Multicomponent indices to predict survival in COPD: the COCOMICS study

Jose M. Marin[1], Inmaculada Alfageme[2], Pere Almagro[3], Ciro Casanova[4], Cristobal Esteban[5], Juan J. Soler-Cataluña[6], Juan P. de Torres[7], Pablo Martínez-Camblor[8], Marc Miravitlles[9], Bartolome R. Celli[10] and Joan B. Soriano[11]

Affiliations: [1]Respiratory Dept, Hospital Universitario Miguel Servet, Zaragoza, [2]Respiratory Dept, Valme University Hospital, Seville, [3]Internal Medicine Unit, Hospital Universitari Mútua de Terrassa, Barcelona, [4]Respiratory Dept, Hospital Nuestra Señora de la Candelaria, Tenerife, [5]Respiratory Dept, Hospital Galdakao-Usansolo, Bizkaia, [6]Respiratory Unit, Hospital General de Requena, Valencia, [7]Respiratory Dept, Clínica Universidad de Navarra, Pamplona, [8]Oficina de Investigación Biosanitaria de Asturias, Oviedo, [9]Pneumology Department, Hospital Universitari Vall d'Hebron, Barcelona, and [11]Program of Epidemiology and Clinical Research, Fundación Caubet-Cimera Illes Balears, Bunyola, Spain. [10]Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard University, Boston, MA, USA.

Correspondence: J.B. Soriano, Program of Epidemiology and Clinical Research, Fundación Caubet-CIMERA Illes Balears, Recinte Hospital Joan March, Carretera Palma-Soller Km12, Bunyola 07110, Spain. E-mail: jbsoriano@caubet-cimera.es

ABSTRACT Guidelines recommend defining chronic obstructive pulmonary disease (COPD) by airflow obstruction and other factors, but no studies have evaluated the ability of existing multicomponent indices to predict mortality up to 10 years.

We conducted a patient-based pooled analysis. Survival analysis and C statistics were used to determine the best COPD index/indices according to several construct variables and by varying time-points. Individual data of 3633 patients from 11 COPD cohorts were collected, totalling the experience of 15 878 person-years.

Overall, there were 1245 death events within our cohorts, with a Kaplan–Meier survival of 0.963 at 6 months, which was reduced to 0.432 at 10 years. In all patients, ADO (age, dyspnoea and forced expiratory volume in 1 s), BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) and e-BODE (BODE plus exacerbations) were the best indices to predict 6-month mortality. The ADO index was the best to predict 12-month (C statistic 0.702), 5-year (C statistic 0.695) and 10-year mortality (C statistic 0.698), and was significantly better than BODE (all $p<0.05$). The best indices to predict death by C statistics when adjusting by age were e-BODE, BODEx (substitution of exacerbations for exercise capacity) and BODE.

No index predicts short-term survival of COPD well. All BODE modifications scored better than ADO after age adjustment. The ADO and BODE indices are overall the most valid multicomponent indices to predict time to death in all COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is considered a common, preventable and treatable disease, characterised by airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1]. The COPD population burden will increase in the near future [2, 3]. It is widely acknowledged that efficacy of current treatments is limited [4, 5]. The assessment of COPD phenotypes, irrespective of the way they are defined, is and will be a topic of interest, and to determine the short- and long-term clinical outcomes in COPD patients requires either large studies or pooling multiple data, as it is often the case that individual studies are small and/or have a short duration and, therefore, lack representativity [6]. Spirometry is recognised by international clinical guidelines as the essential test to diagnose COPD and stage severity based on different transformations of the forced expiratory volume in 1 s (FEV_1) and other lung function variables. However, a growing number of multicomponent indices have been proposed beyond lung function to determine time-to-death probability and other clinically relevant outcomes.

Multidimensional indices of COPD can be used either to predict death in general or to stratify the severity of COPD patients. Initially, the BODE (body mass index (BMI), airflow obstruction, dyspnoea, exercise capacity) index [7], aimed to classify the severity of COPD better than FEV_1 alone, and it used total and respiratory mortality as "marker" of such severity. It did not include age and comorbidities because these were independent but nonmodifiable factors that affect all individuals, either having COPD or not, although some comorbidities can be treated/managed, even cured. However, conflicting opinions remain [8, 9].

A global, pooled assessment of different studies with many COPD patients and with longer follow-up, and therefore more patient-years, would allow a more accurate assessment of these indices. The Collaborative Cohorts to assess Multicomponent Indices of COPD in Spain (COCOMICS) study is pooling a number of cohort studies at the individual level, all with different stages of COPD severity, from hospitalised to discharged patients, with and without comorbidities, and some who are frequent exacerbators. We are aiming to determine the prognostic value to predict death in the short- and very long-term of a number of COPD multicomponent indices.

Methods

Study design

This study is a pooled analysis of individual patient-data [10], from the following COPD patient cohorts, all in Spain (online supplementary material, fig. S1): Galdakao [11], Pamplona [12], Requena [13], Seville [14], Tenerife [15], Terrassa [16–18] and Zaragoza [19]. A minimum data set with age, sex, spirometry and follow-up data in all patients was required. Data were provided by the primary investigator of each of the participating cohorts. Given that all are published/on-going studies with mostly consistent data, a summary of baseline characteristics of all these cohorts is presented in table 1, representing the varied inclusion/exclusion criteria of each study.

Indices calculations

We calculated for the whole cohort the following indices: the original BODE index [7], which incorporates dyspnoea by the modified Medical Research Council (mMRC), BMI, FEV_1 and exercise capacity as measured by 6-min walking distance (6MWD). We also calculated modifications of the BODE index, including the mBODE (which replaces 6MWD with oxygen uptake) [20], e-BODE (BODE plus exacerbations) [21], and BODEx (substitution of exacerbations for exercise capacity) [21]. We also calculated the ADO index (age, dyspnoea and FEV_1) [22], the COPD Prognostic Index (CPI) (quality of life standardised by the Chronic Respiratory Questionnaire (CRQ) or St George's Respiratory Questionnaire (SGRQ), FEV_1, age, sex, BMI, exacerbation history and cardiovascular disease history) [23], the SAFE index (quality of life by SGRQ, FEV_1 and 6MWD) [24], the HADO index (health status, activity, dyspnoea and FEV_1) [25], the COPDSS-COPD severity score (respiratory symptoms, systemic corticosteroid use, other COPD medication use, previous hospitalisation or intubation for respiratory disease and home oxygen use) [26, 27], TARDIS (age, BMI, dyspnoea, airflow obstruction, hospitalisations and influenza vaccination) [28], and the DOSE index (dyspnoea, smoking status, FEV_1 and prior exacerbation history) [29]. Comorbidities were quantified by means of the Charlson index, excluding COPD [30]. Calculation of all indices differs by variable and threshold (available in online supplementary material, table S1).

Statistical analysis

All data was quality controlled centrally and a homogeneous template to translate all coding was applied. Variables were then double-checked by each principal investigator. Comprehensive tabulations with ranges, mean $\pm$ SD of all quantitative variables and percentages of all qualitative variables were available for each study.

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TABLE 1 Demographic and clinical characteristics of patients at baseline/enrolment by cohort

	Galdakao	Pamplona	Requena I	Requena II	Seville	Tenerife	Terrassa I	Terrassa II	Terrassa III	Zaragoza I	Zaragoza II	Total
Study years	2003–2009	2004–2009	1998–2004	1999–2004	1999–2010	1997–2010	1996–2010	1998–2010	2003–2010	1998–?	1997–2007	
Cohort entry	Stability	Stability	Stability	Stability	Stability	Stability	Discharge	Re-admitted	Discharge	Stability	Stability	
Subjects n	543	190	174	186	596	275	135	66	181	137	1150	3633
Person-years	2303.67	795.58	561.25	557.83	1567.50	1271.00	584.00	301.75	704.17	717.17	6520.25	15878.17
Age years	68.3±8.3	65.2±8.4	72.1±8.9	70.9±8.0	65.8±9.6	62.9±9.9	72.2±9.2	71.7±8.9	71.9±9.8	65.8±7.6	63.4±9.4	66.4±9.7
Sex male	522 (96)	159 (84)	173 (99)	185 (99)	564 (95)	217 (79)	124 (92)	65 (98)	172 (95)	136 (99)	1072 (93)	3389 (93)
Pack-years of smoking	48±26	53±27	61±33	63±36	50±22	65±27	NA	NA	58±36	57±25	52±25	54±36
Smoking status												
Former	414 (76)	119 (63)	131 (76)	151 (81)	453 (76)	140 (57)	96 (72)	57 (86)	132 (75)	99 (73)	740 (66)	2532 (71)
Current	114 (21)	71 (37)	39 (22)	32 (17)	143 (24)	103 (43)	23 (17)	9 (14)	41 (23)	37 (27)	384 (34)	996 (28)
Never	15 (3)	0 (0)	3 (2)	3 (2)	0 (0)	0 (0)	14 (11)	0 (0)	3 (2)	0 (0)	0 (0)	38 (1)
BMI	28±4	27±5	28±4	28±5	29±6	27±5	26±5	26±4	28±5	28±5	28±5	28±5
FEV1 % pred	55±13	69±19	48±17	46±17	43±13	56±21	41±13	30±13	45±14	48±18	62±20	54±19
GOLD stage												
Mild	1 (0.2)	64 (34)	5 (3)	10 (5)	1 (0.2)	41 (15)	0 (0)	1 (2)	0 (0)	6 (5)	239 (20)	368 (10)
Moderate	357 (66)	92 (48)	63 (42)	47 (25.4)	202 (34)	112 (41)	31 (23)	2 (3)	63 (35)	59 (43)	584 (51)	1612 (45)
Severe	167 (31)	28 (15)	57 (38)	100 (54.1)	292 (49)	95 (34)	79 (58)	21 (34)	94 (53)	50 (37)	272 (24)	1255 (35)
Very severe	18 (3)	6 (3)	25 (17)	28 (15.1)	101 (17)	27 (10)	25 (19)	38 (61)	22 (12)	21 (15)	55 (5)	366 (10)
mMRC dyspnoea score	2.4±0.9	2.0±1.1	2.8±1.2	3.1±1.1	2.4±1.0	2.1±1.2	3.4±1.3	3.0±1.0	3.7±1.2	2.7±1.1	2.6±1.1	2.6±1.1
6MWD m	409±92	463±114	434±125	380±112	NA	487±87	NA	218±77	330±106	449±92	456±154	397±130
Past year exacerbations	0.6±0.7	NA	0.3±0.6	0.6±0.9	1.2±1.9	0.4±0.7	1.0±1.4	1.8±1.2	1.3±2.0	NA	0.9±2.2	0.9±1.8
Charlson index	1.4±1.4	1.6±1.3	1.1±1.6	0.8±0.9	1.1±1.8	2.0±1.7	1.2±1.0	0.6±0.9	1.2±1.3	2.5±1.1	0	1.3±1.5
SGRQ total	39±20	NA	55±25	47±19	NA	34±22	51±19	56±16	49±13	45±19	NA	43±20

Data are presented as n (%) or mean±SD, unless otherwise stated. BMI: body mass index; FEV1: forced expiratory volume in 1 s; % pred: % predicted; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire; NA: not available. Note: The Zaragoza II cohort selected COPD patients without comorbidities at baseline, so Charlson is 0 by definition.

We focused all analyses on time to death for all causes, as other outcomes (*i.e.* exacerbations of different types) were considered to be less reliably recorded. Most related publications to date have focused on 5-year mortality. However, given the substantial patient-year exposure within the database, indices were also tested in the short-term (at 6 and 12 months) up to the very long-term (up to 10 years) to predict time to death. Standard Cox semi-parametric proportional hazards models were employed to model the time-to-death data [31]. The C statistic, a measure of discrimination for survival analysis, was employed to assess the performance of the time-to-death models of all indices *versus* spirometry and BODE [32]. Time-specific variations of the C statistic were also calculated [33]. Heterogeneity and potential study effects were handled by running models with the individual study as an additional stratification variable, and inferences were by the bootstrap method [34]. In all analyses, a p-value <0.05 was considered to be statistically significant.

Results

Individual data of 3633 patients from 11 COPD cohorts in Spain was collected, totalling the experience of 15 878 person-years, with a wide range of values in all domains of COPD (table 1). Patients had an mean±SD age of 66.4±9.7 years, and 93.3% were male and 6.7% female. At study entry, smoking exposure was substantial (53.6±36.0 pack-years), and 71.0% were former-smokers while 27.9% were still current-smokers. Most participants were of moderate or higher severity with an FEV1 of 53.8±19.4% predicted and a Charlson index of 1.35±1.54.

Overall, there were 1245 deaths within our cohorts, with a Kaplan–Meier survival (number of deaths) by different time-points of 0.963 (131) at 6 months, 0.935 (230) at 1 year, 0.780 (726) at 3 years, 0.676 (975) at 5 years and 0.432 (1225) at 10 years.

The actual mortality rates observed for different times to follow-up and cut-off points of selected COPD multicomponent indices are presented in table 2, ranging from a 0.3% death rate at 6 months of a first quartile score in e-BODE of 1 or 2, up to a 88.0% death rate at 10 years of a fourth quartile score in SAFE of $\geqslant 6$. Moreover, these tabulations could be used for the individual assessment of prognosis of individual patients.

Many indices share construct variables, and all indices were highly autocorrelated (table 3). ADO and SAFE indices were the closest to FEV1 only, while there was a cluster of all BODE-like indices with SAFE, mathematically explaining more variance than the other indices.

There was great heterogeneity in the time to death within each of the eleven COPD cohorts (fig. 1), due to the varying entry criteria at each specific cohort. The distribution of the calculated COPD multicomponent

TABLE 2 Actual mortality rates observed for different times to follow-up and cut-offs of selected chronic obstructive pulmonary disease (COPD) multicomponent indices

Time	Quartile	BODE	e-BODE	BODEx	ADO	SAFE	DOSE
6 months	Q1	0.007 (5)	0.003 (1)	0.012 (9)	0.008 (7)	0.005 (2)	0.012 (9)
	Q2	0.013 (4)	0.028 (9)	0.020 (7)	0.016 (10)	0.044 (9)	0.028 (15)
	Q3	0.036 (10)	0.026 (4)	0.039 (25)	0.030 (32)	0.024 (7)	0.039 (15)
	Q4	0.034 (14)	0.027 (7)	0.062 (25)	0.076 (31)	0.075 (11)	0.067 (28)
1 year	Q1	0.015 (11)	0.010 (3)	0.024 (18)	0.014 (12)	0.078 (7)	0.025 (18)
	Q2	0.025 (8)	0.040 (13)	0.043 (15)	0.034 (21)	0.108 (22)	0.062 (33)
	Q3	0.073 (20)	0.072 (11)	0.076 (49)	0.059 (62)	0.058 (17)	0.070 (27)
	Q4	0.081 (33)	0.092 (24)	0.119 (48)	0.161 (58)	0.144 (21)	0.095 (47)
3 years	Q1	0.066 (51)	0.066 (18)	0.131 (85)	0.068 (51)	0.112 (43)	0.148 (93)
	Q2	0.126 (35)	0.141 (42)	0.208 (66)	0.161 (93)	0.207 (42)	0.219 (106)
	Q3	0.191 (50)	0.217 (31)	0.28 (168)	0.228 (222)	0.248 (73)	0.274 (98)
	Q4	0.298 (115)	0.328 (83)	0.28 (168)	0.522 (180)	0.466 (68)	0.392 (185)
5 years	Q1	0.148 (94)	0.111 (27)	0.181 (105)	0.102 (68)	0.206 (76)	0.208 (116)
	Q2	0.231 (63)	0.282 (75)	0.290 (82)	0.256 (131)	0.320 (63)	0.322 (138)
	Q3	0.329 (80)	0.370 (49)	0.444 (233)	0.355 (313)	0.446 (127)	0.409 (129)
	Q4	0.485 (177)	0.390 (99)	0.568 (198)	0.697 (219)	0.662 (96)	0.551 (236)
10 years	Q1	0.359 (126)	0.253 (38)	0.346 (136)	0.210 (92)	0.532 (99)	0.361 (144)
	Q2	0.575 (91)	0.523 (96)	0.547 (105)	0.456 (165)	0.611 (81)	0.600 (178)
	Q3	0.658 (109)	0.671 (63)	0.684 (266)	0.601 (395)	0.860 (158)	0.637 (158)
	Q4	0.778 (225)	0.675 (161)	0.707 (235)	0.862 (242)	0.880 (115)	0.777 (283)
Cut-off points#	Q1	1–2	1–2	1–2	1–3	1–2	1–2
	Q2	3	3–4	3	4	3	3
	Q3	4	5	4–5	5–6	4–5	4
	Q4	+5	+6	+6	+7	+6	+5

Data are presented as 1-Kaplan–Meier (number of deaths). BODE: body mass index, airflow obstruction, dyspnoea, exercise capacity; e-BODE: BODE plus exacerbations; BODEx: substitution of exacerbations for exercise capacity as measured by incremental exercise test; ADO: age, dyspnoea and forced expiratory volume in 1 s (FEV_1); SAFE: quality of life by St George's Respiratory Questionnaire, FEV_1 and 6-min walking distance; DOSE: dyspnoea, smoking status, FEV_1 and prior exacerbation history; Q: quartile. #: cut-off points of each COPD multicomponent index correspond with the values given.

indices and their C statistic to predict 5-year total survival, in all participants and by cohort are presented in table 4. When compared to the gold standards of per cent predicted FEV_1 and GOLD COPD staging, it can be seen that numerically ADO, and then e-BODE and BODE had the highest C statistics, 0.695, 0.681, and 0.673 respectively, while the lowest was DOSE (C statistic 0.628) and then SAFE (C statistic 0.648), and all comparisons were significant *versus* FEV_1 ($p<0.05$).

As detailed in the Methods section, the validity of all indices to predict time to death in the short-term (6- and 12-months) up to the very long-term (up to 10-years) is presented in table 5 and figures 2 and 3b. Predictors of short-term mortality were first assessed. In all patients, ADO (C statistic 0.7015), BODE (C statistic 0.6808) and e-BODE (C statistic 0.6808 but $p=0.07$ *versus* FEV_1 only) were the best indices to

TABLE 3 Correlation matrix of chronic obstructive pulmonary disease multicomponent indices

Index	FEV_1	BODE	e-BODE	BODEx	ADO	SAFE	DOSE
FEV_1	1.0000000	0.7277113	-0.7038642	-0.7653869	-0.6633867	-0.5998811	-0.6443202
BODE		1.0000000	0.9683475	0.8886048	0.7887521	0.8173834	0.8495256
e-BODE			1.0000000	0.9333513	0.7734677	0.8289571	0.8740556
BODEx				1.0000000	0.7666853	0.7420591	0.9295135
ADO					1.0000000	0.6216816	0.7366796
SAFE						1.0000000	0.7379466
DOSE							1.0000000

BODE: body mass index, airflow obstruction, dyspnoea, exercise capacity; e-BODE: BODE plus exacerbations; BODEx: substitution of exacerbations for exercise capacity as measured by incremental exercise test; ADO: age, dyspnoea and forced expiratory volume in 1 s (FEV_1); SAFE: quality of life by St George's Respiratory Questionnaire, FEV_1 and 6-min walking distance; DOSE: dyspnoea, smoking status, FEV_1 and prior exacerbation history.

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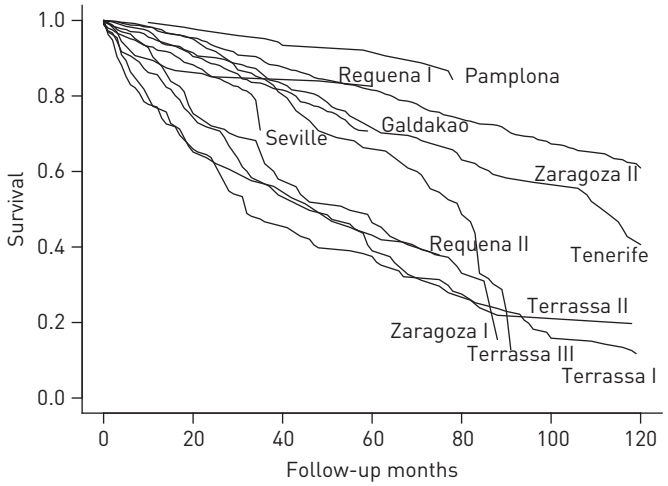

FIGURE 1 High heterogeneity (variability) in overall short- and long-term survival within the 11 cohorts in the Collaborative Cohorts to Assess Multicomponent Indices of COPD in Spain study.

predict 6-months mortality. The ADO index was the best to predict 12-month mortality (C statistic 0.702), 5-year mortality (C statistic 0.695) and 10-year mortality (C statistic 0.679), significantly better than BODE ($p=0.0479$, $p=0.0186$ and $p=0.0177$, respectively). However, both ADO and BODE showed superiority *versus* the other multicomponent indices in separate analyses and all bivariate comparisons (table 5). In all patients, the ADO and BODEx indices were the best to predict moving C statistics continuously from short- to long-term follow-up, but when adjusting by age, e-BODE, BODEx and BODE had superiority (online supplementary material, fig. S2).

Discussion

We have found that no COPD multicomponent index predicts well short-term survival at 6- and up to 12 months. The index with best prognostic value to death appears to be ADO. However, huge variability exists in survival within cohorts, which is substantially deemed when controlling by ADO and/or BODE. The ADO and BODE indices are overall the most valid multicomponent indices to predict time to death in all COPD patients, but when controlling by age, all BODE modifications show superiority.

Brief literature review

The course of COPD and the relationship between COPD, decline in lung function over time and exacerbations is a complex issue. It has been proposed that each COPD exacerbation reduces at least 10 mL of FEV_1 in individual COPD patients, accounting for a 1.2% to 1.4% relative decline from baseline FEV_1 and that, overall, probably ~25% of the fall in lung function can be attributed to the effects of exacerbations [35]. Data from VESTBO *et al.* [36] quantified that each COPD exacerbation accounted for 2 ± 0.5 mL in the annual rate of change in FEV_1. A recent meta-analysis of published data concluded that each exacerbation increases the risk of immediate death (case-fatality rate) by 16%, although there was a variability from 11.4% to 19.0% in the six studies included [37]. We believe that in addition to excluding all Spanish cohorts, the study of HOOGENDOORN *et al.* [37] assesses only admitted COPD patients and it has a rather simplistic statistical analysis given that computes aggregated data, and therefore our current approach is improved in form and substance. We used a relatively new tool, pooled analysis, which collects individual patient-level data and analyses studies as a single, new study. This has advantages over classical meta-analyses as it avoids many of the methodological pitfalls related to classical meta-analytic techniques that rely exclusively on published data. It is of note that the CPI index was constructed by pooling individual data from 12 trials, involving a total of 8802 patients and amounting to >6000 patient-years of information [23], but the representativity of trial participants of real-life patients is debatable [38].

Clinical relevance

To what extent is each multicomponent index better than FEV_1 alone? First, C statistics do not have a direct application to the clinic. It is a mathematical summary measure that estimates the probability when comparing two given patients. The relevance of the conceptual discussion about the inclusion of age in COPD multicomponent indices *versus* other factors to determine individual clinical prognosis is exemplified in table 6. [39]. According to the ADO index, the older patient has a higher risk of death than the younger one (see table 2 for predicted mortality at different time-points). However, this has little to do with COPD and all to do with life itself. The addition of the 6MWD and BMI (both predictors of

TABLE 4 Overall distribution of chronic obstructive pulmonary disease multicomponent indices and their C statistic to predict 5-year total survival by cohort

	Galdakao	Pamplona	Requena I	Requena II	Seville	Tenerife	Terrassa I	Terrassa II	Terrassa III	Zaragoza I	Zaragoza II	Total
GOLD stage												
Mild	1 (0.2)	64 (34)	5 (3)	10 (5)	1 (0.2)	41 (15)	0 (0)	1 (2)	0 (0)	6 (5)	239 (20)	368 (10)
Moderate	357 (66)	92 (48)	63 (42)	47 (25.4)	202 (34)	112 (41)	31 (23)	2 (3)	63 (35)	59 (43)	584 (51)	1612 (45)
Severe	167 (31)	28 (15)	57 (38)	100 (54.1)	292 (49)	95 (34)	79 (58)	21 (34)	94 (53)	50 (37)	272 (24)	1255 (35)
Very severe	18 (3)	6 (3)	25 (17)	28 (15.1)	101 (17)	27 (10)	25 (19)	38 (61)	22 (12)	21 (15)	55 (5)	366 (10)
FEV1 % pred	55±13	69±19	48±17	46±17	43±13	56±21	41±13	30±13	45±14	48±18	62±20	54±19
Multicomponent indices												
BODE	2.7±1.6	1.8±1.8		4.3±1.9		2.2±1.7		6.4±1.6	4.2±1.8	3.1±1.7	2.4±2.0	3.1±2.0
e-BODE	4.2±1.6			4.7±2.0		2.5±1.8		7.5±1.8	4.6±1.9		3.8±2.4	3.9±2.3
BODEx	3.7±1.4		4.0±2.4	4.3±1.7	4.0±2.1	2.4±1.7	4.4±1.7	5,9±1.4	4.2±1.5		2.9±2.1	3.5±2.1
ADO	4.5±1.4	3.4±1.7	6.0±2.3	5.7±1.5	4.8±1.7	3.4±1.6	5.6±1.5	6.2±1.4	5.8±1.4	4.5±1.5	3.9±1.7	4.4±1.7
SAFE	3.0±1.6		2.0±1.4	4.2±2.1		2.5±1.7	1.6±0.7	7.0±1.5	4.4±1.4	3.3±1.7		3.3±1.9
DOSE	3.1±1.1		3.8±1.6	3.9±1.3	3.5±1.5	2.4±1.9	3.7±1.4	4.9±1.4	3.9±1.3		3.0±1.6	3.3±1.6
C statistic												
GOLD stage	0.539	0.591	0.623	0.568	0.5	0.666	0.575	0.571	0.534	0.572	0.584	0.629
FEV1 % pred	0.559	0.608	0.670	0.585	0.5	0.683	0.571	0.598	0.546	0.606	0.621	0.670
BODE	0.634	0.558		0.640		0.623		0.681	0.587	0.593	0.694	0.673
e-BODE	0.605			0.669		0.627		0.657	0.615		0.694	0.681
BODEx	0.556		0.75	0.641	0.5	0.623	0.582	0.668	0.606		0.650	0.652
ADO	0.645	0.616	0.75	0.715	0.5	0.674	0.625	0.715	0.618	0.599	0.681	0.695
SAFE	0.631			0.634		0.623	0.585	0.555	0.507	0.621		0.648
DOSE	0.582		0.75	0.633	0.5	0.610	0.564	0.667	0.583		0.637	0.628

Data are presented as n (%) or mean±SD, unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted; BODE: body mass index, airflow obstruction, dyspnoea, exercise capacity; e-BODE: BODE plus exacerbations; BODEx: substitution of exacerbations for exercise capacity as measured by incremental exercise test; ADO: age, dyspnoea and FEV1; SAFE: quality of life by St George's Respiratory Questionnaire, FEV1 and 6-min walking distance; DOSE: dyspnoea, smoking status, FEV1 and prior exacerbation history. All indices but mBODE, CPI, HADO, COPDSS, and TARDIS.

outcome) provide clinical dimensions that ADO does not have. These two clinical factors are also predictors of mortality independent of age. Patient 1 was referred for lung transplantation, whereas patient 2 was prescribed bronchodilators. Therefore, it is our understanding that age, as many other nonmodifiable factors, should have limited value in the clinical stratification of a specific disease process, such as COPD.

The 6MWD adds substantial value to any COPD prognostic assessment [40], yet we agree that performing the 6MWD could be cumbersome to some practising doctors and settings, particularly to family physicians that care mostly for mild COPD patients, or busy internal medicine wards. Nevertheless, the 6MWD alone is an important tool as predictor of mortality in patients with pulmonary fibrosis, pulmonary hypertension, and those with both heart and respiratory failure. We think that most or all patients under specialist care should have some type of exercise capacity assessed, and the 6-MWD is the simplest test. It is of interest that

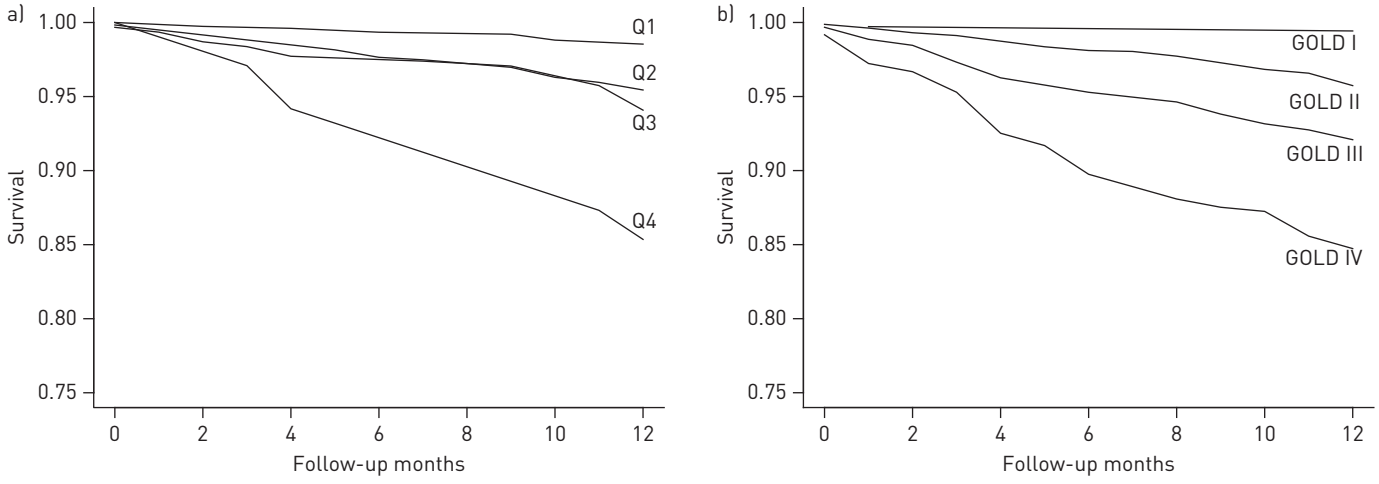

FIGURE 2 Kaplan–Meier curves showing 12-month survival of a) BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) quartiles and b) forced expiratory volume in 1 s staging. The y-axis is truncated from 75% survival.

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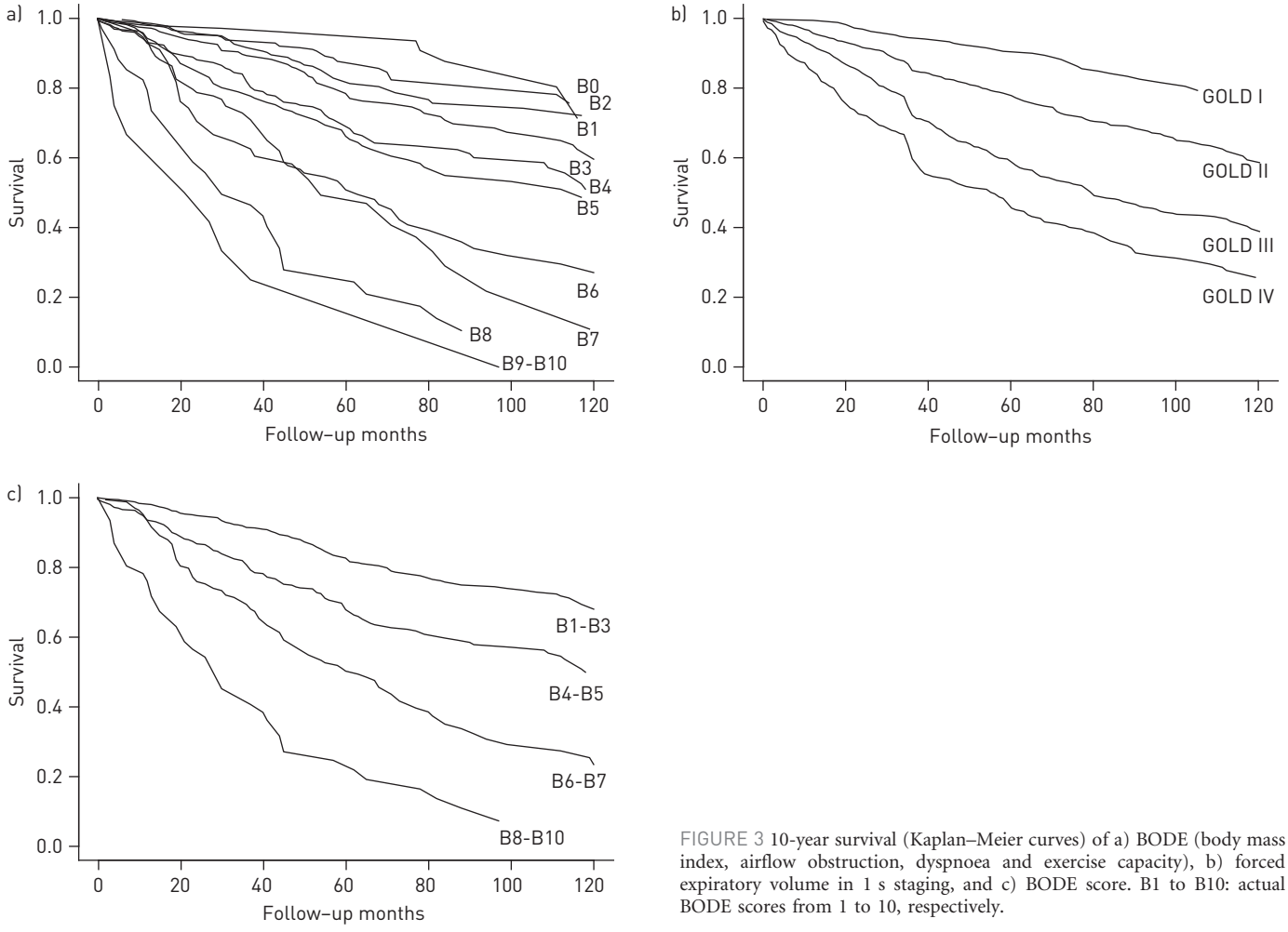

FIGURE 3 10-year survival (Kaplan–Meier curves) of a) BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity), b) forced expiratory volume in 1 s staging, and c) BODE score. B1 to B10: actual BODE scores from 1 to 10, respectively.

those indices that do not include exercise capacity, such as the BODEx index, also demonstrated good predictor ability and could be a good surrogate when the 6MWD is not available, which is a recent GOLD 2011 recommendation [1].

Strengths and limitations

The strengths of the COCOMICS study include, first, a large sample size of nearly 16 000 person-years, allowing for statistical power in most subanalyses; very few participants were lost to follow-up, as cohorts were built from clinical practices in elite, prestigious hospital centres managing these patients. Homogeneity is also a strength, as all COPD patients are Spanish, granted by law with guaranteed universal, free-of charge health coverage, and therefore giving robustness to the interpretation or assessment of health outcomes. Another strength is internal consistency, as all investigators follow the same COPD clinical guidelines for pharmacological and nonpharmacological treatments. As mentioned above, the analytical approach is not a meta-analysis of published results, but a pooled analysis of individual data collected for this project. Finally, by including cohorts of patients with different origins, and severity of disease, all indices have been tested in a diverse population.

One limitation of our study is that not all participants have data in all variables, and key variables such as exacerbations or cause of death were not collected either consistently or in all participants. Indeed, about two-thirds of our COPD patients died of comorbidities, mainly cardiovascular and lung cancer. To date, it seems that apart from the newly available COTE (COPD-specific comorbidity test) index [41], no index reflects the variable contribution of specific causes of death, which changes with lung function and the natural history of COPD [42]. All cohorts used protocols and collected data in a similar, but not identical, way, given the nature of ''real life'' usual care rather than the ''research-only'' origin of these cohorts. All our participants were Caucasian and extrapolation of results (table 2) should apply to those COPD patients cared for in systems with public health services. However, the use of different cohorts grouped to compare

TABLE 5 C statistics for the comparison of multicomponent indices

Time-point	Statistic	FEV_1 % pred	BODE	e-BODE	BODEx	ADO	SAFE	DOSE
6 months	C statistic	0.657	0.680	0.680	0.651	0.701	0.641	0.632
	p-value	1.0000	0.0332	0.0734	0.7587	0.0001	0.1482	0.0062
	p-value		1.0000	0.9943	0.0384	0.0509	0.0057	0.0001
	p-value			1.0000	0.0019	0.1158	0.0118	0.0001
	p-value				1.0000	0.0002	0.7309	0.2026
	p-value					1.0000	0.0011	0.0001
	p-value						1.0000	0.4409
	p-value							1.0000
1 year	C statistic	0.656	0.682	0.683	0.651	0.702	0.642	0.631
	p-value	1.0000	0.0174	0.0462	0.8312	0.0001	0.7707	0.0048
	p-value		1.0000	0.8947	0.0520	0.0479	0.0498	0.0001
	p-value			1.0000	0.0025	0.1408	0.0668	0.0001
	p-value				1.0000	0.0019	0.9534	0.2675
	p-value					1.0000	0.0001	0.0001
	p-value						1.0000	0.7847
	p-value							1.0000
5 years	C statistic	0.670	0.673	0.681	0.652	0.695	0.648	0.628
	p-value	1.0000	0.7495	0.3646	0.4271	0.0036	0.4891	0.0001
	p-value		1.0000	0.3342	0.3118	0.0186	0.3385	0.0001
	p-value			1.0000	0.0108	0.2288	0.1681	0.1302
	p-value				1.0000	0.0125	0.9947	0.2147
	p-value					1.0000	0.0006	0.0001
	p-value						1.0000	0.5156
	p-value							1.0000
10 years	C statistic	0.664	0.647	0.664	0.642	0.679	0.671	0.618
	p-value	1.0000	0.2324	0.9860	0.3528	0.2133	0.6005	0.0001
	p-value		1.0000	0.0626	0.8914	0.0177	0.1366	0.0386
	p-value			1.0000	0.3215	0.3326	0.6737	0.0009
	p-value				1.0000	0.1029	0.3779	0.2949
	p-value					1.0000	0.5879	0.0001
	p-value						1.0000	0.0001
	p-value							0.0001

FEV_1: forced expiratory volume in 1 s; % pred: % predicted; BODE: body mass index, airflow obstruction, dyspnoea, exercise capacity; e-BODE: BODE plus exacerbations; BODEx: substitution of exacerbations for exercise capacity as measured by incremental exercise test; ADO: age, dyspnoea and forced expiratory volume in 1 s (FEV_1); SAFE: quality of life by St George's Respiratory Questionnaire, FEV_1 and 6-min walking distance; DOSE: dyspnoea, smoking status, FEV_1 and prior exacerbation history.

TABLE 6 Comparison of ADO (age, dyspnoea and forced expiratory volume in 1 s (FEV_1)) *versus* BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) indices of two individual patients

	Patient 1	Patient 2
Age years	48	91
BMI kg·m^{-2}	19.7	26
FEV_1 % pred	43	65
MRC dyspnoea score	3	2
6MWD m	274	196
ADO index	3 points	7 points
BODE index	7 points	4 points

BMI: body mass index; % pred: % predicted; MRC: Medical Research Council; 6MWD: 6-min walking distance. Adapted from [39].

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different staging systems or recommendations is considered useful if methodology is applied to all patient data [43]. Regrettably, history of past COPD exacerbations and/or prospective use of health resources (emergency department and hospitalisations) were not collected in all cohorts, and in the few who collected them consistently, it was considered that methods were too diverse to be pooled together. As has already been noted, numbers of female COPD patients were scant. It was not possible to make an analysis of treatments or of time-dependant variables to assess changes in medication, smoking habits and other factors. Even in the very long-term, our analyses assumed that the patients' condition did not change from baseline, which in some variables may not be so (change in medication, becoming a frequent exacerbator or developing a new comorbidity). Although some COPD variables show stability and repeatability, these analyses had no regular monitoring and re-staging. Finally, we are analysing the COPD multicomponent indices available to us at the onset of the COCOMICS study. However, other indices have been newly proposed, such as the NIAF (physiological functioning, complaints, functional impairment and quality of life) study [44]. As recently proposed by Rossi and Zanardi [45], given the growing number of multidimensional indices for assessing COPD multiple phenotypes, we cannot expect a single variable or index to assess the heterogeneity of COPD, but multiple variables for different COPDs.

We conclude that no COPD multicomponent index predicts well short-term survival up to 6-months. It appears the index with the best prognostic value is ADO, but after age adjustment, all BODE modifications score better. The ADO and BODE indices are overall the most valid multicomponent indices to predict time to death in all COPD patients.

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