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Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index☆

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ABSTRACT

Purpose: The purpose of the study is to describe early predictors and to develop a prediction tool that accurately identifies the need for mechanical ventilation (MV) in pneumonia patients with hypoxemic acute respiratory failure (ARF) treated with high-flow nasal cannula (HFNC).
Materials and methods: This is a 4-year prospective observational 2-center cohort study including patients with severe pneumonia treated with HFNC. *High-flow nasal cannula failure* was defined as need for MV. *ROX index* was defined as the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate.
Results: One hundred fifty-seven patients were included, of whom 44 (28.0%) eventually required MV (HFNC failure). After 12 hours of HFNC treatment, the ROX index demonstrated the best prediction accuracy (area under the receiver operating characteristic curve 0.74 [95% confidence interval, 0.64-0.84]; $P < .002$). The best cutoff point for the ROX index was estimated to be 4.88. In the Cox proportional hazards model, a ROX index greater than or equal to 4.88 measured after 12 hours of HFNC was significantly associated with a lower risk for MV (hazard ratio, 0.273 [95% confidence interval, 0.121-0.618]; $P = .002$), even after adjusting for potential confounding.
Conclusions: In patients with ARF and pneumonia, the ROX index can identify patients at low risk for HFNC failure in whom therapy can be continued after 12 hours.

1. Introduction

Heated humidified high-flow nasal cannula (HFNC) has been described as a safe and useful therapy for hypoxemic acute respiratory failure (ARF) patients [1-7]. Compared with conventional oxygen therapy, it may improve comfort and oxygenation [2,5,8-9]. It has also been shown that it may decrease the need for mechanical ventilation (MV) in ARF lung transplant patients readmitted to the intensive care unit (ICU) [3] and may decrease reintubation rates as well [9]. More recently, the first large randomized control trial comparing the effectiveness of conventional oxygen therapy, noninvasive ventilation (NIV) combined with HFNC, and HFNC alone in hypoxemic ARF [1] demonstrated that HFNC alone reduced need for MV in the most severe (Pao_2/fraction of inspired oxygen [Fio_2], ≤200 mm Hg) subgroup of patients. High-flow nasal cannula patients also had the higher 90-day survival rate of the entire cohort.

However, one of the most challenging decisions in the management of ARF patients is to decide when to move from a spontaneous breathing oxygenation therapy to invasive MV [10]. In this regard, although HFNC may avoid further need for MV in some patients with ARF [1,3], it may unduly delay initiation of MV in others and worsen their outcome [11], as already evidenced for NIV [12–15]. Therefore, to identify and describe accurate early predictors of the need for MV in spontaneously breathing patients with ARF are of special interest.

Some clinical or oxygenation variables have been associated with HFNC failure and subsequent need for MV. For example, absence of

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oxygenation improvement [5,16] or significant decrease in the respiratory rate and persistence of thoracoabdominal asynchrony [5] were early indicators of treatment failure. They were, however, not discriminant enough to unequivocally identify patients that would require subsequent intubation. In addition to respiratory parameters, presence of additional organ failures such as hemodynamic [3,4,16] or neurologic failure has also been considered as a significant determinant of HFNC failure.

Indexes are commonly and widely used to help or guide physicians in the bedside decision-making process of patients' management. This is particularly true in critically ill patients to predict their probability of death [17,18] and assess their systemic severity [19] or the severity of some specific diseases, such as lung injury [20] or pneumonia [21,22]. Because the latter is by far the main indication for HFNC [1,3,5-6,16], the aim of the present study was to describe a feasible and reliable easy-to-use index that accurately predicted the need for MV in patients with pneumonia and hypoxemic ARF treated with HFNC.

2. Materials and methods

2.1. Study design

This is a 2-center prospective observational cohort study performed over a 4-year period (from 2009 to 2012), including patients with pneumonia admitted to the 32-bed medicosurgical ICU of Vall d'Hebron University Hospital, Barcelona (Spain), and the 12-bed medicosurgical ICU of Louis Mourier University Hospital, Colombes (France), who were treated with HFNC (Optiflow; Fisher & Paykel, Auckland, New Zealand). Some patient data were extracted from previously published prospective observational studies [4-6]. Local ethics committee approved the studies, and patient's informed consent was obtained before inclusion.

2.2. Patients

All patients admitted to the ICU with pneumonia and treated with HFNC were included. Pneumonia was diagnosed according to Infectious Diseases Society of America/American Thoracic Society 2007 guidelines [23]. Exclusion criteria were age younger than 18 years, indication for immediate MV [24] upon admission, and absence of commitment to pursue full life support. Patients electively intubated for diagnostic or therapeutic procedures (fibrobronchoscopy and surgery) were also not included. Patients were followed up until death or hospital discharge.

2.3. Data collection

Demographic variables and severity scores were recorded at the moment of inclusion. Acute Physiology and Chronic Health Evaluation (APACHE) II [17] was calculated in the first 24 hours of ICU admission. Sequential Organ Failure Assessment (SOFA) [19] score was recorded once a day during the first 5 days of HFNC therapy. We also recorded Pneumonia Severity Index (PSI) [22] and type of pneumonia (community acquired [23] vs health care associated [25]). To assess radiologic severity, chest x-ray findings were evaluated at the beginning of HFNC therapy. Clinical respiratory and pulmonary gas exchange variables in patients with arterial line were recorded 2, 6, 12, 18, and 24 hours after initiation of HFNC therapy. After the first 24 hours, the same variables were recorded once daily until HFNC withdrawal. *Failure of HFNC* was defined as subsequent need for invasive MV because, in the participating units, NIV is not used as second-line ventilatory support in case of HFNC failure where tracheal intubation is the preferred option and thus performed if necessary. The presence of an organ failure before and during HFNC therapy was also registered. Briefly, *shock* was defined as need for vasopressors [3]; *renal failure* was defined as increased serum creatinine × 1.5 and/or urine output less than 0.5 mL/kg per hour during 6 hours [26]. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [27] with the presence of bilateral infiltrates in chest x-ray and no evidence of heart failure but modified by using the ratio pulse oximetry (Spo_2)/Fio_2 less than 315 to assess hypoxemia [28]. We also recorded length of HFNC therapy, MV, and ICU and hospital stay and survival.

2.4. Device description and management

The HFNC device (Optiflow system, MR850 heated humidified RT202 delivery tubing, and RT050/051 nasal cannula; Fisher and Paykel Healthcare, Ltd) consists of a low-resistance nasal cannula that can deliver up to 60 L/min of totally conditioned (37°C and 100% of relative humidity) gas admixture. It was initiated with a minimum flow of 30 L/min with an Fio_2 of 1. Then, Fio_2 was set to maintain a pulse oximetry (Spo_2) greater than 92%, and flow rate was set according to the physician judgment. The parameters used to assess the level of respiratory support provided were Fio_2 and total flow delivered, adjusted to the individual patient's needs. The parameters used to assess respiratory failure were respiratory rate (RR), Spo_2/Fio_2 ratio, and arterial carbon dioxide ($Paco_2$). The criteria for intubation and MV [1,4] were decreased level of consciousness (Glasgow Coma Scale score, <12), cardiac arrest/arrhythmias, and severe hemodynamic instability (norepinephrine >0.1 μg/kg per minute) or persisting or worsening respiratory condition defined as at least 2 of the following criteria: failure to achieve correct oxygenation (Pao_2 <60 mm Hg despite HFNC flow ≥30 L/min, and Fio_2 of 1), respiratory acidosis ($Paco_2$ >50 mm Hg with pH <7.25), RR greater than 30 beats per minute, or inability to clear secretions.

2.5. ROX index description

The index predicting the need for MV was calculated from the measured respiratory variables assessing respiratory failure that significantly differ among groups (success vs failure). It aimed to obtain an additive effect, increasing their capacity to discriminate between patients who would succeed on HFNC and those who would fail. In the numerator were placed the variables with a positive association with HFNC success, such as oxygenation, assessed by the ratio Spo_2/Fio_2. In contrast, RR was placed in the denominator as it has an inverse association with HFNC success. We used the name ROX (Respiratory rate-OXygenation) for the index, as the ratio of Spo_2/Fio_2 to RR.

2.6. Statistical analysis

Quantitative variables were expressed as mean and SD or median and interquartile range if normality criteria, as tested with Kolmogorov-Smirnov test, were not met. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Differences in categorical variables were assessed with χ^2 or Fisher exact test, as appropriate. To assess the accuracy of different variables for correctly classifying patients who would succeed or fail on HFNC, receiver operating characteristic (ROC) curves were performed, and the area under the curves was calculated (AUROC). The optimal threshold of continuous variables was chosen to maximize the sum of sensitivity and specificity. According to the cut-point described in the ROC curve analysis for ROX index, Kaplan-Meier curves were used to determine the probability of MV for patients with higher ROX index and those with lower ROX index. These curves were compared using the log-rank test. To identify if the ROX index was associated with higher need for MV, Cox proportional hazards modeling was chosen, while simultaneously adjusting for other covariates. Variables with *P* value less than .2 in the univariate analysis were considered as potential covariates. We also adjusted by severity scores (APACHE and PSI). To prevent model overfitting, we introduced all potential confounding one at a time. A 2-sided *P* value of .05 or less was considered statistically