

PREDICTING WALKING-INDUCED OXYGEN DESATURATIONS IN COPD PATIENTS: A STATISTICAL MODEL

A Risk Score for Walking Desaturation

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ABSTRACT

Background

Oxygen desaturation during walking can have important consequence on prognosis of COPD patients. However, a standard 6-minute walking test (6MWT) useful to detect walking desaturators (WD⁺), can be difficult to execute in some settings of COPD management, as in the community health care service. Aim of our study was to validate and evaluate the accuracy of a newly composed score of risk of oxygen desaturation during walking in COPD patients: the Walking Desaturation Score-WDS.

Methods

Data on symptomatic COPD inpatients admitted for rehabilitation (derivation cohort) and outpatients referred to the local community health service (validation cohort) were recorded. By pulse-oximetry oxygen saturation (SpO₂) was monitored during 6MWT to obtain minimal values (SpO₂ nadir); patients were thus divided into WD⁺ or non-desaturators (WD⁻). By a regression analysis model we have assigned a weighted score proportional to the measured percentage of explained variance for each variable. Risk estimate was computed by odds ratio (OR). A Receiver Operating Curve (ROC) analysis and a Hosmer-Lemeshow (HL) goodness of fit test were then performed to measure discrimination and calibration of WDS.

Results

Baseline characteristics in derivation (n=435, WD⁺ 74%) and validation (n=238, WD⁺ 37%) cohorts were different. Resting arterial oxygen saturation-SO₂, arterial partial pressure of oxygen-PaO₂ and forced expiratory volume in the 1st second-FEV₁ % pred. were the variables predicting walking desaturation. The proportion of WD⁺ patients (and OR estimate) gradually increased according to WDS (range 0 to 6) and associated categories of desaturation risk (*low* 0-1 in total score of WDS, *high* 2-3, and *very high* 4-6) ($\chi^2 < 0.001$). A considerable predictive

discrimination (area under curve-AUC 0.90, 95% CI 0.86 to 0.93, $P < 0.001$) and calibration (HL χ^2 1.31, $P=0.859$) values have been shown.

Conclusions

WDS accurately predicts and classifies the risk of walking desaturation in COPD patients.

Keywords

6-minute walking test, COPD, oxygen desaturations, community health care, decision making, risk score.

INTRODUCTION

The increase of expiratory flow resistance and mismatch of lung ventilation to perfusion ratio are common patho-physiological features in patients with Chronic Obstructive Pulmonary Disease (COPD) leading to oxygen desaturation during exercise or activities of daily living [1-4].

The standardized 6-minute walking test (6MWT) [5] provides several responses regarding the walking capacity of COPD patients [6] [7] and it is useful and sensitive to identify those individuals specifically showing desaturation by the pulse-oximetry monitoring [8-11]; this finding may inform on prognosis, since COPD patients with walking desaturation have a higher mortality rate than patients without [12] [13].

In the daily clinical practice a standard 6MWT can be difficult to execute in non specialistic settings, as such as in the community (i.e. general practitioner, or health care service with low expertise) [14-16].

The aim of this study therefore is to elaborate and to validate a walking desaturation score (WDS) in a pure COPD population, using the combination of variables in the 6MWT and to report about its validation and accuracy figures as an identifier and stratifier of COPD patients who are likely to desaturate during 6MWT.

METHODS

This is a mono-centric prospective study, executed following the approval of the Institutional Review Board (registered at the clinicaltrials.gov website with code-number NCT01303913) and according to any conformity of good clinical practice. Patients gave their written informed consent to participate into the study. No external funding source supports this study.

Patients

Figure 1 shows the flow diagram indicating patients' recruitment in the study cohorts.

Derivation cohort

Consecutive and symptomatic COPD patients (n=435) admitted for a hospital-based pulmonary rehabilitation (PR) course at our institution were selected between January 2010 and June 2011. The study coordinator confirmed the diagnosis and severity of COPD according to the GOLD guidelines [17].

Exclusion criteria: a) patients recovering from exacerbation or with a change in medications over the previous 4 weeks; b) subjects with other underlying pulmonary disease (either obstructive or restrictive); c) subjects with chronic respiratory failure (CRF) and resting hypoxemia (arterial partial pressure of oxygen- $\text{PaO}_2 \leq 60$ mm Hg or arterial oxygen saturation- $\text{SO}_2 \leq 90\%$ on room air in a sitting position), with associated chronic and clinically evident non-respiratory conditions (such as chronic heart failure, morbid obesity, peripheral and/or cerebrovascular disease); d) subjects unable to perform the 6MWT in a correct manner, due to major neuro-motorial limitations.

Validation cohort

A sample of COPD outpatients (n=238) were collected in the period between January 2006 and December 2010 and served as the validation cohort (Figure 1); these patients were naïve from PR and referred to the local community health service.

Criteria for inclusion and exclusion were the same as in the derivation study cohort.

Measurements

General measurements

These data included primary demographic, anthropometric and functional variables.

Body mass index (BMI) has been calculated by dividing body weight for the squared height in meters (kg/m^2) [18].

Co-morbidities were assessed based on the reported anamnesis and/or clinically evident signs or symptoms and without any formal functional assessment. The Charlson index [19], an individual's self-reported score, has been used to determine the degree of co-morbidity; this index was computed and recorded not adjusted for age and diagnosis of COPD.

Arterial blood sample was obtained from the radial artery to obtain resting PaO_2 , SO_2 and partial pressure of carbon dioxide- PaCO_2 values by means of an automated analyzer (Model 850; Chiron Diagnostics; Medfield, MA).

Forced lung volumes to obtain forced expiratory volume in the 1st second (FEV_1) and forced vital capacity (FVC) were assessed by means of an automated spirometer (Masterscope; Jaeger; Hoechberg, Germany) with predicted values according to the Quanjer equation [20].

Assessment of both BODE [21] and ADO [22] index as validated prognostic measures in COPD patients was also computed in the study populations.

Six-minute Walking Test and correlated variables

This test was conducted according to the current recommendations [5] and performed indoor (in a corridor 50 m length and 3 m width) under quiet conditions. Standardized instructions were provided to patients by two trained physiotherapists unaware of the study purpose. A pre-test evaluation (at least 30 minutes) was performed in order to minimize the possible learning effects [23]; the distance walked in meters (m) was recorded for analysis using the best of two consecutive tests.

Oxygen saturation (SpO_2) was continuously registered during the test by a handheld and lightweight pulse-oximeter (Pulsox 3; Minolta; Tokyo, Japan) with a finger clip. To minimize

artefacts, the physiotherapist verified the signal quality and paid special attention when positioning the probe; every lost or fall in recorded signal was excluded from the analysis. Saturation nadir (SpO₂ nadir) value was then recorded.

A fall $\geq 4\%$ in SpO₂ and a value of SpO₂ nadir $\leq 89\%$ during 6MWT were considered as clinically significant for walking desaturation during exercise and activities of daily living [24]. According to this parameter, COPD patients were categorized into walking desaturators (WD⁺) or non-desaturators (WD⁻).

Statistical analysis

Analysis was carried out by specific tools (SPSS ver. 8.0 and Analyse-it[®] software Ltd). For all analysis a probability value (P) less than 0.05 was considered to be statistically significant.

We estimated the sample of patients in the derivation cohort based on the consecutive referral of patients to our centre during a defined temporal range (18 months). Since the minimal significant difference to observe a size effect was not known in the validation cohort, we have established *a priori* that patients allocated in derived and validated cohorts should have been 65% and 35% of total, respectively. In the derivation cohort all the considered variables were expressed as median (5th-95th percentiles), mean \pm standard deviation (SD) or frequency (No, %). Comparisons between WD⁺ and WD⁻ were made by two-way analysis of variance (ANOVA), chi-square (χ^2), Fisher's exact or Mann-Whitney U test as appropriate. In the same cohort, a bivariate correlation among all the considered variables and SpO₂ nadir was estimated by Pearson (r) or Spearman rho (ρ); the variables showing strong significant relationship (P < 0.01) then entered into a multivariate stepwise regression test with SpO₂ nadir as the dependent variable.

To develop a prognostic score for walking desaturation (WDS), we have assigned to each variable significant at the regression analysis a weighted score that was proportional to each single percentage of explained variance (R^2) [25]. The cut-off level for allocating points was based on percentile distribution within each variable.

Populations were then divided into three categories (*low*, *high* and *very high*) according to the associated risk score. The estimate of risk was computed by odds ratio (OR) in a 2x2 table; as previously described in [26], the formula $(P_{HR} - P_{LR}) \div 100$ was calculated to determine the difference in the probability of walking desaturation among categories, where P was the predicted probability and HR-LR the higher and lower risk in each category [27].

Finally, the diagnostic discrimination and calibration properties of score (in the detection of walking desaturation event according described criteria [24]) were measured by the area (AUC) under Receiver Operating Curve (ROC) [28] and a Hosmer-Lemeshow (HL) goodness-of-fit test, respectively.

RESULTS

Table 1 shows the characteristics of the study cohorts. Sixty-five % of patients in the derivation cohorts were male and 74% of them resulted in walking-induced desaturation (WD^+). Most of these patients (85%) were in moderate to severe degree of COPD (stage II and III, FEV_1 52.3 ± 16.0 % of pred.) with normal arterial oxygen pressure (PO_2 69 mmHg) at rest. In contrast, patients in the validation cohort showed a less severe impairment in both lung function (FEV_1 64% of pred. and PO_2 73 mmHg), walking capacity (416 metres at 6MWT), and WD^+ rate (37%).

Scoring system and categories of desaturation risk

In the derivation cohort, the bi-variate correlation (Table 2) and the following multivariate regression (Table 3) between anthropometric and functional variables and SpO₂ nadir as the dependent variable have shown that resting SO₂ ($r = 0.65$ and $b = 1.18$), PaO₂ ($r = 0.50$ and $b = 0.12$) and FEV₁ % pred. ($r = 0.41$ and $b = 0.08$) significantly predict walking desaturation.

After correlating each R² of the significant variables in this cohort (see in Figure 2) a total weighted score of 6 (100%) was determined and specified as follows: 3/6 point (50%) for SO₂, 2/6 point (33%) for PaO₂, and 1/6 point (17%) for FEV₁ % pred. WDS system ranged 0 to 6 as illustrated in Table 4. A range score 0-1 in the WDS was assigned to patients at *low* risk, 2-3 to patients at *high* risk, and 4-6 to patients at *very-high* risk for walking desaturation.

The distribution of COPD patients according WDS has shown that WD⁺ patients gradually increased according to the score level (from 2% at WDS score 1 to 92%, 97% and 100% at WDS score 4, 5 and 6, respectively) ($\chi^2 < 0.001$) with a similar behaviour regarding the categories of desaturation risk and OR estimate (Figure 3).

Accuracy of WDS

The accuracy analysis of the WDS in the validation cohort has demonstrated a considerable predictive discrimination (AUC 0.90, 95% CI 0.86 to 0.93, SE 0.018, $P < 0.001$, Z-Measure of sensitivity 22.57) (Figure 4) and calibration (HL χ^2 1.31, $P = 0.859$) capacities.

Correlation of WDS with validated prognostic scores

In the validation cohort, the score distribution of the BODE (mean 1.85, 95%CI 1.66 to 2.04) and the ADO indexes (mean 2.03, 95%CI 1.79 to 2.27) has shown a progressive increase according to the WDS and different categories of desaturation risk (see Figure 5); the correlation

analysis indicated a significant value ($P < 0.001$) between WDS and risk categories and the other prognostic indexes ($r = 0.44$ and 0.23 for BODE and $r = 0.43$ and 0.22 for ADO, respectively).

DISCUSSION

The key message from our study is that a score (WDS) derived from variables easily and usually recorded in COPD patients can predict and classify the risk associated with walking-induced desaturation. Interestingly, WDS and three categories of desaturation risk significantly correlates with other validated prognostic index such as BODE and ADO within this population.

The findings of our research could be able to offer a new and possibly clinically relevant information on how the degree of oxygen desaturation during usual daily physical activities may result in a different risk of prognosis among pure COPD patients by directly linking the likelihood of desaturation during physical exercise with a workable indicator of risk [12] [13].

Walking is the most common patter of activity in the daily life of COPD patients [7]. Thus, to indirectly evaluate the prognostic significance of WDS we have also considered its relation to other multidimensional grading scores including assessment of walking ability (but not oxygen desaturation) [21, 22], which have clearly demonstrated their ability to predict the risk of death from respiratory and any cause.

The high discrimination and calibration power of WDS (Figure 4) demonstrates its ability to identify WD^+ COPD patients in a cohort taken from the “real life”. In a practical approach we have appropriately considered three risk categories of WD^+ . COPD patients with higher WDS score (4 to 6 as *very-high* risk) almost certainly show walking desaturation; in contrast, patients with WDS score 0 to 1 (*low* risk) have a very low possibility to desaturate (difference in probability 0.97) (see in Figure 3). In addition to this, a high risk difference in probability (0.61) was seen between first (*low*) and mid (*high*) risk class categories: this was the main reason why

we have decided in any case to rename this category characterised by intermediate values as in a *high* (and not mild or moderate) range of risk.

From a clinical point of view, such an easy application starting from an extra semi-laboratory assessment may be of special interest for managing COPD patients at every level of care, also in the extra-hospital based setting [14-16]. Indeed, in “a very first approach to the COPD patients”, the early screening of patients who are at *high* and *very-high* risk to desaturate may support physicians in their decision making process within the area of diagnostic and therapeutic options, such as additional laboratory tests and/or ambulatory oxygen (although still questioned) [24].

Previous studies have demonstrated that forced volumes [29], diffusion capacity for carbon monoxide-DL_{CO} [30-32] and resting SO₂ [29] [33] may behave as predictors of exercise desaturation during 6MWT. In some of these, a drop in SpO₂ between 2 to 4% from the baseline level was used as the diagnostic criterion [30] [31]; notwithstanding, the fall in SpO₂ by 4% to a value $\leq 89\%$ more strictly defines exercise desaturators and enables physicians to consider ambulatory oxygen therapy [24] in patients with chronic lung disease. However, in none of those studies was introduced the method of multiple correlation and integration among variables which were only defined as single predictors of that phenomenon. Statistically, to confirm the importance of this aspect, the predictive discrimination power of our score (measured by AUC in ROC analysis) was very high (AUC 0.90, $P < 0.001$).

With regard to the oxygen desaturation exercise-induced tests, preview studies [30] [32] did not refer to validated and 6MWT-correlated tests (e.g. 3-min step-test [32]) for assessing desaturation, nor indicated any clear criteria. In recent years, 6MWT has been used more widely in clinical practice, showing to be the most sensitive test to identify any exercise-induced desaturation [8-11] and to evaluate the short-term response to supplemental oxygen [24].

Furthermore, and in contrast with other non-walking exercise test, 6MWT reproduces more typical efforts of the daily life [34] and this aspect has an excellent relationship with the ability of COPD patients to perform daily activities: from this point of view, the ability of our WDS to define desaturation likelihood by 6MWT, adds new information that may help in the daily management of COPD's life.

In our study, baseline characteristics were clearly different among the two cohorts (stratified by temporal and spatial technique [28]) (see Table 1). We infer that this was due to patients coming from different scenarios; in particular, for example, the network of ambulatories in the community care is clearly a setting where less severe and disabled patients are normally observed and treated. A potential benefit stemming from the baseline variability in the two cohorts extends the validation data to a wider set of COPD stages, facilitating the process of recording relatively easy-to-catch variables directly able to predict the patient's complexity. Especially in this cohort of patients, the chance to accurately identify WD^+ individuals can eventually lead to very relevant prognostic consequences and clinical options in the long-term management of patients.

Despite our original findings, our study has two limitations which need to be kept in consideration when assigning a clinical value to the reported evidences.

First, the selection criteria adopted to identify any possible co-morbidity (likely present in COPD patients and causing oxygen perturbations) in our patients for the derivation and the validation cohort was exclusively based on reported (by Charlson items) or clinically evident disease. For this reason we have excluded *a priori* all COPD patients with associated diseases (median score of un-adjusted Charlson index=1). Thus, we cannot exclude that COPD patients with associated co-morbidities at a sub-clinical level might have a theoretically biased set of

results. However, we were not in the ability to specifically assess any of the co-morbidities usually present in a COPD patient in our clinical setting. In any case, this would have even lead to a possible under-estimation of the true prevalence of the co-morbidities themselves.

Second, diffusion lung capacity (DL_{CO}) measurement was not planned for assessment in our study population. At this regard, two studies [30,32] , previously conducted in an unselected population including different chronic lung diseases, shown DL_{CO} as a functional variable able to predict oxygen desaturation during exercise. Even if this variable has demonstrated to play a prevalent role in interstitial lung diseases [35] we cannot exclude that COPD with an emphysema phenotype might have a reduced value of DL_{CO} . Another study [31], showing DL_{CO} as the screening test to identify desaturators among COPD patients, was unfortunately conducted in only 48 patients and, in addition, did not consider the standard walking test to properly assess desaturation while on exercise. Future studies specifically designed to answer this question will clarify the point.

To conclude, our study report an original attempt aimed at identifying statistically derived stratifiers to model the risk of desaturation during 6MWT in a pure COPD population by a simple score (WDS) calculated from basal functions. To our best knowledge, this information was never elaborated before but could be of relevant usefulness in the COPD management at the community level outside any specialistic setting. Finally, this approach might be really useful and easy to use to obtain rapid information along the clinical decision making process in these patients.

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FIGURE LEGENDS

Figure 1. Study Flow Diagram.

Legend

PR: Pulmonary rehabilitation; COPD: Chronic obstructive pulmonary disease; CRF: Chronic respiratory failure; SpO₂: Oxygen saturation; 6MWT: 6-minute walking test.

Figure 2. Regression Analysis in the Derivation Cohort.

Legend

FEV₁ % pred.: Forced expiratory volume in the 1st second, % predicted; PaO₂: Partial pressure of oxygen; SO₂: Oxygen saturation; R²: Squared regression coefficient as measure of explained variance.

Figure 3. Distribution of Risk Estimate according WDS (Panel A) and Categories of Risk (Panel B) among WD⁺ COPD Patients in the Validation Cohort.

Legend

WDS: Walking Desaturation Score.

[#]OR-Odds ratio estimate for walking desaturation according a fall $\geq 4\%$ from SpO₂ to a value of SpO₂ nadir $\leq 89\%$ (WD⁺ and grey bars) or $\geq 90\%$ (WD⁻ and black bars). 95% CI: Confidence interval of OR.

[†]NA-not applicable, risk estimate analysis cannot be computed for empty cells in a 2x2 table.

[§]Analysis of difference in the probability of walking desaturation between the difference risk groups calculated by the formula $(P_{HR} - P_{LR}) \div 100$ (see methods).

Figure 4. Receiver Operating Curve (ROC) in the Validation Cohort.

Legend

WDS: Walking Desaturation Score.

Figure 5. Mean Distribution of BODE and ADO Score according to the WDS and Categories of Risk.

Legend

WDS: Walking Desaturation Score; BODE (Index composed by Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity values); ADO (Index composed by Age, Dyspnoea and airflow Obstruction values); 95% CI: Confidence interval.

[§]Analysis of mean comparison between groups.

****P<0.001.**

Table 1. Descriptive Data of Enrolled Patients.

Variables	Derivation cohort (<i>n</i> = 435)	Validation cohort (<i>n</i> = 238)
Age, yr.	72 (56-84)	72 (53-82)
Male/Female, No	286/153	176/62 [*]
Body mass index, kg/m ²	26.5 ± 5.2	26.5 ± 3.7
Charlson index [†]	1 (1-2)	1 (1-2)
GOLD stage I/II/III/IV, %	6.9/48.0/36.6/8.5	17.6/59.7/21.0/1.7 ^{**}
FEV ₁ , liters	1.13 ± 0.44	1.54 ± 0.54 ^{**}
FEV ₁ , % predicted	52.3 ± 16.0	63.9 ± 16.8 ^{**}
FVC, liters	1.89 ± 0.72	2.66 ± 0.85 ^{**}
FVC, % predicted	80.0 ± 20.6	89.4 ± 48.0 ^{**}
PaO ₂ , mmHg	68.9 ± 7.3	72.9 ± 7.9 ^{**}
PaCO ₂ , mmHg	40.4 ± 5.1	39.3 ± 4.2 [*]
6MWT, meters walked at	378.3 ± 88.5	415.9 ± 76.7 ^{**}
SO ₂ , %	93.6 ± 1.8	94.8 ± 1.6 ^{**}
SpO ₂ nadir, %	86.9 ± 4.4	90.1 ± 4.0 ^{**}
MRC grade, score	3 (2-5)	3 (1-5) [*]
WD [‡] , No (%)	324 (74)	89 (37) ^{**}

Data are presented as median (5th-95th percentiles), mean ± standard deviation or No (%) if appropriate.

^{*}and ^{**} Statistical analysis performed versus derivation cohort with P value <0.05 and <0.01, respectively.

[†]Calculated including COPD and age uncorrected; a higher score of Charlson index indicate more coexisting co-morbidities.

[‡]Defined by a variation ≥ 4% from SpO₂ to a value of SpO₂ nadir ≤ 89% (WD⁺) or ≥ 90% (WD⁻) [24].

Legend

FEV₁: Forced expiratory volume in the 1st second; FVC: Forced vital capacity; PaO₂: Partial pressure of oxygen; PaCO₂: Partial pressure of carbon dioxide; 6MWT: 6-minute walking test; SO₂: Arterial oxygen saturation; SpO₂ nadir: minimum value of oxygen saturation measured by pulse-oximetry; MRC: Medical research council dyspnoea scale with a range 1-5, 5 indicating a major perceived breathlessness; WD⁺: Walking desaturators.

Table 2. Bivariate Correlation between COPD Characteristics and SpO₂ Nadir in the Derivation Cohort.

Variables	No	Correlation coefficient [†]
Age	435	-0.008
Sex	435	0.011
BMI	435	0.087
Charlson index	435	-0.073
FEV ₁ , liters	431	0.311 ^{**}
FEV ₁ , % predicted	431	0.418 ^{**}
FVC, liters	431	0.191 ^{**}
FVC, % predicted	431	0.261 ^{**}
PaO ₂	429	0.508 ^{**}
PaCO ₂	429	-0.244 ^{**}
SO ₂	429	0.653 ^{**}
6MWT	435	0.116 [*]
MRC grade	435	-0.153 ^{**}

* and ** P value <0.05 and <0.01, respectively.

[†]Pearson (*r*) or Spearman rho (*ρ*) analyses were applied depending on the type of variable.

Legend

See Table 1.

Table 3. Multivariate Linear Stepwise Regression Analysis for associated significant factors predicting Walking Oxygen Desaturation in the Derivation Cohort.

Dependent variable: SpO ₂ nadir	Variable	b^{\dagger}	SE †	95% CI	β^{\ddagger}	t	P value
	SO ₂	1.18	0.08	1.01 to 1.34	0.50	13.87	<0.001
	PaO ₂	0.12	0.02	0.07 to 0.16	0.20	5.51	<0.001
	FEV ₁ % pred.	0.08	0.00	0.06 to 0.09	0.29	8.97	<0.001
	(Constant)	-36.34	7.35	-50.79 to -21.89		-4.94	

R²: 0.558; SE of estimate: 2.94; R² change: 0.031; F change: 30.394.

Legend

See Table 1; SE and 95% CI: standard error and 95% confidence interval of b coefficient.

Stepwise criteria: probability of F to enter ≤ 0.05 , probability of F to remove ≥ 0.10 .

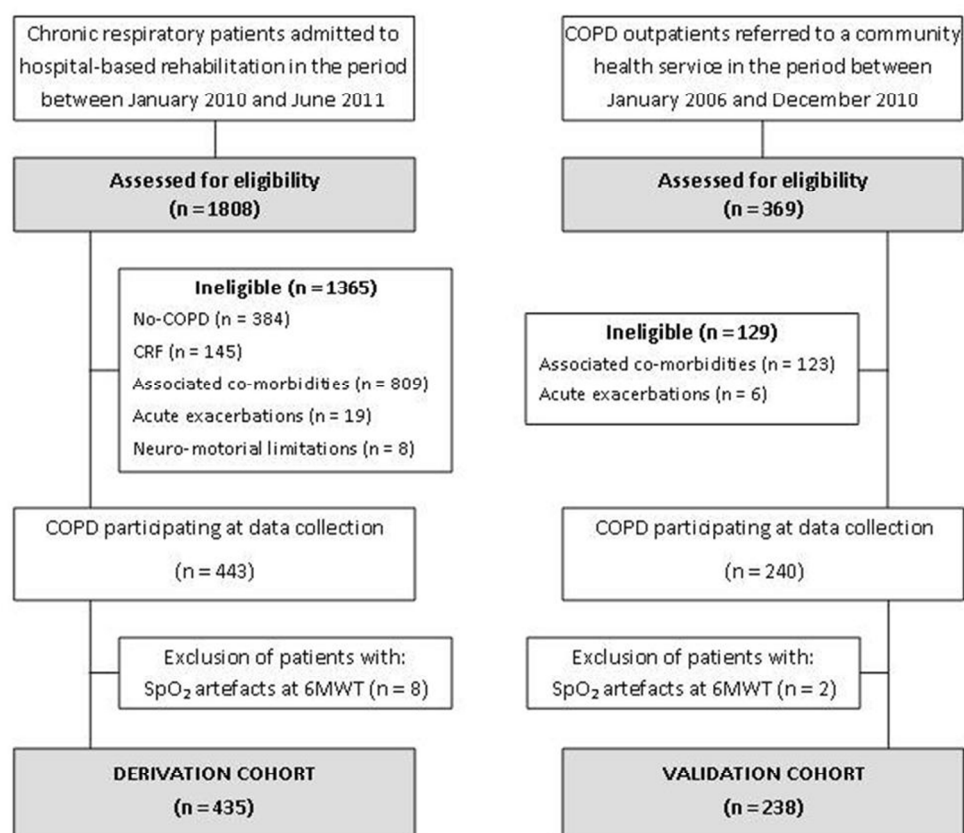
† and ‡ : Unstandardized and standardized coefficients, respectively.

Table 4. The Scoring System of WDS.

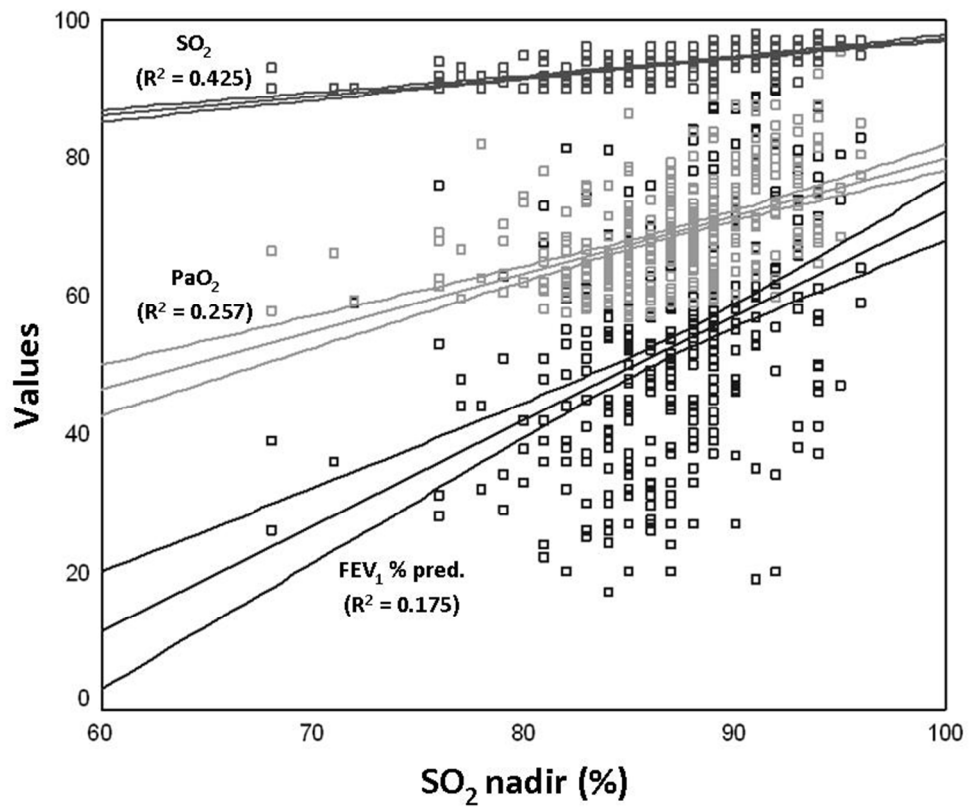
	Points at WDS			
	0	1	2	3
SO ₂ , %	≥ 96	95	94-93	≤92
PaO ₂ , mmHg	≥ 71	66-70	≤ 65	
FEV ₁ , % predicted	≥ 53	< 52		

Legend

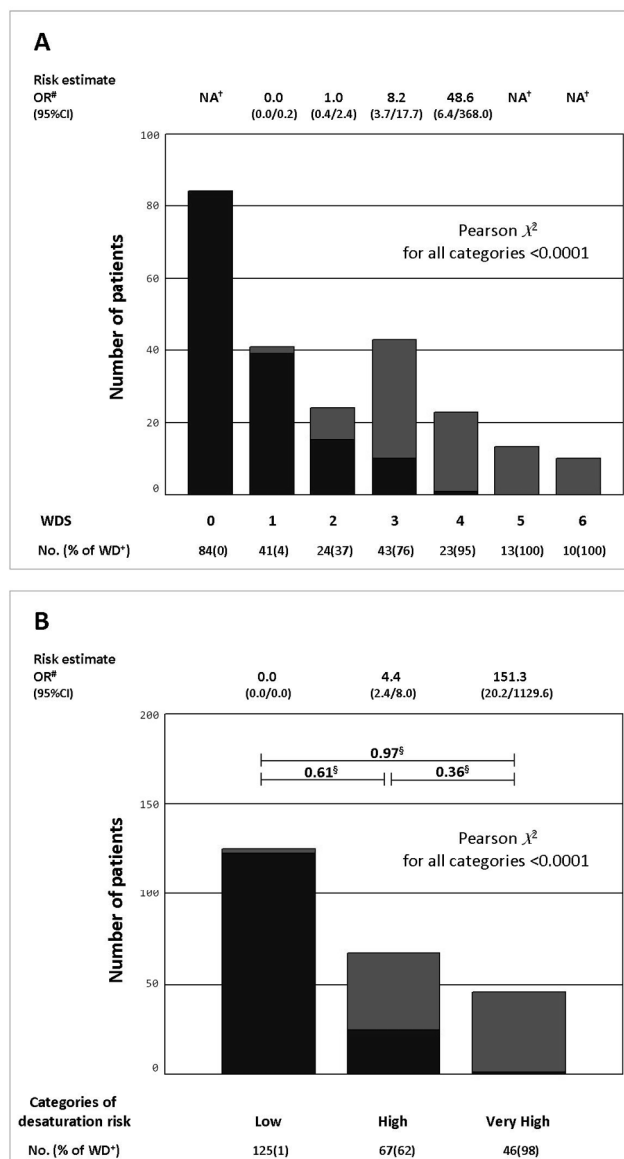
WDS: Walking desaturation score; see also table 1.



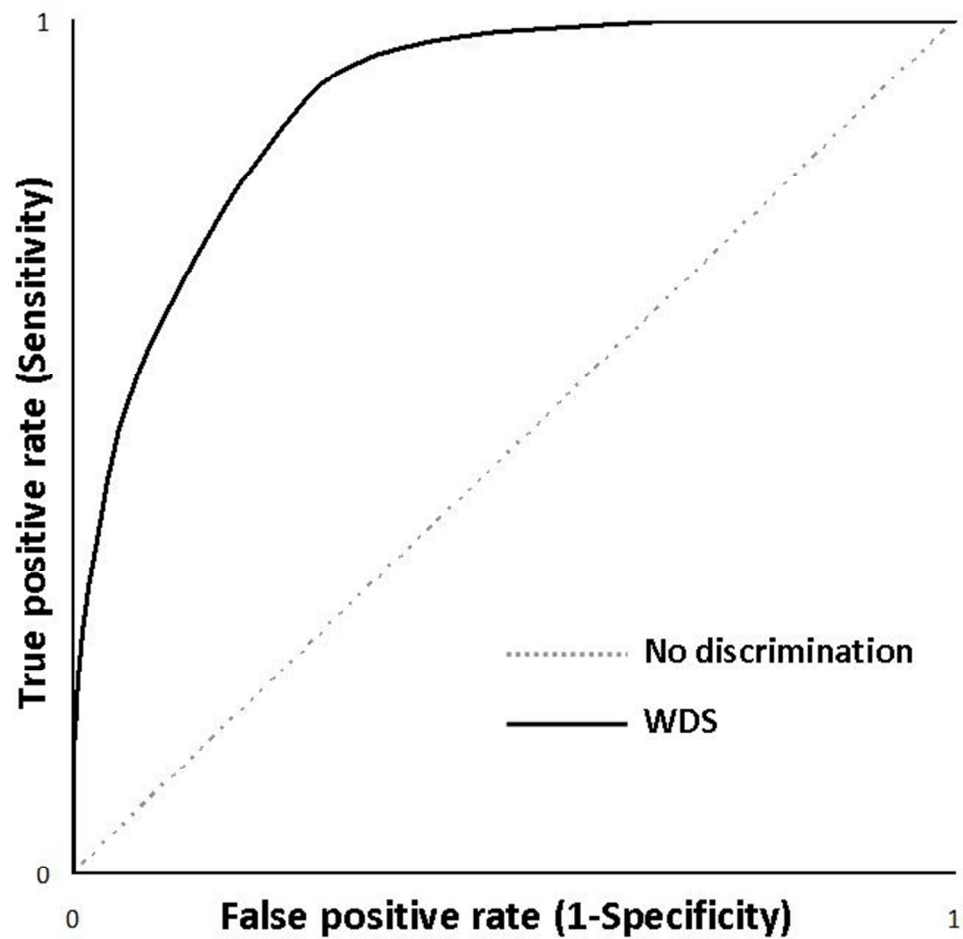
86x75mm (300 x 300 DPI)



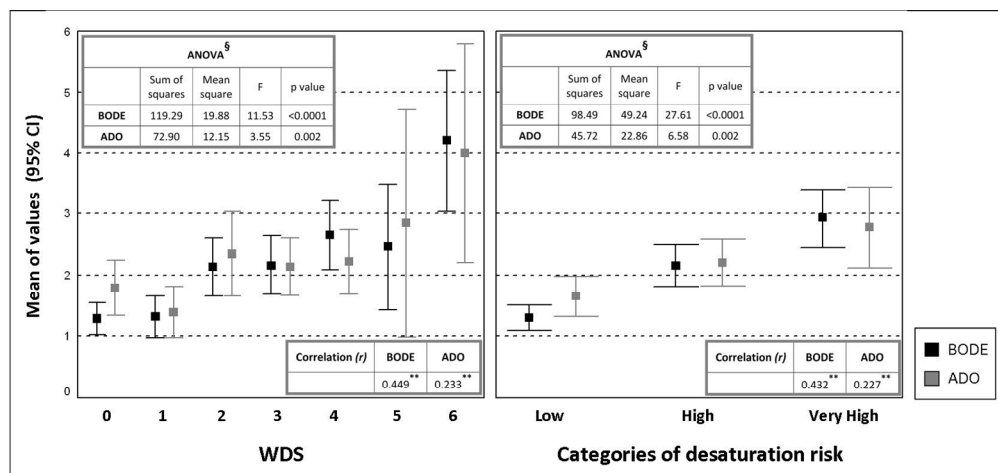
73x60mm (300 x 300 DPI)



103x186mm (300 x 300 DPI)



57x56mm (300 x 300 DPI)



141x66mm (300 x 300 DPI)