High-Flow Nasal Cannula and Prone Positioning in Awake Patients with COVID-19 Related Respiratory Failure: An Observational Study.

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Abstract

Background: We report an observational study on the use of High-flow nasal cannula (HFNC) and awake prone position in patients with Covid-19 related severe ARF.

Methods: chart analysis of consecutive patients with confirmed Covid-19 and severe ARF (PaO2/FiO2 ratio <150) who received HFNC. Patients were systematically encouraged to lie in the prone position if tolerated. We calculated initial ROX index (the ratio of SpO2/FIO2 to respiratory rate) while in supine position and at the end of the first HFNC session whether in prone or supine position, and their difference (delta ROX). The success/failure of HFNC (need for intubation) was recorded. Predictors of HFNC failure were identified using ROC curve and logistic regression.

Results: HFNC was administered to 213 out of 360 patients with COVID-19 related severe ARF (71% male, median age:59 years (IQR:50-68), median PaO2/FIO2: 104(73-143). At the start of HFNC, median ROX index was 4(3.4-5). Among included patients, 178 (83.5%) could tolerate prone position and had a median of 4.4(2-6) prone sessions during a median of 10(4-16) hours/day each, for a median of 4(2-7) days. Overall, HFNC failure occurred in 61 patients (28.1%) with similar proportions in patients who had HFNC in prone position and in patients who did not tolerate prone position (29% and 26%, respectively; relative risk:1.14. 95%CI:0.62-2.1). In the prediction of HFNC outcome, AUC was highest for delta ROX (AUC=0.83); AUC for baseline ROX (0.71), PaO2/FiO2 (0.73), and SpO2 (0.67), were significantly lower. The delta ROX cut-off ≤1.8 had the best Youden index indicating the best combination of sensitivity (0.89) and specificity (0.61) with a PLR (2.33) and a NLR (0.17) to predict HFNC failure. Logistic regression disclosed the following predictors of HFNC failure: delta ROX: RR=0.44, 95%CI=0.32-0.62; p-0.0001); baseline ROX index: RR=0.58, 95% CI:0.39-0.85, p=0.005); SOFA score (RR=1.6 for each point; 95%CI: 1.1-2.2, p=0.007); and PaO2/FiO2 at admission: RR=0.96, 95%CI=0.94-0.99). Prone position was not related to HFNC success.

CONCLUSION: Awake HFNC in prone position is feasible in most patients with severe hypoxemic COVID-19. Indicators of ARF severity and the early response to HFNC, rather than prone position are independently associated with HFNC outcome.

Introduction

Acute respiratory failure (ARF) is an important clinical feature of COVID-19 pneumonitis leading to supplemental oxygen in 76% of hospitalized patients and ventilatory support in the majority of cases[1–3]. Predominant evidence prior to the onset of the Covid-19 pandemic favored the use of high flow nasal cannulas (HFNC) in de novo ARF instead of bilevel NIV[4] [5]. With the advent of Covid-19 pandemic, the so-called "aerosol-generating procedures" such as bilevel NIV and HFNC, were no longer recommended as first-line procedures because of the risk of dispersion of viral particles through droplets and aerosolized particles[6, 7]. However, a paradigm shift has gradually emerged recommending “avoidance of intubation” following both, observations on higher mortality associated with invasive ventilation (up to

90%)[8], and mitigation of the risk associated with "aerosol-generating procedures" by implemented precautions [9–11]. Recent reports show that the ventilatory support in Covid-19 related ARF usually consists in HFNC used in no-less than 55%, bilevel NIV in 16%, whereas invasive mechanical ventilation (IMV) is used in only 9%[3].

The new credit granted to non-invasive ventilation in the context of Covid-19 pandemic has favored the emergence of several studies aiming to assess the feasibility and the comparative performance of non-invasive oxygenation methods[1, 12–16]. Grieco et al reported similar effects on the number of days free of respiratory support within 28 days in COVID-19 related moderate-to-severe hypoxemia, whether oxygenation relied on helmet NIV or HFNC [12]. A study falling within the framework of comparative effectiveness concluded to the superiority of oxygenation by CPAP over standard oxygenation, whereas HFNC was not better than the standard of care[1]. However, in these studies, patients were not ventilated in prone position which has been recently suggested to potentiate the effect of NIV in awake patients[17–21]. In intubated as well as in spontaneously breathing patients, prone positioning improves indeed oxygenation and reduces the risk of lung injury. Increased oxygenation results from improved ventilation/perfusion matching through an improved ventilation in the well-perfused non-dependent areas of the lung [22–24]. The decreased risk of lung injury results from a decrease in chest wall compliance when the juxta-sternal part of the lung relies on the bed surface [24, 25]. In a multinational meta-trial, Ehrmann et al have recently shown that in patients with hypoxemic respiratory failure due to Covid-19, awake prone positioning reduces the risk of treatment failure and the need for tracheal intubation[26].

Nonetheless, the availability of a clinical tool or a score that assists in making a rapid decision to forgo HFNC is of utmost importance to avoid any delay in the intubation decision and prognosis worsening [27, 28]. ROX index, corresponding to the ratio of oxygen saturation as measured by pulse oximetry/FiO2 to respiratory rate has been shown to identify patients at low risk for HFNC failure in patients with ARF and pneumonia [29, 30]. However, there are little published data describing the use of ROX index to guide use of HFNC to treat COVID-19-associated respiratory failure[27, 31–33].

We report herein, the results of an observational study on the use of HFNC associated to prone positioning and the yield of ROX index in patients with Covid-19 related severe ARF.

Methods

This is an observational study with prospective data collection that lasted between September 02, 2020, and July 31, 2021. The study received the approval of the Institutional Review Board under the usual care label, which waived the need for individual consent.

Study population

charts of patients aged ≥18 years consecutively admitted to the medical ICU for confirmed Covid-19 and severe acute hypoxemic respiratory failure were analyzed. Covid-19 pneumonia was confirmed by positive pharyngeal/nasal swab rt PCR. Severe acute hypoxemic respiratory failure was diagnosed on the presence of dyspnea, tachypnea with respiratory rhythm≥26, tachycardia, an SpO2≤92% while breathing ambient air, and a PaO2/FiO2 ratio <150. Our ICU policy does not recommend bilevel NIV in hypoxemic respiratory failure with a preference to oxygenation with HFNC targeting a saturation range of 94-98%. Patients already intubated at admission, or those requiring immediate intubation and invasive mechanical ventilation were not included in the study. Only patients who received HFNC were included in the study.

Oxygenation Protocol:

HFNC is started in supine position with AIRVO 2 (Fisher & Paykel Healthcare) adapted with flowmeters to supply up to 60 l/min of humidified and heated oxygen through heated breathing tube (Air Spiral; Fisher & Paykel Healthcare) and Optiflow interfaces (Fisher & Paykel Healthcare). At HFNC start temperature is set at 33 to 37ºC and the initial flow at 45 L/min in order to fit patient's air demand. The flow might be increased up to 60l/min according to patient's need and tolerance. The fraction of inspired oxygen (FiO2) concentration was set to maintain SpO2 levels ≥ 94%.

All patients were instructed and supported to lie in the prone position daily for as long as was tolerated, ensuring they were predominantly on their chest. Patients who tolerated prone position were asked to remain in that position as long as possible on a 24-h basis. In patients who did not tolerate prone position, HFNC was administered in supine position.

HFNC treatment was continuous, with close monitoring of vital signs and respiratory pattern, and was maintained until either clinical improvement (defined as SpO2 > 94% without dyspnea or clinical signs of distress) allowing the passage of oxygen therapy through a reservoir at 15 Lpm or lower according to SpO2 target[34], or clinical worsening mandating tracheal intubation Intubation and initiation of invasive mechanical ventilation was indicated when respiratory rate was above 30 breaths per min in association with respiratory muscle fatigue, respiratory acidosis (pH below 7·25), severe hypoxemia corresponding to SpO2 below 90% despite an FiO2 of ≥0·8), hemodynamic instability, or deteriorating consciousness level. HFNC failure was defined as the need for tracheal intubation and mechanical ventilation due to deterioration of respiratory function, or death of the patient.

Data Collection: The following information was collected in all patients on ICU admission: age gender, date of onset of symptoms and that of hospital admission, coexisting chronic morbidities.

Collected respiratory variables included peripheral oxygen saturation (SpO2), Respiratory Rate (RR), PaO2/FiO2 ratio, allowing calculation of the ROX index as defined by the ratio of SpO2/FIO2 to respiratory rate, an index that has previously been validated as a predictor of HFNC success or failure[29]. These variables were recorded at admission (in supine position), and at the end of the first HFNC session (whether in prone or supine position in patients who did not tolerate awake prone position). The difference between ROX calculated at the end of the first HFNC session and that calculated at baseline (delta ROX) was calculated.

The duration of the first HFNC session and the number of total HFNC sessions/patient were also recorded in each patient. The final outcome of HFNC (success or failure), the length of ICUstay, and patient's outcomes (hospital discharge, death) were recorded too.

Statistical analysis:

Data are presented as median with Interquartile range (IQR). Comparisons of clinical characteristics of patients were performed by Mann Whitney U Test. Categorical variables are reported as numbers and percentages and analyzed using the Chi-squared test and Fisher's exact test. A p value < 0.05 was considered significant.

Receiver operating characteristic (ROC) curve analysis was performed to test the performance of variables such as SpO2 measured at admission on ambient air, baseline ROX index, delta ROX, and PaO2/FiO2 in the prediction of HFNC outcome. Comparison of ROC curves relied on DeLong et al test[35]. Operative characteristics of various cut-off points were explored with the Youden index which combines sensitivity, specificity, and Likelihood ratios for rating diagnostic tests. Independent predictors of HFNC outcome were identified by Logistic regression which included variables that were significantly different between successful and failing HFNC groups. SPSS 21 for Windows was used for analysis.

Results

During the study-period, 360 patients with acute hypoxemic respiratory failure were admitted to our ICU (Figure 1: flow chart). Of these, 213 had oxygenation with HFNC and were included in the study. Despite the encouragement and support to lie in prone position, the procedure was not actually tolerated in 35 (16%). The major limitations to prone positioning were related to back or shoulder pain (47.1%), obesity (23.5%), delirium (17.6%), or refusal for general discomfort (11.8%).

Baseline characteristics:

Table I depicts the main characteristics of patients included in the study. All patients (median age: 59(IQR:50-68), Male/Female ratio: 152/61, median BMI: 28(26-32), had confirmed molecular diagnosis of COVID-19 (positive rtPCR for viral RNA). They were admitted to the hospital at a median of 10(7-14) days following their first clinical manifestations of Covid-19 disease and transferred to the ICU at a median of 2(1-4) days after hospitalization. At admission, their median PaO2/FIO2 ratio was 104(73-143), and SpO2 on ambient air was 85(77-88). The median respiratory rate was 26(24-30) breaths/min, and the median ROX index when they started HFNC was 4 (3.4-5).

Table I: **Baseline characteristics of patients who had prone HFNC according to their final status (success/failure)**

	All patients n=213	HFNC success n=152	HFNC Failure n=61	
Demographics/Morbidities				
Age, median (IQR), yr	59(50-68)	57(47-65)	64(55-71)	0.02
Sex (Male), n(%)	152(71)	109(72)	44(72)	0.54
BMI, median (IQR), Kg/m2	28(26-32)	28(26-31)	29(27-39)	0.09
Hypertension, n (%)	54(25)	28(18)	26(43)	0.28
Diabetes mellitus, n (%)	69(32)	46(30)	23(38)	0.45
Severity				
Time-interval between first symptom and hospitalization, days	10(7-14)	10(8-14)	10(7-14.5)	0.17
Time-interval to transfer to ICU, days	2(1-4)	2(1-4)	3(1.5-4.5)	0.36
SAPS II, median (IQR)	27(26-32)	25(19-30)	32(27-38)	0.0001
SOFA score, median (IQR)	3(2-4)	3(2-3)	4(3-6)	0.0001
SPO2 AA, median (IQR), %	85(77-88)	86(80-88)	80(70-87)	0.0001
PaO2/FiO2, median (IQR)	104(73-143)	114(82-160)	76(60-109)	0.0001
HR (beats/min), median (IQR)	81(75-95)	80(75-89)	85(80-106)	0.001
RR (breaths/min), median (IQR)	26(24-30)	25(23-29)	30(25-35)	0.0001
ROX Index at baseline, median (IQR)	4(3.4-5.2)	4.2(3.6-5.8)	3.5(3-4.2)	0.0001
pH	7.45(7.42-7.48)	7.45(	7.46()	0.2
CRP, mg/l	128(72-204)	115(60-200)	158(105-216)	0.01
Leucocytes, median (IQR), /mm3	9,470(7,500-12,160)	9,500(7,500-12,180)	9,400(7,050-12,110)	0.96
Lymphocytes, median (IQR), /mm3	720(500-1,075)	800(500-1,100)	610(500-900)	0.07
Platelets/Lymphocytes, median (IQR)	300(218-525)	292(225-495)	309(192-575)	0.9
Duration of stay, median (IQR), days	10(6-14)	9(6-13)	10(7-17)	0.08

Body position and HFNC Outcome:

Overall, 178 patients (83.5%) could tolerate prone position and had a median number of 4.4(2-6) prone positioning sessions which lasted a median of 10(4-16) hours/day each, for a median of 4(2-7) days oxygenation with HFNC. At the end of the first HFNC session which lasted a median of 6(4-9) hours, ROX index increased overall by a median of 1.62(0.45-3.9); $p<0.0001$. In patients who tolerated prone position, the median increase in ROX index at the end of the first prone session was 1.67(0.83-3.5).

Overall, tracheal intubation (HFNC failure) occurred in 61 patients (28.1%). Proportions of HFNC failure were similar in patients who had HFNC in prone position and in patients who did not tolerate prone position (29% and 26%, respectively; relative risk:1.14. 95%CI:0.62-2.1). Comparison between patients successfully managed with HFNC and those who failed shows that the latter group had significantly higher severity scores (SAPSII and SOFA), and lower levels of SpO2, PaO2/FiO2, and baseline ROX (Table I). ROX increase at the end of the first HFNC session (delta ROX) was significantly higher in the group of patients with successful HFNC treatment than in the patients with failing HFNC (medians, IQR): 2.7(-0.7-3.6) and 0.47(-4.3-2.9), respectively.

ROC curves were drawn to explore the performance of indicators of disease severity in predicting HFNC outcome. AUC was highest for delta ROX (AUC=0.83). In comparison, AUC for baseline level of ROX was:0.71 ($p=0.04$ vs delta ROX), AUC for PaO2/FiO2 was0.73 ($p=0.05$ vs delta ROX), and AUC for SpO2 on ambient air was 0.67 ($p=0.003$ vs delta ROX ; Figure 2).The delta ROX cut-off ≤1.8 had the best Youden index indicating the best combination of sensitivity (0.89) and specificity (0.61) with a Positive Likelihood Ratio of 2.33, and a Negative Likelihood Ratio of 0.17 to predict HFNC failure.

The Logistic regression identified the following variables as independent predictors of HFNC failure: delta ROX: OR=0.44 (95%CI=0.32-0.62; $p=0.0001$); baseline ROX index: OR=0.58 (95% CI:0.39-0.85, $p=0.005$); SOFA score: OR=1.6 for each point; 95%CI: 1.1-2.2, $p=0.007$); and PaO2/FiO2 at admission: OR=0.96, 95%CI=0.94-0.99). Prone positioning was not related to HFNC success. Overall, ICU mortality occurred in 52 patients (24.4%).

Dicussion

In this observational study out of 213 patients with Covid-19 related severe hypoxemic respiratory failure and instructed to lie in the prone position while receiving HFNC, 35 patients did not tolerate prone position while the remaining 178 (83.5%) had HFNC in awake prone position. Intubation (HFNC failure) was required in similar proportions in patients who tolerated prone position (52/178; 29%) and in those who had HFNC in the supine position during their ICU stay (9/25; 26%). Delta ROX corresponding to the difference between ROX index calculated at ICU admission and after the first HFNC session was the best predictor of the outcome of HFNC. A ROX cut-off ≤1.8 had the best operative characteristics in predicting the failure of HFNC. HFNC outcome was independently associated with indicators of ARF severity (such as SOFA score, baseline PaO2/FiO2, or baseline ROX) and not with body position.

Since the start of the pandemics, Covid-related severe hypoxemia revealed a great challenge to intensivists, with evolving paradigm regarding the place of non-invasive ventilation in this setting. From the ban unanimously applied on NIV during the first wave, evidence has progressively emerged on the reduced risk incurred by health workers and environment contamination when airways are managed without intubation, authorizing therefore the use of different NIV tools [10, 15, 36–40]. In early ARF, bilevel NIV delivered through helmet interface, and HFNC are deemed more effective than bilevel NIV delivered via facemask [41]. CPAP has recently emerged as the preferred tool of oxygenation in hypoxemic Covid-19 patients[1].

Combining prone position in awake patients under spontaneous ventilation whichever the tool, is an idea that progressively gained scientific ground [12, 17, 19, 20, 42, 43]. Prone positioning is indeed a first-line intervention in patients invasively ventilated for severe ARDS leading to substantial reduction in mortality through both, oxygenation improvement and VILI reduction[25, 44, 45]. Its use in awake and spontaneously breathing patients with ARDS secondary to COVID-19 has recently been reported to improve oxygenation in few retrospective or small sample prospective cohorts[19, 20, 43, 46, 47]. One of the mechanisms that could explain the beneficial effect of ventilation in prone position is the homogenization of the VA/Q mismatch as shown in a case report by Zarontonello et al [46].

The observational nature of our study does not allow reliable assessment of prone impact on hard outcomes such as HFNC success or ICU mortality. The lack of randomization precludes random assignment to prone position and does not exclude statistical imbalance in variables with outcome relevance between patients who did tolerate prone position and those who did not. However, studies of varying sizes can provide information on the magnitude of the benefits associated with the application of awake prone HFNC in hypoxemic Covid-19. Small recent studies on the use of prone position in spontaneously breathing patients with Covid-19 related hypoxemia reported lower success rates of HFNC: 34% in Zucman et al study, and 46.7% in Blez et al study, compared to 64% in our cohort [32, 48]. Conversely, in a retrospective cohort analysis of Covid-19 patients oxygenated with HFNC whether in supine or in prone position, Ferrando et al reported similar rates of intubation in both groups (41% and 40%, respectively) and no significant risk in 28-day mortality[49].

In a landmark multinational meta-trial, Ehrmann et al have recently provided the evidence for the superiority of awake prone positioning over supine, in Covid-19 related hypoxemic respiratory failure[26]. The authors pooled and analyzed in advance the individual observations of patients already included in prospective studies in progress spread across the world. These studies had in common the objective of evaluating the impact of delivery of awake prone HFNC in patients with Covid-19 acute hypoxemic respiratory failure. The meta-trial included 1,121 patients and reported a reduced HFNC failure rate (intubation or death) in patients assigned to awake prone positioning (40%), compared to patients assigned to standard care (46%; Relative risk 0·86 [95% CI 0·75–0·98]). They recommended accordingly routine awake prone position in patients with COVID-19 who require HFNC. They even claimed that equipoise surrounding the prone positioning of patients treated with HFNC does no longer exist recommending therefore to stop ongoing RCTs on the issue as performing HFNC in supine position becomes no longer ethical. Although observational in its design, our study was conducted before the publication of the meta-trial by Ehrmann et al and raises no ethical issue. Moreover, our observation of no significant difference between HFNC in supine or in prone position should not be considered in contradiction with that of Ehrmann et al since 95% CI boundaries surrounding point estimates overlap. Several explanations might account for the lack of statistical significance in our study. First, the lack of randomization cannot exclude an imbalance in baseline risk in patients who tolerated and those who did not tolerate prone position. Second, we cannot exclude a type II error and an underpowered study. Third, the multinational character of Ehrmann's study which on one hand reinforces the result's extrapolation might in the other hand, introduce a center bias. Mexico (and France) provided the highest number of participants whereas Spain, Ireland, and Canada contributed only modestly to the study participants. Discrepancy in study protocols or in clinical practice for procedures that were not standardized by protocols (such as actual prone duration which varied from 1.6 hour in Spain to 8.6 h in Mexico) might have impacted to a certain extent the failure/success rates. Besides, given its sample size, the Mexican subgroup had the highest weight among included subgroups and substantially impacted the final meta-trial result as it was the only positive trial per se. One might speculate that the effect of awake prone position is risk-dependent requiring therefore a risk-stratified analysis. In this connection, the lower failure rate reported in our study compared to that reported in the meta-trial by Ehrmann et al, might suggest a lower overall failure risk in our population compared to that of the meta-trial. However, the rate of HFNC failure reported in our study compares fairly with that usually reported outside the setting of Covid-19 (34.3% in the meta-analysis by Rochwerg et al[4]), or in Covid-19 [3].

In addition to information on feasibility and outcome of awake prone in real life, our study provides information on predictors of HFNC outcome in the specific setting of Covid-19 related hypoxemia. Our study confirms the performance of the ROX index evaluated elsewhere outside the Covid-19 setting. We show that the variation of the ROX index between baseline and the end of the first HFNC session, rather than a unique baseline measurement, is the best indicator of HFNC outcome. An increase by less than a threshold of 1.8 appears to have the best operative characteristics to predict HFNC failure. Early following setting up oxygenation with HFNC, clinicians have a reliable tool on outcome prediction and decision-making.

The usual questions in matters of HFNC arise therefore: in what proportion failure occurs, and how to predict them early enough to avoid the loss of chance related to delayed intubation in these patients. Although non-randomized, our study could answer most these previously enumerated relevant questions. It allowed precision of the rate of ROX index proved effective in the prediction of HFNC failure. In patients ventilated either in prone or in supine position, the cut-off of ROX variation between baseline and the end of the first HFNC session had the best operative characteristics among other physiologic variables such as severity of hypoxemia or general severity scores (SOFA). Our study further clarified the impact of HFNC combined to prone position on patient's survival.

Conclusions

Awake HFNC in prone position is feasible in most patients with severe hypoxemic COVID-19. Indicators of ARF severity and the early response to HFNC, rather than prone position are independently associated with HFNC outcome.

Declarations

Ethics approval and consent to participate: The study received the approval of the Institutional Review Board under the usual care label, which waived the need for individual consent.

Consent for publication : NA

Availability of data and materials : The data sets used and/or analysed in the current study are available from the corresponding author on reasonable request.

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

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Figures

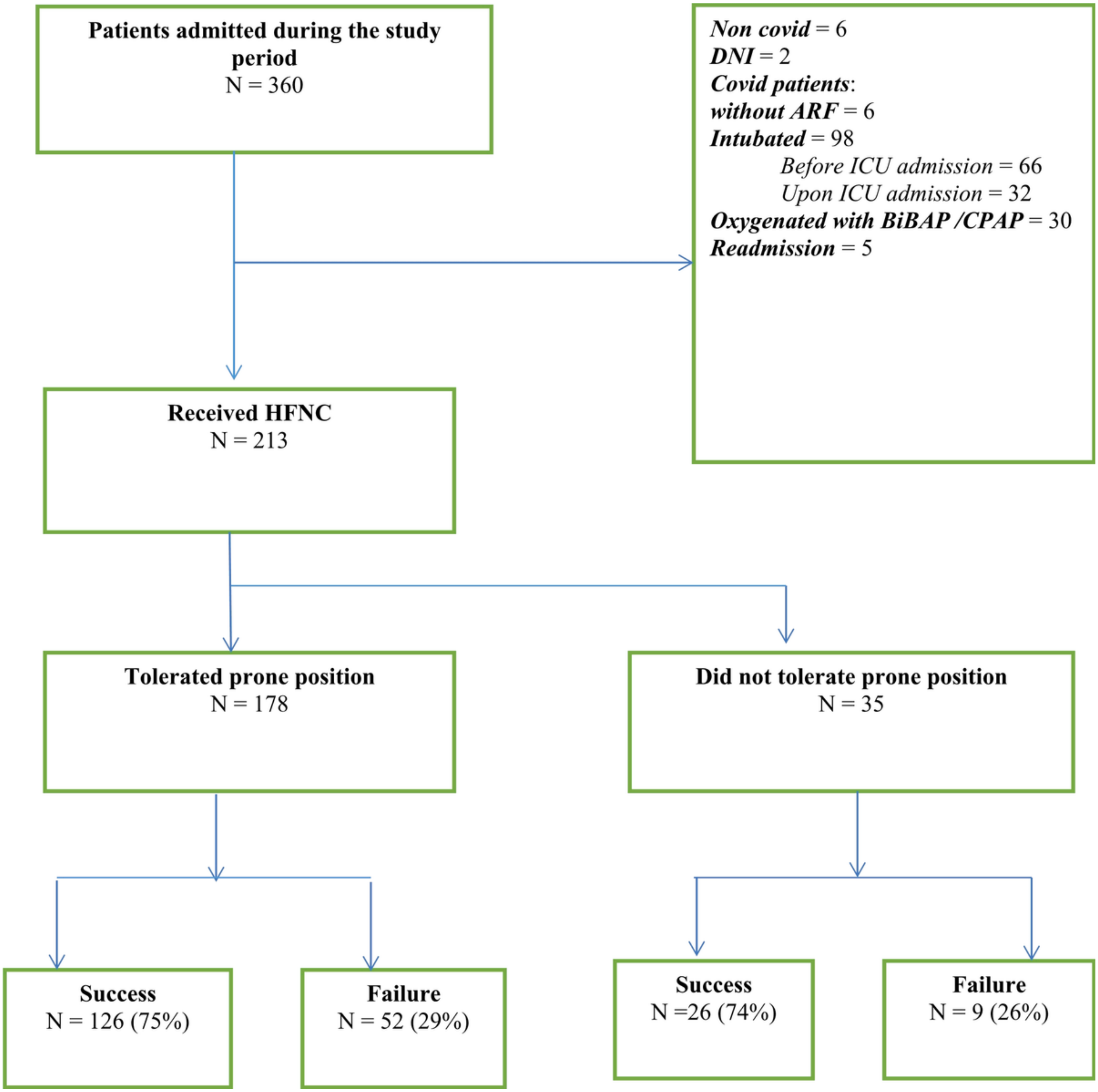

Figure 1

study flow chart

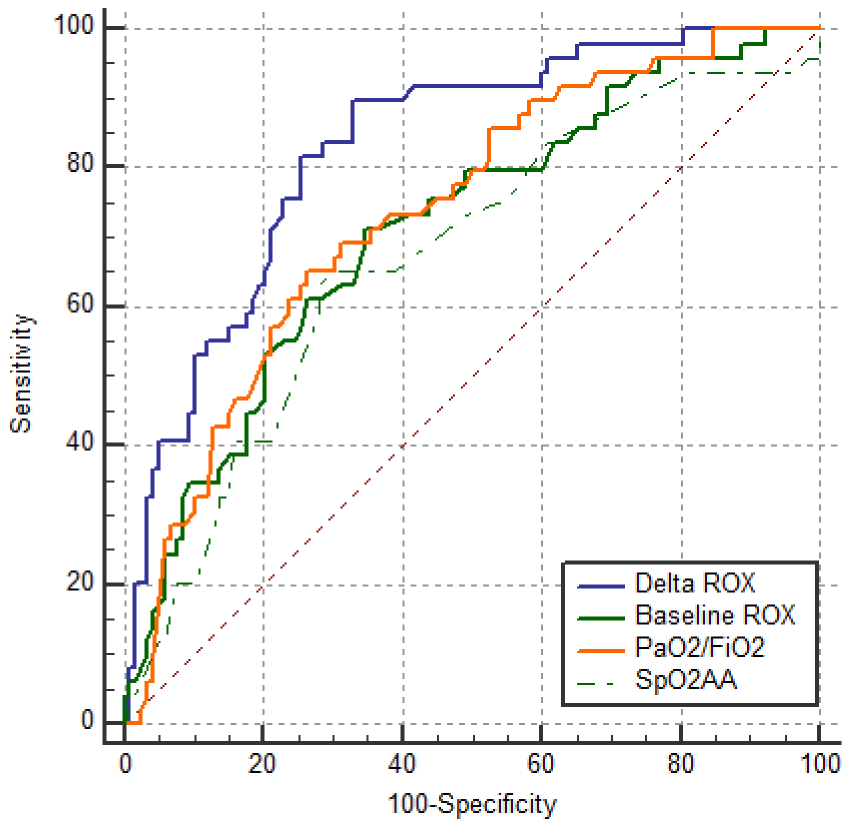

Figure 2

ROC curves of variables with potential for predicting HFNC success. AUC for delta ROX (AUC=0.83) was significantly higher than AUC of baseline ROX (AUC=0.71; p=0.04 vs delta ROX), baseline PaO2/FiO2 (AUC=0.73; p=0.05 vs delta ROX), and SpO2 on Ambient Air (AUC=0.67; p=0.03 vs delta ROX).