Original research

High-flow nasal oxygen versus conventional oxygen therapy in patients with COVID-19 pneumonia and mild hypoxaemia: a randomised controlled trial

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2022-218806).

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Received 3 February 2022
Accepted 26 April 2022

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To cite: Crimi C, Noto A, Madotto F, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2022-218806

ABSTRACT

Rationale In patients with COVID-19 pneumonia and mild hypoxaemia, the clinical benefit of high-flow nasal oxygen (HFNO) remains unclear. We aimed to examine whether HFNO compared with conventional oxygen therapy (COT) could prevent escalation of respiratory support in this patient population.

Methods In this multicentre, randomised, parallel-group, open-label trial, patients with COVID-19 pneumonia and peripheral oxygen saturation (SpO_2) ≤92% who required oxygen therapy were randomised to HFNO or COT. The primary outcome was the rate of escalation of respiratory support (ie, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation) within 28 days. Among secondary outcomes, clinical recovery was defined as the improvement in oxygenation (SpO_2 ≥96% with fractional inspired oxygen (FiO_2) ≤30% or partial pressure of arterial carbon dioxide/FiO_2 ratio >300 mm Hg).

Results Among 364 randomised patients, 55 (30.3%) of 181 patients assigned to HFNO and 70 (38.6%) of 181 patients assigned to COT underwent escalation of respiratory support, with no significant difference between groups (absolute risk difference −8.2% (95% CI −18% to +1.4%); RR 0.79 (95% CI 0.59 to 1.05); p=0.09). There was no significant difference in clinical recovery (69.1% vs 60.8%; absolute risk difference 8.2% (95% CI −1.5% to +18.0%), RR 1.14 (95% CI 0.98 to 1.32)), intensive care unit admission (7.7% vs 11.0%, absolute risk difference −3.3% (95% CI −9.3% to +2.6%)), and in hospital length of stay (11 (IQR 8–17) vs 11 (IQR 7–20) days, absolute risk difference −1.0% (95% CI −3.1% to +1.1%)).

Conclusions Among patients with COVID-19 pneumonia and mild hypoxaemia, the use of HFNO did not significantly reduce the likelihood of escalation of respiratory support.

Trial registration number NCT04655638.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ High-flow nasal oxygen has been widely used worldwide in patients with COVID-19-associated respiratory failure with the aim of reducing the need for invasive mechanical ventilation even without rigorous clinical research proving its benefits in this patient population. No studies evaluating the effects of high-flow nasal oxygen on hospitalised patients with COVID-19 pneumonia and mild hypoxaemia were identified.

WHAT THIS STUDY ADDS

⇒ The COVID-HIGH trial is the first multicentre randomised controlled trial to report results on the use of high-flow nasal oxygen in hospitalised patients with COVID-19 pneumonia and mild hypoxaemia. We found no significant difference on the rate of escalation of respiratory support within 28 days between patients randomised to high-flow nasal oxygen compared with conventional oxygen therapy in this patient population. Secondary clinical outcomes such as the likelihood of clinical recovery, the time to the first escalation of respiratory support, admission to intensive care unit, and mortality at 28 days and 60 days, were concordant with the primary outcome.

INTRODUCTION

Almost 80% of hospitalised patients with COVID-19 need oxygen therapy,[1] and up to one-third develop severe pneumonia[2] that may require non-invasive respiratory support or invasive mechanical ventilation (IMV).[3 4]

In patients with moderate-to-severe acute hypoxaemic respiratory failure, high-flow nasal oxygen (HFNO) has been promoted as an effective means of improving oxygenation and decreasing escalation of respiratory support and intubation when compared with conventional oxygen therapy (COT).[5 6] In non-COVID-19-related acute hypoxaemic respiratory failure, international guidelines recommend using HFNO as the first-line respiratory support intervention with moderate certainty of evidence.[7 8]

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The pathophysiological effects of high-flow nasal oxygen are unlikely to significantly affect the clinical course of COVID-19 pneumonia-related mild hypoxaemia compared with conventional oxygen therapy. Thus, in this patient population, high-flow nasal oxygen should not be used as routine strategy for oxygen supplementation.

HFNO has been used extensively in patients with COVID-19.[9 10] The potential benefits of HFNO in this population include the ability to match inspiratory demand, thus reducing inspiratory resistance, delivery of humidified warm gas mixture with a stable fraction of inspired oxygen (FiO_2), preservation of mucociliary function and dead space wash-out.[11] HFNO can also improve respiratory mechanics[12] and end-expiratory lung volume[13] and reduce respiratory rate and inspiratory effort.[14] Therefore, these effects may theoretically prevent the progression of lung damage.[15] Recently, a trial conducted in patients with severe COVID-19 demonstrated that HFNO compared with COT reduced the need for IMV and time to clinical recovery.[16] In hospitalised patients with COVID-19 pneumonia and mild hypoxaemia, whether HFNO provides similar advantages over COT remains unclear.

The COVID-HIGH multicentre trial was designed to test the hypothesis that in hospitalised patients with COVID-19 pneumonia and mild hypoxaemia, treatment with HFNO compared with COT decreases the likelihood of escalation of respiratory support within 28 days.

METHODS

Study design

We conducted this investigator-initiated, open-label, parallel-group randomised controlled trial (the COVID-HIGH trial) at 27 centres in 6 countries (Italy, Greece, Spain, Portugal, Poland, Turkey). A complete list of the participating sites is available in online supplemental eTable 1. Patients underwent screening and randomisation between 10 February 2021 and 26 August 2021. The trial was overseen by an oversight committee comprised of independent clinicians with no competing interests.

Patients

Eligibility criteria were hospital admission <48 hours in any department managing patients with COVID-19 pneumonia; age ≥18 years old; positive PCR test confirming SARS-CoV-2 infection; clinical signs of acute respiratory infection and radiological evidence of pneumonia; peripheral oxygen saturation (SpO_2) ≤92% or arterial partial pressure of oxygen to fraction of inspired oxygen (arterial oxygen tension (PaO_2)/FiO_2) ratio <300 in room air and need for oxygen therapy[17] according to clinical judgement, at screening.

Exclusion criteria included respiratory rate ≥28 breaths/min and/or severe dyspnoea and/or use of accessory muscles; PaO_2/FiO_2 ratio ≤200; need for immediate intubation, continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) according to clinical judgement; patients already on CPAP/NIV or HFNO at study screening; septic shock; evidence of multiorgan failure; Glasgow Coma Scale <13; neuromuscular disease; presence of partial pressure of arterial carbon dioxide ($PaCO_2$) >45 mm Hg (if blood gas available) or history of chronic hypercapnia. Patients already on long-term oxygen therapy and/or home NIV/CPAP or with limitation of care based on patients' or physicians' decision or with the inability to comprehend the study content and give consent were also excluded. Written informed consent was obtained from all patients or surrogates.

Randomisation and masking

Eligible patients were randomly assigned to a 1:1 ratio to either HFNO or COT throughout their hospitalisation or until reaching the termination criteria. A predefined list with permutation blocks having a fixed size of 4 was created by a statistician using SAS software (PROC PLAN). Block size was concealed. Randomisation was implemented using a web-based electronic system incorporated in the electronic case report form to ensure allocation concealment. Study data were collected, managed and stored using the Research Electronic Data Capture[18] tool hosted at the University of Messina, Italy. The investigators of the study centres entered baseline variables and outcomes data into the electronic case report form from day 1 to 28 and on the 28-day and 60-day follow-up period. Blinding of patients and healthcare staff was not possible.

Procedures

Other than the randomly allocated interventions, all patients received treatments in accordance with the clinical judgement of treating physicians, local protocols and routine clinical practice. The randomly allocated treatments were started within 15 min of randomisation. In the intervention group, HFNO was delivered by any available device able to deliver it. The initial flow rate was set at 40 L/min and increased as required up to 60 L/min, according to patient tolerance. The temperature was set from 37°C to 31°C according to patient comfort. A surgical mask was placed over the HFNO cannula.[19] In the control group, oxygen was delivered preferably by a Venturi mask, but any other device was allowed, and a table of conversion for FiO_2 was provided. FiO_2 and oxygen flow were titrated to maintain SpO_2 between 92% and 96%[20] in both groups.

The criterion for weaning off study interventions was patients' clinical recovery, defined as the improvement in oxygenation with the ability to maintain SpO_2 ≥96% with FiO_2 ≤30% or PaO_2/FiO_2 ratio >300 mm Hg. Any change from COT to HFNO (or vice versa) was considered a protocol violation.

Predefined criteria for considering the escalation of respiratory support to CPAP, NIV or IMV were the presence of SpO_2 ≤92% despite COT or HFNO or PaO_2/FiO_2 ratio ≤180 mm Hg with FiO_2 ≥50%, and at least one of the following: respiratory rate ≥28 breaths/min, severe dyspnoea, signs of increased work of breathing (eg, use of accessory muscles). The type of respiratory support chosen for escalation was selected by treating physicians based on their clinical judgement. Escalation of respiratory support could be performed in the hospital ward where the patient was admitted or after being transferred to the intensive care unit (ICU).

Outcomes

The primary outcome was the rate of escalation of respiratory support to CPAP, NIV or IMV within 28 days of randomisation.

The secondary outcomes included the rate of clinical recovery, time to the escalation of respiratory support, type of respiratory support as the first-line escalation therapy by day 28, admission to ICU, hospital and ICU length of stay, dyspnoea score (range, 0 (no dyspnoea) to 10 (severe dyspnoea)), patient comfort score (range, 0 (severe discomfort) to 10 (perfect comfort)), SpO_2/FiO_2 ratio divided by Respiratory Rate (ROX index), National

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Early Warning Score 2, mortality at 28 and 60 days, and in-hospital, days free from CPAP/NIV/IMV, oxygen free days, treatment intolerance. No blinding of adjudication was performed for outcome assessments.

Prespecified subgroup analyses were performed on the primary outcome according to time from symptoms onset to hospital admission (<5 vs ≥5 days), time from hospitalisation to enrolment (<6 vs ≥6 hours), age (<65 vs ≥65 years old), comorbidities (<1 vs ≥1) and respiratory rate at randomisation (<25 bpm vs ≥25 bpm).

Statistical analysis

We calculated that 346 patients would need to be enrolled for the trial to have an 80% power to show a 15% absolute reduction in the proportion of patients with the escalation of respiratory support (primary outcome) in the HFNO group at a two-sided α level of 5%, assuming that 55% in the COT group would need escalation.[10] As compensation for a possible drop-out rate of 5%, the final study population included 182 subjects in each group, for a total of 364 subjects enrolled in the study.

Scheduled interim analyses were performed after the enrolment of the first 122 and 243 patients considering the Haybittle-Peto boundary, p value threshold of 0.001. Interim analyses were reviewed by the trial oversight committee. No specific (mandatory) stopping rules were defined.

Analysis was based on intention to treat, that is, all patients were analysed in the group they had been allocated, with no exclusions after randomisation other than for withdrawn consent.

The effect size of the dichotomous primary outcome was measured using the risk ratio (RR) of escalation in the intervention versus control arm. Asymptotic normal distribution of RRs was assumed for estimating CI (Wald method). A mixed-effects logistic regression model was used to evaluate a possible centre effect on the primary outcome. OR and 95% CI were estimated as a relative measure of this effect, considering the variable 'centre' as a random intercept. Survival analysis was conducted to evaluate the probability of escalation of respiratory support during the study period and time-to-event, considering death and clinical recovery as competing risks. Cumulative

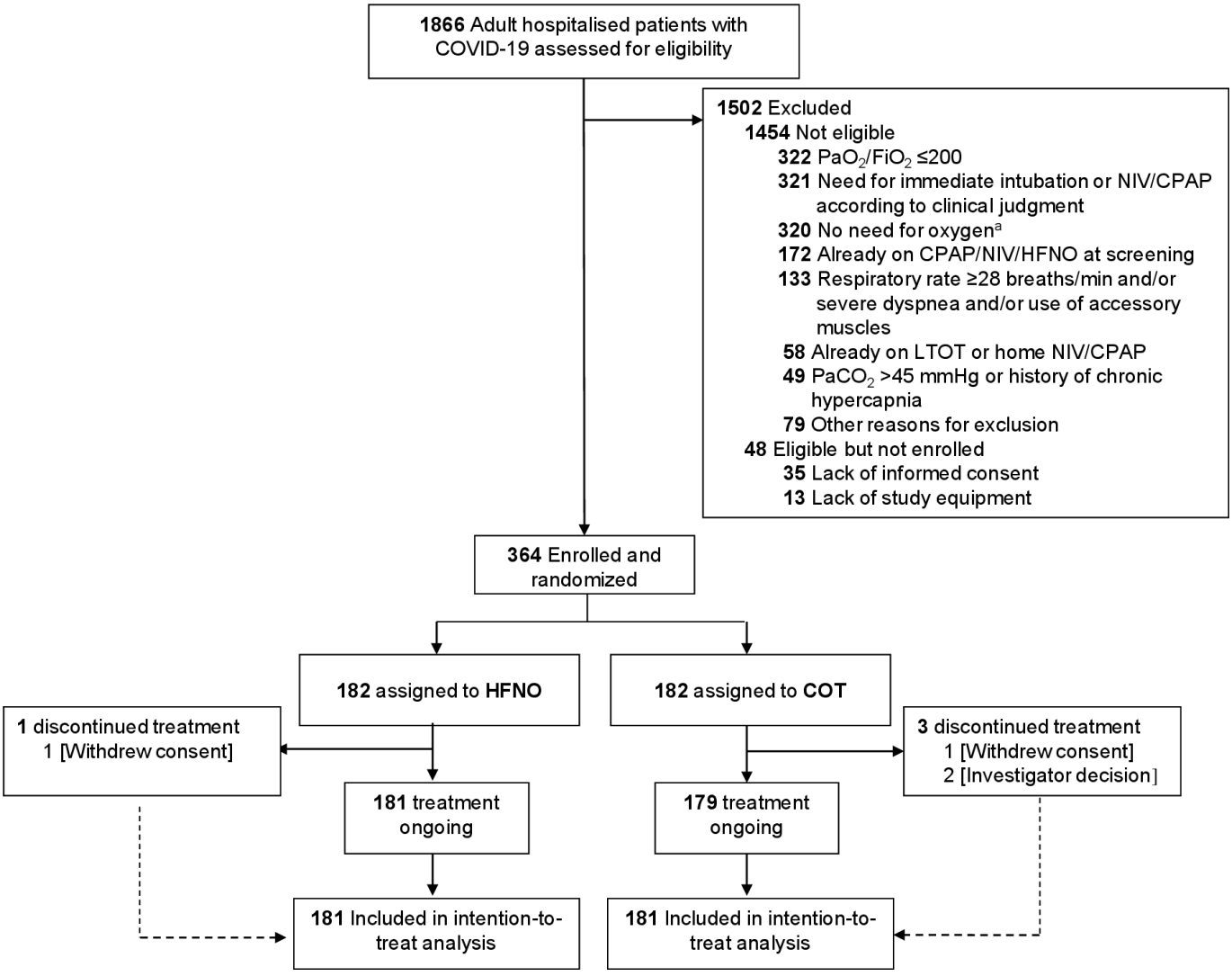

Figure 1 Trial profile. [a]No need for oxygen: SpO_2 >92% or PaO_2/FiO_2 >300 in room air or no need for oxygen therapy according to clinical judgement, at screening. COT, conventional oxygen therapy; CPAP, continuous positive airway pressure; GCS, Glasgow Coma Scale; FiO_2, fraction of inspired oxygen; HFNO, high-flow nasal oxygen; LTOT, long-term oxygen therapy; NIV, non-invasive ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, peripheral oxygen saturation.

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incidence of escalation of respiratory support was estimated in each study group and compared using the Grey test. The effect size was described with the HR (95% CI), using the Fine and Gray subdistribution hazard function. The effect on the primary outcome was also evaluated in each predefined subgroup using the Gail and Simon test to assess qualitative interaction between study treatments and stratification variables.

For dichotomous secondary outcomes, we reported the effect size as described for the primary outcome. For continuous secondary outcomes, the mean difference between groups (and 95% CI) was assessed to evaluate the treatment effect. Differences between treatment groups were assessed each day using unpaired Student's t-test or unpaired Wilcoxon rank-sum test according to data distribution.

A post hoc generalised linear model with log link and binomial distribution (log-binomial regression model) was performed using treatment (HFNO-COT) as independent variable and each variable used for subgroups analyses and sex, due to the predominance of male in our study cohort.

All statistical tests of significance were two sided (α of 0.05). Analyses were performed using R software V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS V.9.4 software (SAS Institute). The trial was prospectively registered with ClinicalTrials.gov on 7 December 2020 (NCT04655638) and no changes were made thereafter.

RESULTS

Between 10 February 2021 and 26 August 2021, 1866 patients were screened, and 364 were randomised (182 received HFNO and 182 received COT; figure 1). Of the 364 participants, 2 withdrew consent for the use of data (one in each group), and 362 patients (mean age, 59 years (SD 14); 131 (36%) women) (online supplemental eTable 2) were included in the final analysis (n=181 in each group) (figure 1). Data for the primary outcome and the subsequent follow-up were obtained for all patients. The final 60-day follow-up date was 25 October 2021. Baseline characteristics and cointerventions were evenly distributed between groups (table 1 and online supplemental eTable 3).

At randomisation, mean SpO_2 was 89% (SD 2) and mean respiratory rate was 21 breaths/min (SD 3) in both groups. The median dyspnoea score was 2 (IQR 2–3) and 3 (IQR 2–3) in the HFNO and COT groups, respectively. The mean Charlson Comorbidity Index[21] was 2.2 (SD 2) in both groups (table 1). Median time from symptoms onset to hospital admission was 7 days (IQR 4–9) and 6 days (IQR 4–8), and the median time from hospital admission to randomisation was 8 hours (IQR 0–21) and 6 hours (IQR 0–22) in the HFNO and COT group, respectively (table 1).

All patients in the intervention group received continuous HFNO starting immediately after randomisation, with a mean flow of 51 L/min (SD 9), mean temperature of 32°C (SD 1) and mean FiO_2 of 45% (SD 16). In the COT group, mean FiO_2 was 42% (SD 14). All the other characteristics of the interventions are described in online supplemental eTable 4. The median treatment duration was 4 days (IQR 2–7) in the HFNO group and 3 days (IQR 1–6) in the COT group. In twenty-eight patients (8%), there were protocol violations as the assigned intervention was changed at least once (n=2 in the HFNO group; n=26 in the COT group) (online supplemental eTable 4).

Interim analyses were performed as planned and yielded p values of 0.059 and 0.12, respectively, for the primary outcome. As there was also no evidence of harm, the trial was continued.

Table 1 Baseline characteristics of the intention-to-treat population

	High flow Nasal oxygen (n=181)	Conventional Oxygen therapy (n=181)
Demographics		
Sex, no (%)		
Female	62 (34.3)	69 (38.1)
Male	119 (65.7)	112 (61.9)
Age (years), mean (SD)	59.01 (14.88)	58.92 (14.77)
BMI (kg/m^2), mean (SD)	28.55 (4.33)	27.99 (4.45)
Clinical characteristics related to acute respiratory failure		
SpO_2 (%), mean (SD)	89.63 (2.62)	89.87 (2.78)
Respiratory rate (breaths/min), mean (SD)	21.53 (3.32)	21.62 (3.56)
Dyspnoea score,* median (IQR)	2 (2–3)	3 (2–3)
Comorbidities, no (%)		
History of acute myocardial infarction	8 (4.4)	8 (4.4)
Chronic heart failure	11 (6.1)	10 (5.5)
Cerebrovascular disease	3 (1.7)	3 (1.7)
Chronic obstructive pulmonary disease	18 (9.9)	19 (10.5)
Diabetes	18 (9.8)	26 (14.2)
Moderate to severe chronic kidney disease†	6 (3.3)	6 (3.3)
Moderate to severe liver disease‡	2 (1.1)	3 (1.7)
Cancer§	6 (3.4)	4 (2.3)
Obesity¶	60 (33.1)	58 (32.0)
At least one comorbidity,** no (%)		
None	80 (44.2)	76 (42.0)
At least one	101 (55.8)	105 (58.0)
Charlson comorbidity index,†† mean (SD)	2.23 (2.06)	2.25 (2.08)
Clinical Frailty scale,‡‡ no (%)		
Very fit	23 (12.7)	27 (14.9)
Well	70 (38.7)	76 (42.0)
Managing well	73 (40.2)	55 (30.4)
Vulnerable	10 (5.5)	16 (8.8)
Mildly frail	3 (1.7)	5 (2.8)
Moderately frail	1 (0.6)	2 (1.1)
Severely frail	1 (0.6)	0 (0.0)
Time from admission to randomisation (hours), median (IQR)	8 (0–21)	6 (0–22)
Time from symptoms onset to hospital admission (days), median (IQR)	7 (4–9)	6 (4–8)

*Data were not available for 25 patients (6.9% of study population).
†Chronic kidney disease was defined as severe in case of being on dialysis, status post kidney transplant, uraemia; moderate=creatinine >3 mg/dL (0.27 mmol/L). These definitions were reported according to the Charlson Comorbidity Index.
‡Chronic liver disease was defined as severe in case of cirrhosis and portal hypertension with variceal bleeding history; moderate in case of cirrhosis and portal hypertension but no variceal bleeding history. These definitions were reported according to the Charlson Comorbidity Index.
§Cancer includes the following comorbid conditions as reported in the Charlson Comorbidity Index: localised solid tumour, metastatic solid tumour, lymphoma or multiple myeloma.
¶Obesity was defined as a body mass index ≥30 kg/m^2.
**The comorbidities were counted on the components of the Charlson Comorbidity Index, including obesity.
††The Charlson Comorbidity Index consists of 17 items. Each item can be scored from 0 to 6 points and each has a different weight. The maximum Charlson comorbidity Index score (adjusted for age) is 37 points. The Charlson comorbidity Index includes the following comorbid conditions: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatoid disease, peptic ulcer disease, mild and moderate/severe liver disease, diabetes mellitus with and without complications, hemiplegia/paraplegia, renal disease, cancer (any malignancy) and metastatic solid tumour, AIDS/HIV. The Charlson comorbidity Index provides a 10-year mortality risk based on weighted comorbid conditions, ranging from 0 (no comorbid conditions) to 29, with a score of 4 associated with an estimates 10-year survival of 53%.
‡‡Degree of fitness and frailty (range, 1–9: 1, very fit; 5, mildly frail; 9, terminally ill).
BMI, body mass index; SpO_2, peripheral oxygen saturation.

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Table 2 Primary and key secondary outcomes

	High flow Nasal oxygen (n=181)	Conventional Oxygen therapy (n=181)	P value	Difference* (95% CI)	Risk ratio (95% CI)
Primary outcome					
Escalation of respiratory support, No. (%)	55 (30.3)	70 (38.6)	0.0973	−8.29 (−18.05 to 1.47)	0.79 (0.59 to 1.05)
Secondary outcomes					
Clinical recovery, No. (%)	125 (69.1)	110 (60.8)	0.0985	8.29 (−1.51 to 18.08)	1.14 (0.98 to 1.32)
Time to first escalation of respiratory support (for patients with escalation), median (IQR)	2 (1–3)	2 (1–3)	0.8904	−0.28 (−1.26 to 0.70)	–
First treatment for escalation of respiratory support, No. (% on escalation)			0.7467		
CPAP	29 (52.7)	39 (55.7)		−2.99 (−20.58 to 14.61)	0.95 (0.68 to 1.31)
NIV	22 (40.0)	24 (34.3)		5.71 (−11.35 to 22.78)	1.17 (0.73 to 1.84)
IMV	4 (7.3)	7 (10.0)		−2.73 (−12.55 to 7.10)	0.73 (0.22 to 2.36)
ICU admission, No. (%)	14 (7.7)	20 (11.0)	0.2797	−3.31 (−9.32 to 2.69)	0.70 (0.37 to 1.34)
Length of stay in hospital,† median (IQR)	11 (8–17)	11 (7–20)	0.9872	−0.99 (−3.16 to 1.17)	–
Deaths within 28 days, No. (%)	14 (7.7)	13 (7.2)	0.8414	0.55 (−4.86 to 5.96)	1.08 (0.52 to 2.23)
Deaths within 60 days, No. (%)	15 (8.3)	15 (8.3)	1.0000	0.00 (−5.68 to 5.68)	1.00 (0.50 to 1.98)

* Absolute risk difference (%) for binary outcomes; mean difference for continuous outcomes.
† Two patients (0.6% of study population) were still hospitalised after 60 days from hospital admission.
CPAP, continuous positive airway pressure; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation.

By day 28 after randomisation, 55 of 181 patients (30.3%) randomised to HFNO and 70 of 181 patients (38.6%) randomised to COT received escalation of respiratory support with no significant difference between groups (absolute risk difference −8.2% (95% CI −18% to +1.4%); RR 0.79 (95% CI 0.59 to 1.05); p=0.09) (table 2). Competing risk analysis of the cumulative incidence of escalation of respiratory support within 28 days according to the intervention showed no significant difference (HR 0.75 (95% CI 0.54 to 1.0); p=0.09) (figure 2). There was no significant centre effect on the primary outcome (OR 0.64 (95% CI 0.40 to 1.03)).

There was no significant difference between HFNO and COT in clinical recovery (69.1% vs 60.8%; absolute risk difference 8.2% (95% CI −1.5% to +18.0%), HR 1.14 (95% CI 0.98 to 1.32)), time to the first escalation of respiratory support (2 (IQR 1–3) vs 2 (IQR 1–3) days, mean difference −0.2 days (95% CI −1.2 to +0.7)), ICU admission (7.7% vs 11.0%, absolute risk difference −3.3% (95% CI −9.3% to +2.6%)) and median hospital length of stay (11 (IQR 8–17) vs 11 (IQR 7–20) days, absolute risk difference −1.0% (95% CI −3.1% to +1.1%)). There was no significant difference in the proportion of patients who received CPAP, NIV or IMV as the first-line strategy for escalation of respiratory support (table 2). Mortality was not significantly different between groups neither within 28 days (7.7% vs 7.2%; absolute risk difference +0.5% (95% CI −4.8% to +5.9%)), nor within 60 days (8.3% vs 8.3%; absolute risk difference +0% (95% CI −5.6% to +5.6%)). A statistically significant difference in median dyspnoea score on the first time point at 2 hours and on days 3, 4 and 5 was found in the HFNO group compare to COT (online supplemental eFigure1). Respiratory rate and comfort score were not significantly different between groups at any time points (online supplemental eFigure1–3). None of the other secondary outcomes differed significantly between the two groups (online supplemental eTable 5).

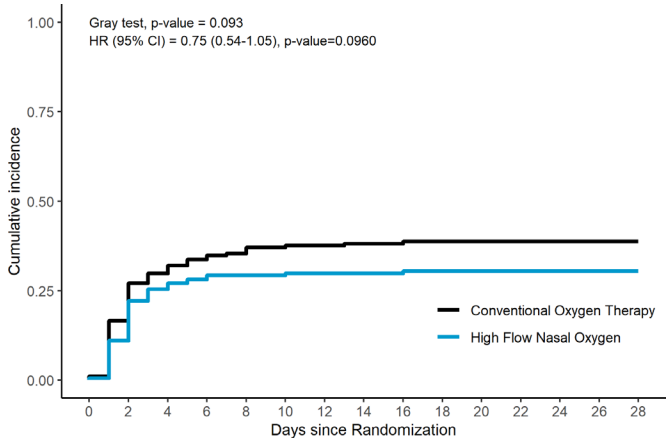

Figure 2 Cumulative incidence of escalation of respiratory support, according to the original assigned intervention.

Prespecified exploratory subgroup analyses showed no qualitative interaction between study interventions and subgroups. However, the risk of escalation of respiratory support may be more pronounced among patients younger than 65 years old (22.5% vs 37.5%; RR 0.60 (95% CI 0.39 to 0.91)) and among patients whose duration of symptoms prior to hospital admission was ≥5 days (29.0% vs 42.5%; RR 0.68 (95% CI 0.49 to 0.95)) (figure 3, online supplemental eTable 6). In the post hoc generalised linear model with log link and binomial distribution, there was no credible effect of the variable used in the subgroups analyses and sex on the associations between study intervention and the occurrence of the primary outcome (online supplemental eTable 7).

DISCUSSION

This randomised controlled trial found no significant reduction in the escalation of respiratory support with HFNO compared with COT. These results suggest that pathophysiological effects

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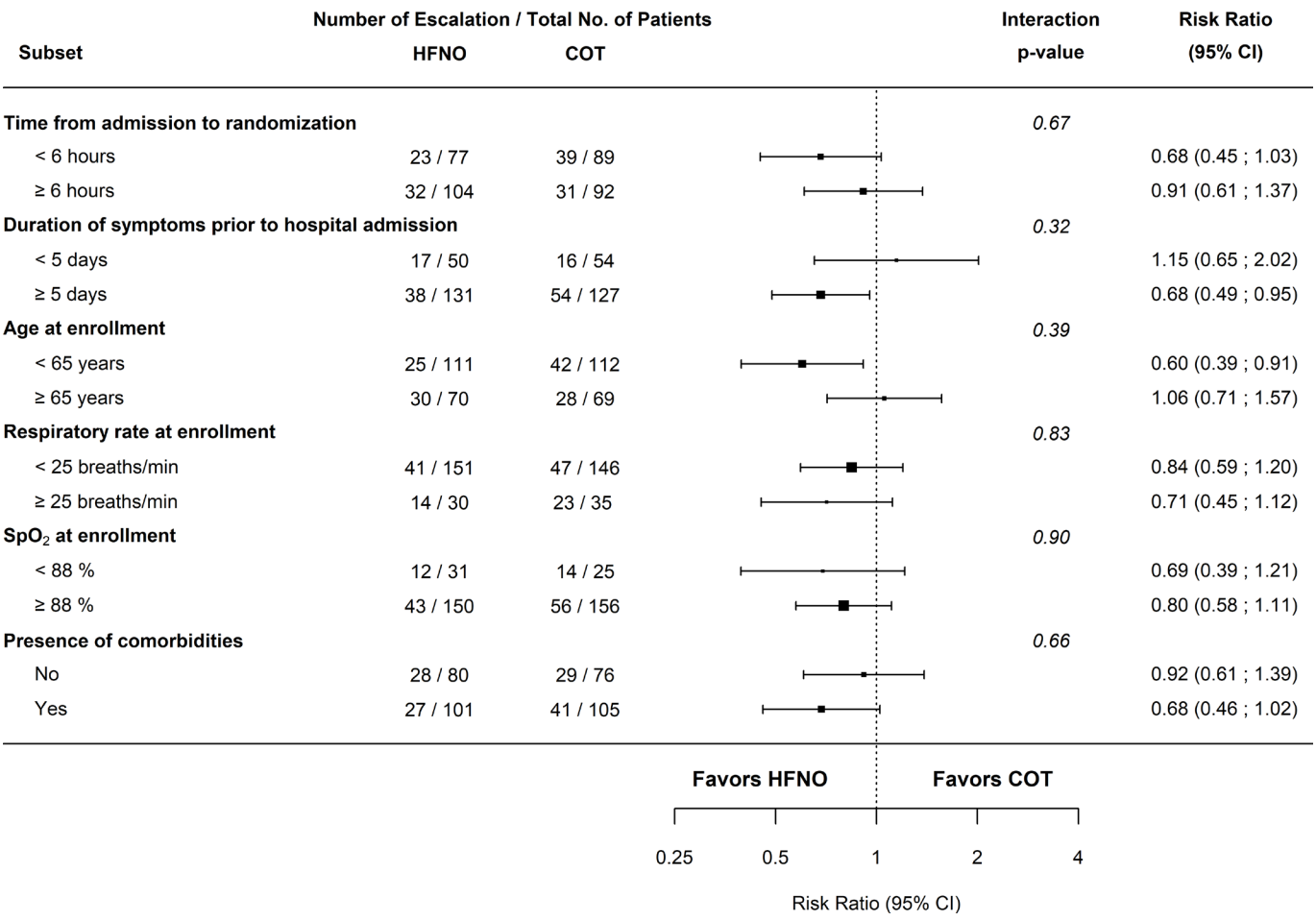

Figure 3 Primary outcome in predefined subgroups of patients, according to the original assigned intervention. Square sides of data markers are proportional to subgroup sizes. Error bars indicate 95% CIs. The Gail and Simon test for interaction was used. COT, conventional oxygen therapy; HFNO, high-flow nasal oxygen; S_pO_2, peripheral oxygen saturation.

of HFNO are unlikely to significantly affect the clinical course of COVID-19 pneumonia-related mild hypoxaemia compared with COT. However, these considerations should be seen in light of a lower than expected event rate and its contribution to the not significant difference in the primary outcome, also taking into account the minimum clinically important difference used for sample size calculation.

HFNO can deliver more stable oxygen supplementation compared with COT, and it can provide several beneficial effects in terms of oxygenation, respiratory mechanics and patient's effort.[22 23] Thus, it is generally considered a form of non-invasive respiratory support.[24] HFNO has been extensively used worldwide for respiratory support of patients with COVID-19 during the pandemic,[9] even outside the ICUs,[25] considering the shortage of intensive care beds and the relative ease of use.[26] However, national and international organisations recommendations relating to the use of HFNO are inconsistent.[27] Unprecedented demands for hospital resources and particularly oxygen requirements during the pandemic have led to oxygen shortages in many centres worldwide.[28] HFNO requires a high amount of oxygen,[29] especially in hypoxaemic patients who require high FiO_2 and flows and, in a pandemic context, a judicious administration of oxygen should be considered. In the HFNO group, a lower proportion of patients underwent escalation of respiratory support and a higher proportion had clinical recovery. Thus, a small but clinically significant improvement associated with HFNO use cannot be excluded. However, considering the higher oxygen consumption and the inherent infection control concerns with HFNO,[30] a substantial clear benefit would be required to support HFNO, which is lacking.

Our trial hypothesis was based on the uncertainty of whether the overall effects of HFNO would provide significant clinical benefits in terms of risk for clinical deterioration compared with standard oxygen in the mild stage of COVID-19 pneumonia-related hypoxaemia. The RECOVERY-RS multicentre trial showed no difference between HFNO and COT for the composite primary outcome of intubation or mortality within 30 days (44.3% HFNO vs 45.1% COT, unadjusted OR 0.97 (95% CI 0.73 to 1.29), p=0.83) in COVID-19 patients.[31] Although our results were in line with these data, our patient population and trial design differed significantly from RECOVERY-RS.[31] The RECOVERY-RS recruited more severe patients with COVID-19 pneumonia-related hypoxaemia, with a SpO_2 ≤94% despite receiving a FiO_2 of at least 40%. Differently from our design, CPAP was one of the RECOVERY-RS study arms.[31] A recent trial conducted in three centres in Colombia demonstrated that HFNO significantly reduced the risk of intubation (HR 0.62 (95% CI 0.39 to 0.96); p=0.03) and time to clinical recovery (HR 1.39 (95% CI 1.00 to 1.92); p=0.047) in patients with severe COVID-19 (FiO_2 <200). The results of these trials suggest that the clinical benefit of HFNO over COT may differ

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according to the severity of COVID-19 pneumonia-related hypoxaemia.[16]

To the best of our knowledge, this is the first trial evaluating HFNO compared with COT in patients with COVID-19 pneumonia-related mild hypoxaemia with the aim of reducing the likelihood of escalation of respiratory support. No patients were lost to follow-up, and the analysis was performed by intention to treat. The participation of 27 centres in 6 countries with different logistic characteristics confers external validity to our results.

The trial has limitations. Due to the nature of the study interventions, blinding was not possible. However, clinical criteria used to decide on the escalation of respiratory support were standardised. Nonetheless, we acknowledge that subjectivity in clinical judgement could not be excluded. It is possible that, in selected cases, clinicians may have considered HFNO as a form of respiratory support and been less likely to escalate to CPAP/NIV compared with COT. Therefore, this may partly explain the higher rate of protocol violations observed in the COT group. The study was designed to detect an absolute difference of 15% (equal to a relative difference of 27%) for the primary outcome, considering an event rate of 55% in the control group that was the most likely at the time of trial design.[10] However, the event rate was lower than expected (40% vs 55%). Therefore, the trial is underpowered to detect the hypothesised difference since it has a 60% of power for detecting a relative difference of 27%. By contrast, the study shows a power of 80% for detecting a relative difference of 35%, that corresponds to an absolute difference of 14%. These considerations suggest that a clinically meaningful benefit from HFNO in this patient population could not be definitely ruled out. In our cohort, 64% of patients were males and this may limit the generalisability of our finding towards the whole patient population. However, the adjusted RR for sex showed no significant effect on the association between occurrence of the primary outcome and study interventions. Due to the multinational and multicentre nature of the study, different surges of the pandemic may have had different indirect consequences on the level of care at the study sites. We did not register data on SARS-CoV-2 variants and the vaccination status of the participants. Finally, the results of the subgroup analyses should be considered exploratory as positive findings may be attributed to repeated testing.

CONCLUSIONS

The COVID-HIGH trial showed that HFNO did not significantly decrease the escalation of respiratory support compared with COT among hospitalised patients with COVID-19 pneumonia with mild hypoxaemia.

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Acknowledgements We thank Professor Sharon Einav and Prof. Nicolino Ambrosino for their invaluable contribution and assistance for this trial and for their commitment as members of the Trial Oversight Committee. None mentioned herein were compensated.

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the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. ACo and CC are responsable for the overall content as the guarantors. The COVID-HIGH trial collaborators consist of local investigators who were responsible for participant recruitment and local ethical board approval.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests ACh, AG and CG declare a patent, in association with the University of Palermo—Italy (No 102019000020532—Italian Ministry of Economic Development), not discussed in the present study. ACa received honoraria for lectures or consultancies from Breas, Philips (outside the submitted work). CC received honoraria for lectures from Philips, Resmed (outside the submitted work). CG received honoraria for lectures or consultancies from Vivisol, Philips, Mindray, Air Liquide (outside the submitted work). JCW received honoraria for lectures from Vitalaire, Nippon Gases, Philips, Breas and Armstrong Medical (outside the submitted work). The remaining authors declared no competing interests.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Ethics Committee of the coordinating centre (Comitato Etico Catania 1, 01/2021/PO, 25/01/2021) and all participating sites before patient inclusion. The study was performed in accordance with Good Clinical Practice guidelines and ethical principles of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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