Predictors of high flow oxygen therapy failure in COVID-19-related severe hypoxemic respiratory failure

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Background: During COVID-19 pandemic, people who developed pneumonia and needed supplemental oxygen, where treated with low-flow oxygen therapy systems and non-invasive methods, including oxygen therapy using high flow nasal cannula (HFNC) and the application of bi-level or continuous positive airway pressure (BiPAP or CPAP). We aimed to investigate the outcomes of critical COVID-19 patients treated with HFNC and unveil predictors of HFNC failure.

Methods: We retrospectively enrolled patients admitted to COVID-19 wards and treated with HFNC for COVID-19-related severe hypoxemic respiratory failure. The primary outcome of this study was treatment failure, such as the composite of intubation or death during hospital stay. The association between treatment failure and clinical features was evaluated using logistic regression models.

Results: One hundred thirty-two patients with a median (IQR) PaO_2/FiO_2 ratio 96 (63–173) mmHg at HFNC initiation were studied. Overall, 45.4% of the patients were intubated. Hospital mortality was 31.8%. Treatment failure (intubation or death) occurred in 50.75% and after adjustment for age, gender, Charlson Comorbidity index (CCI) score and National Early Warning Score 2 (NEWS2) score on admission and PaO_2/FiO_2 ratio and acute respiratory distress syndrome (ARDS) severity at the time of HFNO initiation, it was significantly associated with the presence of dyspnea [adjusted OR 2.48 (95% CI: 1.01–6.12)], and higher Urea serum levels [adjusted OR 1.25 (95% CI: 1.03–1.51) mg/dL].

Conclusions: HFNC treatment was successful in almost half of the patients with severe COVID-19-related acute hypoxemic respiratory failure (AHRF). The presence of dyspnea and high serum Urea levels on admission are closely related to HFNC failure.

Keywords: COVID-19; acute respiratory distress syndrome (ARDS); respiratory failure; high flow nasal cannula (HFNC); intubation

Introduction

Acute hypoxemic respiratory failure (AHRF), resulting from COVID-19 pneumonia, is the hallmark of "severe" and "critical" disease (1) and it is the main reason for SARS-CoV-2-related mortality (2,3). Low-flow oxygen therapy systems can achieve adequate blood oxygenation in early COVID-19 pneumonia, but in up to 20% of hospitalized patients, lung disease may progress to acute respiratory

distress syndrome (ARDS) (2). In that case, patients often need intubation and invasive mechanical ventilation (IMV). However, a proportion of them may be treated with non-invasive methods, including oxygen therapy using high flow nasal cannula (HFNC) and the application of bi-level or continuous positive airway pressure (BiPAP or CPAP) (4).

The value of HFNC in AHRF management was highlighted in the pre-pandemic era, when the emblematic FLORALI trial demonstrated lower mortality in patients treated with HFNC compared to standard oxygen therapy and non-invasive ventilation (NIV) (5). Intubation risk was reduced with HFNC in the sub-group of patients with PaO_2/FiO_2 <200 mmHg. In the same line of evidence, meta-analyses indicate that in patients with AHRF, HFNC is more effective than standard oxygen therapy in avoiding intubation, while a survival benefit is unclear (6-8). Not surprisingly, with the advent of COVID-19 pandemic, clinicians increasingly relied on this method to deal with the unprecedented number of AHRF patients and the restricted Intensive Care Unit (ICU) resources during pandemic surges. HFNC is recommended for the treatment of COVID-19-related AHRF by international authorities (1,9,10). Early observations from common wards or ICUs (11-19) suggest that several HFNC-treated COVID-19 patients with AHRF may avoid intubation, while information on their final outcome and risk factors for treatment failure is relatively poor. We here aimed to study the clinical features, the intubation rates and the overall success (alive and discharged) of HFNC inpatients admitted at common hospital wards and required treatment with HFNC for critical COVID-19 (1) and to identify factors associated with failure of the method. We hypothesized that most of these patients would be successfully treated with HFNC and discharged from the hospital avoiding intubation and mechanical ventilation and that failure of the method could be predicted using patients' features, available on their admission to the hospital or at HFNC initiation.

We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1373/rc).

Methods

Patients and procedures

We retrospectively enrolled patients admitted to the COVID-19 Unit (common isolation wards) of our hospital between September 2020 and January 2021 and treated with HFNC for severe AHRF caused by SARS-CoV-2 pneumonia, anytime during their hospital stay. By protocol, patients failing to maintain an oxygen saturation (SpO_2) >92% while treated with a Venturi mask with FiO_2 50% and not requiring urgent endotracheal intubation were offered HFNC at 60 L/min and appropriate FiO_2 to achieve a pulse SpO_2 92–96%. All patients with COVID-19 pneumonia and respiratory failure treated with HFNC during the defined period were included in the study. Patients' demographics, clinical, imaging, laboratory data and outcomes were extracted from the medical records. The primary outcome of this study was treatment failure, such as the composite of intubation or death during hospital stay. Success was considered discharged from the hospital without the need for intubation and mechanical ventilation. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Evaggelismos Hospital (Protocol No. 44-25/2/2021) and individual consent for this retrospective analysis was waived.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), if they are normally or non-normally distributed, accordingly. Categorical data are presented as percentage frequencies. Failure of the method was defined as intubation or in-hospital death. We applied logistic regression models to estimate the association between HFNC failure (intubation or in-hospital death) and patients' demographic features, comorbidities [including Charlson Comorbidity Index (CCI)], duration of symptoms, clinical symptoms and signs, National Early Warning Score 2 (NEWS2) score, X-ray Lung Field Score (20), laboratory data, admission, PaO_2/FiO_2 ratio on admission and within two hours of HFNC initiation and ARDS severity at HFNC initiation as well. In these models, we applied both unadjusted and adjusted analyses. Data were treated as categorical (such as sex, racial origin, presence of a symptom or presence of a comorbidity, grade of ARDS severity) or continuous (rest of them). In the adjusted analysis, we mutually controlled for confounders including age, gender, CCI score and NEWS2 score on admission and PaO_2/FiO_2 ratio and ARDS severity at the time of HFNO initiation. We applied Student's t-test to compare the duration of HFNC treatment, ICU stay and hospitalization between those intubated and those successfully treated with HFNC.

Table 1 Patients' demographics and co-morbidities

Characteristic	N=132
Age (years)	67±14
Male sex	91 (68.9%)
European origin	121 (91.7%)
Obesity (BMI ≥30 kg/m^2)	34 (25.8%)
Smoking	43 (32.6%)
Hypertension	69 (52.3%)
Coronary artery disease	19 (14.4%)
Asthma/COPD	14 (10.6%)
Diabetes	39 (29.5%)
Cancer	9 (6.8%)
Immunosuppression	12 (9.1%)
Cerebrovascular disease	7 (5.3%)
Chronic hepatic disease	2 (1.5%)
Chronic renal failure	7 (5.3%)
Autoimmune disease	4 (3.0%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Results

One hundred thirty-two patients, with mean ± SD age 67±14 years old were included in the study. Co-morbidities were common (*Table 1*) and the median [IQR] CCI was 3 [2–4]. Five patients had deemed as "do-not-intubate" (DNI) due to serious comorbidities. On admission, 49% had respiratory failure (SaO$_2$<90% while breathing ambient air). HFNC treatment was initiated 2 [0–7] days after hospital admission. The PaO$_2$/FiO$_2$ ratio within the first two hours of HFNC commencement was 96 [63–173] mm Hg. At that time, all patients had bilateral alveolar infiltrates, and PaO$_2$/FiO$_2$ ratio <300 mmHg while receiving HFNC at 60 L/min which generates a positive airway pressure of 5–6 cm H$_2$O (4), thus fulfilling typical ARDS criteria (21,22). ARDS was mild in 8%, moderate in 39% and severe in 53% of them (21). The median (IQR) duration of HFNC treatment was 5 [1–11] days.

Overall, 71.2% of the patients were transferred to the ICU, 45.4% were intubated and 31.8% finally died. NIV was not used as pre-intubation mean of respiratory support in any of the patients. HFNC failed (intubation or death) in 50.7% patients. Un-adjusted logistic regression analysis

revealed a link between treatment failure and advanced age, high CCI score, as well as high respiratory rate, low PaO$_2$/FiO$_2$ ratio, presence of dyspnea, high NEWS2 score and high Urea and Creatinine levels on admission, and low PaO$_2$/FiO$_2$ ratio and ARDS severity soon after HFNC initiation (*Table 2*). However, when adjusted logistic regression analysis was used, only the presence of dyspnea and high Urea serum levels on admission, were found to be significantly associated to the failure of HFNC (*Table 2*). Only 1/10 of patients with mild ARDS were intubated and none died, 23% of those with moderate ARDS were intubated and 21% died and 67% of those with severe ARDS were intubated and 44% died.

Less than half (47.3%) of full-treatment (including intubation) patients were intubated and 29.2% died. Mortality was 58,3% among those intubated. In the full treatment group, 9 of 10 patients with mild ARDS avoided intubation and all survived, 76% of those with moderate ARDS avoided intubation and 82% survived and 30% of those with severe ARDS avoided intubation and 58% survived. Compared to patients who avoided intubation, those intubated had a shorter HFNC treatment duration (4.56±4.7 *vs.* 6.5±3.5 days, P<0.05), longer ICU stay (26±21.4 *vs.* 4.2±5.5 days, P<0.05) and longer hospital stay (34.7±22.7 *vs.* 20.3±9.9 days, P<0.05).

Discussion

We here present the clinical features, the course and the outcome of patients who were admitted at common hospital wards, received treatment for COVID-19-related ARDS based on standard protocol and had definite outcomes (death or discharge). Our main findings are: (I) HFNC treatment succeeded (discharge without intubation) in 49.3 % of the patients and after adjustment for age, gender, CCI score and NEWS2 score on admission and PaO$_2$/FiO$_2$ ratio and ARDS severity at the time of HFNO initiation, this was significantly associated with the presence of dyspnea [adjusted OR 2.48 (95% CI: 1.01–6.12)] and higher Urea serum levels [adjusted OR 1.25 (95% CI: 1.03–1.51), by mg/dL on admission; (II) Intubation was avoided in 52.7% of the patients without a DNI-order (including almost 1/3 of those with severe ARDS); (III) Overall mortality was 31.8%.

We observed that HFNC commenced under a standard treatment protocol in patients with COVID-19-related ARDS admitted at common isolation hospital wards was successful in almost half of the patients who were

Table 2 Clinical parameters associated with High Flow Nasal Oxygen (HFNC) failure (intubation or in-hospital death)

	Unadjusted odd ratios	95% CI		P	Adjusted odd ratios	95% CI		P
Age (per year)	1.04	1.01	1.06	<0.05	1.03	0.99	1.07	NS
CCI score(per unit)	1.19	1.00	1.40	<0.05	1.02	0.80	1.30	NS
Respiratory rate (per breath/min)	1.05	1.00	1.11	<0.05	1.03	0.96	1.11	NS
PaO_2/FiO_2 on admission (per 10 mmHg)	0.96	0.92	0.99	<0.05	1.00	0.94	1.06	NS
Dyspnea	2.72	1.34	5.52	<0.05	2.48	1.01	6.12	<0.05
NEWS2 (per unit)	1.12	1.01	1.25	<0.05	1.04	0.91	1.19	NS
Urea (per 10 mg/dL)	1.30	1.09	1.55	<0.05	1.25	1.03	1.51	<0.05
Creatinine (per mg/dL)	6.37	1.88	21.61	<0.05	3.97	0.92	17.08	NS
PaO_2/FiO_2 at HFNC initiation (per 10 mmHg)	0.77	0.69	0.87	<0.05	0.84	0.68	1.04	NS
ARDS severity (per grade)	5.34	2.68	10.67	<0.05	1.82	0.43	7.72	NS

CCI, Charlson Comorbidity Index; NEWS2, National Early Warning Score 2; ARDS, adult respiratory distress syndrome. Grades for ARDS severity were defined as follows: mild, moderate, severe. All parameters except "PaO_2/FiO_2 at HFNC initiation" and "ARDS severity" refer to patients' condition on admission.

discharged without the need for intubation and mechanical ventilation. Intubation was avoided in 47.3% of patients not deemed DNI and survival in this group was 68.2%. Patients who avoided intubation, had shorter ICU and hospital stay compared to those intubated. Among patients with severe ARDS (21), in which HFNC use is not suggested by the WHO guidelines (1) intubation was avoided in approximately 1/3 of the patients and survival was more than 50%. In our cohort of patients fulfilling ARDS criteria (21), with a median PaO_2/FiO_2 ratio <100 at the time of HFNC initiation, HFNC success rate was similar to those reported, by either retrospective (common wards or ICUs, 45–65% success) (11-16) and prospective (ICUs, 46–48% success) (17-19) observational studies or a clinical trial conducted at the ICU (23). From the data discussed above, it follows that an HFNC trial should be attempted in patients with COVID-19-related AHRF even in those with severe ARDS when urgent intubation is not otherwise required.

Predicting patients' response to the HFNC is of major importance, especially during pandemic surges, when ICUs are overwhelmed, therapeutical means are scarce and optimal allocation of available non-invasive tools to treat severe COVID-19 AHRF and possibly avoid intubation becomes a task of paramount priority. After adjusting for age, gender, CCI score and NEWS2 score on admission

and PaO_2/FiO_2 ratio and ARDS severity at the time of HFNO initiation, we found that the presence of dyspnea and, higher urea serum levels on admission are associated with increased risk of HFNC failure. In agreement with others (15,16) and similarly to an observation made with the use of NIV in COVID-19-related severe respiratory failure (24), increased age was linked to increased risk of HFNC failure (intubation or death) in unadjusted analysis. Previous work has shown that HFNC failure in COVID-19 patients can be predicted using physiological parameters including the ROX index (12,14,15,17,18), SAPS2 (14), SOFA score (16,18), which were not examined at the present study. We demonstrated that other physiological features, such as PaO_2/FiO_2 ratio (on admission and after HFNC initiation), grade of ARDS severity and the NEWS2 score (on admission), were not linked with treatment failure. Interestingly, abnormal renal function, expressed by increased serum urea levels was a robust predictor of HFNC failure. Taken together, the above demonstrates that the presence of dyspnea and abnormal renal function on admission can predict failure or the method.

The main limitations of our study are connected with its retrospective design. In connection to these, incomplete records on the respiratory rate did not permit us to calculate ROX index. It is very challenging to interpret the observed associations as causal because we may have

unmeasured confounding, despite controlling for (I) all the significant variables from the univariate analysis and (II) the 6 most important confounders, i.e., age, gender, CCI score and NEWS2 score on admission and PaO_2/FiO_2 ratio and ARDS severity at the time of HFNO initiation, in the adjusted analysis. In addition, intubation was decided by the attending physicians on case-by-case basis and not according to pre-defined criteria. Nevertheless, it should be stressed that an "early intubation" strategy was unpopular in our institution and during that study period, the decision for intubation and mechanical ventilation was made using traditional criteria, i.e., resistive hypoxemia along with signs of respiratory distress and threatened respiratory arrest, altered mental status and cardiac arrest. On the other hand, advantages of the study include the fact that we used standard criteria for HFNC treatment throughout the study period and that all patients had definite outcomes (death or survival and discharge).

In conclusion, we showed that half of patients with COVID-19-related severe AHRF, treated with HFNC can be safely discharged without the need of intubation. The presence of dyspnea and high serum Urea levels on admission are closely related to HFNC failure. Randomized trials comparing HFNC to standard oxygen therapy are required to clarify its impact on COVID-19-related AHRF.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1373/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1373/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Evaggelismos Hospital (Protocol No. 44-25/2/2021) and individual consent for this retrospective analysis was waived.

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