Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index

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Summary

Background The BODE index (including body-mass index, airflow obstruction, dyspnoea, and exercise capacity) was an important contribution to the prognostic assessment of patients with chronic obstructive pulmonary disease (COPD). However, no study has assessed whether the risk of mortality predicted by the BODE index matches the observed mortality in different populations. We assessed the calibration of the BODE index, updated it to improve its calibration, and developed and validated a simplified index for use in primary-care settings.

Methods We included 232 patients from the Swiss Barmelweid cohort with longstanding and severe COPD and 342 patients from the Spanish Phenotype and Course of COPD cohort study who had had their first hospital admission due to moderate-to-severe COPD. In both cohorts we compared the observed 3-year risk of all-cause mortality with the risk predicted by the BODE index. We then updated the BODE index and developed a simplified ADO index (including age, dyspnoea, and airflow obstruction) from the Swiss cohort, and validated both in the Spanish cohort.

Findings Calibration of the BODE index was poor, with relative underprediction of 3-year risk of mortality by 36% in the Swiss cohort (median predicted risk 21·7% [IQR 12·7–31·7] *vs* 34·1% observed risk; p=0·013) and relative overprediction by 39% in the Spanish cohort (16·7% [12·7–31·7] *vs* 12·0%; p=0·035). The 3-year risk of mortality predicted by both the updated BODE (median 10·7% [8·1–13·8]) and ADO indices (11·8% [9·1–14·3]) matched the observed mortality in the Spanish cohort well (p=0·99 and p=0.98, respectively).

Interpretation Both the updated BODE and ADO indices could lend support to the prognostic assessment of patients with COPD in specialised and primary-care settings. Such assessment enhances the targeting of treatments to individual patients.

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Introduction

The BODE index was an important contribution to prognostic research in chronic obstructive pulmonary disease (COPD).[1] It combines information about several predictors including body-mass index (BMI), airflow obstruction (forced expiratory volume in 1 s [FEV_1]), dyspnoea (Medical Research Council [MRC] dyspnoea scale), and exercise capacity (6-min walk distance) in a score ranging from 0 to 10. This prognostic index predicts mortality significantly better than does lung function—the traditional prognostic COPD indicator—alone. The BODE index contributed to the acceptance that prognostic assessment in patients with COPD should go beyond lung function.[2,3]

Findings from several studies[4–6] have confirmed that the BODE index has better discriminative properties than does lung function. Discrimination refers to the ability of the prognostic index to distinguish between patients who will or will not die over a specific period of time. However, discrimination is not the only property that is relevant for prognostic indices. To be useful in practice, prognostic instruments should accurately predict the absolute risk of an event in individual patients.[7] Guided by these predicted risks, clinicians and patients might decide on more or less comprehensive treatment to modify that risk. The absolute risks as predicted by risk scores should be compared with the observed risks in at least one other population (so-called calibration).[8–10] Without any assessment of calibration, clinicians should be very cautious in applying such scores in practice because treatment selection could be inadequate if the risk is overestimated or underestimated. Unlike widely used risk scores such as the Framingham risk score and the APACHE (acute physiology and chronic health evaluation) scores, the BODE index does not provide absolute risks of mortality and its calibration has never been assessed. As a consequence, the BODE index seems not yet ready for use as a prognostic instrument in patients with COPD.

We aimed to assess the calibration of the BODE index in two different COPD populations, to explore how its

prediction could be improved, and to develop a simplified risk index that is also applicable in primary-care settings.

Methods

Study design and patients

We included all patients with COPD in the Swiss Barmelweid cohort and the Spanish Phenotype and Course of COPD (PAC-COPD) cohort study.[11] Patients in the Swiss cohort had longstanding and, on average, severe COPD (according to criteria from the Global initiative for chronic Obstructive Lung Disease [GOLD]), whereas those in the Spanish cohort study were enrolled after they had had their first hospital admission due to an exacerbation of moderate-to-severe COPD.[11]

In the Swiss cohort we included any patients with COPD with a postbronchodilator ratio of FEV_1 to forced vital capacity (FVC) less than 0·7 predicted and FEV_1 less than 80% predicted (GOLD stages II–IV) after they had followed a respiratory rehabilitation programme at a secondary care hospital (Klinik Barmelweid, Barmelweid, Switzerland) between May, 2004, and December, 2005. During that rehabilitation, 100 patients had participated in a pragmatic randomised respiratory rehabilitation trial, whose main results have been published.[12] Frequent reasons for exclusion were no measurement of 6-min walk distance because of neurological or musculoskeletal comorbidities (n=159), language other than German (n=28), no informed consent (n=13), or miscellaneous reasons (n=33). The ethics committee of the Kantonsspital Aarau (Aargau, Switzerland) approved the study protocol. We obtained written informed consent from all patients, and the Swiss Expert Commission for Release from Doctor-Patient Confidentiality allowed us to contact patients, the patients' partners, or general practitioners of deceased patients to verify survival status and exact date of death.

In the Spanish cohort we recruited all participants when they were admitted to one of the nine participating teaching hospitals because of their first admission for an exacerbation[13] between January, 2004, and March, 2006. We considered any hospital stay or time spent in the emergency room for at least 18 h as an admission. We assessed the patients' clinical characteristics, including a confirmation of COPD by spirometry according to established criteria[14] at least 3 months after discharge and in clinical stability as described previously.[11] Patients who declined to participate (n=262) had similar characteristics to those who were included.[15] The protocol was approved by the ethics committees of all participating hospitals, and we obtained written informed consent from all participants.

Outcome

In both cohorts, survival status (outcome) was obtained by research assistants who were masked to the patients' risk profiles at baseline, including BODE index score. After at least 30 months of follow-up, all patients were contacted by telephone or visited our hospitals, or both. If we were unable to contact patients or their partners after at least five telephone calls, we contacted their general practitioners and obtained information from the hospital registries about survival status. For deceased patients, both hospital and primary-care registries were checked to ensure exact date of death. We registered only all-cause mortality.

Prognostic predictors

In both cohorts, lung function was assessed following standardised procedures as described previously.[11,12] We calculated BMI from the height and weight that was measured by hospital nurses. To measure dyspnoea, patients in the Swiss cohort completed the validated self-administered standardised dyspnoea domain of the German Chronic Respiratory Questionnaire.[16] The dyspnoea domain score correlates strongly with the five-point MRC dyspnoea scale,[17] and both scores can be transformed to one another (webappendix p 1). Patients in the Spanish cohort completed the modified (6-point) MRC scale, and scores were transformed to scores of the 5-point MRC scale.[18] Finally, all patients completed 6-min walk tests according to the criteria of the American Thoracic Society,[19] as previously described.[11,12] For missing predictors we used multiple imputation with age, BMI,

	Swiss cohort (n=232)	Spanish cohort (n=342)
Age (years)	72·2 (9·1)	67·9 (8·6)
Men	139 (60%)	318 (93%)
Pack years*	52·1 (29·4)	68·1 (39·2)
Current smokers	41 (18%)	114 (33%)
BMI (kg/m²)	26·0 (6·3)	28·2 (4·7)
FEV_1 (% predicted)	45·2% (16·2)	52·4% (16·2)
Dyspnoea†	2·2 (1·2)	2·1 (1·0)
6-min walk distance (m)	363 (127)	441 (91)
PaO_2 (mm Hg)	62·7 (11·0)	74·3 (10·6)
Cardiovascular disease‡	88 (38%)	85 (25%)
Diabetes†	42 (18%)	65 (19%)
Inhaled corticosteroid§	210 (91%)	222 (65%)
Longacting β agonist§	198 (85%)	227 (66%)
Longacting anticholinergic§	105 (45%)	191 (56%)
Previous respiratory rehabilitation	232 (100%)	14 (4%)

Data are mean (SD) or number (%). In the Spanish cohort, values were missing for pack years (n=11), dyspnoea (4), 6-min walk distance (33), partial pressure of oxygen in arterial blood (PaO_2) (11), diabetes (5), inhaled corticosteroids (4), longacting β agonists (4), and longacting anticholinergic (4). Missing values were assumed to be randomly distributed and mainly due to the hospital logistics and patients availability (data available from the authors). Missing values in dyspnoea and 6-min walk distance were imputed with multiple imputation. BMI=body-mass index. FEV_1=forced expiratory volume in 1 s. *Pack years=(number of cigarettes smoked per day/20)×number of years as a smoker. †Medical Research Council (MRC) score derived from modified MRC score used in Spanish cohort and chronic respiratory questionnaire dyspnoea score used in Swiss cohort as described in webappendix p 1. ‡Physician diagnosed. §Alone or in combination.

Table 1: **Patients' characteristics in the Swiss and Spanish cohorts**

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See **Online** for webappendix

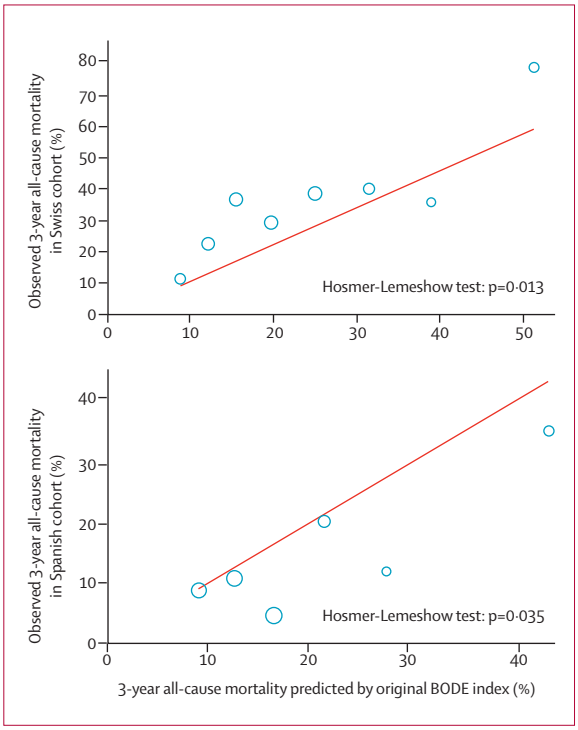

Figure 1: **Calibration plot of the original BODE index in the Swiss and Spanish cohorts**

The x-axis shows the 3-year risk of mortality as predicted by the original BODE index and the y-axis shows the observed risk. Every circle represents a risk class with a corresponding predicted and an observed risk. The solid line represents perfect agreement between predicted and observed risks. Circles above the solid line mean that the predicted risk was lower than the observed risk (underprediction) and circles below the solid line show overprediction of the risk. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes.

	Shrunken* regression coefficients β_s per unit increase	Category (j)†	Reference values W_{ij} (midpoint)	$\beta_s \times (W_{ij} - W_{ireference})$	Risk score ($\beta_s \times [W_{ij} - W_{ireference}]/B$‡)
BMI (kg/m²)	–0·013 (p=0·55)	>21	28 ($W_{1reference}$)	..	0
		≤21	19	0·121	1
FEV_1 (% predicted)	–0·005 (p=0·56)	≥65–80%	72·5 ($W_{2reference}$)	..	0
		≥50–64%	57·0	0·082	1
		≥36–49%	42·5	0·158	1
		≤35%	25·0	0·250	2
Dyspnoea	0·146 (p=0·20)	0–1	0·5 ($W_{3reference}$)	..	0
		2	2	0·218	1
		3	3	0·364	2
		4	4	0·510	3
6-min walk distance (m)	–0·005 (p<0·0001)	≥350	450·0 ($W_{4reference}$)	..	0
		≥250–349	299·5	0·688	4
		≥150–249	199·5	1·146	7
		<150	120·0	1·509	9

Constant of regression equation for patients with longstanding and severe chronic obstructive pulmonary disease (COPD)=1·483. Constant of regression equation for patients after a first hospital admission due to an exacerbation of moderate-to-severe COPD=0·266. BMI=body-mass index. FEV_1=forced expiratory volume in 1 s. *Regression coefficients were multiplied by a shrinkage factor of 0·863. †Original BODE categories. ‡Constant B corresponds to an important change in 6-min walk distance (35 m),[30] which is equivalent to a coefficient=0·1855. Points rounded to the next integer.

Table 2: **Regression coefficients and development of updated BODE index by variable (i)**

MRC dyspnoea scores, 6-min walk distance, cardiovascular disease, and maximal oxygen uptake (VO_2max). We generated 50 datasets and took the median of the 50 values that were imputed for an individual patient.[20]

Statistical analysis

We first validated the BODE index in our two external cohorts; in the case of poor calibration we planned to recalibrate the BODE index. Independently from the performance of the BODE index we developed and validated a simplified index for use in patients with COPD in primary-care settings. The webappendix pp 2–3 provides a detailed description of the statistical analysis.

On the basis of the reported Cox proportional hazard,[1] we calculated the 3-year risk for all-cause mortality for all patients (webappendix p 2).[21] We chose 3-year mortality because we regarded it as clinically meaningful for the management of patients with moderate-to-severe COPD and because we did not have a longer duration of follow-up. Furthermore, the only large COPD trial with mortality as primary outcome had a 3-year follow-up.[22] In every cohort we compared this risk of death predicted by the original BODE index with the observed 3-year mortality, with use of calibration plots and goodness-of-fit statistics (Hosmer-Lemeshow test). Finally, we calculated the *c* statistic for the BODE score as a measure of discrimination.

We updated the original BODE score with recently published methods and our own data.[23–25] For updating we used the Swiss cohort because it had a high mortality incidence, yielding a more stable updated BODE index, and because the Swiss cohort was more similar to the original BODE study cohort than was the Spanish cohort (BMI 26·3 kg/m² in BODE cohort *vs* 26·0 kg/m² in Swiss cohort; FEV_1 42·5% predicted *vs* 45·2% predicted; dyspnoea 2·3 *vs* 2·2; average 6-min walk distances 374 m *vs* 363 m).

We fitted a multivariable logistic regression model with all-cause death at 3 years as outcome and the original BODE variables as predictors. We used the linear forms of the continuous BODE predictors, which were supported by the analysis of their functional form with fractional polynomials and bootstrapping (webappendix p 4).[26] We did not eliminate any predictors, to leave the original BODE index intact. We also used shrinkage to prevent our model from being overoptimistic in future applications of the updated BODE index.[27] We then validated the updated BODE index in the Spanish cohort. Since mortality was substantially lower in the Spanish cohort than in the Swiss cohort, we first recalibrated the intercept with recently reported recalibration methods to allow for an accurate validation.[23–25]

Subsequently, we used the same analytical approach to develop a simpler risk index (ADO index; including age, dyspnoea, and airflow obstruction) for increased applicability outside of specialised respiratory medicine settings. We replaced the 6-min walk distance with age

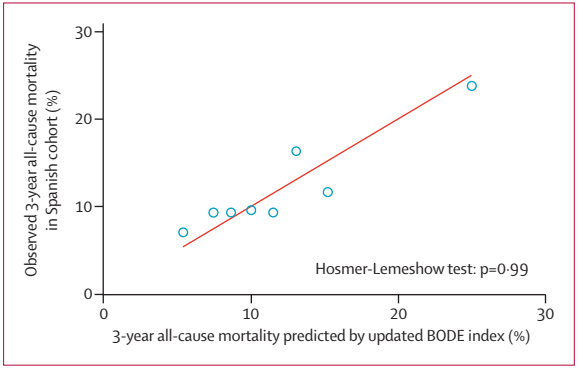

Figure 2: **Calibration plot of the updated BODE index (with data from the Swiss cohort) in the Spanish cohort**
The x-axis shows the 3-year risk of mortality as predicted by the updated BODE index and the y-axis shows the observed risk in the Spanish cohort. Every circle represents a risk class with a corresponding predicted and an observed risk. The solid line represents perfect agreement between predicted and observed risks. Circles above the solid line mean that the predicted risk was lower than the observed risk (underprediction) and circles below the solid line show overprediction of the risk. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes.

because 6-min walk distance is often not available and because age is a strong predictor of mortality. In the multivariable modelling we retained only the predictors associated with 3-year mortality at a significance level of p=0·157 on the basis of the likelihood ratio test.[28]

To enhance the applicability of the final prognostic models for clinicians, we developed a new point system for both the updated BODE and the ADO index following an established approach used for the Framingham risk score.[29] Finally, we calculated the risk of 3-year mortality associated with the points of the updated BODE and the ADO indices for future patients with longstanding and severe COPD (such as those in the Swiss cohort) and patients who have had their first hospital admission due to an exacerbation of moderate-to-severe COPD (such as those in the Spanish cohort). We did all analyses with Stata (version 10.1).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

232 patients were included in the Swiss cohort and 342 in the Spanish cohort. The Swiss cohort included elderly COPD patients with moderate-to-severe chronic airflow obstruction, a moderate degree of dyspnoea, a mean 6-min walk distance of 363 m, and a mean partial pressure of oxygen in arterial blood (PaO_2) of 62·7 mm Hg (table 1). Cardiovascular comorbidity was common, and most patients received one or several inhaled drugs (table 1). Median follow-up was 34 months (range 3–50) and 3-year mortality 34·1% (79/232).

Patients in the Spanish cohort were, on average, 4 years younger, predominantly men, and had less severe disease with moderate degree of airflow obstruction and dyspnoea, a 6-min walk distance of 441 m, and PaO_2 of 74·3 mm Hg (table 1). About 25% had cardiovascular disease, two-thirds received one or several inhaled drugs, and 4% had followed respiratory rehabilitation in the year before enrolment (table 1). Median follow-up was 40 months (range 9–56) and 3-year mortality 12·0% (41/342).

3-year mortality was underpredicted in the Swiss cohort and overpredicted in the Spanish cohort (figure 1). Differences between predicted and observed risks were significant in both cohorts (figure 1). In the Swiss cohort, the median predicted 3-year risk of mortality was 21·7% (IQR 12·7–31·7) compared with 34·1% observed 3-year mortality, corresponding to a relative underprediction of 36% (predicted overobserved ratio=0·64). In the Spanish cohort, the median predicted 3-year risk of mortality was 16·7% (12·7–31·7) compared with 12·0% observed mortality, corresponding to a relative overprediction of 39% (predicted overobserved ratio=1·39). Discrimination of the BODE index was lower in both the Swiss (*c* statistic 0·67) and Spanish cohorts (0·62) than in the original BODE cohort (0·74).[1] Because of the poor calibration and discrimination of the original BODE index in the two external cohorts we updated the BODE index.

Table 2 shows the development of the updated BODE index (from 0 to 15) based on the Swiss cohort. When validated in the Spanish cohort, the updated BODE index predicted the observed 3-year risk of mortality well, with little difference between predicted and observed mortality (p=0·99; figure 2). The *c* statistic (0·61) of the updated BODE index remained unchanged in the Spanish validation cohort compared with the *c* statistic of the original BODE index.

Table 3 shows the new point systems based on the updated BODE index, which directly indicates the strength of association of the four BODE predictors with mortality. A higher number of points are assigned to 6-min walk distance than to other variables because it was the strongest predictor of mortality. Table 4 shows the 3-year risk of death of the updated BODE score for patients with longstanding and severe COPD and for those after their first hospital admission due to an exacerbation of moderate-to-severe COPD. For example,

	0 points	1 point	2 points	3 points	4 points	7 points	9 points
BMI (kg/m²)	>21	≤21	..	..	..	..	..
FEV_1 (% predicted)	≥65%	≥36–64%	≤35%	..	..	..	..
Dyspnoea (MRC scale)	0–1	2	3	4	..	..	..
6-min walk distance (m)	≥350	..	..	..	≥250–349	≥150–249	<150

BMI=body-mass index. FEV_1=forced expiratory volume in 1 s. MRC=Medical Research Council.

Table 3: **Assignment of points for the updated BODE index**

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Patients with longstanding and severe COPD*	15·2% (9·4–23·6)	17·9% (11·9–25·9)	20·8% (14·8–28·5)	24·1% (18·1–31·3)	27·7% (21·8–34·6)	31·7% (25·7–38·4)	35·9% (30·0–42·7)	40·4% (33·3–47·8)	45·0% (36·9–53·3)	49·7% (40·3–59·1)	54·4% (43·5–64·9)	59·1% (47·7–70·4)	63·6% (49·8–75·4)	67·8% (52·8–80·0)	71·8% (55·7–83·8)	75·5% (58·5–87·0)
Patients after first hospital admission due to moderate-to-severe COPD†	6·5% (4·0–10·5)	7·9% (5·2–11·8)	9·5% (6·7–13·4)	11·5% (8·4–15·4)	13·7% (10·2–18·2)	16·3% (11·9–21·9)	19·3% (13·6–26·7)	22·7% (15·2–32·4)	26·5% (16·9–39·1)	30·7% (18·5–46·3)	35·2% (20·2–53·8)	40·0% (22·0–61·2)	45·0% (23·8–68·1)	50·0% (25·7–74·4)	55·0% (27·7–79·8)	60·0% (29·8–84·5)

Data are 3-year risk of mortality per updated BODE score (95% CI). *Odds ratio per point increase in BODE index=1·21 (95% CI 1·12–1·31). †Odds ratio per point increase in BODE index=1·23 (1·10–1·37).

Table 4: **Prediction of 3-year mortality in patients with chronic obstructive pulmonary disease (COPD) by updated BODE score**

	Shrunken* regression coefficients β_s per unit increase	Category (j)†	Reference values W_{ij} (midpoint)	$\beta_s \times (W_{ij} - W_{ireference})$	Risk score ($\beta_s \times [W_{ij} - W_{ireference}]/B$‡)
FEV_1 (% predicted)	−0·012 (p=0·072)	≥65–80%	72·5 ($W_{2reference}$)	..	0
		≥50–64%	57·0	0·183	1
		≥36–49%	42·5	0·354	1
		≤35%	25·0	0·561	2
Dyspnoea	0·193 (p=0·0226)	0–1	0·5 ($W_{3reference}$)	..	0
		2	2	0·289	1
		3	3	0·482	2
		4	4	0·675	3
Age (years)	0·027 (p=0·0183)	40–49	44·5 ($W_{4reference}$)	..	0
		50–59	54·5	0·268	1
		60–69	64·5	0·535	2
		70–79	74·5	0·803	3
		80–89	84·5	1·070	4
		≥90	94·5	1·338	5

Constant of regression equation for patients with longstanding and severe chronic obstructive pulmonary disease (COPD)=−3·436. Constant of regression equation for patients after a first hospital admission due to an exacerbation of moderate-to-severe COPD=−3·663. FEV_1=forced expiratory volume in 1 s. *Regression coefficients were multiplied by a shrinkage factor of 0·674. †Original BODE categories. ‡1 point is assigned per 10 years of change in age; coefficient (B)=0·268. Points rounded to the next integer.

Table 5: **Regression coefficients and development of simplified ADO index by variable (i)**

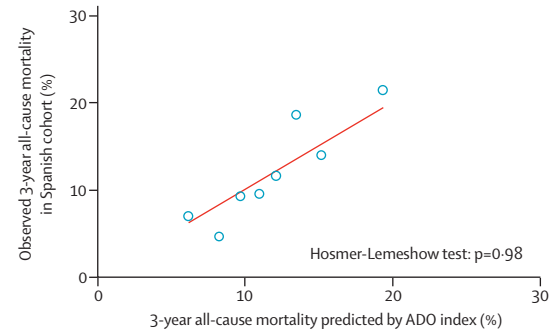

Figure 3: **Calibration plot of the newly developed ADO index (with data from the Swiss cohort) in the Spanish cohort**
The x-axis shows the 3-year risk of mortality as predicted by the ADO index and the y-axis shows the observed risk in the Spanish cohort. Every circle represents a risk class with a corresponding predicted and an observed risk. The solid line represents perfect agreement between predicted and observed risks. Circles above the solid line mean that the predicted risk was lower than the observed risk (underprediction) and circles below the solid line show overprediction of the risk. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes.

a patient with a BMI of 25 kg/m² (0 points), FEV_1 of 45% predicted (1 point), an MRC dyspnoea score of 2 (1 point), and a 6-min walk distance of 380 m (0 points, total updated BODE score of 2 points) had a 3-year mortality risk of between 9·5% (in patients with COPD who had their first hospital admission due to an exacerbation of moderate-to-severe COPD) and 20·8% (in those with longstanding and severe COPD).

In the Swiss cohort, age was most strongly associated with 3-year mortality, followed by dyspnoea and FEV_1 (table 5). BMI showed no association with 3-year mortality. When validated in the Spanish cohort, the calibration plot of the ADO index (from 0 to 10) showed a good match between the 3-year predicted and observed risk (figure 3). The *c* statistic of the ADO index was 0·63 in the Spanish validation cohort.

Table 6 shows the assignment of points for the ADO index, and table 7 shows the absolute 3-year risk of mortality associated with each score (ranging from 0 to 10). For example, a 72-year-old patient (3 points) with an FEV_1 of 56% predicted (1 point) and an MRC dyspnoea score of 1 (0 points, total ADO score of 4 points) had a 3-year mortality risk of between 9·8% (in patients with COPD who had their first hospital admission due to an exacerbation of moderate-to-severe COPD) and 23·9% (in those with longstanding and severe COPD).

Discussion

Our study showed that the original BODE index did not accurately predict mortality in two different COPD populations from Switzerland and Spain. The updated BODE index and the ADO index were similarly accurate in their risk prediction in an external validation cohort, and better than was the original BODE index. The simplified point systems for the updated BODE and ADO indices developed for patients with longstanding severe disease and patients after their first hospital admission due to an exacerbation of moderate-to-severe COPD are easy to use to obtain the 3-year mortality risk in an individual patient.

There are several potential reasons why the original BODE index did not do well in our external validation cohorts, even though the Swiss cohort was fairly similar to the (average of) the original three BODE subcohorts.

First, the method of points assignment in the original BODE index has not been published and might not have followed standard approaches such that the assigned number of points adequately indicates the strength of the underlying associations (regression coefficients).[29] Strong predictors should obviously achieve more weight in risk scores than should weak predictors. For example, assigning the same number of points to dyspnoea or FEV_1 as to 6-min walk distance (0–3 points) does not accord with published work and is not supported by our data, since the 6-min walk distance was a stronger predictor of death than was dyspnoea or FEV_1.[31,32] Second, although the BODE cohort included three substantially different cohorts from the USA, Venezuela, and Spain, the model underlying the BODE index was averaged over these cohorts. This approach might not always be best since prediction often needs to be recalibrated to different cohorts, as our study has shown.[23,33]

Third, the investigators used forward stepwise logistic regression for the development of the original BODE index, which might have led to poor performance of a risk score in a new population.[24,28] Finally, investigators of the original publication[1] claimed that the BODE index had been validated and was ready for use in practice. However, in the validation study the investigators did not assess calibration and discrimination of the initial statistical model that was developed to predict 1-year mortality, as should have been done.[10] Rather, they refitted the BODE index on the data already available and subsequently quantified its accuracy on the same data, thereby also using mortality over a median follow-up of 28 months (rather than 12 months).

We chose two COPD cohorts that differed in terms of the severity of COPD and, as a consequence, in terms of mortality. We noted that both the updated BODE and ADO indices predicted 3-year mortality accurately in the Spanish cohort, but an adjustment of the underlying risk of mortality (adjustment of intercept) was necessary. However, this adjustment is common for prediction models that are applied in different populations.[23,24] For example, the risk for cardiovascular disease as predicted by the Framingham risk score also needed adjustment when applied to cohorts with different underlying outcome incidence.[34] As a result, we separately presented the 3-year risk of mortality of the updated BODE and ADO indices for both patients with longstanding and severe COPD and those who had their first hospital admission due to an exacerbation of moderate-to-severe COPD (table 4 and table 7).

	0 points	1 point	2 points	3 points	4 points	5 points
FEV_1 (% predicted)	≥65%	≥36–64%	≤35%	..	..	..
Dyspnoea (MRC scale)	0–1	2	3	4	..	..
Age (years)	40–49	50–59	60–69	70–79	80–89	≥90

FEV_1=forced expiratory volume in 1 s. MRC=Medical Research Council.

Table 6: **Assignment of points for the ADO index**

The fairly low discriminative ability and the need for recalibration of the updated BODE and ADO indices in other cohorts suggests that important predictors are still missing in both indices, which could further explain observed differences in mortality.[7,23,24] Although 6-min walk distance, age, FEV_1, and dyspnoea are among the strongest predictors of death in patients with COPD, further external validation studies of both indices are needed to assess how they can be applied to other COPD populations and whether additional predictors can improve their discriminative ability. Furthermore, the updated BODE and ADO indices seem to be similarly accurate in predicting 3-year mortality (figure 2 and figure 3), but future validation studies will need to confirm this finding.

Our reporting of the original underlying statistical models facilitates such studies. Investigators should use the regression coefficients and constants reported here to predict and compare 3-year mortality in their validation cohorts. If additional predictors are considered, the focus should be on predictors that are easily obtainable not only in specialised pulmonary medicine but also in primary-care settings in which most patients with COPD are managed. For example, comorbidities such as cardiovascular disease and associated treatments (drugs to lower blood pressure or lipids), blood markers such as C-reactive protein,[35] or the ratio of circulating fibronectin to C-reactive protein[36] could be additional variables to improve the prediction of mortality. Additionally, if COPD treatments prove to modify the risk of mortality, they could also be considered for updating the BODE and ADO indices.[7] Finally, geographic differences could

	0	1	2	3	4	5	6	7	8	9	10
Patients with longstanding and severe COPD*	7·2% (2·7–17·9)	9·9% (4·4–20·6)	13·5% (7·2–23·8)	18·1% (11·4–27·5)	23·9% (17·4–31·8)	30·8% (24·8–37·4)	38·7% (32·0–45·7)	47·2% (37·9–56·6)	55·9% (43·1–68·0)	64·2% (47·8–77·8)	71·8% (52·4–85·4)
Patients after first hospital admission due to moderate-to-severe COPD†	3·0% (0·9–9·0)	4·0% (1·6–10·0)	5·4% (2·7–10·9)	7·3% (4·3–12·1)	9·8% (6·8–13·9)	12·9% (9·6–17·1)	16·9% (12·0–23·3)	21·8% (13·7–32·8)	27·6% (15·2–44·9)	34·3% (16·7–57·9)	41·7% (18·0–70·0)

Data are 3-year risk of mortality per ADO score (95% CI). *Odds ratio per point increase in ADO index=1·42 (95% CI 1·19–1·69). †Odds ratio per point increase in ADO index=1·37 (1·09–1·71).

Table 7: **Prediction of 3-year mortality in patients with chronic obstructive pulmonary disease (COPD) by ADO score**

modify the risk of mortality and need to be considered when updating the BODE and ADO indices, as has been done in cardiovascular medicine.[34,37] If future validation studies further improve the prediction of the updated BODE and ADO indices by considering easily obtainable additional predictors, then the need to present different risk prediction tables might be overcome.

The updated BODE index and the newly developed ADO index might stimulate a debate about how to individualise COPD management according to the underlying risk profile. Until now, clinicians were not supported by an index that accurately estimates the prognosis of patients with COPD in terms of absolute mortality risks. They base their prognostic assessment, if at all, mostly on lung function.[38] The updated BODE and ADO indices provide a more explicit risk assessment than does the original BODE index. They refer to a specific time period (3 years) and provide absolute risks for mortality. Such an explicit risk assessment allows clinicians to identify patients at moderate or high risk of mortality, for which more comprehensive treatment with respiratory rehabilitation, for example, might be appropriate to reduce their risk.

At what thresholds a more or less intensive treatment should be proposed to have an acceptable risk–benefit ratio is unclear. But examples from cardiovascular medicine show that a consensus can be reached on how to treat patients at different risk for mortality.[39] Eventually, randomised trials assessing the effect of using these rules to start subsequent treatments on patient outcome as compared with present care, could inform formal cost-effective analyses that can then be used for treatment decisions.[40] Finally, we believe that risk scores such as the updated BODE and ADO indices should never be used as surrogate outcomes for mortality in trials, as is increasingly being done,[5] because lowering a risk score in the short term might not translate into lower mortality, or because some predictors such as age cannot be modified at all.

A strength of this study is the inclusion of patients from two different cohorts, which allowed us to validate the original BODE index in different populations, and to develop the updated BODE and ADO indices which in turn could immediately be externally validated. Another strength is the use of robust statistical techniques to update existing prediction models to increase the ability of a risk score to perform well in new populations.[23,24] A potential shortcoming of our study is that we did not have identical protocols for the Swiss and the Spanish cohorts, so the measurements differed somewhat. Although such differences make prediction difficult, they do represent the variability of measurements across studies or populations, therefore increasing the generalisability of the findings. Finally, although the development of the updated BODE and ADO indices were based on a cohort with an adequate number of events, both the development and validation cohorts were still relatively small.

We conclude that both the updated BODE and ADO indices could lend support to the prognostic assessment of patients with COPD in specialised and primary-care settings. Such assessment enhances the targeting of treatments to individual patients.

Contributors

MAP conceived the study idea, led the Swiss–Spanish research consortium, contributed to the statistical analysis, and drafted the first version of the report. JG-A led the Spanish part of the research consortium, contributed to the statistical analysis, and revised the report. MF led and oversaw all activities related to the conduct of the Swiss cohort study. GtR and KGMM contributed to the statistical analysis and revised the report. JMA, AGA, FPG, and RR-R led and oversaw all activities related to the conduct of the Spanish cohort study and revised the report. AGK and UH contributed to the statistical analysis and revised the report.

Conflicts of interest

None of the authors has any conflicts of interest with this report. In the past, MAP and MF have received research grants from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline for trials in respiratory rehabilitation and for the development of patient-reported outcomes. RR-R has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Kyorin, Novartis, and Pfizer; consulted with several pharmaceutical companies (Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed, and Pfizer); serves on advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Nycomed, Pfizer, and Procter & Gamble; and has been sponsored for several clinical trials by, and received laboratory research support from, Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Esteve, and Pfizer. AGA served on advisory boards for GlaxoSmithKline, Boehringer Ingelheim, Almirall, AstraZeneca, Nycomed, Sepracor, and Roche; received fees for lecturing from GlaxoSmithKline Boehringer Ingelheim, Almirall, AstraZeneca, Nycomed, Sepracor, and Chiesi; and received grant support from GlaxoSmithKline, Almirall, and Nycomed in relation to the general topic of COPD. GtR has received a research grant from Zambon.

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References

1 Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; **350:** 1005–12.

2 Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; **370:** 797–99.

3 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007; **370:** 765–73.

4 Cote CG, Pinto-Plata VM, Marin JM, Nekach H, Dordelly LJ, Celli BR. The modified BODE index: validation with mortality in COPD. *Eur Respir J* 2008; **32:** 1269–74.

5 Imfeld S, Bloch KE, Weder W, Russi EW. The BODE index after lung volume reduction surgery correlates with survival. *Chest* 2006; **129:** 873–78.

6 Martinez FJ, Han MK, Andrei AC, et al. Longitudinal change in the BODE index predicts mortality in severe emphysema. *Am J Respir Crit Care Med* 2008; **178:** 491–99.

7 Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ* 2009; **338:** b375.

8 Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000; **19:** 453–73.

9 Bleeker SE, Moll HA, Steyerberg EW, et al. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol* 2003; **56:** 826–32.

10 Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009; **338:** b605.

11 Garcia-Aymerich J, Gomez FP, Anto JM. Phenotypic characterization and course of chronic obstructive pulmonary disease in the PAC-COPD study: design and methods. *Arch Bronconeumol* 2009; **45:** 4–11.

12 Puhan MA, Busching G, Schunemann HJ, VanOort E, Zaugg C, Frey M. Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2006; **145:** 816–25.

13 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000; **117** (suppl 2)**:** 398S–401S.

14 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23:** 932–46.

15 Balcells E, Anto JM, Gea J, et al. Characteristics of patients admitted for the first time for COPD exacerbation. *Respir Med* 2009; published online May 7. DOI:10.1016/j.rmed.2009.04.001.

16 Puhan MA, Behnke M, Frey M, et al. Self-administration and interviewer-administration of the German Chronic Respiratory Questionnaire: instrument development and assessment of validity and reliability in two randomised studies. *Health Qual Life Outcomes* 2004; **2:** 1.

17 Duiverman ML, Wempe JB, Bladder G, Kerstjens HA, Wijkstra PJ. Health-related quality of life in COPD patients with chronic respiratory failure. *Eur Respir J* 2008; **32:** 379–86.

18 Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; **154:** 1726–34.

19 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166:** 111–17.

20 Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; **59:** 1087–91.

21 Yang X, So WY, Tong PC, et al. Development and validation of an all-cause mortality risk score in type 2 diabetes. *Arch Intern Med* 2008; **168:** 451–57.

22 Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–89.

23 Janssen KJ, Moons KG, Kalkman CJ, Grobbee DE, Vergouwe Y. Updating methods improved the performance of a clinical prediction model in new patients. *J Clin Epidemiol* 2008; 61: 76–86.

24 Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. *Stat Med* 2004; **23:** 2567–86.

25 van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* 2000; **19:** 3401–15.

26 Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. *Stat Med* 2007; **26:** 5512–28.

27 Copas JB. Using regression models for prediction: shrinkage and regression to the mean. *Stat Methods Med Res* 1997; **6:** 167–83.

28 Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. *BMJ* 2009; **338:** b604.

29 Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med* 2004; **23:** 1631–60.

30 Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *Eur Respir J* 2008; **32:** 637–43.

31 Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;23(1):28-33.

32 Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; **167:** 544–49.

33 Steyerberg EW, Bleeker SE, Moll HA, Grobbee DE, Moons KG. Internal and external validation of predictive models: a simulation study of bias and precision in small samples. *J Clin Epidemiol* 2003; **56:** 441–47.

34 Eichler K, Puhan MA, Steurer J, Bachmann LM. Prediction of first coronary events with the Framingham score: a systematic review. *Am Heart J* 2007; **153:** 722–31.

35 de Torres JP, Pinto-Plata V, Casanova C, et al. C-reactive protein levels and survival in patients with moderate to very severe COPD. *Chest* 2008; **133:** 1336–43.

36 Man SF, Xing L, Connett JE, et al. Circulating fibronectin to C-reactive protein ratio and mortality: a biomarker in COPD? *Eur Respir J* 2008; **32:** 1451–57.

37 Marrugat J, D'Agostino R, Sullivan L, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. *J Epidemiol Community Health* 2003; **57:** 634–38.

38 Puhan MA, Zoller M, ter Riet G. COPD: more than respiratory. *Lancet* 2008; **371:** 27–28.

39 British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; 91 (suppl 5): v1–52.

40 Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009; **338:** b606.