Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19

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Non-invasive respiratory strategies in acute respiratory failure patients with COVID-19: the RECOVERY-RS adaptive randomized clinical trial

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KEY POINTS

Question: what is the clinical effectiveness of continuous positive airway pressure or high-flow nasal oxygen, compared with conventional oxygen therapy in hospitalized adults with acute hypoxemic respiratory failure due to COVID-19?

Findings: In this randomized clinical trial of 1273 patients, CPAP, compared with conventional oxygen therapy reduced the incidence of a composite outcome of tracheal intubation or mortality within 30-days. There was no evidence of a clinical benefit with high-flow nasal oxygen.

Meaning: In patients with acute hypoxemic respiratory failure due to COVID-19, continuous positive airway pressure is a clinically effective strategy. High-flow nasal oxygen is unlikely to be beneficial.

ABSTRACT

Importance

Continuous positive airway pressure and high-flow nasal oxygenation have been recommended for acute hypoxemic respiratory failure in COVID-19. Uncertainty exists regarding effectiveness and safety.

Objective

To determine whether either continuous pressure airway pressure or high-flow nasal oxygen, compared with conventional oxygen therapy, improves clinical outcomes in hospitalized patients with COVID-19 acute hypoxemic respiratory failure.

Design

A parallel group, open-label, three-arm, adaptive, allocation concealed, randomized clinical trial, conducted between April 2020 and May 2021.

Setting

75 acute hospitals across the United Kingdom and Jersey.

Participants

1273 hospitalized adults with COVID-19 acute hypoxemic respiratory failure

Interventions

Participants were randomized to receive continuous positive airway pressure (n=380), high-flow nasal oxygen (n=418), or conventional oxygen therapy (n=475). The randomization system facilitated randomization between one of the two interventions and conventional oxygen therapy, where sites had only one intervention available.

Main outcome and measure

The primary outcome was a composite of tracheal intubation or mortality within 30-days. Secondary outcomes, defined a priori, included tracheal intubation within 30-days, mortality at 30-days, and time to tracheal intubation.

Results

In 1273 randomized patients (mean age 57 years, 66% male, 65% white ethnicity), primary outcome data were available for 99%. The trial stopped prematurely due to declining UK COVID-19 case numbers and the end of the funded recruitment period. The need for intubation or mortality within 30-days was lower with continuous positive airway pressure, compared with conventional oxygen therapy (137 of 377 participants (36.3%) vs 158 of 356 participants (44.4%); unadjusted odds ratio 0.72; 95% confidence interval 0.53 to 0.96, P=0.03). There was no evidence of a difference between high-flow nasal oxygen and conventional oxygen therapy (184 of 415 participants (44.3%) vs 166 of 368 participants (45.1%); unadjusted odds ratio 0.97; 95% confidence interval 0.73 to 1.29, P=0.83).

Conclusions and relevance

Continuous positive airway pressure, compared with conventional oxygen therapy, reduced the composite outcome of tracheal intubation or death within 30 days of randomization in hospitalized adults with acute hypoxemic respiratory failure due to COVID-19. There was no evidence of an effect with high-flow nasal oxygen, compared with conventional oxygen therapy.

Trial registration: ISRCTN.com, registration number ISRCTN16912075.

INTRODUCTION

Acute hypoxemic respiratory failure is a key clinical characteristic of COVID-19 pneumonitis, with 76% of hospitalized patients requiring supplemental oxygen and 9% requiring tracheal intubation and invasive mechanical ventilation.[1] Early in the pandemic, international experiences highlighted the potential risk that intensive care units might become overwhelmed, and high mortality in patients that required invasive mechanical ventilation.[2-4] This drove an urgent public health need to identify strategies to reduce the demand for invasive mechanical ventilation.

In COVID-19 patients with increasing oxygen requirements, non-invasive respiratory strategies, such as continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO), provide a potentially attractive strategy for avoiding invasive mechanical ventilation. In other respiratory diseases, particularly community acquired pneumonia, both CPAP and HFNO may improve clinical outcomes, although those treated with CPAP experience more adverse events.[5,6] In the context of COVID-19, however, there was concern that these strategies might serve only to delay tracheal intubation due to high failure rates, whilst correspondingly exacerbating lung injury through generation of large tidal volumes.[7-10] At a wider system level, there is ongoing uncertainty around the risk of nosocomial infection with aerosol generation and oxygen shortages, due to the high demand placed on hospital oxygen delivery systems.[11,12]

The absence of evidence to support CPAP and HFNO use in patients with COVID-19 led to significant variability both in international guidelines and clinical practice.[9,13] On this basis, we designed a trial to determine whether either CPAP or HFNO, compared with conventional oxygen therapy, reduces the need for the composite outcome of tracheal intubation or mortality within 30-days in hospitalized patients with COVID-19 acute hypoxemic respiratory failure.

METHODS

Study design

Recovery-Respiratory Support was a parallel group, open-label, three-arm, adaptive, randomized controlled trial designed to evaluate the clinical effectiveness of CPAP or HFNO, compared with conventional oxygen therapy, in hospitalized patients with acute hypoxemic respiratory failure due to COVID-19. The adaptive multi-arm multi-stage design allowed the study to stop early if one or both interventions were more effective than conventional oxygen therapy, with the final analysis adjusted to control the overall alpha value (5%).

The trial was conducted across 75 hospitals in the United Kingdom and Jersey. The trial protocol was approved by the London-Brighton & Sussex Research Ethics Committee and the Health Research Authority, sponsored by the University of Warwick, co-ordinated by Warwick Clinical Trials Unit, and funded by the National Institute for Health Research. An independent Trial Steering Committee and Data Monitoring Committee provided trial oversight. The study was conducted in accordance with Good Clinical Practice guidelines, local regulations, and the ethical principles described in the Declaration of Helsinki. Consent from patients or agreement from their surrogates was obtained in keeping with regional regulations.

The trial was prospectively registered (ISRCTN16912075) and its design has been published previously.[14] The trial protocol and statistical analysis plan are available at https://warwick.ac.uk/fac/sci/med/research/ctu/trials/recovery-rs/.

Participants

Adult (≥18-years) hospitalized patients with known or suspected COVID-19 were eligible if they had acute hypoxemic respiratory failure, defined as peripheral oxygen saturations (SpO_2) of 94% or below despite receiving a fraction of inspired oxygen (FiO_2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required. We excluded patients with an immediate (<1-hour) need for invasive ventilation, known pregnancy, or planned withdrawal of treatment. A contraindication to an intervention, based on the judgement of the treating clinician, precluded randomization to that trial arm.

Randomization and masking

Eligible participants were randomized using an internet-based system with allocation concealment. We anticipated that either CPAP or HFNO might be unavailable at sites on a temporary or permanent basis. As such, the randomization system allowed the hospital site to randomize between CPAP, HFNO, and conventional oxygen therapy (on a 1:1:1 basis), or between a single intervention (CPAP/HFNO) and conventional oxygen therapy (on a 1:1 basis). These two systems were integrated and constantly updated to ensure that the allocation ratio was maintained. There was a possibility that this ratio would not be maintained and this was compensated in our sample size, which was inflated accordingly. Sites could not randomize only between CPAP and HFNO. Randomization was stratified by site, sex, and age, and the allocation was generated by a minimization algorithm.

Due to the nature of the trial interventions and context, we were unable to blind patients, treating clinicians, or outcome assessors.

Procedures

Participants randomized to CPAP or HFNO started treatment as soon as possible. Breaks from treatment were permitted for comfort. Participants randomized to conventional oxygen therapy continued to receive oxygen via a face mask or nasal cannulae. In all participants, local policies, and clinical discretion informed decisions regarding choice of device, set-up, titration, treatment targets (e.g. SpO_2) and discontinuation of treatment. Tracheal intubation was performed when clinically indicated, based on the judgement of the treating clinician. We defined crossover as a participant that received a non-allocated intervention (CPAP or HFNO) for a period of over six-hours, unless used as a bridge to tracheal intubation or for palliative care.

At enrolment, we collected information on demographics (including investigator classified sex and ethnicity), co-morbid state, and physiological observations. Collection and reporting of ethnicity was mandated by the funder due to the disproportionate impact of COVID-19 infection on non-white populations.[15] Participants were followed up throughout their hospital stay to record intervention use, crossover, safety events, and outcomes. We undertook data linkage with national datasets to support collection of demographic information and outcomes

Outcomes

The primary outcome was a composite of tracheal intubation or mortality within 30-days of randomization. Tracheal intubation, as an outcome, reflects the need for invasive mechanical ventilation, which is typically delivered in high-resource intensive care units. Secondary outcomes included the incidence of tracheal intubation and mortality at 30 days, time to tracheal intubation, duration of invasive mechanical ventilation, time to death, mortality (critical care, hospital), incidence of intensive care unit admission, and length of stay (critical care, hospital).

Statistical analysis

Early COVID-19 data informed the event rate in the conventional oxygen therapy arm.[16] Assuming a conservative incidence of 15% for the composite outcome of intubation or mortality (with a two-sided 5% significance level and 90% power), a total of 3,000 participants (1,000 per arm across 3 arms) were required. This equated to detecting a reduction of 5% or an odds ratio of 0.625. We inflated this sample size to 4,002, due to the uncertainties in relation to the disease and event rates.

Effectiveness monitoring of each pairwise comparison with conventional oxygen therapy was based on an alpha spending function approach with one-sided pairwise type I error rate of 0.025 and type I error spent at interim analyses proportional to the observed Fisher's information. This allowed the trial to stop early if one or both interventions were more effective than conventional oxygen therapy. Any decision to stop the trial or drop an arm due to futility or safety was left to the Data Monitoring Committee. The sample size calculation assumed the conduct of 11 interim analyses, and one final analysis.

The primary and secondary analyses were performed for the intention-to-treat (ITT) population. Outcome data were compared between each intervention arm and conventional oxygen therapy. Participants in the conventional oxygen therapy arm were only included in a comparison with HFNO or CPAP, if they had the opportunity to be randomized to that intervention. Continuous data were summarized using number of participants, mean, standard deviation (SD), median, and interquartile range (IQR). Categorical data were summarized with frequency count, percentage and missing. Odds ratios (95% confidence interval (CI)) were reported for categorical outcomes using logistic regression models and mean difference (95% CI) reported for continuous outcomes using linear regression models. For time to event analysis, hazard ratios (95% CI) were reported. The number needed to treat (NNT) was obtained for the primary outcome. Where the 95% CI reflected NNT as infinite, number needed to harm was reported. In adjusted analyses, covariates age, sex, morbid obesity, ethnicity, FiO_2, respiratory rate and treatment phases were used, with site included as a random effect.[17,18] Treatment phases were defined as before July 2020, July 2020 to January 2021, after January 2021, based on the introduction of Dexamethasone and Tocilizumab as standard care in June 2020 and January 2021, respectively.[19-21] Due to the non-availability of NHS Digital data, we could not include social deprivation in the adjusted analyses. We used inverse probability weighting to correct for the effect of treatment crossover.The final P value for the primary analysis was corrected for the type I error spent at the interim analyses performed.[22] Thus, $P < 0.05$ was considered as statistically significant for the primary, secondary, and sub-group analyses. Analyses were conducted using SAS and RStudio software.

Trial termination

Over the trial period, trial recruitment closely tracked the number of UK hospitalized COVID-19 patients (Electronic supplement). Trial recruitment stopped early, in line with the end of the 12-month funded recruitment period, and coincided with a rapid decline in hospitalized patients. On this basis, and the need to share accumulated data to inform international treatment of COVID-19 patients, the trial management group proposed to stop recruitment. Prior to stopping, three formal interim analyses had been conducted (36, 160, 387 participants) with the trial continuing after each analysis. The results of interim analyses, other than the decision to continue the trial, were not known to the trial management group, trial steering committee, study sponsor or funder. The decision to stop trial recruitment was agreed by the Trial Steering Committee, study sponsor and funder. It was made independently of the interim analyses.

RESULTS

Between 6th April 2020 and 3rd May 2021, there were 1278 randomizations across 48 hospitals. Five cases underwent double randomisation, leaving 1273 participants (380 CPAP; 418 HFNO; 475 conventional oxygen therapy) (Figure 1). Eight participants withdrew and five patients were lost to follow-up. Primary outcome data were available for 99.0 % (1260/1273) of participants.

We included 733 participants (377 CPAP; 356 conventional oxygen therapy) in the comparison of CPAP with conventional oxygen therapy, and 783 participants (415 HFNO; 368 conventional oxygen therapy) in the comparison of HFNO with conventional oxygen therapy (Electronic supplement).

Participant characteristics were similar at baseline (table one; electronic supplement). The mean age was 57.4 (95% CI, 56.7 to 58.1) years, 66.3% were male, and 65.3% of white ethnicity. Median time from first COVID-19 symptoms to randomisation was 9 days (IQR, 7.0 to 12.0). Baseline mean SpO_2 and FiO_2 were 92.8% (95% CI, 92.6 to 93.1) and 0.61 (95% CI, 0.60 to 0.63) respectively.

The allocated intervention was received by 348/380 (91.6%), 384/418 (91.9%), and 467/475 (98.3%) participants in the CPAP, HFNO, and conventional oxygen therapy arms, respectively (figure one; electronic supplement). In the CPAP group, initial positive end expiratory pressure was set at a mean of 8.3 cmH_2O (95% CI, 8.1 to 8.5) (table two). In the HFNO group, initial flow was set at a mean of 52.4 litres/minute (95% CI, 51.4 to 53.5).

Crossover occurred in 58/380 (15.3%) of participants in the CPAP arm, 48/418 (11.5%) in the HFNO arm, and 112/475 (23.6%) in the conventional oxygen therapy arm (figure one; electronic supplement).

For the comparison of CPAP and conventional oxygen therapy, the primary outcome occurred in 137/377 (36.3%) participants in the CPAP group and 158/356 (44.4%) participants in the conventional oxygen therapy group (unadjusted odds ratio 0.72, 95% CI 0.53 to 0.96, P=0.03, adjusted for interim analyses). For the comparison of HFNO and conventional oxygen therapy, the primary outcome occurred in 184/415 (44.3%) participants in the HFNO group and 166/368 (45.1%) participants in the conventional oxygen therapy group (unadjusted odds ratio 0.97; 95% CI 0.73 to 1.29, P=0.83, adjusted for interim analyses). Findings were consistent across both unadjusted and adjusted analyses (Table 2), and between our primary analysis and inverse probability weighting analysis (electronic supplement). The number needed to treat for CPAP was 12 (95% CI, 7 to 105) and for HFNO was 130 (95% CI, number needed to treat 13 to number needed to harm 16). In unadjusted sub-group analyses, there was no statistical evidence that the treatment effect was modified by baseline characteristics, except for fraction of inspired oxygen in the comparison of HFNO and conventional oxygen therapy (figure two). Findings were broadly consistent between unadjusted and adjusted sub-group analyses (figure two; electronic supplement).

The decrease in the primary outcome in the CPAP group was driven by a decrease in the incidence of tracheal intubation (table 2). Neither CPAP nor HFNO, compared with conventional oxygen therapy, reduced mortality at any time-point. In the CPAP group, fewer participants required admission to critical care and, in those that required tracheal intubation, time to tracheal intubation was longer. There was no evidence of a difference for any other outcome in the comparison of CPAP and conventional oxygen therapy or for any outcome in the comparison of HFNO and conventional oxygen therapy.

Safety events (electronic supplement) occurred most frequently in the CPAP group (CPAP 130/380 (34.2%); HFNO 86/418 (20.6%); conventional oxygen therapy 66/475 (13.9%), p<0.001). The most commonly reported adverse event was hemodynamic instability, occurring in 106 (8.3%) participants. Across all groups, pneumothorax and pneumomediastinum events were reported in 25 (2.0%) and 20 (1.6%) participants respectively. Eight serious adverse events (seven CPAP; one conventional oxygen therapy) were reported. Four were classified as probably or possibly linked to the trial intervention, with all occurring in the CPAP group (surgical emphysema and pneumomediastinum; pneumothorax and pneumomediastinum (two events); and vomiting requiring emergency tracheal intubation).

DISCUSSION

In this open-label, three-arm, adaptive, randomized controlled trial, we included hospitalized adults with acute hypoxemic respiratory failure due to COVID-19 deemed suitable for tracheal intubation if treatment escalation was required. We found that CPAP, compared with conventional oxygen therapy, was effective in reducing the composite outcome of tracheal intubation or mortality within 30-days. In contrast, there was no evidence that HFNO provided a benefit compared with conventional oxygen therapy. This decrease in the incidence of the primary outcome with CPAP was attributable to a decrease in the need for tracheal intubation. Neither HFNO nor CPAP reduced mortality, compared with conventional oxygen therapy. More safety events were reported in the CPAP group.

We designed a pragmatic trial that was deliverable in the context of a pandemic and which tested interventions that precluded blinding of either the participant or treating clinician. The decision to perform tracheal intubation, and thereby commence invasive mechanical ventilation, was not standardised .[13] It is possible that the lower tracheal intubation rate in the CPAP group may have been driven by a greater willingness amongst clinicians and patients to delay intubation, and this may be supported by our finding that time to tracheal intubation was longer in the CPAP group. However, physiology at the time of tracheal intubation was similar across groups, suggesting that, irrespective of treatment strategy, clinicians used a similar threshold to determine the need for tracheal intubation. Furthermore, this effect was not observed with HFNO, which should have been susceptible to the same risk of performance bias.

Our decision to not standardize escalation to tracheal intubation was driven by clinical uncertainty regarding the optimal timing and threshold of tracheal intubation in patients with COVID-19.[13,23] Whilst rapidly building clinical consensus may be achievable in trials recruiting in a small number of hospitals, such as the HENIVOT trial, we determined that any attempt to stipulate specific criteria might influence clinical equipoise and patient acceptability, impact trial recruitment, and, more importantly, reduce trial generalisability.[24] Previous large trials of non-invasive respiratory strategies have differed in their approach to protocolization of tracheal intubation, which likely reflects these specific challenges, even in respiratory conditions where the pathophysiology has been well described.[25-27]

A recent systematic review and meta-analysis of 25 randomized controlled trials (3804 patients) summarised evidence on the clinical effectiveness of non-invasive ventilation (with and without pressure support) and HFNO, compared with conventional oxygen therapy, in acute respiratory failure.[5] Across 14 trials (1275 patients), facemask non-invasive ventilation reduced the risk of both mortality and tracheal intubation. In contrast, HFNO reduced the risk of tracheal intubation (five trials, 1479 patients), but not mortality (three trials, 1279 patients). We found that CPAP reduced tracheal intubation, but not mortality, although our trial was not specifically powered to detect differences in mortality. We found that HFNO did not reduce the need for tracheal intubation. One explanation for these discordant findings is differences in pathophysiology between COVID pneumonitis and other causes of acute respiratory failure[5,28] Furthermore, in our trial, some hospitals modified care pathways to deliver CPAP and HFNO outside of a critical care unit, which may have influenced the clinical effectiveness of the interventions.

Two randomized controlled trials of non-invasive respiratory strategies in COVID-19 have previously reported.[24,29] One trial of 22 patients that compared HFNO with conventional oxygen therapy reported that HFNO improved PaO_2/FiO_2 ratio and reduced ICU length of stay.[29] These data should be interpreted with caution due to the small sample size and high risk of bias. In contrast to our study, the HENIVOT trial directly compared helmet non-invasive ventilation (with pressure support) and HFNO in 110 COVID-19 patients across four intensive care units.[24] No difference was observed in the primary outcome of days free of respiratory support, although fewer patients in the non-invasive ventilation arm required tracheal intubation (odds ratio 0.41, 95% CI 0.18-0.89). However, the trial's highly protocolised approach to the set-up and weaning of trial interventions and the decision to perform tracheal intubation potentially limits its generalisability.

Our trial has several limitations. Firstly, we did not achieve our planned sample size with the decision to stop recruitment driven by practical reasons linked to reducing numbers of COVID-19 in the UK, and an ethical obligation to share accumulated data with the international clinical community. Secondly, we observed crossover between allocated treatment arms, principally from the conventional oxygen therapy arm to one or both interventions. This is a common challenge in trials of non-invasive respiratory strategies, and reduces the observed effect size of a clinically effective treatment.[26,27] Nevertheless, findings from our inverse probability weighting analysis were consistent with our primary analysis. Thirdly, we determined that it would be impractical to collect screening data, meaning we cannot describe the number of non-randomized patients and reasons for non-randomization. Finally, the trial was rapidly set-up early in the pandemic, prior to the development of a core outcome set for COVID-19 trials.[30] Whilst our outcome list aligns closely to most of the core outcomes subsequently identified, we did not capture information on patient recovery following hospital discharge.

In conclusion, in this randomized trial of hospitalized adults with acute hypoxemic respiratory failure due to COVID-19, CPAP, compared with conventional oxygen therapy, reduced the composite outcome of tracheal intubation or death within 30 days of randomization in hospitalized adults with acute hypoxemic respiratory failure due to COVID-19. There was no evidence of an effect, compared with conventional oxygen therapy, with the use of HFNO.

Author contributions

Professors Perkins, Lall, McAuley and Drs Ji and Hee had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of data analysis.

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The sponsor and funder approved the design of the study and monitored the conduct of the study. They played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of interests

Professor Perkins is supported as an NIHR senior investigator and through the NIHR West Midlands Applied Research Collaboration. Professor McAuley is programme director for the NIHR Efficacy and Mechanism Evaluation programme. Dr Connolly is a director of research for the Intensive Care Society. Professors Perkins and McAuley were, until recently (term ended June 2021), directors of research for the Intensive Care Society. Professors Dark and De Soyza are NIHR CRN National Specialty Cluster Leads. Professor Dark is supported by the Manchester NIHR Biomedical Research Centre.

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Respironics, Philips, Resmed, and Fisher and Paykel; and institutional funding for his role on the Philips Global Medical Advisory Board. Dr Messer reports personal fees from Fisher and Paykel. Dr Parekh reports grant funding from the NIHR and Medical Research Council UK Research and Innovation. Professor Steiner reports personal fees from GlaxoSmithKline. Professor McAuley reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis, SOBI and Eli Lilly, and from sitting on DMECs for trials undertaken by Vir Biotechnology and Faron Pharmaceuticals. Professor McAuley also reports grant funding to his institution from several funders (NIHR, Wellcome Trust, Innovate UK, Medical Research Council, and Northern Ireland Health and Social Research and Development division) for studies in patients with ARDS and COVID-19, and a patent (US8962032) issued to his institution as a treatment for inflammatory disease. The remaining authors report no conflicts of interest.

Data sharing

The protocol, statistical analysis plan and other key trial documents are available at https://warwick.ac.uk/fac/sci/med/research/ctu/trials/recovery-rs/. Requests for data sharing will be reviewed on an individual basis by the chief investigators. The study will comply with the good practice principles for sharing individual participant data from publicly funded clinical trials and data sharing will be undertaken in accordance with the required regulatory requirements. Requests for access to deidentified participant-level data should be directed to Professors Perkins (g.d.perkins@warwick.ac.uk) and McAuley (d.f.mcauley@qub.ac.uk).

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FIGURE LEGENDS

Figure 1: Enrolment and outcomes

Figure 2: Unadjusted sub-group analyses

Table 1: Characteristics of participants at baseline

	Conventional Oxygen Therapy	CPAP	HFNO
Age, mean (SD), years	57.6 (12.7)	56.7 (12.5)	57.6 (13.0)
Sex			
Male	312 (65.7%)	260 (68.4%)	272 (65.1%)
Female	163 (34.3%)	120 (31.6%)	146 (34.9%)
Ethnicity – no. (%)			
Asian	90 (19.0%)	73 (19.2%)	77 (18.4%)
Black	19 (4.0%)	16 (4.2%)	14 (3.4%)
Mixed	6 (1.3%)	3 (0.8%)	4 (1.0%)
White	312 (65.7%)	243 (64.0%)	276 (66.0%)
Other	9 (1.9%)	11 (2.9%)	12 (2.9%)
Unknown	35 (7.4%)	33 (8.7%)	34 (8.1%)
Time from symptom onset to hospital admission (days)- Median (IQR)	7.0 (5.0-10.0), n=466	7.0 (5.5-10.0), n=376	8.0 (5.0-10.0), n=407
Time from symptom onset to randomization (days)- Median (IQR)	9.0 (6.0-12.0), n=470	9.0 (7.0-12.0), n=378	9.0 (7.0-12.0), n=414
COVID-19 status – no. (%)			
Confirmed	409 (86.1%)	326 (85.8%)	355 (84.9%)
Suspected	64 (13.5%)	53 (14.0%)	62 (14.8%)
Co-morbidities – no. (%)			
None	188 (39.6%)	148 (39.0%)	141 (33.7%)
ESRF requiring RRT	5 (1.1%)	2 (0.5%)	6 (1.4%)
Congestive cardiac failure	5 (1.1%)	2 (0.5%)	4 (1.0%)
Chronic lung disease	66 (13.9%)	65 (17.1%)	52 (12.4%)
Coronary heart disease	44 (9.3%)	34 (9.0%)	26 (6.2%)
Dementia	3 (0.6%)	4 (1.1%)	1 (0.2%)
Diabetes requiring medication	91 (19.2%)	86 (22.6%)	98 (23.4%)
Hypertension	153 (32.2%)	131 (34.5%)	164 (39.2%)
Uncontrolled or active malignancy	7 (1.5%)	7 (1.8%)	10 (2.4%)
Morbid obesity (BMI >35)	75 (15.8%)	62 (16.3%)	81 (19.4%)
Clinical Frailty Scale (pre-admission) no. (%)			
CFS1 - Very Fit	62 (13.1%)	72 (19.0%)	71 (17.0%)
CFS2 - Well	237 (49.9%)	192 (50.5%)	196 (46.9%)
CFS3 - Managing Well	131 (27.6%)	87 (22.9%)	109 (26.1%)
CFS4 - Vulnerable	30 (6.3%)	12 (3.2%)	27 (6.5%)
CFS5 - Mildly Frail	6 (1.3%)	4 (1.1%)	6 (1.4%)
CFS6 - Moderately Frail	3 (0.6%)	3 (0.8%)	0 (0.0%)
CFS7 - Severely Frail	0 (0.0%)	0 (0.0%)	2 (0.5%)
CFS8 - Very Severely Frail	0 (0.0%)	0 (0.0%)	0 (0.0%)
CFS9 - Terminally Ill	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory rate (breaths per minute)- Mean (SD)	25.0 (6.8), n=472	26.4 (7.5), n=377	25.3 (6.9), n=414
FiO_2- Mean (SD)	0.61 (0.24), n=459	0.62 (0.24), n=363	0.60 (0.24), n=404
SpO_2(%)- Mean (SD)	93.1 (3.8), n=470	92.9 (3.7), n=378	92.6 (3.9), n=409
SpO_2 to FiO_2 ratio (%)- Mean (SD)	186.4 (99.1), n=457	183.5 (95.6), n=363	187.5 (98.5), n=399
PaO_2 (mmHg)- Mean (SD)	73.3 (24.1), n=317	71.0 (17.8), n=238	69.9 (20.0), n=287
PaO_2 to FiO_2 ratio (mmHg)- Mean (SD)	135.3 (82.9), n=308	131.6 (67.7), n=229	138.2 (87.5), n=284
$PaCO_2$ (mmHg)- Mean (SD)	34.3 (6.2), n=331	33.5 (5.3), n=252	33.5 (6.2), n=306
Key- BMI- body mass index; CPAP- Continuous Positive Airway Pressure; ESRF- end-stage renal failure; FiO_2- fraction of inspired oxygen; HFNO- High-flow nasal oxygen; $PaCO_2$ -Partial pressure of carbon dioxide; PaO_2 -Partial pressure of oxygen;			

RRT- Renal replacement therapy; SpO2-Peripheral oxygen saturation.			

Table two: intervention delivery

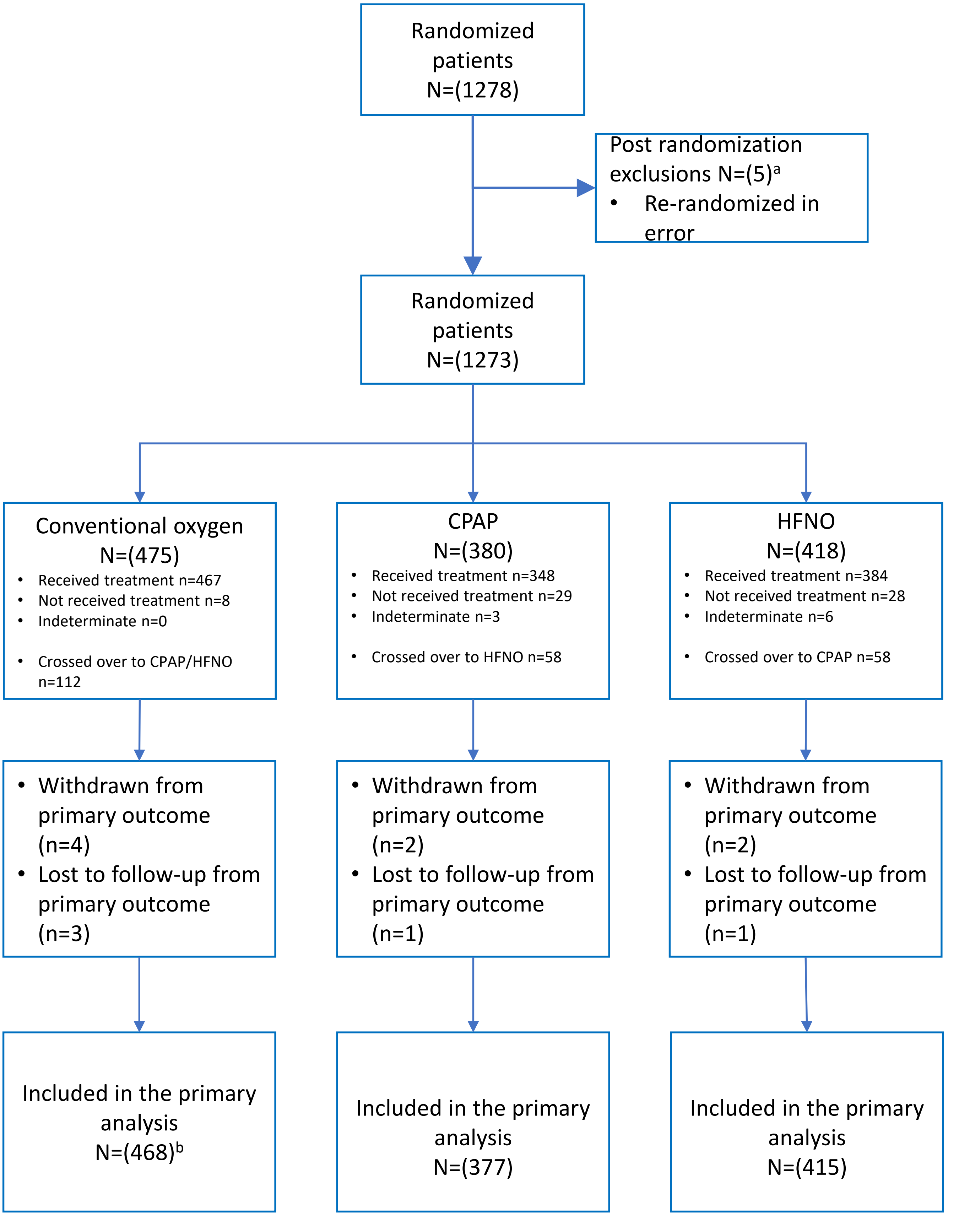
	Conventional Oxygen Therapy	CPAP	HFNO
CPAP set-up PEEP (cmH_20)- Mean (SD)	-	8.3 (2.1), n=304	
CPAP delivery device– no. (%)			
NIV device in CPAP mode		147 (38.7)	
CPAP device		173 (45.5)	
Other		24 (6.3)	
HFNO set-up flow (liters/ minute)- Mean (SD)	-		52.4 (9.8), n=323
Treatment delivery duration (days)- Mean (SD)	-	3.5 (4.6), n=340	3.7 (4.1), n=378
Awake prone positioning – no. (%)			
Yes	252 (53.1%)	207 (54.5%)	243 (58.1%)
No	122 (25.7%)	120 (31.6%)	98 (23.4%)
Unknown	90 (19.0%)	51 (13.4%)	73 (17.5%)
Worst physiology in 60-minutes prior to tracheal intubation			
Respiratory rate (breaths per minute)- Mean (SD)	31.7 (9.5), n=103	33.9 (9.6), n=73	29.8 (9.7), n=86
FiO_2- Mean (SD)	0.84 (0.20), n=117	0.77 (0.19), n=88	0.81 (0.20), n=100
SpO_2(%)- Mean (SD)	90.5 (4.9), n=122	91.5 (5.5), n=86	90.0 (6.2), n=100
SpO_2 to FiO_2 ratio (%)- Mean (SD)	118.8 (62.5), n=109	131.4 (56.7), n=81	119.0 (49.0), n=89
PaO_2 (mmHg)- Mean (SD)	42.3 (11.2), n=97	43.4 (11.7), n=70	40.9 (13.5), n=76
PaO_2 to FiO_2 ratio (mmHg)- Mean (SD)	57.8 (33.4), n=88	62.3 (29.7), n=65	52.7 (27.7), n=69
$PaCO_2$ (mmHg)- Mean (SD)	68.7 (19.7), n=94	71.4 (21.4), n=69	66.0 (14.3), n=71
Conscious level– no. (%)			
Alert	112 (56.3%)	72 (57.1%)	93 (53.9%)
Responsive to Voice	3 (1.5%)	7 (5.6%)	4 (2.4%)
Responsive to Pain	0 (0.0%)	0 (0.0%)	1 (0.6%)
Unresponsive	7 (3.5%)	1 (0.8%)	7 (4.1%)
Unknown	59 (29.7%)	32 (25.4%)	49 (29.0%)
Key- FiO2- fraction of inspired oxygen; HFNO- High-flow nasal oxygen; $PaCO_2$ - Partial pressure of carbon dioxide; PaO2 -Partial pressure of oxygen; PEEP- Positive End Expiratory Pressure; SpO2- Peripheral oxygen saturation.			

Table three: primary and secondary outcomes

	Pairwise Treatment Comparisons				**Odds Ratio/Hazard Odds/Mean Difference (95% CI)**					
	CPAP versus Conventional Oxygen Therapy[f]		HFNO versus Conventional Oxygen Therapy[g]		CPAP versus Conventional Oxygen Therapy [f]			HFNO versus Conventional Oxygen Therapy [g]		
	CPAP	Conventional Oxygen	HFNO	Conventional Oxygen	Unadjusted	Adjusted	P value (unadj/adj)	Unadjusted	Adjusted	P value (unadj/adj)
Tracheal Intubation or mortality within 30 days[a,d]	137/377 (36.3%)	158/356 (44.4%)	184/415 (44.3%)	166/368 (45.1%)	0.72 (0.53-0.96)	0.68 (0.48-0.94)	0.034/0.022	0.97 (0.73 - 1.29)	0.94 (0.68-1.29)	0.829/0.688
Intubation within 30 days[a]	126/377 (33.4%)	147/356 (41.3%)	170/415 (41.0%)	153/368 (41.6%)	0.71 (0.53-0.96)	0.67 (0.48-0.93)	0.028/0.018	0.98 (0.73-1.30)	0.94 (0.69 - 1.30)	0.862/0.724
Mortality at 30 days(%)[a]	63/378 (16.7%)	69/359 (19.2%)	78/416 (18.8%)	74/370 (20.0%)	0.84 (0.58 - 1.23)	0.91 (0.59 - 1.39)	0.367/0.649	0.92 (0.65 - 1.32)	0.97 (0.65 - 1.46)	0.658/0.903
Secondary outcomes										
Tracheal Intubation rate in the study period[a, e]	126/377 (33.4%)	147/356 (41.3%)	169/415 (40.7%)	154/368 (41.8%)	0.71 (0.53-0.96)	0.67 (0.48-0.93)	0.028/0.018	0.95 (0.72-1.27)	0.92 (0.67-1.27)	0.750/0.625
Admission to critical care [a]	204/368 (55.4%)	219/348 (62.9%)	252/408 (61.8%)	214/361 (59.3%)	0.73 (0.54-0.99)	0.69 (0.49-0.96)	0.042/0.030	1.11 (0.83-1.48)	1.04 (0.75-1.45)	0.482/0.810
Duration of invasive ventilation (days)										
All randomized patients	0.0 (0.0 - 8.0)	0.0 (0.0 - 10.0)	0.0 (0.0 - 11.0)	0.0 (0.0 - 10.0)	NA	NA		NA	NA	
Intubated patients [b]	15.0 (8.0 - 25.0)	11.0 (6.0 - 23.0)	15.0 (8.0 - 26.0)	12.0 (6.0 - 23.0)	0.82 (0.61-1.09)	0.83 (0.61-1.12)	0.173/0.221	0.92 (0.71 – 1.20)	1.01 (0.76 - 1.34)	0.558/0.959
Time to intubation (days) [b]	2.0 (1.0 – 4.0)	1.0 (0.0-4.0)	1.0 (0.0-3.0)	1.0 (0.0-3.0)	0.77 (0.61 - 0.98)	0.71 (0.56 - 0.91)	0.034/0.007	0.98 (0.78 - 1.21)	0.92 (0.74 - 1.16)	0.824/0.493
Time to death (days) [b]	17.0 (11.0-26.0)	17.0 (11.0-24.0)	16.5 (9.0-22.5)	17.0 (11.0-24.0)	0.86 (0.61-1.21)	0.93 (0.65-1.33)	0.376/0.690	0.94 (0.68-1.29)	0.94 (0.67 - 1.32)	0.688/0.737
Mortality in critical care [a]	62/204 (30.4%)	66/219 (30.1%)	72/251 (28.7%)	65/214 (30.4%)	1.01 (0.67-1.53)	1.10 (0.69-1.75)	0.955/0.681	0.92 (0.62-1.38)	0.98 (0.63 - 1.54)	0.691/0.941
Mortality in hospital[a]	72/364 (19.8%)	78/346 (22.5%)	86/405 (21.2%)	80/359 (22.3%)	0.85 (0.59 - 1.22)	0.92 (0.62 - 1.38)	0.368/0.689	0.94 (0.67 - 1.33)	0.99 (0.67 - 1.47)	0.726/0.972
Length of critical care stay (days)[c]	9.5 (15.6)	9.6 (13.6)	10.5 (15.6)	9.6 (14.1)	-0.08 (-2.23, 2.07)	-0.16 (-2.30, 1.99)	0.943/0.884	0.95 (-1.16, 3.07)	0.47 (-1.57, 2.50)	0.377/0.653

Length of hospital stay (days)[c]	16.4 (17.5)	17.3 (18.1)	18.3 (20.0)	17.1 (18.0)	-0.96 (-3.59, 1.67)	-1.14 (-3.84, 1.55)	0.474/0.406	1.21 (-1.50, 3.93)	0.33 (-2.28, 2.94)	0.380/0.803

Table legend:
Data are n/N (%), median (IQR), or mean (SD)
Key- CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen
The % are based on excluding missing data (i.e. withdrawals and no data provided).
The footnote in figure two provides details on how data were censored for time-to-event analyses.
a- Reported as odds ratio; b- Reported as hazard odds; c- Reported as mean difference (pairwise comparisons include those with completed critical care/hospital stay. Patients not admitted to critical care were allocated a critical care stay of 0 days)
d- the final p value for the primary analysis is corrected for the interim analyses performed using the method described by Jennison and Turnbull[22]
e- Outcome included tracheal intubation during the index hospital admission- compared with the 30-day analysis, this excluded one patient that was intubated within 30-days, but outside the index hospital admission (HFNO arm) and included one patient that was intubated in the index hospital admission but occurred more than 30-days post-randomization (conventional oxygen therapy arm)- both in the HFNO v conventional oxygen therapy comparison.
f- Includes patients randomized between CPAP and conventional oxygen therapy, or between CPAP, HFNO, and conventional oxygen therapy.
g- Includes patients randomized between HFNO and conventional oxygen therapy, or between CPAP, HFNO, and conventional oxygen therapy



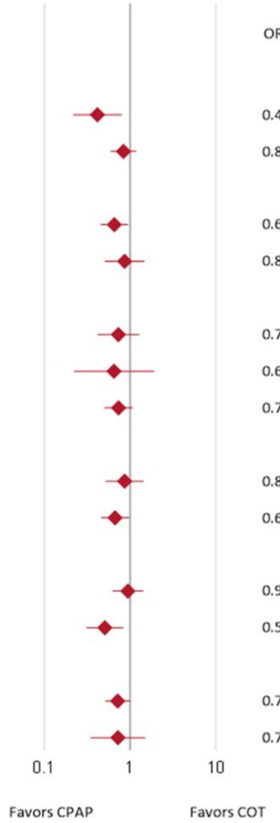
a) Of the 1278 patients randomized, 5 were re-randomized in error and excluded from the summaries and analysis

b) Of the 468 conventional oxygen therapy participants, 356 were included in the comparison with CPAP, and 368 were included in the comparison with HFNO

Key: CPAP- Continuous positive airway pressure; HFNO- High-flow nasal oxygen

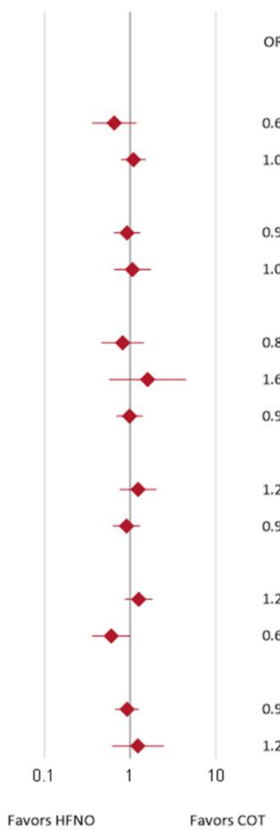
Continuous positive airway pressure v conventional oxygen therapy

Subgroup	Intubation or mortality in 30 days: CPAP	COT	OR (95% CI)	p (interaction)
Age group				0.06
<50 years	34/92 (37%)	20/102 (20%)	0.42 (0.22, 0.79)	
>=50 years	124/264 (47%)	117/275 (43%)	0.84 (0.60, 1.17)	
Sex				0.39
Male	110/239 (46%)	92/257 (36%)	0.65 (0.46, 0.94)	
Female	48/117 (41%)	45/120 (38%)	0.86 (0.51, 1.45)	
Ethnicity				0.98
Black, Asian and minority ethnic	47/101 (47%)	40/103 (39%)	0.73 (0.42, 1.27)	
Unknown	11/30 (37%)	9/33 (27%)	0.65 (0.22, 1.88)	
White	97/221 (44%)	88/241 (37%)	0.74 (0.51, 1.07)	
Time from onset to randomization				0.42
<=7 days	59/119 (50%)	56/122 (46%)	0.86 (0.52, 1.43)	
>7 days	96/233 (41%)	81/254 (32%)	0.67 (0.46, 0.97)	
FiO2				0.06
<=0.6	70/216 (32%)	67/215 (31%)	0.94 (0.63, 1.42)	
>0.6	79/125 (63%)	68/146 (47%)	0.51 (0.31, 0.83)	
BMI				0.99
<=35 kg/m2	127/296 (43%)	110/314 (35%)	0.72 (0.52, 0.99)	
>35 kg/m2	28/56 (50%)	26/62 (42%)	0.72 (0.35, 1.49)	



High-flow nasal oxygen v conventional oxygen therapy

Subgroup	Intubation or mortality in 30 days: COT	HFNO	OR (95% CI)	p (interaction)
Age group				0.13
<50 years	37/97 (38%)	31/108 (29%)	0.65 (0.36, 1.17)	
>=50 years	129/271 (48%)	153/307 (50%)	1.09 (0.79, 1.52)	
Sex				0.63
Male	116/239 (49%)	126/271 (46%)	0.92 (0.65, 1.31)	
Female	50/129 (39%)	58/144 (40%)	1.07 (0.66, 1.73)	
Ethnicity				0.53
Black, Asian and minority ethnic	44/91 (48%)	46/106 (43%)	0.82 (0.47, 1.44)	
Unknown	10/28 (36%)	16/34 (47%)	1.60 (0.57, 4.46)	
White	110/246 (45%)	122/275 (44%)	0.99 (0.70, 1.39)	
Time from onset to randomization				0.31
<=7 days	68/132 (52%)	75/132 (57%)	1.24 (0.76, 2.01)	
>7 days	94/232 (41%)	107/280 (38%)	0.91 (0.64, 1.30)	
FiO2				0.02
<=0.6	83/238 (35%)	106/263 (40%)	1.26 (0.88, 1.81)	
>0.6	75/117 (64%)	72/139 (52%)	0.60 (0.36, 1.00)	
BMI				0.45
<=35 kg/m2	137/309 (44%)	141/333 (42%)	0.92 (0.67, 1.26)	
>35 kg/m2	26/55 (47%)	42/80 (53%)	1.23 (0.62, 2.45)	



Non-invasive respiratory strategies in acute respiratory failure patients with COVID-19: the RECOVERY-RS adaptive randomized clinical trial

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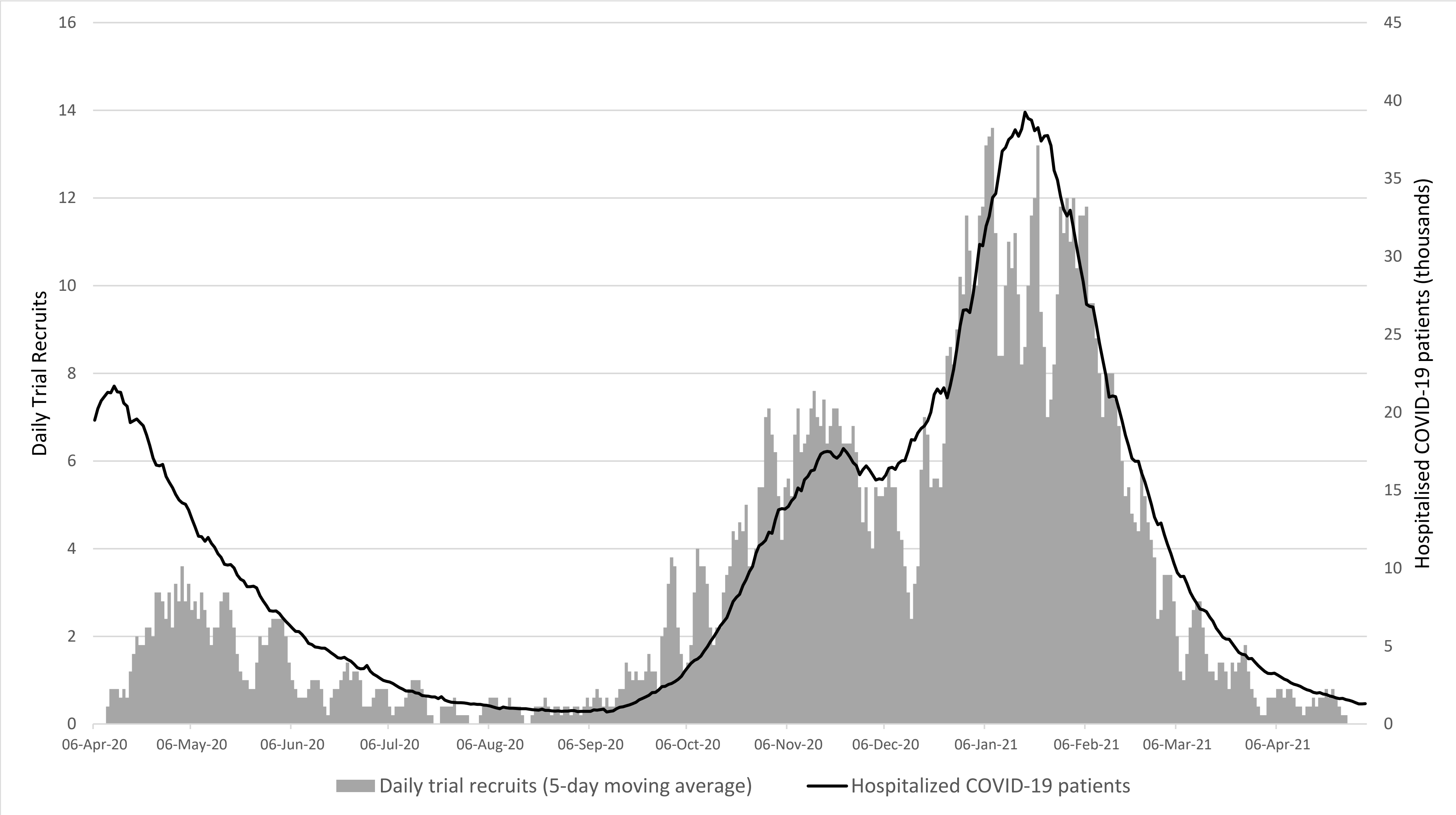
Figure S1: RECOVERY RS trial recruitment and UK hospitalized COVID-19 patients



Data for hospitalized COVID-19 patients extracted from publicly available UK data sources at https://coronavirus.data.gov.uk/details/healthcare

Table S1: Summary of randomizations and data for pairwise comparisons

Randomization	Treatment arm		
	CONVENTIONAL OXYGEN THERAPY	CPAP	HFNO
Device availability			
CPAP and conventional oxygen therapy only	103	114	NA
HFNO and conventional oxygen therapy only	113	NA	109
CPAP, HFNO and conventional oxygen therapy	259	266	309
Total	475	380	418
	Treatment arm		
Pairwise comparison	**CONVENTIONAL OXYGEN THERAPY**	**CPAP**	**HFNO**
CPAP vs CONVENTIONAL OXYGEN THERAPY	362 (48.8%)	380 (51.2%)	NA
HFNO vs CONVENTIONAL OXYGEN THERAPY	372 (47.1%)	NA	418 (52.9%)

Key: CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen

Table S2: Summary of trial crossover by treatment arm

Category of crossover	n/N (%)
Participants randomized to CPAP	
Received HFNO	58/380 (15.3%)
Participants randomized to HFNO	
Received CPAP	48/418 (11.5%)
Participants randomized to conventional oxygen therapy	
Received CPAP	40/475 (8.4%)
Received HFNO	36/475 (7.6%)
Received both CPAP and HFNO	36/475 (7.6%)

Key: CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen

Table S3: Additional participant baseline characteristics

Characteristic	Conventional Oxygen Therapy	CPAP	HFNO
Core body temperature at hospital admission (°C)- Mean (SD)	37.6 (1.0), n=472	37.7 (1.0), n=377	37.7 (1.0), n=414
Heart Rate (per minute)- Mean (SD)	88.7 (16.7), n=469	91.1 (17.0), n=371	90.4 (15.8), n=410
Systolic blood pressure (mmHg)- Mean (SD)	127.3 (18.1), n=473	128.6 (19.0), n=377	128.4 (18.2), n=414
Diastolic blood pressure (mmHg)- Mean (SD)	75.6 (11.2), n=473	75.2 (12.4), n=374	75.4 (12.2), n=414
Urea (mmol/l)- Mean (SD)	39.4 (23.9), n=464	39.4 (23.7), n=372	41.1 (25.0), n=410
Confusion – no. (%)			
Confused	9 (1.9)	14 (3.7)	9 (2.2)
Not confused	461 (97.1)	364 (95.8)	407 (97.4)
N/A- sedated	1 (0.2)	0	1 (0.2)
CURB-65 Score – no. (%)			
0	171 (36.0)	133 (35.0)	136 (32.5)
1	175 (36.8)	129 (34.0)	151 (36.1)
2	89 (18.7)	71 (18.7)	85 (20.3)
3	22 (4.6)	30 (7.9)	29 (6.9)
4	3 (0.6)	2 (0.5)	4 (1.0)
5	1 (0.2)	0 (0.0)	0 (0.0)
Treatment phases – no. (%)			
Before July 2020	47 (9.9)	47 (12.4)	44 (10.5)
July 2020 - January 2021	331 (69.7)	262 (69.0)	289 (69.1)
After January 2021	97 (20.4)	71 (18.7)	85 (20.3)

Key: CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen

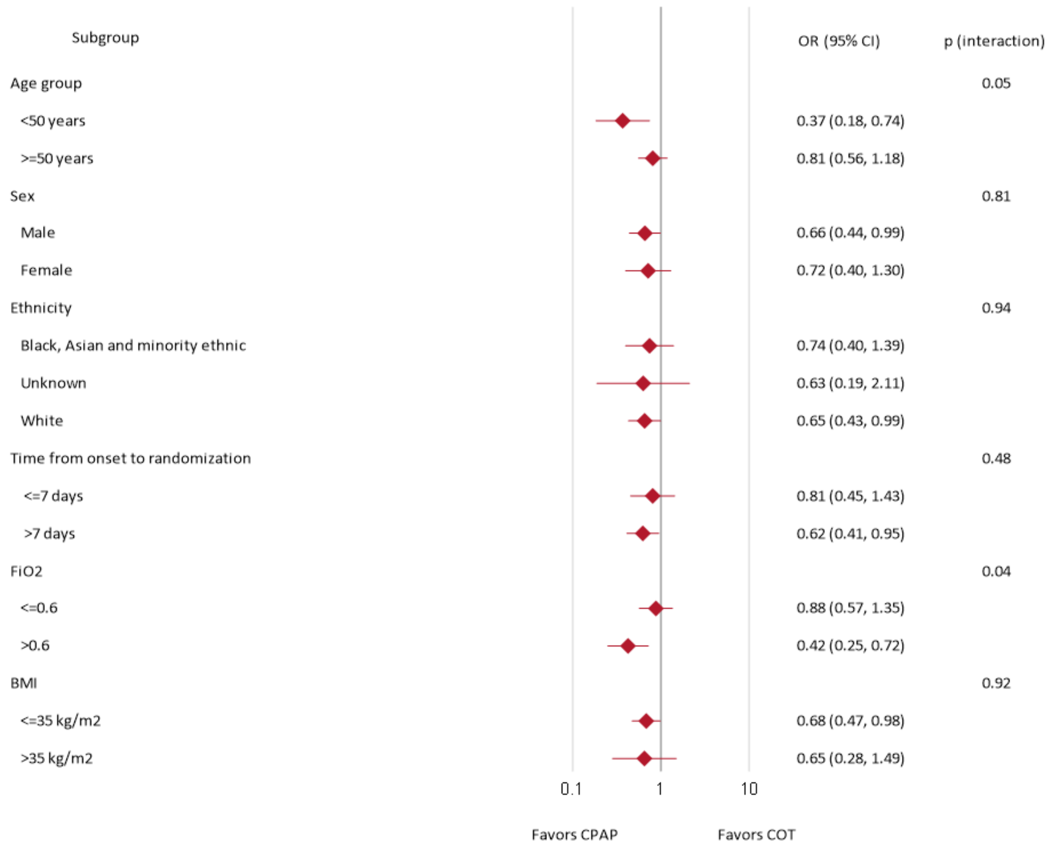
Table S4: Inverse probability weighting analysis

	CPAP versus Conventional Oxygen Therapy [a]		HFNO versus Conventional Oxygen Therapy [b]	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Tracheal Intubation or mortality within 30 days[c] - Odds ratio (95% confidence interval)-	0.65 (0.44, 0.96)	0.62 (0.39, 0.96)	1.05 (0.71, 1.55)	0.98 (0.64, 1.52)

Key: CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen
a) Includes patients randomized between CPAP and conventional oxygen therapy, or between CPAP, HFNO, and conventional oxygen therapy.
b) Includes patients randomized between HFNO and conventional oxygen therapy, or between CPAP, HFNO, and conventional oxygen therapy
c) Inverse probability weighting was used to take into account crossovers in each treatment arm. Weights were estimated using baseline covariates, including age, sex, ethnicity, treatment phases, FiO2, PaO2, comorbidity status, heart rate, respiratory rate, Clinical Frailty Scale. Bootstrapping was used to obtain 95% confidence intervals.

Figure S2: Adjusted sub-group analyses

Panel a- Continuous positive airway pressure v conventional oxygen therapy



Panel b- High-flow nasal oxygen v conventional oxygen therapy

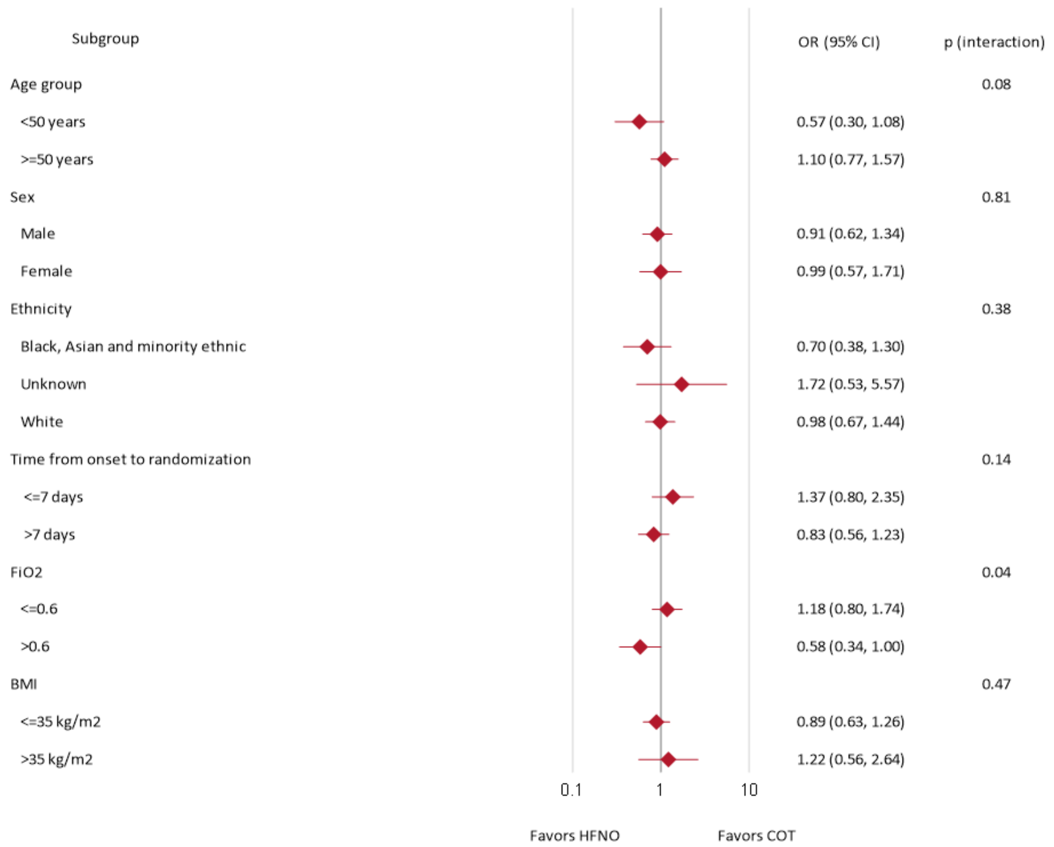
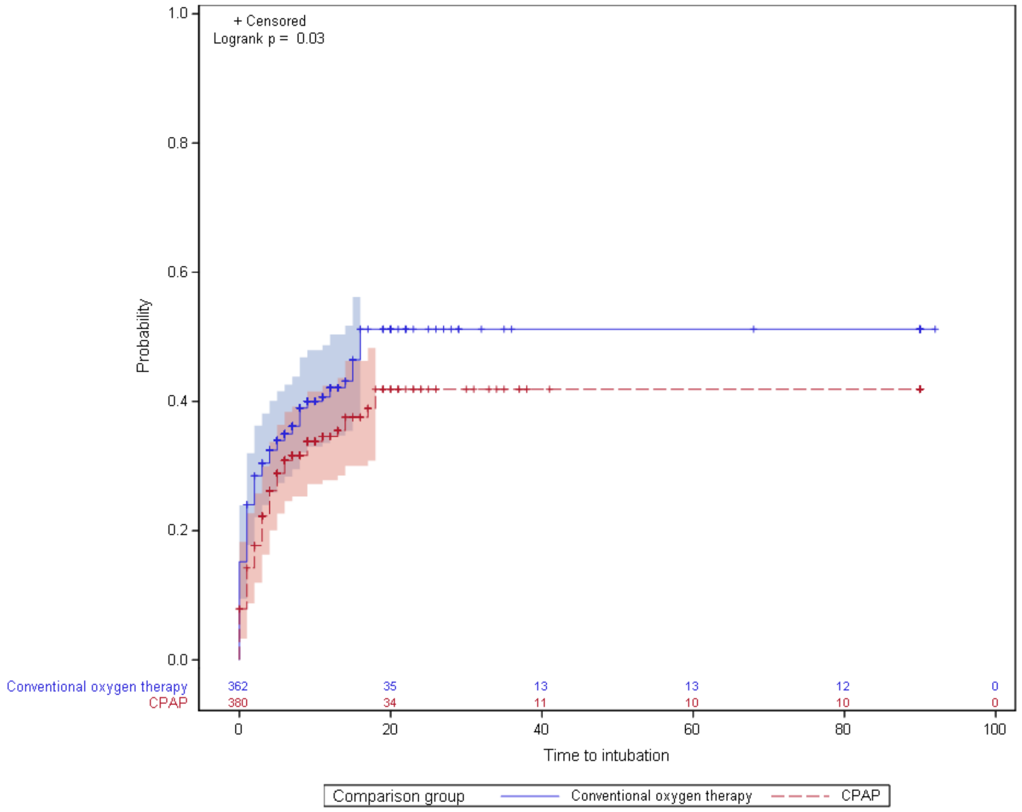
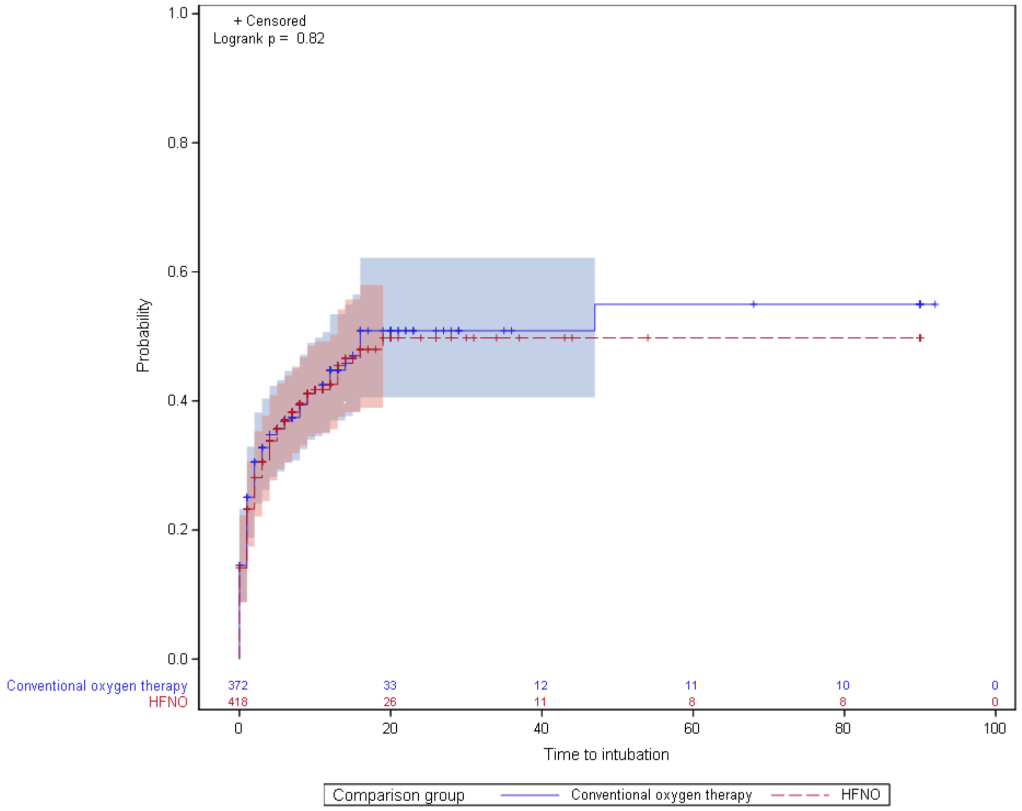


Figure S3: Kaplan Meier curve by treatment arm: time to tracheal intubation (all participants)

Panel a- Continuous positive airway pressure v conventional oxygen therapy



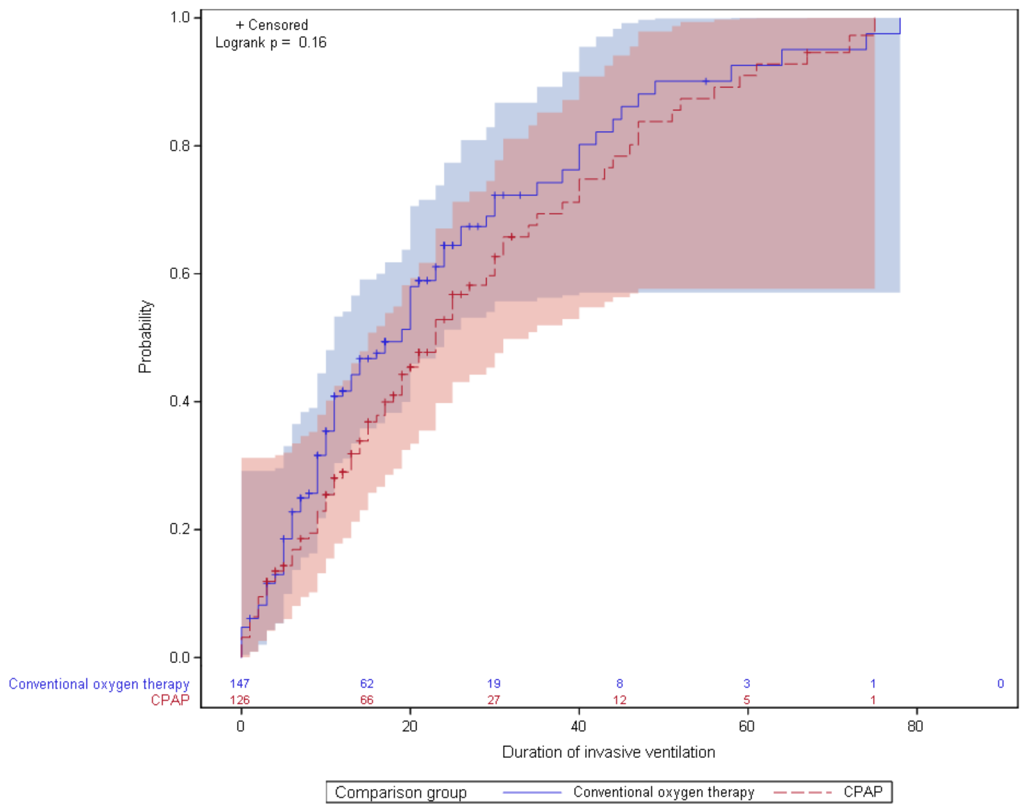
Panel b- High-flow nasal oxygen v conventional oxygen therapy



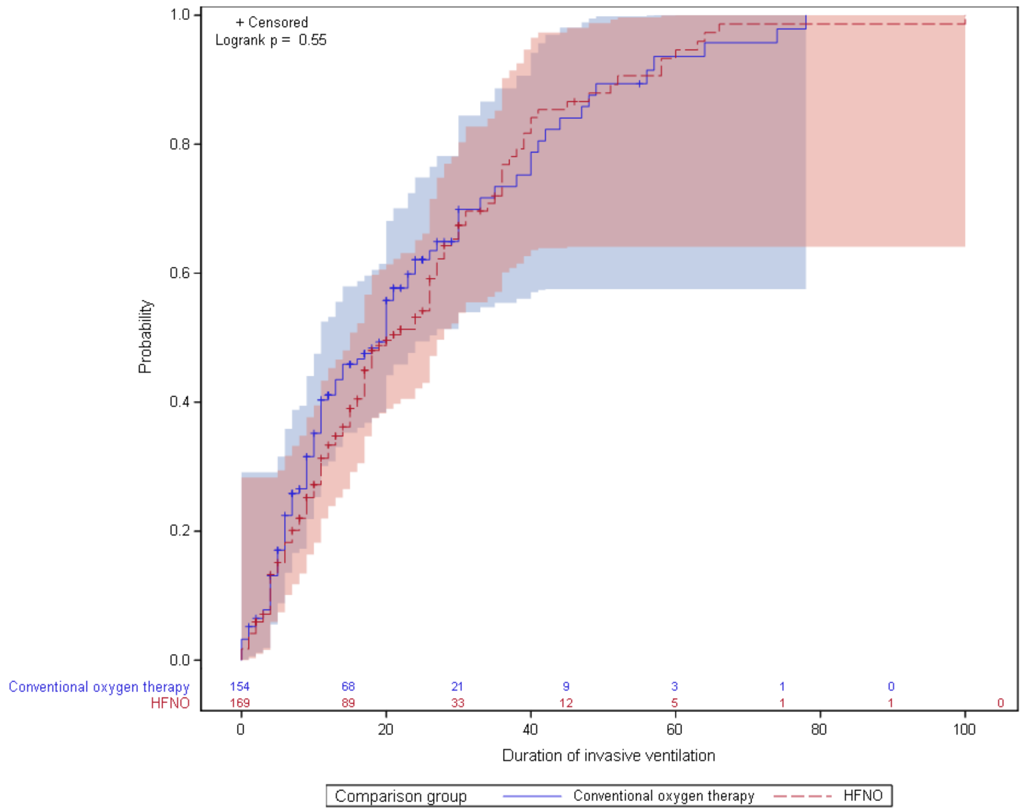
Censored patients include 1) patients died before hospital discharge; 2) patients discharged alive from hospital without intubation; 3) patients lost to follow-up (including complete withdrawals before intubation was given and complete missing in-hospital data).

Figure S4: Kaplan Meier curve by treatment arm: duration of invasive ventilation (intubated participants only)

Panel a- Continuous positive airway pressure v conventional oxygen therapy



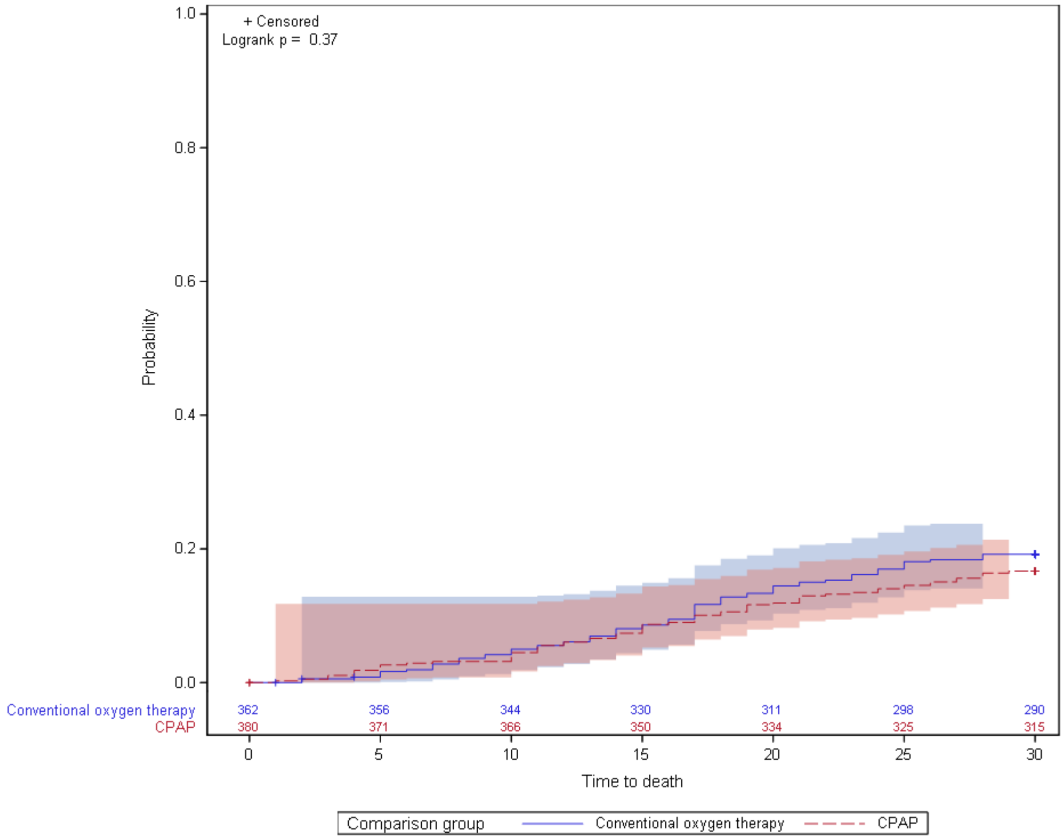
Panel b- High-flow nasal oxygen v conventional oxygen therapy



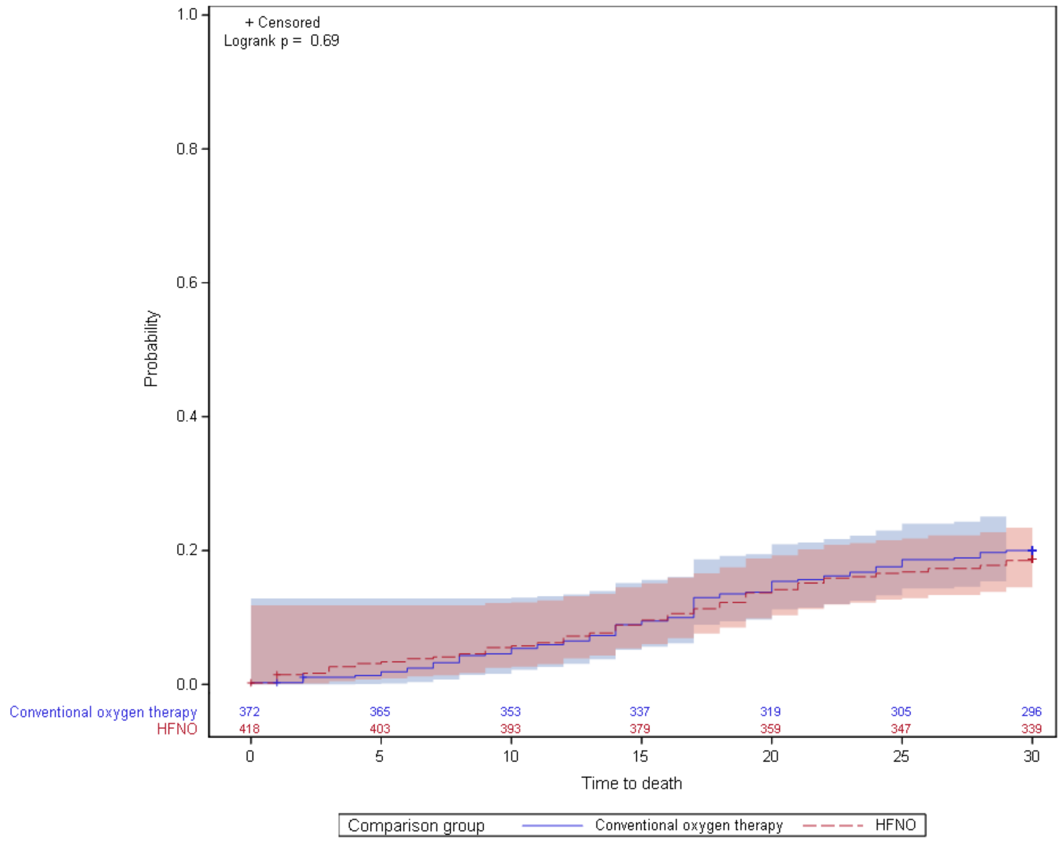
Censored patients include: 1) patients died before coming off invasive ventilation alive; 2) patients withdrew completely before the end of invasive ventilation; 3) patients stayed on invasive ventilation beyond the follow-up period (20th June, 2021); 4) patient died in hospital or discharged alive without intubation

Figure S5: Kaplan Meier curve by treatment arm: time to death (all participants)

Panel a- Continuous positive airway pressure v conventional oxygen therapy



Panel b- High-flow nasal oxygen v conventional oxygen therapy



Censored patients include: 1) patient withdrew completely before 30 days from randomisation; 2) patient survived at 30 days

Table S5: Adverse events and serious adverse events by treatment arm

	Conventional oxygen therapy (n=475)	CPAP (n=380)	HFNO (n=418)	P-value[a]	All participants (n=1273)
Participants with AE/ SAE- n (%)	66 (13.9%)	130 (34.2%)	86 (20.6%)	<0.001	282 (22.2%)
ADVERSE EVENTS					
Participants with AE- n (%)	65 (13.7%)	130 (34.2%)	86 (20.6%)	<0.001	281 (22.1%)
Summary of events- n(%)[b]					
Interface/therapy Intolerance	1 (0.2%)	22 (5.8%)	3 (0.7%)		26 (2.0%)
Pain	6 (1.3%)	21 (5.5%)	10 (2.4%)	-	37 (2.9%)
Cutaneous pressure sore	14 (2.9%)	32 (8.4%)	14 (3.4%)	-	60 (4.7%)
Claustrophobia	9 (1.9%)	46 (12.1%)	10 (2.4%)	-	65 (5.1%)
Oronasal dryness	9 (1.9%)	25 (6.6%)	25 (6.0%)	-	59 (4.6%)
Respiratory acidosis	4 (0.8%)	4 (1.1%)	11 (2.6%)	-	19 (1.5%)
Haemodynamic instability	29 (6.1%)	43 (11.3%)	34 (8.1%)	-	106 (8.3%)
Nausea and vomiting	6 (1.3%)	9 (2.4%)	10 (2.4%)	-	25 (2.0%)
Aspiration of gastric contents	2 (0.4%)	6 (1.6%)	5 (1.2%)	-	13 (1.0%)
Pneumothorax	10 (2.1%)	7 (1.8%)	8 (1.9%)	-	25 (2.0%)
Pneumomediastinum	5 (1.1%)	12 (3.2%)	3 (0.7%)	-	20 (1.6%)
Anxiety and confusion	0	6 (1.6%)	3 (0.7%)	-	9 (0.7%)
Pulmonary embolism	1 (0.2%)	1 (0.3%)	0	-	2 (0.2%)
Surgical emphysema	0	3 (0.8%)	1 (0.2%)	-	4 (0.3%)
Haemoptysis	0	1 (0.3%)	1 (0.2%)	-	2 (0.2%)
Other[c]	1 (0.2%)	5 (1.3%)	8 (1.9%)	-	14 (1.1%)
SERIOUS ADVERSE EVENTS					
Participants with SAE- n (%)[b,d]	1 (0.2%)	7 (1.8%)	0 (0.0%)	0.002	8 (0.6%)
Impact of SAE					
Death	1 (0.2%)	1 (0.3%)	0 (0.0%)		2 (0.2%)
Life Threatening	0 (0.0%)	4 (1.1%)	0 (0.0%)		4 (0.3%)
Hospitalisation	0 (0.0%)	6 (1.6%)	0 (0.0%)		6 (0.5%)
Disability	0 (0.0%)	1 (0.3%)	0 (0.0%)		1 (0.1%)
Birth Defect	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Required Intervention	0 (0.0%)	4 (1.1%)	0 (0.0%)		4 (0.3%)
Causality of SAE					
Definitely	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Probably	0 (0.0%)	1 (0.3%)	0 (0.0%)		1 (0.1%)
Possibly	0 (0.0%)	3 (0.8%)	0 (0.0%)		3 (0.2%)
Unlikely	0 (0.0%)	2 (0.5%)	0 (0.0%)		2 (0.2%)
Unrelated	1 (0.2%)	1 (0.3%)	0 (0.0%)		2 (0.2%)

Key- AE- Adverse event; CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen; SAE- Serious adverse event

a- p-value calculated using chi-square test for AE/SAE and AE comparison, and using Fisher-exact for SAE comparison

b-Multiple events/categories allowed per participants

c-Details of other events:

Conventional oxygen therapy (one event): Nasal cannulae leak

CPAP (five events): Chest tightness; Significant desaturation when eating; CPAP leak; Pneumopericardium; Low tidal volume/hypoxia/dyspnoea (one of each event)

HFNO (eight events): Abdominal distension; Bilateral rupture of tympanic membrane; Monoclonal antibody treatment side-effect (hand pustules); Need for tracheostomy; Ventilator-associated pneumonia and klebsiella meningitis diagnosis; Pleural effusions; Secondary sepsis, intracranial bleed, requirement for renal replacement therapy; Detail not reported (one of each event)

d-Details of serious adverse events:

Conventional oxygen therapy (one event): Pulmonary embolus CPAP (seven events): Type 2 myocardial infarction (one event); surgical emphysema and pneumomediastinum (one event); vomiting requiring emergency tracheal intubation (one event); Intracranial bleed (one event); Perforated bowel (one event); Pneumothorax and pneumomediastinum (two events)