

Comparison Between Normobaric Hypoxia Altitude Simulation Test and Altitude Hypoxia Predictive Equations in Cystic Fibrosis Patients

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Abstract

Background: The Hypoxia Altitude Simulation Test (HAST) is the *Gold Standard* to evaluate hypoxia in response to altitude and to decide on in-flight requirements for oxygen supplementation. Several equations are available to predict PaO₂ in altitude (PaO_{2alt}), but it remains unclear whether their predictive value is equivalent. We aimed to compare the results obtained by the available methods in a population of cystic fibrosis (CF) adults. **Methods:** Eighty-eight adults (58 healthy controls and 30 CF patients) performed a spirometry followed by an HAST. HAST results were compared with the predicted PaO_{2alt} made by five equations: 1st: $PaO_{2alt} = 0,410 \times PaO_{2ground} + 1,7652$; 2nd: $PaO_{2alt} = 0,519 \times PaO_{2ground} + 11,855 \times FEV_1 (L) - 1,760$; 3rd: $PaO_{2alt} = 0,453 \times PaO_{2ground} + 0,386 \times FEV_1 (\%) + 2,44$; 4th: $PaO_{2alt} = 0,88 + 0,68 \times PaO_{2ground}$; 5th: $PaO_{2alt} = PaO_{2ground} - 26,6$. **Results:** None of the controls required in-flight oxygen neither by HAST or by the five predictive equations. Eleven CF-patients had PaO_{2alt} < 50 mmHg, accessed by HAST. The positive predictive value was 50% (1st), 87.5% (2nd and 3rd), 77.78% (4th) and 58.33% (5th). Areas under the curve were 78.95% (1st), 84.69% (2nd), 88.04% (3rd) and 78.95% (4th and 5th). FEV₁ and PaO_{2ground} were correlated with HAST results. **Conclusions:** The 3rd equation gave the best predictions in comparison with results obtained by HAST. However, because the individual differences found were substantial for all equations, we still recommend performing a HAST whenever possible to confidently access in-flight hypoxia and the need for oxygen.

Keywords: Cystic Fibrosis, Altitude, Hypoxia

Introduction

The quality of life and life expectancy of patients with cystic fibrosis (CF) have increased substantially during the past years¹ due to medical improvement and preventive initiatives, which currently enable these patients to participate in activities that were not previously feasible, such as tourism.² As a result, physicians are increasingly requested to evaluate these patients for their ability to fly safely and the need for oxygen supplementation.^{3,4} Commercial flights expose individuals to a lower atmospheric pressure and consequently to a lower oxygen content,² as passenger cabins of commercial aircraft at maximal cruising altitude are pressurized to an altitude equivalent of 2438 m (8000 feet),^{1,3,5-7} which is equivalent to breathing 15% oxygen at sea level.³⁻¹⁰ This altitude hypobaric hypoxia can be tolerated in healthy individuals, but may cause severe hypoxemia in patients with pulmonary disease.^{3,10-14} CF-patients are therefore prone to a substantial and unsafe reduction in the partial arterial oxygen pressure (PaO₂) during the flight^{1,12} that may lead to a severe respiratory decompensation.¹⁵

The Aerospace Medical Association² and British Thoracic Society (BTS)⁴ recommend to perform a hypoxic altitude simulation test (HAST) to assess whether patients need in-flight oxygen supplementation. The HAST is considered the gold standard¹¹ and it can be done by artificially reducing inspired oxygen to similar levels as those experienced at 2438 m (8000 feet) for 20 min by either reducing the fraction of inspired oxygen to 15%^{1,4,7,11} or by reducing atmospheric pressure to 565 Torr (75 kPa) in a hypobaric chamber.^{4,11} The normobaric HAST is usually the preferred technique, as it is more accessible and inexpensive than the HAST performed in a hypobaric chamber. The expected PaO₂ (PaO_{2HAST}) is then determined from measurements of arterial blood gases (ABG).¹¹ A subject is judged to require in-flight oxygen supplementation if the PaO_{2HAST} falls below 50 mmHg, although this arbitrary cut-off value has little supporting evidence.⁴

Security cut-offs have been proposed that can be used when HAST is not available. In the case of CF, patients with FEV₁ > 50% or PaO_{2ground} > 60 mmHg can safely be allowed to travel without oxygen supplementation.^{3,12} In addition, several investigators have developed predictive equations that estimate PaO₂ at altitude (PaO_{2alt}) using measurements made at sea level.^{6,11,14,16,17} The BTS guidelines refers to four of them, but they have been derived almost exclusively from patients with chronic obstructive pulmonary disease who undergone a HAST.⁴ Only one study, performed by

Kamin et al.¹⁷ (in our study referred as 5th equation) testing 12 adults with CF with mild to moderate respiratory insufficiency (mean PaO₂: 79 mmHg) proposed one equation to predict the expected hypoxemia for flights of up to 3,5 hours in duration.¹⁷

The aim of this study was to compare HAST results with those predicted by the available equations in a population of adults diagnosed with CF in order to evaluate their performance in distinguishing those who need in-flight oxygen supplementation from those who do not.

Materials and Methods

CF-patients, followed in our unit, aged over 18 years old, with stable disease, who intent to fly in the future were recruited. Thirty CF-patients were included in our study. To recruit healthy adults, an open call was launched by e-mail among medical students and young medical doctors. The participants had to fill a questionnaire with known diseases, current chronic medication, symptoms during previous flights and intention to fly in future. Individuals aged under 18 years old, with previous known diseases, symptoms during previous flights or with no intention to fly were excluded. We randomly selected 58 healthy adults. For both groups, we recorded age, sex, weight, height, body mass index (BMI) and smoking habits. Both spirometry and HAST was performed in CF-patients in a period of clinical stability with no change in their usual medication.

Spirometry breathing room air at sea level (Lisbon, 2 m above sea level, hereafter referred to as sea level) was performed before HAST using body screen from Viasys (Conshohocken, Pennsylvania, US) and the reference equation of Quanjer et al.¹⁸ to determine forced expiratory volume in 1 second (FEV₁), Forced vital capacity (FVC) and calculate FEV₁/FVC.

The normobaric HAST was performed at sea level and according to the recommendations of the BTS⁴ and Vohra and Klocke method¹⁹. Briefly, following this protocol, participants had to breath a FiO₂ of 15% using a gas mixture with a supply of 99.993% nitrogen (Linde Healthcare, Lisboa, Portugal) through a 40% flow Venturi mask (Intersurgical, Berkshire, UK). Cardiorespiratory monitoring was performed using a polygraph and an oximeter in a hand finger (Alice PDX; Philips-Respironics, Murrysville, PA, USA; Nonin Medical, Plymouth, MN, USA). Parameters monitored included oxygen peripheral saturation, arterial pressure (Classic Check, Pic solution, Artsana, Grandate, Italy) and electrocardiography. As established by BTS, recommended HCT duration is between 20 and 25 min. Immediately before and 30 min after provocation an ABG sample was drawn and immediately analyzed (Rapid point

500, Siemens, Erlangen, Germany), to measure $\text{PaO}_{2\text{ground}}$, oxygen saturation at ground ($\text{SatO}_{2\text{ground}}$), $\text{PaO}_{2\text{HALT}}$ and oxygen saturation after HAST ($\text{SatO}_{2\text{HAST}}$). HAST results were then compared with the predictions made by the following equations:

- 1st equation (Dillard et al.)¹⁴: $\text{PaO}_{2\text{alt}} = 0,410 \times \text{PaO}_{2\text{ground}} + 17,652$;
- 2nd equation (Dillard et al.)¹⁴: $\text{PaO}_{2\text{alt}} = 0,519 \times \text{PaO}_{2\text{ground}} + 11,855 \times \text{FEV}_1 \text{ (L)} - 1,760$;
- 3rd equation (Dillard et al.)¹⁴: $\text{PaO}_{2\text{alt}} = 0,453 \times \text{PaO}_{2\text{ground}} + 0,386 \times \text{FEV}_1 \text{ (\%)} + 2,44$;
- 4th equation (Gong et al.)¹⁶: $\text{PaO}_{2\text{alt}} = 0,88 + 0,68 \times \text{PaO}_{2\text{ground}}$;
- 5th equation (Kamin et al.)¹⁷: $\text{PaO}_{2\text{alt}} = \text{PaO}_{2\text{ground}} - 26,6$.

Statistical analysis

Clinical characteristic, spirometry and ABG results were analyzed and compared in the healthy controls and CF patients. Normal distribution of the data was assessed using Shapiro-Wilk test; Student's *t*-test was performed for data with a normal distribution, and the non-parametric Wilcoxon test when that was not the case. The Chi-square test was preferred for categorical variables. To verify the effectiveness of the five equations in separating who needs oxygen during the flight from those who do not, receiving operator characteristic (ROC) curves were performed and the area under the curve (AUC) was calculated for each equation. This study was approved by the Research Ethics Committee of Centro Hospitalar Lisboa Norte (Lisboa, Portugal).

Results

Out of the 88 randomly selected adults, all were caucasians and the majority were women (52.27%) with a median age of 22 years old. Between CF-patients and the healthy controls, there was a significant difference in weight, height and body mass index (BMI) ($p < 0.001$), with CF-patients being thinner and shorter. In the control group, 18.96% were former smokers and 12.06% current smokers, while all of the CF-patients were non-smoker. No statistically significant difference was found for age and gender. Clinical characteristics of the sample studied are summarized in Table 1.

We found significant differences when comparing the recorded functional respiratory values: CF-patients had lower FVC, FEV_1 and FEV_1/FVC ($p < 0.001$). CF-patients had also lower $\text{PaO}_{2\text{ground}}$, $\text{SatO}_{2\text{ground}}$, $\text{PaO}_{2\text{HALT}}$, $\text{SatO}_{2\text{HAST}}$ and lower minimal oxygen saturation ($\text{SpO}_{2\text{min}}$) measured during HAST ($p < 0.001$). Respiratory functional results are summarized in Table 2.

None of the healthy controls reached a $\text{PaO}_{2\text{HAST}}$ below 50 mmHg, while 11 (36.7%) of the CF-patients had lower values, with 42.7 mmHg being the lowest founded value – Table 3.

When CF-patients were divided by $\text{PaO}_{2\text{HAST}}$ (below or above 50 mmHg), a significant difference was found for weight ($p=0.002$), BMI ($p<0.002$), FVC, FEV_1 ($p<0.001$), FEV_1/FVC ($p=0.003$), $\text{PaO}_{2\text{ground}}$ ($p=0.008$) and $\text{SatO}_{2\text{ground}}$ ($p<0.007$), with patients with $\text{PaO}_{2\text{HAST}} < 50$ mmHg having lower values. No difference was found for age ($p=1$), gender ($p=0.466$) or height ($p=0.219$) between CF-patients.

Adjustment between groups

As the healthy controls and CF-patients have significant differences, we performed an adjustment for tobacco usage, BMI and height. All smokers and former smokers were excluded. Out of the 70 non-smoker adults (40 healthy controls and 30 CF-patients), the majority were women (54.28%) with a median age of 22 years old. Between CF-patients and the healthy controls, as expected, there was a significant difference in weight ($p < 0.001$), height ($p=0.003$) and BMI ($p < 0.001$). No statistically significant difference was found for age ($p= 0.092$) and gender ($p= 1$).

Significant differences were found when analyzing functional respiratory values: CF-patients had lower FVC, FEV_1 and FEV_1/FVC ($p < 0.001$). CF-patients had also lower $\text{PaO}_{2\text{ground}}$, $\text{SatO}_{2\text{ground}}$, $\text{PaO}_{2\text{HAST}}$, $\text{SatO}_{2\text{HAST}}$ ($p < 0.001$) and a lower $\text{SpO}_{2\text{min}}$ measured during HAST ($p < 0.001$).

With all five equations, the mean predicted $\text{PaO}_{2\text{alt}}$ had a significant difference between healthy controls and CF-patients ($p < 0.001$). When the five equations were compared to each other, the mean predicted $\text{PaO}_{2\text{alt}}$ had also a significant difference ($p \leq 0.005$), but when a cut-off of 50 mmHg was used, no difference was found ($p=0,51$).

To prevent a confounding effect by BMI and height, we used a correction based on multiple linear regression. This method allows to take into consideration the variability associated with each factor. A significant difference was still found between the groups on FVC, FEV_1 and FEV_1/FVC , $\text{PaO}_{2\text{ground}}$, $\text{SatO}_{2\text{ground}}$, $\text{PaO}_{2\text{HAST}}$, $\text{SatO}_{2\text{HAST}}$, $\text{SpO}_{2\text{min}}$ and predicted $\text{PaO}_{2\text{alt}}$ by the five equations ($p < 0.001$).

Equation comparison

Healthy adults and CF-patients: When the values of $\text{PaO}_{2\text{alt}}$ in the healthy controls and CF-patients were compared, a significant difference was found in all five equations ($p < 0.001$). The lowest predicted $\text{PaO}_{2\text{alt}}$ was found with the 5th equation, on the CF-

patient group (34.2 mmHg) – Table 3. This value was lower than the respective $\text{PaO}_{2\text{HAST}}$ found. When a cut-off of 50 mmHg for $\text{PaO}_{2\text{alt}}$ was used, none of the control had a predicted $\text{PaO}_{2\text{alt}} < 50$ mmHg. We used a non-parametrical approach for all variables when CF-patients were divided by $\text{PaO}_{2\text{HAST}}$ (below or above 50 mmHg), because the groups became smaller. In this case, a significant difference was found for weight ($p=0.002$), BMI ($p<0.002$), FVC, FEV_1 ($p<0.001$), FEV_1/FVC ($p=0.003$), $\text{PaO}_{2\text{ground}}$ ($p=0.008$) and $\text{SatO}_{2\text{ground}}$ ($p<0.007$). Patients with $\text{PaO}_{2\text{HAST}} < 50$ mmHg had the lowest values. No difference was found on age ($p=1$), gender ($p=0.466$) or height ($p=0.219$) between CF-patients.

Using this cut-off, there were no evidences of significant differences between the case distribution among the equations ($p=0.369$). However, when we compare with the case distribution based on the results from the HAST test, some CF-patients were misclassified – Table 4 and Table 5.

We found no statistically significant difference on the sensibility of each equation (63.64%) and the specificity was 63.16% (1st equation), 94.74% (2nd and 3rd), 89.47% (4th) and 74.68% (5th). The positive predictive value was 50% (1st equation), 87.5% (2nd and 3rd), 77.78% (4th) and 58.33% (5th). The negative predictive value was 75% (1st equation), 81.82% (2nd and 3rd), 80.95% (4th) and 77.78% (5th).

In order to compare the performance of the five equations with the cut-off of 50 mmHg, ROC curves were performed (Figure 1). The 3rd equation had the best performance with an AUC of 88.04%.

Prediction of in-flight oxygen need in CF-patients

To test whether the requirement for in-flight oxygen supplementation could be predicted by $\text{PaO}_{2\text{ground}}$ and/or by FEV_1 (in Liters and predicted percentage), we analyzed the CF-patients with $\text{PaO}_{2\text{HAST}} < 50$ mmHg ($n=11$). Of this sub-group eight (72.73%) had $\text{FEV}_1 < 50\%$, six (54.55%) had $\text{PaO}_{2\text{ground}} < 70$ mmHg, two of which had < 65 mmHg.

A relation between $\text{FEV}_{1(\text{in liters})}/\text{PaO}_{2\text{HAST}}$, $\text{FEV}_{1(\%)}/\text{PaO}_{2\text{HAST}}$ and $\text{PaO}_{2\text{ground}}/\text{PaO}_{2\text{HAST}}$ was found ($p < 0.001$) – Figure 2.

Out of the patients that required in-flight oxygen supplementation, 10 had $\text{FEV}_1 < 2$ Liters, one $\text{FEV}_1 > 3$ Liters, all had $\text{FEV}_1 < 60\%$ of the predicted value and $\text{PaO}_{2\text{ground}} > 60$ mmHg, with one patient having $\text{PaO}_{2\text{ground}} > 90$ mmHg.

Discussion

Guidelines refer to predictive equations of altitude hypoxia as either a screening tool for recommending a HAST or as a replacement when this test is not available,¹¹ but the accuracy and predictive value of the available equation in relation to the HAST *Gold Standard* has not been previously evaluated in CF patients in comparison to healthy individuals. In our sample, we found a significant difference between healthy and CF-patients even when adjusted for tobacco usage, BMI or height. In our sample, 11 CF-patients and none of the healthy controls reached a PaO_{2HAST} below 50 mmHg. Patients who needed in-flight oxygen supplementation were thinner, had lower FVC, FEV₁, FEV₁/FVC, PaO_{2ground} and SatO_{2ground} than those who did not.

While the 3rd equation performed better than the other four, when compared to HAST results, none was able to correctly identify CF-patients that required in-flight oxygen supplementation. In a previous study, Martin et al.⁵ tested the prediction of the first four equations in 15 adults with CF and concluded that the four equations overestimated the need of in-flight oxygen. In our sample, only the first and fifth equations overestimated the HAST results. While overestimation will lead to unnecessary prescription of oxygen in flight with no clinical risk but increasing flight cost, possibly making the trip unfeasible, the opposite could lead a significant clinical risk. Therefore, we do not recommend to use these equations as screening tools or substitute of HAST.

According to some literature,^{3,12} CF-patients with FEV₁ > 50% or PaO_{2ground} > 60 mmHg can safely travel without oxygen supplementation. Therefore, this recommendation would exempt the performance of HAST in these patients. In fact, in our sample, FEV₁ and PaO_{2ground} correlated with HAST results, with FEV₁ in predicted percentage being the most accurate. However, contrary to the recommendations described above, all patients that needed in-flight oxygen had a FEV₁ < 60% while no other cut-off on FEV₁ in Liters or PaO_{2ground} was able to correctly predict those who reached PaO_{2HAST} below 50 mmHg. We do not recommend to use the previous values of FEV₁ (> 50% of the predicted value) or PaO_{2ground} (> 60 mmHg) as, in our sample, tree patients with FEV₁ > 50% and all 11 patients that needed in-flight oxygen had PaO_{2ground} > 60 mmHg.

We found a large variability between the results given by HAST and the values predicted by the different equations studied. The third equation produced predictions closer to the results observed by HAST, but given the individual difference found, the

authors recommend to, whenever possible, perform a HAST to analyze commercial air flights risks.

Table 1 – Clinical characteristics of the sample studied.

Characteristics	Total (n=88)	CF patients (n=30)	Healthy controls (n=58)	p-value
Age, years [†]	22 [21; 24]	23 [21.25; 30.75]	22 [21; 23]	0.099
Gender - Men, n (%)	42 (47.72)	14 (46.66)	28 (48.27)	1
Weight, kg [†]	61 [53.75; 70.5]	53 [50; 61.5]	65 [57.25; 75]	<0.001
Height, cm [*]	167.52 ± 8.94	163.3 ± 7.02	169.71 ± 9.08	<0.001
BMI, kg/m ^{2†}	22.23 [19.84; 23.87]	19.93 [18.99; 21.92]	23.08 [21.81; 23.25]	<0.001
Non-smokers, n (%)	70 (79.54)	30 (100)	40 (69.96)	<0.001

*: mean ± standard deviation; †: median [interquartile range]; BMI: Body mass index.

Table 2 – Respiratory functional results of the sample studied.

Results	Total (n=88)	CF patients (n=30)	Healthy controls (n=58)	p-value
FVC, L [†]	3.74 [3.09; 4.75]	2.76 [2.35; 3.23]	4.21 [3.62; 5.23]	<0.001
FVC, % [†]	95.50 [81.5; 104]	72.5 [60.5; 82]	101 [94.25; 108]	<0.001
FEV ₁ , L [†]	3.32 [2.23; 4.04]	1.7 [1.18; 2.5]	3.66 [3.28; 4.42]	<0.001
FEV ₁ , % [†]	93 [71.75; 104]	56 [37.25; 71.75]	103 [93; 208.75]	<0.001
FEV ₁ /FVC, % ^{†*}	84.9 [72.77; 88.26]	63.3 [53; 73.13]	86.58 [82.58; 91]	<0.001
PaO _{2ground} , mmHg [†]	95.7 [85.9; 99.88]	80.25 [71.68; 90.75]	98.2 [94.98; 109.1]	<0.001
PaO _{2HAST} , mmHg [†]	66.7 [59.13; 70.9]	53.45 [45.9; 59.38]	69.35 [65.48; 73.35]	<0.001
SatO _{2ground} , % [†]	97.5 [96.7; 97.73]	96.05 [94.35; 97]	97.65 [97.4; 97.9]	<0.001
SatO _{2HAST} , % [†]	93.5 [91.35; 97.8]	89.15 [83.85; 91.7]	94.4 [93.13; 95.15]	<0.001
SpO _{2min} , % [†]	88 [85; 93]	83 [80; 85.75]	88.5 [87.25; 90.75]	<0.001

†: median [interquartile range]; *: using the reference equation of Quanjer et al.¹⁸; FVC: Forced volume capacity; L: Liters; FEV₁: Forced expiratory volume in 1 second; PaO_{2ground}: partial arterial oxygen pressure measured at ground; PaO_{2HAST}: partial arterial oxygen pressure measured at the end of the hypoxia challenge test; SatO_{2ground}: oxygen saturation at ground measured by arterial blood gas; SatO_{2HAST}: oxygen saturation at the end of the hypoxia challenge test measured by arterial blood gas; SpO_{2min}: lower minimal oxygen saturation measured during the hypoxia challenge test measured by finger probe.

Table 3 – Mean PaO₂ at altitude (mmHg) by HAST and predicted the five equations.

	Total (n=88)	CF patients (n=30)	Healthy controls (n=58)	p-value
HAST	64.78 ± 11.18	54.31 ± 9.32	70.59 ± 7.21	<0.001
Lowest value	42.70	42.70	59.20	
1st equation *	55.45 ± 4.74	50.81 ± 4.69	57.85 ± 2.44	<0.001
Lowest value	42.58	42.58	51.11	
2nd equation *	83.74 ± 19.21	63.06 ± 16.34	94.44 ± 9.28	<0.001
Lowest value	37.58	37.58	76.54	
3rd equation *	77.46 ± 15.22	60.38 ± 13.54	86.29 ± 5.24	<0.001
Lowest value	38.75	38.75	74.14	
4th equation *	63.57 ± 7.87	55.87 ± 7.77	67.55 ± 4.05	<0.001
Lowest value	42.22	42.22	56.37	
5th equation *	65.59 ± 11.57	54.27 ± 11.43	71.44 ± 5.96	<0.001
Lowest value	34.20	34.20	55	

Table 4 – Division of CF-patients by predicted PaO₂ at altitude (PaO_{2alt}, mmHg) by the five equations.

Equation	Predicted PaO_{2alt}		p-value
	< 50 mmHg	> 50 mmHg	
1st equation	14	16	0.369
2nd equation	8	22	
3rd equation	8	22	
4th equation	9	21	
5th equation	12	18	

Table 5 – Division of CF-patients by HAST results and by predicted PaO₂ at altitude (PaO_{2alt}, mmHg) by the five equations.

		1st equation		2nd equation		3rd equation		4th equation		5th equation	
		<50 mmHg	>50 mmHg	<50 mmHg	>50 mmHg	<50 mmHg	>50 mmHg	<50 mmHg	>50 mmHg	<50 mmHg	>50 mmHg
HAST results	< 50 mmHg	7	4	7	4	7	4	7	4	7	4
	> 50 mmHg	7	12	1	18	1	18	2	17	5	14

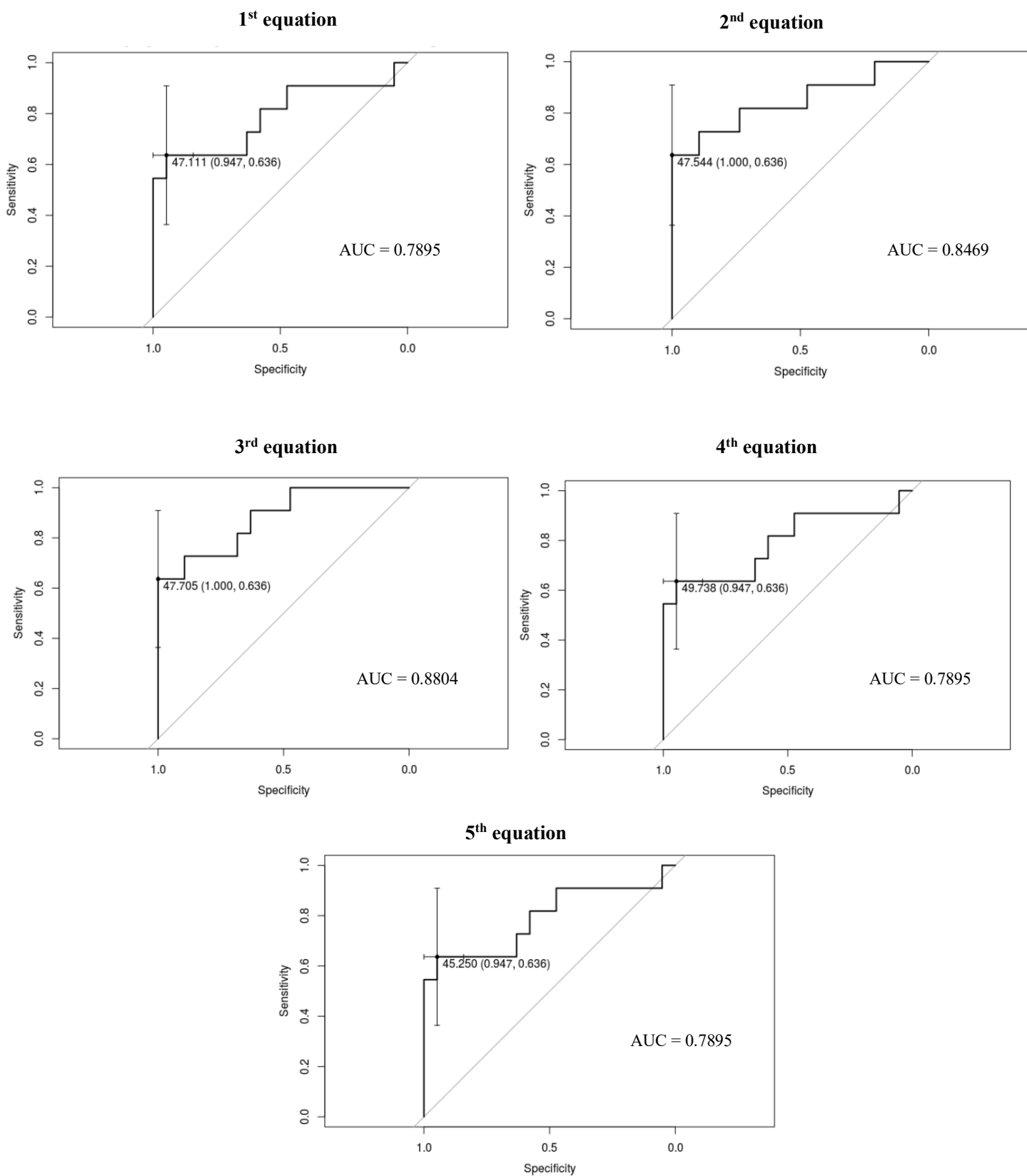
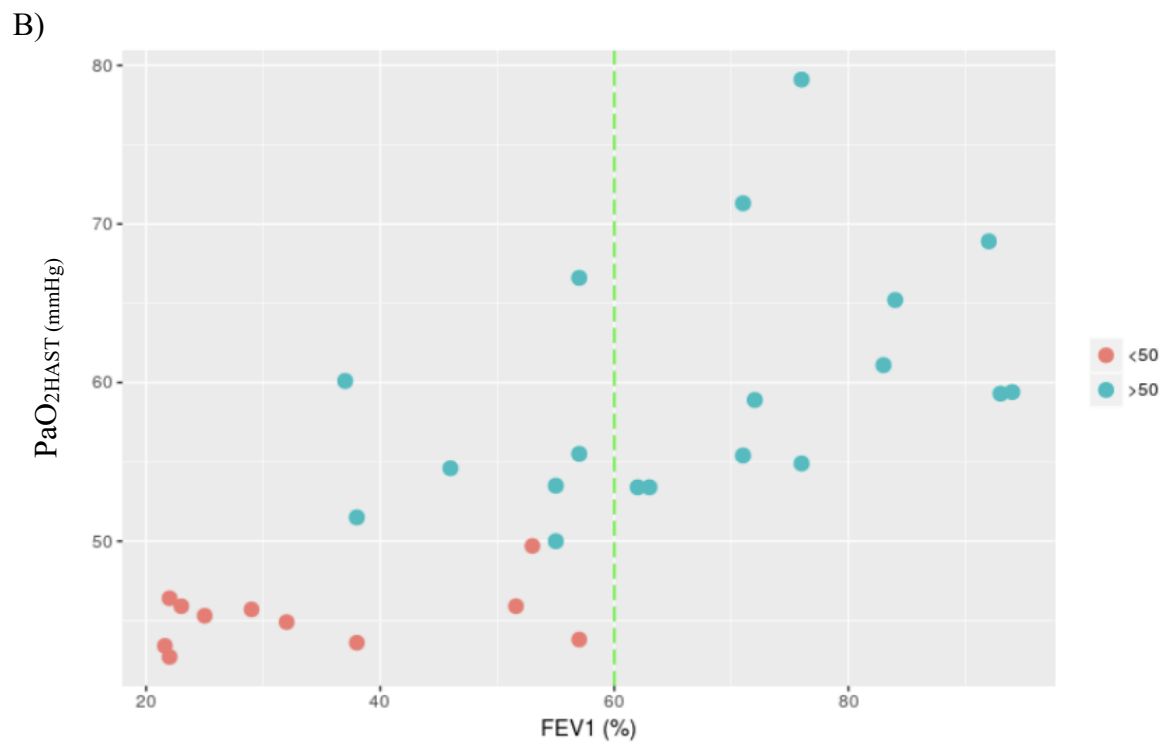
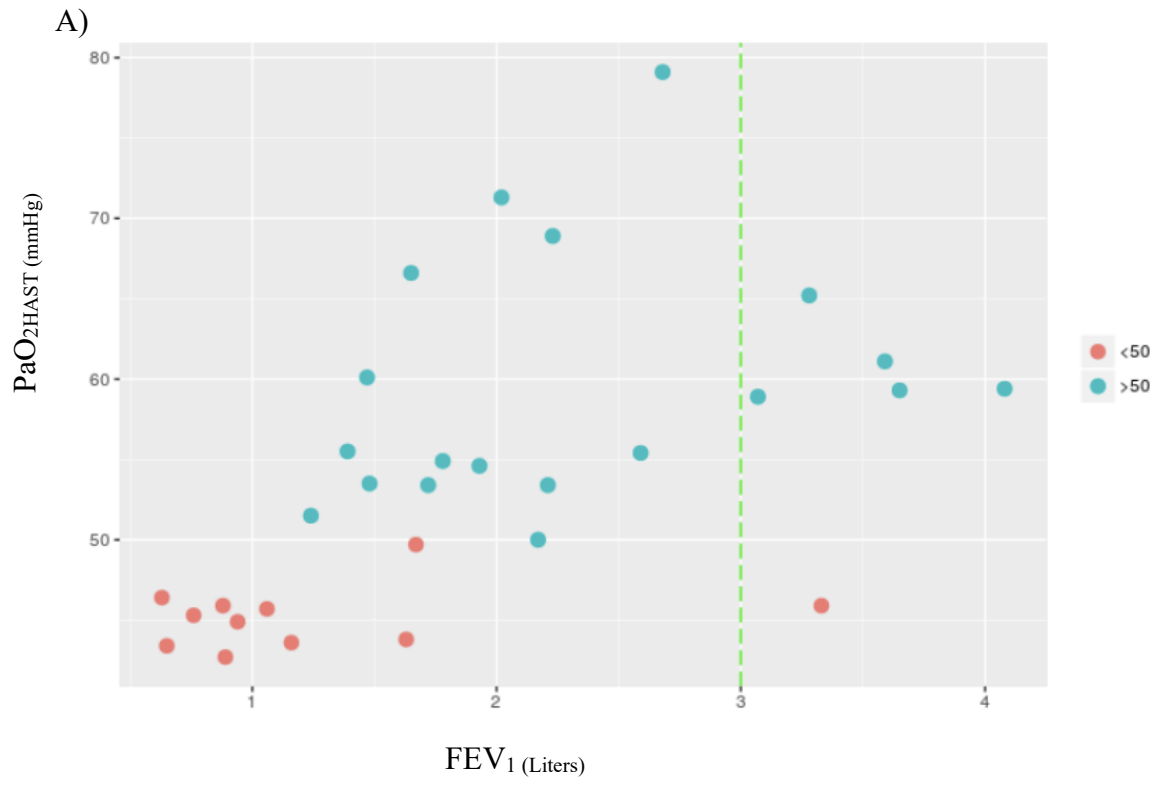


Figure 1- Receiving Operator Characteristic (ROC) curves and Area Under the Curve (AUC) of the five equations analyzed.



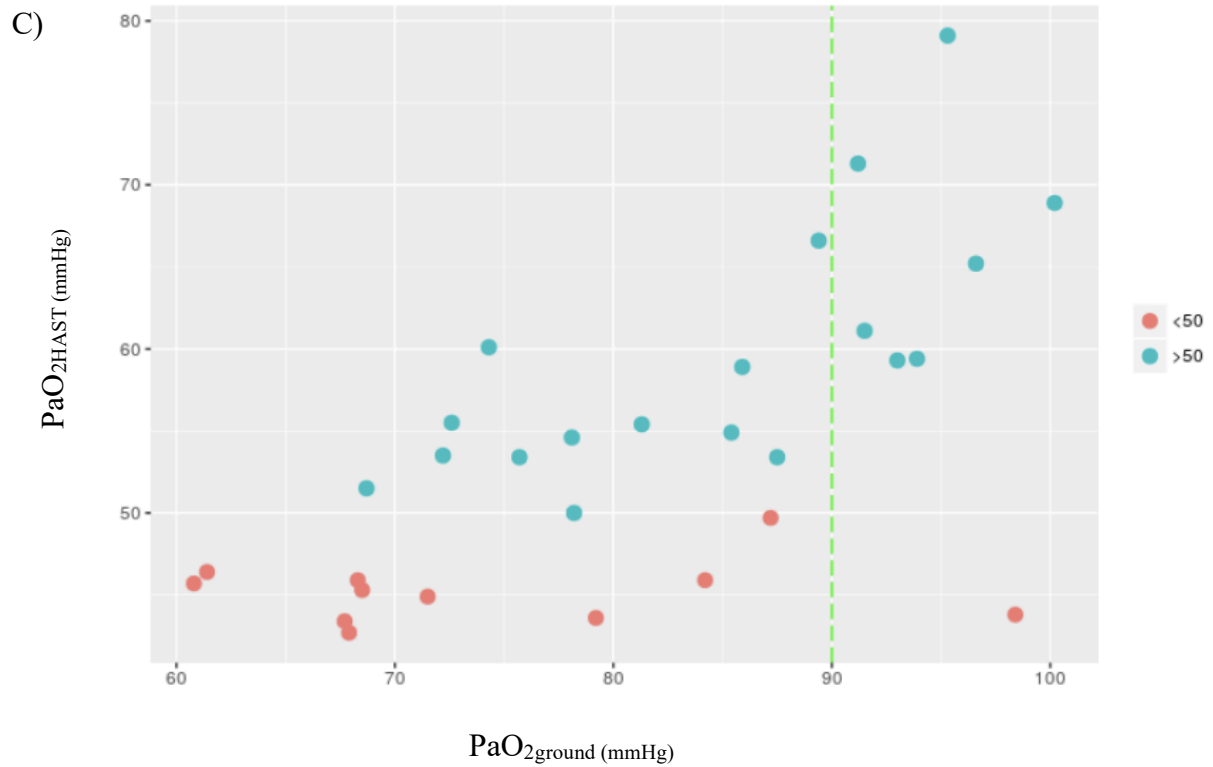


Figure 2- Relation between: (A) $FEV_{1(\text{in liters})} / PaO_{2HAST}$; (B) $FEV_{1(\%)} / PaO_{2HAST}$; (C) $PaO_{2ground} / PaO_{2HAST}$.

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