maintenance oral corticosteroid therapy, and alternative therapeutic approaches might be best, although these are limited for those with no evidence of eosinophilic inflammation.

How can this precision medicine approach be further improved, particularly for those with no evidence of eosinophilic inflammation, to find new treatments? Differential analysis of the omics data characterizing each of these four clusters may provide clues to the pathways that may underlie corticosteroid responsiveness. The other approach would be to first cluster on available transcriptomic or proteomic data. Taking this approach in the U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes project) cohort, Kuo and colleagues clustered transcriptomic pathways associated with inflammatory and immune mechanisms in bronchial biopsies and epithelial cells using machine learning to obtain T2-high molecular phenotypes associated with corticosteroid insensitivity (11). With use of an inference scheme, these molecular clusters could be predicted by using the inflammatory biomarkers of sputum eosinophilia and Fe_{NO} levels, together with oral corticosteroid use, with good sensitivity and specificity. The work of Wu and colleagues emphasizes the need for the unsupervised approach and the application of machine learning techniques that can provide useful tools for the clinician while improving understanding of corticosteroid insensitivity in severe asthma. ■

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Predicting Outcomes of High-Flow Nasal Cannula for Acute Respiratory Distress Syndrome

An Index that ROX

Noninvasive forms of ventilatory assistance, including noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC), have emerged as important modalities to treat acute respiratory failure during the last 2 decades. NIV use grew rapidly during the decade from 2000 through 2010 (1), when NIV as a proportion of initial ventilator starts in the United States rose as high as 40% (2), and HFNC use has risen during the present decade. According to current guidelines (3), NIV is considered the ventilatory modality of first choice to treat acute hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease, as well as cardiogenic pulmonary edema. NIV has not been so successful in patients with *de novo* hypoxemic respiratory failure resulting from pneumonia/acute respiratory distress syndrome (ARDS), with intubation rates as high as 50–66% (2, 4) and with particularly high mortality rates in these NIV failures (5). The European Respiratory Society/American Thoracic Society guideline on NIV made no recommendation on whether NIV should be used or not in *de novo* hypoxemic respiratory failure because of the high failure rates and the conflicting evidence.

In contrast, HFNC has been gaining traction as a therapy for *de novo* hypoxemic respiratory failure. This is partly because HFNC is an effective oxygenator related to its ability to keep up with the high inspiratory flows of dyspneic, hypoxemic

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patients, reducing entrainment of room air that dilutes $F_{I_{O_2}}$ with standard oxygen systems. In addition, the flushing of nasal and oropharyngeal dead space means that the initial bolus of air at the start of inspiration is freshly oxygenated gas rather than oxygen-depleted gas that has just been exhaled (6).

The increasing use of HFNC to treat acute hypoxemic respiratory failure is also partly driven by accumulating evidence, although no guidelines have yet recommended this application. In the FLORALI study (7), a randomized controlled trial consisting of 310 patients with acute hypoxemic respiratory failure allocated to HFNC, NIV using a standard full-face mask, or standard oxygen, roughly 80% of enrollees had pneumonia/ARDS. Overall intubation rate (the primary outcome variable) did not differ between the groups, but in the subgroup with a $Pa_{O_2}/F_{I_{O_2}} \leq 200$, intubation rate was significantly lower in the HFNC group than in the other 2 groups. Moreover, the intensive care unit and 90-day mortality rates were significantly lower in the HFNC than in the standard oxygen and NIV groups (11%, 19%, and 25% for the intensive care unit and 12%, 23%, and 28% for 90-d mortality), respectively.

This and other studies have been influential in encouraging greater use of HFNC to treat hypoxemic respiratory failure. More recently, Patel and colleagues (8) have reported that NIV using a helmet device consisting of a clear plastic hood that fits over the head and affixes to the neck and shoulders drastically reduces intubation rate compared with a standard full-face mask (18% vs. 62%), as well as mortality (34% vs. 56%), raising the possibility that NIV administered via a better interface may still have a role in treating acute hypoxemic respiratory failure. Regardless of the noninvasive modality chosen, however, a major challenge in managing patients is to avoid delay of a needed intubation. In their study on use of NIV for postextubation respiratory insufficiency, Esteban and colleagues (9) found higher intensive care unit mortality in the NIV group, in which reintubations were performed an average of 10 hours later than in the control group. Similar findings were reported for HFNC in a retrospective cohort of 175 patients in whom late failure (after 48 h) was associated with worse outcomes than early failure. Thus, ways of predicting the likelihood of failure could be very helpful clinically, so that at-risk patients can be watched closer or even intubated earlier.

In this issue of the *Journal*, Roca and colleagues (pp. 1368–1376) (10) report results of their validation of the ROX index ([oxygen saturation/$F_{I_{O_2}}$]/respiratory rate) to predict outcomes of patients with hypoxemic respiratory failure resulting from pneumonia/ARDS treated with HFNC. Using a training cohort of 157 patients, they previously reported that a ROX value of >4.88 predicted success of HFNC (11). In the current study, the ROX index was validated in 191 patients enrolled at 5 centers in France and Spain who were sicker (more with shock and a trend toward a higher APACHE II score) and had a higher mortality (27.3%) than the training cohort (14.2%). Still, the ROX index score of >4.88 was as predictive of outcomes in the validation cohort as it was in the training cohort. The area under the curve at 12 hours, a measure of discrimination, was 0.752, which was comparable to the training cohort, and was higher than those of $Sp_{O_2}/F_{I_{O_2}}$ and Sp_{O_2} and $F_{I_{O_2}}$ singly at most points up to 24 hours. A second validation using patients from the FLORALI cohort (7) provided similar findings, although the areas under the curve were consistently lower than those in the first validation. It is worth noting that to fully validate a score, both discrimination (using area under the curve) and calibration (using observed outcomes) are important. Comparing predicted outcomes (based on the training cohort) versus observed outcomes at different levels of ROX in the validation cohort could have strengthened the validation.

The ROX score is likely to be useful clinically because it requires few data points and is simple to calculate at the bedside. It has a positive predictive value for success of HFNC of more than 80% between 12 and 20 hours postinitiation, when most of the intubations occur. For durations of use of less than 12 hours, when the ability to predict HFNC failure and the need for intubation would be important, the cutoff values of 2.85 at 2 hours, 3.47 at 6 hours, and 3.85 at 12 hours had specificities of 98–99% in the main validation cohort. Thus, clinicians could use the ROX score as a way to assess progress in patients receiving HFNC, making serial measurements, and incorporating it when considering decisions to escalate care. During the first 12 hours, scores below the cutoffs given here would prompt consideration of earlier intubation. Once the 12-hour point is reached, a score >4.88 increases clinician confidence that the patient will succeed. Caveats include the fact that the ROX score was developed in cohorts with hypoxemic respiratory failure resulting from pneumonia/ARDS and has not been validated in other populations. Also, no score can replace close bedside observation of critically ill patients with respiratory failure, but it can be helpful in more safely managing these patients, helping to avoid delayed intubations. Additional study would be necessary, however, to demonstrate that use of the ROX index can actually improve clinical outcomes, rather than just predict them. ■

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Respiratory Suffering in the ICU: Time for Our Next Great Cause

Dyspnea, or breathlessness, ranks among the worst suffering that a human being can experience. Although it is similar to pain in many ways, dyspnea differs from pain in its terrifying dimension. Having trouble taking a breath in, experiencing an unquenchable thirst for air, or feeling one's chest constricted immediately summons an existential fear, the fear of dying. This makes the relief of dyspnea a primary concern, anchored not only to clinical obligation but also to universal ethical and moral considerations (1, 2).

Relief of dyspnea implies its recognition. When the dyspneic patient can talk, the patient's own report of having difficulty breathing is emphasized in the current operational definition of dyspnea (3). It is straightforward to elicit, if one takes the trouble to do so (4). When verbal communication is impaired for whatever reason, dyspnea-related clinical manifestations can be missed. Dyspnea then remains occult (5), compounding the perception of an existential threat with a sensation of powerlessness. This leads to panic and is a clear recipe for post-traumatic stress disorder (1). Yet there are many nonverbal dyspnea-related signs (neurovegetative, behavioral, and emotional) that allow the identification of breathlessness in noncommunicative patients (6–9).

In this issue of the *Journal*, Gentzler and colleagues (pp. 1377–1384) confirm that dyspnea is as frequent a problem for patients in the ICU as pain (10). In their study, moderate to severe dyspnea was reported by 47% of patients, and 41% of patients reported pain. One of their most striking findings is that the performance of nurses in identifying dyspnea was relatively poor; personal caregivers performed much better. Personal caregivers' ratings of dyspnea agreed well with the patients' own ratings, but this was far from being the case for the nurses' ratings. The poor aptitude of nurses, physiotherapists, and physicians in identifying dyspnea in their patients has been described before (11–13), but this is the first time that a comparison has been conducted with the corresponding aptitude of personal caregivers, who, notably, never failed to detect dyspnea.

Improving the performance of ICU personnel in identifying dyspnea and evaluating its severity therefore seems necessary. Implementing systematic dyspnea assessments in routine clinical care (as for pain) could be useful (14), and such routine assessments seem readily acceptable to nurses (15). Generalizing the use of observational scales (and particularly their simplified ICU versions [7–9]) could also be useful (16). Specific studies should be designed to determine the potential benefits of such approaches. Electromyographic and electroencephalographic techniques offer the prospect of improving this process by providing surrogate biomarkers of dyspnea (17–19).

But identifying dyspnea is not enough. It is necessary to do something about it. Perhaps the most important finding of the study by Gentzler and colleagues is that nurse detection of moderate-to-severe dyspnea was not associated with any therapeutic action, such as administering bronchodilators or opioids, adjusting ventilator settings, or changing the respiratory device altogether. This stood in contrast to pain, whose detection was significantly associated with opioid treatment. This finding is not completely surprising. A recent survey showed that clinicians confronted with theoretical cases of chronic pain or "chronic breathlessness" (20), or "persistent breathlessness" (21), acted far more on the pain than on the dyspnea (22). The term "invisibility of dyspnea" was coined to describe the lack of response of caregivers to dyspnea, or even their avoidance of it (23, 24). There are several possible reasons for this surprising observation. First, dyspnea, in contrast to pain, is not a universal experience. The shortness of breath that healthy people experience during exertion cannot be compared with pathological breathlessness (25). It is unthreatening—it can even be satisfactory—and it can be controlled by reducing the intensity of exertion. It is thus likely that it is more difficult for a caregiver to identify with the suffering of dyspna than with the suffering of pain. Second, and also in contrast to pain, there are no firmly established guidelines to manage dyspnea in ICU patients. This can make caregivers feel helpless and, as a reaction, favor avoidance. The nurses in Gentzler and colleagues study emphasized that dyspnea presented a greater challenge to symptom management than pain, yet dyspnea in mechanically ventilated patients

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ORIGINAL ARTICLE

An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy

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Abstract

Rationale: One important concern during high-flow nasal cannula (HFNC) therapy in patients with acute hypoxemic respiratory failure is to not delay intubation.

Objectives: To validate the diagnostic accuracy of an index (termed ROX and defined as the ratio of oxygen saturation as measured by pulse oximetry/FI_{O_2} to respiratory rate) for determining HFNC outcome (need or not for intubation).

Methods: This was a 2-year multicenter prospective observational cohort study including patients with pneumonia treated with HFNC. Identification was through Cox proportional hazards modeling of ROX association with HFNC outcome. The most specific cutoff of the ROX index to predict HFNC failure and success was assessed.

Measurements and Main Results: Among the 191 patients treated with HFNC in the validation cohort, 68 (35.6%) required intubation. The prediction accuracy of the ROX index increased over time (area under the receiver operating characteristic curve: 2 h, 0.679; 6 h, 0.703; 12 h, 0.759). ROX greater than or equal to 4.88 measured at 2 (hazard ratio, 0.434; 95% confidence interval, 0.264–0.715; $P = 0.001$), 6 (hazard ratio, 0.304; 95% confidence interval, 0.182–0.509; $P < 0.001$), or 12 hours (hazard ratio, 0.291; 95% confidence interval, 0.161–0.524; $P < 0.001$) after HFNC initiation was consistently associated with a lower risk for intubation. A ROX less than 2.85, less than 3.47, and less than 3.85 at 2, 6, and 12 hours of HFNC initiation, respectively, were predictors of HFNC failure. Patients who failed presented a lower increase in the values of the ROX index over the 12 hours. Among components of the index, oxygen saturation as measured by pulse oximetry/FI_{O_2} had a greater weight than respiratory rate.

Conclusions: In patients with pneumonia with acute respiratory failure treated with HFNC, ROX is an index that can help identify those patients with low and those with high risk for intubation.

Clinical trial registered with www.clinicaltrials.gov (NCT 02845128).

Keywords: high-flow nasal cannula; nasal high flow; acute respiratory failure; pneumonia

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At a Glance Commentary

Scientific Knowledge on the Subject: Delayed intubation of spontaneously breathing patients with hypoxemic acute respiratory failure is associated with an excess mortality. Although several studies have described factors associated with higher risk for intubation in patients treated with high-flow oxygen, none was designed and powered to validate them. We recently described the utility of the ROX index, defined as the ratio of oxygen saturation as measured by pulse oximetry/FI_{O_2} to respiratory rate, for determining which patients treated with nasal high flow will not require intubation.

What This Study Adds to the Field: We confirm the ROX index's accuracy for predicting nasal high-flow oxygen outcome of pneumonia-related respiratory failure: ROX index greater than or equal to 4.88 measured at 2, 6, or 12 hours is a determinant of high-flow success. Additionally, we identified and validated values at different time-points of the ROX index, which predict high-flow failure. Because the ROX index is easily measured and repeated at the bedside, we show that changes of the index over time are also predictive of high-flow outcome. This index can thus be incorporated in the day-to-day clinical decision-making process of critically ill patients treated with nasal high flow.

A growing interest in noninvasive management of acute hypoxemic respiratory failure (AHRF) has been fueled by the advent of high-flow nasal cannula oxygen therapy (HFNC) (1) and by recent data showing that use of HFNC was associated with lower mortality, more ventilator-free days, and lower risk for intubation in subsets of patients with Pa_{O_2}/FI_{O_2} less than or equal to 200 mm Hg or in those who were immunocompromised in comparison with noninvasive ventilation (NIV) or standard oxygen (2, 3). These positive results followed physiologic studies showing improvements in oxygenation, lung mechanics, and comfort associated with HFNC (4–6). Pneumonia, which is a frequent cause of acute respiratory distress syndrome (7), was the most frequent cause of AHRF in these studies (8). This has led clinicians to try this technique in patients with the most severe respiratory failure, those precisely with acute respiratory distress syndrome (9, 10).

A consequence of the increasing use of HFNC is the risk of delaying a needed intubation. This is an important concern because a large body of evidence has shown that patients that fail NIV management of *de novo* AHRF have a worse outcome. This has been convincingly shown with NIV (11), especially in patients treated for pneumonia (12) and also with HFNC (13). The new European Respiratory Society/American Thoracic Society guidelines for acute respiratory failure made no formal recommendation for NIV in this context (14). In addition, there are no prospectively validated and accepted intubation criteria for AHRF. This may lead to considerable differences among clinicians in terms of timing of intubation that could impact outcome (15). A core set of parameters that should prompt intubation are generally agreed on, but precise cutoffs may vary considerably. Therefore, to describe clinical variables that could be easily used at the bedside to help decide on intubation in a timely fashion is a point of special interest to avoid delaying a needed intubation. To address this unmet need, we recently described the ROX index, defined as the ratio of oxygen saturation as measured by pulse oximetry (Sp_{O_2})/FI_{O_2} to respiratory rate (RR). This index outperformed the diagnostic accuracy of the two variables separately (16). Patients who had a ROX index greater than or equal to 4.88 after 12 hours of HFNC therapy were less likely to be intubated, even after adjusting for potential covariates. Like any other scoring system, an independent validation of the score is necessary. We therefore undertook a multicenter, prospective study to validate the ROX index's diagnostic accuracy for determining which patients will succeed and which will fail on HFNC.

Methods

Study Design

This is a multicenter prospective observational cohort study performed over a 2-year period (2016–2017) including patients with pneumonia treated with HFNC who were admitted in five different ICUs in Spain and France (*see* the online supplement for detail). Local ethics committee approved the studies in Spain and written patient's informed consent was obtained before inclusion. For the French centers, the Ethics Committee of the French Intensive Care Society also approved the study. Because of its purely observational design, written consent was not required. Patients were informed of the nature of the study, its purpose and objectives, and of their right to decline participation.

Patients

All consecutive patients admitted to the ICU with pneumonia and treated with HFNC were included. No patients declined to participate. Pneumonia was diagnosed according to Infectious Diseases Society of America/American Thoracic Society 2007 guidelines (17). Patients younger than 18 years old, patients with indication for immediate intubation (18), and those with do-not-intubate order were excluded. Patients electively intubated for diagnostic or therapeutic procedures (fibrobronchoscopy, surgery) were also not included. Patients were followed until death or hospital discharge.

Device Description and Management

Management of HFNC therapy and criteria for mechanical ventilation (MV) did not differ between training (16) and validation studies. High flow was provided either with the Optiflow device (MR850 heated humidified RT202 delivery tubing and RT050/051 nasal cannula; Fisher and Paykel Healthcare) or with Airvo 2 (Fisher and Paykel Healthcare). HFNC was initiated with a minimum flow of 30 L/min with a FI_{O_2} of 1 in those patients that were unable to maintain an Sp_{O_2} higher than 92% and an RR of 25 breaths/min or greater while receiving standard oxygen administered through a face mask at 10 L/min or more. Then, FI_{O_2} was titrated targeting an Sp_{O_2} above 92% and flow rate was adjusted according to the maximum tolerated. In all patients, the maximum tolerated flow was achieved within the first 10 minutes of HFNC treatment.

HFNC failure was defined as the subsequent need for invasive MV. The participating ICUs agreed on a common set of intubation criteria to help the attending

physicians decide when to intubate. These criteria included a decreased level of consciousness (Glasgow coma score <12), cardiac arrest/arrhythmias and severe hemodynamic instability (norepinephrine >0.1 μg/kg/min), or persisting or worsening respiratory condition defined as at least two of the following criteria: failure to achieve correct oxygenation (Pa_{O_2} <60 mm Hg or Sp_{O_2} <90% despite HFNC flow ⩾30 L/min and FI_{O_2} of 1), respiratory acidosis (Pa_{CO_2} >50 mm Hg or Pv_{CO2} >55 mm Hg with pH <7.25), RR >30 breaths/min, or inability to clear secretions.

ROX Index Description

In the previous prospective exploratory study, the ROX index was calculated from the respiratory variables that were significantly different among groups (16), aiming to obtain an additive effect on the accuracy for discriminating between patients who succeeded and those who failed with HFNC. The ROX index was defined as the ratio of Sp_{O_2}/FI_{O_2} (%) to RR (breaths/min). In the numerator were placed the variables with a positive association with HFNC success, whereas in the denominator were placed those variables that had an inverse relation with HFNC success. In the present study, the ROX index was not used to decide on intubation, which was guided by criteria agreed on and defined previously.

Statistical Analysis

Quantitative variables were expressed as median (interquartile range), categorical variables were expressed as frequency (percentage). Continuous variables were compared using the Student's *t* test or Mann-Whitney *U* test, as appropriate. Differences in categorical variables were assessed with chi-square 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 curves (ROCs) were performed and the areas under the curves (AUROCs) were calculated. Differences between ROC curves were estimated using a nonparametric approach to the analysis of areas under correlated ROC curves, by using the theory on generalized U-statistics to generate an estimated covariance matrix (19). Because the effect of RR and FI_{O_2}, and ROX index in predicting HFNC success are the opposite, we have used the AUROC of the inverse of RR and FI_{O_2} for its comparison with ROX index AUROC. Because reported intubation rates in AHRF treated with HFNC range from 28% to 48% (3, 9, 10, 16), the sample size was estimated assuming an intubation rate of 35%. According to the previous reported value of the ROX index after 12 hours, we predicted AUROC value of 0.8 in the validation cohort with a noninferiority margin of 0.08. The noninferiority design included a power of 0.8 and a type I error of 0.05. These conditions required 189 patients.

We have used the previously defined cutoff point described for the ROX index of 4.88 (16). According to this value, Kaplan-Meier curves were used to determine the probability of MV for patients with higher and lower ROX index at different time points. These curves were compared using the log-rank test. To identify if the ROX index was associated with the need for MV, Cox proportional hazards modeling was chosen, while simultaneously adjusting for other covariates. Variables with *P* value less than 0.1 in the univariate analysis and other variables that could influence the value of the ROX index were considered as potential covariates. We have also adjusted by severity scores (Acute Physiology and Chronical Health Evaluation II and Sequential Organ Failure Assessment score). To prevent model overfitting, we introduced all potential confounding one at a time. Moreover, a general model for predicting the need for MV in the overall cohort (validation and training together) was constructed using those variables with a *P* value less than 0.1 in the univariate analysis and the variable ROX index greater than or equal to 4.88 at different time points. Further validation was also performed in the FLORALI cohort (3).

Table 1. Baseline Characteristics of the Validation Cohort (2016–2017) Comparing Success and Failure Patients

	Success (*n* = *123*)	Failure (*n* = *68*)	*P* Value
Sex, male, *n* (%)	76 (61.8)	42 (61.8)	0.997
Age, yr	64 (52–73)	60 (52–71)	0.412
Comorbidities, *n* (%)			
Immunosuppression	32 (26.0)	28 (41.2)	0.031
Chronic heart failure	26 (21.1)	14 (20.6)	0.929
Chronic liver disease	13 (10.6)	3 (4.4)	0.141
Chronic respiratory disease	45 (36.6)	24 (35.6)	0.859
Chronic renal failure	9 (7.3)	6 (8.8)	0.711
Type of pneumonia, *n* (%)			0.177
Bacterial			
Community acquired	78 (63.4)	34 (50.0)	
Health care related	31 (25.2)	25 (36.8)	
Viral pneumonitis	14 (11.4)	9 (13.2)	
Pneumonia severity index	112 (74–153)	121 (94–146)	0.445
APACHE II of 24-h ICU admission	16 (11–21)	18 (14–21)	0.140
SOFA score at ICU admission	5 (2–8)	4 (3–7)	0.198
NIV requirement, *n* (%)	6 (4.9)	4 (5.9)	0.746
Number of quadrants affected on chest X-ray	2.5 (2–4)	3 (2–4)	0.095

Definition of abbreviations: APACHE II = Acute Physiology and Chronical Health Evaluation; NIV = noninvasive ventilation; SOFA = Sequential Organ Failure Assessment.
Data are shown as median (interquartile range) unless otherwise indicated.

Table 2. Respiratory Variables during HFNC Treatment of the Validation Cohort (2016–2017) Comparing Success and Failure Patients

Variable	Time (*h*)	Success (*n* = *123*)	Failure (*n* = *68*)	*P* Value
$Sp_{O_2}/F_{I_{O_2}}$	Prior to HFNC	180 (113–223)	106 (94–190)	0.005
	2	155 (106–165)	109 (96–159)	0.003
	6	160 (127–192)	115 (98–167)	0.001
	12	165 (127–200)	113 (97–190)	0.001
	18	176 (140–203)	118 (98–193)	0.002
	24	194 (152–239)	120 (96–192)	<0.001
RR, breaths/min	Prior to HFNC	28 (26–32)	32 (25–34)	0.778
	2	25 (22–28)	28 (22–32)	0.023
	6	24 (20–27)	26 (22–30)	0.003
	12	23 (19–26)	26 (21–29)	<0.001
	18	22 (18–26)	25 (22–28)	0.001
	24	21 (18–25)	24 (20–30)	0.004
Pa_{CO_2}, mm Hg	Prior to HFNC	36 (31–42)	38 (30–45)	0.468
	2	38 (33–44)	38 (33–47)	0.317
	6	38 (33–46)	37 (32–45)	0.650
	12	38 (32–44)	36 (31–43)	0.940
	18	39 (33–45)	35 (28–43)	0.230
	24	38 (32–43)	34 (28–44)	0.415
Flow, L/min	Prior to HFNC	7 (4–12)	9 (5–15)	0.140
	2	50 (40–60)	50 (40–60)	0.256
	6	50 (40–60)	50 (40–60)	0.729
	12	50 (40–60)	40 (40–55)	0.185
	18	50 (40–60)	40 (40–53)	0.140
	24	50 (40–59)	45 (40–60)	0.495
ROX index	Prior to HFNC	5.81 (4.21–8.00)	4.06 (2.98–6.54)	0.169
	2	5.71 (4.62–7.28)	4.43 (3.57–6.16)	0.001
	6	6.55 (5.44–8.17)	4.86 (3.43–6.64)	<0.001
	12	7.53 (5.83–9.93)	4.78 (3.67–6.99)	<0.001
	18	8.60 (6.30–10.03)	5.10 (3.84–7.31)	<0.001
	24	8.68 (6.93–11.77)	5.05 (4.00–6.74)	<0.001
Sp_{O_2}, %	Prior to HFNC	92 (90–96)	93 (90–96)	0.381
	2	97 (95–99)	96 (94–98)	0.032
	6	97 (96–98)	96 (95–99)	0.015
	12	97 (95–99)	96 (94–97)	<0.001
	18	97 (96–99)	96 (94–98)	0.001
	24	97 (96–99)	96 (95–98)	0.013
$F_{I_{O_2}}$	Prior to HFNC	0.50 (0.40–0.81)	0.89 (0.50–0.98)	0.000
	2	0.60 (0.60–0.90)	0.80 (0.60–1.00)	0.002
	6	0.60 (0.50–0.75)	0.84 (0.60–1.00)	<0.001
	12	0.60 (0.50–0.75)	0.85 (0.50–1.00)	0.291
	18	0.53 (0.45–0.70)	0.80 (0.50–1.00)	0.001
	24	0.50 (0.40–0.63)	0.80 (0.50–1.00)	<0.001
Lactate, mmol/L	Prior to HFNC	—	—	—
	2	1.60 (1.00–2.30)	1.50 (1.00–2.35)	0.363
	6	1.30 (0.88–1.90)	1.40 (1.09–2.08)	0.495
	12	1.40 (1.00–2.00)	1.45 (1.10–2.08)	0.933
	18	1.40 (0.95–1.89)	1.44 (1.00–2.50)	0.644
	24	1.22 (0.90–1.90)	1.27 (1.03–2.48)	0.868

Definition of abbreviations: HFNC = high-flow nasal cannula; RR = respiratory rate; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.
Data are shown as median (interquartile range) unless otherwise indicated.

Finally, we investigated a cutoff of the ROX index with higher specificity for predicting the risk of HFNC failure. Differences in the values of the ROX index at different time points between patients who succeeded and those patients who fail on HFNC were also assessed and their role was confirmed using the Cox proportional hazards modeling and adjusting for the previous value of the ROX index. A two-sided *P* value of 0.05 or less was considered statistically significant. Statistical analyses were performed using the STATA 14 software (Stata Corp. Stata Statistical Software: Release 14. Statistical software; StataCorp LP).

Results

General Characteristics of the Population Included

A total of 191 and 157 patients were treated with HFNC in the validation and in the training cohort, respectively. Their baseline characteristics are reported in Table E1 in the online supplement. Results regarding the training cohort were reported elsewhere (16). Patients included in the validation cohort were older and presented a higher prevalence of chronic heart failure compared with those patients included in the training cohort. Moreover, in the validation cohort, the type of pneumonia was more frequently a healthcare-associated pneumonia and patients also presented a higher prevalence of shock (39 [20.4%] patients vs. 13 [8.4%] patients; $P = 0.002$) and a trend toward high Acute Physiology and Chronical Health Evaluation II score. Higher $Sp_{O_2}/F_{I_{O_2}}$ values were observed and higher flow rates were used in the validation cohort throughout the study period (*see* Table E2). Finally, whereas no differences in ICU mortality or length of stay were observed between the two cohorts, patients included in the validation cohort presented a higher hospital mortality (50 [27.3%] patients vs. 22 [14.2%] patients; $P = 0.003$).

Variables Associated to HFNC Success and ROX Index Validation

In the validation cohort, 68 (35.6%) patients required subsequent intubation and MV. The median duration of HFNC therapy in success and failure groups was 96 (48–144) hours and 24 (12–60) hours, respectively ($P < 0.001$). After 2, 6, and 12 hours, 190 (99.5%), 182 (95.2%), and 169 (88.4%) patients were still on HFNC, respectively. Within the first 2 hours of HFNC therapy only one (0.5%) patient needed to be intubated. Between 2 and 6 hours, six (3.1%) patients were intubated and between

Table 3. Diagnostic Accuracy of Different Respiratory Variables at Different Time Points of Need for MV in Patients Treated with HFNC in the Validation Cohort

Variable	Time	AUROC	95% CI	*P* Value
$Sp_{O_2}/F_{I_{O_2}}$	Prior to HFNC	0.641	0.550–0.731	0.002
	2 h	0.648	0.561–0.734	0.001
	6 h	0.672	0.580–0.764	<0.001
	12 h	0.695	0.598–0.791	<0.001
	18 h	0.685	0.575–0.796	0.001
	24 h	0.749	0.648–0.850	<0.001
RR, breaths/min	Prior to HFNC	0.460	0.367–0.553	0.383
	2 h	0.393	0.303–0.482	0.017
	6 h	0.381	0.293–0.470	0.010
	12 h	0.341	0.246–0.436	0.002
	18 h	0.323	0.227–0.419	0.001
	24 h	0.349	0.243–0.456	0.007
Pa_{CO_2}, mm Hg	Prior to HFNC	0.462	0.358–0.567	0.469
	2 h	0.481	0.388–0.575	0.682
	6 h	0.539	0.442–0.637	0.420
	12 h	0.535	0.434–0.635	0.499
	18 h	0.607	0.505–0.710	0.047
	24 h	0.559	0.445–0.673	0.295
Flow, L/min	Prior to HFNC	—	—	—
	2 h	0.543	0.456–0.631	0.326
	6 h	0.516	0.425–0.607	0.720
	12 h	0.569	0.474–0.664	0.162
	18 h	0.568	0.466–0.670	0.191
	24 h	0.534	0.424–0.643	0.530
ROX index	Prior to HFNC	0.659	0.566–0.751	0.001
	2 h	0.679	0.594–0.763	<0.001
	6 h	0.703	0.616–0.790	<0.001
	12 h	0.752	0.664–0.840	<0.001
	18 h	0.755	0.662–0.847	<0.001
	24 h	0.801	0.709–0.893	<0.001
Sp_{O_2}, %	Prior to HFNC	0.451	0.364–0.537	0.273
	2 h	0.582	0.496–0.668	0.063
	6 h	0.596	0.503–0.689	0.034
	12 h	0.693	0.608–0.778	<0.001
	18 h	0.675	0.575–0.775	0.001
	24 h	0.625	0.517–0.734	0.025
$F_{I_{O_2}}$	Prior to HFNC	0.644	0.558–0.729	0.002
	2 h	0.629	0.544–0.715	0.003
	6 h	0.669	0.579–0.760	<0.001
	12 h	0.672	0.574–0.770	0.001
	18 h	0.676	0.565–0.787	0.001
	24 h	0.747	0.645–0.849	<0.001
Lactate, mmol/L	Prior to HFNC	—	—	—
	2 h	0.506	0.413–0.600	0.894
	6 h	0.432	0.335–0.530	0.195
	12 h	0.505	0.401–0.608	0.931
	18 h	0.501	0.387–0.616	0.984
	24 h	0.483	0.373–0.593	0.768

Definition of abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; HFNC = high-flow nasal cannula; MV = mechanical ventilation; RR = respiratory rate; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

6 and 12 hours, 11 (5.7%) needed to be intubated. The cumulative risk of being free of MV in HFNC failure is represented in Figure E1. HFNC failure was associated with higher ICU and hospital mortality and length of stay (*see* Table E3). HFNC failure patients had a higher prevalence of immunosuppression (Table 1). HFNC success patients had higher $Sp_{O_2}/F_{I_{O_2}}$ and lower RR after HFNC and throughout the study period (Table 2). Likewise, higher ROX index values were observed in those patients who succeeded with HFNC. AUROC values of different variables are reported in Table 3. There was no difference in the diagnostic accuracy of the ROX index between the validation and training cohorts whatever the time point (*see* Table E4). In the validation cohort, AUROC values of ROX index for discriminating those patients who will succeed with HFNC were higher than those found with $Sp_{O_2}/F_{I_{O_2}}$ at 18 hours, RR at 6, 12, and 24 hours, and $F_{I_{O_2}}$ at 12 and 18 hours (*see* Table E5). We considered the same cutoff point for the ROX index than previously reported (16).

The values of sensitivity, specificity, positive and negative predictive value, and the positive and negative likelihood ratio for a ROX index greater than or equal to 4.88 are presented in Table 4. Kaplan-Meier plots showing the probability of MV according to the ROX value at different time points are shown in Figure 1. Patients with ROX index score greater than or equal to 4.88 after 2 hours of HFNC were less likely to need MV. These differences increased throughout the study period. To validate the association between the ROX index during HFNC and the risk of MV, a Cox proportional hazards model was performed. A ROX index greater than or equal to 4.88 was consistently associated with a lower risk of MV, even after adjusting for potential confounding variables (Table 5). Finally, Table E6 shows the cutoff values of the ROX index that have a sensitivity or specificity greater than or equal to 90% and those with the maximum value of positive and negative likelihood ratio for HFNC success.

Analysis of the Two Cohorts

First, to give a clearer statement regarding when the ROX index should be calculated to decide on intubation we determined in the whole sample (the training and validation cohort together) the excess of mortality in different time frames taking as reference the first 6 hours of HFNC therapy. Those patients intubated after 12 hours or more of HFNC had an increased risk of hospital death (Figure 2). Second, variables associated with risk of intubation and MV

Table 4. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Likelihood Positive Ratio, and Likelihood Negative Ratio of ROX Index ⩾4.88 at Different Time Points in the Validation and Training Cohorts

		Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR−
2 h	Validation	69.6	60.0	75.5	52.7	1.74	0.51
	Training	37.1	73.8	76.6	33.7	1.41	0.85
6 h	Validation	83.8	50.0	76.6	61.2	1.68	0.32
	Training	50.5	60.0	76.6	31.8	1.26	0.82
12 h	Validation	86.8	52.2	81.8	61.5	1.82	0.25
	Training	70.1	72.4	89.4	42.0	2.54	0.41
18 h	Validation	87.7	47.4	83.3	56.2	2.00	0.22
	Training	81.0	66.7	88.9	51.6	2.43	0.28
24 h	Validation	89.1	42.9	83.1	55.6	1.56	0.25
	Training	80.7	72.2	93.1	44.8	2.90	0.27

Definition of abbreviations: LR+ = likelihood positive ratio; LR− = likelihood negative ratio; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Sp = specificity.

were also analyzed in the whole sample. HFNC success was associated with a higher ROX index, regardless of the time point considered. In contrast, HFNC failure was associated with a greater number of quadrants affected in chest X-ray (3 [2–4] vs. 2 [2–4]; $P < 0.001$) and a higher prevalence of immunosuppressed patients (39.3% vs. 29.7%; $P = 0.049$). All variables with P less than 0.1 were included in a multivariate model using Cox proportional hazards modeling (number of quadrants involved in chest X-ray, immunosuppression, viral pneumonia and ROX index). Another model was constructed using ROX index measured at 2, 6, and 12 hours after HFNC onset. ROX index was the unique variable constantly associated with the risk of intubation, regardless of the time-point used (*see* Table E7).

Predicting HFNC Failure

Table E8 shows the cutoff value of the ROX index with a higher specificity and the maximum likelihood positive ratio for predicting HFNC failure at 2, 6, and 12 hours. A ROX smaller than 2.85, 3.47, and 3.85 at 2, 6, and 12 hours of HFNC initiation had specificities of 99.2%, 99.2%, and 98.4%, respectively. Kaplan-Meier plot showing the difference in probability of MV between patients with ROX index less than 3.85 and greater than or equal to 4.88 are shown in Figure E2. Patients who failed presented a smaller increase in ROX index values from 2 to 12 and 6 to 12 hours compared with those patients who succeeded (*see* Table E9). The differences in the ROX index were associated with the risk of HFNC failure after adjusting for the value of the ROX index at the beginning of the analyzed period (*see* Table E10). Similar and consistent results were observed in the training cohort (*see* Tables E8–E10).

Validation in the FLORALI Cohort

A second external validation was performed using the FLORALI cohort. No differences were observed in the diagnostic accuracy of the ROX index in the FLORALI cohort compared with both the validation and training cohorts at 2, 6, and 12 hours (*see* Table E11). The values of sensitivity, specificity, the positive and negative predictive values, and the positive and negative likelihood ratios for a ROX index greater than or equal to 4.88 to predict HFNC success and different cutoff values to predict HFNC failure are presented in Tables E12 and E13. Patients who failed presented a lower increase in the values of the ROX index from 1 to 12 hours (*see* Tables E14 and E15).

Discussion

Predicting outcome of noninvasive management of patients with AHRF to avoid delaying a needed intubation is a major and daily challenge for clinicians in the ICU. In the present study, we confirm that a ROX index greater than or equal to 4.88 measured at 2, 6, or 12 hours is a determinant of HFNC success, even after adjusting for potential confounding variables. Similar results are found when applying the ROX index to the FLORALI database. Additionally, we provide specific cutoff points of the ROX index with very high specificity allowing identification of patients who need to be intubated within the first 12 hours of treatment with HFNC. These results have the potential to change and improve practices in the monitoring of patients treated with HFNC.

Consistent data indicate that "late" intubation is associated with worse outcome in patients with acute respiratory failure (20, 21). The same has been found true in patients treated with HFNC (13). However, prediction of HFNC outcome is still challenging. Although many respiratory (oxygenation [5, 22, 23], RR, thoracoabdominal asynchrony [5]) and nonrespiratory (need for vasopressors [22–24], baseline Sequential Organ Failure Assessment score [25, 26], severity of disease [9]) criteria have been found to be associated with HFNC failure, none of them has been tested prospectively to predict HFNC outcome. More and more patients are being treated with HFNC including patients with acute respiratory distress syndrome (9, 10) and a noticeable proportion (30–40%) of them will require subsequent intubation. It is therefore crucial that they may be identified as early as possible by clinicians so as to anticipate intubation. We previously showed that the ROX index measured 12 hours after HFNC initiation was a better predictor of treatment success than Sp_{O_2}/FI_{O_2} or RR alone (16). Furthermore, patients with a ROX index greater than or equal to 4.88 after 12 hours of HFNC therapy were less likely to be intubated, even after adjusting for potential covariates.

To ensure robustness of the ROX index, three different analyses were performed. First, by examining the AUROC of the different variables, we found that ROX index's AUROC measured in the validation cohort was comparable with the one reported in the training cohort (16) and also in the FLORALI cohort (3). In addition, ROX index's AUROC were superior to the ones of other respiratory variables. Second, using a Cox proportional hazards modeling, we found that the ROX

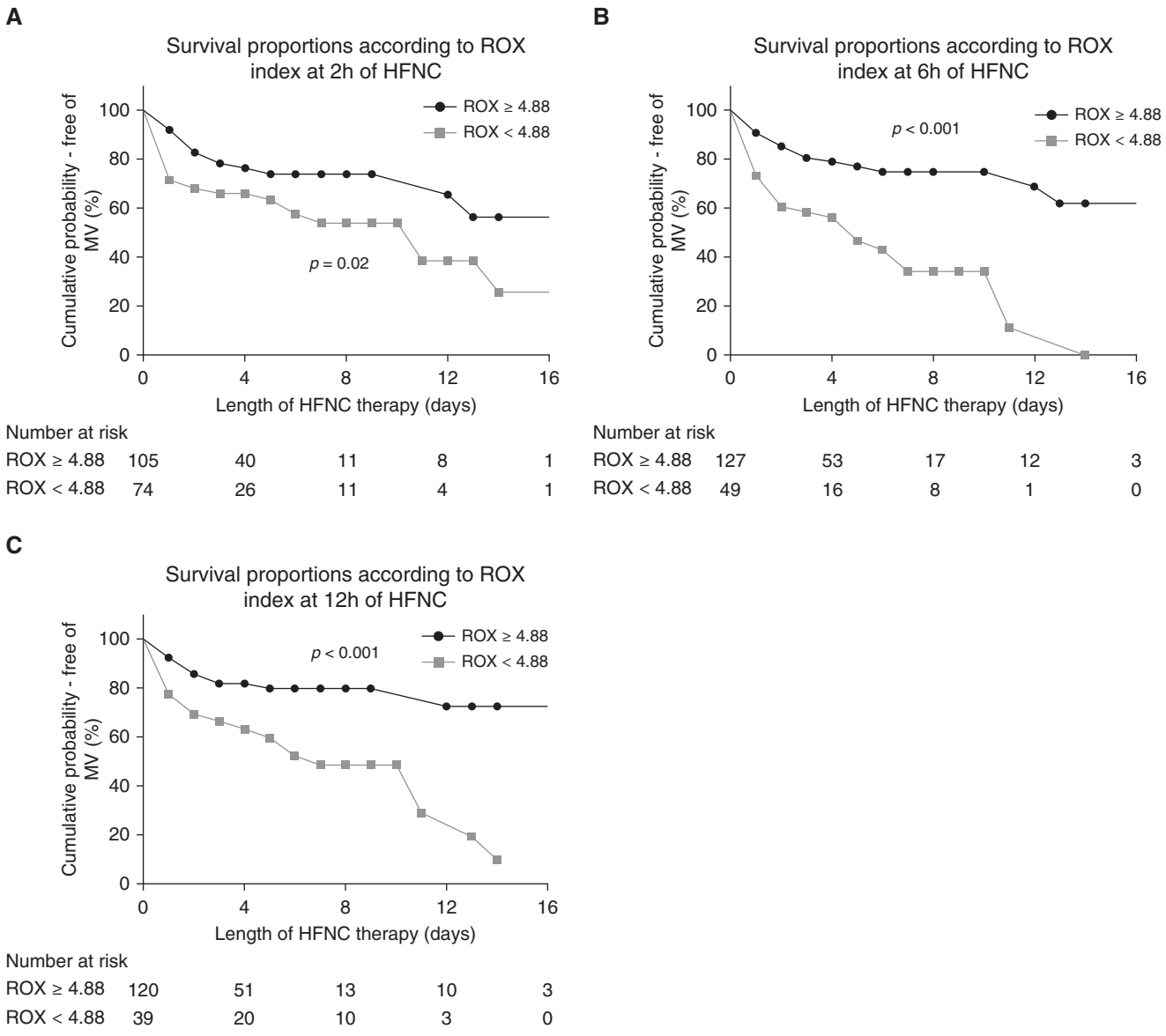

Figure 1. Kaplan-Meier plots showing the probability of mechanical ventilation according to the ROX group at (*A*) 2 hours, (*B*) 6 hours, and (*C*) 12 hours after high-flow nasal cannula onset. HFNC = high-flow nasal cannula; MV = mechanical ventilation.

index less than 4.88 was independently associated with a higher risk of intubation, even after adjusting for the potential confounders. Because predicting success is not the same as predicting failure, we were able to determine ROX index cutoff points with higher specificity and positive likelihood ratio for predicting HFNC failure. Finally, to take into account the dynamic dimension of decision-making, we analyzed the variations in the ROX index over time and observed a lesser increase (and in some instances a decrease) in the ROX index values between different time-points in those patients who failed compared with those who succeeded with HFNC. Interestingly, similar to what was observed with NIV (27), patients who failed on HFNC and were intubated after more than 12 hours of HFNC presented an increased risk of death.

How can these results be applied by the clinician? Data from studies on HFNC that reported the time of intubation shows that most intubations occur between the 12th and the 24th hour. We therefore suggest monitoring the ROX index over time with a special focus from the 12th hour onward: if the ROX is greater than or equal to 4.88, then the patient has a high chance of success, if it is less than 3.85, then the risk of failure is high, and intubating the patient should be discussed. No predictive index is perfect, and a gray zone obviously exists between 3.85 and 4.88 in which it is difficult to conclude. At 12 hours, 21 patients only (11% [21/191] of the entire population) were in this zone. Among them, seven were ultimately intubated. One could imagine that if a patient is in the gray zone at 12 hours, the ROX could be repeated 1 or 2 hours later: *1*) if the score has increased, the patient should be considered with a greater likelihood of success; *2*) if it has

Table 5. Cox Proportional Hazards Model (Cox Regression) to Analyze the Effect of ROX Index ⩾4.88 at Different Time Points of HFNC Therapy and Potential Covariates on the Risk for MV

	Hazard Ratio	95% CI	*P* Value
Unadjusted ROX ⩾ 4.88			
At 2 h after HFNC onset	0.434	0.264–0.715	0.001
At 6 h after HFNC onset	0.304	0.182–0.509	<0.001
At 12 h after HFNC onset	0.291	0.161–0.524	<0.001
Adjusted by immunosuppression			
At 2 h after HFNC onset	0.455	0.274–0.756	0.002
At 6 h after HFNC onset	0.322	0.190–0.546	<0.001
At 12 h after HFNC onset	0.311	0.170–0.569	<0.001
Adjusted by number of quadrants affected in chest X-ray			
At 2 h after HFNC onset	0.449	0.271–0.744	0.002
At 6 h after HFNC onset	0.308	0.184–0.516	<0.001
At 12 h after HFNC onset	0.326	0.178–0.597	<0.001
Adjusted by shock at HFNC onset			
At 2 h after HFNC onset	0.435	0.264–0.717	0.001
At 6 h after HFNC onset	0.300	0.179–0.501	<0.001
At 12 h after HFNC onset	0.303	0.168–0.548	<0.001
Adjusted by SOFA			
At 2 h after HFNC onset	0.444	0.269–0.733	0.001
At 6 h after HFNC onset	0.306	0.183–0.512	<0.001
At 12 h after HFNC onset	0.296	0.164–0.534	<0.001
Adjusted by APACHE II			
At 2 h after HFNC onset	0.442	0.268–0.729	0.001
At 6 h after HFNC onset	0.310	0.184–0.522	<0.001
At 12 h after HFNC onset	0.290	0.158–0.533	<0.001
Adjusted by flow rate			
At 2 h after HFNC onset	0.417	0.252–0.690	0.001
At 6 h after HFNC onset	0.282	0.169–0.472	<0.001
At 12 h after HFNC onset	0.289	0.158–0.528	<0.001
Adjusted by center			
At 2 h after HFNC onset	0.400	0.240–0.668	<0.001
At 6 h after HFNC onset	0.283	0.169–0.474	<0.001
At 12 h after HFNC onset	0.292	0.152–0.698	<0.001

Definition of abbreviations: APACHE II = Acute Physiology and Chronical Health Evaluation; CI = confidence interval; HFNC = high-flow nasal cannula; MV = mechanical ventilation; SOFA = Sequential Organ Failure Assessment.

decreased, then intubation has a greater likelihood to occur; and *3*) if the score is unchanged, then reassessment should be performed after 1 or 2 more hours. Such a strategy obviously requires a prospective evaluation.

The limitations of the study listed below deserve consideration. We deliberately included only patients with pneumonia-related AHRF because pneumonia is by far the leading cause of AHRF and the major indication for HFNC (3) (82% of the FLORALI patients had pneumonia). Our results may thus not be generalizable to other less frequent causes of AHRF. In some instances, $Sp_{O_2}/F_{I_{O_2}}$ was almost as good as ROX. However, adding the RR generally improved the diagnostic accuracy. It is universally accepted as a highly determinant vital sign that is easily measured at the bedside. Patients' dyspnea and discomfort under HFNC were not assessed, although they might be a potential indicator of HFNC failure. Whether they are superior or not to the ROX index requires further assessment. Because of the design of the study and construction of the models, some analyses were retrospective. Application of the ROX index to the FLORALI cohort yielded consistent results with those obtained with the training and validation cohorts, although in some instances weaker than expected. A potential explanation is that the FLORALI criteria for intubation required a 10-point higher RR than in the present study keeping in mind that RR has a strong impact on the ROX index. Finally, we cannot ascertain that the ROX index was not used to make any decision of intubation. However, even though all variables were collected prospectively, the ROX index calculation was performed during the statistical analysis.

In conclusion, our results indicate that the ROX index helps predict outcome of HFNC therapy of patients with AHRF caused by pneumonia. They also suggest that the dynamic of changes of its value may help discriminate those patients who will

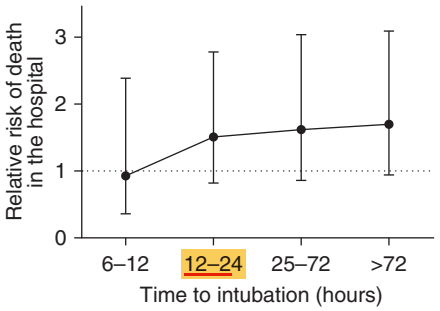

Figure 2. Relative risk of death according to the time of intubation in patients who failed on high-flow nasal cannula.

succeed with HFNC from those patients who will fail. Among the components of the index, Sp_{O_2}/FI_{O_2} has a greater weight than RR. The index can be easily and repeatedly measured at the bedside thereby contributing to the day-to-day clinical decision-making process of critically ill patients treated with HFNC. Further studies are needed to determine whether the use of the ROX index can avoid delaying a needed intubation and improve outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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