Influence of physical activity on the prognosis of COPD patients: the HADO.2 score – health, activity, dyspnoea and obstruction

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Physical activity is a key variable in the evaluation of COPD patients and should be included in the multidimensional prognosis scores of COPD. https://bit.ly/491hOm2

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Abstract

Objective The aim of this study was to create a prognostic instrument for COPD with a multidimensional perspective that includes physical activity (PA). The score also included health status, dyspnoea and forced expiratory volume in 1 s (HADO.2 score).

Methods A prospective, observational, non-intervention study was carried out. Patients were recruited from the six outpatient clinics of the respiratory service of a single university hospital. The component variables of the HADO.2 score and BODE index were studied, and PA was measured using an accelerometer. The outcomes for the HADO.2 score were mortality and hospitalisations during follow-up and an exploration of the correlation with health-related quality of life at the moment of inclusion in the study.

Results 401 patients were included in the study and followed up for three years. The HADO.2 score showed good predictive capacity for mortality: C-index 0.79 (0.72–0.85). The C-index for hospitalisations was 0.72 (0.66–0.77) and the predictive ability for quality of life, as measured by R2, was 0.63 and 0.53 respectively for the Saint George's Respiratory Questionnaire and COPD Assessment Test.

Conclusions There was no statistically significant difference between the mortality predictive capacity of the HADO.2 score and the BODE index. Adding PA to the original BODE index significantly improved the predictive capacity of the index. The HADO.2 score, which includes PA as a key variable, showed good predictive capacity for mortality and hospitalisations. There were no differences in the predictive capacity of the HADO.2 score and the BODE index.

Introduction

COPD is a heterogeneous lung condition in which patients suffer diverse symptoms due to structural changes in the airways and lung parenchyma [1]. Moreover, the consequences of COPD for homeostasis and the function of other organs and systems extend beyond the respiratory system, making this disease a multifaceted condition [2].

This "systemic scenario" impacts the evaluation and treatment of the different subtypes of COPD patient, resulting in a more precise medicine. In this approach, it is essential to establish an accurate prognosis.

In recent years, the use of multidimensional tools in the evaluation and prognosis of COPD patients has become increasingly widespread. The BODE index (body mass index, airflow obstruction, dyspnoea, exercise capacity) has marked a turning point in prediction of the prognosis (mortality) of COPD patients [3]

and is now the most widely used tool for this task. Taking the BODE index as a reference, several other indexes have been created that seek to improve on its prognostic capacity and usability [4–6].

On the presumption that there is no one gold-standard predictive instrument, we should all, ideally, "speak the same language" (for example, BODE). However, given that there are multiple facets to the disease that are being overlooked in the predictive indexes currently being used, it is essential to improve the predictive capacity of these tools until such time as new forms of evaluation can be implemented, based on new technologies.

Physical activity (PA) plays a key role in health and disease. In COPD its importance has been established in epidemiological and observational studies and through measurement with questionnaires and accelerometers [7–9]. Indeed, PA has been indicated to be the main predictor of mortality in COPD patients [10]. The HADO (health, activity, dyspnoea, obstruction) score was created to be a predictive instrument of mortality at least as good as BODE [11] that uses self-reported PA as a key element for scoring (C-statistic 0.682) [12]. Surprisingly, given that PA is a key element in COPD prognosis, no other index has incorporated this measurement from the original HADO.

The aims of this study were to emphasise the importance of PA in COPD; to improve the usability of the original HADO score in daily clinical practice and its predictive capacity by including objectively-measured PA (HADO.2 score); and to compare its predictive capacity to the reference tool, the BODE index.

Methods

Participants and data collection

This was a prospective, observational, non-intervention study. Patients were recruited after being treated for COPD in one of six outpatient respiratory clinics run by the Respiratory Service of Galdakao University Hospital. Functional inclusion criteria were forced expiratory volume in 1 s (FEV_1) <80% of the predicted value and a FEV_1/forced vital capacity ratio <70%. Patients were enrolled consecutively in the study if they had been diagnosed with COPD for at least 6 months and had been stable for at least 6 weeks. Patients were not eligible for the study if they had been diagnosed with asthma, any other major respiratory diseases, or psychiatric or neurological problems that might hinder effective collaboration. The protocol was approved by the hospital's ethics and research committees (16/2014). All candidate patients were given detailed information about the study, and all those included provided written informed consent.

Study protocol

Sociodemographic variables were recorded. The level of dyspnoea was established using the modified Medical Research Council (mMRC) dyspnoea scale [13]. Comorbidities were identified by reviewing the patients' entire electronic medical record and summarised using the Charlson comorbidity index [14]. Health-related quality of life (HRQoL) was assessed using the validated Spanish versions of the Saint George's Respiratory Questionnaire (SGRQ) [15] and the COPD assessment Test (CAT) [16].

Complete pulmonary function tests were carried out. These tests were performed in accordance with the standards of the Spanish Society of Respiratory Medicine and Thoracic Surgery (SEPAR) [17]. For theoretical values, we considered the values of the European Community for Steel and Coal [18].

Two 6-min walk tests (6MWT) were performed as per American Thoracic Society guidelines [19]. PA was measured using an accelerometer (SenseWear Pro 3; Body Media Inc, Pittsburgh, PA, USA). Patients wore the armband for 7 consecutive days, at all times except during their daily personal hygiene.

Self-reported general health was assessed with the question "How is your health status in general?" with a 5-option response "excellent, very good, good, fair, or poor" [20].

Follow-up

Patients were followed up for 3 years. The interview and assessments were then repeated yearly amongst survivors. No interventions were performed related to this study, and the research team did not take part in patients' routine care or the treatment of any exacerbations.

Patient medical records and the hospital database on hospitalisations were reviewed at each assessment during the 3-year follow-up period. Vital status was established by reviewing medical records, the hospital database and public death registries.

HADO and variations of HADO and BODE

To construct the new HADO (HADO.2 score) we used the 12-point score of the original HADO and, importantly, with a higher score indicating better clinical condition [11]. In the HADO.2 score the patient-reported PA of the original tool was substituted for PA as measured by an accelerometer. The four categories of PA ranged from <3500 steps to >12 000 steps. These were established as <3500 ("sedentary"=3 points), 3500–6499 ("low active"=2 points), 6500–11 999 ("somewhat active"=1 point) and ⩾12 000 ("active"=0 points). These cut-off points have been selected using descriptive analysis techniques such as quartiles.

These four categories of PA were kept in the three other different variations which were analysed in the study (adding 6MWT in the HADO; adding PA in the BODE and replacing 6MWT for PA in the BODE). We also used the categories of the BODE index original [3].

Statistical analysis

Descriptive statistics of all the variables were performed, using frequencies and percentages for categorical variables and mean and standard deviation or median and 1st and 2nd quartiles for continuous variables. The characteristics of live and dead participants after 3 years of follow-up were compared using the Chi-square test for categorical variables and non-parametric Wilcoxon test for continuous variables.

We categorised the scores into four different levels of risk. The optimal thresholds in the continuous risk score were determined with the CatPredi function of the R package CatPredi [21].

Cox proportional hazard regression analyses were performed to assess the capacity of the different scores to predict mortality at 3 years. Hazard ratio, 95% CI and p-value were calculated for the categories of each score. We also calculated the C-statistic to study the predictive ability of the score, where the null value for the C-statistic is 0.5 with a maximum value of 1.0. Internal validation was carried out using the bootstrap method. Significant differences between C-statistics of each score were also analysed using the bootstrap method.

Survival and linear models for the prediction of mortality and HRQoL (CAT and SGRQ) at 3 years have been created adjusted for baseline characteristics. The goodness-of-fit of the linear models was calculated using the R^2 statistic. Differences between the number of hospitalisations and HADO were analysed using the Chi-square test.

Kaplan–Meier curves were performed for mortality after 3 years of follow-up for the different scores. All statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Carey, NC, USA) and R, version 4.1.1.

Results

We included 401 consecutive patients in our study. Women represented 26.4% of the cohort. The cohort had a mean±SD age of 64.2±8.4. Current smokers represented 29.7% of the cohort. Other clinical and functional characteristics of the cohort were body mass index (BMI) 27.5±5.4 $kg \cdot m^{-2}$, FEV_1 56.9±17.6% predicted and 6MWT 476.7±108.3 m; the median PA was 6330 (3573–9586) $steps \cdot day^{-1}$, and 43.9% considered their health status to be "good" and 41.4% "fair". The median HADO.2 score of the cohort was 6 (4–8) and the BODE index 2 (1–3). Mortality at 3 years was 11%.

The bivariate analysis showed statistical differences between those that remained alive and those who died during the 3-year follow-up period (table 1).

Table 2 shows the predictive ability of all the variables making up the HADO.2 score and the BODE index for 3-year survival. Dyspnoea and PA ($steps \cdot day^{-1}$) were the variables with the highest predictive capacity (C-statistics 0.757 and 0.753 respectively). By contrast, the lowest predictive capacity was for BMI (C-statistic 0.562).

A 1-point decrease in the continuous HADO.2 score increased mortality by almost 60% (HR: 1.598), similar to the BODE index (HR: 1.602) (table 3). The C-statistic for the categorised HADO.2 score was 0.79 (0.725–0.855) and for the BODE index 0.767 (0.692–0.842). There were no significant differences between the c-index of the different models except between the BODE index and BODE (+PA) index. Figure 1 shows the survival curve of the HADO.2 score categories.

TABLE 1 Baseline characteristics of study participants and characteristics by vital status after 3 years follow-up

	All	Patients		p-value
		Alive	Dead	
Total	401 (100.00)	357 (89.03)	44 (10.97)	
Age years	64.19±8.41	63.59±8.36	69.00±7.26	<0.0001
Male	295 (73.57)	255 (71.43)	40 (90.91)	0.0057
BMI kg·m^{-2}	27.50±5.44	28.25±12.27	26.18±5.69	0.1304
BMI >21	358 (89.95)	326 (91.32)	32 (78.05)	0.0074
Hospital admission (2 previous years)	132 (32.92)	102 (28.57)	29 (65.91)	<0.0001
Smoking habit pack-years	44 (31–65)	43 (30–60)	62 (39–77.50)	0.0038
FEV_1 L	1.47±0.51	1.52±0.50	1.05±0.44	<0.0001
FEV_1 % pred	56.95±17.61	58.63±16.89	43.51±17.64	<0.0001
FEV_1/FVC	51.20±10.11)	51.92±9.87	45.40±10.28	<0.0001
6-min walk distance m	476.73±108.34	493.03±95.49	340.98±114.66	<0.0001
Dyspnoea (mMRC) scale	1 (1–2)	1 (1–2)	2 (2–3)	<0.0001
Physical activity steps·day^{-1}	6330 (3573–9586)	6687 (4188–9782)	2618 (997–4000)	<0.0001
Health status				0.0075
Bad	42 (10.47)	32 (8.96)	10 (22.73)	
Fair	166 (41.40)	145 (40.62)	21 (47.73)	
Good	176 (43.89)	163 (45.66)	13 (29.55)	
Very good/excellent	17 (4.24)	17 (4.76)	0 (0.00)	
Charlson Comorbidity Index	1 (1–2)	1 (1–2)	2 (1.50–3)	<0.0001
St George's Respiratory Questionnaire total	41.18±17.57	39.54±17.27	52.79±15.45	0.0012
COPD Assessment Test	12.74±7.66	12.14±7.40	17.59±8.07	<0.0001
Hospital Anxiety and Depression Scale				
Anxiety	5 (2–8)	5 (1–8)	7 (3–10.50)	0.0124
Depression	3 (1–6)	3 (1–5)	5 (2–8.50)	0.0005
HADO.2 score (steps·day^{-1})	6 (4–8)	7 (5–8)	3 (2–4.5)	<0.0001
BODE index	2 (1–3)	1 (1–2)	4 (2–6)	<0.0001

Data are presented as n (%), mean±SD or median (interquartile range). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: modified Medical Research Council dyspnoea scale; HADO: health, activity, dyspnoea, obstruction; BODE: body mass index, obstruction, dyspnoea, exercise.

Indexes variations

Given that each index includes one of two variables related to PA accepted as being very important for COPD management (PA and 6MWT), we performed the exercise of exchanging the variable between the tools. When 6MWT was added to the continuous HADO.2 score, the C-statistic was 0.796 (0.727–0.866). Exchanging 6MWT for PA, the C-statistic for the continuous BODE index was 0.805 (0.734–0.877), while adding PA it was 0.807 (0.735–0.879). Among all the scores analysed, the only statistical differences found were between the HADO with the 6MWT score *versus* the BODE with PA index and between the BODE index *versus* BODE with PA index (table 3). Internal validation was performed by bootstrap; the C-index achieved through this internal validation was 0.791 for the HADO.2 score and 0.769 for the BODE index (table 3).

HADO.2 score properties

Adjusted by age and comorbidities (Charlson index), the HADO.2-score showed a good predictive capacity for mortality (C-index 0.85) with an increasing HR risk of death by HADO.2 severity categories. Moreover, the HADO.2 score categories were also associated with an increasing HR of hospitalisation during the 3-year follow-up (table 4). We also looked at the relationship of the HADO.2 with two HRQoL measures, the CAT and SGRQ, where the adjustment by the respective baseline HRQoL score in each case was also added to each model, with increasingly worse scores in each HADO.2 increasing the severity category in each HRQoL tool (SGRQ and CAT) and with good predictive ability, as measured by R2 of 0.63 and 0.53 respectively.

Discussion

In our cohort of COPD patients: 1) the HADO.2 score – which uses PA measured by an accelerometer, as opposed to a questionnaire as in the original version of the HADO – showed better predictive capacity for

TABLE 2 3-year death survival univariable analysis for the variables of the HADO and BODE scores

Variables	n (%)	HR (95% CI)	p-value	C-statistic
HADO variables				
FEV_1 %				0.722
⩽35	17 (40.48)	Ref.	Ref.	
36–49	13 (14.13)	0.311 (0.151–0.642)	0.0017	
50–64	6 (4.41)	0.091 (0.036–0.231)	<0.0001	
⩾65	8 (6.11)	0.128 (0.055–0.296)	<0.0001	
Dyspnoea (mMRC) scale				0.757
3–4	21 (45.65)	Ref.	Ref.	
2	14 (10.53)	0.181 (0.092–0.357)	<0.0001	
1	7 (4.55)	0.076 (0.032–0.178)	<0.0001	
0	2 (2.94)	0.049 (0.011–0.209)	<0.0001	
Physical activity				0.753
0 (<3500 steps·day^{-1})	28 (29.47)	Ref.	Ref.	
1 (3500–6499 steps·day^{-1})	10 (9.01)	0.274 (0.133–0.563)	0.0004	
2 (6500–11 999 steps·day^{-1})	4 (2.84)	0.083 (0.029–0.236)	<0.0001	
3 (⩾12 000 steps·day^{-1})	2 (3.70)	0.108 (0.026–0.455)	0.0024	
Health status				0.631
Bad	10 (23.81)	Ref.	Ref.	
Fair	21 (12.65)	0.497 (0.234–1.056)	0.0689	
Good	13 (7.39)	0.279 (0.122–0.637)	0.0024	
Very good/excellent	0 (0.00)	-	0.9963	
6MWT m				0.706
⩽149	2 (100.00)	Ref.	Ref.	
150–249	8 (44.44)	0.378 (0.080–1.790)	0.2200	
250–349	13 (38.24)	0.288 (0.064–1.287)	0.1030	
⩾350	21 (6.04)	0.040 (0.009–0.171)	<0.0001	
BODE variables				
FEV_1 %				0.727
⩾65	8 (6.11)	Ref.	Ref.	
50–64	6 (4.41)	0.712 (0.247–2.053)	0.5300	
36–49	13 (14.13)	2.442 (1.012–5.891)	0.0470	
⩽35	17 (40.48)	7.843 (3.381–18.193)	<0.0001	
Dyspnoea (mMRC) scale				0.753
0–1	9 (20.46)	Ref.	Ref.	
2	14 (31.82)	2.687 (1.163–6.209)	0.0207	
3	13 (29.55)	13.460 (5.748–31.521)	<0.0001	
4	8 (18.18)	17.733 (6.823–46.092)	<0.0001	
6MWT m				0.706
⩾350	21 (6.04)	Ref.	Ref.	
250–349	13 (38.24)	7.293 (3.649–14.580)	<0.0001	
150–249	8 (44.44)	9.558 (4.226–21.620)	<0.0001	
⩽149	2 (100.00)	25.316 (5.865–109.28)	<0.0001	
BMI kg·m^{-2}				0.562
⩽21	9 (22.50)	2.696 (1.287–5.649)	0.0086	
Physical activity				0.753
0 (⩾12 000 steps·day^{-1})	2 (3.70)	Ref.	Ref.	
1 (6500–11 999 steps·day^{-1})	4 (2.84)	0.765 (0.140–4.174)	0.7565	
2 (3500–6499 steps·day^{-1})	10 (9.01)	2.524 (0.553–11.519)	0.2320	
3 (<3500 steps·day^{-1})	28 (29.47)	9.227 (2.198–38.743)	0.0024	

HADO: health, activity, dyspnoea, obstruction; BODE: body mass index, obstruction, dyspnoea, exercise; HR: hazard ratio; FEV_1: forced expiratory volume in 1 s; mMRC: modified Medical Research Council dyspnoea scale; 6MWT: 6-min walk test; BMI: body mass index.

mortality at 3 years; 2) at the same time, the HADO.2 score showed a similar predictive capacity to the BODE index; and 3) adding our proposal of measuring PA by accelerometer to the BODE (BODE+PA) also improved the predictive capacity of the original BODE.

The HADO.2 score was made up of several variables which had already been shown to be important in the prognosis of COPD patients. Variables such as FEV_1% and dyspnoea are well-known predictive factors of

TABLE 3 3-year death survival analysis for the different scores

Variables	n (%)	HR (95% CI)	p-value	C-statistic (95% CI)
HADO.2 score (cont.)#	3 (2–4.5)	1.598 (1.409–1.812)	<0.0001	0.800 (0.735–0.864)
HADO.2 score				0.790 (0.725–0.855)
7–12	3 (2.03)	Ref.	Ref.	
0–1	11 (7.14)	32.850 (9.749–110.700)	<0.0001	
2–4	10 (17.24)	9.206 (2.533–33.450)	0.0007	
5–6	20 (48.78)	3.595 (1.003–12.890)	0.0495	
Bootstrap (cat.)				0.791 (0.720–0.848)
HADO.2 score (+6MWT) (cont.)#	4 (2–6)	1.463 (1.327–1.614)	<0.0001	0.796 (0.727–0.866)
HADO.2 score (+6MWT)				0.773 (0.703–0.843)
10–15	7 (3.41)	Ref.	Ref.	
7–9	6 (6.52)	19.383 (7.888–47.627)	<0.0001	
4–6	16 (21.62)	7.053 (2.901–17.148)	<0.0001	
0–3	15 (50.00)	1.948 (0.655–5.796)	0.2310	
Bootstrap (cat.)				0.775 (0.698–0.842)
BODE index (cont.)#	4 (2–6)	1.583 (1.421–1.763)	<0.0001	0.792 (0.719–0.865)
BODE index				0.767 (0.692–0.842)
0–2	11 (3.90)	Ref.	Ref.	
3–4	10 (13.33)	3.593 (1.526–8.460)	0.0034	
5–6	13 (46.43)	15.233 (6.815–34.050)	<0.0001	
7–10	7 (53.85)	18.395 (7.103–47.640)	<0.0001	
Bootstrap (cat.)				0.769 (0.693–0.845)
BODE index (−6MWT+PA) (cont.)#	7 (5–7)	1.687 (1.479–1.924)	<0.0001	0.805 (0.734–0.877)
BODE index (−6MWT+PA)				0.773 (0.698–0.848)
0–3	5 (3.31)	Ref.	Ref.	
4–5	10 (5.59)	1.718 (0.587–5.027)	0.3230	
6–7	16 (31.37)	11.222 (4.109–30.645)	<0.0001	
8–10	10 (58.82)	25.433 (8.661–74.683)	<0.0001	
Bootstrap (cat.)				0.777 (0.704–0.846)
BODE index (+PA) (cont.)#	7 (5–9)	1.488 (1.356–1.634)	<0.0001	0.807 (0.735–0.879)
BODE index (+PA)				0.804 (0.735–0.873)
0–3	6 (2.69)	Ref.	Ref.	
4–5	7 (7.14)	2.737 (0.920–8.143)	0.0704	
6–7	9 (21.95)	9.064 (3.226–25.469)	<0.0001	
8–13	19 (52.78)	26.629 (10.609–66.841)	<0.0001	
Bootstrap (cat.)				0.806 (0.728–0.875)

Significant differences only found between BODE index and BODE (+PA) index and HADO (+6MWT) score and BODE (+PA) index, where the confidence interval of the difference is (−0.077 to −0.001) and (−0.042 to −0.006) respectively. HR: hazard ratio; HADO: health, activity, dyspnoea, obstruction; CI: confidence interval; 6MWT: 6 min walk test; BODE: body mass index, obstruction, dyspnoea, exercise; Cont: continuous score; Bootstrap (cat.): refers to the C-statistic results of the internal validation of each score by bootstrap. #: the probability of death is calculated for each unit the score decreases in the HADO.2, while in the BODE the probability of death is calculated for each unit the score increases.

mortality in COPD patients [22, 23]. Indeed, both variables, especially FEV_1, are frequently included in the prognosis scores [24].

It has been shown that HRQoL, which globally reflects patients' general and subjective respiratory clinical condition, was associated with short-term prognosis [25]. However, we sought to incorporate this aspect by using a simpler tool, in this case in the form of a single question. We based this choice on a number of other studies, summarised in a meta-analysis of all-cause mortality prediction based on 14 studies comparing individuals reporting their health status as "fair" and "poor" *versus* "excellent", giving a result of OR 1.44 (95% CI 1.21–1.72) and 1.92 (95% CI 1.64–2.25) [20]. Considering that this subjective measurement is correlated with other objective measurements [26], it should be noted that in our cohort, self-reported health status did not have the highest predictive capacity (table 2), but was better than BMI, which had the lowest predictive capacity. This aspect of BMI has been noted in other studies; Soler-Cataluña *et al.* [4] found that the only variable not significantly associated with mortality in their cohort was BMI.

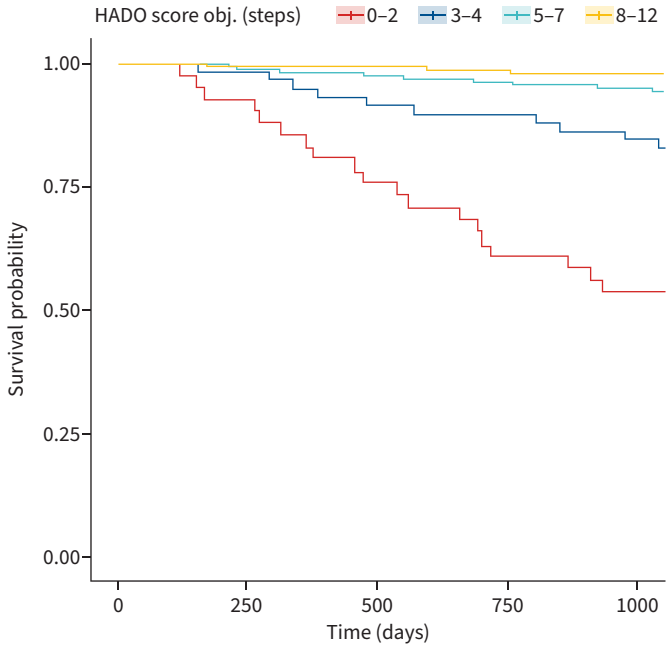

FIGURE 1 3-year survival curve of the HADO.2 score categories. obj: objective.

What deserves more attention in this study is PA and its relationship with exercise capacity (6MWT). Previous evidence has determined several key aspects in exercise capacity and PA. Exercise capacity measured by 6MWT has proved to be an important prognostic tool in different scenarios. Indeed, 6MWT was an independent predictor of mortality in a cohort of severe COPD patients, with a risk-of-death rate of 0.82 per 50-m increase in 6MWT [27]. 6MWT was a predictor of mortality in a retrospective study that included observational studies and clinical trials, with an area under the curve from the receiver operating characteristic curve of 0.725 and 0.684 at 6 and 12 months respectively [28]. In women with COPD a threshold of 350 m in the 6MWT was a valid differentiator of survival [29].

PA also has an important role in COPD. Watz *et al*. [8] showed that PA is reduced in the mild level of COPD and continues to deteriorate increasingly over time [30]. Furthermore, PA was distinguished as an important predictor of several outcomes in COPD. Waschki *et al*. [10], using PA level or steps per day, identified it as the strongest predictor of all causes of mortality. Moreover, PA has been linked to mortality in studies based on different methodologies and designs [7, 8], and even a relationship to dose response has been demonstrated [9].

Starting from this scenario, it is clear that PA and exercise capacity settle in different constructs. In COPD patients, the relationship between PA *versus* exercise capacity measured with an incremental cycle ergometer test and incremental and endurance shuttle walking test was established from moderate to weak [31]. In another cross-sectional study that included mild–moderate patients from primary care, there was no significant correlation between several variables of PA and 6MWT [32]. Furthermore, exercise training was associated with a small effect on PA, as demonstrated in a systematic review and meta-analysis [33]. Furthermore, after a rehabilitation programme, an immediate improvement in exercise capacity (6MWT and incremental shuttle walking test) ensued, with no change in PA performance [34].

Summarising, PA and exercise capacity contribute to a better perspective of the clinical situation of the patient and thus to better management of COPD patients [35]. These two perspectives should be considered together, not only with regard to the aspects discussed above, but also in the prognosis evaluation, as demonstrated in our study. Strikingly, a recent study found that the higher the level of 6MWT, the lower the risk of mortality in the 6-year follow-up [36]. In this study, PA seems to play a minor role in the predictive role of mortality.

In our study it is worth noting that the C-statistics of the HADO.2 score, which can be qualified as good, are 0.80 when the score is considered as continuous and 0.79 when categorised, without losing predictive

TABLE 4 3-year death survival model, hospitalisation logistic regression and linear models for the CAT and SGRQ scores changes from baseline to 3 years

Variables	n (%)	3-year mortality			Hospitalisations			CAT changes			SGRQ changes		
		n	HR (95% CI)	p-value	n	OR (95% CI)	p-value	n	β (95% CI)	p-value	n	β (95% CI)	p-value
HADO-score													
8–12	148 (36.91)	3	Ref.	Ref.	16	Ref.	Ref.	145	Ref.	Ref.	143	Ref.	Ref.
5–7	154 (38.40)	11	2.97 (0.82–10.70)	0.0963	43	3.24 (1.71–6.12)	0.0003	143	1.62 (0.40–2.83)	0.0095	140	3.38 (0.44–6.32)	0.0424
3–4	58 (14.46)	10	8.00 (2.20–29.18)	0.0016	20	4.28 (2.00–9.18)	0.0002	50	4.74 (3.00–6.49)	<0.0001	50	9.85 (5.60–14.11)	<0.0001
0–2	41 (10.22)	20	29.32 (8.67–99.16)	<0.0001	21	9.47 (4.13–21.73)	<0.0001	22	3.57 (1.14–6.00)	0.0041	22	6.31 (0.24–12.38)	0.0249
C-index (95% CI)			0.85 (0.80–0.89)			0.72 (0.66–0.77)							
R^2									0.53			0.63	

All models have been adjusted by age, Charlson comorbidity index and baseline health-related quality of life respective scores. CAT: COPD Assessment Test; SGRQ: Saint George's Respiratory Questionnaire; HR: hazard ratio; HADO: health, activity, dyspnoea, obstruction.

ability. In our original HADO we did not get a particularly good predictive capacity (C-statistic 0.682) by using a questionnaire for PA. But what is also remarkable is the improvement in the score of BODE+PA as opposed to BODE. This could be interpreted as the complementarity of PA and exercise capacity in COPD evaluation and reinforces the role of PA as a mortality predictor, contributing to the debate on its importance and providing another perspective on the results of Vaes *et al*. [10, 35, 36]. Indeed, there was a statistical difference in the C-statistics between the BODE+PA *versus* the BODE (table 3). That finding reinforces the importance of PA.

Differences between HADO.2 score and BODE cohorts should be mentioned. The BODE cohorts come from hospitals [3], but the HADO.2 cohort was built from patients from a monographic COPD surgery (hospital patients), and patients from other surgeries in our service (which involves patients neither in hospital nor in primary care but in outpatient respiratory surgeries). Our patients are therefore milder in severity than those from the BODE cohort, but both the HADO.2 score and the BODE index work well in our cohort in the mid-term.

Our study has some limitations: 1) the HADO.2 score was cross-sectional and other clinical and therapeutic circumstances that occurred during the follow-up in this study were not taken into consideration; 2) there was a low number of deaths during the study, which may have conditioned the results; 3) an external validation was not carried out, although an internal validation by bootstrap was performed; 4) the long-term predictive capacity in the HADO.2 score was not established, although this was not the aim of the study and the prognosis of each patient should probably be evaluated bearing in mind the constant change in factors having some influence on these patients' life expectancy; 5) other variables related to PA obtained from accelerometers could have been used in order to improve the predictive capacity of the model, but the objective was to use easily obtainable parameters to provide the easiest tool for use in clinical practice; 6) in the study an analysis of subgroups like bronchitis and emphysema were not carried out, due to a lack of a precise diagnosis of both entities and their overlap in some patients; and 7) the measurement of PA by accelerometers imply a limitation in its implementation; however measurement of PA is day by day becoming more accessible for everyone, so this kind of measurement (mobile phone) just needs a validation and PA will become an easy-to-use tool with very important clinical implications for the patients.

Among the strengths of this study, apart from the quality of the records, we have shown that the HADO.2 score has a good association with the most important outcomes in COPD, namely mortality, hospitalisations during the follow-up and change in quality of life measured by two well-known specific tools for COPD patients, which supports the suitability of the tool (table 4).

We need to be aware that the task of establishing a precise prognosis has not been concluded, given that several facets of COPD must still be explored. Patients' evaluation should be based mainly on objective measurements (metabolic, hormonal, inflammatory, etc.), but humans are unable to capture the entire complex relationship between the mix of variables that play a role in COPD (genetics, exposome, microbiome, metabolomics, etc.). We therefore need to recruit other agents (*i.e.*, artificial intelligence) for the task. Until such time, we propose incorporating PA in the prognosis scores of the COPD patients, since it improves the efficacy of these prognosis scores and will probably make health professionals (at all levels of care) and patients more aware of the importance of keeping moving.

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