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# Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19

## A Randomized Clinical Trial

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 Supplemental content

**IMPORTANCE** The effect of high-flow oxygen therapy vs conventional oxygen therapy has not been established in the setting of severe COVID-19.

**OBJECTIVE** To determine the effect of high-flow oxygen therapy through a nasal cannula compared with conventional oxygen therapy on need for endotracheal intubation and clinical recovery in severe COVID-19.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, open-label clinical trial conducted in emergency and intensive care units in 3 hospitals in Colombia. A total of 220 adults with respiratory distress and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of less than 200 due to COVID-19 were randomized from August 2020 to January 2021, with last follow-up on February 10, 2021.

**INTERVENTIONS** Patients were randomly assigned to receive high-flow oxygen through a nasal cannula (n = 109) or conventional oxygen therapy (n = 111).

**MAIN OUTCOMES AND MEASURES** The co-primary outcomes were need for intubation and time to clinical recovery until day 28 as assessed by a 7-category ordinal scale (range, 1-7, with higher scores indicating a worse condition). Effects of treatments were calculated with a Cox proportional hazards model adjusted for hypoxemia severity, age, and comorbidities.

**RESULTS** Among 220 randomized patients, 199 were included in the analysis (median age, 60 years; n = 65 women [32.7%]). Intubation occurred in 34 (34.3%) randomized to high-flow oxygen therapy and in 51 (51.0%) randomized to conventional oxygen therapy (hazard ratio, 0.62; 95% CI, 0.39-0.96; *P* = .03). The median time to clinical recovery within 28 days was 11 (IQR, 9-14) days in patients randomized to high-flow oxygen therapy vs 14 (IQR, 11-19) days in those randomized to conventional oxygen therapy (hazard ratio, 1.39; 95% CI, 1.00-1.92; *P* = .047). Suspected bacterial pneumonia occurred in 13 patients (13.1%) randomized to high-flow oxygen and in 17 (17.0%) of those randomized to conventional oxygen therapy, while bacteremia was detected in 7 (7.1%) vs 11 (11.0%), respectively.

**CONCLUSIONS AND RELEVANCE** Among patients with severe COVID-19, use of high-flow oxygen through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT04609462](https://clinicaltrials.gov/ct2/show/study/NCT04609462)

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Infection with COVID-19, the disease caused by SARS-CoV-2, commonly results in asymptomatic or mild disease.<sup>1</sup> Nevertheless, the number of infected patients progressing to acute hypoxemic respiratory failure might become substantially high during pandemic circumstances, thus challenging health care system capacities.<sup>2,3</sup>

Arterial hypoxemia is the leading feature of severe cases of COVID-19.<sup>4,5</sup> Consequently, its management should rely on oxygen supplementation aiming to improve oxygenation and to assist respiratory effort throughout different support modalities. Early observational studies during the COVID-19 pandemic reported a very high mortality in patients subjected to invasive mechanical ventilation,<sup>3</sup> while some investigators warned about early intubation and mechanical ventilation.<sup>4</sup> Conversely, patient self-inflicted lung injury might occur during spontaneous breathing in nonintubated patients with acute respiratory failure because of high respiratory drive and potentially injurious transpulmonary pressure swings.<sup>6</sup> Meanwhile, in agreement with both views, noninvasive respiratory support techniques could limit self-inflicted lung injury while preventing adverse events associated with intubation and mechanical ventilation.

High-flow oxygen therapy through a nasal cannula is a technique whereby a mixture of heated and humidified oxygen and air are delivered to the nose at high flow rates.<sup>7-9</sup> Data suggest that high-flow oxygen therapy might decrease need for endotracheal intubation and risk of escalation of therapy in patients with acute hypoxemic respiratory failure,<sup>10,11</sup> but with no apparent effect on mortality rates.<sup>11,12</sup> Even though international guidelines and early observational studies proposed using high-flow oxygen therapy through a nasal cannula to initially treat patients with severe COVID-19,<sup>13-15</sup> evidence supporting this is very limited. Thus, this current trial was conducted to assess the effect of high-flow oxygen therapy through a nasal cannula vs conventional oxygen therapy on need for intubation and mechanical ventilation and time to clinical recovery in patients with severe COVID-19.

## Methods

### Study Design and Oversight

This open-label randomized clinical trial was conducted in 3 hospitals in Colombia between August 13, 2020, and January 12, 2021, with last follow-up on February 10, 2021. The trial protocol is available in [Supplement 1](#) and the statistical analysis plan is available in [Supplement 2](#). The trial was designed by the steering committee ([Supplement 1](#) and eAppendix in [Supplement 3](#)) and was approved by the ethical and biomedical research committee (EBRC) of the coordinating center (Fundación Valle del Lili; protocol number 1635; approval number 259-2020) and then by local ethical/research committees at each participating hospital. Electronic written informed consent was obtained from all patients, their next of kin, or another surrogate decision maker as appropriate. An independent data quality surveillance committee, research assistants from the coordinating center, and members of the steering committee regularly monitored all participating centers to

## Key Points

**Question** Does the use of high-flow oxygen therapy through a nasal cannula, compared with conventional oxygen therapy, reduce requirement of intubation and time to clinical improvement among patients with severe COVID-19?

**Findings** In this randomized clinical trial that included 220 patients with severe COVID-19, the rate of intubation and mechanical ventilation for those treated with high-flow oxygen therapy through a nasal cannula vs with conventional oxygen therapy was 34.3% vs 51.0%, respectively; the median time to clinical recovery was 11 days vs 14 days. Both comparisons were statistically significant.

**Meaning** Among patients with severe COVID-19, treatment with high-flow oxygen therapy compared with conventional oxygen therapy reduced the likelihood of invasive mechanical ventilation and decreased time to clinical recovery.

check adherence to protocol and to evaluate the accuracy of information recorded in the electronic case report form ([Supplement 1](#) and eAppendix in [Supplement 3](#)). An independent data and safety monitoring board (DSMB) was in charge of conducting a single interim analysis on enrollment of 50% of the sample (eAppendix in [Supplement 3](#)).

Participating patients could not be masked because of the nature of the intervention. Nevertheless, main investigators were unaware of the study group outcomes until the database was locked after the end of follow-up on February 10, 2021. An independent statistician performed all the analyses. All respiratory support devices (ie, conventional oxygen cannulas, face masks, high-flow nasal cannulas, and all consumable materials) were provided by each participating center in the context of the pandemic emergency.

### Patients

Adult patients admitted to the emergency department, general ward, or intensive care unit were enrolled if they met all of the following eligibility criteria: aged 18 years or older; suspected or confirmed infection with SARS-CoV-2 (confirmation via reverse transcriptase-polymerase chain reaction test from a nasopharyngeal swab); acute respiratory failure with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) of less than 200, accompanied by clinical signs of respiratory distress (eg, use of accessory muscles and respiratory rate greater than 25/min); and less than 6 hours elapsed since fulfilling the criteria of acute respiratory failure ([Supplement 1](#) and eAppendix in [Supplement 3](#)).

Exclusion criteria were need for immediate endotracheal intubation (see [Supplement 1](#) for detailed prespecified intubation criteria); a partial pressure of arterial carbon dioxide greater than 55 mm Hg; pregnancy; high suspicion or confirmation of acute cardiogenic pulmonary edema; history of or current left ventricular ejection fraction of less than 45%; history of chronic heart failure (New York Heart Association class III-IV)<sup>16</sup>; clinical suspicion or confirmation of peripheral demyelinating disease; history of advanced chronic obstructive pulmonary disease (Global Initiative for Chronic

Obstructive Lung Disease grade C-D)<sup>17</sup> or hospitalization due to chronic obstructive pulmonary disease decompensation within the last year; advanced liver cirrhosis (Child-Pugh class C)<sup>18</sup>; anatomical or other conditions precluding the use of a high-flow nasal cannula; do-not-intubate or do-not-resuscitate orders; imminent death; and refusal of study participation by a patient or their next of kin.

### Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive respiratory support with high-flow oxygen therapy through a nasal cannula vs conventional oxygen therapy. Randomization was centrally performed through a web-based system using computer-generated random numbers with blocks of 2 and 4, unknown to the investigators, and was stratified by study site to ensure allocation concealment. Site investigators were unaware of block size. Baseline was defined as the time of randomization.

### Interventions

Randomly allocated treatments were delivered within 30 minutes after randomization. In the high-flow oxygen therapy group, respiratory support was continuously applied through large-bore binasal prongs using heated and humidified gas at an initial flow of 60 L/min and an  $\text{FIO}_2$  of 1.0. The  $\text{FIO}_2$  was subsequently adjusted to maintain pulse oxygen saturation ( $\text{SpO}_2$ ) values of 92% or greater. Flow rate was decreased in patients reporting discomfort due to high-flow oxygen therapy until its resolution. High-flow oxygen therapy was continuously applied until intubation or when criteria for weaning of high-flow oxygen therapy were achieved, namely, improvement in clinical signs of respiratory distress, a  $\text{PaO}_2/\text{FIO}_2$  ratio higher than 200, and ability to maintain  $\text{SpO}_2$  values of 92% or greater with less than 9 L/min of conventional oxygen therapy. Patients experiencing hypoxemia after weaning from high-flow oxygen therapy recommenced high-flow oxygen therapy with a nasal cannula unless immediate intubation was necessary.

In the conventional oxygen therapy group, oxygen was applied continuously through any low-flow oxygen device or combination thereof (nasal prongs, mask with or without oxygen reservoir, Venturi mask systems). Rates of gas flow and  $\text{FIO}_2$  were adjusted to maintain  $\text{SpO}_2$  values of 92% or greater until patient intubation or recovery.

Prone position while awake was allowed in both study groups at the discretion of attending physicians. Intubation decisions for patients included in the study were based on prespecified criteria (Supplement 1 and eAppendix in Supplement 3). High-flow oxygen therapy was used during laryngoscopy and intubation only in patients randomized to the high-flow oxygen therapy group. Use of a high-flow nasal cannula was allowed after extubation in both groups according to decisions of attending physicians. Noninvasive mechanical ventilation with a face-mask interface was not used in this open-label clinical trial according to local infection control authority recommendations during the time of trial planning. The use of steroids, antibiotics, antivirals, or other antimicrobial agents was allowed at the discretion of medical attending teams.

All participants were evaluated daily from day 1 through day 28 (while remaining hospitalized) by the local study coordinators and research assistants. Trial data were recorded in the electronic case report form from randomization until day 28 (or until hospital discharge if it occurred before day 28). When hospital discharge happened before day 28, patients or family representatives were contacted via a structured telephone call to verify vital and clinical status at day 28 (Supplement 1 and eAppendix in Supplement 3).

### Outcomes

The co-primary outcomes were need for intubation and time to clinical recovery within 28 days after randomization. The latter was defined as the time elapsed from randomization until the first day during the 28 days after enrollment on which a patient attained a reduction of 2 or more points from their score at randomization on a modified 7-category ordinal scale. Scores on the ordinal scale were defined as follows: 1, discharged from the hospital, resuming complete daily-life activities; 2, discharged from the hospital but with limitation of activities, home oxygen requirement, or both; 3, hospitalized in a general ward (not intensive care unit), not requiring supplemental oxygen, and no longer requiring ongoing medical care (used if hospitalization was extended for infection control reasons); 4, hospitalized in a general ward (not intensive care unit), requiring supplemental oxygen or requiring ongoing medical care (for COVID-19-related or other medical conditions); 5, hospitalized in the intensive care unit, requiring any supplemental oxygen; 6, hospitalized in the intensive care unit, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation; and 7, death (eTable 1 in Supplement 3).

Eight secondary outcomes included proportion of patients requiring early intubation and mechanical ventilation; mechanical ventilation-free days within 28 days; kidney replacement therapy-free days; hospital and intensive care unit lengths of stay; overall mortality by day 28; proportion of serious adverse events; and proportion of bacterial and fungal infections. Tertiary outcomes included evolution of oxygen flow requirement and  $\text{PaO}_2/\text{FIO}_2$  ratio; time from randomization to intubation; evolution of multiorgan and extrapulmonary organ dysfunction; relationship between the HACOR (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) scale and the ROX (respiratory rate oxygenation) index and requirement of intubation; and time courses of pre-specified blood markers. A detailed description of all secondary outcomes and prespecified subgroup analysis is available in the statistical analysis plan (Supplement 2).

### Sample Size

Assuming an intubation rate of 60% in patients with acute respiratory hypoxemic failure undergoing conventional oxygen therapy,<sup>10</sup> which was in agreement with data obtained from the first 75 patients with COVID-19-related severe hypoxemic respiratory failure treated in the coordinating center, it was estimated that enrollment of 196 patients would be necessary to demonstrate an absolute reduction of 20% in the rate of intubation between the high-flow oxygen

therapy and conventional oxygen therapy groups with 80% power and a 2-sided  $\alpha = .05$ . In addition, according to such initial data, 160 patients would be necessary to demonstrate a reduction of 2 days in time to recovery, with 80% power and a 2-sided  $\alpha = .05$ . Consequently, the sample size target was 196 patients (for details, see the eAppendix in [Supplement 3](#)). Nevertheless, because of particular hospital conditions during the pandemic period, an unexpected number of patients were transferred for administrative reasons (related to health insurance) to other hospitals within 72 hours after enrollment. Due to the limitation of providing further protocolized management and the impossibility of ensuring adequate follow-up after transferring to nonparticipating hospitals, and in agreement with the recommendation stated by the Fundación Valle del Lili EBRC, these patients were excluded from the main analysis (eAppendix in [Supplement 3](#)). Consequently, because of the unexpected number of lost participants and in agreement with the EBRC recommendation, the number of randomized patients was extended to 220 participants (eAppendix in [Supplement 3](#)).

### Statistical Analysis

All analyses were conducted according to the statistical analysis plan ([Supplement 2](#)) elaborated and approved by the Fundación Valle del Lili EBRC prior to locking the trial database and analyzing data. Patients were analyzed according to their randomization group, excluding those withdrawing consent. There were no missing data for the co-primary outcomes.

Continuous variables are described herein as medians and interquartile ranges and categorical variables as counts and proportions. Follow-up data on the co-primary outcomes were available for all patients included in the analysis. The effect of treatment on need for endotracheal intubation and clinical recovery was calculated with a Cox proportional hazards model adjusted for hypoxemia severity, age, and comorbidities ([Supplement 1](#), [Supplement 2](#), and eAppendix in [Supplement 3](#)). Results of the co-primary outcomes were not adjusted for multiplicity. The proportional hazards assumption was tested with the Grambsch and Therneau method.<sup>19</sup> Results are reported as hazard ratios (HRs) with 95% confidence intervals and represented in Kaplan-Meier curves. No correction was made in *P* values and confidence intervals for the 2 primary outcomes. Analysis of treatment effect on the co-primary outcomes is also shown according to the baseline 7-category ordinal scale (ie, scores of 4 or 5 at enrollment). In addition, HRs estimated from Cox regression models for predefined subgroups (ie, age  $\geq 60$  years vs  $< 60$  years,  $\text{PaO}_2/\text{FiO}_2$  ratio  $\geq 100$  vs  $< 100$ , and interleukin 6 level  $\geq 100$  pg/mL vs  $< 100$  pg/mL) are provided in forest plots. We included interaction terms between each specified subgroup and the treatment groups in Cox proportional hazards models adjusted by hypoxemia severity, age, and comorbidities to calculate *P* values for interaction. Results of secondary outcomes were not adjusted for multiplicity; therefore, these should be considered exploratory and cannot be used to infer treatment effects.

A scheduled interim analysis was performed by the independent DSMB when the first 100 patients were enrolled. Haybittle-Peto stopping boundaries were used,<sup>20</sup> with a thresh-

old of  $P < .001$  to interrupt the trial for safety and a threshold of  $P < .0001$  to interrupt the trial for efficacy.

Post hoc sensitivity analyses to assess the treatment effect on the co-primary outcomes were repeated with similar models considering all randomized patients providing consent to use data including those who were transferred to other institutions within 72 hours after randomization. There was no loss to follow-up for co-primary outcome data among these participants up to the point at which they were transferred to nonparticipating hospitals. A post hoc sensitivity analysis was performed to evaluate the site-by-treatment effects by using a mixed-effects model with site (participating hospital) as a random effect.

A 2-tailed  $P < .05$  was considered to be statistically significant. We used Stata software version 14.0 (StataCorp) and R software version 4.0.3 (R Foundation) for all analyses. Additional information about the planned statistical analysis is provided in [Supplement 2](#) and the eAppendix in [Supplement 3](#).

## Results

### Patients

From August 2020 through January 2021, 650 patients with acute hypoxemic respiratory failure due to suspected or confirmed COVID-19 were screened; 250 were eligible for inclusion and 220 underwent randomization ([Figure 1](#)). The 28-day follow-up was completed on February 10, 2021. After exclusion of 8 patients who withdrew consent and 13 patients transferred to other hospitals (for administrative reasons) within the first 72 hours of randomization, a total of 199 were included in the analysis, with 99 randomized to high-flow oxygen therapy through a nasal cannula and 100 to conventional oxygen therapy. Baseline patient characteristics were similar between groups ([Table 1](#); eTable 2 in [Supplement 3](#)).

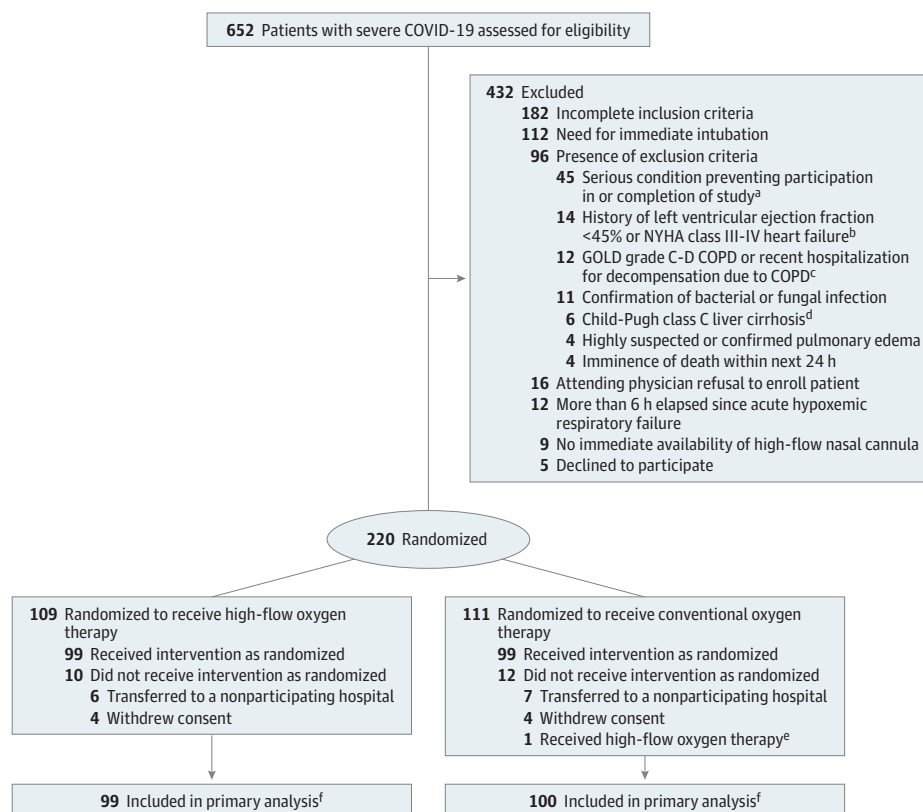
### Interventions

Allocated therapies were always commenced within 30 minutes after randomization. All patients completed their treatment as randomized except 1 patient randomized to conventional oxygen therapy who underwent high-flow oxygen therapy on the decision of the attending physician. This patient was included in the conventional oxygen therapy group for the primary analysis.

High-flow oxygen therapy was continuously delivered for a total of 6 (IQR, 3-9) days in patients randomized to this therapy, and it was successfully weaned to conventional oxygen therapy by 6 (IQR, 4-7) days in 65 (65.7%) of 99 patients. Patients' respiratory condition at 2 and 4 hours after starting randomized interventions is shown in eTable 3 in [Supplement 3](#). Cumulative time in prone position while awake was not significantly different between groups (21 [IQR, 8-40] hours for high-flow oxygen therapy vs 18 [IQR, 8-35] hours for conventional oxygen therapy;  $P = .35$ ) (eTable 4 in [Supplement 3](#)). Systemic steroids were used in 93 patients (93.9%) in the high-flow oxygen therapy group vs 92 (92.0%) of those



Figure 1. Flow of Participants Through the Trial



<sup>a</sup> Defined as any serious medical condition or clinical laboratory test result abnormality that, in an investigator's judgement, could prevent safe patient participation and completion of the study. Patients for whom therapeutic limitations were anticipated or moribund patients were included in this category.

<sup>b</sup> New York Heart Association (NYHA) class I indicates no symptoms with normal physical activity (asymptomatic); class II, mild symptoms with normal physical activity; class III, moderate symptoms with activities of daily living; and class IV, symptoms at rest.<sup>16</sup>

<sup>c</sup> COPD indicates chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD) airflow limitations are determined by spirometry and divided into 4 grades: 1, mild (forced expiratory volume in first second of expiration [FEV<sub>1</sub>] ≥80% predicted); 2, moderate (FEV<sub>1</sub> 50%-79% predicted); 3, severe (FEV<sub>1</sub> 30%-49% predicted); and 4, very severe (FEV<sub>1</sub> <30% predicted).<sup>17</sup> GOLD C corresponds to patients with severe or very severe airflow limitation (spirometric grades 3 and 4) and/or 2 or more exacerbations per year and/or 1 or more hospitalized exacerbations per year, and a Modified British Medical Research Council (mMRC) questionnaire on breathlessness grade of 0 to 1 or a Chronic Obstructive Pulmonary Disease Assessment Test (CAT) score less than 10. GOLD D corresponds to patients with severe or very severe airflow limitation (spirometric grades 3 and 4) and/or 2 or more exacerbations per year and/or 1 or more hospitalized exacerbations per year, and an mMRC grade of 2 or higher or a CAT score of 10 or higher.

<sup>d</sup> Child-Pugh scores are calculated by assessing ascites (1 point for none, 2 points for slight, and 3 points for moderate), serum bilirubin level (1 point for <2.0 mg/dL, 2 points for 2.0-3.0 mg/dL, and 3 points for >3.0 mg/dL), serum albumin level (1 point for ≥3.5 g/dL, 2 points for 2.8-3.5 g/dL, and 3 points for <2.8 g/dL), prolongation of prothrombin time (1 point for <4 seconds, 2 points for 4-6 seconds, and 3 points for >6 seconds), and encephalopathy (1 point for none, 2 points for grade 1 or 2, and 3 points for grade 3 or 4). Child-Pugh class C is a total score of more than 9 points.<sup>18</sup>

<sup>e</sup> One patient randomized to conventional oxygen therapy received high-flow oxygen therapy according to the decision of the attending physician. This patient was included in the conventional oxygen therapy group for the primary analysis.

<sup>f</sup> Patients were analyzed according to their randomization group, excluding those withdrawing consent and those transferred to nonparticipating hospitals. Because of the hospital emergency situation during the pandemic and in agreement with the recommendation by the ethical and biomedical research committee of the coordinating center, patients who were transferred to other hospitals (for health insurance-related reasons) before 72 hours had elapsed since enrollment were excluded from the primary analysis because of limitations on providing further protocolized management and impossibility of ensuring adequate follow-up. All co-primary outcome data were recorded for these patients until transfer.

randomized to conventional oxygen therapy. Other respiratory and pharmacological interventions are described in eTable 4 in Supplement 3.

### Interim Analysis

The interim analysis was performed as planned, when the first 100 patients were enrolled. Based on this analysis, the DSMB found no reason to recommend halting the study and

thus suggested continuing the trial until the planned sample size was reached.

### Primary Outcomes

By day 28 after randomization, 34 (34.3%) of 99 patients randomized to high-flow oxygen therapy and 51 (51.0%) of 100 randomized to conventional oxygen therapy had been intubated (HR, 0.62; 95% CI, 0.39-0.96;  $P = .03$ ) (Table 2 and

Table 1. Baseline Participant Characteristics

Characteristics	High-flow oxygen therapy (n = 99) <sup>a,b</sup>	Conventional oxygen therapy (n = 100) <sup>a,c</sup>
Age, median (IQR), y	60 (50-69)	59 (49-67)
Sex, No. (%)		
Female	28 (28)	37 (37)
Male	71 (72)	63 (63)
Body mass index, median (IQR) <sup>d</sup>	28.7 (26.3-32.1)	29.4 (26.2-33.1)
APACHE II score, No. (%) <sup>e</sup>	10 (8-12)	10 (8-12)
Test results for SARS-CoV-2, No. (%)		
Positive RT-PCR result	98 (99)	100 (100)
RT-PCR result unavailable	1 (1)	0
Comorbidities, No. (%)		
Hypertension	35 (35)	44 (44)
Diabetes	18 (18)	20 (20)
Liver cirrhosis (Child-Pugh class A-B) <sup>f</sup>	35 (35)	44 (44)
Chronic obstructive pulmonary disease	3 (3)	1 (1)
Chronic heart failure	3 (3)	4 (4)
Chronic kidney disease	0	1 (1)
Cancer	1 (1)	0
Medications on hospital admission, No. (%)		
Steroids	4 (4)	10 (10)
Angiotensin-converting enzyme inhibitors	5 (4)	8 (8)
Angiotensin II receptor antagonists	24 (24)	20 (20)
Statins	7 (7)	3 (3)
Time from symptom onset to randomization, median (IQR), d	10 (7-11)	8 (7-11)
Time from admission to randomization, median (IQR), d	1 (0-1)	1 (0-1)
SOFA score at randomization, median (IQR) <sup>g</sup>	4 (3-4)	4 (3-4)
Respiratory rate, median (IQR), /min	28 (27-32)	28 (26-31)
PaO <sub>2</sub> , median (IQR), mm Hg	78 (66-97)	73 (63-92)
Paco <sub>2</sub> , median (IQR), mm Hg	32 (30-35)	32 (30-36)
PaO <sub>2</sub> /Fio <sub>2</sub> ratio, median (IQR)	104 (85-132)	105 (85-141)
Seven-category ordinal scale score at randomization, No. (%) <sup>h</sup>		
Hospitalized and receiving supplemental oxygen (score of 4)	18 (18)	20 (20)
Hospitalized in ICU and receiving oxygen supplementation (score of 5)	81 (82)	80 (80)

Abbreviations: Fio<sub>2</sub>, fraction of inspired oxygen; ICU, intensive care unit; Paco<sub>2</sub>, partial pressure of arterial carbon dioxide; PaO<sub>2</sub>, partial pressure of arterial oxygen; RT-PCR, reverse transcriptase-polymerase chain reaction.

<sup>a</sup> Percentages may not total 100% because of rounding.

<sup>b</sup> High-flow oxygen indicates therapy with high-flow oxygen through a nasal cannula.

<sup>c</sup> Conventional oxygen therapy was given through a Venturi or nonrebreather face mask at a flow rate up to 15 L/min.

<sup>d</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup> The Acute Physiology and Chronic Health Evaluation (APACHE II) score ranges from 0 to 71; higher scores indicate greater severity of illness and risk of in-hospital death (eg, a score of 12 for a patient with pneumonia predicts an in-hospital mortality risk of 15%).

<sup>f</sup> Child-Pugh scores are calculated by assessing ascites (1 point for none, 2 points for slight, and 3 points for moderate), serum bilirubin level (1 point for <2.0 mg/dL, 2 points for 2.0-3.0 mg/dL, and 3 points for >3.0 mg/dL), serum albumin level (1 point for ≥3.5 g/dL, 2 points for 2.8-3.5 g/dL, and 3 points for <2.8 g/dL), prolongation of prothrombin time (1 point for <4 seconds, 2 points

for 4-6 seconds, and 3 points for >6 seconds), and encephalopathy (1 point for none, 2 points for grade 1 or 2, and 3 points for grade 3 or 4). Child-Pugh class A is a total score of 5 or 6 points and class B is a total score of 7 to 9 points.<sup>18</sup>

<sup>g</sup> The Sequential Organ Failure Assessment (SOFA) 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).

<sup>h</sup> Scores on the 7-category ordinal scale are as follows: 1, discharged from the hospital, resuming complete daily-life activities; 2, discharged from the hospital with limitation of activities, home oxygen requirement, or both; 3, hospitalized in a general ward (not ICU), not requiring supplemental oxygen, and no longer requiring ongoing medical care (used if hospitalization was extended for infection control reasons); 4, hospitalized in a general ward (not ICU), requiring supplemental oxygen or requiring ongoing medical care (for COVID-19-related or other medical conditions); 5, hospitalized in the ICU, requiring any supplemental oxygen; 6, hospitalized in the ICU, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation; and 7, death. See eTable 1 in Supplement 3.

Figure 2A). Causes of intubation were similar between groups (eTable 5 in Supplement 3). Clinical recovery occurred in 77 patients (77.8%) randomized to high-flow oxygen therapy vs 71 (71.0%) of those randomized to conventional oxygen

therapy. The median time to recovery among patients in the high-flow oxygen therapy group was 11 (IQR, 9-14) days vs 14 (IQR, 11-19) days in the conventional oxygen therapy group. Patients randomized to high-flow oxygen therapy had early

Table 2. Primary and Secondary Outcomes

Outcomes	High-flow oxygen therapy (n = 99)	Conventional oxygen therapy (n = 100)	Unadjusted absolute difference (95% CI)	Effect estimate, OR or HR (95% CI) <sup>a</sup>	P value
<b>Primary outcomes</b>					
Intubation within 28 d, No. (%)	34 (34.3)	51 (51.0)	-16.7 (-30.2 to -3.1) <sup>b</sup>	HR, 0.62 (0.39-0.96) <sup>c</sup>	.03
Clinical recovery within 28 d, No. (%)	77 (77.8)	71 (71.0)	6.8 (-5.3 to 18.9) <sup>b</sup>	HR, 1.39 (1.00-1.92) <sup>d</sup>	.047
Time to clinical recovery, median (IQR), d <sup>e</sup>	11 (9-14)	14 (11-19)	-3.0 (-7.5 to 1.0) <sup>f</sup>		
<b>Secondary outcomes</b>					
Intubation within 7 d, No. (%)	31 (31.3)	50 (50.0)	-18.7 (-32.1 to -5.3) <sup>b</sup>	HR, 0.59 (0.38-0.94) <sup>c</sup>	.03
Intubation within 14 d, No. (%)	34 (34.3)	51 (51.0)	-16.7 (-30.2 to -3.1) <sup>b</sup>	HR, 0.63 (0.41-0.97) <sup>c</sup>	.04
Ventilation-free days at day 28, median (IQR)	28 (19-28)	24 (14-28)	4.5 (0.0 to 7.8) <sup>g</sup>	OR, 2.08 (1.18-3.64)	.01
Kidney replacement therapy-free days, median (IQR) <sup>h</sup>	28 (28-28)	28 (28-28)	0 (0 to 0) <sup>g</sup>	OR, 1.78 (0.67-4.68)	.24
Length of stay, median (IQR), d					
Intensive care unit	7 (5-13)	9 (5-18)	-2.0 (-6.0 to -1.0) <sup>g</sup>	OR, 0.74 (0.45-1.22)	.24
Hospital	12 (9-20)	14 (9-23)	-2.0 (-4.0 to -1.0) <sup>g</sup>	OR, 0.77 (0.47-1.25)	.29
Mortality at day 14, No. (%)	6 (6.1)	6 (6.0)	0.1 (-6.6 to 6.7) <sup>b</sup>	HR, 0.93 (0.29-2.93) <sup>c</sup>	.90
Mortality at day 28, No. (%)	8 (8.1)	16 (16.0)	-7.9 (-16.9 to 1.1) <sup>b</sup>	HR, 0.49 (0.21-1.16) <sup>c</sup>	.11
Serious adverse events, No. (%)					
Cardiac arrest	2 (2.0)	6 (6.0)			
Supraventricular tachycardia or ventricular arrhythmia	3 (3.0)	1 (1.0)			
Atelectasis	1 (1.0)	0			
Other reported adverse events, No. (%)					
Suspected bacterial pneumonia	13 (13.1)	17 (17.0)			
Bacteremia	7 (7.1)	11 (11.0)			

Abbreviations: HR, hazard ratio; OR, odds ratio.

<sup>a</sup> Proportional odds models are adjusted for age ( $\geq 60$  or  $< 60$  years), ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) at randomization, and comorbidities (arterial hypertension, diabetes, obesity [body mass index  $> 30$ ], chronic obstructive pulmonary disease, kidney failure, heart failure, and Child-Pugh class A-B liver cirrhosis). Odds ratios greater than 1 indicate benefit with use of high-flow oxygen therapy. Adjusted hazard ratios were calculated from a Cox proportional hazards model. Variables used for adjustment were the same as those listed above for odds ratios. See footnote "f" in Table 1 for Child-Pugh score and class descriptions.<sup>18</sup>

<sup>b</sup> Absolute incidence differences in percentage points (percentage intubated, clinically recovered, requiring kidney replacement therapy, or who died, as appropriate).

<sup>c</sup> A hazard ratio for intubation or mortality less than 1 indicates benefit with use of high-flow oxygen therapy.

<sup>d</sup> A hazard ratio for clinical recovery greater than 1 indicates benefit with use of

high-flow oxygen therapy. A reported lower confidence bound of 1.00 is a consequence of rounding.

<sup>e</sup> Kaplan-Meier estimates of median time to clinical recovery. Time to clinical recovery was defined as the time elapsed from randomization until the first day during the 28 days after enrollment on which a patient attained a reduction of 2 or more points from their score at randomization on the modified 7-category ordinal scale (see footnote "h" in Table 1 for description of the ordinal scale).

<sup>f</sup> Bootstrap 95% CI of the median difference from Kaplan-Meier estimates.

<sup>g</sup> Median time-difference 95% CIs were estimated based on 5000-bootstrap resampling.

<sup>h</sup> Need for kidney replacement therapy occurred in 7 patients (7.1%) randomized to high-flow oxygen therapy vs 14 (14.0%) randomized to conventional oxygen therapy (OR, 0.49; 95% CI, 0.18-1.28;  $P = .16$ ).

clinical improvement as assessed by the 7-category ordinal scale (HR, 1.39; 95% CI, 1.00-1.92;  $P = .047$ ) (Table 2 and Figure 2B). The proportional hazards assumption was not violated as examined by the Grambsch and Therneau method (eTable 10 in Supplement 3).

### Secondary Outcomes

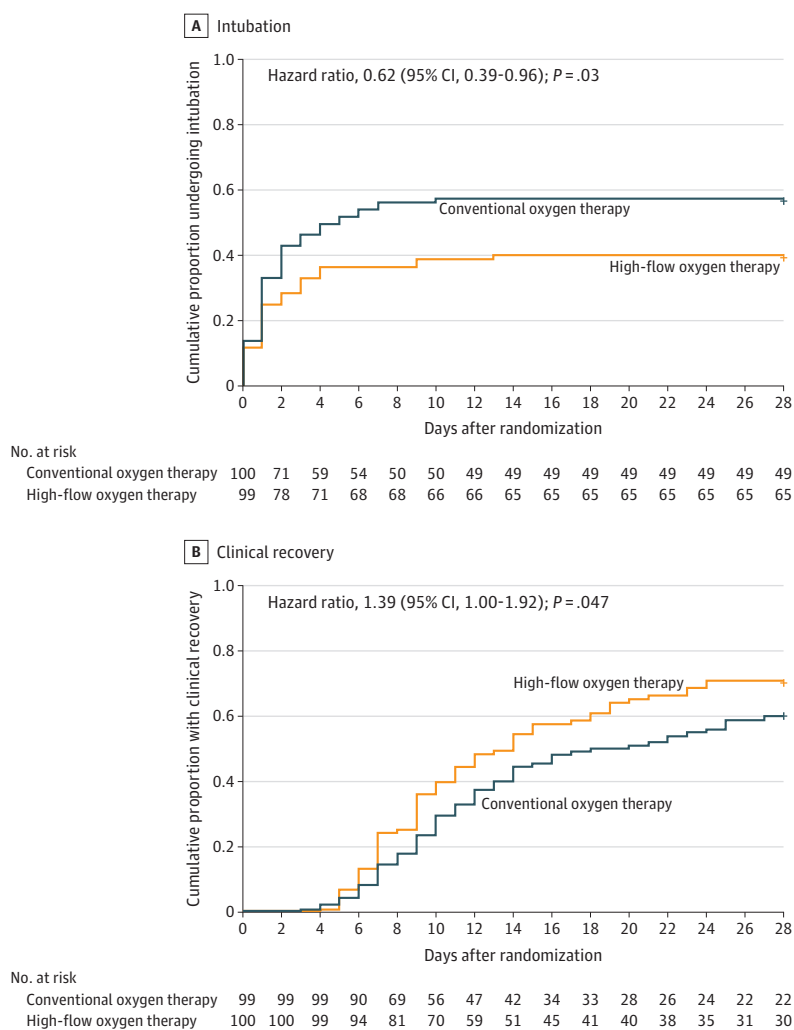
This trial included 8 secondary outcomes. High-flow oxygen therapy was related to lower risk of intubation at days 7 and 14 (Table 2). Median ventilator-free days within the first 28 days after randomization were 28 (IQR, 19-28) days in the high-flow oxygen therapy group vs 24 (IQR, 14-28) days in the conventional oxygen therapy group (adjusted odds ratio, 0.77; 95% CI, 0.33-1.68;  $P = .01$ ) (Table 2). Need for kidney replacement

therapy was not significantly different between groups (Table 2). Similarly, in-hospital and intensive care unit length of stay were not significantly different between groups and neither was the proportion of adverse events (Table 2). The HR for death at day 28 was 0.49 (95% CI, 0.21-1.16;  $P = .11$ ) in the high-flow oxygen therapy group compared with the conventional oxygen therapy group (Table 2). Causes of death are given in eTable 5 in Supplement 3.

### Tertiary Outcomes

Time courses of  $\text{PaO}_2/\text{FiO}_2$  ratio and oxygen flow in the study groups are shown in eFigures 1 and 2 in Supplement 3. Patients received a median of 22.3 (IQR, 13.2-60.7) hours of high-flow oxygen therapy vs 29.2 (IQR, 14.4-58.3) hours

Figure 2. Cumulative Intubation and Clinical Recovery Through Day 28 (Co-Primary Outcomes)



The effect of treatments on cumulative incidence of intubation and recovery rates was calculated with a Cox proportional hazards model adjusted for hypoxemia severity, age, and comorbidities.

of conventional oxygen therapy prior to intubation ( $P = .69$ ) (eTable 3 in Supplement 3). Median time spent at an  $\text{FIO}_2$  greater than 0.70 from randomization to intubation was 11.5 (IQR, 4.2-21.0) hours for high-flow oxygen therapy vs 25.8 (IQR, 13.5-46.5) hours for conventional oxygen therapy ( $P < .001$ ) (eTable 3 in Supplement 3). There were no significant differences in the involvement of multiple and extrapulmonary organ dysfunction as evaluated by the Sequential Organ Failure Assessment score during the first 7 days after randomization (eFigures 3 and 4 in Supplement 3). Time courses for predefined laboratory measures are depicted in eFigures 11-17 in Supplement 3.

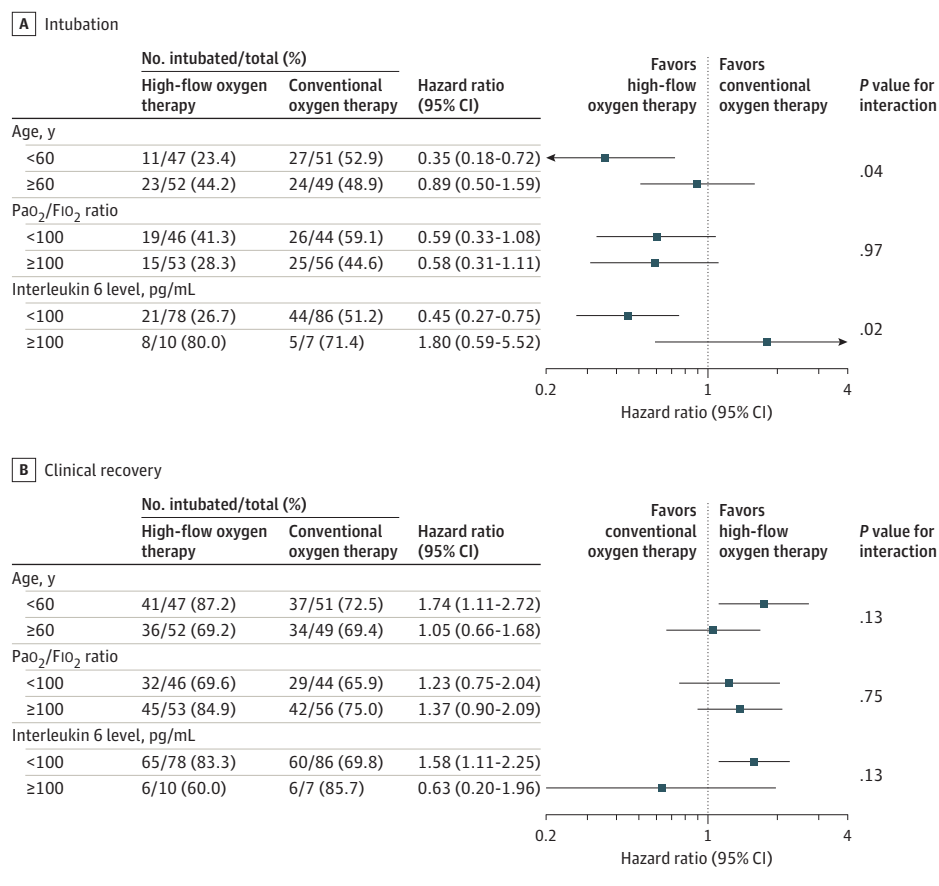
### Subgroup and Sensitivity Analyses

Results of the prespecified subgroup analysis are reported in Figure 3 and eFigures 5-10 in Supplement 3. There were no significant differences in treatment effect on the prespecified subgroup analyses, with the possible exceptions of age and interleukin 6 level at baseline. The effect on intubation in the high-flow oxygen therapy group may be more pronounced among patients younger than 60 years (HRs:  $<60$  years, 0.35

[95% CI, 0.18-0.72];  $\geq 60$  years, 0.89 [95% CI, 0.50-1.59];  $P = .04$  for interaction) and those with interleukin 6 levels less than 100 pg/mL (HRs: interleukin 6  $<110$  pg/mL, 0.45 [95% CI, 0.27-0.75]; interleukin 6  $\geq 110$  pg/mL, 1.80 [95% CI, 0.59-5.52];  $P = .02$  for interaction). Nevertheless, these findings are exploratory because of lack of adjustment for multiplicity of hypothesis tests. Analyses of primary and secondary outcomes according to the baseline 7-category ordinal scale for clinical recovery as well as clinical status at 28 days are shown in eTables 6 and 7 in Supplement 3. Post hoc sensitivity analyses considering all randomized patients who provided consent to use data including those who were transferred to other institutions within 72 hours after randomization provided results similar to the main analyses (eTable 8 in Supplement 3). Similarly, post hoc sensitivity mixed-model analysis with site as a random effect was consistent with the main analysis: high-flow oxygen therapy through a nasal cannula decreased need for mechanical ventilation support (HR, 0.62; 95% CI, 0.40-0.96;  $P = .03$ ) and increased the probability of clinical recovery (HR, 1.42; 95% CI, 1.03-1.97;  $P = .04$ ) compared with conventional oxygen therapy (eTable 9 in Supplement 3).



Figure 3. Results of the Prespecified Subgroup Analysis on Intubation and Clinical Recovery



## Discussion

In this open-label, multicenter randomized clinical trial among patients with acute hypoxemic respiratory failure due to severe COVID-19, the use of high-flow oxygen therapy through a nasal cannula significantly decreased the need for intubation and invasive mechanical ventilation and also led to earlier clinical recovery within 28 days.

Arterial hypoxemia is the leading feature of severe cases of SARS-CoV-2 infection.<sup>4</sup> In general, management of acute hypoxemic respiratory failure relies on oxygen supplementation and supporting respiratory effort, and management of COVID-19-related moderate and severe hypoxemic respiratory failure should be based on similar principles. Analogous to previous studies on acute hypoxemic respiratory failure due to other etiologies,<sup>10-12</sup> high-flow oxygen therapy through a nasal cannula was also able to decrease the requirement of intubation and mechanical ventilation in severe cases of COVID-19, but with no effect on mortality rates. The HiFLo-Covid trial did not use an “oxygen escalation strategy,” but instead, high-flow oxygen therapy was immediately applied in patients fulfilling inclusion criteria. In this sense, a strategy providing high-flow oxygen therapy at very early stages of respiratory failure could theoretically offer some physiological advantages including improvement of inspiratory effort, minute volume, re-

spiratory rate, lung volumes, dynamic lung compliance, transpulmonary pressure, and lung homogeneity.<sup>21</sup>

Avoiding systematic intubation in COVID-19 could prevent complications related to invasive mechanical ventilation, sedation, delirium, and neuromuscular paralysis.<sup>21</sup> In addition, successful prevention of intubation could optimize resources during pandemic conditions. In the current trial, both intubation and extubation procedures were performed according to well-prespecified criteria, which probably limited delays in providing protective invasive mechanical ventilation. Time elapsed from randomization to intubation and reasons for intubation were similar between study groups. Although previous studies have suggested that delay in intubation is related to increased mortality rates in patients with acute hypoxemic respiratory failure,<sup>22,23</sup> high-flow oxygen therapy seems to be safe, as it is not associated with higher mortality rates or longer recovery times despite nonimmediate intubation in cases that eventually require it. Conversely, longer periods of high FIO<sub>2</sub>, as observed in most patients receiving conventional oxygen therapy, could have negatively influenced time to recovery such as has been suggested by experimental models in which hyperoxia was related to exacerbated lung injury.<sup>24</sup>

Patients receiving high-flow oxygen therapy showed earlier clinical recovery, although the mechanisms involved are less obvious than those implied in avoiding intubation. Very

early relief of inspiratory effort could theoretically limit patient self-inflicted lung injury, which should influence clinical outcomes. Improvement of respiratory mechanics and limitation of lung injury could reduce time to clinical recovery, assuming that part of such injury might appear as a consequence of increased respiratory load that is inadequately supported during spontaneous breathing.<sup>6</sup>

Although the HiFlo-Covid trial was constructed under the assumption of physiological effects of high-flow oxygen therapy, measurements or estimations of the metabolic work of breathing, esophageal pressure monitoring, dynamic measurements of transpulmonary pressures, minute volume measurements, and estimations of nonhomogeneous distribution of tidal ventilation were not performed. Thus, the current trial evaluated only clinical outcomes, assuming that mechanisms involved in preventing the progression of lung injury, relief of respiratory effort, and improvement of gas exchange should be improved by high-flow oxygen therapy.

A recent clinical trial comparing high-flow oxygen therapy through a nasal cannula vs noninvasive ventilation through a helmet interface resulted in no significant difference in the number of days free of respiratory support within 28 days.<sup>25</sup> In addition, the rate of endotracheal intubation was significantly lower in the noninvasive ventilation group, while the number of days free of invasive ventilation was significantly higher in the noninvasive ventilation group compared with high-flow oxygen therapy. However, these last findings should be further evaluated, as they are results of secondary outcomes.

This trial has several strengths. First, group randomization was consistently maintained until intubation and invasive mechanical ventilation support was started or until clinical recovery was reached. Second, the results are in agreement with studies of acute hypoxemic respiratory failure due to other etiologies.<sup>10-12</sup> Third, this study had a well-defined protocol including prespecified criteria for endotracheal intubation and extubation, with only 1 violation regarding therapy allocation.

Fourth, results were consistent even after sensitivity analysis including patients transferred to other centers due to administrative reasons within 72 hours after randomization. Fifth, sensitivity analysis evaluating the site-by-treatment effects also found similar results favoring high-flow oxygen therapy.

### Limitations

This study has several limitations. First, because of its nature, this open-label trial lacked the possibility of blinding, which may affect the assessment of outcomes. Second, all participants were recruited in only 3 centers from 1 country, which restricts the generalizability of the results. Third, the trial design considered 2 co-primary end points, raising the potential for type I error. Fourth, analysis of secondary outcomes was not adjusted by multiplicity; these results should be considered exploratory. Fifth, the sample size of this trial and the number of events were relatively small, and therefore small variations in the number of events would have rendered treatment effect on the co-primary outcomes nonsignificant. Sixth, measurements or estimations for the metabolic work of breathing, transpulmonary pressures, minute volume, or estimations of nonhomogeneous distribution of tidal ventilation were not performed; thus, potential mechanisms mediating the effect of high-flow oxygen therapy through a nasal cannula on the co-primary outcomes remain theoretical. Seventh, this trial was not powered to demonstrate differences in mortality; nevertheless, the effect of high-flow oxygen therapy on need for intubation and clinical recovery could encourage its use.

### Conclusions

Among patients with severe COVID-19, use of high-flow oxygen through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy.

### ARTICLE INFORMATION

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