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Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts

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ABSTRACT

Background: Little evidence on the validity of simple and widely applicable tools to predict mortality in patients with chronic obstructive pulmonary disease (COPD) exists.

Objective: To conduct a large international study to validate the ADO index that uses age, dyspnoea and FEV_1 to predict 3-year mortality and to update it in order to make prediction of mortality in COPD patients as generalisable as possible.

Design: Individual subject data analysis of 10 European and American cohorts (n=13 914).

Setting: Population-based, primary, secondary and tertiary care.

Patients: COPD GOLD stages I–IV.

Measurements: We validated the original ADO index. We then obtained an updated ADO index in half of our cohorts to improve its predictive accuracy, which in turn was validated comprehensively in the remaining cohorts using discrimination, calibration and decision curve analysis and a number of sensitivity analyses.

Results: 1350 (9.7%) of all subjects with COPD (60% male, mean age 61 years, mean FEV_1 66% predicted) had died at 3 years. The original ADO index showed high discrimination but poor calibration (p<0.001 for difference between predicted and observed risk). The updated ADO index (scores from 0 to 14) preserved excellent discrimination (area under curve 0.81, 95% CI 0.80 to 0.82) but showed much improved calibration with predicted 3-year risks from 0.7% (95% CI 0.6% to 0.9%, score of 0) to 64.5% (61.2% to 67.7%, score of 14). The ADO index showed higher net benefit in subjects at low-to-moderate risk of 3-year mortality than FEV_1 alone.

Interpretation: The updated 15-point ADO index accurately predicts 3-year mortality across the COPD severity spectrum and can be used to inform patients about their prognosis, clinical trial study design or benefit harm assessment of medical interventions.

ARTICLE SUMMARY

Article focus
- We aimed to conduct a large international study to validate the ADO index that uses age, dyspnoea and FEV_1 to predict 3-year mortality and to update it in order to make prediction of mortality in chronic obstructive pulmonary disease (COPD) patients as generalisable as possible.

Key messages
- The updated 15-point ADO index accurately predicts 3-year mortality across the COPD severity spectrum (GOLD stage I–IV), settings (general population, primary care and specialised care) and geographical area.
- The updated ADO index can be used to inform patients, clinical trial study design and benefit harm assessment of medical interventions on a population level or individual level.
- In addition, the ADO index could serve as a reference standard for risk prediction against which the additional value of various biomarkers to predict mortality could be assessed.

Strengths and limitations of this study
- The study includes a large sample size from 10 European and American cohorts and covers the entire COPD severity spectrum, which increases external validity.
- The study uses information readily available in routine clinical practices.
- Focus on mortality and easily available predictors.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is among the leading causes of death worldwide.[1][2] Although the substantial excess mortality associated with COPD is well

recognised from a public health standpoint, relatively little evidence is available on how to estimate the risk of mortality for an individual patient. Tools to accurately project the clinical course of the disease, including prediction of outcomes such as mortality, exacerbations or quality of life, would inform patients and their caregivers about prognosis and allow for a better understanding of the benefits and harms of possible treatments.[3–6] Also, tools that incorporate prognostic information from easily available parameters could serve as reference against which the additional prognostic value of biomarkers could be assessed.

Current international COPD guidelines provide little guidance on how to assess a patient's prognosis.[7 8] This is likely due, in large part, to the scarcity of evidence on how to accurately estimate prognosis in patients with COPD; however, this is in contrast to other chronic disease guidelines that have clear recommendations on the use of prognostic indices to inform patients and to guide treatment decisions.[9–13] Prognostic indices for COPD have recently received increased attention, but have seen little application in clinical practice. This may be because indices, to date, have either required information not readily available in routine clinical practice,[14] do not provide explicit outcome risks[15 16] or have received minimal validation.[15–17] A recently developed index, the ADO index, combines age, dyspnoea and airflow obstruction to predict the risk of mortality. It may have great potential for widespread application because of its simplicity. However, formal testing of its accuracy across a variety of COPD patient cohorts following standard methods has not yet been done.[6 18–21] The original index was derived in a cohort of moderate-to-severe COPD patients from specialised care, therefore, it requires validation in larger and notably more diverse COPD populations. We conducted such large-scale international validation of the ADO index to determine how well it predicts mortality for individual subjects with COPD from diverse settings, and updated the index as needed.

METHODS
Cohorts and patients
Investigators from 10 COPD and population-based cohort studies in Europe and the Americas agreed to collaborate in the International COPD Cohorts Collaboration Working Group. These cohorts include the Barmelweid cohort (Switzerland, clinic based),[17] the Basque study (Spain, clinic based),[22] the Cardiovascular Health Study (CHS, USA, population based),[23] the Copenhagen City Heart Study (CCHS, Denmark, population based),[24] the Jackson Heart Study (JHS, USA, population based),[25] the Lung Health Study (LHS, USA, clinic based),[26] the cohort from which patients for the National Emphysema Treatment Trial were recruited (NETT, USA, clinic based),[27] the Phenotype and Course of COPD PAC-COPD Study (PAC-COPD, Spain, clinic

based),[28] the PLATINO study (Uruguay, population based),[29] and the Quality of Life of COPD Study Group (SEPOC, Spain, clinic based).[30] Details about the cohorts are provided in the online supplement (see online supplementary appendix 1). From this international pool of cohorts we selected participants with at least 40 years of age and with COPD defined by spirometry as a post-bronchodilator (BD) $FEV_1/FVC \leq 0.7$, except for the CHS and CCHS cohorts where post-BD was not available and pre-BD values were used. Thus, our large pool of cohorts represents a heterogeneous group of subjects, combining (1) COPD patients from clinical cohorts and (2) subjects with evidence of airway limitation from the population-based cohorts, but without a confirmed diagnosis of COPD. Ethics Board approval was obtained in all cohorts.

Mortality and candidate predictors of mortality
All-cause mortality at 3 years was defined as the outcome. It was obtained from personal follow-up of patients or relatives, national registries, or hospital records, yielding no missing information with respect to mortality. We considered potential predictors of mortality which are easy to obtain across diverse medical settings. These variables included age, sex, smoking status, prebronchodilator or postbronchodilator FEV_1 as available, dyspnoea score (Medical Research Council Dyspnea scale), respiratory signs and symptoms (cough, sputum and wheezing), body mass index (BMI), asthma and cardiovascular disease (CVD, which included ischaemic heart disease, stroke, congestive heart failure or peripheral vascular disease). As in previous analyses,[17] we explicitly excluded potential predictors of mortality which are more burdensome to measure such as exercise capacity (eg, 6 min walked distance) or arterial blood gases, since these are unlikely to be available consistently in clinical practice outside academic centres. Missing values were imputed using 10-fold multiple imputation for each cohort, using the remaining variables as predictors.[31 32] Methods used for collecting and harmonising data, and for handling missing data are detailed in the appendix (see online supplementary appendices 2–4).

Statistical analysis
A detailed version of statistical analysis including sample size assessment is available in the appendix (see online supplementary appendix 5).

We first validated the original ADO index[17] through the assessment of its discrimination (area under curve) and calibration (comparison of predicted vs observed risk) properties in all subjects except for those included in the original derivation cohort (ie, the Barmelweid study).

In order to make the risk estimation tool as generalisable to different international populations as possible, we then updated the ADO index following standardised procedures that first included an updating or adjustment

of the intercept only followed by, if necessary, more extensive updates including model revision (refitting the predictor-outcome associations) and model extension (adding new predictors).[21][32] Model refitting of the ADO index was performed using all subjects from the CCHS, LHS, NETT, PLATINO and PAC-COPD cohorts (update cohort, n=10 221), applying logistic regression with death as the outcome variable and age, dyspnoea and FEV_1 as predictors. Then the validation (discrimination and calibration) of the final updated ADO index was done with the subjects from the Barmelweid study, CHS, Basque Study, JHS and SEPOC cohorts (validation cohort, n=3693). Thus, both update and validation sets included a large number of subjects with COPD or airflow limitation, diverse in terms of disease severity (GOLD I–IV) and settings (general population, primary care and specialised care). We translated the final model into a simple-to-use 15-point scale.[33]

To further quantify the accuracy of the updated ADO index, we performed a decision curve analysis that compares the net benefit of different approaches. Net benefit is defined as the difference between the proportion of subjects that are correctly identified to be at or above a certain risk threshold (eg, 5% risk) and the proportion of subjects incorrectly identified to be at or above that threshold. We focused on subjects with COPD at low-to-moderate risk for 3-year mortality (<20%) where most uncertainty about the balance between benefits and harms of treatments may exist so that risk thresholds may be specifically useful.[34][35]

Finally, we explored whether adding new predictors (eg, CVD, BMI and sex) improved the updated (refitted) models' discrimination and calibration and we conducted three sensitivity analyses that tested how susceptible our results were to analytical approaches taken. All analyses were repeated: (1) using multilevel (rather than conventional) logistic regression analysis; (2) excluding subjects with mild COPD (GOLD stage I) and (3) excluding subjects with a physician diagnosis of asthma from cohorts where only prebronchodilator spirometry was available. We also considered restricting the analyses to subjects with an FEV_1/FVC ratio below their lower limit of normal level according to local prediction equations, but the number of subjects not fulfilling this criterion was very low (<1%).

We conducted all analyses using Stata for Windows (V.11.1, College Station, Texas, USA) and R, V.2.12 (R Foundation for Statistical Computing, Vienna, Austria, 2011).

RESULTS

In total, 13 914 subjects with COPD (60% men) were included in the analysis (table 1). On average, subjects were approximately 61 years old, with moderate airflow limitation and mild dyspnoea; however, there was a wide range of disease severity within and across cohorts. The majority of subjects were former or current smokers (89%) and 22% had concomitant CVD. After 3 years 1350 (9.7%) subjects had died.

The original ADO index showed high discrimination (see online supplementary appendix 6) but poor calibration with a substantial mismatch between predicted and observed risks across the entire risk spectrum. Updating the intercept only did not substantially improve this miscalibration. Therefore, we decided to update the original ADO index.

In the update cohort, the updated ADO model showed very good agreement between predicted and observed 3-year mortality risk across 10 equally sized groups of subjects with increasing predicted risk (figure 1: mean predicted risk 9.1%). More importantly, in the validation cohort, the updated index still had good prediction across all risk categories, in particular in subjects at mortality risks below 20%. There was only a slight overprediction among subjects at very high risk. This validation did not indicate a need for further adjustment of the intercept or regression coefficients of the updated ADO model, which indicated good generalisability across countries and settings. Discrimination was, as expected, somewhat lower in the validation cohort but still 0.73 (95% CI 0.70% to 0.76%). Further extensions of the updated ADO index by adding CVD, BMI and sex did not substantially improve the model's discrimination or calibration, even though all three predictors were significantly associated with mortality in the multivariate model (all p values <0.05). The area under the curve remained 0.85 in the update cohort and 0.74 in the validation cohort, and the calibration also remained good (see online supplementary appendix 7).

Tables 2 and 3 show the updated ADO index where the strength of association of age, dyspnoea and FEV_1 with 3-year mortality is reflected in the regression coefficients and the corresponding integer point score. The 3-year risks of mortality associated with ADO scores are shown in table 4 and range from 0.7% (95% CI 0.6% to 0.9%) with a score of zero to 64.5% (95% CI 61.2% to 67.7%) at a point score of 14. The area under the curve of the updated ADO index is 0.81 (95% CI 0.80% to 0.82%).

Figure 2A shows that, from 1% to 20% risk of 3-year mortality, using the updated ADO index (regression equation) is consistently more accurate to classify patients correctly above or below certain risk thresholds than using either of the three predictors alone. Figure 2B shows the consequences of more accurate risk classification. For example at a risk threshold of 5%, using the ADO index would result in a reduction of the number of patients classified incorrectly to be above 5% by 33/100 subjects compared with considering all patients to be above 5% (ie, without using any predictors), and compared with using only FEV_1 (18 per 100 subjects), age (24 per 100 subjects) or dyspnoea (10 per 100 subjects). At higher risk thresholds, the updated ADO index and FEV_1 perform similarly.

Discrimination, calibration and the analysis of accuracy for risk thresholds remained essentially

Table 1 Description of sociodemographic and clinical characteristics of 13 914 subjects with COPD from the cohorts

	Total n=13914	Barmelweid cohort Switzerland, Europe n=231	Basque study Spain, Europe n=106	Cardio-vascular Health Study USA, North America n=2619	Copenhagen City Heart Study Denmark, Europe n=2287	Jackson Heart Study USA, North America n=419	Lung Health Study USA, North America n=5167	National Emphysema Treatment Trial USA, North America n=2252	PAC-COPD Study Spain, Europe n=342	PLATINO study Uruguay, South America n=173	SEPOC study Spain, Europe n=318
Age (years), mean (SD)	60.8 (11.6)	72.4 (8.8)	70.5 (8.9)	73.6 (5.9)	60.7 (9.4)	62.4 (11.0)	50.1 (5.7)	66.7 (6.3)	67.9 (8.6)	67.2 (11.3)	65.2 (9.2)
Sex: male, n (%)	8324 (60)	138 (60)	104 (98)	1341 (51)	1235 (54)	184 (44)	3223 (62)	1366 (61)	318 (93)	97 (56)	318 (100)
Working status: active, n (%)	5297 (63)	n.a.	n.a.	n.a.	n.a.	413 (99)	4538 (88)	178 (8)	61 (18)	63 (36)	51 (16)
Smoking											
Never, n (%)	1452 (11)	9 (5)	0 (0)	930 (36)	215 (9)	215 (52)	0 (0)	12 (1)	2 (1)	57 (33)	12 (5)
Former, n (%)	4751 (34)	138 (73)	82 (77)	1245 (48)	443 (19)	102 (25)	73 (1)	2240 (100)	220 (67)	60 (35)	148 (58)
Current, n (%)	7590 (55)	41 (22)	24 (23)	444 (17)	1626 (71)	99 (24)	5094 (99)	0 (0)	109 (33)	56 (32)	97 (38)
Body mass index(kg/m^2), mean(SD)	25.7 (4.5)	25.9 (6.1)	26.1 (4.9)	26.2 (4.8)	25.0 (4.2)	29.6 (7.5)	25.6 (3.9)	24.9 (4.2)	28.2 (4.7)	27.4 (5.3)	26.4 (4.2)
Dyspnoea (MRC, 0–4), mean (SD)	1.1 (1.3)	2.2 (1.2)	2.0 (0.6)	0.8 (1.1)	1.1 (1.3)	0.2 (0.6)	0.6 (0.8)	2.7 (1.0)	2.2 (1.0)	0.6 (0.6)	2.1 (1.5)
Cough, n (%)	4009 (59)	n.a.	n.a.	444 (17)	n.a.	108 (26)	3259 (100)	n.a.	138 (41)	60 (35)	n.a.
Sputum, n (%)	4289 (52)	n.a.	n.a.	656 (25)	908 (40)	107 (26)	2400 (100)	n.a.	172 (51)	46 (27)	n.a.
Wheeze, n (%)	4352 (53)	n.a.	n.a.	187 (9)	n.a.	73 (18)	3897 (75)	n.a.	125 (37)	70 (40)	n.a.
FEV$_1$ (% pred), mean (SD)*	65.9 (24.8)	45.1 (16.1)	46.9 (11.4)	77.3 (22.4)	70.5 (23.7)	71.2 (20.5)	77.8 (9.1)	27.5 (8.9)	52.4 (16.2)	84.3 (18.1)	45.0 (18.3)
Inhaler steroid use, n (%)	1833 (33)	-	103 (100)	55 (2)	n.a.	n.a.	n.a.	1376 (61)	266 (79)	33 (19)	n.a.
6-min walk distance, mean (SD)	357.8 (111.7)	363.1 (127.0)	442.9 (95.4)	n.a.	n.a.	n.a.	n.a.	340.6 (106.3)	435.5 (90.6)	n.a.	n.a.
Asthma,† n (%)	920 (8)	0 (0)	0 (0)	148 (6)	246 (11)	74 (18)	373 (7)	n.a.	30 (9)	49 (28)	0 (0)
Diabetes,† n (%)	262 (7)	41 (18)	n.a.	n.a.	60 (3)	71 (19)	n.a.	n.a.	65 (19)	7 (4)	18 (6)

Table 1 Continued

	Total n=13914	Barmelweid cohort Switzerland, Europe n=231	Basque study Spain, Europe n=106	Cardio-vascular Health Study USA, North America n=2619	Copenhagen City Heart Study Denmark, Europe n=2287	Jackson Heart Study USA, North America n=419	Lung Health Study USA, North America n=5167	National Emphysema Treatment Trial USA, North America n=2252	PAC-COPD Study Spain, Europe n=342	PLATINO study Uruguay, South America n=173	SEPOC study Spain, Europe n=318
Cardiovascular disease,†‡ n (%)	3007 (22)	165 (71)	25 (29)	747 (29)	813 (34)	79 (19)	278 (5)	704 (31)	85 (25)	37 (21)	74 (23)
Death during 3-year follow-up, n (%)	1350 (10)	79 (34)	16 (15)	232 (9)	186 (8)	29 (7)	58 (1)	632 (28)	41 (12)	16 (9)	61 (19)

*Prebronchodilator FEV₁ used where postbronchodilator FEV₁ not available (Cardiovascular Health Study and Copenhagen City Heart Study).
†Cocomorbidities are self-reported, self-report of a doctor diagnosis, or doctor diagnosed (according to medical chart and physical examination) depending on the cohort.
‡Cardiovascular disease is defined as at least one of the following: ischaemic heart disease, stroke, congestive heart failure or peripheral vascular disease.
COPD, chronic obstructive pulmonary disease.

unchanged in all sensitivity analyses (see online supplementary appendix 8).

DISCUSSION

Our study showed that the updated ADO index, ranging from 0 to 14, accurately predicts 3-year mortality in subjects with COPD. We found that adding CVD, BMI or sex does not significantly improve prediction of mortality when added to age, dyspnoea and FEV₁. Importantly, these results were consistent in sensitivity analyses and across very diverse COPD populations. Based on these results, the updated ADO index has the potential to provide COPD patients with accurate prognostic information on mortality.

The interest in prognostic assessment of COPD has resulted in several prognostic tools.[15–17] The latter had, however, little impact on clinical guidelines or practice so far. The current study overcomes potentially important barriers to the use of previously published prognostic tools by providing an extensive, international validation of a simple tool. The first step of our analysis, the large-scale validation of the original ADO index, showed that mortality could not be predicted accurately but that the combination of age, dyspnoea and FEV₁ is highly discriminative. Therefore, a more extensive update than just an adjustment for different underlying risks was necessary and we updated the entire regression model in our very diverse update cohort that represented the entire disease spectrum. The resulting updated ADO index showed excellent calibration and discrimination in both the update and validation cohorts. An additional adjustment was not deemed necessary for the validation cohort, which may be due to the great diversity of the update and validation cohorts in terms of disease severity, clinical setting and geographical area. Our results confirm that CVD and low BMI are important comorbidities in COPD patients and are significantly associated with mortality; however, they did not provide additional accuracy in risk prediction when added to age, dyspnoea and FEV₁, as shown by the fact that the performance of the ADO index was not improved by adding CVD, sex and BMI to the statistical model.

Informing patients about their prognosis is a core task of clinicians. Patients with chronic disease are particularly interested in the potential course of their disease in order to better understand what a diagnosis such as COPD implies for them. Important outcomes that characterise prognosis are exacerbations, quality of life and mortality.[36] With the ADO index, we now provide a simple tool that clinicians from any setting can use to estimate the risk of mortality. We propose that such multivariable tools can also be used to balance the benefits and harms of possible treatments since the benefit harm balance depends heavily on the patients' prognosis.[4 37] Thus, estimation of prognosis is of key importance for patients but also for policy makers, regulatory agencies and clinical guideline developers. Our data suggest that

Figure 1 Update and validation of the ADO index in 13 914 subjects with chronic obstructive pulmonary disease (COPD). The upper part of the figure shows the predictive performance of the updated ADO index in 10 221 subjects with COPD from the Copenhagen City Heart Study, Lung Health Study, National Emphysema Treatment Trial, PLATINO and the Phenotype and Course of COPD Study. The calibration plot shows the predicted and observed risks for 10 equally sized group with increasing risk of 3-year mortality. The discrimination plot shows the area under the curve. The lower part of the figure shows the predictive performance of the updated ADO index in the validation cohort with 3693 subjects from the Cardiovascular Health Study, Basque COPD study, Jackson Heart Study, Barmelweid Study and the Quality of Life of Chronic Obstructive Pulmonary Disease Study (SEPOC).
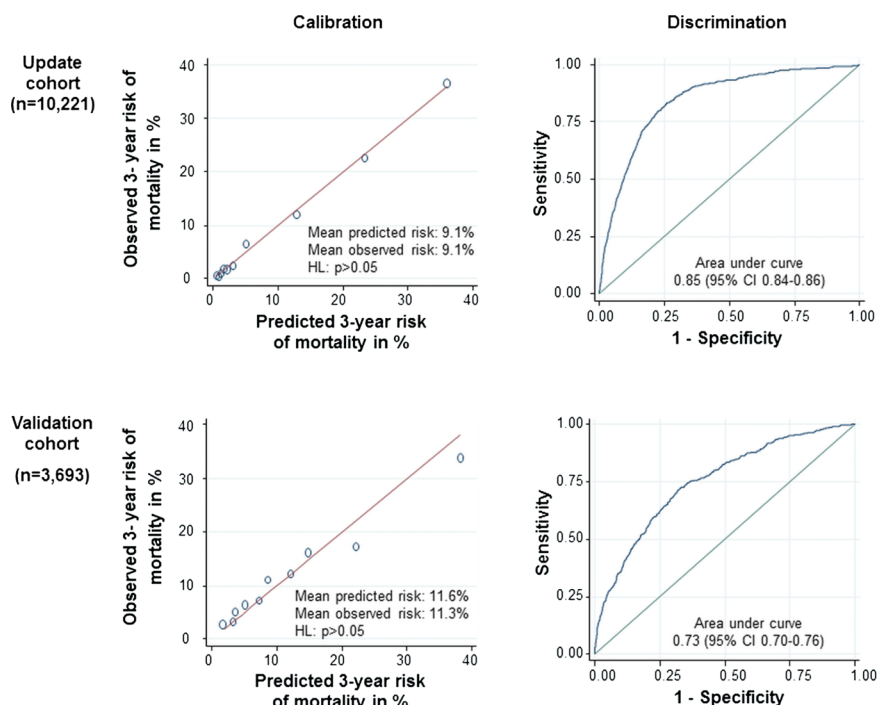
Table 2	Regression coefficients and development of updated ADO index				
Variable	**Regression coefficients β_s per unit increase**	**Categories**	**Reference values W_{ij} (mid point)**	**β_s* (W_{ij}-*$W_{1reference}$)**	**Risk score=β_s* (W_{ij}-*$W_{1reference}$)/B†**
FEV$_1$ (% predicted)	−0.0288 (SE 0.0023, p<0.0001)	≥81	87.0 ($W_{2reference}$)		0
		≥65–80	72.5	0.418	1
		≥50–64	57.0	0.864	2
		≥36–49	42.5	1.282	3
		≤35	25.0	1.786	4
Dyspnoea (mMRC, 0–4)	0.2585 (SE 0.0406, p<0.0001)	0	0 ($W_{3reference}$)		0
		1	1	0.259	1
		2	2	0.517	1
		3	3	0.776	2
		4	4	1.034	3
Age (years)	0.0703 (SE 0.0048, p<0.0001)	40–49	44.5 ($W_{4reference}$)		0
		50–59	54.5	0.703	2
		60–69	64.5	1.406	4
		70–79	74.5	2.109	5
		≥80	84.5	2.812	7

†1 Point is assigned per 15% in FEV$_1$=coefficient of 0.40. Points rounded to the next integer. Constant of regression equation=−5.640. MRC, Medical Research Council.

Table 3 Assignment of points for the updated ADO index, compared with the original ADO index

Assignment of points	0	1	2	3	4	5	7
Updated ADO index							
FEV$_1$ (% predicted)	≥81	65–80	51–64	36–50	≤35		
Dyspnoea (mMRC, 0–4)	0	1–2	3	4			
Age (in years)	40–49		50–59		60–69	70–79	≥80
Original ADO index							
FEV$_1$ (% predicted)	≥65	36–64	≤35				
Dyspnoea (mMRC, 0–4)	0–1	2	3	4			
Age (years)	40–49	50–59	60–69	70–79	80–89	≥90	

the ADO index classifies patients more correctly above or below certain risk thresholds than only FEV$_1$, and this gain is especially relevant in subjects with very low and low risk of 3-year mortality where the benefit harm balance may be unfavourable.[3][4] Although most COPD treatments are not prescribed to modify mortality risk, but to reduce exacerbations, and improve symptoms and quality of life, similar estimates for the benefit harm balance could be made for patients at low risk for exacerbations. Therefore, in the future, the ADO index should be complemented by other widely validated risk tools that make accurate projections about the risk for important outcomes in COPD, including exacerbations or worsening quality of life, in order to balance the benefits and harms of possible treatments.

In addition, accurate prediction of mortality by the ADO index can be used in clinical trials to base sample size calculations on realistic estimates of expected event rates, to target treatments to specific risk groups, for pre-stratification or to adjust for potential baseline imbalances. Also, the ADO index could be useful for the evaluation of biomarkers. Currently, major studies are being carried out to identify biomarkers that might help to improve outcome prediction and response to treatments. The use of such biomarkers in clinical practice seems justified if they add significantly to the prediction based on easily available information. The ADO index is a simple tool that could serve as reference against which the additional value of biomarkers to predict mortality could be assessed. Therefore, the ADO index is likely to be useful for both medical practice and research.

A limitation to the current study is the use of mortality as the only assessed outcome, since COPD morbidity includes other relevant outcomes such as exacerbations, hospital admissions, or quality-of-life. Thus, our study should be considered a simplification of the clinical setting but it may pave the way for similar research evaluating risk prediction of additional outcomes. Once risk tools for various important outcomes and improved evidence about benefit and harm of treatments to modify these risks are available, informed decisions for providing the most appropriate care can be better supported. Our study was confined to a limited number of readily available predictors; therefore, variables with potential relevance to mortality risk such as exacerbation frequency or measures of exercise capacity were not included. This may also be perceived as strength of our study because it uses information readily available in routine clinical practices, including primary care settings, where most COPD patients are treated. Additional strengths of our study include the already mentioned large sample size and diversity of the populations. This increases external validity, which in this context means that recalibrations in populations different from those included in our analyses do not seem necessary. Lastly, by using decision curve analysis we looked beyond standard metrics for the performance of risk tools (discrimination and calibration) by providing an interpretation of the risk model that refers to different risk thresholds that may be used to inform treatment decisions.

In conclusion, the updated 15-point ADO index is a simple tool that can be used in diverse settings to inform patients and their caregivers about prognosis. Using risk tools in clinical COPD research may also help to design clinical trials and to inform policy makers, regulatory agencies or guideline developers when estimating the benefit harm balance and to serve as a reference standard for risk prediction against which the

Table 4 The ADO index—prediction of 3-year mortality in chronic obstructive pulmonary disease subjects

Three-year risk of mortality per ADO score in % (95% CI)	
0	0.7 (0.6 to 0.9)
1	1.0 (0.9 to 1.2)
2	1.6 (1.3 to 1.8)
3	2.3 (2.0 to 2.6)
4	3.4 (3.0 to 3.7)
5	4.9 (4.5 to 5.4)
6	7.2 (6.7 to 7.7)
7	10.3 (9.7 to 10.9)
8	14.5 (13.8 to 15.3)
9	20.1 (19.1 to 21.1)
10	27.2 (25.8 to 28.6)
11	35.7 (33.7 to 37.7)
12	45.1 (42.6 to 47.7)
13	55.0 (52.0 to 58.0)
14	64.5 (61.2 to 67.7)

OR per 1 point increase in ADO index: 1.48 (95% CI 1.45 to 1.52).
Area under the curve: 0.81 (95% CI 0.80 to 0.82).

Figure 2 Accuracy of four strategies to classify subjects into risk categories. The upper part (A) of the figure shows the net benefit of six strategies to classify subjects with chronic obstructive pulmonary disease. The higher the values for net benefit the more patients are correctly classified. Two strategies do not use any predictors but assume that all patients would be above or below a risk threshold. The four other strategies use the ADO index, age, dyspnoea or FEV_1 and associated risks of 3-year mortality to classify patients. Net benefit is defined as the difference between the proportion of correctly classified subjects and the proportion of subjects classified incorrectly to be at or above a risk threshold (eg, 5% risk). The line for considering all patients to be above a risk threshold crosses that line for considering all patients to be below a risk threshold at the death rate observed (9.7%). The lower part of the graph (B) shows that, for example at a threshold of 5% mortality risk, using the ADO index would result in a net benefit similar to the reduction of 33 incorrectly classified patients per 100 subjects compared to considering all patients to be above a 5% mortality risk. Using age, dyspnoea or FEV_1 only would reduce it by only 24, 10 and 18 per 100 subjects, respectively. The graph is restricted to subjects at low to moderate risk for 3-year mortality (<20%) where most uncertainty about the balance between benefits and harms from treatment may exist.
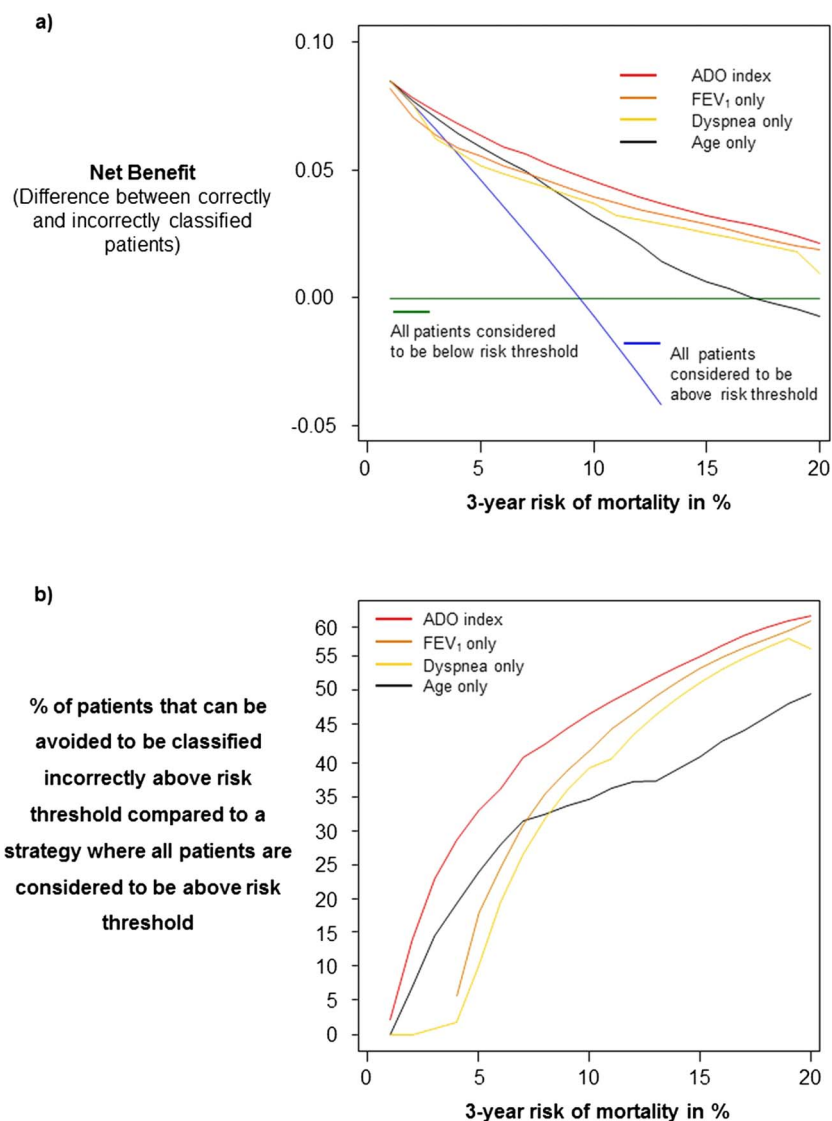
additional value of various biomarkers to predict mortality could be assessed.

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