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Effect of High-Flow Nasal Cannula Oxygen vs Standard Oxygen Therapy on Mortality in Patients With Respiratory Failure Due to COVID-19
The SOHO-COVID Randomized Clinical Trial

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IMPORTANCE The benefit of high-flow nasal cannula oxygen (high-flow oxygen) in terms of intubation and mortality in patients with respiratory failure due to COVID-19 is controversial.

OBJECTIVE To determine whether the use of high-flow oxygen, compared with standard oxygen, could reduce the rate of mortality at day 28 in patients with respiratory failure due to COVID-19 admitted in intensive care units (ICUs).

DESIGN, SETTING, AND PARTICIPANTS The SOHO-COVID randomized clinical trial was conducted in 34 ICUs in France and included 711 patients with respiratory failure due to COVID-19 and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen equal to or below 200 mm Hg. It was an ancillary trial of the ongoing original SOHO randomized clinical trial, which was designed to include patients with acute hypoxemic respiratory failure from all causes. Patients were enrolled from January to December 2021; final follow-up occurred on March 5, 2022.

INTERVENTIONS Patients were randomly assigned to receive high-flow oxygen (n = 357) or standard oxygen delivered through a nonrebreathing mask initially set at a 10-L/min minimum (n = 354).

MAIN OUTCOMES AND MEASURES The primary outcome was mortality at day 28. There were 13 secondary outcomes, including the proportion of patients requiring intubation, number of ventilator-free days at day 28, mortality at day 90, mortality and length of stay in the ICU, and adverse events.

RESULTS Among the 782 randomized patients, 711 patients with respiratory failure due to COVID-19 were included in the analysis (mean [SD] age, 61 [12] years; 214 women [30%]). The mortality rate at day 28 was 10% (36/357) with high-flow oxygen and 11% (40/354) with standard oxygen (absolute difference, −1.2% [95% CI, −5.8% to 3.4%]; $P = .60$). Of 13 prespecified secondary outcomes, 12 showed no significant difference including in length of stay and mortality in the ICU and in mortality up until day 90. The intubation rate was significantly lower with high-flow oxygen than with standard oxygen (45% [160/357] vs 53% [186/354]; absolute difference, −7.7% [95% CI, −14.9% to −0.4%]; $P = .04$). The number of ventilator-free days at day 28 was not significantly different between groups (median, 28 [IQR, 11-28] vs 23 [IQR, 10-28] days; absolute difference, 0.5 days [95% CI, −7.7 to 9.1]; $P = .07$). The most common adverse events were ventilator-associated pneumonia, occurring in 58% (93/160) in the high-flow oxygen group and 53% (99/186) in the standard oxygen group.

CONCLUSIONS AND RELEVANCE Among patients with respiratory failure due to COVID-19, high-flow nasal cannula oxygen, compared with standard oxygen therapy, did not significantly reduce 28-day mortality.

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Visual Abstract

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Supplemental content

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Group Information: The SOHO-COVID Study Group and the REVA Network investigators are listed in Supplement 4.

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As of 2022, the COVID-19 pandemic has caused more than 6 million deaths around the world due to unfavorable outcome of acute hypoxemic respiratory failure.[1-3] During successive waves, up to 80% of patients admitted to the hospital and 45% to intensive care units (ICUs) with COVID-19 have been treated with standard oxygen as first-line therapy.[3-6] Several other noninvasive oxygenation supports have been proposed as treatment for patients with respiratory failure due to COVID-19 with the aim of avoiding intubation, including high-flow nasal cannula oxygen (high-flow oxygen), noninvasive ventilation with pressure support, and continuous positive airway pressure.[7-11] Retrospective observational studies suggested a decreased risk of intubation with high-flow oxygen as compared with standard oxygen, without improved survival.[7,8] A randomized clinical trial showed similar results with decreased risk of intubation with high-flow oxygen as compared with standard oxygen, but no significant difference in mortality.[11] However, a recent clinical trial did not report a significant difference in intubation rates with high-flow oxygen as compared with standard oxygen.[12] No study has reported improved survival of patients with COVID-19 treated with high-flow oxygen or any other oxygenation support compared with standard oxygen, while results are conflicting on the risk of intubation.

Before the COVID-19 pandemic, 2 randomized clinical trials reported conflicting results between high-flow oxygen and standard oxygen in the management of critically ill patients with acute hypoxemic respiratory failure.[13,14] One showed decreased risk of death and intubation with high-flow oxygen compared with standard oxygen,[13] but a second trial did not show a significant difference in terms of intubation or mortality in the specific population of immunocompromised patients with acute respiratory failure.[14]

This multicenter, randomized, clinical trial was conducted to determine whether high-flow oxygen, compared with standard oxygen, could reduce the rate of mortality in patients admitted to an ICU with respiratory failure due to COVID-19.

Key Points

Questions In patients with respiratory failure due to COVID-19, does the use of high-flow nasal cannula oxygen reduce the risk of mortality compared with standard oxygen therapy?

Findings In this randomized clinical trial that included 711 patients, mortality at day 28 was 10% in the high-flow oxygen group and 11% in the standard oxygen therapy group, a difference that was not statistically significant.

Meaning In patients with respiratory failure due to COVID-19, high-flow nasal cannula oxygen did not significantly reduce mortality at day 28 compared with standard oxygen therapy.

Methods

Study Design and Oversight

The SOHO-COVID (Standard Oxygen Versus High Flow Cannula Oxygen Therapy in Patients With Acute Hypoxemic Respiratory Failure) trial was a multicenter, open-label, parallel-group randomized clinical trial conducted in 34 ICUs in France. It was an ancillary study of the SOHO trial, which was originally designed to include patients with acute hypoxemic respiratory failure from all causes. The SOHO trial started on January 19, 2021, while the third wave of COVID-19 was occurring. Therefore, we decided to focus the trial on patients with respiratory failure due to COVID-19. At the time we submitted the SOHO-COVID trial to the ethics committee (on April 16, 2021), 319 of the 333 randomized patients (96%) had respiratory failure due to COVID-19. The SOHO-COVID trial was approved by the ethics committee on April 27, 2021. Because silent hypoxemia seemed common in the participating ICUs,[15,16] the ethics committee approved the proposition to broaden inclusion for patients with a low respiratory rate by stratifying randomization on respiratory rate equal to or below 25 breaths per minute.

The study protocol (Supplement 1) was approved for all centers by the central ethics committee (Comité de Protection des Personnes Sud Méditerranée III). The statistical analysis plan is provided in Supplement 2. Written informed consent was obtained from all patients, their next of kin, or another surrogate decision-maker as appropriate before inclusion in the study. The trial was overseen by a steering committee (REVA Network) that met every 6 months. According to French law and the decision of the ethics committee, no safety committee was required because the interventions carried out in the study were noninvasive oxygen supports that are commonly used in clinical practice. Research assistants regularly monitored all centers on-site to check compliance with the protocol and accuracy of the data recorded. An investigator at each center was responsible for enrolling patients in the study, ensuring adherence to the protocol, and completing the electronic case-report form.

Patients

Consecutive adult patients with respiratory failure due to COVID-19 were randomly assigned to receive either high-flow oxygen or standard oxygen. Eligible critically ill patients could be enrolled if they met all the following criteria: age older than 18 years, suspected or confirmed diagnosis of COVID-19 (via reverse transcriptase–polymerase chain reaction test from a nasopharyngeal swab), a pulmonary infiltrate, and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (Pao_2:Fio_2) equal to or below 200 mm Hg while breathing oxygen at a flow rate of 10 L/min or more for at least 15 minutes. Fio_2 was estimated as follows: $Fio_2 = 0.03 \times (\text{oxygen flow L/min}) + 0.21$.[13,17]

The main exclusion criteria were as follows: partial pressure of arterial carbon dioxide more than 45 mm Hg, exacerbation of chronic lung disease, cardiogenic pulmonary edema, hemodynamic instability defined by signs of hypoperfusion or use of vasopressors at doses greater than 0.3 µg/kg/min, Glasgow Coma Scale score equal to or below 12 points, urgent need for endotracheal intubation, do-not-intubate order, and refusal to participate. The study exclusion criteria are detailed in the eMethods in Supplement 3.

Randomization and Masking

Randomization was computer-generated in permuted blocks of 4 (unknown to investigators), with stratification according to immunosuppression status (eMethods in Supplement 3) in the original SOHO trial for patients included from January 19 to April 27, 2021, and according to COVID-19 status and respiratory rate (>25 breaths per minute or ≤25 breaths per minute) in the ancillary SOHO-COVID trial for patients included from April 27 to December 6, 2021.[15,16] Within the first 3 hours following validation of inclusion criteria, using a centralized web-based management system, patients were randomly assigned in a 1:1 ratio (ENNOV EDC) to the high-flow oxygen or standard oxygen groups. Although individual patient assignments could not be masked, the coordinating center and all the investigators remained unaware of the study group outcomes until the data were locked in March 2022. All analyses were performed by the study statistician in line with the International Conference on Harmonization Good Clinical Practice guidelines.

Interventions

In the standard oxygen group, oxygen was continuously delivered through a nonrebreathing mask, with oxygen flow set at 10 L/min or more, adjusted for oxygen saturation measured by pulse oximetry (Spo_2) between 92% and 96% until recovery or intubation.

In the high-flow oxygen group, oxygen was continuously delivered via large bore binasal prongs with gas flow of 50 L/min or more through a heated humidifier (MR850, Fisher & Paykel Healthcare). The fraction of oxygen was adjusted to maintain Spo_2 between 92% and 96% (Optiflow or Airvo-2, Fisher & Paykel Healthcare; or an ICU ventilator with a high-flow oxygen therapy option). High-flow oxygen therapy was applied for at least 48 hours and was stopped and switched to standard oxygen therapy when the patient maintained Spo_2 of at least 92% and a respiratory rate equal to or below 25 per minute with a Fio_2 equal to or below 40%.[18]

Outcomes

The primary outcome was the proportion of patients who died within 28 days following randomization.

Thirteen secondary outcomes included the proportion of patients who required endotracheal intubation within 28 days following randomization, number of ventilator-free days (ie, number of days alive without invasive mechanical ventilation) between randomization (day 1) and day 28, mortality at various predefined times (in the ICU, in the hospital, and up until day 90), length of stay in the ICU and hospital, level of oxygenation at 1 hour, dyspnea (using a 5-point Likert scale model, indicating marked improvement, slight improvement, no change, slight deterioration, and marked deterioration), comfort (using a 100-mm visual analog scale, 0 meaning no discomfort to 100 mm, maximal imaginable discomfort), intervals between randomization and intubation, intervals between intubation criteria and intubation procedure, and Sepsis-related Organ Failure Assessment score during the first 48 hours after intubation. The overall incidence of serious adverse events, including cardiac arrest, pneumothorax during spontaneous breathing, septic shock, and ventilator-associated pneumonia, were also assessed (eMethods in Supplement 3).

Post hoc exploratory outcomes included application of awake prone position, use of noninvasive ventilation as rescue therapy, the proportion of patients who met criteria for intubation, reasons for intubation, and mortality in patients who required endotracheal intubation.

To ensure the consistency of intubation indications across participating centers and to reduce the risk of delayed intubation, patients were immediately intubated if 1 of the following criteria was fulfilled: severe respiratory failure; life-threatening hypoxemia defined as recurrent episodes of Spo_2 below 80% or persisting Spo_2 below 88% with maximal oxygen support; cardiac arrest; hemodynamic instability with signs of hypoperfusion; or deterioration of neurologic status with Glasgow Coma Scale score below 12 points or agitation.

Severe respiratory failure leading to intubation was defined by at least 2 of the following criteria: (1) respiratory rate greater than 40 breaths per minute, (2) appearance or worsening of signs of respiratory-muscle fatigue, (3) acidosis with pH less than 7.35, or (4) hypoxemia defined as need for oxygen flow equal to or greater than 15 L/min (standard oxygen group) or of Fio_2 equal to or greater than 80% (high-flow oxygen) to maintain Spo_2 equal to or greater than 92% or Pao_2:Fio_2 ratio less than 100 mm Hg (eMethods in Supplement 3).

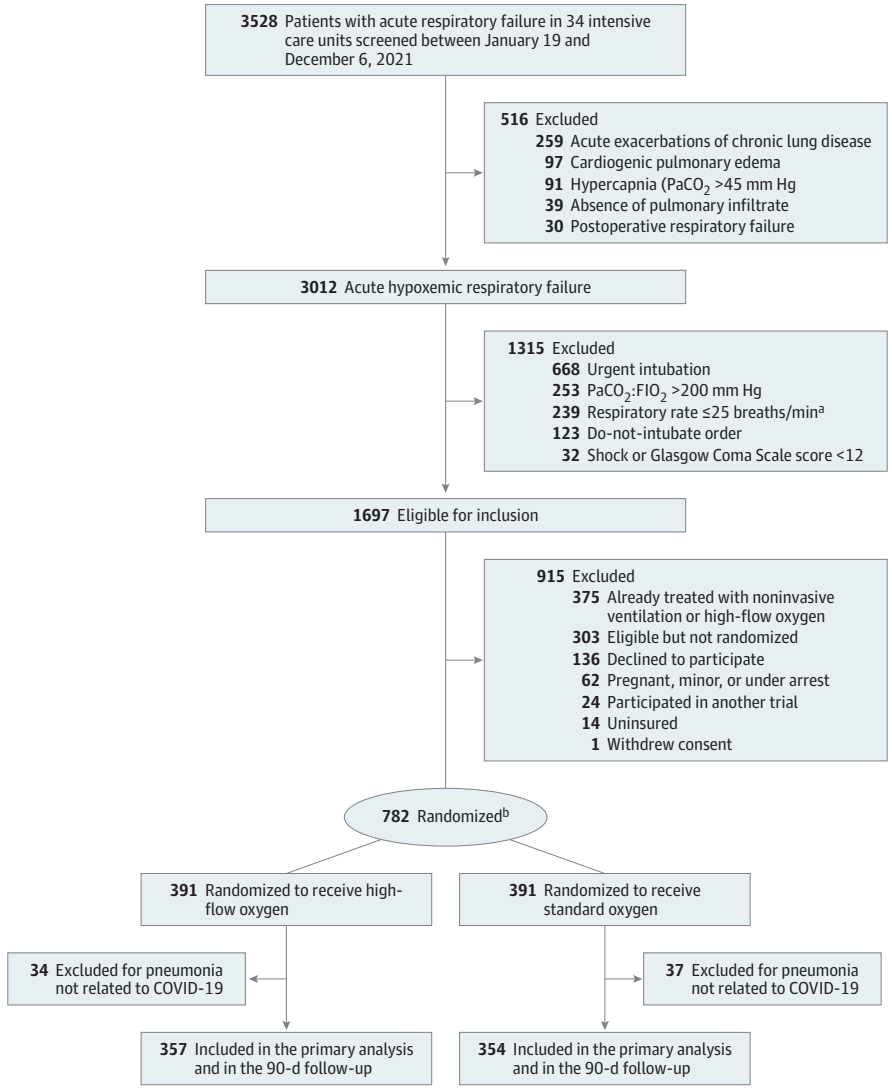
Sample Size Calculation

Assuming a mortality rate of 25% in patients with respiratory failure due to COVID-19 treated with standard oxygen,[7,8,19] we determined that enrollment of 670 patients would provide power of 90% to highlight an absolute difference of 10% in the primary outcome between the standard oxygen group and the high-flow oxygen group (estimated mortality rate at 15%)[8,9,13,20] at a 2-sided α level of .05. To allow for potential secondary exclusions and take into account rapid inclusions and difficulties in monitoring centers during the pandemic period, we planned to increase the number to 720 patients with respiratory failure due to COVID-19 (including patients from the original and ancillary trials).

Statistical Analysis

Analyses pooled all patients with COVID-19 (from the original and ancillary trials) together. All analyses were performed in patients according to their randomization group (statistical analysis plan is detailed in Supplement 2). The proportions of patients who died within the 28 days following randomization were compared between the 2 groups by means of the χ^2 test. Kaplan-Meier curves were plotted to assess time from randomization to death and compared by means of the log-rank test at day 28. Hazard ratio was calculated by means of a Cox proportional-hazard regression analysis. The proportional hazards assumption was checked using a test based on the scaled Schoenfeld residuals, and the assumption was not violated. The rate of intubation at day 28 and mortality rates in the ICU, in the hospital, at day 28, and day 90 were compared between the 2 groups by means of the χ^2 test. Kaplan-Meier curves were plotted to assess the time from randomization to endotracheal intubation at day 28 and were compared by means of the

Figure 1. Flow of Patients in the SOHO-COVID Trial



FIO_2 indicates fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide.

[a] After April 27, 2021, inclusion criteria were broadened with the aim of including patients with silent hypoxemia having a low respiratory rate.

[b] A total of 389 patients in the original SOHO trial (with stratification on immunosuppression status) and 393 in the ancillary SOHO-COVID trial (with stratification on COVID-19 status and respiratory rate).

log-rank test. Comparisons of the other secondary and exploratory outcomes were performed with the χ^2 test for qualitative variables and with *t* test or nonparametric Mann-Whitney U test if appropriate for quantitative variables. A secondary multiple logistic regression analysis was performed for mortality and intubation at day 28 to adjust on the stratification variables (immunocompromised status and respiratory rate), and on potential baseline unbalanced variables after testing for interaction. Lack of balance was defined if the comparison test between the 2 randomized interventions (χ^2 test for qualitative variables or *t* test/Mann-Whitney U test for quantitative variables) yielded $P < .05$. To take into account a potential study site effect, a mixed-effects logistic regression model was performed in a post hoc analysis. The missing data were sparse and not replaced.

For all outcomes, effect sizes were expressed as absolute differences and odds ratios with 95% CIs.

Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. A 2-tailed *P* value of less than .05 was considered statistically significant. We used SAS software version 9.2 (SAS Institute Cary) and R statistical package version 4.0.4 (The R Foundation for Statistical Computing) for all analyses.

Results

Patients

From January 19, 2021, through December 6, 2021, a total of 1697 patients admitted to the 34 participating ICUs had acute hypoxemic respiratory failure from all causes, and 782 patients with acute hypoxemic respiratory failure underwent randomization (**Figure 1**). After exclusion of 71 patients who had pneumonia not related to COVID-19, 711 patients (mean [SD] age, 61 [12] years; 214 women [30%]) were retained in the analysis, including 357 assigned to high-flow oxygen and 354 to standard oxygen. The median interval between ICU admission and

Table 1. Baseline Patient Characteristics

Characteristic	High-flow oxygen (n = 357)	Standard oxygen (n = 354)
Age, mean (SD), y	61 (12)	61 (12)
Sex, No. (%)		
Male	250 (70)	247 (70)
Female	107 (30)	107 (30)
Body mass index, mean (SD)[a]	29 (5)	29 (6)
Current smoker, No. (%)	15 (4)	17 (5)
Coexisting illness, No. (%)		
Immunosuppression[b]	44 (12)	31 (9)
Ischemic heart disease	31 (9)	32 (9)
Chronic lung disease	17 (5)	18 (5)
Kidney replacement therapy	5 (1)	4 (1)
Confirmed COVID-19, No. (%)[c]	354 (99)	350 (99)
Interval between symptom onset and ICU admission, median (IQR), d	10 (7-12)	10 (8-12)
Interval between hospital and ICU admission, median (IQR), d	2 (1-3)	2 (1-3)
Use of glucocorticoids, No. (%)	338 (95)	335 (95)
Clinical parameters		
Respiratory rate, mean (SD), breaths/min	28 (6)	29 (6)
Respiratory rate ≤25 breaths/min, No. (%)	79 (22)	67 (19)
Heart rate, mean (SD), beats/min	81 (15)	81 (17)
Systolic arterial pressure, mean (SD), mm Hg	134 (20)	134 (20)
Mean arterial pressure, mean (SD), mm Hg	94 (13)	93 (14)
Bilateral pulmonary infiltrates, No. (%)[d]	348 (99)	342 (98)
Arterial blood gas, mean (SD)[e]		
pH	7.46 (0.04)	7.46 (0.05)
Pao_2, mm Hg	73 (15)	76 (15)
FIO_2[f]	0.58 (0.08)	0.58 (0.07)
Pao_2:FIO_2 ratio, mm Hg	128 (31)	132 (31)
$Paco_2$, mm Hg	35 (5)	35 (4)
Simplified Acute Physiology Score II, mean (SD), points[g]	31 (10)	29 (13)
Score of Clinical Frailty Scale, median (IQR), points[h]	2 (1-3)	2 (1-2)

Abbreviations: FIO_2, fraction of inspired oxygen; high-flow oxygen, high-flow nasal cannula oxygen therapy; ICU, intensive care unit; $Paco_2$, partial pressure of arterial carbon dioxide; Pao_2 partial pressure of arterial oxygen; standard oxygen, oxygen given initially through a nonrebreathing face mask at a flow rate of 10 L or more per minute.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Immunosuppression, defined as use of long-term steroids (>3 months) or high-dose (≥20 mg/d of prednisone or equivalent for at least 14 days) steroids, use of other immunosuppressant/immunomodulatory drugs, solid organ transplant, active solid cancer, hematologic malignancy (active or remitting for less than 5 years), leukopenia <1 ×10^9/L or neutropenia ≤0.5 ×10^9/L after chemotherapy, allogenic stem cell transplantation within the last 5 years, AIDS, or primary immune deficiency.

[c] Diagnosis of COVID-19 was confirmed via reverse transcriptase–polymerase chain reaction test from a nasopharyngeal swab.

[d] Bilateral pulmonary infiltrates refer to chest x-ray in 328 patients (46%) and computed tomographic scan in 383 patients (54%).

[e] Reference values are the following: pH, 7.35-7.45; Pao_2, 80-100 mm Hg; and $Paco_2$, 35-45 mm Hg.

[f] FIO_2 was estimated as follows: (oxygen flow L/min) × 0.3 + 0.21.

[g] The Simplified Acute Physiology Score II is calculated from 17 variables at inclusion, information about previous health status, and from information obtained at admission. Scores can range from 0 to 163, with higher scores indicating more severe disease.

[h] The score of Clinical Frailty Scale is a way to summarize the overall level of fitness or frailty after clinical evaluation. Scores can range from 1 to 9, ie, very fit to terminally ill.

randomization was 2.6 hours (IQR, 1.3-6.3), and allocated treatment was applied 5 minutes (IQR, 0.0-26) after randomization.

The characteristics of the patients at enrollment were similar in the 2 groups, except for Pao_2, which was lower in the high-flow oxygen group (mean [SD] of 73 [15] vs 76 [15] mm Hg; absolute difference, -3 mm Hg [95% CI, -5.2 to -0.8]; P = .03) (**Table 1**). The mean (SD) baseline respiratory rate was 29 (6) breaths per minute and Pao_2:FIO_2 ratio of 130 (31) mm Hg with FIO_2 at 0.58 (0.07).

Interventions

The initial mean (SD) settings were as follows: gas flow of 51 (10) L/min and FIO_2 of 0.68 (0.17) in the high-flow oxygen group and oxygen flow of 13 (3) L/min in the standard oxygen group. High-flow oxygen was continuously delivered for a median of 4 days (IQR, 2-6) and was successfully weaned to standard oxygen by 5 days (IQR, 4-8) in the 197 (55%) of 357 patients who did not need intubation. Standard oxygen through a mask was continuously delivered for a median of 4 days (IQR, 2-6) and

Table 2. Primary and Secondary Outcomes

Outcomes	High-flow oxygen (n = 357)	Standard oxygen (n = 354)	Absolute difference (95%CI)	Unadjusted odds ratio (95%CI)	*P* value for unadjusted odds ratio	Adjusted odds ratio[a,b] (95% CI)	*P* value for adjusted odds ratio
Primary outcome							
Mortality at day 28, No. (%)	36 (10)	40 (11)	-1.2 (-5.8 to 3.4)	0.88 (0.55 to 1.42)	.60	0.78 (0.48 to 1.28)	.32
Secondary outcomes							
Intubation at day 28, No. (%)	160 (45)	186 (53)	-7.7 (-14.9 to -0.4)	0.73 (0.55 to 0.99)	.04	0.65 (0.48 to 0.89)	.007
ICU mortality, No. (%)	42 (12)	52 (15)	-2.9 (-7.9 to 2.1)	0.77 (0.50 to 1.20)	.25	0.68 (0.42 to 1.05)	.08
Hospital mortality, No. (%)	46 (13)	53 (15)	-2.1 (-7.2 to 3.0)	0.84 (0.55 to 1.29)	.42	0.74 (0.48 to 1.15)	.18
Mortality at day 90, No. (%)	48 (13)	53 (15)	-1.5 (-6.7 to 3.6)	0.88 (0.58 to 1.34)	.56	0.79 (0.51 to 1.23)	.30
Ventilator-free days at day 28 median (IQR), d[c,d]	28 (11 to 28)	23 (10 to 28)	0.5 (-7.7 to 9.1)[b]		.07		

Abbreviations: ICU, intensive care unit; high-flow oxygen, high-flow nasal cannula oxygen therapy; Pao_2 partial pressure of arterial oxygen; standard oxygen, oxygen given initially through a nonrebreathing face mask at a flow rate of 10 L or more per minute.

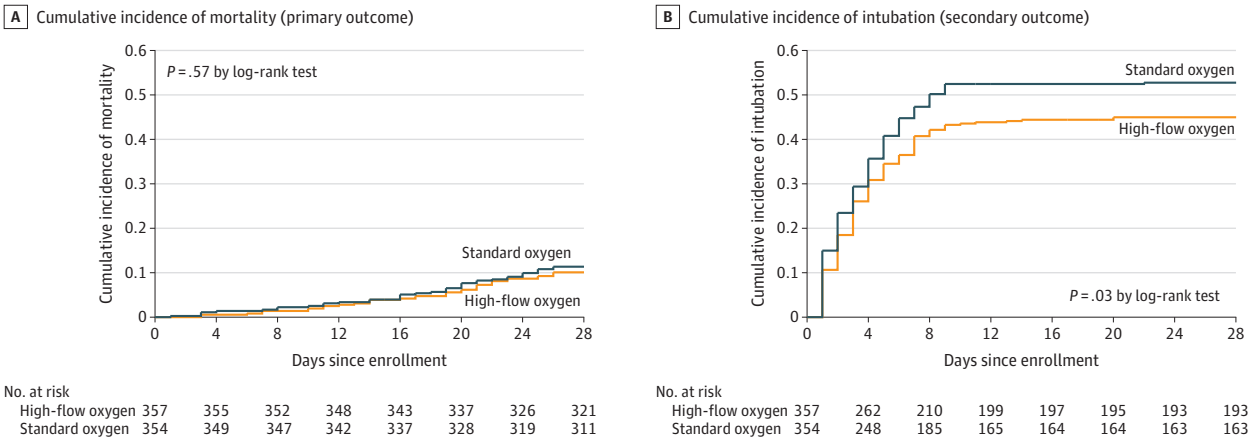
[a] An odds ratio less than 1 indicates benefit with use of high-flow oxygen therapy.

[b] Multivariable logistic regression was performed with adjustment for baseline group differences (Pao_2) and stratification variables (respiratory rate and immunosuppression). There were no significant differences between the groups in any of the characteristics listed except for Pao_2 (*P* = .03).

[c] The number of ventilator-free days was defined as the number of days alive without invasive mechanical ventilation from randomization (day 1) at day 28.

[d] 95% CI of the difference of medians were estimated based on 5000 bootstrap resampling.

Figure 2. Kaplan-Meier Plot of the Cumulative Incidence of Mortality (Primary Outcome) and Intubation (Secondary Outcome) From Randomization to Day 28



The median observation time was 28 days (IQR, 28-28) in all treatment groups.

was successfully weaned by 4 days (IQR, 3-6) in the 168 (47%) of 354 patients who did not need intubation.

With regard to adherence with the allocated treatment, 21 patients (6%) randomized to the high-flow oxygen group were switched to standard oxygen due to intolerance and 12 patients (3%) randomized to the standard oxygen group were switched to high-flow oxygen.

Primary Outcome

The mortality rate at day 28 was 10% (36 of 357 patients) in the high-flow oxygen group and 11% (40 of 354) in the standard oxygen group (absolute difference, -1.2% [95% CI, -5.8% to 3.4%]; *P* = .60) (**Table 2**). After adjustment on baseline Pao_2, respiratory rate, and immunosuppression status, the mortality rate at day 28 remained not significantly different between the 2 groups (odds ratio, 0.78 [95% CI, 0.48 to 1.28]; *P* = .32). Moreover, in a post hoc analysis taking into account site as a random effect, the difference remained nonsignificant (*P* = .32). The hazard ratio for mortality at day 28 was 0.88 (95% CI, 0.56 to 1.38; *P* = .57) in the high-flow oxygen group compared with the standard oxygen group (**Figure 2**).

Secondary Outcomes

The intubation rate by day 28 was 45% (160 of 357 patients) in the high-flow group and 53% (186 of 354) in the standard oxygen group (absolute difference, -7.7% [95% CI, -14.9% to -0.4%]; *P* = .04; hazard ratio, 0.77 [95% CI, 0.63 to 0.96]; *P* = .03 by log-rank test) (Figure 2 and Table 2). The intubation rate remained significantly lower in the high-flow oxygen group after adjustment for the baseline Pao_2 and stratification variables (*P* = .007) (Table 2). The median time of intervals between randomization and intubation did not significantly differ

between groups (36 hours [IQR, 12-84] with high-flow oxygen and 26 hours [IQR, 12-54] with standard oxygen; absolute difference, 9.6 hours [95% CI, -2.8 to 20.1]; P = .10) (**Table 3**). The median number of ventilator-free days at day 28 was 28 (IQR, 11 to 28) in the high-flow oxygen group and 23 (IQR, 10 to 28) in the standard oxygen group (absolute difference, 0.5 days [95% CI, -7.7 to 9.1]; P = .07). There was no significant difference in mortality at day 90 (13% [48 of 357 patients] vs 15% [53 of 354]; absolute difference, -1.5% [95% CI, -6.7% to 3.6%] in the high-flow oxygen and standard oxygen groups, respectively; P = .56) or mortality in the ICU (12% [42 of 357 patients] vs 15% [52 of 354]; absolute difference, -2.9% [95% CI, -7.9% to 2.1%] in the high-flow oxygen and standard oxygen groups, respectively; P = .25) (Table 2). Six patients died in the ICU without intubation (3 patients in each group).

One hour after treatment initiation, Pao_2 was lower in the high-flow oxygen group than in the standard oxygen group (mean [SD], 75 [27] vs 80 [22] mm Hg in the high-flow oxygen and standard oxygen groups, respectively; absolute difference, -5.0 mm Hg [95% CI, -8.6 to -1.4]; P = .006). Change in respiratory patient discomfort did not differ significantly between groups (median, 0.0 mm [IQR, -0.42 to 0.30] in high-flow oxygen group and 0.0 mm [IQR, -0.33 to 0.03] in standard oxygen group; P = .21), while the dyspnea score significantly improved with the use of high-flow oxygen (44% of patients [123 of 276] had slight or marked improvement in the high-flow oxygen group vs 28% [76 of 273] in the standard oxygen group; P < .001) (Table 3; and eTable in Supplement 3).

Post Hoc Exploratory Outcomes

Awake prone positioning was performed within the first 48 hours in 73 patients (20%) in the high-flow oxygen group and in 64 patients (18%) in the standard oxygen group. Noninvasive ventilation was applied as rescue therapy in 7 patients (2%) in the high-flow oxygen group and in 9 patients (3%) in the standard oxygen group (Table 3).

Among the 346 patients who required intubation in the ICU, all met prespecified criteria for intubation. Reasons for intubation were similar between groups and included severe respiratory failure in 290 patients (84%), life-threatening hypoxemia in 107 patients (31%), deterioration of neurologic status in 24 patients (7%), and hemodynamic instability or cardiac arrest in 18 patients (5%) (Table 3).

Adverse Events

The most common adverse events were ventilator-associated pneumonia, occurring in 58% (93/160) of patients in the high-flow oxygen group and 53% (99/186) in the standard oxygen group (Table 3). Seven patients had cardiac arrest leading to intubation (2 in the high-flow oxygen group and 5 in the standard oxygen group).

Discussion

In this multicenter, randomized, open-label trial, high-flow oxygen did not result in lower mortality rates than standard oxygen when administered as first-line therapy in critically ill patients with respiratory failure due to COVID-19.

When planning the study, a 25% mortality rate was assumed in the standard oxygen group and 15% in the high-flow oxygen group, based mainly on previous data from the first wave of the COVID-19 pandemic.[7-9,13,19,20] Despite high intubation rates (49%), mortality rates (11%) were markedly lower than expected, though consistent with recent clinical trials.[11,21] This may be explained by improved management of patients with COVID-19, particularly the widespread use of steroids since 2020.[22] As a result, to achieve adequate power to assess for a statistically significant difference in mortality rates in this setting would require a large number of patients. A previous trial suggested the superiority of high-flow oxygen over standard oxygen in terms of mortality (secondary outcome) in a smaller sample of patients.[13] However, these patients mainly had bacterial pneumonia as the main cause of acute respiratory failure, were more likely to have underlying comorbidities or immunosuppression status, and consequently had markedly higher mortality (exceeding 20% in the standard oxygen group) than patients with COVID-19 in this trial.[13]

All patients met the prespecified intubation criteria at the time of the intubation procedure and the reasons for intubation were similar in the 2 groups. Therefore, the decreased intubation rate in the high-flow oxygen group cannot be explained by any inconsistency in intubation indications. Moreover, high-flow oxygen did not improve oxygenation compared with standard oxygen. Consequently, the beneficial effects of high-flow oxygen on intubation could be due to decreased inspiratory effort[23] and washout of the upper airways[24] as suggested by an improved grade of dyspnea and lower carbon dioxide values 1 hour after treatment initiation.

To our knowledge, only 1 clinical trial, which was conducted in Colombia, has reported a decreased risk of intubation with high-flow oxygen compared with standard oxygen in 199 patients with respiratory failure due to COVID-19.[11] The present trial confirms these findings of decreased risk of intubation without decreased risk of death. This contrasts with a multicenter trial conducted in the United Kingdom and Jersey, which showed no significant difference in either intubation rates or mortality.[12] However, this trial had weaknesses including a high proportion of treatment crossover, and intubation indications were left to the discretion of the attending physician without the criteria for intubation having been expressly defined.[12] Although high-flow oxygen had no significant effect on the primary outcome of mortality, the decreased risk of intubation and need for invasive mechanical ventilation may be considered an important outcome for patients with acute respiratory failure. In addition, it may also help avoid the use of ICU ventilators in resource-constrained settings during a pandemic.

The present trial has several strengths, which suggest that the results may be generalized to patients admitted for respiratory failure due to COVID-19 in other ICUs and countries. They include the large scale of the study and participating centers, a well-defined study protocol including prespecified intubation criteria, and low crossover treatment.

Table 3. Additional Secondary and Exploratory Outcomes

Outcomes	High-flow oxygen (n = 357)	Standard oxygen (n = 354)	Absolute difference (95% CI)	*P* value
Secondary outcomes				
1 h after treatment initiation, mean (SD)				
Respiratory rate, breaths/min	25 (7)	27 (7)	-2.0 (-3.0 to -1.0)	<.001
Pao_2, mm Hg	75 (27)	80 (22)	-5.0 (-8.6 to -1.4)	.006
Fio_2[a]	0.68 (0.17)	0.58 (0.08)	0.10 (0.08 to 0.12)	<.001
Pao_2:Fio_2 ratio, mm Hg	116 (43)	141 (47)	-25 (-32 to -18)	<.001
$Paco_2$, mm Hg	34 (5)	35 (4)	-1.0 (-1.7 to -0.3)	<.001
pH	7.47 (0.04)	7.46 (0.04)	0.01 (0.00 to 0.02)	.001
Grade of dyspnea 1 h after treatment initiation, No. (%)[b]	n = 276	n = 273		<.001
Marked improvement	28 (10)	16 (6)	4.3 (-0.3 to 9.0)	
Slight improvement	95 (34)	60 (22)	12.4 (4.9 to 19.8)	
No change	119 (43)	188 (69)	-25.7 (-33.5 to -17.5)	
Slight deterioration	30 (11)	6 (2)	3.2 (0.7 to 6.3)	
Marked deterioration	4 (1)	3 (1)	0.3 (-1.9 to 2.7)	
Respiratory patient discomfort[c]				
Baseline, mean (SD), mm	29.0 (26.4)	22.8 (23.0)	6.2 (2.5 to 9.8)	.002
1 h after treatment initiation, mean (SD), mm	28.0 (25.0)	20.7 (22.4)	7.3 (3.8 to 10.8)	<.001
Change between 1 h after treatment initiation and baseline, median (IQR), mm[d,e]	0.0 (−0.42 to 0.30)	0.0 (−0.33 to 0.03)	0.0 (-0.33 to 0.03)	.21
Interval between randomization and intubation, median (IQR), h[e]	n = 160	n = 186		
Median (IQR), h[e]	36 (12-84)	26 (12-54)	9.6 (-2.8 to 20.1)	.10
Interval between meeting intubation criteria and intubation procedure, No. (%)	n = 160	n = 186		.99
<1 h	56 (36)	66 (36)	-0.4 (-10.5 to 9.9)	
1 to 3 h	70 (45)	82 (45)	-0.2 (-10.1 to 10.4)	
>3 h	30 (19)	34 (19)	0.5 (-7.7 to 9.1)	
Sepsis-related Organ Failure Assessment score, median (IQR), points[e,f]	(n = 160)	(n = 186)		
Within 24 h after intubation	6 (4-7)	6 (4-7)	0 (0 to 2)	.82
Within 48 h after intubation	5 (3-7)	5 (3-7)	0 (0 to 2)	.53
Length of stay, median (IQR), d[e]				
In the ICU	8 (5-16)	9 (4-18)	-1 (-2 to 1)	.91
In the hospital	16 (10-24)	16 (10-25)	-1 (-2 to 3)	.54
Serious adverse events[g]				
Ventilator-associated pneumonia, No./total (%)	93/160 (58)	99/186 (53)		
Septic shock after intubation, No./total (%)	29/160 (8)	34/186 (10)		
Pneumothorax during spontaneous breathing, No. (%)	5 (1)	4 (1)		
Cardiac arrest leading to intubation, No. (%)	2 (1)	5 (1)		

(continued)

Table 3. Additional Secondary and Exploratory Outcomes (continued)

Outcomes	High-flow oxygen (n = 357)	Standard oxygen (n = 354)	Absolute difference (95% CI)	*P* value
Post hoc exploratory outcomes				
Awake prone positioning within the first 48 h, No. (%)	73 (20)	64 (18)	2.4 (-3.4 to 8.2)	
Duration, median (IQR), h	6 (3-11) [n = 73]	7 (2-11) [n = 64]	-1 (-4 to 3)	
Noninvasive ventilation as rescue therapy within the first 48 h, No. (%)	7 (2)	9 (3)	-0.6 (-3.0 to 1.8)	
Duration, median (IQR), h[e]	3.0 (2.0-12.0) [n = 7]	2.0 (1.0-2.0) [n = 9]	1 (0 to 15)	
Met intubation criteria at time of intubation, No. (%)	160 (100)	186 (100)		
Reason for intubation, No. (%)	[n = 160]	[n = 186]		
Severe respiratory failure	136 (85)	154 (83)	2.2 (-5.7 to 9.9)	
Life-threatening hypoxemia	45 (28)	62 (33)	-5.2 (-14.7 to 4.6)	
Deterioration of neurologic status	10 (6)	14 (8)	-1.3 (-6.8 to 4.4)	
Hemodynamic instability	6 (4)	5 (3)	0.9 (-2.5 to 4.8)	
Cardiac arrest	2 (1)	5 (1)	-1.4 (-5.0 to 2.1)	

Abbreviations: FIO_2, fraction of inspired oxygen; ICU, intensive care unit; high-flow oxygen, high-flow nasal cannula oxygen therapy; PaO_2 partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; standard oxygen, oxygen given initially through a nonrebreathing face mask at a flow rate of 10 L or more per minute.

[a] FIO_2 was estimated in standard oxygen group as follows: (oxygen flow L/min) × 0.3 + 0.21.

[b] The response to strategy was collected by asking patients to grade the effect of the strategy assigned on their dyspnea during spontaneous breathing: +2, marked improvement; +1, slight improvement; 0, no change; −1, slight deterioration; and −2, marked deterioration.

[c] The intensity of respiratory patient discomfort was collected immediately after the end of each oxygenation strategy during spontaneous breathing, by use of an unmarked 100-mm visual analog scale that had ends marked with "no discomfort" and "maximal imaginable discomfort."

[d] Changes between 1 hour after treatment initiation and randomization were calculated as follows: measurement at 1 hour after treatment initiation minus measurement at baseline divided by measurement at baseline.

[e] For all values expressed in medians, absolute differences are in medians and 95% CIs of the difference of medians were estimated based on 5000 bootstrap resampling.

[f] Sepsis-related Organ Failure Assessment score assesses the presence and intensity of respiratory, coagulation, hemodynamic, neurologic, liver, and kidney failure. Each organ is assessed on a scale from 0 (no failure) to 4 (worst possible failure); the total score ranges from 0 (no organ failure) to 24 (all organ failure).

[g] The diagnoses of septic shock and ventilator-associated pneumonia were established by the physician in charge of the patient.

Limitations

This study has several limitations. First, all enrolled patients had respiratory failure due to COVID-19, which means that the results may not be fully generalizable to acute hypoxemic respiratory failure due to other causes. Second, this trial failed to demonstrate a significant difference in mortality rates, due to overestimation of mortality rates when designing the trial, which were based on available data at the time the study was planned. Third, the change in study enrollment criteria and randomization stratification factors during the study is a limitation that may complicate study interpretation. However, all patients had respiratory failure due to COVID-19, and the interventions and outcomes were the same in the original and ancillary studies. Fourth, imbalances in baseline factors across the 2 groups also complicate study interpretation; that said, they disfavored the high-flow oxygen group, in which Pao_2 was lower. Fifth, considering the large number of secondary outcomes, the findings for these outcomes should be interpreted as exploratory.

Conclusions

Among patients with respiratory failure due to COVID-19, high-flow nasal cannula oxygen, compared with standard oxygen therapy, did not significantly reduce 28-day mortality.

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