Comparison of COVID-19 survival in relation to CPAP length of treatment and by comorbidity and transmission setting (community or hospital acquired) in a medium-sized UK hospital in 2020: a retrospective study

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ABSTRACT

Objective To estimate continuous positive airway pressure (CPAP) length of treatment effect on survival of hospitalised COVID-19 patients in a medium-sized UK Hospital, and how this effect changes according to the patient’s comorbidity and COVID-19 route of acquisition (community or nosocomial) during the two waves in 2020.

Setting The acute inpatient unit in Wrightington, Wigan and Leigh Teaching Hospitals National Health Service (NHS) Foundation Trust (WWL), a medium-sized NHS Trust in north-west of England.

Design Retrospective cohort of all confirmed COVID-19 patients admitted in WWL during 2020.

Participants 1830 patients (568 first wave, 1262 s wave) with antigen confirmed COVID-19 disease and severe acute respiratory syndrome admitted between 17 March 2020 (first confirmed COVID-19 case) and 31 December 2020.

Outcome measure COVID-19 survival rate in all patients and survival rate in potentially hospital-acquired COVID-19 (PHA) patients were modellled using a predictor set which include comorbidities (eg, obesity, diabetes, chronic ischaemic heart disease (IHD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD)), wave, age, sex and care home residency, and interventions (remdesivir, dexamethasone, CPAP, intensive care unit (ICU), intubation). Secondary outcome measure was CPAP length, which was modelled using the same predictors of the survival rate.

Results Mortality rate in the second wave was significantly lower than in the first wave (43.4% vs 28.1%, p<0.001), although for PHA COVID-19 patients mortality did not reduce, remaining at very high levels independently of wave and CPAP length. For all cohort, statistical modelling identified CPAP length (HR 95% CI 0.86 to 0.96) and women (HR 95% CI 0.71 to 0.81) were associated with improved survival, while being older age (HR 95% CI 1.02 to 1.03) admitted from care homes (HR 95% CI 2.22 to 2.39), IHD (HR 95% CI 1.13 to 1.24), CKD (HR 95% CI 1.14 to 1.25), obesity (HR 95% CI 1.18 to 1.28) and COPD-emphysema (HR 95% CI 1.18 to 1.57) were associated with reduced survival. Despite the detrimental effect of comorbidities, patients with CKD (95% CI 16% to 30% improvement in survival), IHD (95% CI 1% to 10% improvement in survival) and asthma (95% CI 8% to 30% improvement in survival) benefitted most from CPAP length, while no significant survival difference was found for obese and patients with diabetes.

Conclusions The experience of an Acute Trust during the COVID-19 outbreak of 2020 is documented and indicates the importance of care home and hospitals in disease acquisition. Death rates fell between the first and second wave only for community-acquired COVID-19 patients. The fall was associated to CPAP length, especially for some comorbidities. While uncovering some risk and protective factors of mortality in COVID-19 studies, the study also unravels how little is known about PHA COVID-19 and the interaction between CPAP and some comorbidities.

INTRODUCTION

A large body of literature is emerging on the effectiveness of continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV) therapy interventions during both the first and second waves of the COVID-19

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A case–control study from an entire population during the first and second waves of COVID-19 presenting to a single Acute Trust.
⇒ Retrospective case note review of 1830 COVID-19 cases.
⇒ Outcome modelling using a predictor set that included obesity, diabetes, chronic ischaemic heart disease, chronic kidney disease and chronic obstructive pulmonary disease.
⇒ Outcome measure of effectiveness of continuous positive airway pressure therapy to COVID-19 patients.
Compliance with Public Health England’s guidance on the management of COVID-19 patients with hypoxaemic respiratory failure in whom gas exchange and radiological findings are similar to those generally considered to be indications for invasive mechanical ventilation. Invasive mechanical ventilation showed higher mortality rates than NIV, reflecting that only severely affected patients with little chance to survive should be sent for intubation. For all these reasons CPAP is now considered first-line therapy by the Italian Association of Hospital Pulmonologists and the National Health Service (NHS) while High Flow Nasal Cannulae (HFNC) were found in a smaller trial (367 patients) in Spain where CPAP was compared with high-flow nasal cannula and NIV. During the second wave, a growing number of studies concurred that CPAP had beneficial effects and was well tolerated by patients with only few of them dropping out. For example, describe better preparation, increased knowledge, improved CPAP equipment and early commencement of CPAP as being the essential factors during the second wave to improve respiratory rate and oxygenation while reducing the number of patients requiring intubation. Examples from this literature show that CPAP can be successfully used to treat COVID-19 patients with hypoxaemic respiratory failure in whom gas exchange and radiological findings are similar to those generally considered to be indications for invasive mechanical ventilation. Invasive mechanical ventilation showed higher mortality rates than NIV, reflecting that only severely affected patients with little chance to survive should be sent for intubation. For all these reasons CPAP is now considered first-line therapy by the Italian Association of Hospital Pulmonologists and the National Health Service (NHS) while High Flow Nasal Cannulae (HFNC) or CPAP is recommended by the Portuguese Society of Pulmonology.

Improvements from CPAP and other treatments on mortality are hindered by hospital-acquired COVID-19 that has proven to be an additional challenge both within the UK and internationally. In the first two waves in UK, 32,307 patients are thought to have been infected in hospitals in England and Wales from which an estimated 414 healthcare workers died, while 8700 patients died in English hospitals. Towards the end of 2020 officially classified ‘hospital-acquired’ COVID-19 levels were alarming with one in four to one in two COVID-19 cases probably caught by hospital inpatients initially admitted for other reasons. These proportions are comparable to those of other UK and European studies. Hospital-acquired COVID-19 reduced to 4% after summer 2021, corresponding with the rollout of vaccines in the UK. The causes lay in building design, ventilation of rooms, huge pressure on overcrowded beds, short staffed and overwhelmed clinical teams, a lack of testing and inadequate patient and public involvement in the early months of the COVID-19 pandemic. Major deficiencies in compliance with Public Health England’s guidance on good practice in preventing nosocomial COVID-19 transmission were also found, such as routine allocation of patients to beds before negative tests were confirmed, not testing clinical staff regularly and not using protective screens between patients. It was estimated that 6000 additional patients caught COVID-19 in NHS hospital trusts with non-respiratory protective equipment. Staff were less likely to initiate hospital transmission chains in wave 2, accounting for 31.3% of index cases compared with 50.6% in wave 1.

Apart from occasional exceptions, most of the published studies on CPAP are based on small/medium sample size (up to 400 patients). In addition, there are no previous studies that analysed the effect of CPAP length of treatment on the difference of survival of COVID-19 patients according to the different comorbidities and potentially hospital-acquired (PHA)/non-PHA status. Given the opportunities provided by CPAP and the challenges of hospital-acquired COVID-19 whose impact is still not fully deciphered, an overall analysis on more than 2000 patients of mortality and its relationship with CPAP, non-CPAP interventions (ICU, intubation, remdesivir and dexamethasone), comorbidities and hospital-acquired COVID-19, can provide timely information for the management of a future likely endemic COVID-19.

Objective
The main aim of this study is to evaluate the effect of CPAP length on the survival of hospitalised COVID-19 patients, and if any difference existed in this outcome according to the patient’s comorbidity and COVID-19 acquisition (community or nosocomial). The primary outcome of this work is:

- Survival in COVID-19 patients based on CPAP length;
- The secondary outcomes are:
  - Effect of comorbidity on the survival from CPAP length.
  - Effect of hospital-acquired COVID-19 on the patients’ outcome.

METHODS
Study design
This study is based on detailed retrospective case note review of 2141 cases of COVID-19 PCR positive patients admitted to Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation (WWL) during 2020 (from 17 March to 31 May for wave 1 and from 1 November to 31 December for wave 2).

The CPAP protocol used variable oxygen delivery at 5–15 L/min through the face mask to produce CPAP pressure of 5–15 cm H₂O. This delivers 50%–70% FiO₂ varying according to oxygen flow and CPAP pressure. Stellar 150 CPAP machines were used because of their availability at a time of very limited ability to purchase additional equipment.

Criteria for commencing CPAP were provided by protocol. CPAP was commenced in patients where there was type 1 respiratory failure in whom there was failure...
of nasal oxygen at 4 L/min. CPAP was commenced at a pressure of 5 cm H2O and reviewed every 8 hours. Pressure was increased to maintain saturations over 94% with a maximal pressure at 15 cm H2O. Patients were also assessed for a ceiling of care and where that was considered to be ward based with oxygen only, escalation to CPAP was not offered.

The CPAP unit was an 8 bedded bay, providing isolation. Aerosol generation required the clinical team to wear full personal protective equipment and remain within the area during their shifts other than for breaks. The ratio of staff to patients was 2:1.

The case reviews were all completed within a week of the patients being admitted. All data were checked for accuracy at the time that the patients were identified and errors such as double counting were identified and rectified. Patients then had a further case review to identify features of the COVID-19 presentation and comorbidities.

During the case reviews, decisions were made as to whether the patient potentially was infected with COVID-19 during their hospital stay (defined as ‘PHA COVID-19’). WWL created a definition for hospital-acquired COVID-19 prior to the one from NHS. The WWL definition is ‘a patient attending the hospital with an initial negative COVID-19 PCR test and with a second (or later) COVID-19 PCR test positive after 7 days (the recommended screening swab for negative asymptomatic patients), and that was not admitted with symptoms or tests typical of COVID-19 (respiratory illness, lymphopenia or classic CT changes)’. Importantly, this definition also included patients who were admitted with symptomatic

| Table 1 | Baseline information for patients admitted with COVID-19 in wave 1 and wave 2 |
|---------|----------------------------------|
| **Predictor (continuous)** | Wave 1 (n=568) | Wave 2 (n=1262) | Difference test (P values) |
| Age | 74.188 (15.355) | 71.418 (16.915) | 0.001 |
| CPAP start (days) | 4.385 (5.761) | 2.311 (4.986) | 0.062 |
| CPAP length (days) | 4.077 (3.215) | 4.478 (3.953) | 0.318 |
| **Predictor (categorical)** | Proportion (%) | SD | Proportion (%) | SD |
| Time from attended to COVID-19 results <8 days | 81.3 (39.1) | 61.7 | 48.6 | 0.1 10\textsuperscript{-15} |
| CPAP start <4 days | 69.2 (46.7) | 88.2 | 32.4 | 0.007 |
| CPAP start <7 days | 84.6 (36.5) | 93.8 | 23.0 | 0.117 |
| From care home | 31.9 (46.6) | 9.4 | 29.2 | 0.8 10\textsuperscript{-32} |
| Obesity | 13.6 (34.3) | 22.1 | 41.5 | 0.2 10\textsuperscript{-4} |
| Morbid obesity | 1.6 (12.5) | 3.6 | 18.7 | 0.025 |
| IHD | 15.5 (36.2) | 18.2 | 38.6 | 0.173 |
| Diabetes.NIDDM | 25.0 (43.3) | 24.6 | 43.1 | 0.887 |
| Diabetes.IDDM | 0.9 (9.3) | 1.4 | 11.9 | 0.457 |
| CKD | 13.9 (34.6) | 16.5 | 37.1 | 0.183 |
| Asthma | 10.6 (30.8) | 9.8 | 29.8 | 0.688 |
| COPD-emphysema | 18.8 (39.1) | 20.2 | 40.2 | 0.537 |
| Dementia: Alzheimer’s disease | 14.6 (35.4) | 8.7 | 28.2 | 0.001 |
| ICU | 6.5 (24.7) | 3.7 | 18.9 | 0.012 |
| Intubated | 5.6 (23.1) | 2.7 | 16.2 | 0.003 |
| Dexamethasone | 8.8 (28.4) | 61.3 | 48.7 | 0.1 10\textsuperscript{-95} |
| Remdesivir | 0.5 (7.3) | 37.1 | 48.3 | 0.4 10\textsuperscript{-60} |
| Mortality | 43.3 (49.6) | 28.1 | 45.0 | 0.2 10\textsuperscript{-9} |
| Sex (female) | 46.7 (49.9) | 46.1 | 49.9 | 0.871 |
| CPAP | 6.9 (25.3) | 12.8 | 33.4 | 0.003 |
| Hospital acquired | 6.2 (24.1) | 12.7 | 33.3 | 0.4 10\textsuperscript{-4} |

The p values for the test of difference between the mean or proportion for each predictor between the two waves are shown in ‘difference test’.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ICU, intensive care unit; IHD, ischaemic heart disease; NIDDM, Non Insulin Dependent Diabetes Mellitus.
COVID-19 within 2 weeks of being discharged from an incidental (COVID-19 PCR tested negative) admission. The NHS definition was not adopted because it was limited to patients testing positive for COVID-19 after 7 days after admission with an initial negative test, therefore, excluding patients who were readmitted and potentially caught COVID-19 in the first admission.

**Patient and public involvement**

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

**Outcomes and predictors**

The following variables, at individual level, were part of the analyses: COVID-10 PHA; wave (first or second); sex; age at time of admission (years); date of confirmed COVID-19 by PCR test; date the patient was discharged from hospital; date the patient died; date of admission to hospital; whether the patient was admitted from a care home (‘from care home’ variable thereafter); whether the patient spent part or all of their stay on ICU; whether the patient was intubated during their stay (intubated); whether the patient was treated on the CPAP unit (CPAP); date the patient was admitted to the CPAP unit; date the patient was discharged from CPAP unit; if the patient was given dexamethasone during admission (dexamethasone); if the patient was given remdesivir during admission (remdesivir); obesity (International Classification of Disease version 10 (ICD10) codes E66.0); morbid obesity (ICD10 code E66.8); chronic ischaemic heart disease (IHD, ICD10 codes I25.0–I25.9); type 1 diabetes mellitus (diabetes.IDDM, E10.0–E10.9); type 2 diabetes mellitus (Diabetes.NIDDM (Non Insulin Dependent Diabetes Mellitus), E11.0–E11.9); chronic kidney disease (CKD, ICD10 codes N18.0–N18.9); asthmas (Asthma, ICD10 codes J45.0–J45.9); chronic obstructive pulmonary disease, COPD-emphysema (COPD: emphysema, ICD10 codes J43.0–J43.9); and Alzheimer’s disease (dementia: Alzheimer, ICD10 codes G30.1–G30.9). ICD10 (International Classification of Diseases and Related Health Problems, 10th Revision) is the medical classification list by the WHO and are obtained from Clinical Coding, a process which is the translation of written medical terminology from the patient’s health records into searchable ICD10 codes by trained clinical coders.

**Statistical analyses**

The effect of CPAP length of treatment (simply CPAP length) on the survival of hospitalised COVID-19 patients at WWL and its relationship with comorbidities and PHA in wave 1 and wave 2 comprised the following analyses:

- Analyses of the differences in baseline characteristics between wave 1 and wave 2.
- Survival analysis and model selection for the hospitalised COVID-19 patients.
- Estimation of the survival effect of CPAP length on COVID-19 patients affected by a comorbidity.
- Survival analysis of hospital-acquired COVID-19.

The baseline characteristics of the wave 1 and wave 2 patients and timings are compared by $\chi^2$ proportion test for discrete data and two sided t-test for continuous data. Proportions and averages are reported with their SD. Specifically, regarding timings, the multiple $\chi^2$ proportion tests evaluated if between first and second wave any difference in the proportion of patients that started CPAP 1, 2, ..., n days from admission was statistically significant. Similarly, the test was applied for the number of days from attendance to COVID-19 results and for the length of CPAP.

To model CPAP length, we have employed a generalised Poisson linear mixed effects model to identify important variables associated to this outcome. Forward and backward stepwise approaches were used to select the best survival model based on the lowest Bayesian information criteria (BIC), which indicates better fit within parsimonious models. For the survival analyses, we have employed a stratified Cox proportional hazards models (CPHM) to estimate unadjusted and adjusted hazard ratios for the associations between COVID-19 survival (for all cohort and separately for comorbidity and the PHA) and the independent variables of interest. A stratified CPHM assumes that the hazard ratio(s) of the stratified predictor(s) is (are) constant across strata. The time to mortality is recorded from the date of hospital admission to the date of death. Within the CPHM, the wave information (first or second) was included as cluster term in order to compute a robust variance estimation for the model (known as the Huber sandwich estimator).
Predictor selection for survival models followed the same method described above for the generalised linear mixed model. Each predictor was tested for non-proportionality via Schoenfeld proportional hazard test.35

Data are analysed using R V.4.0.4 (15 February 2021)—‘Lost Library Book’.36

RESULTS
Baseline characteristics
During 2020, there were two waves to the COVID-19 pandemic in WWL. The first wave was from March to end of May and the second wave from November to the end of the year. The second wave was larger than the first but had a significant lower death rate, which almost halved (table 1). In the first wave, patients were generally provided with COVID-19 test results earlier than in the second wave (table 1). The demographics of the two waves differ in age, proportion of patients from care homes and some comorbidities (obesity and dementia), but not sex, COPD- emphysema, asthma, CKD, IHD and diabetes (table 1). While there were no differences in proportion of patients in ICU, other interventions such as intubation, drugs and CPAP differed between the two waves, with the latter being provided significantly earlier in the second wave than in the first wave during the first 7 days in hospital (table 1).

Analysis of the CPAP length revealed that ‘from care home’, ICU, obesity and asthma are importantly (as selected) predictors for it. Specifically, obese and asthmatic patients are associated with shorter CPAP length, while being in ICU and ‘from care home’ are associated with longer CPAP length (figure 1). The largest difference in CPAP length was between first wave female (shorter CPAP length) and second wave male (longer CPAP length), both without IHD condition. No difference in CPAP length between waves was found (table 1).

Effect of CPAP length on survival in hospitalised COVID-19 patients
In general, survival in hospital increased for female or for patients in the second wave, and for patients with longer CPAP (table 2); while older age, residency in care home, IHD, obesity, CKD and COPD- emphysema reduced survival. These HRs are all robust apart ‘from care home’ with longer admittance in the hospital (>14 days). In

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Table 2  Unadjusted and adjusted survival HR for the all cohort

| Predictor          | Reference | Unadjusted HR | Lower  | Upper  | Adjusted HR | Lower  | Upper  |
|--------------------|-----------|---------------|--------|--------|-------------|--------|--------|
| Age                |           | 1.0243        | 1.0189 | 1.0298 | 1.0275      | 1.0192 | 1.0358 |
| Sex                | Male      | 0.8117        | 0.7642 | 0.8622 | 0.7594      | 0.7112 | 0.8109 |
| Wave               | 1         | 0.6264        | 0.4853 | 0.8086 | cluster     | cluster| Cluster|
| Care home (T>14)   |           | 1.0193        | 0.9375 | 1.1083 | 1.0091      | 0.9360 | 1.0878 |
| Care home (T<14 hours) |      | 2.7985        | 2.7743 | 2.8228 | 2.3022      | 2.2191 | 2.3885 |
| IHD                | No        | 1.3844        | 1.2858 | 1.4905 | 1.1896      | 1.1345 | 1.2374 |
| Obesity            | No        | 1.0237        | 0.9887 | 1.0600 | 1.2262      | 1.1774 | 1.2771 |
| CKD                | No        | 1.6159        | 1.5249 | 1.7123 | 1.1966      | 1.1419 | 1.2539 |
| Asthma             | No        | 1.0098        | 0.9358 | 1.0896 | 1.1833      | 1.0398 | 1.3464 |
| COPD- emphysema    | No        | 1.5950        | 1.3254 | 1.9195 | 1.3613      | 1.1766 | 1.5749 |
| CPAP length        |           | 0.9110        | 0.8590 | 0.9642 | 0.9183      | 0.8916 | 0.9458 |
| CPAP start         | No        | 0.9856        | 0.9549 | 1.0173 | Variable not included |
| ICU                | No        | 1.1516        | 0.8687 | 1.5275 | Variable not included |
| Intubated          | No        | 1.2045        | 0.8940 | 1.6229 | Variable not included |
| Dexamethasone      | No        | 1.1129        | 0.9482 | 1.3062 | Variable not included |
| Remdesivir         | No        | 0.9754        | 0.8161 | 1.1659 | Variable not included |
| Morbid obesity     | No        | 0.4896        | 0.2619 | 0.9151 | Variable not included |
| Diabetes.NIDDM     | No        | 1.0283        | 0.8598 | 1.2299 | Variable not included |
| Diabetes.IDDM      | No        | 0.5904        | 0.2446 | 1.4251 | Variable not included |
| Dementia: Alzheimer| No        | 1.2458        | 0.9891 | 1.5691 | Variable not included |

The adjusted model is a stratified mixed effect Cox proportional hazards model with dummied ‘from care home’ (T is time from admission) predictor and clustered by wave. Unadjusted survival HR for predictors not included in the best model are also shown.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; IHD, ischaemic heart disease.
addition, obesity and asthma become insignificant when not adjusted for the rest of the factors (see unadjusted columns in table 2).

**Figure 2** Stratified by wave and adjusted by age, sex and care home residency, CPAP length effect (HR) on each comorbidity. Lines represent 95% CI around the HR (blue point). CPAP length was set to 0 for patients who were not treated with CPAP. CPAP treated counts (not threatened in parenthesis): obesity 74 (282), CKD 15 (272), IHD 31 (287), diabetes_NIDDM 61 (391), asthma 29 (155), COPD-Ephysema 33 (329) and morbid obesity 74 (282). CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; IHD, ischaemic hearth disease; NIDDM, non insulin dependent diabetes melitus.

**Effect of CPAP length on survival in hospitalised COVID-19 patients with a comorbidity**

The average CPAP length was very similar for each comorbidity: 4 days for asthma (SD±2 days), COPD-emphysema (± 4 days), IHD (± 3 days), obesity (±3 days); 5 days for diabetes NIDDM (±3 days) and morbid obesity (±4 days); and finally, 6 days for CKD (±5 days). While there are similarities in CPAP length, analysis of the effect of CPAP length on the survival of patients for each comorbidity differed between comorbidity, as shown in figure 2. In this figure, survival gains from CPAP length on COVID-19 patients presenting a comorbidity were adjusted for confounders (age, sex and care home residency). CPAP length was a protective factor for CKD, IHD, asthma and COPD-emphysema, but not for obesity and diabetes. The largest difference was between CKD and IHD, with the former having better outcomes under CPAP length than the latter.

**Survival in PHA COVID-19 patients**

PHA COVID-19 patients’ survival did not benefit from CPAP length since this variable was not found significant. Figure 3 shows the survival curves relative to the model that minimised the BIC and which summary results are shown in table 3. While in the second wave patients had a better survival rate (red line) than in the first wave (green line), for PHA patients the survival was the worst and independent from the wave (blue and purple lines). By employing important variable selection methods, we found seven variables associated to survival based on the PHA status: age, sex, CKD, IHD, obesity, ‘from care home’ and COPD-emphysema (table 3). Female had a better survival while being older and with comorbidities increased mortality. The PHA group is older with a slightly larger proportion of males and patients with IHD.

**Figure 3** Survival curves for potentially hospital-acquired COVID-19 patients (PHA=1) and non (PHA=0) and wave obtained from the model described in table 3. PHA, potentially hospital acquired.
CKD, obesity and COPD-emphysema but not ‘from care home’ (Table 3). Compared with the NHS definition of hospital-acquired COVID-19 (Table 4), the main difference is registered during the second wave. The WWL method suggests more than double the rate of PHA for deaths in the second wave when compared with the NHS method.

**DISCUSSION**

The data demonstrate two waves of infection in a similar pattern to that seen within other UK hospitals.37 There are differences demonstrated between the first and second waves (Table 1). Our data indicate that there was a significant change in the age and admission source between waves in part due to the outbreaks within care homes during the first wave.38–40 During the second wave, in WWL patients were younger and more likely to have obesity and dementia, similar findings were identified on a comparable size cohort in London, including the significant reduction in mortality found in this study.37 As in Bechman et al,37 the improvements in survival seem not to be driven by the use of drugs (remdesivir and dexamethasone), which may be more effective in younger cohorts of patients. In fact, other studies have shown that corticosteroid treatment was associated with decreased in-hospital mortality in patients with severe and critical COVID-1941 in younger hospitalised patients than those of our study.

Despite the seemingly insignificant role of drug treatment, we estimated that CPAP length was a protective factor for the mortality of the hospitalised COVID-19 patients in particular for those with certain comorbidities (Table 2 and Figure 2) although not for PHA patients (Table 3). By accounting for confounders, we found that CPAP length was effective in improving COVID-19 survival for patients presenting CKD, IHD, COPD-emphysema and asthma, but not for obesity and diabetes. Obesity was found to be a key clinical risk factor for being admitted to ICU by previous studies,42 while diabetes has been associated with severe COVID-1943 44 that is likely to have reduced the efficacy of CPAP length.

Although improved outcomes by the use of CPAP are now recognised,45 the CPAP length treatment received little attention.11 12 It is likely that CPAP length is combining the advantages of CPAP5 with additional interventions carried out during the CPAP treatment (eg, anticoagulant and other drug).12

There are no other studies modelling the effect of CPAP length on individual comorbidities. Certainly, these results confirmed the difficulty in improving survival for comorbidities such as obesity and diabetes.46 Other studies have shown that patients with comorbidities such as asthma, COPD-emphysema, tuberculosis, pneumonia, acute respiratory distress syndrome, diabetes mellitus, hypertension, renal disease, hepatic disease, cardiac

| Table 3 | Adjusted HR for a multivariate Cox proportional hazards model stratified by PHA and clustered by Wave and CPAP |
|-----------------------|-----------------------------------------------|-----------------------|-----------------------|-----------------------|
| Predictor | Reference | HR | Lower | Upper | Proportion in non-PHA (n=1635) | Proportion in PHA (n=195) |
| Age* | 1.0248 | 1.0205 | 1.0291 | 71.5076* | 78.7384* |
| Sex | Male | 0.8130 | 0.7964 | 0.8299 | 0.4666 | 0.4307 |
| IHD | No | 1.1305 | 1.0277 | 1.2435 | 0.1657 | 0.2411 |
| CKD | No | 1.1839 | 1.1119 | 1.2606 | 0.1449 | 0.2564 |
| Obesity | No | 1.2464 | 1.1144 | 1.3940 | 0.1939 | 0.2000 |
| COPD–emphysema | No | 1.5491 | 1.3796 | 1.7395 | 0.1908 | 0.2564 |
| Care home | No | 2.2131 | 1.7625 | 2.7789 | 0.1682 | 0.1282 |

The last two columns show the proportion (or the mean*) of patients with the important characteristic for the PHA group and the rest of the patients.

*For the variable age, the mean age is provided instead of proportion.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; PHA, potentially hospital acquired.

| Table 4 | Numbers of deaths where COVID-19 infection is potentially hospital acquired shown according to WWL method of assessment and NHS method of assessment |
|-----------------------|-----------------------------------------------|-----------------------|-----------------------|-----------------------|
| Method of PHA calculation | First wave | Second wave | First and second wave total |
| WWL PHA deaths | 35 | 158 | 193 |
| WWL % PHA deaths | 18 | 44 | 32 |
| NHS PHA deaths | 27 | 65 | 92 |
| NHS % PHA deaths | 11 | 18 | 15 |

NHS, National Health Service; PHA, potentially hospital acquired; WWL, Wrightington, Wigan and Leigh.
disease, male gender and age greater than 60 years, and including history of smoking and history of substance use, were more likely to die or develop undesirable outcomes and that hospitalised women are less likely to die from COVID-19 but once severe disease occurs, the risk of dying is similar to men. Obesity and asthma were the comorbidities most strongly associated to CPAP length (figure 1) in which average length was one of the shortest. However, this may simply reflect the high risk of death in obese patients. For asthmatic patients who are likely to develop severe COVID-19 admission to ICU earlier would lead to shorter CPAP length.

While there was a general improvement in survival during the second wave, this improvement did not affect the PHA group in which mortality stays higher and is similar within the two waves (figure 3) despite CPAP length treatment. This mortality is much higher than the one found in other studies, however, the similar mortality between both waves has been reported elsewhere as well. The higher mortality in PHA patients than patients with community-acquired COVID-19 is also shown in recent studies, although some literature has provided conflicting results. The data presented indicate that PHA infections were common during the outbreak. Our finding is in line with a recent work on more than 70,000 hospital patients in UK with a model-based definition of PHA. However, much larger PHA proportions were estimated for UK hospitals than the one presented here. By accounting for readmissions within 2 weeks, we found a larger mortality rate in PHA patients based on the WWL definition than those PHA based on the NHS definition, exclusively during the second wave (table 4). We recognise that readmission could be inflated by community-acquired COVID-19, however, the 2 weeks are inclusive of the median incubation period (between 5 and 14 days) and therefore PHA cannot be ruled out. questioned whether hospital-acquired COVID-19 cases could have been avoided, and if they could, what we need to do better in future rather than just seeking to appor tion blame. One major factor highlighted was that of ageing hospital estate with a relatively low percentage of single side rooms in all but the newest facilities, close bed spacing in bays shared by 4–6 patients. The author also raised the issue of suboptimal ventilation, inadequate staff areas for breaks, shared working spaces, overwhelmed infection control teams and variability in the rigour of applying correct procedures. For example, in WWL, patients were identified within the emergency department as being possible COVID-19 patients and those patients were cared for in one area until results were available. This was an open area and its ventilation was not built to manage an airborne respiratory disease. However, there is evidence of the effectiveness of stringent infection control programmes in other countries, as for example, in Taiwan and USA. For the latter, it has been reported that dedicated COVID-19 units with airborne infection isolation rooms, wearing correct PPE, donning and doffing monitors, universal masking, restriction of visitors, and liberal RT-PCR (specific COVID test) testing of symptomatic and asymptomatic patients resulted in only two cases of hospital diagnosed COVID-19 from over 9000 admissions over a 12-week period. Health systems adopting systematic approaches made hospital-acquired COVID-19 far rarer. Finally, PHA definition will need to be revised since including patients who became positive after 7 days is likely to underestimate COVID-19 variants with shorter incubation period.

CPAP is a valuable non-invasive respiratory support to treat acute hypoxic respiratory failure associated with COVID-19, however, delaying invasive ventilation in non-responders to CPAP may increase mortality. Further studies need to identify measures to predict CPAP and CPAP length efficacy on patients or which specific non-invasive treatment could be better for a patient. At the moment, only pilot studies have explored it, as for example, the use of Lactate, Oxygenation and Temperature score, Single Breath Counting Test and heart rate, acidosis, consciousness, oxygenation, respiratory rate. However, until future research provides clinically significant evidence of these measures a systems-based approach should be preferred.

We have confirmed the positive effect of CPAP although these analyses have their own limitations in the number of considered confounders, which require further consideration and the fact that not all COVID-19 patients can be treated with CPAP. Therefore, we need to account for the fact that some improvement in survival has different source independent of the CPAP or the considered treatments. For example, the protective effect associated with the wave period itself (first or second wave) indicates the presence of hidden factors that enhanced survival and that are potentially related to admission, treatment, discharge or changes in healthcare infrastructure.

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