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

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Research

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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. Main exposure was the use of high flow nasal oxygen (conservative group), while early invasive mechanical (within the first day of critical care admission; early intubation group) served as the comparator. The primary outcome was ventilator-free days at 28 days. Intensive care unit length of stay and all-cause in hospital mortality served as secondary outcomes. We used propensity score matching to adjust for measured confounding.

Results

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 intensive care unit 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 intensive care 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 intensive care unit length of stay, when compared to early initiation of invasive mechanical ventilation. Future studies should confirm our findings.

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 far, the use of HFNO has been limited, despite 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 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 mechanical ventilation in these patients thus remains unknown. In this study, we aimed to estimate the effect of HFNO on ventilator-free days (VFD), 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 strategies and the rational allocation of invasive mechanical ventilation.

Methods

Study design and setting

We conducted a prospective, multicenter, 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, a total of 1129 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 (≥ 18 years old) admitted to the ICU between March 12th and August 13th, 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 above 35 breaths/min, a Glasgow Coma Score lower than 13 and pH lower than 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 hours of critical illness, under the framework of a target randomized trial (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 by physicians trained in critical care 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 since ICU admission[31]. Patients were followed-up until hospital discharge.

Study exposure and outcomes

The main exposure was the use of HFNO as the initial oxygenation strategy in the first 24 hours (conservative group), and the comparison was the use of invasive mechanical ventilation in the first 24 hours (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 ventilator-free days 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).

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 effect 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 was based on those potentially affecting the likelihood of outcome occurrence and receipt of study treatments[34], and was carried out based on subject matter knowledge with the help of a direct acyclic graph (DAG) (see e-figure 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 in 4 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 was handled using multiple imputation with a Monte Carlo Markov Chain method (see 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 ventilator free days 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, ninety-five percent confidence intervals (95% 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-hour 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.

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).

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 e-table 2 in additional file 1. 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 and active cancer (Table 1). Of the 61 included patients that initially received a conservative strategy with HFNO, 23 (38%) were intubated from day 2 onward.

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

Covariate	Early intubation (N = 61)	High flow nasal oxygen (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 [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

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.

Covariate	Early intubation (N = 61)	High flow nasal oxygen (N = 61)	SMD
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 (11944)	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

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.

Study outcomes

When compared to an early intubation strategy, the use of HFNO was associated with an increase in ventilator free days (mean difference 8.0 days; 95% CI, 4.4 to 11.7 days), and with 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 the 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); see Table 2.

Table 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.

Outcome of interest	Mean (95%CI) in conservative group (HFNO)	Mean (95%CI) in early intubation group	Mean difference (95%CI)
Ventilator-free days	20.7 (17.9–23.4)	12.6 (10.2–15.1)	8.0 (4.4, 11.7)
Intensive care unit length of stay	11.4 (8.8–14.2)	19.7 (16.0–23.3)	-8.2 (-12.7, – 3.6)
In-hospital mortality[1]	14.8 (5.8–23.7)	21.3 (12.0–31.6)	-6.6 (-20.2, 7.1)
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. **Odds ratio (95% confidence interval) of all-cause mortality for the comparison of HFNO vs. early intubation: 0.64 (0.25–1.64)**			

Sensitivity analysis

All sensitivity analysis yielded similar results to the presented main estimates (e-table 3 in additional file 1). 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 in hospital mortality (OR: 1.64; 95% CI, 0.40 to 6.66). Furthermore, after adjusting for imbalanced covariates, namely the presence of an active cancer, Glasgow Coma Scale, ROX index and inspired oxygen fraction, 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 in hospital mortality (OR: 0.75; 95% CI, 0.22 to 2.55). Furthermore, the estimated E-value for the primary analysis for the effect of HFNO on VFD was 3.28 (see e-figure 2 in additional file 1). Finally, no modification of the effect of HFNO on VFD was evident by baseline PaO_2/FiO_2 ratio (see e-table 4 in additional file 1).

Discussion

In this multicentre observational cohort study of 122 matched, critically ill adult patients with COVID-19 associated acute hypoxemic respiratory failure, the use of HFNO was associated with an increase in ventilator-free days and shorter ICU length of stay when compared to an early intubation strategy. No differences were evident in the occurrence of 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 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 population.[43] However, 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 ventilator-free days and shorter duration of ICU length of stay without any significant difference in mortality.

Of note, overall, patients receiving early intubation in our cohort were sicker at baseline as defined 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 inspired oxygen fraction 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 also 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 ventilator-free days as the primary outcome could be considered to favour upfront the HFNO group, given that a significant proportion of patients on HFNO were 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 ventilator-free days 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 ventilator free days 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 ventilator-free days 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, 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. Fourth, 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. Fifth, 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[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 ventilator-free days and a reduction in the duration of ICU stay; without a significant difference in all-cause in-hospital mortality. Future studies should corroborate our findings, as a way of optimizing the ventilation strategy for patients with COVID-19 associated acute respiratory failure.

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 oxyhemoglobin saturation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
VFD
Ventilator-free days

Declarations

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Conflicts of interest: Dr. Torres reports lecturing or consultancy fees from Pfizer, MSD, Basilea, Biomerieux. Jansen. Dr. 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 from General Electric, outside the submitted work. The remaining authors declare no conflicts of interest in relation to this manuscript.

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

Consent to participate: This is an observational study. The need for written informed consent from participants was considered by each participating center.

Consent for publication: Not applicable.

Availability of data and material: By request to the corresponding author.

Code availability: Not applicable.

Notation of prior abstract publication/presentation: A preliminary communication has been submitted in form of an abstract to the European Respiratory Society annual conference 2020.

Author's 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 approved the submitted manuscript.

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Figures

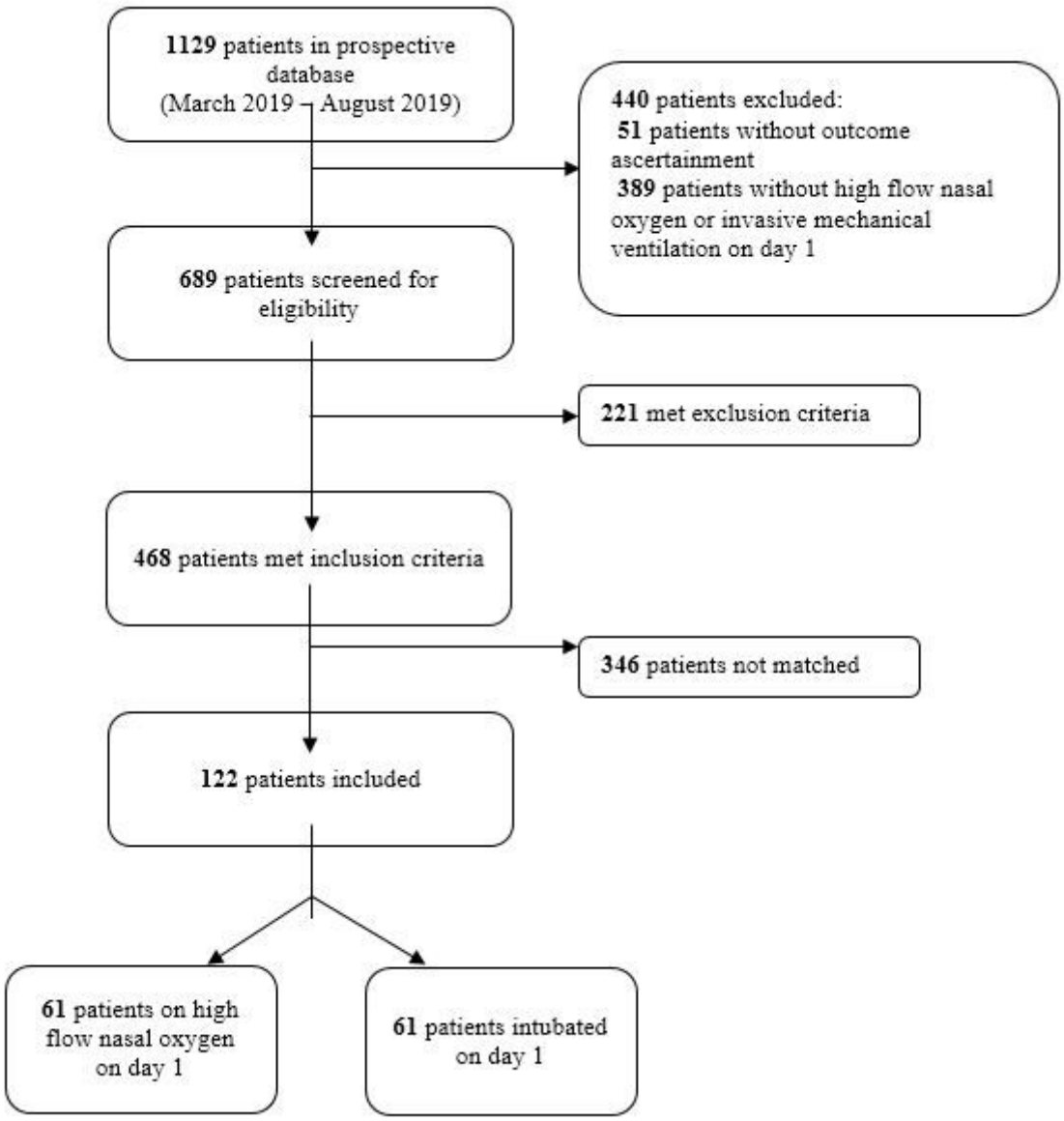

Figure 1

Study flow chart

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