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Early View

Original research article

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OXIMETRY NEITHER TO PRESCRIBE LONG-TERM OXYGEN THERAPY NOR TO SCREEN FOR SEVERE HYPOXAEMIA

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Take home message: Although transcutaneous pulse oximetry is widely used to diagnose severe hypoxaemia and prescribe long-term oxygen therapy in COPD, up to 40% of patients who qualify for this therapy would be denied treatment using the saturation threshold of ≤ 88%.

ABSTRACT

Background and Objective: Transcutaneous pulse oximetry saturation (SpO_2) is widely used to diagnose severe hypoxaemia and to prescribe long-term oxygen therapy (LTOT) in chronic obstructive pulmonary disease (COPD). This practice is not based on evidence. The primary objective of this study was to determine the accuracy (false positive and false negative rates) of oximetry for prescribing LTOT or for screening for severe hypoxaemia in patients with COPD.

Methods: In a cross-sectional study, we correlated arterial oxygen saturation (SaO_2) and SpO_2 in patients with COPD and moderate hypoxaemia (n = 240), and calculated the false positive and false negative rates of SaO_2 at the threshold of ≤88% to identify severe hypoxaemia (PaO_2 ≤55 mmHg or PaO_2 <60 mmHg) in 452 patients with COPD with moderate or severe hypoxaemia.

Results: The correlation between SaO_2 and SpO_2 was only moderate (intra-class coefficient of correlation: 0.43; 95% confidence interval: 0.32 – 0.53). LTOT would be denied in 40% of truly hypoxemic patients on the basis of a SaO_2 > 88% (i.e., false negative result). Conversely, LTOT would be prescribed on the basis of a SaO_2 ≤ 88% in 2% of patients who would not qualify for LTOT (i.e., false positive result). Using a screening threshold of ≤ 92%, 5% of severely hypoxemic patients would not be referred for further evaluation.

Conclusions: Several patients who qualify for LTOT would be denied treatment using a prescription threshold of saturation ≤88% or a screening threshold of ≤92%. Prescription of LTOT should be based on PaO_2 measurement.

INTRODUCTION

Two landmark trials conducted more than 40 years ago provided scientific evidence that long-term oxygen therapy (LTOT) may prolong life [1, 2]. These two trials targeted patients with chronic obstructive pulmonary disease (COPD) and severe daytime hypoxaemia documented by direct arterial blood gas (ABG) measurement. The inclusion criteria of both studies still serve as current indications for LTOT in COPD, with minor variations worldwide [3].

In several jurisdictions, LTOT is actually prescribed and reimbursed on the basis of the measurement of oxygen saturation by transcutaneous pulse oximetry (SpO_2) alone. For instance, in the United States, clinicians may use either a partial pressure in oxygen in arterial blood (PaO_2) $\leq$ 55 mmHg or a $SpO_2 \leq$ 88% (or a PaO_2 of 56 to 59 mm Hg, or SpO_2 of 89% with evidence of cor pulmonale or erythrocytemia) at rest in establishing severe hypoxaemia [4]. The authors of the recently published American Thoracic Society clinical practice guidelines for home oxygen therapy in adults with chronic lung disease recognised the limitations of SpO_2 for oxygen prescription. Nevertheless, the panel supported its use to "improve the usability of the guideline report in circumstances in which arterial blood gas measurements (are) not available" [5]. In Canada, the use of SpO_2 as a criterion for funding is inconsistent among provinces [6]. Although convenient, the practice of using pulse oximetry to determine the need for LTOT is not based on clinical evidence. The most recent British Thoracic Society guidelines for home oxygen use in adults suggested that pulse oximetry may be used for screening patients who might be candidates for LTOT. The guidelines recommend that patients with a resting stable saturation measured by transcutaneous pulse oximetry (SpO_2) $\leq$ 92% should be referred for arterial blood gas assessment in order to assess eligibility for LTOT.[7] A good practice is also to elevate this threshold to $\leq$ 94% if end-organ damage (cor pulmonale or erythrocytemia) is noted [7].

SaO_2 and PaO_2 are predictably related from the oxygen-haemoglobin dissociation curve. Although clinicians often use SpO_2 as a substitute for SaO_2, several studies reported that SaO_2 and SpO_2 are only moderately correlated [8-10]. Consequently, SpO_2 may not be as reliable as measuring PaO_2 to establish the presence of hypoxaemia [11]. By using pulse oximetry alone for LTOT prescription, clinicians and patients should be aware of the potential for misclassification, that is denying LTOT in truly hypoxemic patients on the basis of a $SpO_2 > 88\%$ (i.e., false negative result), or prescribing LTOT on the basis of a $SpO_2 \leq 88\%$ in patients who would not qualify for LTOT if ABG were actually measured (i.e., false positive result). Accordingly, our primary objectives were (1) to demonstrate the correlation between SpO_2 and SaO_2, and (2) to determine the false positive and false negative rates of LTOT prescriptions in patients with COPD if it was based on SaO_2 alone. A secondary objective was to determine the SaO_2 thresholds at which the indication of LTOT can be ruled in or ruled out.

MATERIAL AND METHODS

Design, and patients

In a cross-sectional study, the results of ABG obtained from three separate groups of patients were analysed. First, we extracted the results of baseline ABGs of patients who participated in the International Nocturnal Oxygen (INOX) trial, a 4-year, multicenter, randomised, placebo controlled trial of nocturnal oxygen therapy in patients with COPD [12]. To be included in the trial, patients had to have nocturnal oxygen desaturation without qualifying for LTOT. These patients usually have moderate hypoxaemia at rest (i.e., PaO_2 approaching the threshold of LTOT prescription [13]). ABGs were available in 240 of 243 patients who were randomised in the INOX trial; (Cohort 1). Arterial blood was drawn from patients in sitting position. As per

protocol, SpO_2 was also measured within one hour of arterial blood sampling using PalmSAT 2500™ oximeter only (Nonin Medical Inc., Plymouth, MN, USA).

Second, we obtained from the respiratory home care program of the Quebec City area (province of Quebec, Canada) the result of the ABG of patients registered in the program as of January 1, 2015 with a main diagnosis of COPD who were prescribed LTOT (Cohort 2; n = 212). To be admitted to the program, severe hypoxaemia ($PaO_2 \leq 55$ mmHg or PaO_2 in the range of 56 to 59 mm Hg with clinical evidence of cor pulmonale or erythrocytemia [1]) must be strictly demonstrated in stable condition. Patients were not allowed in the program on the basis of SpO_2 alone, so that SpO_2 was not recorded in this cohort.

We also retrieved from the laboratory of biochemistry of our institution the results of all consecutive ABG measured between January 2009 and June 2017 in outpatients or inpatients while breathing room air (Cohort 3; n = 848). ABG of patients in an intensive care unit or in the recovery room, or those receiving supplemental oxygen were therefore excluded. Each patient contributed only one sample of arterial blood. The underlying diagnoses and indication of ABG measurement were irrelevant to the objectives of this study.

Measurements

Modern blood gas analysers measure PaO_2 using an amperometric electrode and SaO_2 using spectrophotometry [14]. SaO_2 is obtained by dividing the concentration of oxyhemoglobin by the sum of the concentrations of oxyhemoglobin and deoxyhemoglobin in the sample. Patients in Cohorts 1 and 2 came from several locations and ABG were analysed using different blood gas analysers across institutions. In Cohort 3, all ABG were analysed on an ABL 800 Flex blood gas analyser (Radiometer, Copenhagen, Denmark). Patient temperature was not noted; in all measurements, it was assumed to be 37 degrees Celsius.

Patient and public involvement

Patients were not directly involved in this study which is a secondary analysis of data obtained from the INOX trial and a retrospective analysis of data kept in files at the respiratory home care program of the Quebec City area and at the laboratory of biochemistry of our institution. It received approval from the Research Ethics Committee of our institution (CER-IUCPQ-UL: 2021-3592, 22044).

Statistics

We used simple descriptive statistics (proportions, means and standard deviations, medians and interquartile ranges) throughout the study. Clinical characteristics of patients in the 3 cohorts were compared using chi-square tests for dichotomous variables and analyses of variance for continuous variables. We first correlated SaO_2 and SpO_2 in Cohort 1 using an intraclass coefficient of correlation (ICC) calculated from a two-way mixed effect model, with its 95% confidence interval (CI). We also assessed graphically the agreement between the two measures using a Bland-Altman diagram [15]. In the 3 cohorts, we then plotted SaO_2 against PaO_2 to represent oxygen-haemoglobin dissociation curves. We also cross-tabulated the results of SaO_2 and PaO_2. In order to demonstrate the effect of arterial pH on the affinity of oxygen for haemoglobin [16], separate dissociation curves were also plotted after separating the cohorts into two groups at the median value of pH and summarised using local polynomial regression (locally estimated scatterplot smoothing [17]). By combining Cohort 1 and 2 (i.e., the 2 cohorts of patients with COPD), we calculated the false positive and false negative rates of SaO_2 at the thresholds of $\leq$ 88% (i.e., the American prescription threshold) and $\leq$ 92% (i.e., the British screening threshold) to identify severe hypoxaemia defined according to (1) the Nocturnal Oxygen Therapy Trial **(**NOTT [1]) criteria, (2) $PaO_2 \leq 55$ mmHg, or (3) $PaO_2 < 60$ mmHg regardless of oedema, hematocrit or ECG findings. From the same 2 cohorts, we constructed

receiver-operating characteristics (ROC) curves to determine the thresholds of saturation at which severe hypoxaemia is either ruled in or ruled out (i.e., false positive or negative results of 0%). Finally, we used Cohort 3 to validate the results obtained from patients with COPD (Cohorts 1 and 2). All the analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

Patient characteristics are summarised in Table 1. As expected, patients on LTOT (Cohort 2) had more severe hypoxaemia than those with nocturnal oxygen desaturation alone (Cohort 1). Although patients on LTOT were on average mildly hypercapnic, mean pH was normal (median: 7.42; interquartile range: 7.38 - 7.44), presumably indicating clinical stability when LTOT was initiated. Among the 240 patients who participated in the INOX trial (Cohort 1) and the 212 patients on LTOT (Cohort 2), 33 (14%) and 56 (26%) had a PaO_2 in the range of 56 to 59 mmHg, respectively.

Correlation between SaO_2 and SpO_2

SaO_2 and SpO_2 were moderately correlated (ICC: 0.43; 95% CI: 0.32 – 0.53; n = 240, all from Cohort 1; Figure 1S, Supplementary file). On average, the difference between the two measures was 0.6% (standard deviation [SD]: 2.0%). The Bland-Altman diagram indicates that the difference did not vary in a systematic pattern over the range of measurements (Figure 1).

SaO_2 to predict PaO_2

The relation between SaO_2 and PaO_2 in patients with COPD (Cohort 1 and Cohort 2) and in the validation cohort (Cohort 3) is shown in Figure 2. They represent in effect oxygen-haemoglobin dissociation curves. Cross-tabulation of SaO_2 and PaO_2 is presented in Table 1S and 2S in the

Supplementary file. The dissociation curves and the cross-tabulation of SaO_2 and PaO_2 indicate the wide variability of PaO_2 for a given SaO_2, and conversely, the wide variability of SaO_2 for a given PaO_2. The significant effect of pH on the affinity of oxygen for haemoglobin is also demonstrated in Figure 2S, Supplementary file.

Saturation to prescribe LTOT (≤ 88%) or to screen for patient selection (≤ 92%)

Scatter plots of SaO_2 values in patients with severe hypoxaemia and those with isolated nocturnal desaturation are presented in Figure 3. Among the 240 patients fulfilling the indication for nocturnal oxygen alone, 4 had a $SaO_2 \leq 88\%$ (false positive rate: 1.7%). SaO_2 was > 88% in 84 of the 212 patients on LTOT (false negative rate for LTOT prescription: 39.6%) (Table 2). Table 2 also includes the false positive and false negative rates of SaO_2 at the threshold of ≤ 88% to detect severe hypoxaemia defined as $PaO_2 \leq 55$ mmHg or $paO_2 < 60$ mmHg (regardless of oedema, hematocrit and ECG findings). At the SaO_2 screening threshold of ≤ 92%, 4.7% (10/212) of the truly hypoxemic patients would not have been referred for further evaluation.

Saturation thresholds to rule in or rule out the indication of LTOT

From the ROC analysis, we determined in Cohorts 1 and 2 that a SaO_2 threshold of ≤ 87% rules in the indication of LTOT according to the NOTT criteria (i.e., false positive rate = 0%) while a SaO_2 threshold of ≥ 96% rules out the indication of LTOT (i.e., false negative rate = 0%) (Figure 4 and Table 6S, Supplementary file).

Validation study

The false positive and false negative rates in the determination of severe hypoxaemia ($PaO_2 \leq 55$ mmHg or $PaO_2 < 60$ mmHg) at a SaO_2 threshold of ≤ 88% are shown in Table 2. We determined, from the ROC analysis, that a $SaO_2 \leq 82\%$ rules in severe hypoxaemia defined as

$PaO_2 \leq 55$ mmHg (i.e., false positive rate = 0%) while a $SaO_2 \geq 92\%$ rules out severe hypoxaemia (i.e., false negative rate = 0%) (Table 7S, Supplementary file). Similarly, a $SaO_2 \leq 88\%$ rules in severe hypoxaemia defined as $PaO_2 < 60$ mmHg, while a $SaO_2 \geq 94\%$ rules out severe hypoxaemia (Table 8S, Supplementary file).

DISCUSSION

Our findings question the validity of using oxygen saturation alone for the prescription of LTOT in COPD. First, as others [8-10], we observed that SpO_2 and SaO_2 were only moderately correlated. Also, in a recent study [18], the mean difference between SpO_2 and SaO_2 (SaO_2 - SpO_2) was remarkably similar to what we found (-0.6, SD 2.6 in Ekström's study vs. -0.6, SD: 2.0 in ours). Second, although not measured with pulse oximetry, pH may have, as predicted by physiology, a significant effect on the relation between SaO_2 and PaO_2 as demonstrated by the dissociation curves (Figure 1 and Figure 1S, Supplementary file). Third, by using saturation alone, patients are much more often denied LTOT (false negative rate: 40%) than they are prescribed LTOT when it is not indicated (false positive rate: 2%). Fourth, our data suggest that the thresholds of $\leq 82\%$ or $\geq 96\%$ to either rule in or rule out the indication of LTOT may be considered. Even at these thresholds, several factors limit the accuracy of cutaneous pulse oximetry to determine whether LTOT is indicated. These factors include (1) the precision of the currently available pulse oximeters [19], (2) the potential for technical errors with their use, (3) the shape of the oxygen-haemoglobin dissociation curve which may vary due to several unknown or unmeasured variables such as arterial blood pH and temperature [20], and (4) the imperfect correlation between SaO_2 and SpO_2.

The reasons why arterial puncture to determine the indication of LTOT has been abandoned in several jurisdictions are unclear since other reports have also underlined the limitations of pulse oximetry [11, 21, 22]. Yet, arterial puncture, most often of the radial artery,

is a safe and simple procedure. With the exception of local pain, bruising and hematoma, clinically significant complications are rare [23, 24]. Local pain may be decreased by local anaesthetic infiltration or the application of ice prior to the puncture [25, 26]. Topical anesthetics do not seem to be effective to reduce pain [27]. The technique can be performed by several health professionals after minimal training [28-30]. Successful punctures may be obtained in almost 90% of cases [8]. The use of ultrasonography to guide arterial puncture of the radial artery does not seem to improve success rate compared with the conventional technique [31]. Blood gas analysers are found in most hospitals. Portable blood gas analysers are also available, with performance similar to that of conventional laboratory blood gas analysers [32]. Cost of arterial puncture is minimal and hardly an issue when the outcome is LTOT, a major cost driver in the management of COPD [33].

ABG measurement has its own limitations. It does not provide continuous data. Measurement errors are also possible. Air bubbles in syringe increases PaO_2 while elevated temperature and delayed analysis has the opposite effect [34, 35]. Transient hyperventilation occurring during arterial puncture may be sufficient to acutely increase PaO_2, a situation that will not reflect the chronic state of hypoxaemia [36]. Acute respiratory alkalosis on ABG measurement must alert clinicians to this possibility. The analysis of capillary blood, either arterialised or not, has been proposed as an alternative to ABG measurement. At least two separate meta-analyses comparing capillary and arterial blood gas have been published [37, 38]. Richter et al. developed regression models to predict arterial blood gas (including PaO_2) from capillary blood gas values. The authors found excellent predictability of the models and emphasised the potential of capillary blood gases in the management of acute respiratory conditions [38], without mentioning chronic conditions. Zavorsky and colleagues found that earlobe sampling better predicts PaO_2 (adjusted $r^2 = 0.88$, mean bias = 3.8 mmHg compared to arterial) than fingertip sampling (adjusted $r^2 = 0.48$, mean bias = 11.5 mmHg compared to

arterial). The authors concluded that, in most circumstances, sampling blood from earlobe, but not from the fingertip may be, in some circumstances, appropriate as a replacement for PaO_2, unless precision is required [37].

A limitation of our study is that we determined the false positive and negative rates of saturation to identify severe hypoxaemia as well as the saturation thresholds to rule in or rule out the indication of LTOT on the basis of SaO_2 (not SpO_2). Also, ABG in our cohorts of patients with COPD were obtained from different analysers. In this regard, a study has found that differences in PaO_2 values from measurements performed on different blood gas analysers in different laboratories are negligible [39]. Temperature, a significant factor affecting the binding of oxygen to haemoglobin, was not taken into account.

CONCLUSION

Our study confirmed that SaO_2 and SpO_2 are only loosely correlated. We found that several patients who qualify for LTOT would be denied treatment using a SaO_2 prescription threshold $\leq$ 88% or a screening threshold $\leq$ 92%. We therefore conclude that oxygen saturation (SaO_2, and a fortiori SpO_2) is not an adequate replacement of direct PaO_2 measurement for prescribing LTOT or for screening for further assessment of eligibility for LTOT. If chronic hypoxaemia is suspected, patient evaluation should rely on ABG measurement. This practice has its own limitations since it represents a static and instantaneous measure that may not reflect patients' long-term oxygenation status. However, it has the merit to be aligned with the current indications for LTOT that were defined by the NOTT and the British Medical Research Council trial.

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Contributorship statement: conception and design: YL, FS, FM; acquisition of data: ST, BSP, SB; analysis: YL, HJB; interpretation of data: YL, FS, HJB, FM; writing: YL, ST, FS, FM.

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Table 1. Baseline characteristics

	Cohort 1: patients with COPD and isolated nocturnal desaturation (n = 240)	**Cohort 2: patients with COPD and severe hypoxaemia (n = 212)**	**Cohort 3: unselected patients (n = 848)**
Age, years (SD)	69 ± 8	72 ± 10	72 ± 12
Gender, male (n, %)	157 (65%)	97 (46%)	460 (54%)
PaO_2, mmHg (SD)	67 ± 7	52 ± 5	57 ± 10
SaO_2, % (SD)	93 ± 2	87 ± 4	89 ± 5
SpO_2, % (SD)	93 ± 2	N/A	N/A
$PaCO_2$, mmHg (SD)	42 ± 6	47 ± 8	44 ± 8
pH (SD)	7.42 ± 0.03	7.41 ± 0.04	7.43 ± 0.04

N/A: not available; SD: standard deviation. 1 mmHg = 0.133 kPa; 1 kPa = 7.50 mmHg.

Table 2. False positive and false negative rates of oxygen saturation (SaO_2) at the threshold of ≤ 88% to identify severe hypoxaemia in COPD

	$SaO_2 \leq 88\%$ False positive rate		**$SaO_2 \leq 88\%$** False negative rate	
Severe hypoxaemia defined as:	COPD (Cohort 1 + 2)	Validation (Cohort 3)	COPD (Cohort 1 + 2)	Validation (Cohort 3)
NOTT criteria [1]	1.7%*	-	39.6%*	-
$PaO_2 \leq 55$ mmHg	4.7%†	3.3%‡	21.9%†	15.7%‡
$PaO_2 < 60$ mmHg	0.5%†	0%‡	45.4%†	40.3%‡

* Details are provided in Table 3S, Supplementary file.
† Details are provided in Table 4S, Supplementary file.
‡ Details are provided in Table 5S, Supplementary file.

LEGEND FOR FIGURES

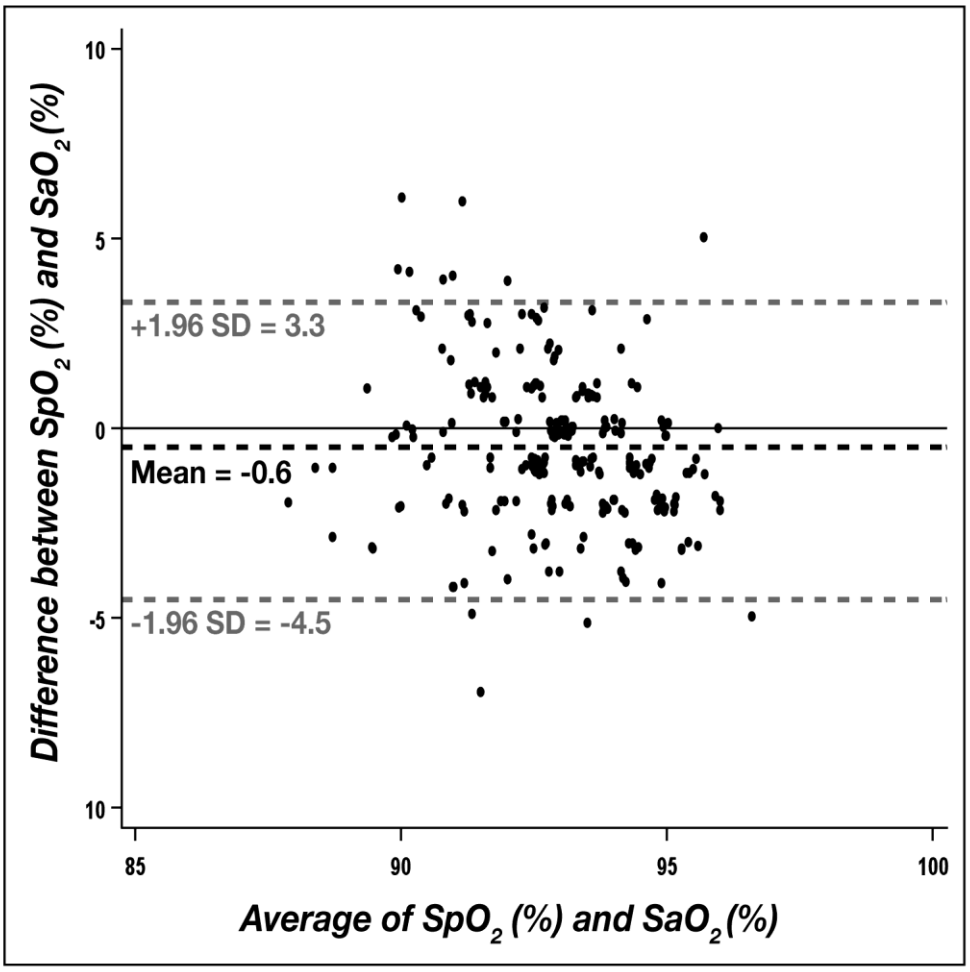

Figure 1

Bland-Altman diagram: agreement between SpO_2 and SaO_2 in the cohort of patients with isolated nocturnal oxygen desaturation (n = 240).

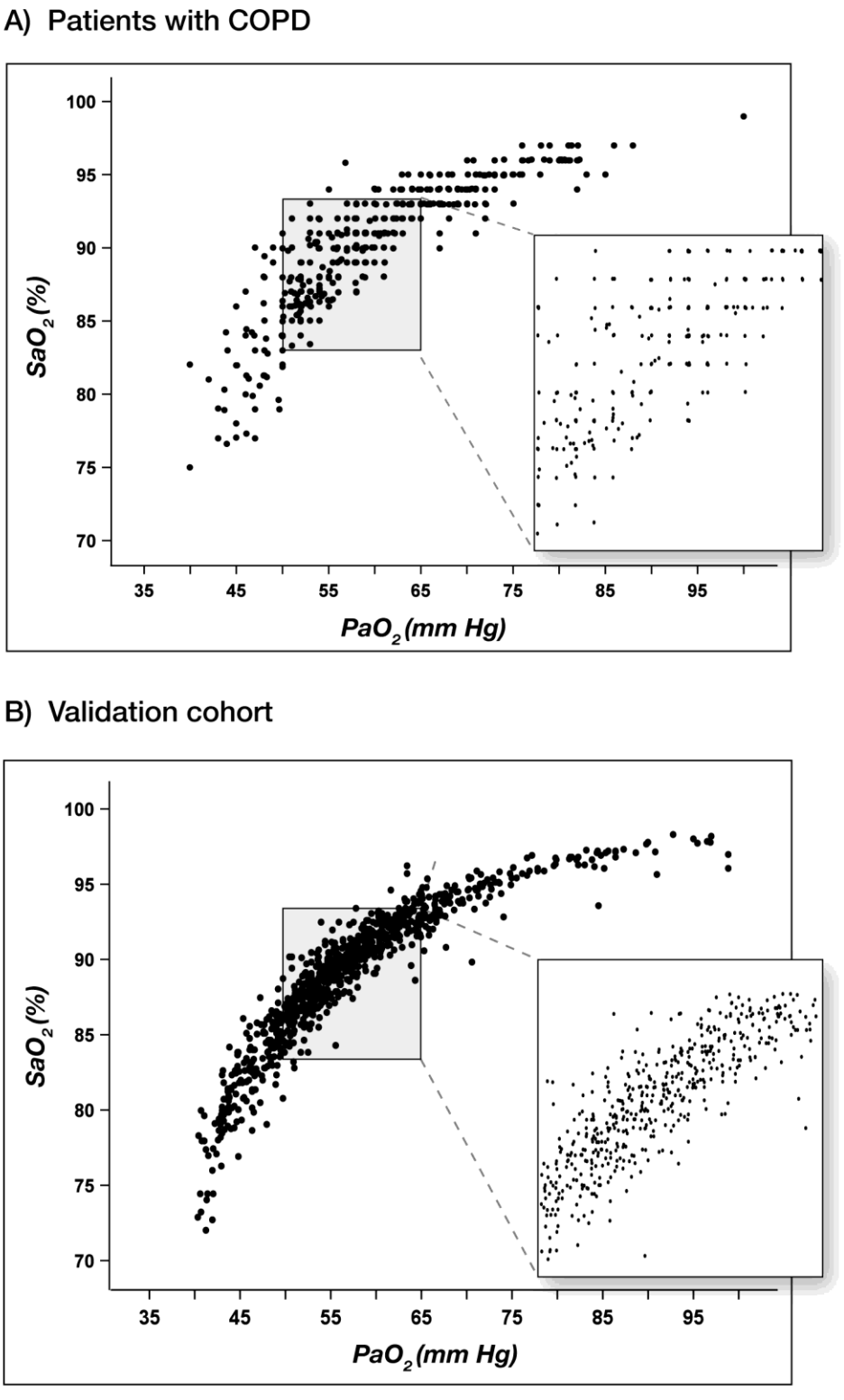

Figure 2

The relation between SaO_2 and PaO_2. Panel A: Patients with COPD: n = 452; Panel B: Validation cohort: n = 848. .

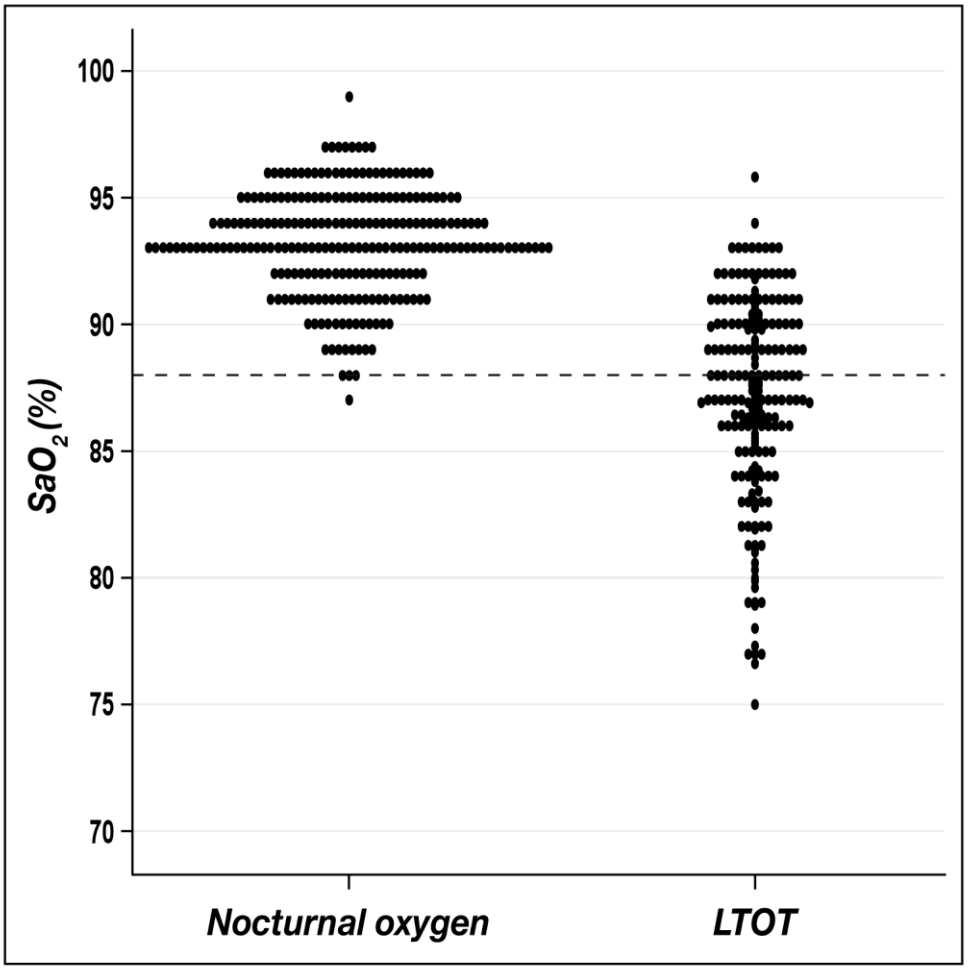

Figure 3

Scatter plot of the individual saturation values in patients on LTOT (n = 212) and those with isolated nocturnal oxygen desaturation (n = 240). The dash line is located at the saturation threshold of 88%.

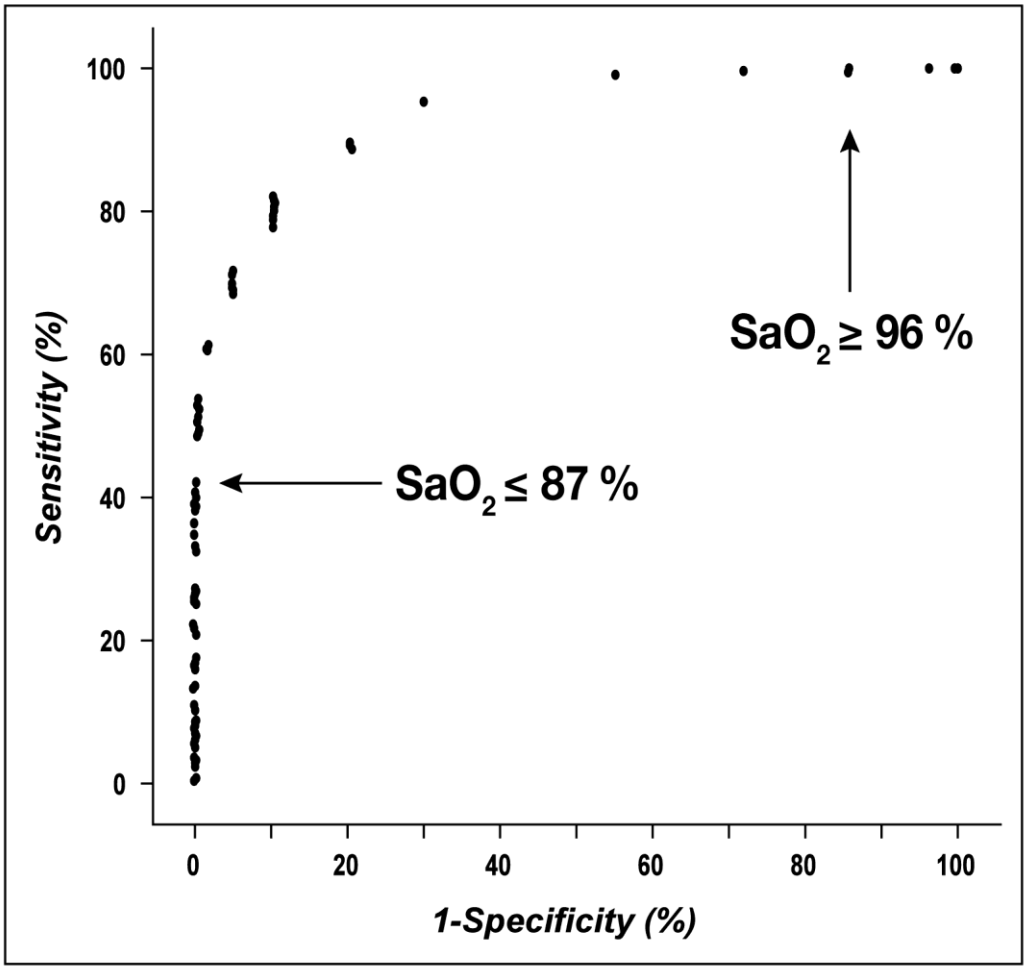

Figure 4

Receiver operating characteristics (ROC) curve: sensitivity and specificity of SaO_2 at varying thresholds to detect severe hypoxaemia ($PaO_2 \leq 55$ mmHg or PaO_2 of 56 to 59 mm Hg with evidence of cor pulmonale or erythrocytaemia) at the level to which LTOT is indicated according to the NOTT criteria. This analysis combined Cohort 1 and 2 (i.e., the 2 cohorts of patients with COPD). The arrows indicate the saturation thresholds at which the false positive rate ($SaO_2 \leq 87\%$) and false negative rate ($SaO_2 \geq 96\%$) are null.

OXIMETRY NEITHER TO PRESCRIBE LONG-TERM OXYGEN THERAPY NOR TO SCREEN FOR SEVERE HYPOXAEMIA

Supplementary file

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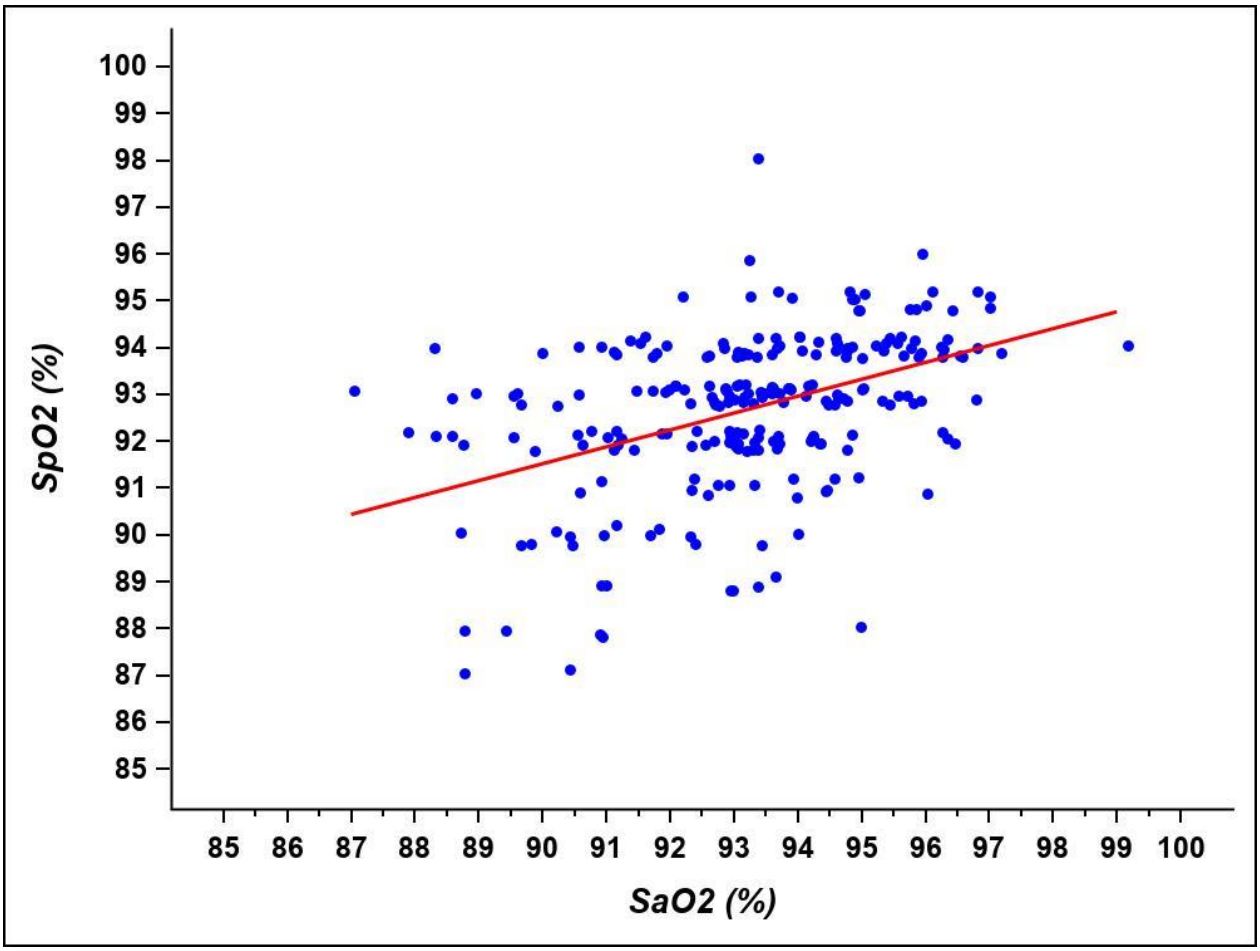
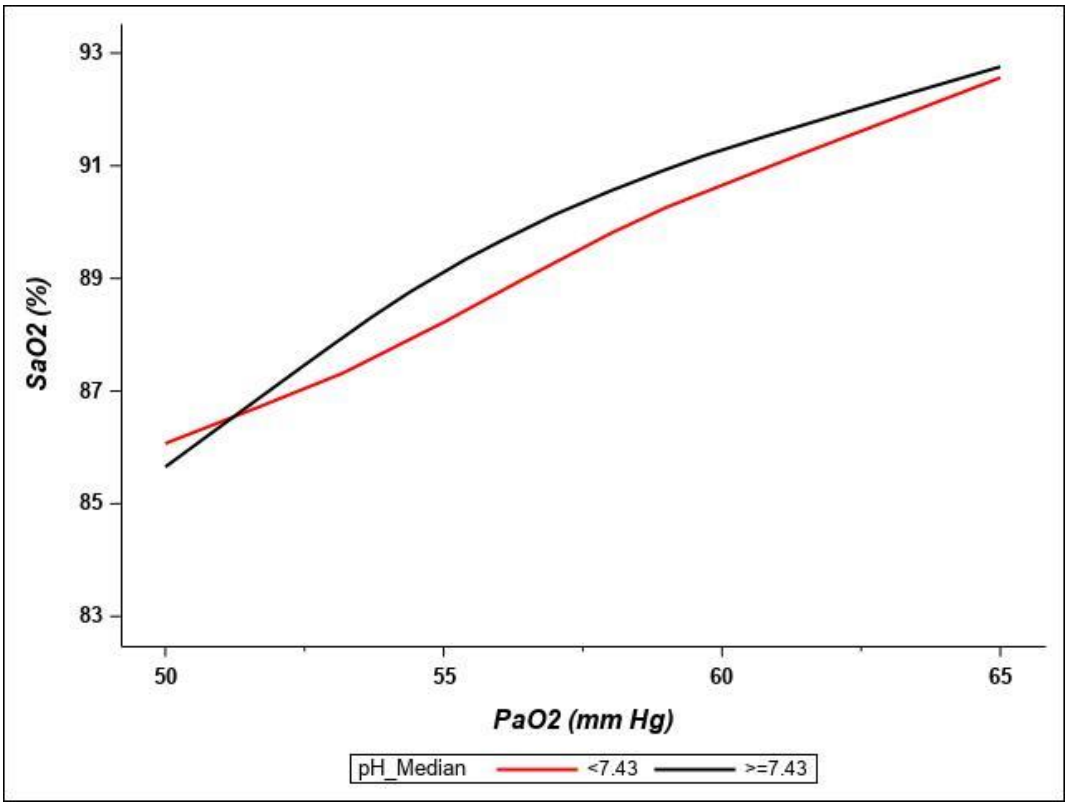
Figure 1S: Correlation between SaO2 and SpO2 in patients with COPD (Cohort 1; n = 240)



Intraclass coefficient of correlation: 0.43; 95% CI: 0.32 – 0.53

Figure 2S: Effect of pH on the affinity of oxygen for hemoglobin



In order to demonstrate the effect of arterial pH on the affinity of oxygen for hemoglobin, separate dissociation curves were also plotted after separating the cohorts into two groups at the median value of pH (7.43) and summarized using local polynomial regression (locally estimated scatterplot smoothing). In this analysis, data from the 3 cohorts (n = 1300) were combined.

Table 1S. Distribution of oxygen saturations (SaO_2) according to PaO_2

A) Patients with COPD (Cohort 1 and 2)

		SaO_2			
PaO_2 (mmHg)	Number of patients	Mean (SD)	Range	Median	Interquartile range
50	21	86 (3)	82 – 91	86	84 – 88
51	18	87 (2)	83 – 92	87	86 – 88
52	25	87(2)	84 – 91	87	86 – 88
53	15	89 (3)	83 – 93	89	87 – 90
54	16	88 (2)	85 – 92	88	87 – 90
55	16	89 (2)	86 – 94	88	87 – 90
56	17	90 (2)	87 – 96	90	89 – 91
57	16	91 (1)	89 – 93	91	90 – 92
58	30	90 (2)	87 – 93	90	89 – 91
59	18	91 (1)	88 – 93	91	90 – 91
60	15	92 (2)	89 – 94	91	91 – 93
61	15	91 (1)	88 – 93	92	91 – 92
62	11	92 (1)	90 – 94	92	91 – 93
63	12	93 (1)	91 – 95	93	92 – 94
64	12	93 (1)	92 – 94	93	93 – 94
65	20	93 (1)	92 – 95	93	93 – 94

Table 1S. Distribution of oxygen saturations (SaO_2) according to PaO_2

B) Validation cohort (Cohort 3)

		SaO_2			
PaO_2 (mmHg)	Number of patients	Mean (SD)	Range	Median	Interquartile range
50	42	86 (2)	82 – 90	86	85 – 86
51	28	87 (1)	83 – 90	87	86 – 87
52	48	87 (2)	83 – 90	87	86 – 88
53	41	88 (2)	85 – 92	88	87 – 88
54	48	88 (1)	86 – 91	88	87 – 89
55	43	89 (1)	83 – 92	89	88 – 90
56	36	89 (1)	87 – 92	89	89 – 90
57	39	90 (1)	87 – 93	90	89 – 91
58	40	90 (1)	88 – 92	90	90 – 91
59	33	91 (1)	89 – 93	91	90 – 92
60	31	91 (1)	89 – 93	92	91 – 92
61	22	92 (1)	90 – 95	92	91 – 92
62	22	92 (1)	90 – 93	92	91 – 93
63	23	93 (1)	91 – 96	93	92 – 93
64	19	92 (2)	88 – 94	92	92 – 93
65	24	93 (1)	90 – 95	93	92 – 94

Table 2S. Distribution of PaO_2 according to oxygen saturation (SaO_2)

A) Patients with COPD (Cohort 1 and 2)

		PaO_2			
SaO_2 (%)	Number of patients	Mean (SD)	Range	Median	Interquartile range
80	3	46 (2)	44 – 48	46	44 – 48
81	7	47 (3)	42 – 50	48	46 – 48
82	6	46 (4)	40 - 50	45	45 – 48
83	8	48 (3)	44 – 53	48	46 – 51
84	10	48 (3)	44 – 52	49	46 – 50
85	11	51 (2)	48 – 54	52	50 – 52
86	31	52 (2)	45 – 55	52	51 – 54
87	26	53 (3)	46 – 58	53	52 – 55
88	19	54 (4)	48 – 61	54	51 – 56
89	30	56 (4)	48 – 61	57	53 – 58
90	35	57 (4)	47 – 67	57	54 – 59
91	40	59 (4)	50 – 71	59	57 – 61
92	35	60 (4)	51 – 72	61	57 – 63
93	68	65 (4)	53 – 75	65	63 – 67
94	42	67 (4)	55 – 82	68	65 – 70
95	34	71 (6)	57 – 85	72	67 – 75

Table 2S. Distribution of PaO_2 according to oxygen saturation (SaO_2)

B) Validation cohort (Cohort 3)

		PaO_2			
SaO_2 (%)	Number of patients	Mean (SD)	Range	Median	Interquartile range
80	17	45 (2)	43 – 49	45	44 – 46
81	22	46 (2)	43 – 51	46	44 – 47
82	22	48 (2)	45 – 53	48	46 – 49
83	30	49 (2)	44 – 57	49	48 – 50
84	33	49 (2)	46 – 54	49	48 – 51
85	44	50 (2)	45 – 55	50	49 – 52
86	54	52 (2)	47 – 58	52	51 – 54
87	57	53 (2)	49 – 58	53	52 – 54
88	72	55 (2)	50 – 65	55	54 – 56
89	82	57 (3)	50 – 71	57	55 – 58
90	76	58 (3)	53 – 68	58	57 – 60
91	62	61 (3)	55 – 67	61	59 – 63
92	73	63 (3)	54 – 75	63	61 – 65
93	41	66 (4)	58 – 85	66	64 – 68
94	36	68 (3)	62 – 74	68	66 – 71
95	22	74 (5)	64 - 92	74	72 - 75

Table 3S. Accuracy of oximetry to identify severe hypoxemia that meets the indication of LTOT according to the NOTT [1] at the threshold of $SaO_2 \leq 88\%$ (Cohort 1 and 2)

		Requirement for LTOT*		
		Yes	No	**Total**
Saturation on arterial blood gas	≤ 88%	128	4	132
	> 88%	84	236	320
	Total	212	240	452

*According to the NOTT [1]
False negative rate: 84 / 212 = 39.6%; False positive rate: 4 / 240 = 1.7%
True positive rate: 128 / 212 = 60.4%; True negative rate: 236 / 240 = 98.3%

Table 4S (A). Accuracy of oximetry to identify severe hypoxemia ($PaO_2 \leq 55$ mmHg) at the threshold of $SaO_2 \leq 88\%$ in patients with COPD (Cohort 1 and 2)

		PaO_2		
		≤ 55 mmHg	> 55 mm Hg	**Total**
Saturation on arterial blood gas	≤ 88%	118	14	132
	> 88%	33	287	320
	Total	151	301	452

False negative rate: 33 / 151 = 21.9%; False positive rate: 14 / 301 = 4.7%
True positive rate: 118 / 151 = 78.1%; True negative rate: 287 / 301 = 95.3%

Table 4S (B). Accuracy of oximetry to identify severe hypoxemia ($PaO_2 < 60$ mmHg) at the threshold of $SaO_2 \leq 88\%$ in patients with COPD (Cohort 1 and 2)

		PaO_2		
		< 60 mmHg	≥ 60 mm Hg	**Total**
Saturation on arterial blood gas	≤ 88%	131	1	132
	> 88%	109	211	320
	Total	240	212	452

False negative rate: 109 / 240 = 45.4%; False positive rate: 1 / 212 = 0.5%
True positive rate: 131 / 240 = 54.6%; True negative rate: 211 / 212 = 99.5%

Table 5S (A). Oxygen saturation (SaO_2) to identify severe hypoxemia defined as $PaO_2 \leq 55$ mmHg in the validation cohort of unselected patients (Cohort 3)

		PaO_2		
		≤ 55 mmHg	> 55 mmHg	**Total**
Saturation on arterial blood gas	≤ 88%	332	15	347
	> 88%	62	439	501
	Total	394	454	848

False negative rate: 62 / 394 = 15.7%; False positive rate: 15 / 454 = 3.3%
True positive rate: 332 / 394 = 84.3%; True negative rate: 15 / 454 = 96.7%

Table 5S (B). Oxygen saturation (SaO_2) to identify severe hypoxemia defined as $PaO_2 < 60$ mmHg in the validation cohort of unselected patients (Cohort 3)

		PaO_2		
		< 60 mmHg	≥ 60 mmHg	**Total**
Saturation on arterial blood gas	≤ 88%	347	0	347
	> 88%	234	267	501
	Total	581	267	848

False negative rate: 234 / 581 = 40.3%; False positive rate: 0 / 267 = 0%
True positive rate: 347 / 581 = 59.7%; True negative rate: 267 / 267 = 100%

Table 6S (A). Saturation threshold (≤ 87) at which the false positive rate is of 0% when severe hypoxemia is defined according to the NOTT criteria for LTOT requirement (Cohort 1 and 2)

		Requirement for LTOT*		
		Yes	No	**Total**
Saturation arterial blood gas	≤ 87	89	0	89
	> 87	123	240	363
	Total	212	240	452

False negative rate: 123 / 212 = 58.0%; False positive rate: 0 / 240 = 0%
True positive rate: 89 / 212 = 42.0%; True negative rate: 240 / 240 = 100%

Table 6S (B). Saturation threshold (≥ 96) at which the false negative rate is 0% when severe hypoxemia is defined according to the NOTT criteria for LTOT requirement (Cohort 1 and 2)

		Requirement for LTOT*		
		Yes	No	**Total**
Saturation on arterial blood gas	< 96	212	206	418
	≥ 96	0	34	34
	Total	212	240	452

False negative rate: 0 / 212 = 0%; False positive rate: 206 / 240 = 85.8%
True positive rate: 212 / 212 = 100%; True negative rate: 34 / 240 = 14.2%

Table 7S (A). Saturation threshold (≤ 82%) at which the false positive is 0% when severe hypoxemia is defined as $PaO_2 \leq 55$ mmHg (Cohort 3)

		PaO_2		
		≤ 55 mmHg	> 55 mm Hg	**Total**
Saturation arterial blood gas	≤ 82%	129	0	129
	> 82%	265	454	719
	Total	394	454	848

False negative rate: 265 / 394 = 67.3%; False positive rate: 0 / 454 = 0%
True positive rate: 129 / 394 = 32.7%; True negative rate: 454 / 454 = 100%

Table 7S (B). Saturation threshold (≥ 92%) at which the false negative rate is 0% when severe hypoxemia is defined as $PaO_2 \leq 55$ mmHg (Cohort 3)

		PaO_2		
		≤ 55 mmHg	> 55 mm Hg	**Total**
Saturation on arterial blood gas	< 92%	394	272	347
	≥ 92%	0	182	501
	Total	394	454	848

False negative rate: 0 / 394 = 0%; False positive rate: 272 / 454 = 59.9%
True positive rate: 394 / 394 = 100%; True negative rate: 182 / 454 = 40.1%

Table 8S (A). Saturation threshold (≤ 88%) at which the false positive is 0% when severe hypoxemia is defined as PaO_2 < 60 mmHg (Cohort 3)

		PaO_2		
		< 60 mmHg	≥ 60 mm Hg	**Total**
Saturation on arterial blood gas	≤ 88%	347	0	347
	> 88%	234	267	501
	Total	581	267	848

False negative rate: 234 / 581 = 40.3%; False positive rate: 0 / 267 = 0%
True positive rate: 347 / 581 = 59.7%; True negative rate: 267 / 267 = 100%

Table 8S (B). Saturation threshold (≥ 94%) at which the false negative rate is 0% when severe hypoxemia is defined as PaO_2 < 60 mmHg (Cohort 3)

		PaO_2		
		< 60 mmHg	≥ 60 mm Hg	**Total**
Saturation on arterial blood gas	< 94%	581	168	749
	≥ 94%	0	99	99
	Total	581	267	848

False negative rate: 0 / 581 = 0%; False positive rate: 168 / 267 = 62.9%
True positive rate: 581 / 581 = 100%; True negative rate: 99 / 267 = 37.1%

REFERENCES

1. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980;**93**:391-8.