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# High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure

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## Abstract

**Purpose:** Whether the use of high-flow nasal oxygen in adult patients with COVID-19 associated acute respiratory failure improves clinically relevant outcomes remains unclear. We thus sought to assess the effect of high-flow nasal oxygen on ventilator-free days, compared to early initiation of invasive mechanical ventilation, on adult patients with COVID-19.

**Methods:** We conducted a multicentre cohort study using a prospectively collected database of patients with COVID-19 associated acute respiratory failure admitted to 36 Spanish and Andorran intensive care units (ICUs). Main exposure was the use of high-flow nasal oxygen (conservative group), while early invasive mechanical ventilation (within the first day of ICU admission; early intubation group) served as the comparator. The primary outcome was ventilator-free days at 28 days. ICU length of stay and all-cause in-hospital mortality served as secondary outcomes. We used propensity score matching to adjust for measured confounding.

**Results:** Out of 468 eligible patients, a total of 122 matched patients were included in the present analysis (61 for each group). When compared to early intubation, the use of high-flow nasal oxygen was associated with an increase in ventilator-free days (mean difference: 8.0 days; 95% confidence interval (CI): 4.4 to 11.7 days) and a reduction in ICU length of stay (mean difference: − 8.2 days; 95% CI − 12.7 to − 3.6 days). No difference was observed in all-cause in-hospital mortality between groups (odds ratio: 0.64; 95% CI: 0.25 to 1.64).

**Conclusions:** The use of high-flow nasal oxygen upon ICU admission in adult patients with COVID-19 related acute hypoxemic respiratory failure may lead to an increase in ventilator-free days and a reduction in ICU length of stay, when compared to early initiation of invasive mechanical ventilation. Future studies should confirm our findings.

**Keywords:** COVID-19, Acute hypoxemic respiratory failure, High-flow nasal oxygen, Ventilator-free days

## Introduction

High-flow nasal oxygen (HFNO) reduces the need for intubation in adult patients with acute respiratory failure [1–4]. This may in turn help to avoid the associated risks of invasive mechanical ventilation, such as delirium and cognitive impairment, intensive care unit (ICU) acquired weakness and secondary infections. However, through vigorous breathing efforts, spontaneous ventilation could theoretically promote further lung injury (e.g., patient self-inflicted lung injury) [5–9].

A novel coronavirus disease (COVID-19) has spread worldwide causing thousands of cases of acute respiratory failure with a high mortality rate [10, 11]. Thus

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far, the use of HFNO has been limited, despite the fact it may represent an appropriate initial therapy [12, 13]. Conversely, several studies have shown that the use of invasive mechanical ventilation remains high in this population, and patients usually receive it for prolonged periods of time [14–16]. In daily clinical practice, the decision to intubate is usually based on several clinical markers, including blood oxygenation [17], and may differ across institutions [18]. Furthermore, based on experimental [19, 20] and observational data [5, 6], a so-called "early approach" to invasive mechanical ventilation has been advocated for patients with non-COVID related ARDS [5]. Critically ill patients with COVID-19 often have profound hypoxemia which may partially explain the extremely high use of invasive ventilatory support in this patient population. This scenario, combined with the sharp rise in the incidence of COVID-19, has led to an unprecedented pressure on healthcare systems [14, 15, 21–23].

Previous reports on the use of HFNO in patients with COVID-19 have been mainly limited by small sample sizes and the reporting of unadjusted effect estimates [24]. Whether HFNO decreases the need for invasive mechanical ventilation in these patients remains unknown. In this study, we aimed to estimate the effect of HFNO on ventilator-free days (VFDs), ICU length of stay and in-hospital mortality, when compared to an early intubation strategy in adult patients with COVID-19 related acute respiratory failure. Our overall aim is to better inform the use of non-invasive oxygenation/ventilation strategies and the rational allocation of invasive mechanical ventilation.

## Methods

### Study design and setting

We conducted a prospective, multicentre, cohort study of consecutive patients with COVID-19 associated acute respiratory failure admitted to 36 hospitals from Spain and Andorra (see Supplementary file) [16]. The study was approved by the referral Ethics Committee of Hospital Clínic, Barcelona, Spain (#HCB/2020/0399), and conducted according to the amended Declaration of Helsinki. This report follows the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guidelines for observational cohort studies [25]. Gathering of data is ongoing and as of August 13, 2020, a total of 1,129 patients have been included. A preliminary communication was presented as an abstract at the annual European Respiratory Society conference in September 2020 [26].

### Study population

We included adult patients ($\geq$ 18 years old) admitted to the ICU between March 12 and August 13, 2020. Patients were included if they had positive confirmatory nasopharyngeal or pulmonary tract sample and received support with either HFNO or intubation on the first day of ICU admission. Main exclusion criteria were intubation outside the ICU, a $PaO_2/FiO_2$ ratio > 300 mmHg, a respiratory rate on day 1 > 35 breaths/min, a Glasgow Coma Score < 13, and pH < 7.25 [18, 27]. The rationale for the aforementioned eligibility criteria was based on a population that (with equipoise) could theoretically be randomized to a strategy of early intubation or HFNO in the first 24 h of critical illness, under the framework of a target randomized trial (Additional file 1: e-Table 1) [28]. The final analytical cohort was obtained by propensity score matching based on potential confounders measured at baseline.

### Data collection

Patients' characteristics were collected prospectively according to a previously standardized common protocol. Each investigator had a personal username/password and entered data into a specifically pre-designed online data acquisition system (CoVid19.ubikare.io) endorsed and validated by the Spanish Society of Anesthesiology and Critical Care (SEDAR) [29]. Patient confidentiality was protected by assigning a de-identified code. Recorded data included patients' demographics [age, gender, body mass index (BMI)], comorbidities, time from onset of symptoms and from hospital admission to initiation of respiratory support and vital signs (temperature, mean arterial pressure, heart rate), laboratory parameters (complete blood count, coagulation tests, electrolytes, creatinine) and severity assessment scales such as the Sequential Organ Failure Assessment (SOFA) [30] and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [31]. Site investigators collected what they considered to be the most representative data of each day from ICU admission to ICU discharge. Patients were followed up until hospital discharge to assess for in-hospital mortality.

### Study exposure and outcomes

The main exposure was the use of HFNO as the initial oxygenation strategy in the first 24 h (conservative group), and the comparison was the use of invasive mechanical ventilation in the first 24 h (early intubation group) [6]. Because data were collected once per day and the duration of HFNO use was not recorded, patients that were switched from HFNO to invasive-mechanical ventilation on day 1 were considered as part

of the early intubation group [6]. We considered that, in these patients, the HFNO use may have been too short to have a meaningful effect in a patient's outcome [6]. The decision to intubate was left at the discretion of the treating physicians at each participating centre. The primary outcome of interest was VFDs at day 28, calculated as 28 *minus* the days that a particular patient remained mechanically ventilated [32]. To account for the competing risk of death, deceased patients were considered to have 0 VFDs. Secondary outcomes included ICU length of stay, intubation rate and all-cause in-hospital mortality (and up to 60 days). A subgroup analysis considering patients intubated early (on day 1) versus those intubated late (from day 2 and onwards) was performed.

### Statistical analysis

Demographics, comorbidities, vital signs and laboratory markers at ICU admission were compared between both treatment groups using standardized mean differences. To account for potential confounding of the effects of HFNO on all outcomes of interest, we performed a propensity-score matched analysis [33]. Specifically, we built a multivariable logistic regression model to estimate the log-odds of receiving HFNO on the first day of ICU. The criteria to include variables in this model were based on those potentially affecting the likelihood of outcome occurrence and receipt of study treatments [34] and were performed based on subject matter knowledge with the help of a direct acyclic graph (DAG) (e-Fig. 1 in Additional file 1) [35, 36]. Selected variables included gender, APACHE II, SOFA, Glasgow Coma Scale, systolic blood pressure, pH, respiratory rate, arterial partial pressure of carbon dioxide ($PaCO_2$), body mass index (BMI), creatinine, bilirubin, platelet, leucocyte and lymphocyte count, lactate, immunosuppression and hospital group (divided into quartiles based on the proportion of patients receiving intubation from the total). The matching procedure was conducted on a 1:1 fashion without replacement and with the calliper of the logit (propensity score) set at 0.2 [33]. Proper adjustment was assessed with standardized mean differences (SMD) in the matched population, and covariate imbalance defined using a SMD > 0.2 threshold [33]. Missing data on important confounders were handled using multiple imputations with a Monte Carlo Markov chain method (details in Additional file 1) [37].

Once the matched cohort was constructed and after balance assessment, we used simple linear regression to assess mean differences in VFDs at 28 days and ICU length of stay (in days) between treatment groups. For all-cause in-hospital mortality, we used generalized linear models (with identity link and binomial distribution) to estimate risk differences and a crude logistic regression model to estimate odds ratios. For all models, 95% confidence intervals (CI) were constructed based on robust standard errors to account for the matching procedure.

### Sensitivity analyses

Several sensitivity analyses were performed to assess the robustness of our findings for the study outcomes. First, we performed a complete case analysis, excluding patients that had any missing data on the selected variables to construct the propensity score. Second, we repeated our primary analysis for the treatment effect by adjusting for those baseline variables that were not balanced (i.e., SMD > 0.2) by our matching procedure [38]. Third, given that treatment assignment was not random, both residual and unmeasured confounding remain possible. Hence, we estimated the E-value as a way to determine the association between an unmeasured confounder with both the exposure (HFNO) and outcome that would fully explain the estimated effect (see details in Additional file 1). Fourth, we changed our exposure classification, keeping patients who initially received HFNO and switched within the 24-h window to invasive mechanical ventilation as part of the conservative strategy (HFNO). This was done to evaluate whether the initial classification yielded optimistic estimates by assigning sicker patients with early HFNO failure to the early intubation group. Finally, we assessed the modification of the effect of HFNO on the primary outcome of interest according to baseline severity measured by the $PaO_2/FiO_2$ ratio. For subgroup analysis, we used Wilcoxon rank-sum test and Fisher's test as appropriate.

We used a threshold of 0.05 for statistical significance. All reported tests are two-sided. The R software (R Foundation for Statistical Computing, Vienna, Austria; packages mice, lme4 and sjstats packages) and STATA v.14.2 were used for all analysis. The E-value was computed using a freely available online calculator (www.evalue-calculator.com). Graphs were constructed using BioRender.com.

## Results

### Study population

From March 12 to August 13, 2020, 468 critically ill patients with COVID-19 patients fulfilled the inclusion criteria for the present study (Fig. 1). Three-hundred and twelve (67%) patients were intubated on day 1 (37 of them after a HFNO trial). The remaining 156 patients received HFNO, of whom 49 (31%) received intubation from day 2 and onward. Baseline characteristics for the entire population (before matching) are shown in Additional file 1: e-table 2. After propensity score matching, 61 patients in each group were included. Overall, we observed adequate balance between most of baseline characteristics with the

exception of baseline ROX index, systolic blood pressure, Glasgow Coma Scale, pH, inspired oxygen fraction ($FiO_2$) and active cancer (Table 1).

### Study outcomes

When compared to an early intubation strategy, the use of HFNO was associated with an increase in VFDs (mean difference 8.0 days; 95% CI 4.4 to 11.7 days), and a reduction in ICU length of stay (mean difference -8.2 days; 95% CI -12.7 to -3.6 days). Intubation rate was 38% in the conservative group (compared to an expected 100% in the early intubation group). No difference was observed in all-cause in-hospital mortality between groups (OR 0.64; 95% CI 0.25 to 1.64) (Fig. 2).

### Sensitivity analysis

All sensitivity analysis yielded similar results to the main estimates (Additional file 1: e-table 3). Specifically, in the complete-case analysis, the use of HFNO remained associated with an increase in VFDs (mean difference 6.8 days; 95% CI 1.5 to 12.1 days) and shorter ICU length of stay (mean difference 12.3 days; 95% CI 19.8 to 4.7). No difference was observed in all-cause hospital mortality (OR 1.64; 95% CI 0.40 to 6.66). Furthermore, after adjusting for imbalanced

**Table 1 Baseline characteristics of the matched sample of adult patients with COVID-19 related acute respiratory failure**

| Covariate | Early intubation (N = 61) | HFNO (N = 61) | SMD |
|---|---|---|---|
| *Demographic characteristics* | | | |
| Age, *years*—mean (SD) | 61 (11) | 62 (11) | 0.06 |
| Female gender, n (%) | 36 (48) | 27 (40) | 0.14 |
| BMI, *kg/m2* – mean (SD) | 28.8 (4.3) | 28.8 (5.5) | 0.01 |
| Time to ICU admission, *days* – median [IQR] | 2 [1–4] | 2 [1–4] | 0.11 |
| *Baseline comorbid disease* | | | |
| Number of comorbidities – median [IQR] | 1 [0–1] | 1 [0–2] | 0.00 |
| Immunosupression, (n, %) | 2 (3.3) | 4 (6.6) | 0.15 |
| Active cancer, (n, %) | 0 (0) | 6 (9.8) | 0.47 |
| *Initial severity of disease* | | | |
| SOFA score—median [IQR] | 5 [3–7] | 4 [4–7] | 0.00 |
| Glasgow coma score—median [IQR] | 15 [15] | 15 [15] | 0.41 |
| APACHE II score—median [IQR] | 11 [9–14] | 10 [9–113] | 0.11 |
| $PaO_2$:$FiO_2$ ratio—mean (SD) | 117 (51) | 121 (49) | 0.09 |
| Respiratory rate, r*pm*—mean (SD) | 25 (5) | 25 (5) | 0.04 |
| Oxygen saturation, %—mean (SD) | 88 (7) | 89 (6) | 0.09 |
| ROX index—median [IQR] | 4.4 [3.4–6.4] | 5 [4–6.2] | 0.25 |
| $PaCO_2$, *mmHg*—mean (SD) | 37 (8) | 38 (12) | 0.02 |
| Gas flow, L/min—mean (SD) | – | 55 (12) | – |
| $FiO_2$, %—mean (SD) | 79 (18) | 72 (16) | 0.45 |
| Heart rate (bpm)—mean (SD) | 81 (18) | 82 (15) | 0.03 |
| Systolic blood pressure (mmHg)—mean (SD) | 128 (21) | 124 (18) | 0.21 |
| Use of steroids, n (%) | 47 (77) | 45 (73.8) | 0.08 |
| *Laboratory values* | | | |
| pH—mean (SD) | 7.4 (0.1) | 7.44 (0.06) | 0.66 |
| Creatinine, *mg/dL*—mean (SD) | 1.0 (0.8) | 1.0 (0.7) | 0.01 |
| Bilirrubin, *mg/dL*—mean (SD) | 0.7 (0.5) | 0.7 (0.3) | 0.01 |
| Lactate, *mmol/L*—mean (SD) | 0.3 (0.6) | 0.4 (0.7) | 0.13 |
| D-dimer, *U/L*—mean (SD) | 4025 (11,944) | 2235 (4724) | 0.19 |
| Leucocyte count, *10^9/L*—mean (SD) | 8.1 (3.6) | 8.3 (4.8) | 0.04 |
| Lymphocyte count, *10^9/L*—mean (SD) | 0.7 (1.0) | 0.7 (0.5) | 0.09 |
| Platelet count, *10^12/L*—mean (SD) | 223 (88) | 241 (126) | 0.16 |

HFNO: high-flow nasal oxygen; IQR: interquartile range; SD: standard deviation; SMD: standardized mean difference; $PaCO_2$: arterial pressure of carbon dioxide; $FiO_2$: inspired oxygen fraction; ROX: ratio of oxygen saturation to $FiO_2$, divided by respiratory rate: (Saturation/$FiO_2$)/Respiratory rate. APACHE: Acute Physiology And Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment

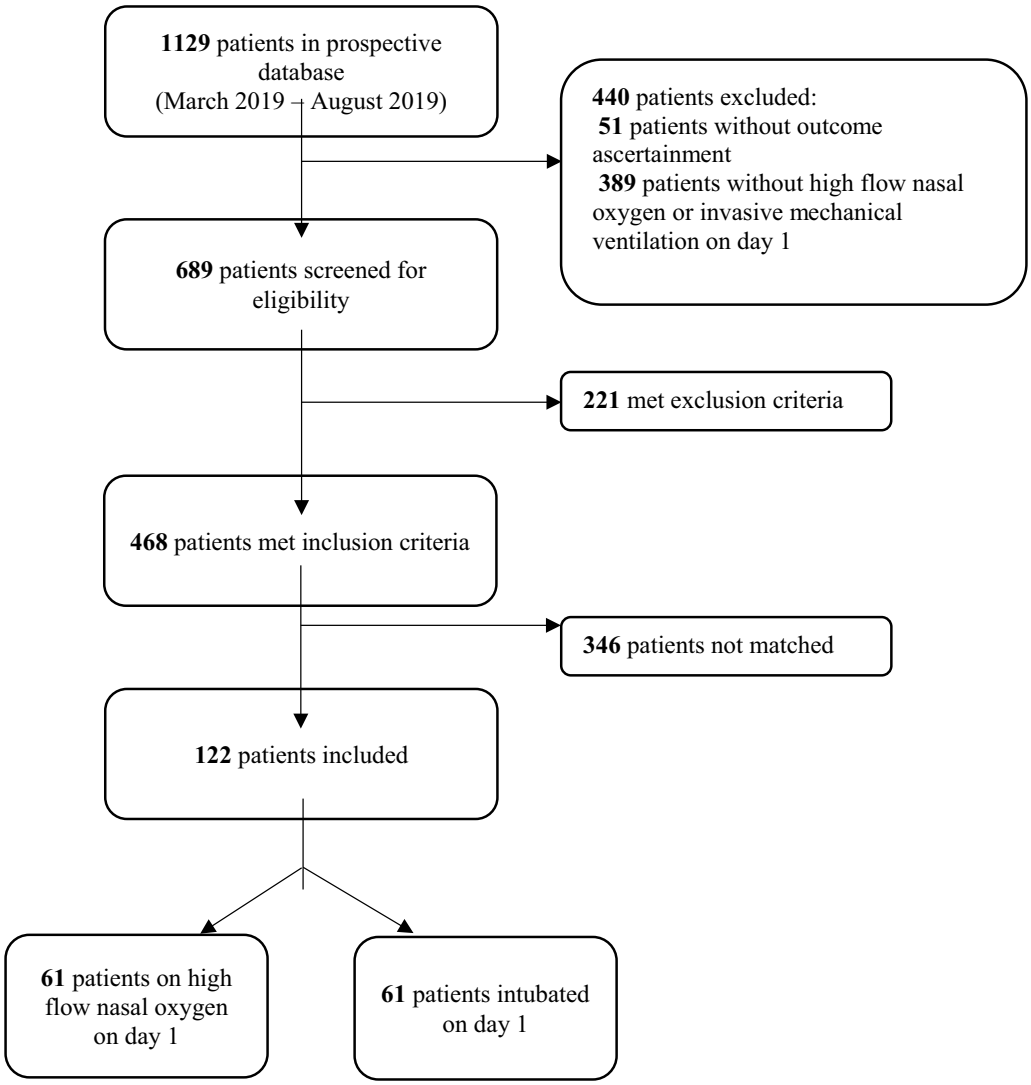


**Fig. 1** Study flowchart

covariates, namely the presence of an active cancer, Glasgow Coma Scale, ROX index and $FiO_2$, the use of HFNO remained associated with an increase in VFDs (mean difference 7.7 days; 95% CI 3.6 to 11.9) and shorter ICU length of stay (mean difference -9.4; 95% CI -14.7 to -4.0) when compared to an early intubation approach. No difference was observed in all-cause hospital mortality (OR 0.75; 95% CI 0.22 to 2.55). The estimated E-value for the primary analysis for the effects of HFNO on VFDs was 3.28 (e-Fig. 2 in Additional file 1). Finally, no modification of the effects of HFNO on VFDs was evident by baseline $PaO_2/FiO_2$ ratio (Additional file 1: e-table 4).

### Subgroup analysis by the time of intubation

Of the 61 included patients who initially received a conservative strategy with HFNO, 23 (38%) were intubated from day 2 onward. When compared to patients intubated early in their ICU course, VFDs (median 10 vs 15 days, p = 0.88), ICU length of stay (12 vs 17 days, p = 0.41) and in-hospital mortality (26% vs 21%, p = 0.77) did not differ (Additional file 1: Table S5).

## Discussion

In this multicentre observational cohort study of 122 matched, critically ill adult patients with COVID-19 associated acute hypoxemic respiratory failure, the use

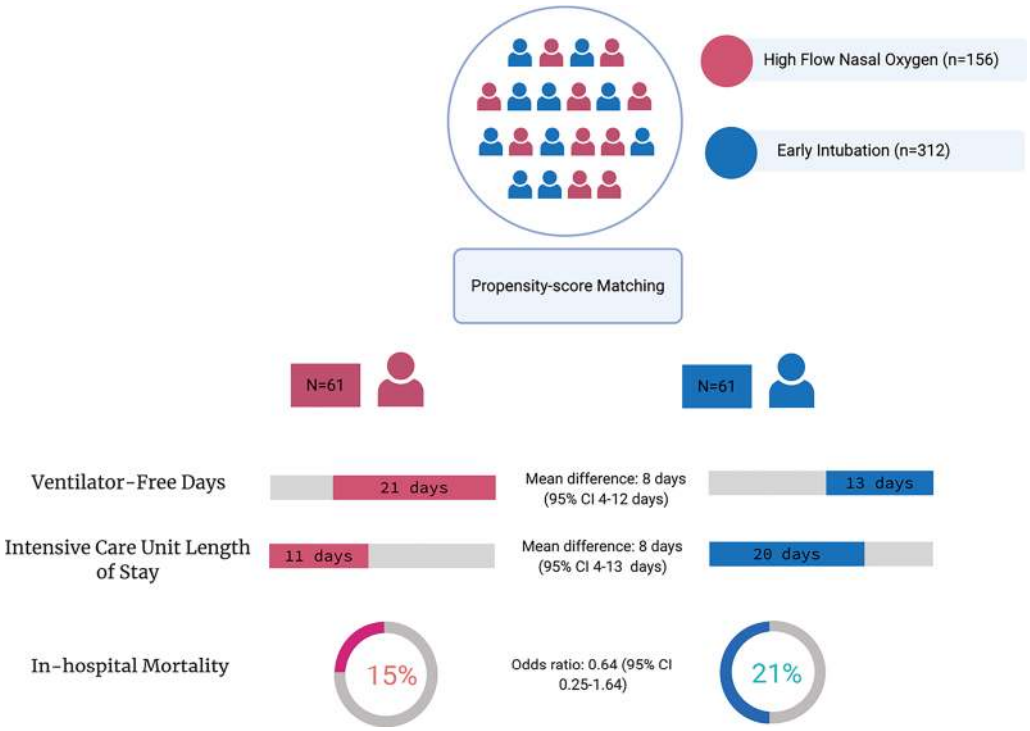


**Fig. 2** Effect of a conservative approach (use of high-flow nasal oxygen) compared to early intubation on main outcomes of interest for patients with COVID-19 associated acute respiratory failure. Difference is expressed as mean difference for continuous variables or absolute risk difference for in-hospital mortality. In-hospital mortality in both groups expressed as cumulative incidence. CI: Confidence interval. HFNO: high-flow nasal oxygen. (1) Cumulative incidence and cumulative incidence difference (i.e., risk difference; 95% CI) reported for both groups. Results for ventilator-free days and intensive care unit length of stay were rounded up or down to the closest whole number

of HFNO was associated with an increase in VFDs and shorter ICU length of stay when compared to an early intubation strategy. No significant differences were evident in all cause in-hospital mortality.

The COVID-19 pandemic has unveiled the ongoing uncertainty and resulting discussions as to whether patients presenting with significant hypoxemia should undergo an early intubation strategy or whether, on the contrary, a conservative non-invasive approach could be offered [39–41]. Importantly, the benefits of the use of non-invasive oxygenation/ventilation strategies in the context of acute respiratory failure need to be balanced against the risk of treatment failure, given its potential association with worse clinical outcomes in non-COVID-19 populations [6, 7]. The results of this analysis are consistent with other studies showing potential beneficial effects of HFNO in the context of COVID-19 associated acute respiratory failure [42] and reinforce recent evidence showing that HFNO was associated with a reduced risk of intubation in this patient population [43].

To the best of our knowledge, this is the first study specifically comparing HFNO with an early intubation strategy. This study provides additional evidence that in a population with similar baseline characteristics and a potential to be randomized to any of these interventions, the use of HFNO may be associated with an increase in VFDs and shorter duration of ICU length of stay without any significant difference in mortality. Of note, on average, patients receiving early intubation in our cohort were sicker at baseline, as assessed by higher SOFA and APACHE II scores. However, matching achieved good balance in most of the covariates assessed and our results were robust to a variety of sensitivity analysis, including a secondary analysis in which adjustment by imbalanced variables was performed. Further, in the matched population, hypoxemia was profound despite the use of high $FiO_2$ and the benefit spanned across the entire spectrum of $PaO_2/FiO_2$ values, as shown by our sensitivity analysis stratifying by oxygenation levels. This finding suggests that moderate-to-severely hypoxemic patients affected by COVID-19 may benefit from HFNO and that HFNO could potentially decrease the need and duration of mechanical ventilation and ICU length of stay without a negative impact in hospital mortality.

Several limitations need to be taken into account when interpreting the findings of our study. First, since

treatment was not randomly allocated, both residual and unmeasured confounding are likely even after careful covariate adjustment. Nonetheless, the moderately robust E-value, together with a pre-planned emulation of a target trial increase the confidence in our study findings. Second, the use of VFDs as the primary outcome could be considered to favour upfront the HFNO group, given that a significant proportion of patients on HFNO was not subsequently intubated. As reported elsewhere, this endpoint encompasses both the time spent on mechanical ventilation as well as mortality and, for any given value in a population, both components should be provided to avoid misleading conclusions [32]. Given the similar mortality risk in both groups, the observed differences in VFDs between groups may be mostly driven by a reduction in the need for intubation among those initially treated with HFNO or, as previously stated, may also be due to unmeasured or residual confounding (e.g., patients who are sicker at baseline predominantly receive early invasive mechanical ventilation and have lower VFDs than those who have less severe disease and initially receive HFNO). Although an untestable assumption, our E-value and robustness to a variety of sensitivity analysis may point towards a potential causal effect rather than confounding as the main explanation for this finding. Explicitly, if both the HFNO and early invasive mechanical ventilation groups are considered comparable at baseline (e.g., regarding their initial severity), then the reduction in VFDs remains informative as it points towards a reduction in intubation as the likely mechanistic pathway—something that has been shown elsewhere in the broad population of critically ill patients with acute respiratory failure. Third, sample size was limited due to the inability to match a significant proportion of patients. This has to be understood in the context of populations differing significantly (the overall group of patients receiving early intubation was sicker) and the choice of very strict adjustment criteria to improve the precision of the estimates. In light of this fact, clinicians should keep in mind that the potential benefit of the treatment might be limited to patients with similar characteristics to the matched cohort (moderate-to-severe hypoxemic patients without concomitant non-pulmonary organ dysfunction) although two additional sensitivity analysis using the whole population also favoured HFNO. Fourth, missing information was present for several covariates of interest possibly resulting in both information bias and residual confounding. However, our multiple imputation-based results were consistent with the complete case analysis. Fifth, misclassification of relevant covariates and potential predictors is also likely. However, a concise operational manual was provided to all researchers at the study initiation, and two investigators checked for the accuracy of the data and unreliable values for all included patients. Sixth, criteria for intubation were not uniformly defined, and hence, the reported rate of failure and the effect of HFNO may not be generalizable to other settings with distinct clinical practice patterns. Sixth, code status at admission was not recorded and this might have impacted the rate of intubation in the conservative group. Indeed, despite achieving good balance between groups after matching, the presence of cancer was still more common in the conservative group. However, the mortality risk was similar across groups, our results were robust across sensitivity analysis adjusting for imbalanced covariates, and the intubation risk in the conservative group was 38%, which is in line with previous reports [27]. Finally, this study cannot offer any information regarding a potential increased risk of COVID-19 infection in healthcare professionals with HFNO use although studies have not been able to show an increase risk with this therapy [44].

## Conclusion

In this observational study of 122 matched adult critically-ill patients with COVID-19-associated acute respiratory failure receiving either HFNO or early intubation upon ICU admission, the use of HFNO was associated with increased VFDs and a reduction in the duration of ICU stay, with no differences in all-cause in-hospital mortality. However, caution is warranted before drawing definite conclusions since, in the whole population, those intubated early were sicker, and even the most thorough statistical adjustment cannot eliminate confounding entirely. Future studies should corroborate our findings, as a way of optimizing the ventilation strategy for patients with COVID-19 associated acute respiratory failure.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-021-03469-w.

**Additional file 1.** It contains further information on methodology as well as 4 tables and 2 figures.

### Abbreviations

APACHE: Acute physiological and Chronic Health disease Classification System; ARDS: Acute respiratory distress syndrome; ARF: Acute respiratory failure; BMI: Body mass index; CI: Confidence interval; COVID-19: Coronavirus Disease 19; CRP: C-Reactive protein; DAG: Direct acyclic graph; HFNO: High-flow nasal oxygen therapy; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; MV: Mechanical ventilation; $PaO_2/FiO_2$: Partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; P-SILI: Patient self-inflicted lung injury; OR: Odds ratio; RR: Respiratory rate; SBP: Systolic blood pressure; SD: Standard deviation; SMD: Standardized mean difference; SOFA: Sequential organ failure assessment; SpO2: Peripheral oxyhaemoglobin saturation; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; VFD: Ventilator-free day.

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COVID-19 Spanish ICU network investigators wish to have their names listed in PubMed. These collaborators are listed below:

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**Authors' contributions**

RMA and CF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RMA participated in the research question and was the responsible for both performing data analysis and drafting the manuscript. BLF and FA participated in the research question, data analysis and in manuscript drafting. EA was the responsible for creating the dataset. MHS and CF participated in the research question and corrected the manuscript. AT, JV and LB offered critical appraisal during manuscript preparation and participated in the writing of manuscript drafts and final manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

By request to the corresponding author.

**Code availability**

Not applicable.

**Ethics approval and consent to participate**

The study was approved by the referral Ethics Committee of Hospital Clínic, Barcelona, Spain (#HCB/2020/0399).

**Consent for publication**

Not applicable.

**Competing interests**

A. Torres reports lecturing or consultancy fees from Pfizer, MSD, Basilea, Biomerieux. Jansen. L. Brochard's laboratory reports grants from Medtronic Covidien, grants and non-financial support from Fisher Paykel, non-financial support from Air Liquide, Sentec, Philips, and a patent with General Electric, outside the submitted work. The remaining authors declare no conflicts of interest in relation to this manuscript.

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