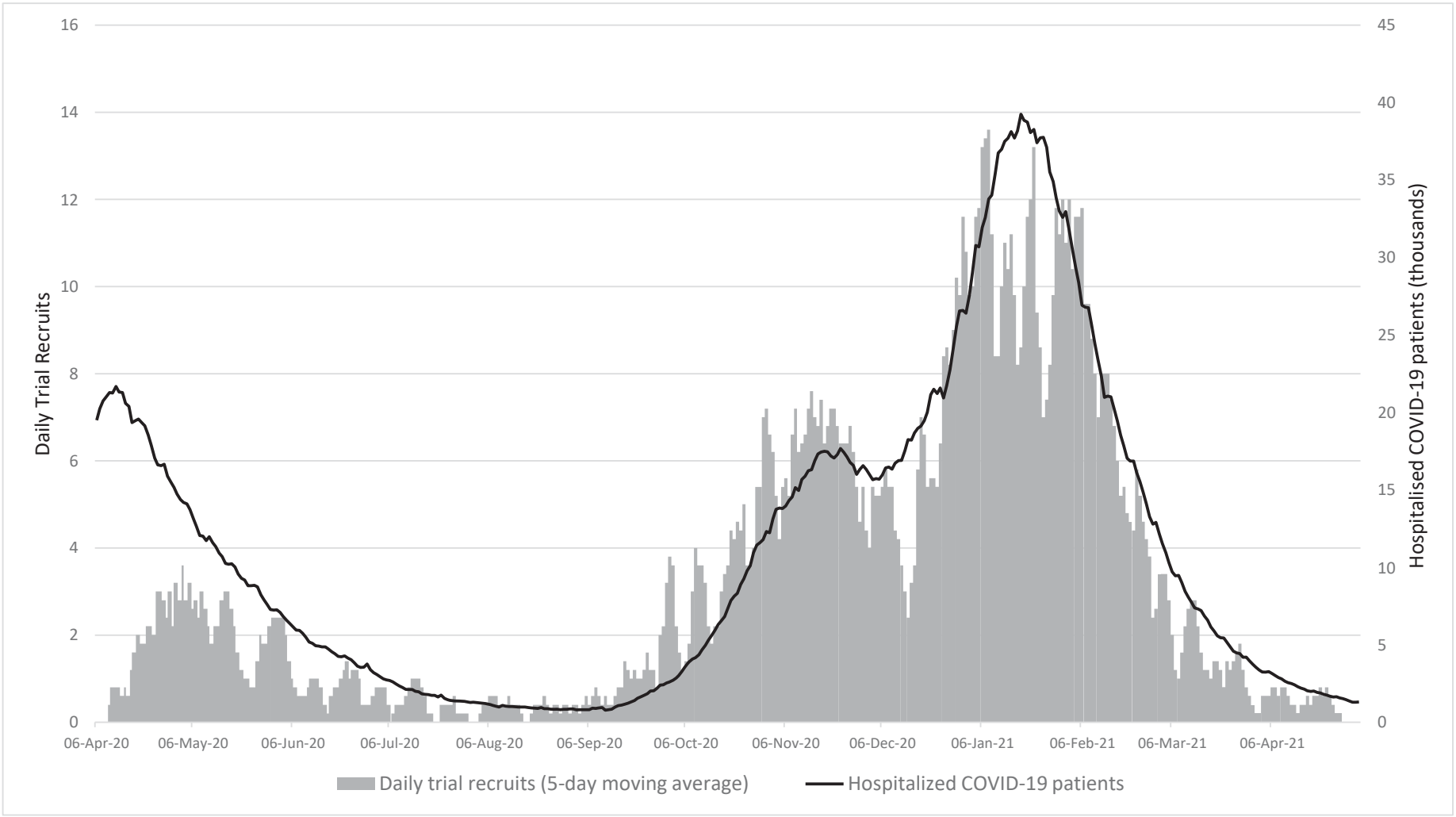
Supplemental Online Content

Perkins GD, Ji C, Connolly BA, et al; RECOVERY-RS Collaborators. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. *JAMA*. Published January 24, 2022. doi:10.1001/jama.2022.0028

This supplemental material has been provided by the authors to give readers additional information about their work.

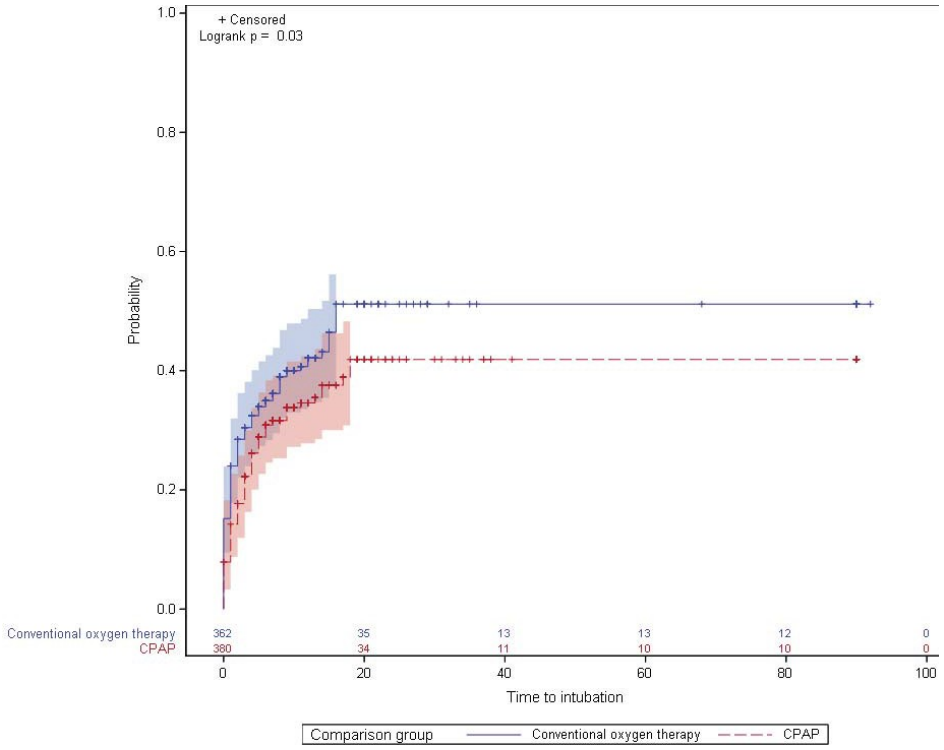
eFigure 1. RECOVERY-RS trial recruitment and UK hospitalized COVID-19 patients



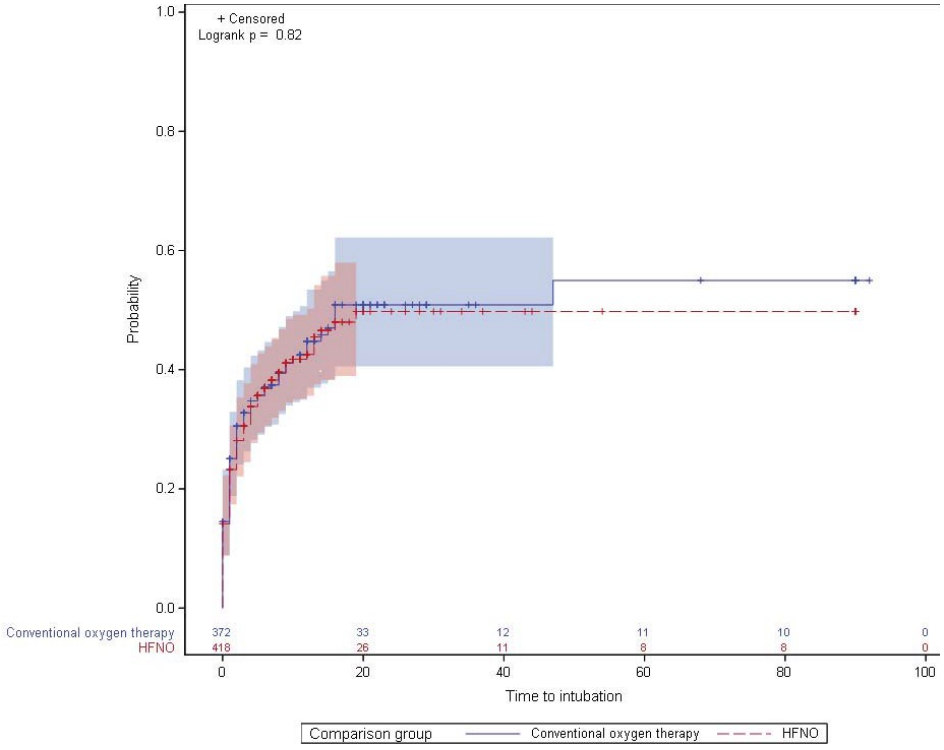
Data for hospitalized COVID-19 patients extracted from publicly available UK data sources at https://coronavirus.data.gov.uk/details/healthcare

eFigure 2. Kaplan Meier curve by treatment arm: time to tracheal intubation (all participants)

Panel a- Continuous positive airway pressure v conventional oxygen therapy



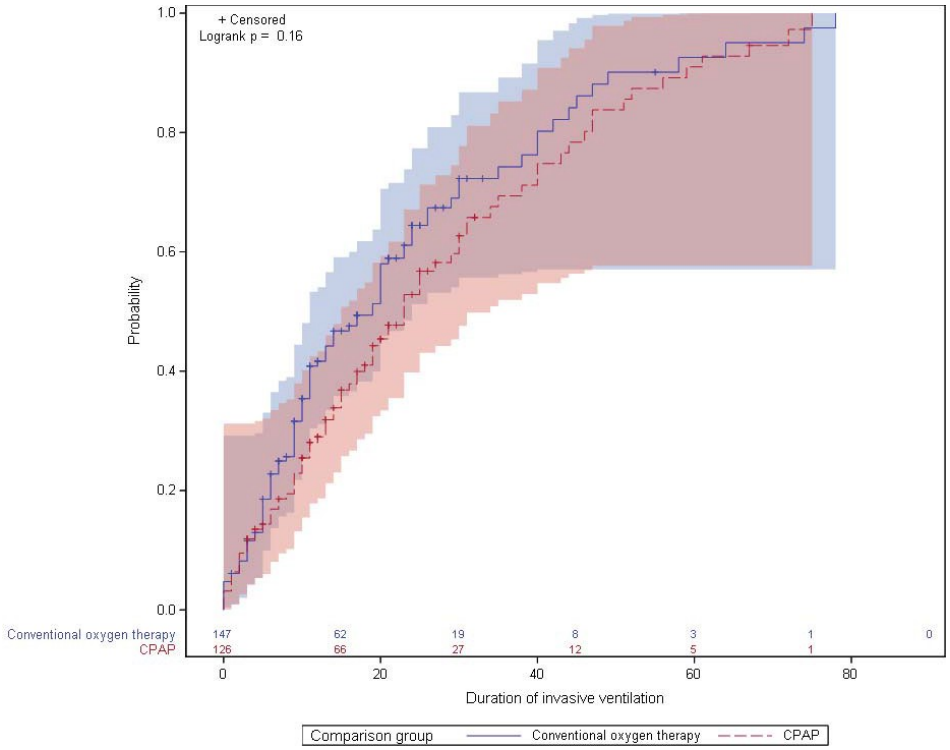
Panel b- High-flow nasal oxygen v conventional oxygen therapy



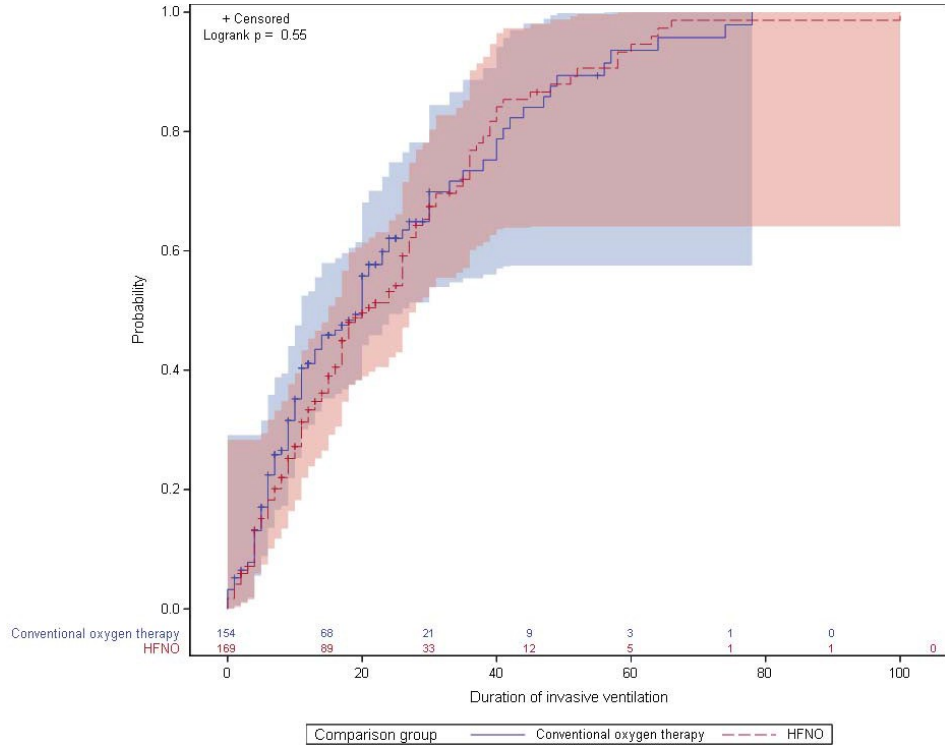
Censored patients include 1) patients died before hospital discharge; 2) patients discharged alive from hospital without intubation; 3) patients lost to follow-up (including complete withdrawals before intubation was given and complete missing in-hospital data).
Proportional hazard assumption was not violated in HFNO vs Conventional oxygen therapy (p=0.81). The test p value was 0.01 in CPAP vs Conventional oxygen therapy, respectively, indicating violation of assumption.

eFigure 3. Kaplan Meier curve by treatment arm: duration of invasive ventilation (intubated participants only)

Panel a- Continuous positive airway pressure v conventional oxygen therapy



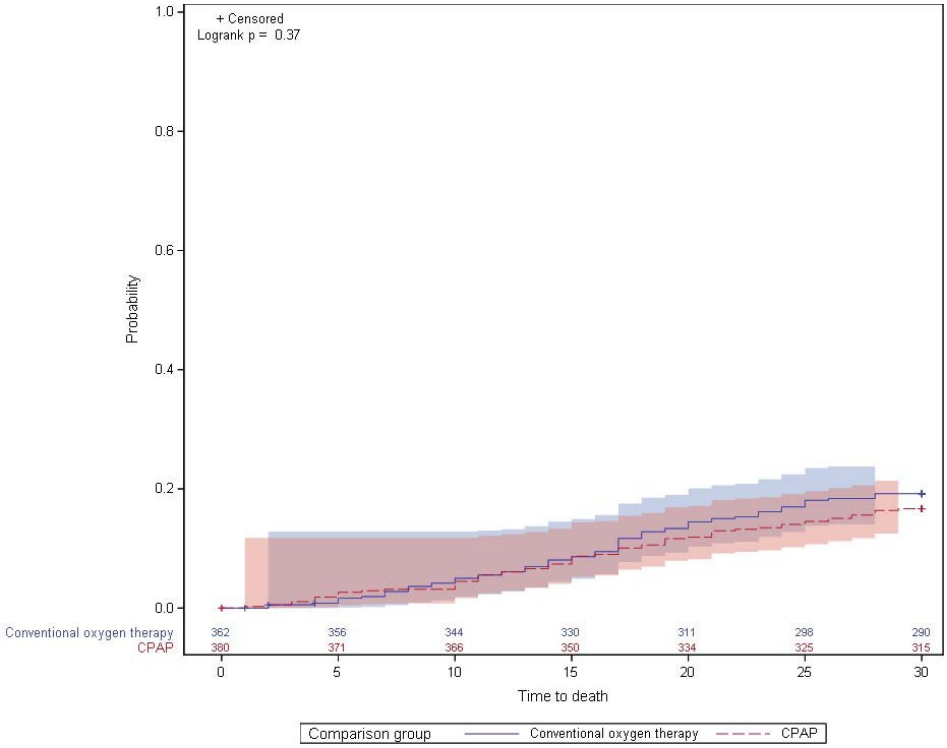
Panel b- High-flow nasal oxygen v conventional oxygen therapy



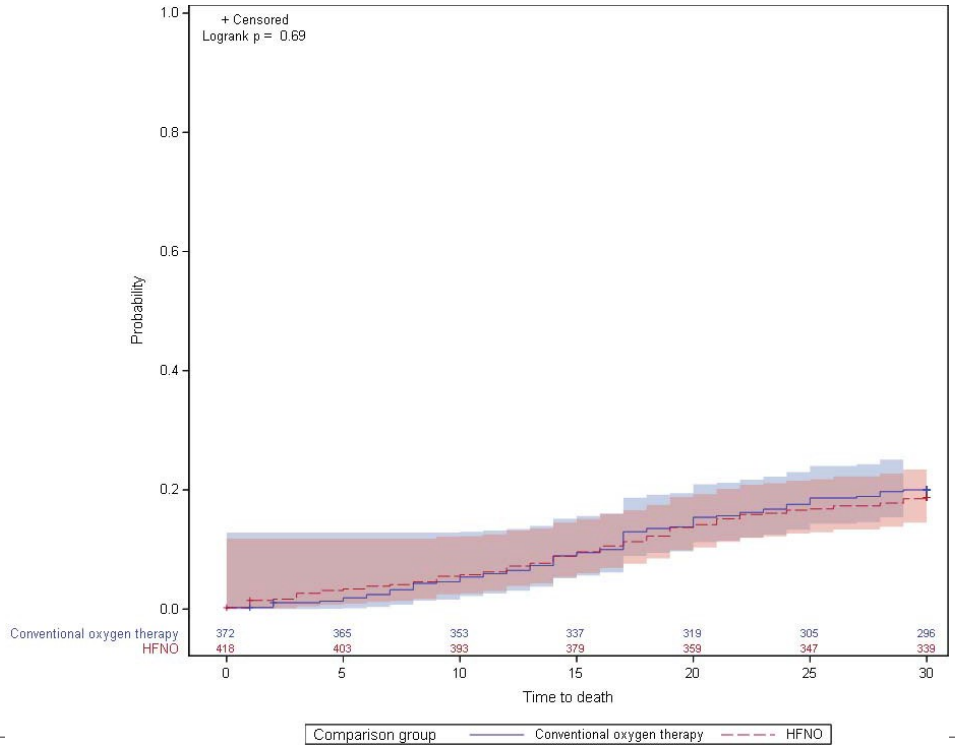
Censored patients include: 1) patients died before coming off invasive ventilation alive; 2) patients withdrew completely before the end of invasive ventilation; 3) patients stayed on invasive ventilation beyond the follow-up period (20th June, 2021); 4) patient died in hospital or discharged alive without intubation.
Proportional hazard assumption was not violated (p=0.54 and 0.32 in CPAP vs Conventional oxygen therapy and HFNO vs Conventional oxygen therapy, respectively.

eFigure 4. Kaplan Meier curve by treatment arm: time to death (all participants)

Panel a- Continuous positive airway pressure v conventional oxygen therapy



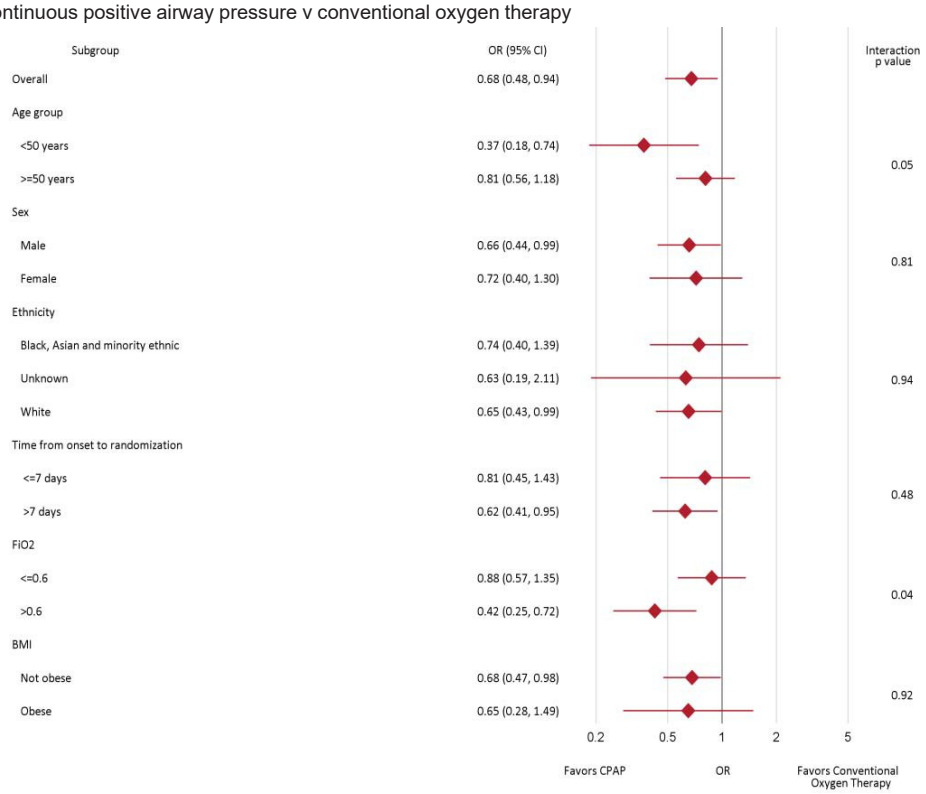
Panel b- High-flow nasal oxygen v conventional oxygen therapy



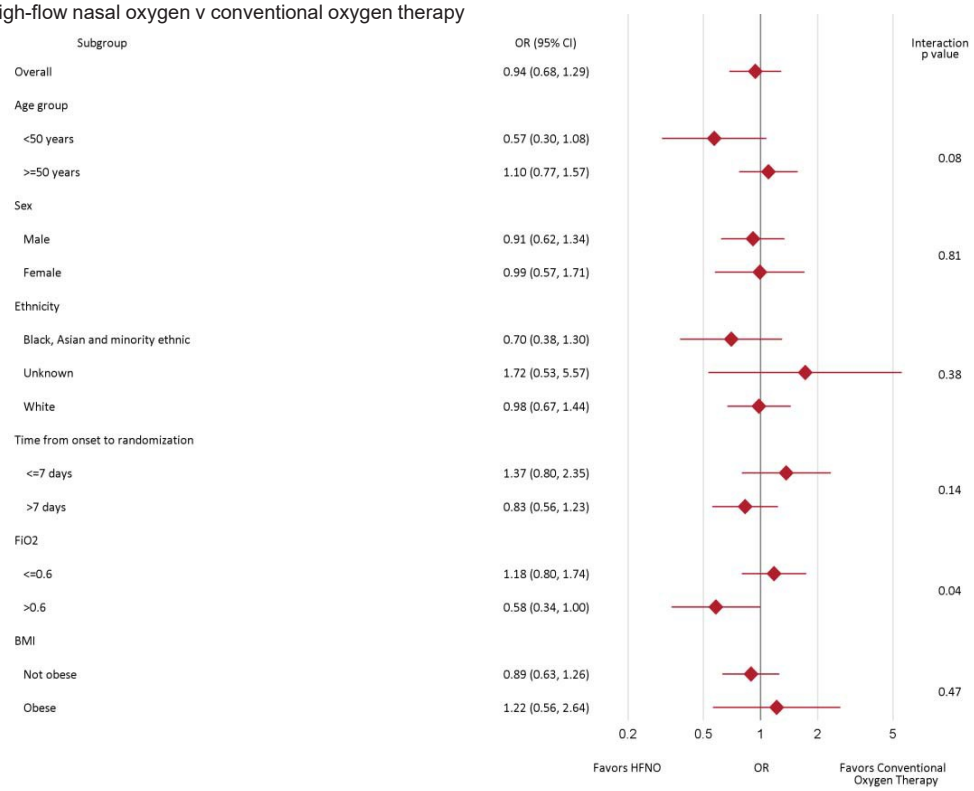
Censored patients include: 1) patient withdrew completely before 30 days from randomisation; 2) patient survived at 30 days. Proportional hazard assumption was not violated (p=0.89 and 0.64 in CPAP vs Conventional oxygen therapy and HFNO vs Conventional oxygen therapy, respectively.

eFigure 5. Adjusted sub-group analyses: tracheal Intubation or mortality within 30 days

Panel a- Continuous positive airway pressure v conventional oxygen therapy



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



Obese defined as body mass index >35 kg/m2. Models adjusted for age, sex, morbid obesity, ethnicity, FiO2, respiratory rate and treatment phases, with site included as a random effect. The Unknown ethnicity refers to a participant selected category of “not given”. The p values are calculated using the test for interaction between the sub-group and treatment variables. Key: BMI- body mass index; CPAP- Continuous Positive Airway Pressure; FiO2- fraction of inspired oxygen; HFNO- High-flow nasaloxygen

eTable 1. Summary of randomizations and data for pairwise comparisons

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

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

eTable 2. Additional participant baseline characteristics

Characteristic	CPAP	HFNO	Conventional Oxygen Therapy
Core body temperature at hospital admission (°C)- Mean (SD)	37.7 (1.0), n=377	37.7 (1.0), n=414	37.6 (1.0), n=472
Heart Rate (per minute)- Mean (SD)	91.1 (17.0), n=371	90.4 (15.8), n=410	88.7 (16.7), n=469
Systolic blood pressure (mmHg)- Mean (SD)	128.6 (19.0), n=377	128.4 (18.2), n=414	127.3 (18.1), n=473
Diastolic blood pressure (mmHg)- Mean (SD)	75.2 (12.4), n=374	75.4 (12.2), n=414	75.6 (11.2), n=473
Urea (mmol/l)- Mean (SD)	39.4 (23.7), n=372	41.1 (25.0), n=410	39.4 (23.9), n=464
Confusion – no. (%)			
Confused	14 (3.7)	9 (2.2)	9 (1.9)
Not confused	364 (95.8)	407 (97.4)	461 (97.1)
N/A- sedated	0	1 (0.2)	1 (0.2)
CURB-65 Score – no. (%)			
0	133 (35.0)	136 (32.5)	171 (36.0)
1	129 (34.0)	151 (36.1)	175 (36.8)
2	71 (18.7)	85 (20.3)	89 (18.7)
3	30 (7.9)	29 (6.9)	22 (4.6)
4	2 (0.5)	4 (1.0)	3 (0.6)
5	0 (0.0)	0 (0.0)	1 (0.2)
Clinical Frailty Scale (pre-admission) no. (%)[a]			
CFS1 - Very Fit	72 (18.9%)	71 (17.0%)	62 (13.1%)
CFS2 - Well	192 (50.5%)	196 (46.9%)	237 (49.9%)
CFS3 - Managing Well	87 (22.9%)	109 (26.1%)	131 (27.6%)
CFS4 - Vulnerable	12 (3.2%)	27 (6.5%)	30 (6.3%)
CFS5 - Mildly Frail	4 (1.1%)	6 (1.4%)	6 (1.3%)
CFS6 - Moderately Frail	3 (0.8%)	0 (0.0%)	3 (0.6%)
CFS7 - Severely Frail	0 (0.0%)	2 (0.5%)	0 (0.0%)
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%)

a- The clinical frailty score is based on pre-admission functional status and determined through notes review or patient assessment. It is measured on a nine-point score (very fit to terminally ill), with lower scores indicating a lower level of frailty.

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

eTable 3. Summary of trial crossover by treatment group

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

eTable 4. 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.

eTable 5. Primary outcome comparison between continuous positive airway pressure and high-flow nasal oxygen

CPAP versus HFNO	CPAP	HFNO	Absolute difference (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[b] (95% CI)	P value (unad, adj)
Primary composite outcome						
Tracheal Intubation or mortality within 30 days[a,]	91/263 (34.6%)	136/307 (44.3%)	-10% (-18%- -2%)	0.67 (0.47, 0.93)	0.68 (0.47, 0.99)	0.02, 0.04
Primary composite outcome components						
Intubation within 30 days	84/263 (31.9%)	125/307 (40.7%)	-9% (-17%- -1%)	0.68 (0.48, 0.96)	0.68 (0.46, 0.99)	0.03, 0.05
Mortality at 30 days(%)	43/264 (16.3%)	58/308 (18.8%)	-3% (-9%- 4%)	0.84 (0.54, 1.29)	1.00 (0.61, 1.63)	0.43, 0.99

Data are n/N (%)
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).
a- The final critical p value is 5%;
b- Models were adjusted for age, sex, morbid obesity, ethnicity, FiO2, respiratory rate and treatment phases, with site included as a random effect.

eTable 6. Adverse events and serious adverse events by treatment group

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