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Original Article

Identifying COPD patients with poor health status and low exercise tolerance through the five-repetition sit-to-stand test and modified Medical Research Council Dyspnea Score

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ABSTRACT

Background: The objective of this study was to determine whether the concomitant presence of poor health status (COPD Assessment Test, CAT $\geq$ 10 points) and low exercise tolerance (6-Minute Walking Test, 6MWT $<$ 350 m) is associated with worse clinical characteristics in patients with COPD. In addition, we aimed to develop a readily applicable diagnostic model to discriminate COPD patients with these conditions.
Methods: A cross-sectional multicenter study involving 208 stable COPD patients (FEV1/FVC $<$ 0.7, smoking history of at least 10 pack-years, and chronic respiratory symptoms) was carried out. The outcome measures were the 6MWT, CAT score, 5-repetition sit-to-stand test (5STS) and modified Medical Research Council Dyspnea Scale (mMRC). Patients were categorized into three groups: no condition (6MWT $\geq$ 350 m and CAT $<$ 10 points), one condition (6MWT $<$ 350 m or CAT $\geq$ 10 points), and both conditions (6MWT $<$ 350 m and CAT $\geq$ 10 points).
Results: A total of 26 patients (12,5%) presented both conditions. These patients experienced a higher degree of dyspnea (p = 0.001), smoking pack-years (p = 0.011), severe obstruction (p = 0.006), and time on 5STS (p = 0.001). The probability of having both conditions directly increased with the time spent on the 5STS (β=0.188; p = 0.010) and the degree of dyspnea (β=1.920; $p < 0.001$) (R^2=0.413). The scoring system, using the 5STS and dyspnea as surrogate measures, demonstrated adequate calibration between the predicted and observed risk (linear R^2=0.852).
Conclusions: COPD patients with concurrent conditions have worse clinical status. The diagnostic model developed to discriminate these patients shows good internal validation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous and systemic condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways and/or alveoli that cause persistent, often progressive, airflow obstruction. COPD is a major cause of morbidity because affected individuals experience chronic and progressive respiratory symptoms [1]. In 2019, the global prevalence of COPD among subjects in a 30-to-79 age range, according to the case definition provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2], was 10.3% (95% CI 8.2–12.8), and it is currently the third leading cause of death worldwide, causing 3.23 million deaths in 2019 [3]. Moreover, COPD has an important economic burden, with high direct and indirect costs [4].

Patients with COPD present a wide variety of symptoms, from reduced mobility to psychosocial problems. Due to the multidimensionality of the disease, the evaluation and management of patients represents a handicap for clinicians and health managers. Thus, there is a growing tendency to use measures based on scoring systems in which different instruments are applied concurrently, such as the BODE index

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[5] and the GOLD classification [1]. These scoring systems include, in addition to “more classical” pulmonary markers (FEV_1), other important non-pulmonary markers, such as exercise tolerance measured by the 6-minute walk test (6MWT) and health status measured by the COPD Assessment Test (CAT) score. These two measures have also been shown to be individually relevant for patients with COPD. Low exercise tolerance, defined by a performance of less than 350 m in the 6MWT, is associated with a significant increase in mortality, a high risk of exacerbation, and rehospitalization [6–8]. Futhermore, poor health status, defined by a CAT score $\geq$ 10 points, is associated with the severity of airflow limitation [9], dyspnea [10], and severity of exacerbations [11, 12].

Despite their relevance as individual measures and as part of international scoring systems, the concurrent occurrence of poor health status and low exercise tolerance (measured by means of the CAT score and 6MWT, respectively) has not been explored yet. Thus, data on the prevalence of COPD patients with both conditions, as well as differences in their clinical profile, remain unknown. Since one of the potential limitations of the concurrent use of both measures (CAT and 6MWT) is time and space constraints in clinical practice, the implementation of easier and faster measures could be more useful for the identification of these patients in research and clinical routine. In this sense, the 5-repetition sit-to-stand test (5STS) and the modified Medical Research Council Dyspnea Scale (mMRC) are feasible surrogate measures for exercise tolerance and health status, respectively. The 5STS has been shown to be a reliable predictor of poor performance on the 6MWT [13]. On the other hand, the mMRC has demonstrated a clear relationship with health status scores, and high mMRC scores are associated with impaired health status [10].

The main objective of the current study was to identify patients with COPD who present poor health status (CAT $\geq$ 10 points) and low exercise tolerance (6MWT $<$ 350 m) concurrently, and to determine whether they display worse pulmonary and non-pulmonary characteristics. Additionally, we sought to develop an easily applicable diagnostic model that can correctly discriminate these patients.

2. Material and methods

2.1. Design and participants

Data for this cross-sectional study were extracted from the primary study “AST-SAQ-2017–01″ (Spanish Activity Questionnaire in COPD), a prospective, observational, multicenter study involving 13 centers (11 specialist care centers and 2 primary care centers) in eight Spanish autonomous communities. The study was conducted for the development and validation of a physical activity questionnaire in patients with COPD [14]. The study protocol was approved by the ethics committees of all the centers involved in the research. All patients signed informed consent prior to their inclusion in the study.

Inclusion criteria for participation in the study were: diagnosis of COPD ($FEV_1/FVC < 0.7$, smoking history of at least 10 pack-years, and chronic respiratory symptoms) and stable condition of the disease (absence of occurrence of moderate-to-severe COPD exacerbations in the four weeks prior to the study onset). Patients with severe physical and/or cognitive limitations due to their inability to perform the physical tests and/or complete the questionnaires were excluded.

Patients were consecutively recruited from the participating centers, controlling for a similar patient proportion based on the severity of airflow restriction according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease [15]. We estimated the sample size based on the rule of thumb that at least 15 subjects per predictor are needed for a reliable equation in multiple regression models [16]. As such, 208 subjects were recruited, assuming a maximum of 11 predictors and 18 subjects per predictor.

Further information on the design and recruitment of participants is available in the research article on the observational study AST-SAQ-2017–01 [14].

2.2. Health status and exercise tolerance

The main outcome measures were health status and exercise tolerance. Health status was measured by the CAT. This reliable and validated tool is composed of eight items, and the score for each item ranges from 0 to 5 (maximum total score = 40 points), with higher scores indicating a higher burden of symptoms. A cut-off score of 10 points was used to differentiate health status ($\geq$10 = "poor health status") [1]. Exercise tolerance was measured by means of the 6MWT. It was performed indoors, along a flat, straight, 30-meter walking course, supervised by well-trained nurses (mean experience of 19 years) according to the American Thoracic Society guidelines [17]. Performance below 350 m in the 6MWT was considered “low exercise tolerance” [17].

2.3. Demographic and clinical characteristics

Demographic variables included age, sex, and education level. Clinical variables included airflow limitation based on the% FEV_1 post-BD according to the American Thoracic Society guidelines [17], smoking pack-years, current smoking status (yes/no); body mass index (kg/m^2), number of comorbidities (Charlson Comorbidity Index) [18], history of heart disease, the 5STS, and the severity of dyspnea based on the mMRC [19], which was developed by the American Thoracic Society as a modification of the originally proposed British Medical Research Council Dyspnea Index. In the 5STS, participants were asked to rise from a chair five times as fast as possible with their arms folded across their chests. The chair was of a standard height (0.43 m) without armrests [13].

2.4. Statistical analyses

A chi-squared test for independence was performed to explore the association between health status and exercise tolerance. Descriptive statistics were used to characterize our whole sample and the three groups of patients, i.e. no condition (patients with 6MWT $\geq$ 350 m and CAT $<$ 10 points), one condition (patients with 6MWT $<$ 350 m or CAT $\geq$ 10 points), and both conditions (patients with 6MWT $<$ 350 m and CAT $\geq$ 10 points). One-way ANOVA with Tukey post-hoc analysis was used to examine between-group differences.

Univariate analysis and multivariate binary logistic regression (forward method) were used to preselect and define variables for the diagnostic model, respectively. Across all analyses, the dependent variable had two categories: patients with both conditions vs. others. To prevent omission bias, variables with $p \leq 0.10$ in the univariate models were retained and considered for further multivariable forward logistic regression analysis. That analysis underwent a two-tailed test using critical p-values for entry ($p \leq 0.05$) and removal ($p \geq 0.10$). The regression coefficients of the multivariate model were used to develop the scoring system. P-values $<$ 0.05 were considered significant in all analyses.

Collinearity statistics (e.g., tolerance, which is associated with each independent variable and ranges from 0 to 1, with smaller values of tolerance denoting higher levels of multicollinearity) were calculated to explore intercorrelations among independent variables and to prevent spurious relationships in that analysis. Whenever the tolerance of a variable was $\leq$0.10, the aforementioned variable was excluded from the multivariate analysis [20].

Next, variables were integrated into a simplified scoring system. To create this scoring system, four categories were defined for each variable based on their discriminative ability to identify patients with low exercise tolerance and poor health status, generating a point-assignment system. Briefly, to define the different categories, a ROC curve was used to examine the ability of each variable and, therefore, its underlying test to discriminate individual participants with both conditions.

Three cut-off points were selected on the curve: the two extreme values were the maximum Youden index and the highest specific value of poor health status, and the intermediate point was established in the middle of the aforementioned values in order to have the same number of units in each one of the two intermediate categories. To build-up the point-assignment system for these categories, scores were generated by a methodology based on the regression coefficients obtained for each variable in the corresponding multivariable model, which is a methodology widely used for indices [21,22].

The discriminant ability of the index was quantified using the area under the ROC curve (AUC). Finally, to calibrate the point system, the probability of having both conditions predicted by the index was compared to the actual observed proportion in the sample using calibration plots.

All analyses were performed using SPSS software version 28.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Sample characteristics

A total of 208 patients were included in the sample. Mean age (standard deviation, SD) was 67.38 (8.19) years, and 154 patients (74%) were male. A total of 125 patients (60.1%) had poor health status, including 26 patients (20.8%) who also presented low exercise tolerance. In contrast, only 5 (6.1%) of the 83 patients with good health status (i.e., CAT<10) had that impairment. A chi-squared test for independence indicated a significant association between health status and exercise tolerance (χ^2=8.58; df =1; p = 0.003).

A total of 26 patients presented both conditions: low exercise tolerance (6MWT: mean 291.93 ± 94.21) and poor health status (CAT: mean 20.53 ± 6.52), whereas 78 (35%) patients did not present any of these impairments, and 104 individuals had either poor 6MWT performance (<350 m) or poor health status (CAT ≥10 points). Patients with both conditions (vs. one or none) displayed higher mean scores of dyspnea (3.38 ± 0.49 *vs* 2.65 ± 0.69 and 1.95 ± 0.60; p = 0.001), higher figures of smoking pack-years (63.67 ± 38.72 *vs* 50.88 ± 31.99 and 44.25 ± 18.04; p = 0.011), worse performances on the 5STS (13.92 ± 3.05 *vs* 11.24 ± 2.91 and 10.35 ± 2.68; p = 0.001), and higher proportion of patients with severe obstruction based on the GOLD criteria (76.9% vs 50.0% and 35.9%; p = 0.006). Concerning airflow limitation, in the group of 26 patients with 6MWT < 350 m and CAT ≥ 10 points, 20 participants (76.9%) showed FEV_1<50%. Further information on the sociodemographic and clinical (pulmonary- and non-pulmonary-related variables) characteristics of the sample is provided in Table 1.

3.2. Development and presentation of the model

Table 2 shows the two characteristics that were included in the final multivariable model. The model significantly fitted the data [χ^2 (df=2, N = 74) = 63.25, p < 0.001], and it explained 41.3% of the variance (R^2=0.413). The AUC of the model was 0.910 [95% confidence interval (CI): 0.869–0.951]. According to the model, the probability of having both poor health status and low exercise tolerance increased with the time spent performing the 5STS (β=0.188; p = 0.010) and the degree of dyspnea (β=1.920, p < 0.001; Table 2). Collinearity statistics revealed an absence of a high association between these significant variables (tolerance for each independent variable > 0.25). The estimated model with bootstrapping techniques evidenced the absence of over-optimism, as the shrinkage factor was 0.9 (i.e., >0.85), and no adjustment was applied for overfitting.

The scoring system developed from the final model is shown in Table 3. Scores were assigned to categories of dyspnea and 5STS, and the total score ranged from 0 to 6. Table 3 also provides the probabilities of the outcome (i.e., having poor health status and low exercise tolerance) corresponding to the total points. The probability corresponding to a “0”

Table 1
Sociodemographic and Clinical Characteristics of Participants.

Variables	All patients (n = 208)	Good tolerance and health status[1] (n = 78)	Low tolerance or poor health status[2] (n = 104)	Low tolerance and poor health status[3] (n = 26)	p-value
Demographic					
Age (years)	67.38 ± 8.19	67.10 ± 8.04	67.01 ± 8.60	68.62 ± 8.21	0.667
Sex (male)	154 (74.0)	57 (73.1)	78 (75.3)	20 (76.9)	0.915
Education level					0.872
No formal education	9 (4.3)	3 (3.8)	6 (5.6)	0 (0.0)	
Primary	61 (29.3)	24 (30.8)	26 (24.7)	11 (42.3)	
Secondary	85 (40.8)	31 (39.7)	44 (42.7)	10 (38.5)	
University	53 (25.5)	20 (25.6)	28 (26.9)	5 (19.2)	
Clinical: Pulmonary					
Dyspnea	2.46 ± 0.78	1.95 ± 0.60	2.65 ± 0.69	3.38 ± 0.49	0.001*
Airflow limitation (GOLD)					0.006*
FEV1 (%) ≥80%	39 (18.8)	20 (25.6)	19 (18.2)	0 (0.0)	
FEV1 (%) 50–80%	69 (33.2)	30 (38.5)	33 (31.7)	6 (23.1)	
FEV1 (%): <50%	100 (48.1)	28 (35.9)	52 (50.0)	20 (76.9)	
Smoking pack-years	49.22 ± 28.20	44.25 ± 18.04	50.88 ± 31.99	63.67 ± 38.72	0.011**
Current smoker	39 (18.8)	12 (15.3)	24 (23.0)	3 (11.5)	0.253
CAT	12.35 ± 7.22	5.29 ± 2.29	17.31 ± 5.55	20.53 ± 6.52	0.001*
Clinical: Non-pulmonary					
Number of comorbidities	1.61 ± 1.11	1.42 ± 0.86	1.64 ± 1.06	1.76 ± 0.96	0.190
Heart failure	9 (4.3)	5 (6.4)	2 (1.9)	2 (7.6)	0.225
5STS	11.26 ± 3.26	10.35 ± 2.68	11.24 ± 2.91	13.92 ± 3.05	0.001**
6MWT	463.79 ± 106.17	510.74 ± 75.49	429.12 ± 109.20	291.93 ± 94.21	0.001*
BMI (kg/m2)	27.02± 4.58	26.73 ± 3.82	27.12 ± 5.11	27.35 ± 5.98	0.798

Data presented in frequencies (percentage) or mean ± standard deviation.

[1] Patients with 6MWT > 350 m and CAT < 10;.

[2] Patients with 6MWT < 350 m or CAT >10;.

[3] Patients with 6MWT < 350 m and CAT < 10.

* All groups differ in paired comparisons (Tukey post-hoc analysis for Dyspnea, CAT, and 6MWT; Dunn’s post-analysis for Airflow limitation).

** Group of patients with 6MWT < 350 m and CAT > 10 (n = 26) differs from the extant two groups (Tukey post-hoc analysis).

Table 2
Regression Coefficients and risk score for the scoring system.

Variable	Regression coefficients β_s	Category	Reference values W_{ij} (midpoint)	β_sx (W_{ij}-$W_{ireference}$)	Risk Score* [β_sx(W_{ij}-$W_{ireference}$)]/B
5 STS	0.188 ($p <$ 0.001)	< 12	10 (W_1 reference)	N/A	0
		12–16	14	0.768	1
		16–20	18	1.53	1
		> 20	23	2.49	2
Dyspnea	1.920 ($p =$ 0.01)	0	0 (W_1 reference)	N/A	0
		1	1	1.920	1
		2	2	3.840	2
		3	3	5.760	3
		4	4	7.680	4

N/A: Non Applicable.
B: B corresponds to an important change in the performance of the 5STS test, which is equivalent to a coefficient of 0.188. As for dyspnea, B corresponds to an important change in the degree of dyspnea, which is equivalent to a coefficient of 1.920.
* Points rounded to the next integer.

Table 3
Point-Score System (a) and Probabilities (b) corresponding to the Points Total.

(a)

Predictor Categories	Points
5STS (*sec*)	
<12	0
12–19.9	1
>20	2
Dyspnea (mMRC)	
0	0
1	1
2	2
3	3
4	4

(b)

Point total	Probability
0	0.000
1	0.002
2	0.016
3	0.072
4	0.255
5	0.639
6	0.894

score was 0% because none of the participants scored “0″ according to the newly developed scoring system.

3.3. Performance of the scoring system

Concerning the discrimination of the scoring system, the AUC was 0.883 (95% CI: 0.829–0.938). The probability of having both conditions predicted by the scoring system was compared to the actual observed proportion in the sample using calibration plots. Fig. 1 displays the calibration plot of the index for both conditions, showing excellent calibration between the predicted and observed risks.

The actual relationship between both risks showed a calibration intercept close to 0, a slope of 0.92, and a linear R^2 of 0.852, corresponding to an almost perfect calibration in which the predicted risk equals the observed risk for patients with both low exercise tolerance and poor health status.

4. Discussion

Our main objective was to identify those patients with stable COPD concurrently showing poor health status and exercise tolerance (measured through the CAT and 6MWT, respectively), and to explore whether these patients exhibited worse pulmonary and non-pulmonary characteristics. Subsequently, we developed a scoring system from regression models, using two more practical surrogate measures, the 5STS and mMRC, to discriminate these patients.

More than 10% of the patients in the current study presented both conditions (i.e., CAT ≥ 10 points and 6MWT < 350 m). However, this prevalence could be higher in other contexts or among patients with exacerbations. These patients had a worse clinical profile than patients in the group with one or no condition, with greater airflow limitation, higher levels of dyspnea, greater smoking pack-years, and more time needed to perform the 5STS.

Although airflow limitation and smoking pack-years were associated with having both conditions in the univariate analyses, they were not retained in the final model. Thus, the results stemming from our research confirm that airflow limitation may be less relevant for determining health status in stable COPD patients than other variables, as expounded by other authors [23,24], The mMRC and 5STS were independent predictors and explained 41% of the variance in the model. The 5STS has already shown an excellent discriminative capacity for exercise tolerance [13] and it has been identified as a predictive factor of severe exacerbations in COPD [25]. Its prognostic value for mortality in COPD has also been reported [26]. Notably, the mMRC is easily applicable, and the CAT and mMRC scores can be used interchangeably and reliably as better objective scales [27], though caution has been suggested in using the mMRC as a surrogate measure for the CAT [28]. Our results confirm that these measures can be applied to identify patients with low exercise tolerance and poor health status concomitantly.

Previous models developed with the aim of predicting health status in COPD patients [29–31] solely included the assessment of either symptoms or exercise tolerance. The current research presents a model based on combined measures: symptom assessment by the CAT and a performance-based test, the 6MWT. Furthermore, both surrogate measures (mMRC and 5STS) are highly efficient, as they require less time, resources, and initial expertise than the former measures.

4.1. Implications for clinical practice

The early identification of individuals with both low physical performance and poor health status is of paramount importance to adequate define their therapeutic approach. The predictive model developed in the current research, alongside its associated point system, may assist clinicians, physiotherapists, and health professionals in understanding the patient’s condition and predicting its evolution, improving the therapeutic management and/or referral of the patient. For instance, it can ease the identification of those patients who could benefit from early receiving preventative strategies or treatments for improving functional performance, and thus, for providing motivation for coping. Since the surrogate measures suggested (mMRC and 5STS) are cost-efficient in terms of effort and time, the use of this assessment could be systematically implemented in daily clinical practice and in future research in the field.

4.2. Study limitations

The results stemming from the current study should be interpreted in light of its methodological limitations. First, as our study represents the starting point for the suggested model, its external validation has not yet been performed. Further data should be collected and used by other researchers and at different clinical sites to generalize the model. Second, some specific aspects on the history of the disease (v.g. years from the initial diagnosis) were not considered in the current study, and it

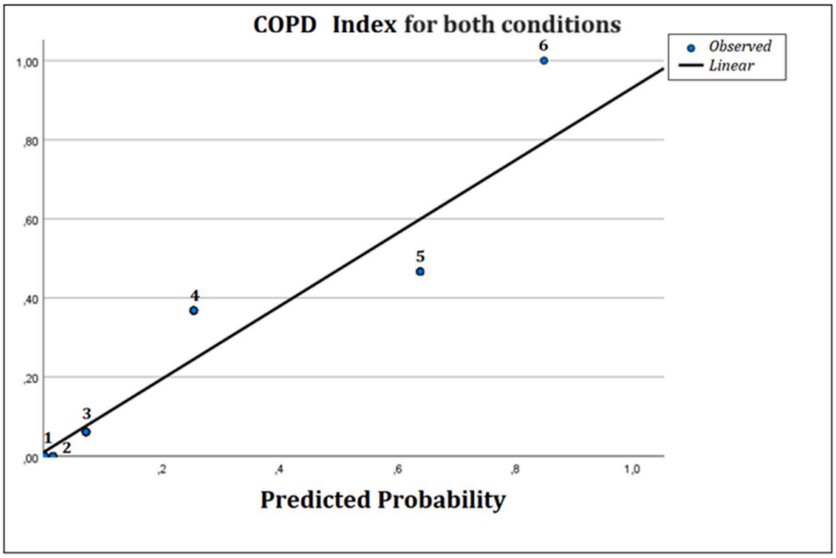

Fig. 1. Calibration Plot of the Scoring System.

could have a potential impact on the extrapolation of our findings. Finally, our model was based on a 10-point cut-off concerning the CAT score as proposed by the GOLD guidelines; future research could explore different points, as reported by other researchers. Also, the potential categorization of patients in future research could be based on their predicted scores and performance of the 6MWT instead of adopting an standardized and "universal" cut-off point.

5. Conclusion

Patients with stable COPD who present poor health status and low exercise tolerance display worse pulmonary and non-pulmonary characteristics. The predictive model developed and its associated point system shows good internal validation in identifying these patients. The assessment instruments included in our model require little time and resources, fact that supports and endorses its clinical implementation.

Declaration of competing interest

None.

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