

Predictors of failure with high-flow nasal oxygen therapy in COVID-19 patients with acute respiratory failure: a multicentre observational study

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Abstract

Purpose

We aimed to describe the use of high-flow nasal oxygen (HFNO) in patients with COVID-19 acute respiratory failure and factors associated with a shift to invasive mechanical ventilation.

Methods

This is a multicentre, observational study from a prospectively collected database of consecutive COVID-19 patients admitted to 36 Spanish and Andorran intensive care units (ICUs) who received HFNO on ICU admission during a 22-week period (March 12-August 13, 2020). Outcomes of interest were factors on the day of ICU admission associated with the need for endotracheal intubation. We used multivariable logistic regression and mixed effects models. A predictive model for endotracheal intubation in patients treated with HFNO was derived and internally validated.

Results

From a total of 259 patients initially treated with HFNO, 140 patients (54%) required invasive mechanical ventilation. Baseline non-respiratory Sequential Organ Failure Assessment (SOFA) score [odds ratio (OR) 1.78; 95% confidence interval (CI) 1.41–2.35], and the ROX index calculated as the ratio of partial pressure of arterial oxygen to inspired oxygen fraction divided by respiratory rate (OR 0.53; 95% CI: 0.37–0.72), and pH (OR 0.47; 95% CI: 0.24–0.86) were associated with intubation. Hospital site explained 1% of the variability in the likelihood of intubation after initial treatment with HFNO. A predictive model including non-respiratory SOFA score and the ROX index showed excellent performance (AUC 0.88, 95%CI 0.80–0.96).

Conclusions

Among adult critically ill patients with COVID-19 initially treated with HFNO, the SOFA score and the ROX index may help to identify patients with higher likelihood of intubation.

Background

High-flow nasal oxygen (HFNO) reduces the need for endotracheal intubation in patients with acute respiratory failure^{1,2}. This may avoid the risks associated with invasive mechanical ventilation, such as delirium, intensive care unit (ICU) acquired weakness, and secondary infections³. However, through vigorous breathing efforts and the fostering of further lung injury (e.g., patient self-inflicted lung injury (P-

SILI))⁴, delaying intubation may be associated with worse outcomes in patients with the acute respiratory distress syndrome (ARDS)⁵⁻⁸.

The novel coronavirus 2019 (COVID-19) infection has spread worldwide causing thousands of cases of acute respiratory failure with an associated high mortality rate^{9,10}. The use of HFNO has been limited despite being a suitable and appropriate initial therapy^{11,12}. Conversely, several studies have shown that the use of invasive mechanical ventilation remains high in patients with COVID-19, and patients usually receive it for long periods of time¹³⁻¹⁵. Although the decision to intubate is based on several clinical markers, including blood oxygenation¹⁶, ICUs may have different policies towards the initiation of invasive mechanical ventilation¹⁷. Based on experimental^{18,19} and observational data^{4,5}, a so-called “early approach” to invasive mechanical ventilation is advocated by some experts in patients with non-COVID-19 related ARDS⁴. In addition, critically-ill patients with COVID-19 often have profound hypoxemia which may partially explain the extremely high use of invasive ventilatory support in these subjects. This issue, combined with the sharp rise in the incidence of this disease, has led to an unprecedented pressure on many healthcare systems and hospitals worldwide^{13,14,20,21}.

In the last few months, several studies have reported experiences with HFNO therapy in patients with COVID-19^{22,23}. Also, a recent publication suggested that HFNO could decrease the requirements for invasive mechanical ventilation in these patients²⁴. If validated, the use of HFNO would not only be beneficial for individual patients treated noninvasively, but also to those planned for invasive mechanical ventilation through the rational allocation of resources. However, identifying those at higher risk of failure could be highly valuable for avoiding delays in choosing the best management approach. In this study, we sought to describe the use of HFNO in adult patients with COVID-19 acute respiratory failure and to identify factors associated with a greater risk of intubation. We also aimed to derive a parsimonious predictive score for intubation as an aid in daily clinical decision making.

Material And Methods

Study design and setting

We conducted a prospective, multicenter, cohort study of consecutive patients with COVID-19 related acute respiratory failure admitted to 36 hospitals from Spain and Andorra (see Supplementary file)¹⁵. The study was approved by the referral Ethics Committee of Hospital Clínic, Barcelona, Spain (code #HCB/2020/0399) and was 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 studies²⁵. Gathering of data is ongoing and as of August 13, a total of 1129 patients were included.

Study population

For the present study, all consecutive patients included in the database from March 12 to August 13, 2020 that fulfilled the following inclusion criteria were analysed: age ≥ 18 years, ICU admission with a diagnosis of COVID-19 related acute respiratory failure, positive confirmatory nasopharyngeal or pulmonary tract sample, and HFNO initiated on ICU admission day. Exclusion criteria were the use of oxygen therapy and non-invasive or invasive mechanical ventilation prior to HFNO or the absence of data regarding respiratory management on day 1 after ICU admission.

Data collection

Patients' characteristics were collected prospectively from electronic medical records by physicians trained in critical care according to a previously standardized consensus 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)²⁶. Patient confidentiality was protected by assigning a de-identified code. Recorded data included demographics [age, gender, body mass index (BMI)], comorbidities and disease chronology [time from onset of symptoms and from hospital admission to initiation of respiratory support, ICU length of stay], vital signs [temperature, mean arterial pressure, heart rate], laboratory parameters (blood test, coagulation, biochemical), ratio of oxygen saturation to inspired oxygen fraction, divided by respiratory rate (ROX) index, as well as severity scores such as the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. After ICU discharge, patients were followed-up until hospital discharge.

Study outcomes

The primary outcome was the assessment of factors at ICU admission (ICU day 1) associated with the need for endotracheal intubation up to 28 days after HFNO initiation. The decision to intubate was made at the discretion of the attending physician at each participating site. Secondary goals were the development of a predictive model to estimate the probability of endotracheal intubation after HFNO and the assessment of between-centre variability in the likelihood of receiving intubation after HFNO had been started.

Statistical analysis

We used descriptive statistics to summarize patients' baseline characteristics. We compared the baseline characteristics of patients who required intubation with those who did not require intubation. Specifically, continuous variables were compared with the T-test with unequal variances or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the Chi-square tests or Fisher's exact test as appropriate. In order to identify factors associated with the likelihood of intubation, we fitted a multivariable logistic regression model with endotracheal intubation as the dependent variable. *A priori* selected variables were those considered of clinical relevance as well as variables that were significantly associated with the outcome in the bivariate analysis (at a p-value threshold of 0.2 or less). We report odds ratios (OR) with their associated 95% confidence intervals (CI).

Then, we sought to derive a parsimonious predictive model for intubation among patients treated with HFNO on the first day of ICU admission. Thus, we randomly split the full dataset in two parts: 1) a training dataset including 70% of the patients, and 2) a validation dataset including the remaining 30% of subjects. In the derivation step, all variables showing statistical significance with the outcome were chosen, and a final model based on the best accuracy was selected after performing 10-fold cross-validation. The final model calibration was tested in the split validation cohort with the use of the Brier score. A receiver operating characteristic (ROC) curve was constructed to display the area under the curve (AUC) for the predictive model. The optimal cutoff was considered as the one showing the best accuracy. At this cutoff, the performance of the model is presented as sensitivity, specificity, positive and negative predictive values as well as positive and negative likelihood ratios and their accompanying 95% CI. An online calculator is shown to estimate the likelihood of HFNO failure for each individual patient.

Additionally, since one of the goals of the present study was to assess centre-related variability regarding the clinical decision to intubate, a mixed-effects multivariable logistic regression was fitted as a secondary analysis. We fitted a logistic model with a random intercept (for each centre that recruited more than 10 patients), to account for possible correlation and differences in the baseline risk of intubation based on practice variation between sites. The proportion of variance explained by all fixed factors is presented as the marginal R^2 and the proportion of variance explained by the whole model is presented as the conditional $R^{2,27}$.

To account for missing data, which occurred in 6% of the observations of interest, we performed multiple imputation based on Markov chain Monte Carlo methods²⁸. Specifically for regression analysis, we removed subjects with extensive missing data (> 50%). Briefly, for every missing value, we created 5 matrices, each one with 1,000 imputations. Final imputed values for each missing observation were calculated as the median of all imputations. Imputation of the dependent variable (intubation) was not performed. We used a threshold of 0.05 for statistical significance and all reported tests are two-sided. For statistical analysis, we used the R software (R Foundation for Statistical Computing, Vienna, Austria) and included mice, lme4, caret, OptimalCutpoints, performance and pROC packages.

Results

From March 12 to August 13, 2020, 259 critically ill patients with COVID-19 related acute respiratory failure were initially treated with HFNO and were included in the present study (Fig. 1). From those, 140 (54.0%) patients were intubated and mechanically ventilated after ICU admission, of whom 74 patients (52.9%) were intubated on the ICU admission day. SOFA score and APACHE II were higher in patients requiring intubation while respiratory rate, $\text{PaO}_2/\text{FiO}_2$ ratio and ROX index were lower (Table 1).

Table 1
Baseline characteristics of 259 patients with COVID-19 acute respiratory failure.

	Intubation			P-value ¹
	ALL (n = 259)	NO (n = 119)	YES (n = 140)	
Patients demographics and comorbidities				
Age, years	62 (55–70)	62 (53–69)	63 (55–70)	0.39
Gender, male	185 (71%)	90 (76%)	95 (68%)	0.16
BMI, kg/m ²	28 (25–32)	27 (25–31)	28 (25–32)	0.11
Number of comorbidities	1 (0–2)	1 (0–2)	1 (0–1)	0.73
Hypertension	109 (42%)	47 (42%)	62 (44%)	0.45
Ischemic heart disease	15 (6%)	8 (7%)	7 (5%)	0.60
Diabetes	45 (17%)	20 (16%)	25 (18%)	0.87
Chronic respiratory disease	14 (5%)	6 (5%)	8 (6%)	1
Chronic kidney disease	22 (8%)	10 (8%)	12 (9%)	1
Malignancy	12 (4%)	9 (8%)	3 (2%)	0.07
Days from Hospital to ICU admission.	2 (1–4)	3 (1–4)	2 (0–4)	< 0.01
Scores				
SOFA	4 (3–7)	4 (3–5)	6 (4–8)	< 0.01
Non-respiratory SOFA	1 (0–3)	0 (0–1)	3 (0–4)	< 0.01
APACHE II	11 (8–16)	9 (6–13)	13 (10–18)	< 0.01
Glasgow Coma Scale	15 (15–15)	15 (15–15)	15 (15–15)	0.03
Vital signs				
Respiratory rate, rpm	26 (22–30)	24 (20–28)	29 (25–34)	< 0.01
Heart rate	80 (72–93)	78 (70–90)	84 (75–95)	0.01

Continuous covariates are shown as mean (SD) or median (IQR). Categorical variables are presented as n (%). ¹Means are compared with the Student's T test, medians with Mann-Whitney U-test and proportions with either the Chi² or Fisher exact test. ROX index was calculated as [(SpO₂/inspired oxygen fraction)/respiratory rate (RR)]. BMI: body mass index; ICU: intensive care unit; SOFA: sequential organ failure assessment; APACHE: Acute Physiology and Chronic Health Evaluation II; SBP: systolic blood pressure; SpO₂: peripheral oxyhemoglobin saturation; PaO₂/FiO₂: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; PaCO₂: partial pressure of carbon dioxide.

	Intubation			P-value ¹
	ALL (n = 259)	NO (n = 119)	YES (n = 140)	
SBP, mmHg	126 (22)	126 (18)	125 (23)	0.33
SpO ₂ , %	90 (87–93)	91 (89–94)	89 (85–92)	< 0.01
PaO ₂ /FiO ₂	109 (83–151)	124 (95–166)	96 (78–144)	< 0.01
ROX index	4.4 (3.3–6.1)	5.4 (5.1–7.3)	3.5 (3.2–5.1)	< 0.01
pH	7.45 (7.40–7.47)	7.46 (7.44–7.49)	7.40 (7.39–7.40)	< 0.01
PaCO ₂ , mmHg	36 (31–41)	34 (31–38)	36 (30–47)	0.01
Laboratory findings				
Creatinine, mg/dL	0.8 (0.7–1.1)	0.8 (0.7–1)	0.9 (0.7–1.2)	0.32
Leucocyte count, 10 ⁹ /μL	7.5 (5.6–11.5)	7.1 (5.8–10.8)	7.7 (5.6–12.3)	0.16
Platelet count, 10 ¹² / μL	235 (175–319)	248 (197–342)	234 (164–300)	0.03
D-dimer, U/L	985 (600–2200)	915 (600–1970)	1100 (680–2620)	0.12
<p>Continuous covariates are shown as mean (SD) or median (IQR). Categorical variables are presented as n (%). ¹Means are compared with the Student's T test, medians with Mann-Whitney U-test and proportions with either the Chi² or Fisher exact test. ROX index was calculated as [(SpO₂/inspired oxygen fraction)/respiratory rate (RR)]. BMI: body mass index; ICU: intensive care unit; SOFA: sequential organ failure assessment; APACHE: Acute Physiology and Chronic Health Evaluation II; SBP: systolic blood pressure; SpO₂: peripheral oxyhemoglobin saturation; PaO₂/FiO₂: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; PaCO₂: partial pressure of carbon dioxide.</p>				

Associated factors and predictive model for intubation

After excluding 3 subjects for extensive missing data, 256 patients were included in the multivariable logistic regression analysis. Baseline non-respiratory SOFA score (OR 1.78; 95% CI 1.41–2.35), ROX index (OR 0.53; 95% CI 0.38–0.72) and pH (OR 0.47; 95% CI: 0.24–0.86) were associated with the need for intubation (Table 2). A model including the non-respiratory SOFA, the ROX index and cancer showed the best accuracy in the training dataset (see additional file 1, table S1). However, given that cancer was a protective factor for intubation, which probably meant treatment escalation limitation, a simpler model including non-respiratory SOFA and the ROX index was selected. In the validation subset, this model had excellent calibration (Brier score of 0.14) and discrimination (AUC of 0.88, 95% CI 0.80–0.96) (see Table 3 in main text and figure S1 in additional file 1).

Table 2
Associated factors with intubation in 256 patients with COVID-19 treated with HFNO.

	Odds ratio (95% CI)	P-value ¹
Non-respiratory SOFA score	1.78 (1.41–2.35)	< 0.01
ROX index	0.53 (0.38–0.72)	< 0.01
pH, per 0.1-unit increase	0.47 (0.24–0.86)	0.03
Leucocyte count, 10 ⁹ /μL	1.07 (1.001–1.13)	0.01
Malignancy	0.14 (0.02–0.88)	0.04
BMI, kg/m ²	1.05 (0.97–1.14)	0.23
PaO ₂ /FiO ₂ (per 10-point increase)	1.04 (0.97–1.11)	0.21
Gender (female)	1.60 (0.73–3.54)	0.24
D-dimer, U/L	1.00 (0.99-1.00)	0.31
APACHE II	0.95 (0.87–1.04)	0.26
Glasgow Coma Scale	0.51 (0.10–1.08)	0.34
Respiratory rate, rpm	0.97 (0.90–1.04)	0.50
Heart rate, bpm (per 10-bpm increase)	1.08 (0.87–1.35)	0.46
Time from symptom onset to ICU admission (per 1-day increase)	1.02 (0.95–1.12)	0.64
SBP, mmHg (per 10-mmHg increase)	0.96 (0.80–1.14)	0.66
PaCO ₂ , mmHg (per 5-mmHg increase)	1.03 (0.87–1.21)	0.76

¹Based on a multivariable logistic regression model after multiple imputation. 2 subjects were excluded for extensive missing data (> 50% variables). CI: confidence interval; HFNO: high flow nasal oxygen treatment; SOFA: sequential organ failure assessment; SBP: systolic blood pressure; BMI: body mass index; SpO₂: peripheral oxyhemoglobin saturation; ICU: intensive care unit; PaO₂/FiO₂: partial pressure of arterial oxygen to inspiratory oxygen ratio; APACHE: Acute Physiology and Chronic Health Evaluation II; PaCO₂: partial pressure of carbon dioxide; AIC: Akaike information criterion.

Table 3
Discrimination ability of the model in the test dataset using a 50% probability-of-intubation cut-off.

Parameter	Value (95% CI)
Sensitivity	83% (68–91%)
Specificity	89% (74–95%)
Positive predictive value	89% (76–96%)
Negative predictive value	82% (67–91%)
Positive likelihood ratio	7.3 (2.9–18.4)
Negative likelihood ratio	0.20 (0.09–0.38)
CI: confidence interval	

Additionally, 216 patients, enrolled in 7 centres with 10 or more cases, were included in a mixed-effect analysis (see additional file 1, table S2). Baseline non-respiratory SOFA score and ROX index remained as independent predictors of intubation (see additional file 1, table S2). Overall, fixed effects explained 63% of the variability of the outcome while individual centres explained an additional 1% (see additional file 1, table S3 and figure S2). An online calculator to predict the likelihood of intubation given baseline non-respiratory SOFA score and ROX index was developed (see <https://desbancar.shinyapps.io/DESBANCAR/>)

Discussion

In this multicentre cohort study of 259 critically ill adult patients with COVID-19 initially treated with HFNO, the need for intubation and invasive mechanical ventilation was frequent and occurred in more than 50% of patients. Non-respiratory SOFA and the ROX index were the main predictors of endotracheal intubation.

Unlike previous studies in non-COVID patients^{2,29}, poor oxygenation at baseline, as measured by $\text{PaO}_2/\text{FiO}_2$, was not a reliable predictor of intubation. While hypoxemia seems often homogeneously noticeable in this population, its mechanisms may be multifactorial and might change over time as the disease progresses³⁰. Cressoni et al. described the distinction between anatomic to functional shunt in ARDS, and Gattinoni et al. have recently reported that the ratio of the shunt fraction to the gasless compartment in COVID-19 subjects is often higher than the values found in ARDS^{31,32}. Recently, Chiumello et al. highlighted the differential radiologic pattern of COVID-19 patients as compared to non-COVID-19 ARDS. Similar to previous studies in both non-COVID and COVID patients, our study supported how ROX index, which encompasses information from both oxygenation and respiratory rate, was useful to predict intubation^{23,33}. In the absence of non-pulmonary involvement, a ROX index of 3.5 at admission

conferred a 50% chance of intubation, which was 83% sensitive and 89% specific for HFNO failure. Of note, the present study differs from previous reports in the percentage of patients receiving HFNO from the total population of patients with COVID-19 related acute respiratory failure^{13,14}. Specifically, the patient population in the present study comprised 24% of the whole database, potentially showing that clinicians seemed to be keener (compared to previously published reports) on using this non-invasive oxygenation strategy in this patient population. This in turn may also explain the lower PaO₂/FiO₂ ratios that were often observed^{13,14} and potentially, the lack of impact on the initial decision to switch from HFNO to invasive mechanical ventilation.

Our parsimonious model, which included non-respiratory SOFA and the ROX index, to predict intubation among patients with COVID-19 treated with HFNO showed excellent discrimination and may be helpful in the decision-making process at the bedside. The model also shows strong clinical rationale. It is plausible that as lung mechanics deteriorated in some patients, respiratory drive increased, making the ROX index a valuable tool to predict HFNO failure. Likewise, pH was often lower and PaCO₂ higher in subjects who later became intubated, suggesting fatigue or increased lung injury in failing subjects. Non-respiratory SOFA score was higher in intubated patients and this was mostly related to hemodynamic impairment. Finally, our mixed-effects analysis showed that most of the variability for the need of invasive mechanical ventilation can be explained by baseline factors at admission, while differential “ICU culture” does not appear to play a major role in this decision. This needs to be analysed in comparison to previous research showing fairly strong centre effects, both in the care of patients with septic shock and mechanically ventilated critically ill adults^{17,34}.

Our study has several strengths. First, data were collected prospectively in a nationwide project and one of its main goals was to specifically study the relationship between respiratory treatment and outcome. Second, we were able to derive a parsimonious, potentially easy-to-use model that could aid in the identification of patients who may need intubation while being treated with HFNO. However, we acknowledge some limitations of our findings. First, observational studies, especially those multicentre in nature, as our study, are prone to misclassification of relevant covariates and potential predictors. However, a concise manual of procedures was provided to all the participating researchers at the beginning of the study, and two independent investigators checked for the accuracy of the data and unreliable values for all included patients. Second, missing data on candidate predictors was present in the final sample, rendering our reported associations subject to information bias and potentially decreasing the precision of our estimates. However, our results were robust while using multiple imputation.

Conclusions

In conclusion, in this observational study of 259 adult critically-ill patients with COVID-19 related acute respiratory failure receiving HFNO, approximately 1 out of 2 patients were intubated during the subsequent ICU stay. Oxygenation at baseline was not a good predictor of HFNO failure, while non-respiratory SOFA, pH and ROX index were independently associated with intubation. Little variation on the

decision to intubate was observed across included centres. Future studies should confirm our findings and evaluate the performance of our model in external cohorts.

Abbreviations

APACHE: Acute physiological and Chronic Health disease Classification System

ARDS: Acute respiratory distress syndrome

ARF: acute respiratory failure

BMI: Body mass index

COVID-19: Coronavirus Disease 19

CRP: C-Reactive protein

HFNO: High flow nasal oxygen therapy

ICU: Intensive Care Unit

IQR: Interquartile range

LOS: Length of stay

MV: mechanical ventilation

NIV: Non-invasive ventilation

PaO₂/FiO₂: Partial pressure of arterial oxygen to inspiratory oxygen fraction ratio

P-SILI: Patient self-inflicted lung injury

RR: respiratory rate

SBP: systolic blood pressure

SOFA: Sequential organ failure assessment

SpO₂: Peripheral oxyhemoglobin saturation

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

V/Q: ventilation-perfusion

Declarations

Ethics approval and consent to participate: The study was approved by the referral Ethics Committee of Hospital Clínic, Barcelona, Spain. The need for written informed consent from participants was considered by each participating center.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest: The authors declare that they have no competing interests

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Authors contributions: R. Mellado-Artigas and C. Ferrando had full access to all the data in the study and take responsibility for the integrity of data and the accuracy of data analysis. R. Mellado-Artigas participated in the research question and was responsible for drafting the first version of the manuscript. R. Mellado-Artigas, L.E. Mujica and M. Ruiz performed the statistical analysis. E. Arruti was responsible for creating the database. B. L. Ferreyro, F. Angriman, E. Barbeta and C. Ferrando participated in the research question and corrected the manuscript. A. Torres and J. Villar provided critical appraisal during manuscript preparation and revised all versions of the manuscript.

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Figures

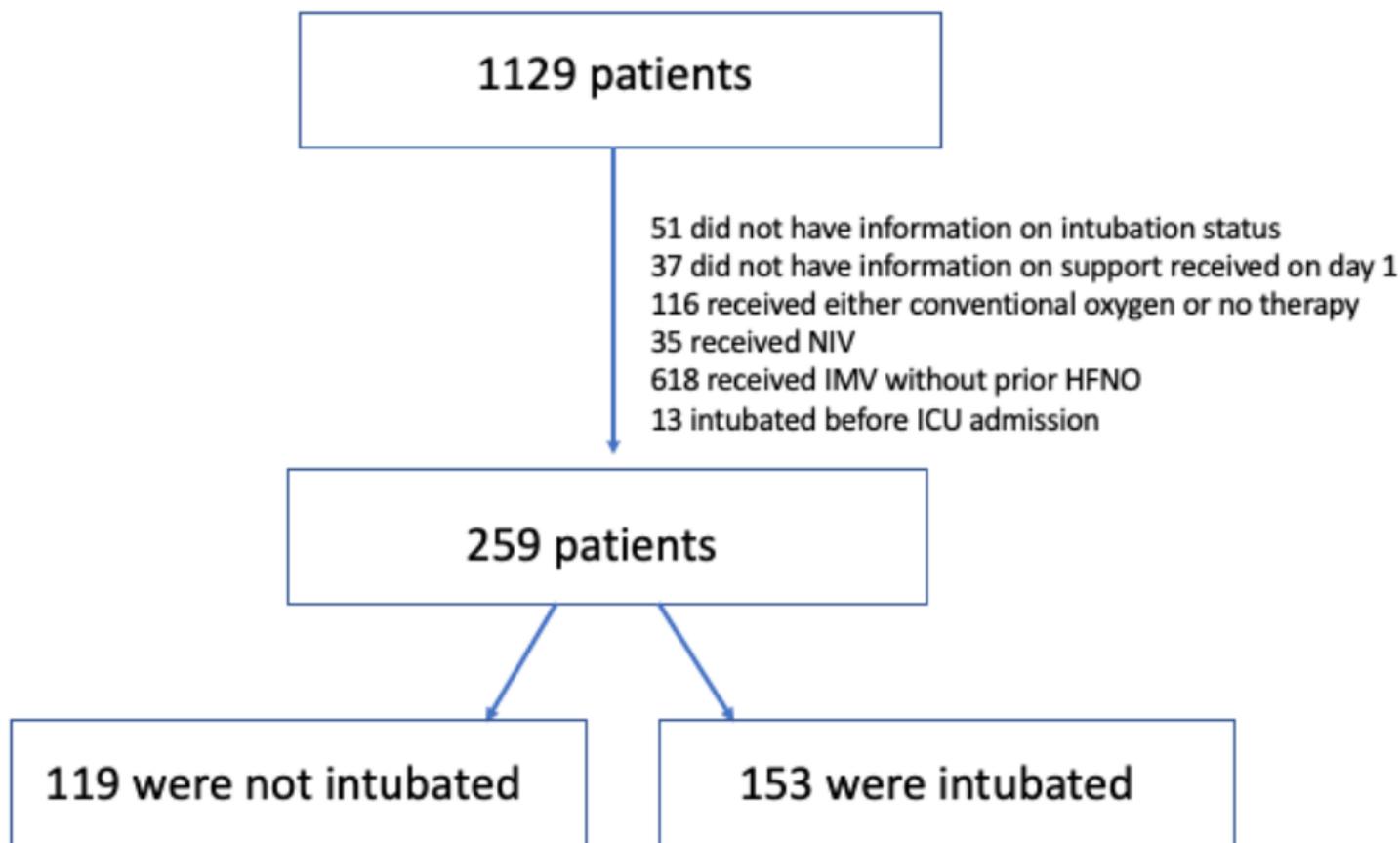


Figure 1

Patient flowchart. 259 patients were included and followed up until ICU discharge or death. NIV: Non-invasive ventilation. IMV: mechanical ventilation.

Supplementary Files

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