV had the highest mortality at 95.65% and the highest LOS. Despite having a higher average ICNARC score on admission, patients who received IV only, had a lower mortality (76.92%) than the patients escalated from CPAP. Additionally, patients who were escalated to IV, started IV with a lower PaO₂/FiO₂ ratio than the patients who started IV directly.

The highest mortality was in the group of patients who 'failed CPAP' and were subsequently invasively ventilated. Potential explanations of this are many. Firstly this is a small group analysis; there may also be significant patient selection bias involved, as many were patients who were elderly or had multiple comorbidities in whom prolonged CPAP may have been used as it was understood that the mortality from IV may have been high. Alternatively, patients may have suffered ill effects of prolonged CPAP before intubation, such as hypoxia and exhaustion. IV was only commenced once all conservative interventions were given. CPAP response was measured by PaO₂/FiO₂ ratios and work of breathing. Additionally, our analysis showed that there was a strong and significant association between a higher ICNARC score and a worse outcome. When the escalated patients were placed on IV, their PaO₂/FiO₂ ratio before IV was lower than the patients who received IV only. As such, it may be argued that in commencing CPAP before IV, we allowed their PaO₂/FiO₂ ratio to deteriorate further and gave them a worse chance of survival due to their lowered P/F ratio.

However, it is clear that many patients survived to hospital discharge from prolonged CPAP alone and it may simply be that the high mortality of the group who received IV after prolonged CPAP, were those patients in whom the disease was relentlessly progressive with ongoing inflammation despite treatment. We were

unable to identify studies from other centers that analyzed their patient subset that had to be escalated and thus were unable to compare our escalated cohort outcome.

We feel this study prompts further questions into the selection criteria and monitoring of patients with COVID-19 who are being managed on CPAP.

Despite serving a significantly more socially deprived population with a higher prevalence of comorbidities than the UK national average, JCUH ICU had a higher discharge rate, and patients had a shorter length of stay by 1.7 days compared to the national ICU average in this time period [19]. Of the 67 patients admitted to ICU and commenced on CPAP, excluding those limited to level 2 care, 58% of patients avoided IV. At JCUH, we put 15% more of our patients on basic respiratory support compared to the ICNARC national average [15]. This reflected the thinking at JCUH ICU that CPAP was the adequate treatment for many patients. Our cohort supports a growing body of retrospective evidence [20-24] suggesting that initial CPAP may prevent the need for sedation and intubation and provide better outcomes for many patients with COVID-19 with type 1 respiratory failure. Again, we look to a well designed randomized control trial such as the Recovery “Respiratory Support” trial [25] to establish the therapeutic benefit of CPAP, high flow oxygen and IV in the treatment of Covid-19.

Several limitations may affect the generalizability of our results. This is an uncontrolled retrospective study in a single center with a small cohort size. There are a number of potential confounders. These include the cohort demographic, timeliness of intervention and disease severity before admission. Additionally, missing BMI and ABG values may have had an impact on average BMI and PaO₂/FiO₂ ratios and significance values. Patients who had COVID-19 who were managed with CPAP

solely on a ward were not included in this study.

Conclusion:

Patients with COVID-19 whose hypoxia was treated with CPAP alone had a significantly reduced mortality in this retrospective analysis. Patients who were escalated from CPAP to IV in our cohort had a 95% mortality rate, higher than patients intubated at an earlier stage. A significant proportion of patients in our cohort were treated with CPAP against early guidance to intubate, and this may have offered them a lower mortality, corroborating evidence found at other clinical sites. Additionally, we found lower PaO₂/FiO₂ ratios and higher ICNARC score on admission to be significantly associated with poor outcomes, while more days on CPAP to be significantly associated with a positive outcome. This study adds to the evidence base that prolonged use of CPAP may be beneficial in the management of Covid-19 pneumonitis and supports the need for more research, such as being currently undertaken by the Recovery RS trial.

Conflict of Interest:

No potential conflict of interest relevant to this article was reported.

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The authors confirm **that the submitted paper has not been published in its current form or substantially similar form elsewhere including on a web site and also, it has not been accepted for publication elsewhere.**

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Conceptualization: KCR, TC, DB, AD, SB. Data Curation: KCR, TC, DB. Formal

analysis: TC. Methodology: TC, AD. Writing – original draft: KCR, AD. Writing – review & editing: KCR, SB.

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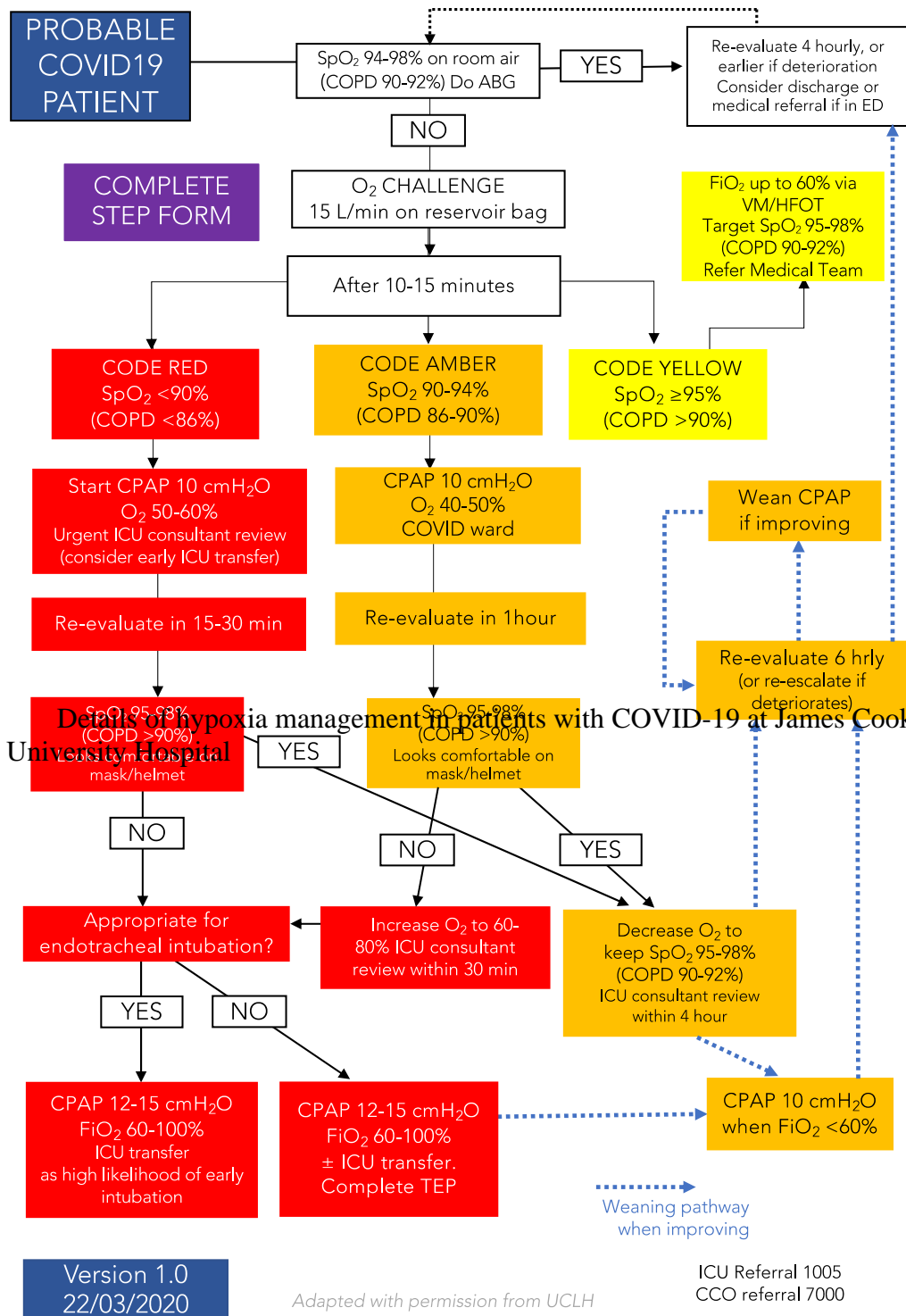
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Appendix A

COVID19 Acute Respiratory Care Pathway

South Tees Hospitals NHS Foundation Trust



CPAP use and outcomes in COVID patients

خلفية الدراسة

تقترح الإرشادات والفحوصات الأولية بخصوص التعامل مع المضاعفات التنفسية الناجمة عن جائحة كوفيد-19 أهمية الاستخدام المبكر للأنابيب (التنبيب) علي المرضى الذين تدهورت حالتهم الصحية ومع هنا كانت المحاولة التي قامت بها مستشفى جامعة جيمس كوك باستخدام جهاز الضغط التنفسي الإيجابي المتواصل (CPAP) خاصة عندما يكون المرضى في حاجة إلي أكثر من 15 لتر أوكسجين .

طريقة البحث

لقد قمنا بدراسة شاملة لمعرفة ماذا كان استخدام (CPAP) له خصائص وقائية من كوفيد-19 علي المرضى في وحدات العناية المركزة ICU. وشملت الدراسة المرضى الذين دخلوا وحدة الرعاية المركزة في مستشفى جامعة جيمس كوك (GCUH-ICU) في أو بعد الأول من فبراير 2020 والذين خرجوا من المستشفى في أو قبل 31 مايو 2020 وكان السبب الرئيس لدخولهم العناية المركزة هو "انفلونزا معدية". ولقد تم إستبعاد المرضى الذين تم إستخدام نظام الأنابيب (التنبيب) عليهم قبل دخولهم مستشفى جامعة جيمس كوك أو تم إستخدام نظام التهوية الغازية قبل إستخدام (CPAP) أو إستخدام (CPAP) من خلال القصبه الهوائية.

النتائج

بتطبيق المعايير السابقة شمل مجتمع الدراسة 86 مريضاً (ن=86) منهم 6 مرضي لم يتلقوا (CPAP) أو التهوية الغازية، و 67 مريضاً تلقوا (CPAP) ومن هؤلاء 23 مريضاً إستخدموا التهوية الغازية في مرحلة تالية، و 13 مريضاً تلقوا التهوية الغازية بدون إستخدام (CPAP) في مرحلة سابقة. ولقد تبين أن المعدل الأكبر للوفاة (حوالي 95,56%) كان بين المرضى الذين تم تصعيدهم من (CPAP) إلي التهوية الغازية. كما أن الفرق في النتائج بين المرضى الذين تلقوا والذين لم يتلقوا (CPAP) كان غير معنوي من الناحية الإحصائية (مستوي معنوية = $p=0,885$). كما وجد أن معامل الارتباط بين الزيادة في عدد الأيام التي تم فيها إستخدام (CPAP) وعدد المرضى الذين خرجوا من المستشفى أحياء كان ارتباطاً ضعيفاً ($r=0.25$).

الخلاصة :

تخلص الدراسة إلي أنه لا يوجد ارتباط بين إستخدام (CPAP) ومعدل التحسن في معدل الوفيات ومع ذلك فإن المرضى الذين تلقوا (CPAP) لعدد أكبر من الأيام زادت نسبة بقائهم أحياء. بالإضافة إلي ذلك فإن نسبة شدة المرض ($P002/FiO2$ ratio) كانت العامل الأكثر ارتباطاً بنتائج المرضى (الوفاة أو البقاء أحياء).