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To cite this article: A. Protti, R. Tonelli, F. Dalla Corte, D.L. Grieco, E. Spinelli, S. Spadaro, D. Piovani, L.S. Menga, G. Schifino, M.L. Vega Pittao, M. Umbrello, G. Cammarota, C.A. Volta, S. Bonovas, M. Cecconi, T. Mauri & E. Clini (2025) Development of clinical tools to estimate the breathing effort during high-flow oxygen therapy: A multicenter cohort study, *Pulmonology*, 31:1, 2416837, DOI: [10.1016/j.pulmoe.2024.04.008](https://doi.org/10.1016/j.pulmoe.2024.04.008)

To link to this article: <https://doi.org/10.1016/j.pulmoe.2024.04.008>



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Published online: 25 Oct 2024.



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ORIGINAL ARTICLE

Development of clinical tools to estimate the breathing effort during high-flow oxygen therapy: A multicenter cohort study

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Received 5 March 2024; accepted 22 April 2024

Available online xxx

Abbreviations: AUROC, area under the receiver operating characteristics curve; AVEN, Area Vasta Emilia Nord; BEa, arterial base excess concentration; COVID-19, coronavirus disease 2019; Δ Pes, maximal inspiratory deflection of the esophageal pressure; FiO₂, inspiratory fraction of oxygen; HFNC, high-flow nasal cannula; ICU, intensive care unit; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; pHa, arterial pH; SaO₂, arterial oxygen saturation; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.

Prior presentations: Some results of this work have been presented at the 33rd SMART Meeting Anesthesia, Resuscitation, and Intensive Care held on May 4th-6th, 2023, in Milan, Italy, and at the 1st Jordi Mancebo PLUG Physiology Symposium held on September 28th-30th, 2023, in Barcelona, Spain.

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<https://doi.org/10.1016/j.pulmoe.2024.04.008>

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Please cite this article in press as: A. Protti, R. Tonelli, F. Dalla Corte et al., Development of clinical tools to estimate the breathing effort during high-flow oxygen therapy: A multicenter cohort study, Pulmonology (2024), <https://doi.org/10.1016/j.pulmoe.2024.04.008>

KEYWORDS

Esophageal pressure;
Breathing effort;
High-flow oxygen therapy;
Acute respiratory failure;
Prediction model;
BREF

Abstract

Introduction and objectives: Quantifying breathing effort in non-intubated patients is important but difficult. We aimed to develop two models to estimate it in patients treated with high-flow oxygen therapy.

Patients and Methods: We analyzed the data of 260 patients from previous studies who received high-flow oxygen therapy. Their breathing effort was measured as the maximal deflection of esophageal pressure (ΔP_{es}). We developed a multivariable linear regression model to estimate ΔP_{es} (in cmH_2O) and a multivariable logistic regression model to predict the risk of ΔP_{es} being $>10 \text{ cmH}_2\text{O}$. Candidate predictors included age, sex, diagnosis of the coronavirus disease 2019 (COVID-19), respiratory rate, heart rate, mean arterial pressure, the results of arterial blood gas analysis, including base excess concentration (BEa) and the ratio of arterial tension to the inspiratory fraction of oxygen ($\text{PaO}_2:\text{FiO}_2$), and the product term between COVID-19 and $\text{PaO}_2:\text{FiO}_2$.

Results: We found that ΔP_{es} can be estimated from the presence or absence of COVID-19, BEa, respiratory rate, $\text{PaO}_2:\text{FiO}_2$, and the product term between COVID-19 and $\text{PaO}_2:\text{FiO}_2$. The adjusted R^2 was 0.39. The risk of ΔP_{es} being $>10 \text{ cmH}_2\text{O}$ can be predicted from BEa, respiratory rate, and $\text{PaO}_2:\text{FiO}_2$. The area under the receiver operating characteristic curve was 0.79 (0.73–0.85). We called these two models BREF, where BREF stands for BREathing EFFort and the three common predictors: BEa (B), respiratory rate (RE), and $\text{PaO}_2:\text{FiO}_2$ (F).

Conclusions: We developed two models to estimate the breathing effort of patients on high-flow oxygen therapy. Our initial findings are promising and suggest that these models merit further evaluation.

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Introduction

Strong breathing effort made by critically ill patients may cause harm in various ways.^{1,2} It can fatigue the respiratory muscles and increase whole-body oxygen consumption and carbon dioxide production,³ which may be relevant in patients with cardiopulmonary dysfunction. It can cause pulmonary edema, for example, in patients with severe chronic obstructive pulmonary disease undergoing weaning from mechanical ventilation.⁴ It might also directly injure the diaphragm and the lungs, but this concept has yet to be validated in humans.^{5,6} All these reasons suggest that strong breathing effort should be recognized and treated.^{1,2,7,8} Based on small physiological studies, different interventions may be considered, from titrating the sedation and the ventilatory support to instituting controlled mechanical ventilation with full neuromuscular blockade.⁹⁻¹³ Indeed, the primary goal of positive pressure ventilation is to relieve excessive work of breathing.¹⁴

During spontaneous breathing, inspiratory muscle contractions produce simultaneous deflections of the esophageal pressure (ΔP_{es}), which reflect the magnitude of the effort.¹⁵ In healthy subjects, ΔP_{es} is only a few cmH_2O during quiet breathing but $>10-15 \text{ cmH}_2\text{O}$ during vigorous exercise or carbon dioxide inhalation.¹⁶⁻¹⁹ In critically ill patients, the upper limit for a “safe” ΔP_{es} is unknown. Nonetheless, according to experts’ opinions (summarized in Table A.1 in the supplemental digital content),^{8,10,20-29} breathing effort with a $\Delta P_{es} >10-15 \text{ cmH}_2\text{O}$ is probably too strong to be tolerated for a long time.

However, esophageal manometry is not widely available.³⁰ Estimating breathing effort without it is complex, especially in non-intubated patients, when tidal volume and ventilator waveforms cannot help.³¹⁻³³ Doctors mostly rely

on their gestalt or overall impression,¹⁴ which is subjective and prone to inaccuracies. For instance, in a previous study from our group, the efforts of non-intubated critically ill patients were often misclassified:²² many of those with a $\Delta P_{es} >10-15 \text{ cmH}_2\text{O}$ were considered “normal”, while some of those with a $\Delta P_{es} \leq 10 \text{ cmH}_2\text{O}$ were considered “strong” despite their lower ΔP_{es} . Another study reported only fair to moderate agreement among doctors in deciding whether their patients passed a spontaneous breathing trial and could thus be extubated.³⁴

This study had two objectives. First, to create a model that could estimate ΔP_{es} (i.e., the effort to breathe) in patients who are not intubated and receiving high-flow oxygen therapy. Second, to simplify this model into another one that could predict the likelihood of ΔP_{es} being $>10 \text{ cmH}_2\text{O}$ (i.e., strong breathing effort).

Material and methods

In this multicenter cohort study, we combined the data of 273 adult patients from seven prospective studies conducted in our mixed or respiratory Intensive Care Units (ICUs) and described in Tables A.2 and A.3 in the supplemental digital content. One hundred and eight patients were from six completed studies,³⁵⁻⁴⁰ and 165 from an ongoing study (NCT03826797). Most of these studies enrolled patients with acute hypoxemic respiratory failure and without a history of chronic lung disease, acute cardiogenic pulmonary edema, and hemodynamic instability. All the completed studies have been approved by the appropriate Institutional Review Committees.³⁵⁻⁴⁰ The ongoing study was approved by the Area Vasta Emilia Nord (AVEN) Ethics Committee in Modena, Italy, in December 2016 under protocol number 266/2016.

The present analysis, which includes patients enrolled until the end of 2022, was approved by the same AVEN Ethics Committee in May 2023. Written informed consent was obtained from all the patients.

In all studies, Δ Pes was the average of three or more consecutive readings during high-flow oxygen therapy through nasal cannula (HFNC). In one study,³⁶ data were recorded from the same patients more than once, on the same occasion, but with different gas flows. All repeated measures were averaged so that each patient contributed one data set to the analysis.

We conducted two analyses. In the first analysis, we used multivariable linear regression to develop a model for Δ Pes. In the second analysis, we used multivariable logistic regression to develop a model for the risk of Δ Pes being >10 cmH₂O. We validated this model internally and simplified it into a score.

We prepared our manuscript following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.⁴¹

Model for Δ Pes in cmH₂O

The outcome to be predicted was Δ Pes (in cmH₂O). The candidate predictors were all measured within a few minutes of Δ Pes by the same investigators. They included age, sex, diagnosis of the coronavirus disease 2019 (COVID-19), heart rate, mean arterial pressure, respiratory rate, arterial pH (pHa), arterial carbon dioxide tension (PaCO₂), arterial oxygen tension (PaO₂), arterial bicarbonate concentration (HCO₃⁻a), arterial base excess concentration (BEa), arterial oxygen saturation (SaO₂), and arterial tension to the inspiratory fraction of oxygen ratio (PaO₂:FiO₂). The product term or interaction between COVID-19 and PaO₂:FiO₂ was also considered based on scientific reasoning.⁴² Unfortunately, other potentially relevant predictors, such as the recruitment of accessory muscles or the severity of dyspnea, were unavailable in the dataset. Only 260 patients with complete data were considered for further analysis. The proportion of patients with missing data (5 %) was deemed negligible and may not have yielded significant biases.

Statistical analysis methods

Data are reported as median (Q1-Q3) and count (percentage).

Firstly, we studied the association between each candidate predictor and outcome separately with univariable linear regression. We used fractional polynomial regression analysis to explore potentially meaningful non-linear associations. We selected the most appropriate second-degree function by minimizing deviance in polynomial regression. However, we observed only a slight improvement in the model fit. To maintain simplicity and avoid overfitting, we opted to develop a model based on linear associations between the candidate predictors and the outcome. Afterward, we built a multivariable linear regression model. In cases of high correlation among candidate predictors (i.e., Spearman's $\rho > |0.80|$), we excluded the variable that was least important based on mechanistic reasoning. Predictors were selected using a backward stepwise elimination strategy, with a $p < 0.05$ at the Wald test as the stopping

rule. Based on the residual analysis, the linearity and normality assumptions were met, but the equal variance assumption was not. Therefore, we computed robust standard errors for the regression coefficients. The fit of the model was evaluated both in terms of calibration and overall performance. Calibration was assessed by plotting the observed Δ Pes against the predicted Δ Pes. In a well-fitting model, the predictions cluster around the 45° diagonal, or identity line, and the slope of the plot is close to 1.^{41,43} Overall performance was evaluated with the adjusted R², which reflects the amount of outcome variability explained by the model adjusted for the number of predictors included.^{41,43}

Model for Δ Pes >10 cmH₂O

We built a multivariable logistic regression model using the same candidate predictors and variable selection technique mentioned previously. The dichotomous outcome to be predicted was strong breathing efforts, defined as those with a Δ Pes >10 cmH₂O as in our previous work.²² The apparent predictive performance of the model was assessed in terms of calibration, discrimination, and overall performance.^{41,43} Calibration was evaluated by plotting the observed proportion of patients with strong breathing efforts against the predicted risk. In a perfectly calibrated model, this plot has an intercept of 0 and a slope of 1. Discrimination was assessed with the area under the receiver operating characteristics curve (AUROC). This area can range from 0 to 1, where 0.5 indicates random guessing, and 1 indicates perfect discrimination. Overall performance was assessed with the scaled Brier score, computed as $1 - \text{Brier score} / \text{Brier score max}$. It ranges from 0 % to 100 %, with higher values indicating a better-performing model.^{41,43}

Internal model validation

When testing performance, using the same dataset used to develop a model often leads to overly optimistic results. To obtain unbiased estimates, we used a bootstrap resampling technique. Firstly, we repeated the entire modeling process, including variable selection, on 200 bootstrap samples drawn with replacement from the original dataset. Secondly, we computed the optimism of each bootstrap model by comparing its performance in the same bootstrap sample or the original dataset. Finally, we subtracted the average optimism of the 200 bootstrap samples from the initial apparent performance of the model under validation to obtain its optimism-corrected performance.^{41,43}

Model presentation

We created a score by dividing each regression coefficient by the smallest one and produced a table to transform each possible total point score into an outcome probability.^{41,43}

All statistical analyses were run with Stata/SE 17.0 (StataCorp LLC; College Station, TX). A two-tailed p -value <0.05 was considered statistically significant.

Other details on methods are presented in the supplementary material.

Table 1 Main characteristics of the study population.

Variable	Study population
Subjects, n	260
Variables recorded at ICU admission	
Age, years	67 (56–75)
Male/Female, n	174/86
With pneumonia, n (%)	225 (87)
Other than COVID-19	143 (55)
COVID-19	82 (32)
Variables recorded on the day of the study	
Time from ICU admission to study, days	0 (0–1)
HFNC settings	
FiO ₂ , %	50 (45–65)
Gas flow, L/min	60 (50–60)
ΔPes, cmH ₂ O	12 (8–18)
Respiratory rate, bpm	26 (22–30)
Heart rate, bpm	91 (79–103)
Mean arterial pressure, mmHg	83 (73–93)
pHa	7.46 (7.44–7.48)
PaCO ₂ , mmHg	34 (31–36)
PaO ₂ , mmHg	69 (61–79)
HCO ₃ ⁻ a, mmol/L	23 (22–24)
BEa, mmol/L	-1 (-2–1)
SaO ₂ , %	94 (93–96)
PaO ₂ :FiO ₂ , mmHg	135 (100–184)
Variable recorded at ICU discharge	
ICU mortality, n (%)	54 (21)

Continuous variables are presented as medians (Q1-Q3). Categorical variables are reported as absolute numbers and percentages. BEa: arterial base excess concentration. COVID-19: novel coronavirus disease 2019. ΔPes: maximal inspiratory deflection of the esophageal pressure. FiO₂: inspiratory fraction of oxygen. HCO₃⁻a: arterial bicarbonate concentration. HFNC: high-flow nasal cannula (oxygen therapy). ICU: Intensive Care Unit. PaCO₂: arterial carbon dioxide tension. PaO₂: arterial oxygen tension. PaO₂:FiO₂: arterial tension to the inspiratory fraction of oxygen ratio. pHa: arterial pH. SaO₂: arterial oxygen saturation.

Results

260 patients were included in the study (Table 1). Most of them had a PaO₂:FiO₂ ≤ 300 mmHg (245 [94 %]) and pneumonia (225 [87 %]). On average, ΔPes was 12 (8–18) cmH₂O. It was ≤ 10 (7 [6–9]) cmH₂O in 107 (41 %) and > 10 (16 [13–25]) cmH₂O in 153 (59 %).

Model for ΔPes in cmH₂O

In univariable linear regression analysis, ΔPes decreased with a diagnosis of COVID-19 but increased with a higher respiratory rate, higher heart rate, and lower PaCO₂, PaO₂, HCO₃⁻a, BEa, SaO₂, and PaO₂:FiO₂. It was not strongly associated with age, sex, mean arterial pressure, and pHa. The product term between COVID-19 and PaO₂:FiO₂ was significant (Table 2).

In multivariable model development, SaO₂ and HCO₃⁻a were excluded because of collinearity issues with PaO₂ and BEa. Age, sex, heart rate, mean arterial pressure, pHa, PaCO₂, and PaO₂ were eliminated by backward selection. A diagnosis of COVID-19, BEa (mmol/L), respiratory rate (bpm), and PaO₂:FiO₂ (mmHg), and the product term between COVID-19 and PaO₂:FiO₂ remained in the model (Table 2). We found that in patients without COVID-19, ΔPes (in cmH₂O) can be estimated as $14.25 - 0.52 \times \text{BEa} + 0.36 \times \text{respiratory rate} - 0.05 \times \text{PaO}_2:\text{FiO}_2$. In those with COVID-19, ΔPes (in cmH₂O) can be estimated as $3.52 - 0.52 \times \text{BEa} + 0.36 \times \text{respiratory rate} - 0.01 \times \text{PaO}_2:\text{FiO}_2$. The calibration slope was 1, and the adjusted R² was 0.39 (Fig. 1 and Fig. A.1).

Model for ΔPes > 10 cmH₂O

On univariable logistic regression analysis, variables associated with the risk of strong breathing efforts were the same

Table 2 Linear regression analysis to predict ΔPes.

Variable	Univariable analysis			Multivariable analysis		
	β	95%-CI	p-value	β	95%-CI	p-value
Age, years	0.067	-0.016 to 0.151	0.114			
Sex, ref.: male	0.881	-1.458 to 3.219	0.459			
With COVID-19, ref.: no	-2.731	-5.098 to -0.364	0.024	-10.734	-16.442 to -5.025	<0.001
Heart rate, bpm	0.082	0.025 to 0.140	0.005			
Mean arterial pressure, mmHg	-0.060	-0.128 to 0.009	0.089			
Respiratory rate, bpm	0.583	0.452 to 0.714	<0.001	0.362	0.233 to 0.491	<0.001
pHa, 0.1 unit	-0.814	-3.161 to 1.533	0.495			
PaCO ₂ , mmHg	-0.332	-0.552 to -0.112	0.003			
PaO ₂ , mmHg	-0.108	-0.161 to -0.055	<0.001			
HCO ₃ ⁻ a, mmol/L	-0.576	-0.883 to -0.268	<0.001			
BEa, mmol/L	-0.538	-0.836 to -0.240	<0.001	-0.520	-0.767 to -0.272	<0.001
SaO ₂ , %	-0.696	-1.093 to -0.299	0.001			
PaO ₂ :FiO ₂ , mmHg	-0.055	-0.069 to -0.041	<0.001	-0.054	-0.068 to -0.040	<0.001
COVID-19 and PaO ₂ :FiO ₂	-0.021	-0.037 to -0.004	0.013	0.048	0.009 to 0.088	0.016

Univariable and multivariable linear regression analysis to predict ΔPes (in cmH₂O) during high-flow nasal cannula oxygen therapy. BEa: arterial base excess concentration. β: regression coefficient. CI: confidence interval. COVID-19: novel coronavirus disease 2019. ΔPes: maximal inspiratory deflection of the esophageal pressure. FiO₂: inspiratory fraction of oxygen. HCO₃⁻a: arterial bicarbonate concentration. PaCO₂: arterial carbon dioxide tension. PaO₂: arterial oxygen tension. PaO₂:FiO₂: arterial tension to the inspiratory fraction of oxygen ratio. pHa: arterial pH. SaO₂: arterial oxygen saturation.

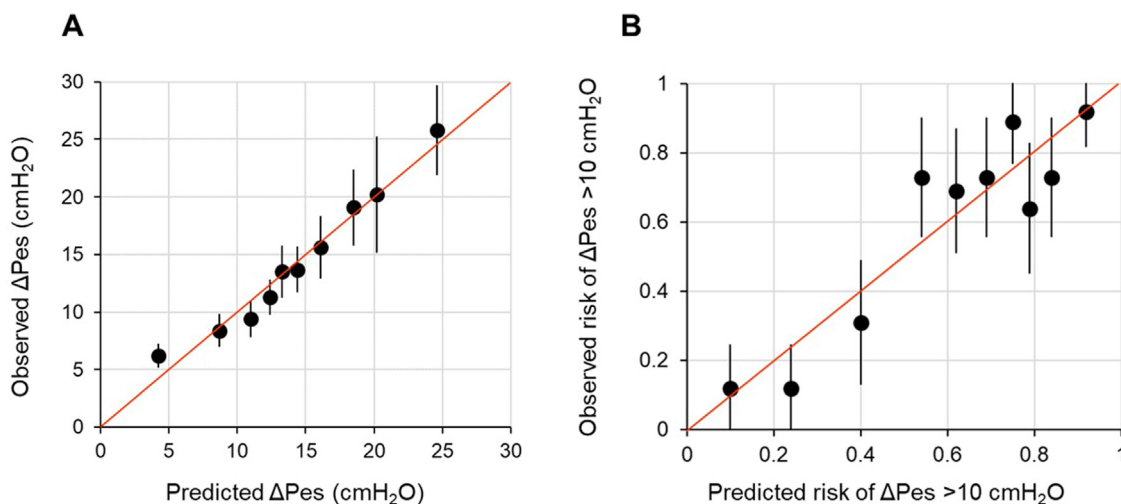


Fig. 1 Calibration plot of observed against predicted outcomes. Panel A shows the calibration plot for the linear regression model for ΔPes (in cmH_2O) tested on the development population, while Panel B shows the calibration plot for the logistic regression model for breathing efforts with a $\Delta\text{Pes} > 10 \text{ cmH}_2\text{O}$ tested on the development population. Each dot on the plot represents a tenth of the predicted values, each one based on data from 26 patients. The bars represent the 95 % confidence intervals, and the red line is the identity line.

as those associated with ΔPes , except for heart rate and the product term between COVID-19 and $\text{PaO}_2:\text{FiO}_2$, which were not significant (Table 3).

During multivariable model development, BEa (mmol/L), respiratory rate (bpm), and $\text{PaO}_2:\text{FiO}_2$ (mmHg) remained in the model while all other variables, including a diagnosis of COVID-19 and the product term between COVID-19 and $\text{PaO}_2:\text{FiO}_2$, were removed (Table 3). We found that the individual probability of outcome can be calculated as $1 / \{1 + \exp[-(0.461 - 0.145 \times \text{BEa} + 0.075 \times \text{respiratory}$

$\text{rate} - 0.014 \times \text{PaO}_2:\text{FiO}_2)]\}$. The corresponding percentage risk can be obtained by multiplying this probability by 100.

When the fit of the model was tested on the same data set used to develop it (apparent performance), the calibration intercept was -0.00 (-0.29 to 0.29), the calibration slope was 1.00 (0.72 to 1.28), the AUROC was 0.79 (95 % CI, 0.73 – 0.85), and the scaled Brier score was 29 % (Fig. 1). On internal validation (optimism-corrected performance), the calibration intercept was 0.00 (-0.33 to 0.33), the calibration slope was 0.85 (0.60 to 1.12), the AUROC was 0.76

Table 3 Logistic regression analysis to predict the risk of strong breathing efforts.

Variable	Univariable analysis			Multivariable analysis		
	β	95%-CI	p-value	β	95%-CI	p-value
Age, years	0.011	-0.008 to 0.030	0.242			
Sex, ref.: male	0.167	-0.352 to 0.686	0.529			
With COVID-19, ref.: no	0.747	0.188 to 1.307	0.009			
Heart rate, bpm	0.006	-0.007 to 0.019	0.352			
Mean arterial pressure, mmHg	0.007	-0.009 to 0.022	0.386			
Respiratory rate, bpm	0.116	0.071 to 0.161	<0.001	0.075	0.028 to 0.122	0.002
pHa, 0.1 unit	0.026	-0.496 to 0.548	0.923			
PaCO_2 , mmHg	-0.080	-0.132 to -0.027	0.003			
PaO_2 , mmHg	-0.026	-0.041 to -0.011	0.001			
HCO_3^- a, mmol/L	-0.126	-0.204 to -0.049	0.001			
BEa, mmol/L	-0.131	-0.207 to -0.054	0.001	-0.145	-0.234 to -0.056	0.001
SaO_2 , %	-0.180	-0.282 to -0.077	0.001			
$\text{PaO}_2:\text{FiO}_2$, mmHg	-0.015	-0.020 to -0.010	<0.001	-0.014	-0.019 to -0.009	<0.001
COVID-19 and $\text{PaO}_2:\text{FiO}_2$	0.004	-0.000 to 0.008	0.063			

Univariable and multivariable logistic regression analysis to predict the risk of breathing efforts with a $\Delta\text{Pes} > 10 \text{ cmH}_2\text{O}$ during high-flow nasal cannula oxygen therapy. BEa: arterial base excess concentration. β : regression coefficient. COVID-19: novel coronavirus disease 2019. ΔPes : maximal inspiratory deflection of the esophageal pressure. FiO_2 : inspiratory fraction of oxygen. HCO_3^- a: arterial bicarbonate concentration. PaCO_2 : arterial carbon dioxide tension. PaO_2 : arterial oxygen tension. $\text{PaO}_2:\text{FiO}_2$: arterial tension to the inspiratory fraction of oxygen ratio. pHa: arterial pH. SaO_2 : arterial oxygen saturation.

(0.71–0.81), and the scaled Brier score was 23 % (Fig. A.2). The prediction model was simplified into the following score: $33.7 - 10.6 \times \text{BEa} + 5.5 \times \text{respiratory rate} - \text{PaO}_2: \text{FiO}_2$. The outcome probabilities of different total points scores are reported in Fig. A.3.

Discussion

We developed two models that can estimate the breathing effort (ΔPes in cmH_2O) or the risk of strong efforts (probability of ΔPes being >10 cmH_2O) in patients with high-flow oxygen therapy. These models are based on a few variables readily available in an ICU, and yet their performance was fairly good, which makes them suitable for further evaluation.

Research on how to estimate the breathing effort in patients has been primarily limited to those receiving invasive mechanical ventilation. There is very little evidence on this topic for non-intubated patients. Therefore, doctors evaluating non-intubated patients rely mostly on their clinical impression.¹⁴ They look for signs that suggest an elevated effort, such as diaphoresis, hypoxia, tachycardia, tachypnea, altered mentation, shortness of breath, and recruitment of accessory and expiratory muscles. However, these signs are poorly defined,⁴⁴ and their relative importance is unclear. Reaching a definite conclusion when they conflict with each other can be difficult. Furthermore, none of these signs alone is accurate, particularly in critically ill patients, due to many confounding factors. On the other hand, doctors also rely on criteria derived from their experience, which are inherently vague and arbitrary.¹⁴ This often leads to clinical decisions being based more on implicit and subjective than explicit and objective rules.⁴⁵ Therefore, it is not surprising that doctors may disagree when rating the breathing effort made by their patients, or when debating whether to proceed to intubation.^{22,34,46-49}

Strengths of our models and their potential clinical applications

This was our first attempt at filling this gap in research. We developed two simple but composite models to estimate the effort of breathing during high-flow oxygen therapy when esophageal manometry is unavailable. One model predicts the actual ΔPes while the other predicts the risk of ΔPes being >10 cmH_2O . The association between the selected variables and breathing effort is biologically plausible.^{1,2} Other variables, such as PaCO_2 , had some predictive value on their own but did not ameliorate model performance. We use the acronym BREF to refer to these models. BREF stands for BReathing Effort but also reminds the common predictors: BEa (B), respiratory rate (RE), and $\text{PaO}_2:\text{FiO}_2$ (F). Doctors may use these models, as well as any updated version, as an aid for their decision-making process. For instance, to determine whether a patient requires admission to the intensive care unit, how often he or she should be reassessed, and whether to increase ventilatory support or proceed to intubation. Those with limited experience or working outside the ICU may find them particularly helpful.⁵⁰ In other fields of medicine, clinical prediction rules are used this way.^{51,52} Results may be interpreted as follows: breathing efforts with ΔPes up to 10 cmH_2O are probably

safe; those with ΔPes from 11 to 15 cmH_2O warrant close monitoring as they can lead to fatigue; those with ΔPes higher than 15 to 20 cmH_2O should not be tolerated for long. These values reflect our current best practices and may be revised as new knowledge becomes available.

Limitations of our models and implications for future research

This work also has several limitations that need to be addressed. Firstly, our models require performing an arterial blood gas analysis, which is invasive and resource-consuming. Secondly, the performance was only moderately good and needs to be validated in a new study population.^{41,43} However, the models may be updated into a second version, including other predictors, and this will hopefully improve their accuracy. Thirdly, the clinical usefulness of any prediction model depends on the accuracy of the unaided doctor and the consequences of decisions based on it, which are yet to be determined. Fourthly, these models may not be suitable for patients excluded from our study population, including those with acute cardiogenic pulmonary edema or a history of chronic lung disease. Lastly, having a dichotomous outcome can facilitate the interpretation of the results but with many drawbacks.^{41,43} For instance, it carries the risk of characterizing patients with a ΔPes slightly lower or higher than 10 cmH_2O as being very different rather than very similar. The exact threshold of ΔPes that separates normal and strong efforts, if such a threshold exists, remains unknown. Various suggestions have been proposed, ranging from 8 to 18 cmH_2O (see Table A.1), but none of them is supported by solid evidence. Also, it may cause a loss of information, which may explain why a diagnosis of COVID-19 was associated with ΔPes at linear regression analysis but not with strong breathing efforts at logistic regression analysis. For these reasons, dichotomizing a continuous outcome is generally discouraged.^{41,43} Hence, our model for ΔPes in cmH_2O should be preferred over the other.

Conclusions

We have developed two models to estimate the breathing effort of critically ill patients on high-flow oxygen therapy. Our initial findings are promising and suggest that these models merit further evaluation. This may include testing them on a new population, updating them, and determining their clinical usefulness.

Conflicts of interest

R.T. received travel support from SEDA Ltd, owns the patent n. 02021000007478 released by the Italian Ministry of Enterprises and Made in Italy, and is a co-founder of IREC Ltd (VAT number 02959080355); G.M.C. received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Getinge e MSD; E.C. owns the patent n. 02021000007478, released by the Italian Ministry of Enterprises and Made in Italy, and is a co-founder of IREC Ltd (VAT number 02959080355). All other authors declare no conflicts of interest related to this manuscript.

Acknowledgments

We are grateful to Davide T. Andreis (SC Rianimazione e Anestesia, ASST Ovest Milanese, Ospedale Civile di Legnano, Legnano, Milan, Italy), Fabiana Madotto (Department of Anesthesia, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), and Emanuele Rezoagli (School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy and Department of Emergency and Intensive Care, Fondazione IRCCS Ospedale San Gerardo dei Tintori, Monza, Italy) for critically reviewing a previous version of the manuscript.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.pulmoe.2024.04.008](https://doi.org/10.1016/j.pulmoe.2024.04.008).

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