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Outcomes and characteristics of COVID-19 patients treated with CPAP/ HFNO outside of the intensive care setting

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Abstract

Background

Continuous Positive Airway Pressure (CPAP) and High Flow Nasal Oxygen (HFNO) have been used to manage hypoxaemic respiratory failure secondary to COVID-19 pneumonia. Limited data are available for patients treated with non-invasive respiratory support outside of the intensive care setting.

Methods

In this single-centre observational study we observed the characteristics, physiological observations, laboratory tests, and outcomes of all consecutive patients with COVID-19 pneumonia between April 2020 and March 2021 treated with non-invasive respiratory support outside of the intensive care setting.

Results

We report the outcomes of 140 patients (Mean Age = 71.2 [SD=11.1], 65% Male [n=91]) treated with CPAP/HFNO outside of the intensive care setting. Overall mortality was 59% and was higher in those deemed unsuitable for mechanical ventilation (72%). The mean age of survivors was significantly lower than those who died (66.1 vs 74.4 years, $p<0.001$). Those who survived their admission also had a significantly lower median Clinical Frailty Score than the non-survivor group (2 vs. 4, $p<0.001$). We report no significant difference in mortality between those treated with CPAP (n=92, mortality: 60%) or HFNO (n=48, mortality: 56%). Treatment was well tolerated in 86% of patients receiving either CPAP or HFNO.

Conclusions

CPAP and HFNO delivered outside of the intensive care setting are viable treatment options for patients with hypoxaemic respiratory failure secondary to COVID-19 pneumonia, including those considered unsuitable for invasive mechanical ventilation. This provides an opportunity to safeguard intensive care capacity for COVID-19 patients requiring invasive mechanical ventilation.

Introduction

Continuous positive airway pressure (CPAP) and High-flow nasal oxygen (HFNO) are recommended by the British Thoracic Society (BTS) as the mainstay of non-invasive respiratory support for COVID-19 patients with severe hypoxaemic respiratory failure who are deemed unsuitable for mechanical ventilation (1). The role of these non-invasive therapies has been examined in previous studies (2-5) with variation in the reported outcomes. Predominantly these report outcomes from inside intensive care units, however, there is also data from patients treated outside of this setting (6-8).

In this study we observed the characteristics and outcomes of consecutive patients with hypoxaemic respiratory failure secondary to COVID-19 pneumonia who received CPAP and HFNO on a Respiratory Support Unit (RSU) between April 2020 and March 2021. The RSU is located on a standard COVID respiratory ward but has enhanced staffing ratios, non-invasive patient monitoring and infection control precautions to facilitate the safe delivery of aerosol generating procedures. We aimed to evaluate the utility of these methods of non-invasive respiratory support as a management option outside of the intensive care setting.

Methods

We undertook a single-centre, prospective observational study of consecutive patients treated for hypoxaemic respiratory failure with either CPAP or HFNO on a designated COVID-19 RSU at Hull University Teaching Hospitals NHS Trust (HUTH) between April 2020 and March 2021. We recorded patient characteristics, physiological observations, laboratory tests, and clinical outcomes.

Patients were identified as requiring non-invasive respiratory support on clinical grounds and supported using a management algorithm designed and implemented at HUTH, based on current BTS recommendations (9). Prior to the initiation of CPAP/HFNO, patients were assessed for suitability for invasive mechanical ventilation by the hospital's critical care outreach team including a senior intensive care physician and/or a senior respiratory physician. The decision-making process was holistic and included assessment of the patients' premorbid condition, likelihood of a positive outcome, and the views of the patients and/or next of kin. The Clinical Frailty Score (CFS)(10), a 7-point scale which measures a patient's frailty based on their comorbid status as well as ability to carry out activities of daily living, was utilised as part of the holistic assessment to predict the likelihood of successful treatment with CPAP/HFNO. All decisions were documented as an advanced care plan in the clinical case records. This pathway can be visualised in Figure 1. Individual patient

care and advanced care planning was ultimately the responsibility of the treating clinical team. Both CPAP and HFNO were delivered in accordance with BTS guidelines and was overseen by specialists in respiratory medicine.

The primary outcome of interest in our study was inpatient mortality. Patient characteristics, modality of respiratory support received, and outcome data were collected prospectively. Treatment tolerance was ascertained on a post-hoc basis through review of patients' adherence to therapies as documented in their clinical case records. In event of missing data, retrospective case record and electronic patient record review was undertaken to input missing data items. All physiological parameters and laboratory markers included in the study are those taken prior to the initiation of CPAP/HFNO. Data collection was approved by the HUTH clinical governance committee.

Data are presented descriptively. Comparison of means were performed using student's t-tests, comparison of medians were performed using Mann Whitney U testing, and comparison of proportions were compared using Chi Squared testing. Statistical significance was defined as a p-value of less than 0.05. All statistical analysis was performed using IBM SPSS Statistics 26. Outcomes were analysed with patients assigned to HFNO or CPAP groups in 2 ways: firstly, based on initial treatment choice (intention to treat analysis [ITT]); and secondly, based on the highest level of support received (patients that received both HFNO and CPAP during their admission were analysed in the CPAP group).

Results

Patient characteristics and outcomes

Outcomes for 140 patients were observed, 65% (n=91) were male and mean (SD) age was 71.2 (11.1) years. Overall inpatient mortality was 59% (n=82). In the 98 patients that were considered unsuitable for invasive ventilation, inpatient mortality was 72% (n=71). Of the 42 patients deemed suitable for invasive mechanical ventilation, 48% (n=20) were admitted to the intensive care unit (ICU) and 11 were treated with invasive mechanical ventilation. All 11 patients treated with mechanical ventilation died, reflecting 26% of all patients treated with non-invasive respiratory support that were considered suitable for invasive ventilation.

Comorbidities

Frequently observed comorbidities included hypertension (HTN) (59%, n=83), obesity (37%, n=52), diabetes mellitus (DM) (29%, n= 40), and ischaemic heart disease (IHD) (27%, n=38). When compared to the survivor group, there was a significantly higher proportion of patients with IHD and

obesity in the non-survivor group (12% vs 38%, p=0.001 and 45% vs. 71%, p=0.022, respectively). There were also differences between the survivor and non-survivor groups in the prevalence of respiratory diseases, with non-survivors having a higher prevalence of chronic obstructive pulmonary disease (COPD) (33% vs 16%, p=0.031) and the survivor group having a higher proportion of patients with asthma (17% vs 6%, p=0.026). We also observed a higher proportion of patients with previous cancer in the non-survivor group (15% vs 3%, p=0.037).

Survivors vs Non-survivors

The mean age of survivors was significantly lower than those who died (66.1 vs 74.4 years, p<0.001). The survivor group also had a significantly lower median CFS than the non-survivor group (2 vs. 4, p<0.001). Patients in the non-survivor group had a significantly higher mean respiratory rate (RR) prior to CPAP/HFNO initiation when compared to survivors (28.7 vs. 25.3, p=0.003). In those who received CPAP, higher initial peak end-expiratory pressures (PEEP) were required in the non-survivor group to attain target oxygen saturation (mean PEEP 9.7 cmH2O vs. 8.4 cmH2O, p=0.021). The non-survivors who received CPAP also required a higher initial fraction of inspired oxygen (FiO2) to attain target oxygen saturation (59.6 vs 71.1, p=0.002). We did not observe any difference in white cell count (WCC), lymphocyte count or C-reactive protein (CRP) between those who survived and those who did not. All patient data and comparison between survivors and non-survivors is displayed in Table 1.

There was no difference in time from hospitalisation to initiation of CPAP/HFNO between survivors and non-survivors (median time to initiation [range] 2 days [1-30] vs 2 days [1-14]). The median duration of CPAP/HFNO treatment for all patients was 3.5 days (range 1 - 24); there was no difference between survivors and non-survivors (median [range] = 4 [1-24] days vs. 3.5 [1-18] days, p=0.454).

Patients considered unsuitable for invasive mechanical ventilation – survivors vs non-survivors

There was no significant difference in age between survivors and non-survivors in the group of patients deemed unsuitable for invasive mechanical ventilation, although the mean age was numerically lower in survivors (Mean age 72.4 vs 76.3 years, p=0.053). The survivor group had a significantly lower median CFS score (3.5 vs. 4, p=0.022). The survivor group had a significantly higher proportion of patients with obesity (48% vs 34%, p=0.033). Patients that did not survive their admission had a significantly higher white cell count prior to the initiation of CPAP/HFNO (Mean

WCC = 11.5 vs 7.4, p=0.036). Data for patients that were considered unsuitable for invasive mechanical ventilation is displayed in Table 2.

CPAP vs HFNO

Highest level of treatment analysis

92 patients received CPAP and 28 patients received HFNO as the highest level of their treatment, where CPAP is considered a more advanced modality of respiratory support. There was no difference in inpatient mortality between the CPAP and HFNO groups (60% [n=55] vs 56% [27], p=0.477). The CPAP group had a significantly higher proportion of patients with HTN (65% vs 48%, p=0.044), however there were no other significant differences in patient characteristics, physiological parameters, or laboratory results prior to initiation of respiratory support. Data are presented in Table 3.

Intention-to-treat analysis

69 patients received CPAP and 71 patients received HFNO as their initial modality of respiratory support. There was no difference in inpatient mortality between the CPAP and HFNO groups (58% [n=40] vs 64% [n=44], p=0.530). There were no significant differences between the two groups with regards to baseline data, patient characteristics, physiological parameters, or laboratory results prior to initiation of respiratory support. All patient data comparing those who received CPAP or HFNO on an intention-to-treat basis can be found in Table 3.

Treatment tolerance

86% (n=120) of patients were documented as tolerating their treatment with either CPAP or HFNO. There was no significant difference in tolerability of CPAP/HFNO between survivors and non-survivors, there was also no significant difference between tolerability between the different modalities of respiratory support when analysed by highest level of support and on an intention-to-treat basis.

Discussion

We observed that 41.4% of patients who were treated for hypoxaemic respiratory failure secondary to COVID-19 pneumonia were discharged home after receiving either CPAP or HFNO on an RSU. We also observed that 27.6% of patients deemed unsuitable for invasive ventilation were able to be discharged home after such treatment. Many patients in our cohort had comorbidities, with more

than half having at least one, and were deemed frail upon holistic assessment. Despite this, many were treated successfully on the RSU with non-invasive respiratory support.

CPAP is a non-invasive form of positive airway pressure ventilation. It delivers a constant pressure throughout the respiratory cycle, preventing small airway collapse and allowing patient-initiated breaths to recruit more lung capacity (11). HFNO is a method of oxygen supplementation which provides humidified oxygen with a flow rate of up to 100 litres min-1 and an FiO2 of between 21% and 100%. It is believed to offer respiratory support by reduction in work of breathing, providing a low level of PEEP, and by improving mucociliary clearance through humidification of the oxygen (12). Early in the course of the COVID-19 pandemic, these modalities were deemed controversial due to the lack of quality evidence for their use in the treatment of bacterial Pneumonia (13,14). However, these modalities are now being utilised frequently worldwide for COVID-19 pneumonia and recent studies have aimed to evaluate their utility.

Our findings are comparable to other studies reporting outcomes of non-invasive respiratory support outside of the ICU setting. A study by *Coppadoro et al.* observed outcomes of patients treated with helmet CPAP outside of the ICU, they report 72% mortality in patients deemed unsuitable for invasive mechanical ventilation and similarly reports that younger age was significantly associated with better outcomes. (15) Another study by *Vaschetto et al.* reported 34% mortality among 397 patients treated with CPAP outside of the ICU, as well as 73% mortality in the 140 patients who were deemed unsuitable for invasive ventilation. (8) Conversely, Bruassco et al. (16) reported 83% survival in 64 patients treated with CPAP on a general respiratory ward, although patient demographics were unavailable. Data from patients treated with HFNO also paint a mixed picture. Patel et al. (5) report low inpatient mortality of 14.4% in 104 patients treated with HFNO, although the mean age of patients included in the study was 60.6 years which is lower than in our cohort. In contrast, Calligaro et al. (17) report a mortality rate of 48% for 293 patients treated with HFNO. Indeed, the overall mortality rates reported for different cohorts will vary based on the case mix of patients studied; however, all studies mentioned indicate that both treatment strategies are useful in both the prevention of progression to mechanical ventilation and as definitive treatment for respiratory failure in COVID-19 patients. A strength of our study is that we did not select patients to be included, we analysed data from all patients that received non-invasive respiratory support outside intensive care in our hospital over the course of the pandemic, providing an accurate representation of the patient population presenting to hospital with COVID-19 in the UK.

Our observed inpatient mortality is higher than that published by the UK Intensive Care National Audit and Research Centre (ICNARC), which reports 38.3% mortality in patients over the age of 70

treated with advanced respiratory support (CPAP and HFNO are included in this definition) in the ICU. (18) This is numerically lower than the 58.6% mortality observed in our cohort (mean age 71.2 years), However, our data and that of the ICNARC cohort are not directly comparable. Co-existent co-morbidities are a well-recognised risk factor for mortality in hospitalised COVID-19 patients (19,20); our cohort has a much higher prevalence of co-morbidities as compared to the ICNARC cohort, though how these are defined varies between the two. Similarly, there would be differences between frailty levels of patients as well as proportion considered suitable for invasive mechanical ventilation in the event of deterioration on CPAP/HFNO. We believe that in the setting of the provision of critical care in the UK, our patient cohort includes many who may not conventionally be considered for treatment on the ICU. We feel as though this cohort has been seldom observed and our data help to inform management decisions of older, more frail, and comorbid patients with COVID-19 pneumonia.

We do not yet know which modality of respiratory support is superior (if either) in the treatment of these patients. Our data do not portray any differences in outcomes for either CPAP or HFNO and meaningful conclusions regarding treatment superiority cannot be drawn from observational data alone. RECOVERY-RS (21) aims to assess the effectiveness of CPAP, HFNO and standard oxygen delivery in a randomised controlled trial and will hopefully provide definitive data to inform decision making about which respiratory support strategy is most likely to be of benefit to individual patients.

A recent study by *Voshaar et al.* (22) expressed an argument for 'permissive hypoxaemia', where they did not enforce a target for oxygen saturation, which allowed them to reduce the number of patients intubated. This resulted in a treatment success rate for CPAP of 83% in patients who were deemed suitable for invasive mechanical ventilation, and they concluded that we should perhaps treat more patients with non-invasive methods of respiratory support. This report has been the topic of some discussion since its publication (23,24). Although our data are not sufficient to draw conclusions regarding the comparison of invasive mechanical ventilation and non-invasive ventilation, we did observe 31 patients who were deemed suitable for mechanical ventilation who survived to discharge without invasive mechanical ventilation. This would suggest that this cohort of patients can be safely and effectively managed on a specialised RSU, thus preserving intensive care capacity for COVID-19 patients requiring intubation and non-COVID-19 patients with intensive care requirements.

There are limitations to our study, including the lack of a control or comparison group and that patient outcomes beyond hospital discharge are not known.

Conclusions

CPAP and HFNO are viable treatment options for patients with hypoxaemic respiratory failure secondary to COVID-19 pneumonia, including those considered unsuitable for invasive ventilation. Patients that are deemed suitable for invasive mechanical ventilation can also be treated safely and effectively outside of ICUs through appropriate use of RSUs; thereby preserving intensive care capacity for COVID-19 patients requiring intubation and non-COVID-19 patients with intensive care requirements.

Conflicts of Interest

We report no conflicts of interest.

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	All Patients (n=140)	Survivors (n=58)	Non-Survivors (n=82)	p-value
Age - Mean (SD)	71.24 (11.1)	66.1 (12.4)	74.4 (9.0)	<0.001
Male – n (%)	91 (65)	34 (59)	55 (67)	0.433
Clinical frailty score – Median (range)	3 (1-7)	2 (1-5)	4 (1-7)	<0.001
CPAP/ HFNO duration in days – Median (range)	3.5 (1-24)	4 (1-24)	3.5 (1-18)	0.642
CPAP/HFNO well-tolerated - n (%)	120 (86)	50 (85)	67 (79)	0.098
Comorbidities - n (%)				
HTN	83 (59)	33 (57)	50 (61)	0.909
Diabetes Mellitus	40 (29)	15 (26)	25 (30)	0.685
COPD	36 (26)	9 (16)	27 (33)	0.031
Asthma	15 (11)	10 (17)	5 (6)	0.026
Home NIV/ CPAP	15 (11)	5 (9)	10 (12)	0.568
Previous Cancer	14 (10)	2 (3)	12 (15)	0.037
IHD	38 (27)	7 (12)	31 (38)	0.001
Smoking History	70 (50)	24 (41)	46 (56)	0.127
Obesity	52 (37)	17 (29)	35 (43)	0.022
Laboratory Results - mean (SD)				
Admission WCC ($x10^9$/L)	9.7 (4.4)	7.8 (3.4)	10.6 (5.1)	0.185
Admission lymphocyte count ($x10^9$/L)	1.02 (0.64)	1.07 (0.89)	0.98 (0.69)	0.631
Admission C-reactive Protein (mg/L)	155 (95.5)	154 (76)	147 (107)	0.129
Observations pre-CPAP/HFNO – Mean (SD)				
Respiratory Rate	25.9 (6.0)	25.3 (5.9)	28.7 (6.8)	0.003
Heart Rate	89.4 (17.0)	89.9 (19.1)	97.3 (21.9)	0.147
Oxygen Saturations	88.8 (6.9)	86.9 (8.1)	87.0 (5.3)	0.387
PaO2/FiO2 Ratio	76.5 (39.1)	78.6 (35.9)	75.2 (41.3)	0.652
CPAP/ HFNO Settings – Mean (SD)				
Starting CPAP PEEP	9.2 (1.8)	8.4 (2.1)	9.7 (1.9)	0.012
Starting CPAP FiO2	66.9 (17.5)	59.6 (16.7)	71.1(16.7)	0.002
Starting HFNO flow rate (L/ min)	54.0 (10.1)	53.9 (10.1)	54.1 (10.3)	0.887
Starting HFNO FiO2	70.0 (14.6)	70.4 (15.9)	69.7 (14.0)	0.966

Table 1. *Comparison of physiological, biochemical, and admission data in patients who survived and those who did not.*

	All patients considered not suitable for IMV (n=98)	Not suitable for IMV Survivors (n=27)	Not suitable for IMV Non-Survivors (n=71)	p-value
Age - Mean (SD)	76.1 (4.6)	72.4 (4.1)	76.3 (4.8)	0.053
Male – n (%)	58 (59)	14 (52)	44 (62)	0.362
Clinical frailty score – Median (range)	4 (1-6)	3.5 (2-5)	4 (1-6)	0.022
CPAP/ HFNO duration in days – Median (range)	4 (1-24)	7 (1-24)	4 (1-11)	0.172
CPAP/HFNO well-tolerated - n (%)	81 (83)	25 (93)	56 (79)	0.053
Comorbidities - n (%)				
HTN	63 (64)	18 (67)	45 (58)	0.593
Diabetes Mellitus	29 (30)	9 (33)	20 (31)	0.539
COPD	32 (33)	5 (19)	27 (38)	0.081
Asthma	6 (6)	1 (4)	5 (6)	0.563
Home NIV/ CPAP	12 (12)	4 (15)	8 (11)	0.585
Previous Cancer	12 (12)	2 (7)	10 (19)	0.397
IHD	32 (33)	5 (19)	27 (38)	0.081
Smoking History	49 (50)	11 (41)	38 (54)	0.258
Obesity	37 (38)	13 (48)	24 (34)	0.033
Laboratory Results - mean (SD)				
Admission WCC (x10^9/L)	10.5 (5.2)	7.4 (4.3)	11.5 (5.1)	0.036
Admission lymphocyte count (x10^9/L)	0.98 (0.68)	0.81 (0.46)	1.04 (0.75)	0.425
Admission C-reactive Protein (mg/L)	160 (105)	191 (78)	150 (113)	0.160
Observations pre-CPAP/HFNO – Mean (SD)				
Respiratory Rate	28.5 (6.6)	26.3 (5.8)	29.2 (6.8)	0.052
Heart Rate	97.9 (21.9)	89.8 (17.1)	100.6 (23.0)	0.089
Oxygen Saturations	88.6 (7.5)	88.4 (7.6)	88.6 (5.9)	0.899
PaO2/FiO2 Ratio	75.7 (40.1)	75.1 (38.8)	75.9 (40.9)	0.932
CPAP/ HFNO Settings – Mean (SD)				
Starting CPAP PEEP	9.4 (1.6)	8.5 (2.0)	9.7 (1.4)	0.111
Starting CPAP FiO2	70.0 (19.7)	75.0 (13.8)	68.3 (21.4)	0.073
Starting HFNO flow rate (L/ min)	54.2 (9.2)	51.3 (9.9)	55.2 (9.1)	0.308
Starting HFNO FiO2	68.3 (14.4)	66.6 (16.7)	69.0 (13.8)	0.702

Table 2. *Comparison of physiological, biochemical, and admission data between survivors and non-survivors in the group of patients deemed unsuitable for invasive mechanical ventilation. .*

IMV: Invasive Mechanical Ventilation

	CPAP - Highest Level of Treatment (n=92)	HFNO – Highest Level of Treatment (n=48)	CPAP - Intention to treat (n=69)	HFNO - Intention to treat (n=71)
Age – Mean (SD)	70.7 (10.0)	71.3 (13.9)	71.1 (9.7)	71.3 (12.3)
Male – n (%)	55 (60)	36 (75)	44 (64)	45 (63)
Inpatient Death – n (%)	55 (60)	27 (56)	40 (58)	44 (64)
Clinical frailty score - median (range)	3 (1-6)	3 (1-7)	3.5 (1-7)	3 (1-7)
CPAP/ HFNO duration in days – median (range)	4 (1-24)	3 (1-14)	4 (1-24)	3 (1-14)
CPAP/HFNO well-tolerated - n (%)	76 (83)	44 (92)	56 (81)	64 (90)
Comorbidities – n (%)				
HTN	60 (65)*	23 (48)*	42 (61)	41 (58)
Diabetes Mellitus	29 (32)	11 (23)	21 (30)	19 (27)
COPD	27 (29)	9 (19)	20 (29)	16 (23)
Asthma	9 (10)	6 (13)	5 (7)	10 (14)
Home NIV/CPAP	12 (13)	3 (6)	10 (14)	5 (7)
Cancer	7 (8)	7 (15)	4 (6)	10 (14)
IHD	27 (29)	11 (23)	19 (28)	19 (27)
Smoking History	51 (55)	19 (40)	31 (45)	39 (55)
Obesity	35 (38)	17 (35)	29 (42)	24 (34)
Laboratory Results – Mean (SD)				
Admission WCC ($x10^9$/L)	9.4 (4.9)	10.1 (4.1)	9.0 (4.6)	8.8 (4.2)
Admission lymphocyte count ($x10^9$/L)	0.97 (0.76)	1.01 (0.54)	0.99 (0.75)	1.04 (0.54)
Admission C-reactive Protein (mg/L)	138.3 (82.1)	144.7 (96.6)	143.0 (82.9)	138.1 (91.0)
Observations pre-CPAP/HFNO – Mean (SD)				
Respiratory Rate	27.8 (6.8)	24.4 (4.9)	26.1 (6.0)	25.8 (5.9)
Heart Rate	89.6 (17.7)	88.7 (15.3)	91.7 (17.7)	87.3 (16.0)
Oxygen Saturations	88.3 (6.8)	90.6 (6.9)	87.9 (7.5)	90.0 (6.1)
FiO2	79.5 (23)	83.8 (26.1)	82.0 (23.5)	83.9 (20.5)
PaO2/FiO2 Ratio	76.0 (34.5)	77.3 (38.2)	77.3 (38.2)	75.9 (40.3)

Table 3. *Admission data, comorbidities, and physiological parameters of patients treated with either CPAP or HFNO, displayed by highest level of treatment and intention to treat analysis.*

**=p<0.05*

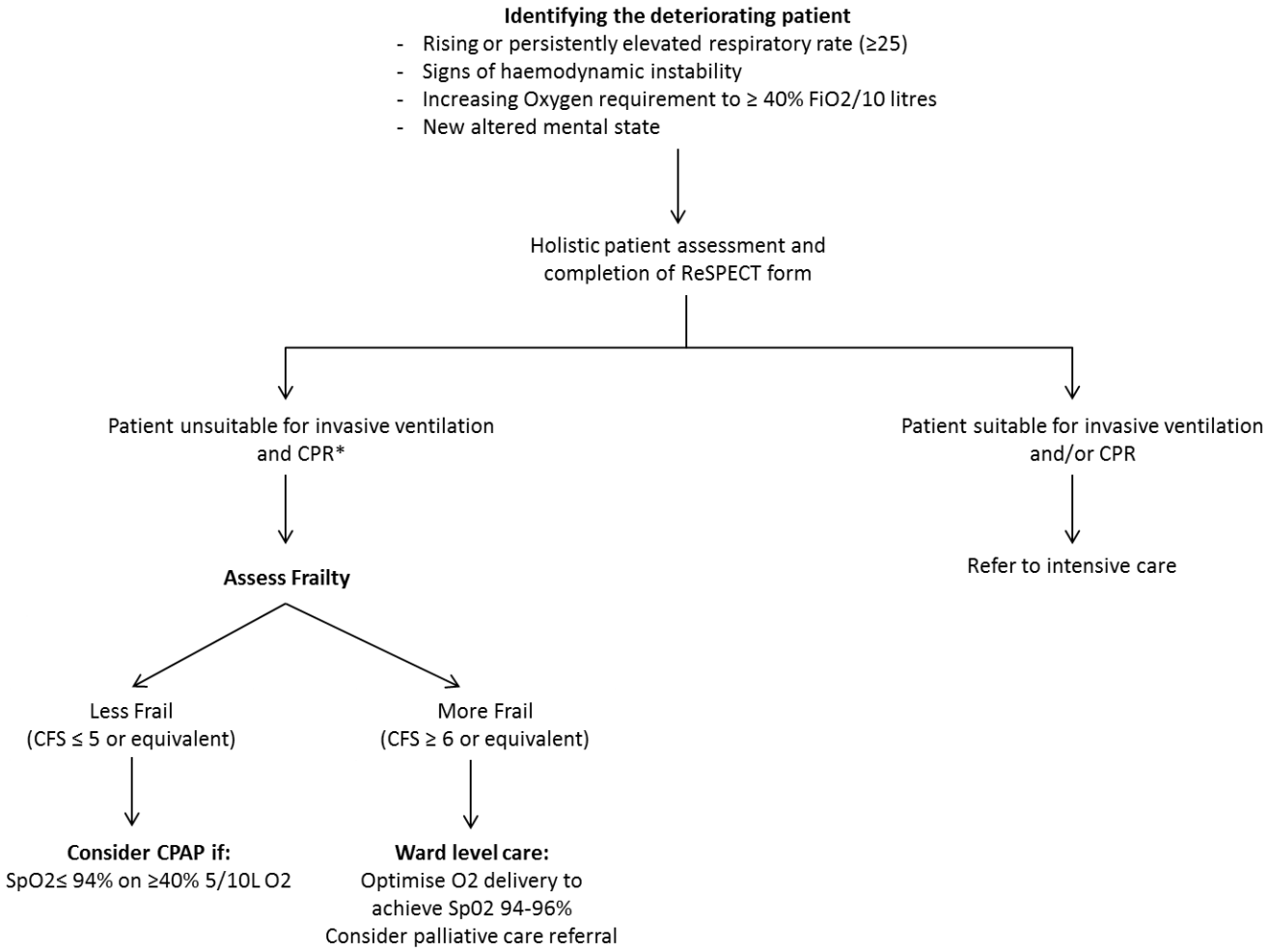

Figure 1. *Hull University Teaching Hospitals (HUTH) treatment algorithm for treating the deteriorating COVID-19 patient. Broadly, patients with CFS score ≥6 were treated for ward-based care (not CPAP) only. Patients with a CFS score of ≤5 were to be discussed with a Respiratory Medicine consultant, for consideration of CPAP/HFNO.*
**Cardiopulmonary Resuscitation*

**ReSPECT = Recommended Summary Plan for Emergency Care and Treatment*