SPO2/FiO2 as a predictor of high-flow nasal cannula outcomes in children with acute hypoxemic respiratory failure: A retrospective study

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Research

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Abstract

Background: High-flow nasal cannula (HFNC) is a useful treatment modality for respiratory distress in children, as it provides effective oxygenation and reduces the work required for breathing. This study aimed to determine whether the oxygen saturation to fraction of inspired oxygen ratio (S/F) is a better predictor of HFNC outcomes than the arterial oxygen partial pressure to fraction of inspired oxygen ratio (P/F) in children with acute hypoxemic respiratory failure (AHRF).

Methods: This study included children treated with HFNC for AHRF between April 2013 and March 2019 at the Severance Children's Hospital in Korea. HFNC failure was defined as the need for mechanical ventilation due to worsening respiratory distress, whereas HFNC success was defined as the improvement of respiratory distress. We analyzed trends in S/F and P/F during HFNC oxygen therapy. A nomogram was constructed based on predictive factors identified via univariate analysis, and was externally validated using independent data.

Results: A total of 139 patients with arterial blood gas data were included in the S/F and P/F analysis. There was a good correlation between S/F and P/F (P<0.001). The S/F at HFNC initiation was <230 and showed a high prediction accuracy for HFNC failure (area under the receiver operating characteristic curve: 0.751). Univariate analyses identified S/F <230 at HFNC initiation, S/F <200 at 2 h (odds ratio, 12.83; 95% confidence interval, 5.06-35.84), and hemato-oncologic disease (odds ratio, 3.79; 95% confidence interval, 1.12-12.78) as significant predictive factors for HFNC failure. These factors were used to construct a nomogram, which was shown to be highly predictive of HFNC outcomes; the concordance index of the exploratory and validation groups were 0.765 and 0.831, respectively.

Conclusions: S/F may be used as a predictor of HFNC outcomes. Our nomogram with S/F for HFNC failure within 2 h may be used to prevent delayed intubation in children with AHRF.

Background

High-flow nasal cannula (HFNC) treatment has been described as a safe and useful technique to deliver heated and humidified oxygen to patients with acute hypoxemic respiratory failure (AHRF) [1]. Its reported beneficial effects include decreases in dyspnea and physiological dead space, as well as improved oxygenation. As such, it may be used as a next-step respiratory support after nasal prongs or an oxygen mask in patients with respiratory failure [2, 3]. HFNC administration in patients with AHRF has been associated with a reduced need for intubation and mechanical ventilation (MV) [2]. However, if a patients' respiratory symptoms, signs, or laboratory findings (including blood gas) do not improve after HFNC implementation, a more aggressive ventilation technique, such as invasive MV, may be considered. Predicting which patients may respond to HFNC and who may require MV can be challenging [3]. The decision to initiate MV is a critical one, as delayed intubation has proven to be a concern during HFNC treatment [3]. Therefore, predicting HFNC outcomes at an optimal time is crucial.

Current evidence indicates that improvements in gas exchange and respiratory rates (RRs) are predictors of successful HFNC outcomes [4, 5]. In contrast, clinical parameters that warrant a subsequent need for intubation include the following: additional organ failure, persistence of thoraco-abdominal asynchrony, and the lack of oxygenation improvement and significant decrease in RR [5, 6]. The ratio of arterial oxygen partial pressure and fraction of inspired oxygen (PaO_2/FiO_2; P/F) has been suggested as an outcome predictor for noninvasive ventilation (NIV) in patients with AHRF [7]. However, the determination of P/F requires arterial blood gas sampling, which is invasive and not readily available in clinical practice, especially for children [8]. In contrast, the procedure for determining the oxygen saturation (SpO_2)/FiO_2 (S/F) ratio is noninvasive and easily performed; S/F is a readily available parameter that may be used as a surrogate marker for P/F in children [8–10]. Furthermore, low S/F has been reported in cases of severe AHRF [11].

The prediction of HFNC outcomes may help clinicians make a timely and optimal decision to intubate children with AHRF. Given that P/F may predict HFNC outcomes, we sought to identify whether S/F could predict HFNC outcomes as well. We also aimed to construct a nomogram as a shortcut prediction tool for HFNC outcomes.

Methods

Subjects

A retrospective chart review of children treated with HFNC due to AHRF was conducted at the Severance Children's Hospital, a single tertiary center, between April 2013 and March 2019. All patients who received HFNC treatment for AHRF were included in the study. Exclusion criteria comprised age > 18 years, indication for endotracheal intubation within 1 h of HFNC initiation, post-extubation state, and congenital heart disease [12, 13]. Patients were divided into two groups: HFNC success and HFNC failure. HFNC failure was defined as the need for invasive MV due to progressive respiratory failure; HFNC success was defined as an improvement in respiratory distress with HFNC. A total of 419 children were treated using HFNC during the aforementioned period. Among these, 165 patients were excluded for the following reasons: 47 patients needed endotracheal intubation within 1 h of HFNC initiation; 52 patients were in the post-extubation state; 60 patients had congenital heart disease; and 6 patients were treated with NIV due to progressive respiratory failure. Among the remaining 254 children, 139 who had available arterial blood gas data during the HFNC treatment were assigned to the exploratory group, and 114 without arterial blood gas data were included in the validation group. This study was approved by the Institutional Review Board of the Severance Hospital, Seoul, Korea (Institutional Review Board 4-2020-0036).

Variable measurement and definition

Demographic data such as age, sex, weight, underlying condition, and etiology of respiratory failure were recorded. Physiologic clinical variables such as the SpO_2, FiO_2, RR, heart rate (HR), and flow rate of gas delivered (L/min) were also obtained at HFNC initiation. The P/F was obtained from the arterial blood gas analysis at the time of HFNC initiation.

To estimate oxygenation, we calculated the S/F as a noninvasive alternative to the P/F [9]. The SpO_2 and FiO_2 were recorded at 1, 2, 4, and 12 h after HFNC initiation, and the corresponding S/F values were calculated. HFNC initiation was defined as the point at which HFNC treatment was started.

We evaluated the S/F as either a continuous or categorical variable, based on whether the patients achieved the therapeutic goal of S/F > 200 [14]. The continuous S/F variable was categorized for the construction of the nomogram model.

Device description and management

HFNC was implemented using the Optiflow® (Fisher & Paykel Healthcare, Auckland, New Zealand) device, which comprises the following components: air mixing device, heated humidifier, heated gas humidification chamber (MR290), high-performance breathing circuit (900PT561), and unique wide bore nasal cannula. The HFNC settings were determined by each attending physician.

Statistical analyses

The patients' characteristics are summarized using numbers and percentages for categorical variables, and medians (interquartile ranges) for continuous variables. For intergroup comparisons, the Mann-Whitney U test was used for continuous variables, and the Chi-squared test or Fisher's exact test was used for categorical variables.

Receiver operating characteristic (ROC) curve analyses were performed to assess the S/F and P/F cutoffs for HFNC outcomes. The area under the ROC curve (AUC) was calculated as a measure of predictive capacity. The difference inAUC was determined using the Delong's method [15].

Univariate logistic regression analysis was used to identify independent predictive risk factors for HFNC outcomes. Factors with a P value < 0.05 in the univariate analyses were included in the prediction model. The effect of each potential risk factor was denoted by the odds ratio (OR) and its 95% confidence interval (CI).

A nomogram was constructed based on selected predictive factors identified using the multivariate logistic regression model of the exploratory group data. The goodness of fit for each nomogram was verified using the Hosmer–Lemshow test. The discrimination ability of the nomogram was analyzed using the AUC. The calibration curve was generated to assess the discriminative performance and predictive accuracy of the nomogram. The proposed prediction model was verified through external validation of the independent data. Statistical analyses were performed using Statistical Package for the Social Sciences version 25 and R (version 3.6.1, The R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value < 0.05 was considered statistically significant.

Results

General characteristics

A total of 139 children with AHRF were included in the exploratory cohort. Baseline characteristics of the study population are presented in Table 1. (Table 1 is not included with this version) Fifty-nine (42.4%) patients who required intubation with MV were categorized as the HFNC failure group. The median time of HFNC treatment was 14.1 h (interquartile range, 4.5–17.9), and 50 (83%) patients were intubated within 24 h. The leading cause for AHRF was pneumonia, which accounted for 67% of the total cases. Other etiologies for AHRF were bronchiolitis, bronchospasm, and acute respiratory distress syndrome. The number of children in the HFNC success group was significantly greater than that in the HFNC failure group, among those with bronchiolitis ($P = 0.041$); a marginally significant difference was observed among children with bronchospasm. The most frequent underlying diseases associated with AHRF were neuromuscular disease (61.1%) and respiratory disease (12.2%); 17 children did not have any underlying disease. Patients with AHRF and underlying hemato-oncologic diseases frequently required intubation with MV after HFNC treatment ($P = 0.021$).

The validation cohort comprised 114 patients. No significant differences were found between the exploratory and validation groups. The results in the validation group were consistent with the exploratory group, and S/F was significantly lower in the HFNC failure group ($P < 0.001$). The number of HFNC failure cases was significantly greater than that of HFNC success among children with hemato-oncologic disease in the validation group ($P = 0.039$) (Additional file 1, Supplementary Table 1).

Respiratory variables and serial S/F monitoring during HFNC

Comparisons of the respiratory variables at initiation and serial S/F monitoring between the HFNC success and failure groups during HFNC treatment are shown in Table 2.

Table 2
Respiratory variables and serial S/F monitoring between HFNC success and failure groups during HFNC

	HFNC success	HFNC failure	*P* value
	(n = 80)	(n = 59)	
Respiratory rate	35 (27.5, 42.5)	29 (24.7, 40.7)	0.424
Heart rate	152 (125.5, 163.0)	153.0 (137, 167.7)	0.077
HFNC setting at initiation			
FiO_2	0.4 (0.3, 0.5)	0.45 (0.38, 0.6)	0.001
Flow/weight	1.0 (0.8, 1.3)	1.0 (0.6, 1.4)	0.503
SpO_2 at initiation	97.0 (95.0, 99.0)	89.0 (86.2, 92.7)	< 0.001
P/F at initiation	263.6 (213.4, 340.0)	191.7 (143.5, 286.5)	0.004
S/F			
Initiation (n = 139)	242.5 (200.0, 320.0)	202.5 (153.3, 229.3)	< 0.001
1 h (n = 139)	243.7 (200.0, 306.4)	214.1 (161.8, 236.8)	< 0.001
2 h (n = 136)	247.5 (226.2, 323.3)	196.0 (153.9, 246.2)	< 0.001
4 h (n = 126)	250.0 (283.1, 326.7)	221.1 (168.5, 270.7)	< 0.001
12 h (n = 102)	250.0 (212.4, 330.0)	212.4 (146.4, 245.6)	< 0.001

Data expressed as n (%) or medians (interquartile ranges).

n, numbers; HFNC, high flow nasal cannula; FiO_2, fraction of inspired oxygen; SpO_2, pulse oximetry oxygen saturation; P/F, PaO_2/FiO_2; S/F, SpO_2/FiO_2

The SpO_2 at HFNC initiation was significantly lower in the HFNC failure group than in the HFNC success group ($P < 0.001$). Patients in the HFNC failure group were treated with higher FiO_2 at initiation compared with the patients in the HFNC success group ($P = 0.001$). Signs of respiratory distress such as RR and HR at HFNC initiation did not significantly differ between the two groups.

The P/F at initiation in the HFNC failure group was significantly lower than that in the HFNC success group ($P = 0.004$). We confirmed that S/F was positively correlated with P/F, which showed a linear relationship using the regression equation (S/F at initiation = 135.199 + 0.375 × P/F at initiation, $P < 0.001$, Additional file 2, Supplementary Fig. 1). Therefore, S/F was recorded as a respiratory oxygenation variable through serial monitoring. The serial S/F displayed significant differences between the groups during HFNC treatment ($P < 0.001$). The mean S/F profile plot over time is shown using a linear mixed model in Additional file 3, Supplementary Fig. 2. The S/F of patients in the HFNC success group improved

consistently during the initial 12 h after HFNC treatment. In the HFNC failure group, the S/F fluctuated within the first 4 h after HFNC initiation, with the lowest value being 197.72 (185.4–209.9) at 2 h.

The AUC of S/F at initiation for predicting HFNC failure was 0.759, and the optimal cutoff was 230 (Fig. 1). The S/F cutoff of < 230 showed 78.0% sensitivity and 68.7% specificity. The AUC for P/F at HFNC initiation was 0.643, and the cutoff of < 195 showed 54.2% sensitivity and 81.2% specificity for predicting HFNC failure. The prediction power of S/F was observed to be better than that of P/F (P = 0.005)

Univariate logistic regression analysis of predictor of HFNC

Predictive Potential predictors for HFNC failure were identified using univariate logistic regression analyses in the exploratory group. The following variables were included in the analysis: RR, HR, flow/weight of HFNC setting at initiation, underlying disease, and newly categorized variables using a S/F cutoff of < 230 at HFNC initiation and < 200 at 2 h (Table 3).

Table 3
Univariate analysis of predictive factor for HFNC failure

	Odds ratio	95% CI	*P* value
Respiratory rate	0.988	0.959–1.018	0.424
Heart rate	1.013	0.998–1.026	0.055
Flow/weight of HFNC setting	1.055	0.597–1.862	0.8541
Achievement of therapeutic goal of S/F			
S/F at initiation ≥ 230 and S/F at 2 h < 200	1 [Ref]		
S/F at initiation < 230 and S/F at 2 h ≥ 200	3.967	1.286–8.136	0.002
S/F at initiation < 230 and S/F at 2 h < 200	13.067	5.06–35.84	< 0.001
Underlying disease			
Neuromuscular disease	1.072	0.540–2.130	0.841
Pulmonology	0.515	0.171–1.551	0.384
Hemato-oncology	3.799	1.129–12.78	0.031
Data expressed as odds ratios with 95% confidence intervals.			
HFNC, high flow nasal cannula; S/F: SpO2/FiO2			
*Therapeutic goals: S/F ≥ 200 after initiation of HFNC			

These variables were identified based on the result of an analysis using various S/F cutoffs (Additional file 4, Supplementary Table 2). A combination of S/F < 230 at HFNC initiation and S/F < 200 at 2 h (OR 13.067; 95% CI 5.06–35.84, P < 0.001), and hemato-oncologic disease (OR 3.799; 95% CI 1.129–12.78, P =

0.031) were significantly associated with HFNC failure. Therefore, we included these two variables (combination of S/F < 230 at initiation and S/F < 200 at 2 h), and the presence of hemato-oncologic disease in the multiple logistic regression analysis for the construction of a nomogram.

Nomogram construction and validation with HFNC

Figure 2a shows a nomogram that was constructed according to two independent predictors from the multiple logistic regression analysis. The Hosmer–Lemshow test showed that the fit of the multiple logistic regression model was good *(P* >0.9999). The ROC curve (according to the predicted probability of the multiple logistic regression analysis) of the exploratory group is shown in Fig. 2b; the AUC was 0.765 (95% CI, 0.687–0.844). The calibration curve showed that the model was close to ideal (Fig. 2c). A higher score calculated in the nomogram was associated with a higher likelihood of HFNC failure. For example, a patient with a hemato-oncologic disease whose initial S/F was 190, and 210 at 2 h, would have a total score of 90; this would correspond to an HFNC failure risk of approximately 70%.

The accuracy of the nomogram was also demonstrated in the validation group: AUC = 0.831 (95% CI, 0.728–0.933) (Fig. 3a). The calibration curve indicated an optimal agreement between the predicted and actual probabilities in the validation group (Fig. 3b).

Discussion

Our study showed that S/F, a noninvasive continuous monitoring variable, might be a good predictor for HFNC outcomes in children with AHRF. We created a nomogram to serve as a shortcut prediction tool for HFNC failure using S/F as a variable at initiation and 2 h after HFNC implementation, as well as the presence of hemato-oncologic disease.

Multiple studies have shown that S/F has a good correlation with P/F in patients with respiratory failure [10, 16]. Our study showed similarly consistent results with a good correlation between S/F and P/F. Furthermore, we showed that S/F had a better predictive power for HFNC failure than P/F. The best predictive S/F cutoff at HFNC initiation was 230 in our study; this was higher than that reported in a previous study in which a S/F cutoff of < 195 during the first hour of treatment was associated with HFNC failure [17]. While the aforementioned study included patients with cardiac comorbidities, we excluded children with congenital heart diseases because they have distinct S/F levels. We acknowledge that our inclusion criteria might have led to different S/F cutoff levels for the prediction of HFNC failure. Fine-tuning of the S/F cutoff is essential to achieve an excellent prediction power for HFNC failure. Accordingly, we used a previously reported therapeutic goal for S/F and combined it with our initial S/F cutoff to create a categorical variable [14]. Finally, a S/F cutoff of < 230 at initiation and < 200 at 2 h was observed to have a remarkable prediction power (OR, 13.067; 95% CI 5.06–35.84).

An emerging issue for HFNC implementation in patients with AHRF is the concern of delayed intubation, which might worsen the clinical deterioration [18, 19]. Therefore, timely and appropriate identification of HFNC failure is crucial. Several indices, such as P/F and S/F, have been reported to be predictors for

HFNC outcomes [14, 20]. The RR oxygenation index (the ratio of SpO_2/FiO_2 to RR) has recently been proposed to be a better predictor for HFNC failure than S/F alone in adults [3, 21]. However, the RR oxygenation index is difficult to apply in children with AHRF due to the variability of RR with age in children. Our categorical S/F variable may help clinicians decide whether endotracheal intubation should be performed within 2 h, which, in turn, would prevent delayed intubation.

Our study showed that the presence of an underlying hemato-oncologic disease was independently associated with HFNC failure, suggesting the deleterious effect of such a disease on HFNC outcomes. Our findings support those of a previous study which reported that HFNC neither improved discomfort nor decreased the need for intubation in patients with hemato-oncologic diseases [22]. In our study, 70% of patients with hemato-oncologic diseases in the HFNC failure group had a severe AHRF with a P/F of 150 mm Hg at HFNC initiation, and pneumonia was the cause of AHRF in all patients with hemato-oncologic diseases. This result parallels that of a previous study, which showed that the etiology of AHRF (pneumonia, OR 11.2) was a significant risk factor for HFNC failure [23]. HFNC failure in children with hemato-oncologic diseases might lead to various clinical conditions, complications, and problems unrelated to AHRF [24]. Further, the conditions associated with the hemato-oncologic diseases might not be influenced by the mode of oxygen delivery [25]. Moreover, supporting evidence has shown that the time needed to improve oxygenation during AHRF might be longer in patients with hemato-oncologic diseases than in other patients [26]. These findings may explain why the presence of underlying hemato-oncologic disease was identified as an independent parameter for HFNC failure in our study. As such, HFNC in patients with hemato-oncologic diseases and AHRF should be monitored with more caution.

Our study is the first to build a nomogram that predicts HFNC failure in children with AHRF. With the help of our nomogram, which was constructed using a combination of S/F and hemato-oncologic disease as predictors, clinicians may estimate the individual probability of an HFNC outcome in a patient without the need for an invasive examination. This, in turn, may help clinicians make a timely decision for intubation. Furthermore, we included both internal and external validation procedures, which demonstrated strong discrimination and calibration. With the ability to estimate individual risk in an easy to use and straight forward manner, we believe that our nomogram has an advantage over simple predictors.

Our results should be interpreted with caution, as six patients who required escalation to NIV were not assessed. NIV was actively implemented during the middle of the study period; consequently, patients receiving NIV were excluded to maintain the homogeneity of the study. We also acknowledge the inclusion of measurements in the analysis that were performed with > 97% SpO_2, where the oxyhemoglobin dissociation curves might have been unchanged [16]. However, children with AHRF who receive appropriate oxygen therapy have been shown to have an SpO_2 > 97% [27]. While additional real-world clinical evidence in children with AHRF is necessary, it was reasonable to include patients with > 97% SpO_2 in the present study to reflect current practice. A good correlation between S/F and P/F using data with S/F > 97% has also been demonstrated, which is consistent with our results [28].

Conclusions

In conclusion, S/F may be an easy-to-use predictor of HFNC outcomes in children with AHRF. We constructed a nomogram using S/F for HFNC failure within 2 h, which may prevent delayed intubation in children with AHRF.

List Of Abbreviations

AHRF: acute hypoxemic respiratory failure

AUC: area under the curve

CI: confidence interval

HFNC: high-flow nasal cannula

HR: heart rate

MV: mechanical ventilation

NIV: noninvasive ventilation

OR: odds ratio

P/F: arterial oxygen partial pressure to fraction of inspired oxygen ratio (PaO_2/FiO_2)

ROC: receiver operating characteristic

RR: respiratory rate

S/F: Oxygen saturation to fraction of inspired oxygen ratio (SpO_2)/FiO_2

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Severance Hospital (Seoul, Korea, Institutional Review Board 4-2020-0036).The need to obtain informed consent was waived due to the retrospective nature of the study.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during 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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Authors' contributions: GE Kim, SY Kim, MJ Kim, KW Kim and MH Sohn designed the study, implemented the project and manuscript, and managed the submission. MJ Lee performed the statistical analyses. JH Jung and MR Park collected the data. All authors revised the manuscript for important intellectual content and gave final approval of the version to be published.

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Figures

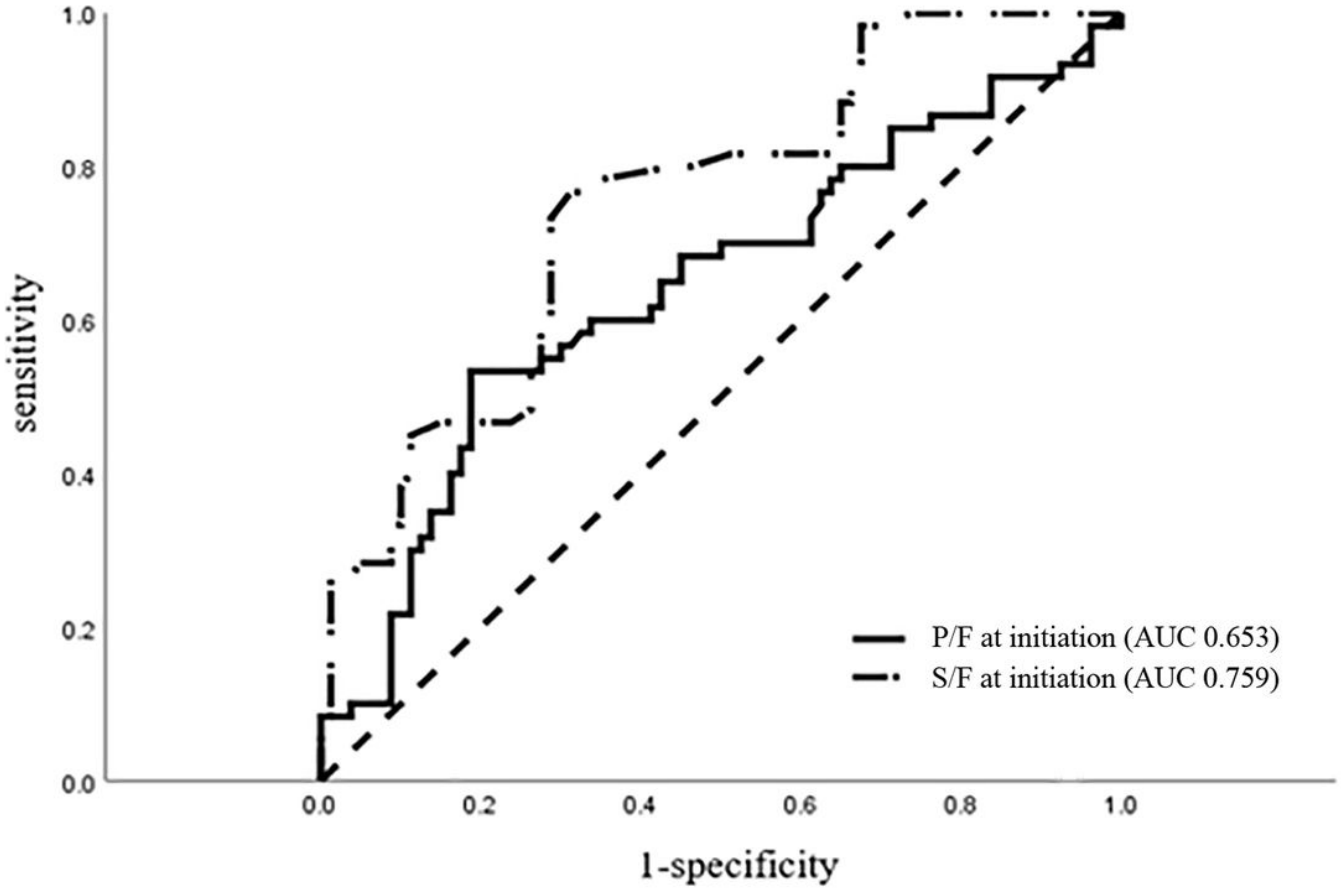

Figure 1

Comparison of P/F and S/F receiver operating characteristic curves for predicting HFNC failure, AUC was 0.653 for P/F at initiation and 0.759 for S/F at initiation. The difference between the AUCs was statistically significant (P=0.005 by Delong's method). P/F, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; S/F, ratio of oxygen saturation to fraction of inspired oxygen; AUC, area under the curve; HFNC, high-flow nasal cannula

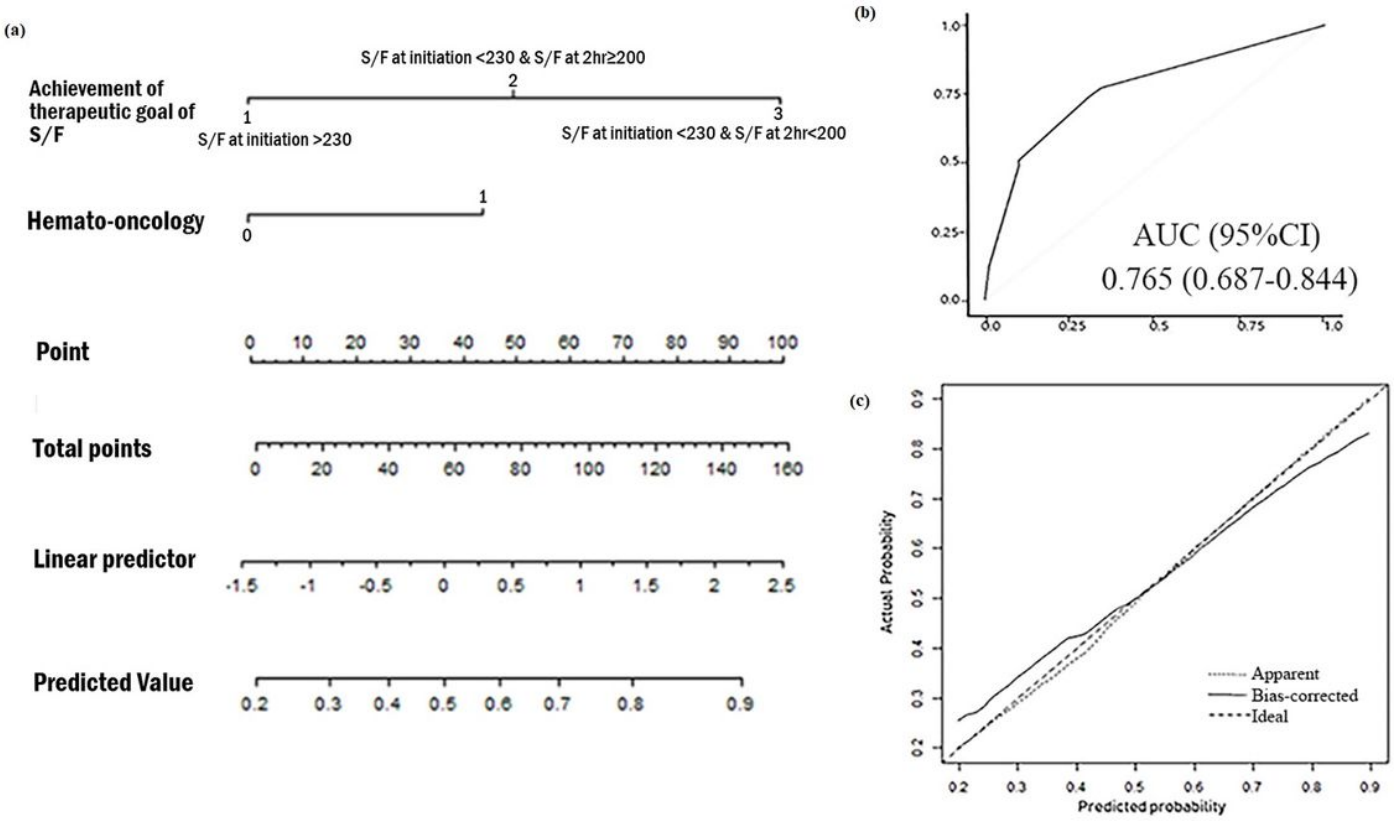

Figure 2

Prediction of HFNC outcomes in the training cohort with the constructed nomogram. (a) The nomogram according to clinical indices for predicting HFNC outcomes. The nomogram is used by adding up points identified on the points scale for each variable. The points of the three predictors are added to calculate the total points. The straight edge is aligned to the “total points,” and the predicted value is visible on the last line. (b) The ROC curve of the nomogram for predicting HFNC failure in the training cohort. The AUC indicates the ability of the nomogram to predict HFNC failure. (c) Calibration curve of the nomogram in the training cohort. The x-axis is the predicted probability from the nomogram, and the y-axis is the actual probability. The dashed line represents the performance of the ideal nomogram (predicted outcome perfectly corresponds with actual outcome). The dotted line represents the apparent accuracy of our nomogram without correction. The solid line represents the bootstrap corrected performance of our nomogram. AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating characteristic; HFNC, high-flow nasal cannula; S/F, ratio of oxygen saturation to fraction of inspired oxygen

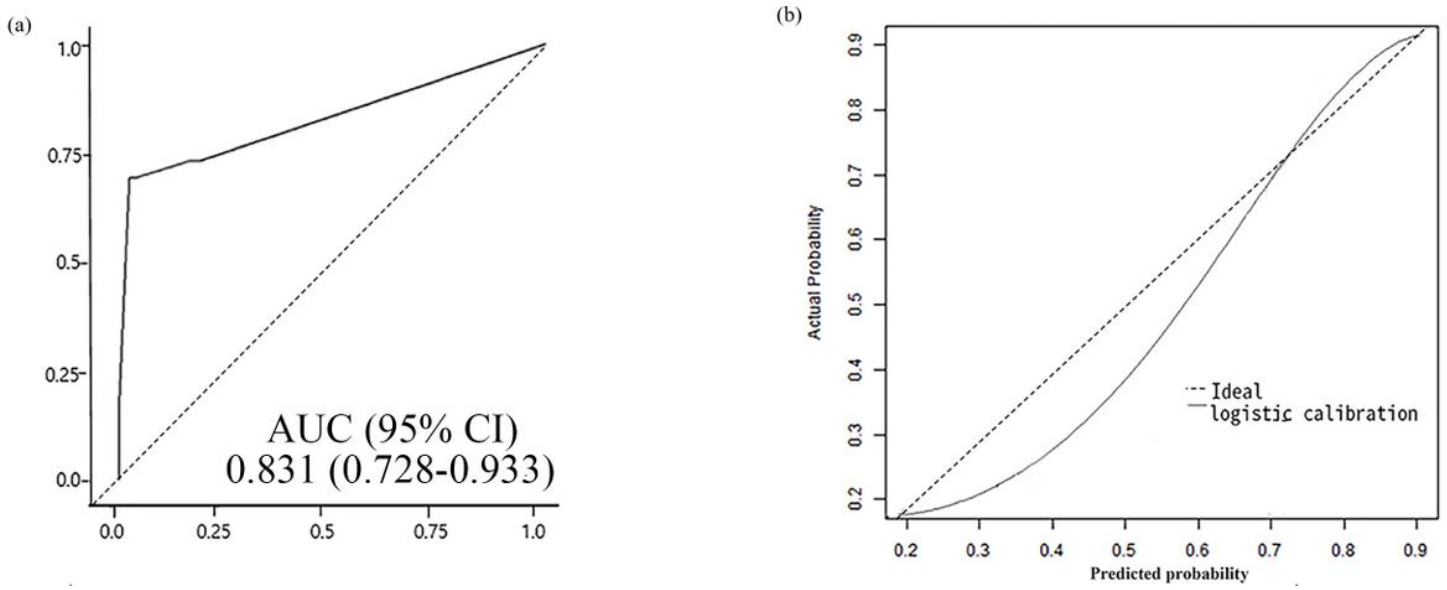

Figure 3

Validation of nomogram for predicting HFNC outcomes in patients with AHRF. (a) The ROC curve of the nomogram with 114 patients in the validation cohort. (b) Calibration plot of the nomogram in the validation cohort. The black line indicates logistic calibration of the validation cohort. The x-axis is the predicted probability from the nomogram, and the y-axis is the actual probability. The dashed line represents the performance of an ideal nomogram (predicted outcome perfectly corresponds with actual outcome). CI, confidence interval; ROC, receiver operating characteristic; HFNC, high-flow nasal cannula; AHRF, acute hypoxemic respiratory failure oxygen saturation to fraction of inspired oxygen; HFNC, high-flow nasal cannula

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