



Adrenomedullin refines mortality prediction by the BODE index in COPD: the “BODE-A” index

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ABSTRACT The BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) index is well-validated for mortality prediction in chronic obstructive pulmonary disease (COPD). Concentrations of plasma pro-adrenomedullin, a surrogate for mature adrenomedullin, independently predicted 2-year mortality among inpatients with COPD exacerbation.

We compared accuracy of initial pro-adrenomedullin level, BODE and BODE components, alone or combined, in predicting 1-year or 2-year all-cause mortality in a multicentre, multinational observational cohort with stable, moderate to very severe COPD.

Pro-adrenomedullin was significantly associated ($p < 0.001$) with 1-year mortality (4.7%) and 2-year mortality (7.8%) and comparably predictive to BODE regarding both (C statistics 0.691 *versus* 0.745 and 0.635 *versus* 0.679, respectively). Relative to using BODE alone, adding pro-adrenomedullin significantly improved 1-year and 2-year mortality prognostication (C statistics 0.750 and 0.818, respectively; both $p < 0.001$). Pro-adrenomedullin plus BOD was more predictive than the original BODE including 6-min walk distance. In multivariable analysis, pro-adrenomedullin (likelihood ratio Chi-squared 13.0, $p < 0.001$), body mass index (8.5, $p = 0.004$) and 6-min walk distance (7.5, $p = 0.006$) independently foretold 2-year survival, but modified Medical Research Council dyspnoea score (2.2, $p = 0.14$) and forced expiratory volume in 1 s % predicted (0.3, $p = 0.60$) did not.

Pro-adrenomedullin plus BODE better predicts mortality in COPD patients than does BODE alone; pro-adrenomedullin may substitute for 6-min walk distance in BODE when 6-min walk testing is unavailable.



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Pro-adrenomedullin improves BODE prediction of mortality in COPD patients and may substitute for 6-min walk distance <http://ow.ly/qV5M3>

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Introduction

A major goal of assessing patients with chronic obstructive pulmonary disease (COPD) is determining risk of adverse outcomes including mortality, so as to guide interventions [1, 2]. Initially, forced expiratory volume in 1 s (FEV₁) was the main factor used in mortality prognostication in COPD, but increasing recognition of the predictive power of systemic and perceptible variables prompted development of multidimensional risk assessment tools [2, 3]. One well-validated multidimensional tool is the BODE (body mass, airflow obstruction, dyspnoea, exercise capacity) index, determined based on the body mass index, FEV₁ % predicted, modified Medical Research Council (mMRC) dyspnoea grade, and 6-min walk distance (6MWD) [2]. However, BODE may incompletely capture the impact of the systemic manifestations and comorbidities of COPD; indeed, the tool's originators recognised the latter limitation by introducing a comorbidity index described as complementing BODE [4]. Furthermore, time, space, staffing and equipment requirements make BODE's 6-min walk test (6MWT) component cumbersome in primary care or other busy or resource-constrained settings, driving development of alternative or additional multidimensional tools [5, 6].

Therefore, interest has mounted in applying systemic biomarkers to adverse outcome prediction in COPD patients [7–9]. One candidate is plasma pro-adrenomedullin, the stable, apparently biologically-inactive midregional fragment of the adrenomedullin prohormone [10, 11]. Adrenomedullin is a pluripotent regulatory peptide acting as both a hormone and a cytokine to exert extensive vascular, immunomodulatory and metabolic effects [11, 12]. The finding of circulating adrenomedullin elevation in end-stage lung disease [13] prompted a prospective, single-centre observational cohort study of pro-adrenomedullin in adverse outcome prediction in inpatients with COPD exacerbation [14]; in multivariate analysis incorporating 12 demographic, clinical, spirometric and laboratory factors, this study found that admission pro-adrenomedullin concentration was the only independent predictor of 2-year all-cause mortality [14].

This observation led us to hypothesise that pro-adrenomedullin might have similar predictive ability for 1- and 2-year all-cause mortality in patients with clinically stable COPD. We also hypothesised that pro-adrenomedullin might provide additional prognostic information to that offered by BODE and BODE components. We therefore envisioned that combining pro-adrenomedullin and BODE might improve long-term mortality prediction compared to use of the latter alone. Furthermore, we speculated that pro-adrenomedullin plus the non-6MWT BODE components ("BOD") might have comparable prognostic accuracy to that of the original BODE including 6MWD.

Therefore, we conducted the present prospectively planned analysis with the primary aim of evaluating the accuracy of a single baseline circulating pro-adrenomedullin estimation, alone or combined with BODE or BOD, to predict 1-year or 2-year all-cause mortality in a multinational, multicentre, prospective, longitudinal, observational cohort study of patients with clinically stable COPD.

Methods

Study overview

Designed to be inclusive, exploratory and hypothesis-generating, the Predicting Outcome using Systemic Markers in Severe Exacerbations of Chronic Obstructive Pulmonary Disease (PROMISE-COPD) Study evaluated variables potentially identifying poor outcomes during and outside exacerbations in patients with moderate to very severe COPD, *i.e.* post-bronchodilator FEV₁/forced vital capacity <70% and FEV₁ <80% pred or Global Initiative for Chronic Obstructive Lung Disease grade II–IV airway obstruction. Enrollees had a baseline examination, and then were followed for ≥2 years in scheduled semi-annual visits. Additionally, as necessary, patients made outpatient visits or were hospitalised for treatment of COPD exacerbation; follow-up visits were specified for 4 weeks post-exacerbation onset. Throughout the study, patients were treated as clinically warranted, without restriction.

PROMISE-COPD was approved by the participating centres' ethics committees, and registered at www.controlled-trials.com (identifier ISRCTN99586989). Patients provided prior written informed consent for all study assessments.

Patients

638 patients were consecutively recruited and followed at 11 European hospital pneumology departments from November 2008 to October 2011. Inclusion criteria comprised: 1) at baseline, clinically stable, moderate to very severe COPD based on anamnesis, physical examination and spirometry ≥4 weeks after the latest exacerbation resolved; 2) age ≥40 years; and 3) smoking history ≥10 pack-years. Exclusion criteria were: 1) main respiratory disorder other than COPD; 2) death expected within 6 months;

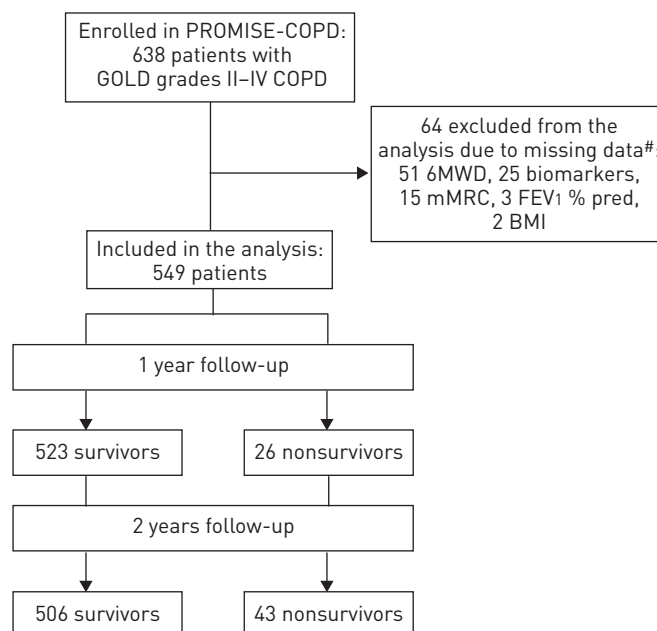


FIGURE 1 Flow chart for the present analysis. Missing data, which led to exclusion from the present analysis, were as follows: pro-adrenomedullin (n=24), procalcitonin (n=24), copeptin (n=24), pro-atrial natriuretic peptide (n=25), body mass index (BMI) (n=2), forced expiratory volume in 1 s (FEV₁) (n=3), modified Medical Research Council (mMRC) dyspnoea score (n=15) and 6-min walk distance (6MWD) (n=51). Of the 43 nonsurvivors, 26 died during the first year of follow-up, 17 during the second year. PROMISE-COPD: Predicting Outcome using Systemic Markers in Severe Exacerbations of Chronic Obstructive Pulmonary Disease Study; GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; % pred: % predicted. #: some patients were missing data for more than one variable.

3) immunosuppression, including AIDS, organ transplantation or chronic steroids (>20 mg·day⁻¹ prednisolone equivalent); and 4) musculoskeletal or neuromuscular disorder preventing walking.

Baseline assessment

For each patient, we performed a physical examination, registered vital signs and obtained a detailed history. Spirometry and 6MWTs were administered by trained technicians following American Thoracic Society guidelines [15, 16]. Patients completed the mMRC dyspnoea questionnaire in local languages, in validated versions when available. BODE scoring employed original methods [2].

Biomarkers

Besides pro-adrenomedullin, PROMISE-COPD evaluated several plasma biomarkers (online supplementary material). Biomarker quantification was performed in duplicate within one run in a central, accredited laboratory by technicians unaware of patients' clinical data, using automated sandwich immunoassays (Kryptor; Thermo Scientific Biomarkers, Hennigsdorf, Germany). The pro-adrenomedullin assay had a 0.05–100 nmol·L⁻¹ measurement range and 0.25 nmol·L⁻¹ functional sensitivity. The pro-adrenomedullin assay has been shown to exhibit low intra-assay variability, and concentrations of pro-adrenomedullin appear stable in samples that are stored at room temperature for up to 72 h, undergo multiple freeze–thaw cycles or are drawn from patients in a nonfasting state [11].

The reference interval of pro-adrenomedullin in a healthy subset is 0.23–0.64 nmol·L⁻¹ (median 0.41 nmol·L⁻¹). Age, measures of obesity (body mass index and body fat percentage), blood lipids (cholesterol, low-density lipoprotein and triglycerides), glucose tolerance (haemoglobin A1c), smoking, alcohol, inflammation (C-reactive protein), renal function (cystatin C) and cardiac wall stress (N-terminal pro-brain natriuretic peptide) were significantly associated with circulating pro-adrenomedullin levels [17].

Outcome assessment

1-year and 2-year vital status, the outcomes of interest in this analysis, were confirmed at the time of scheduled study visits. If needed for this purpose, we contacted relatives, family physicians or insurers, and checked medical records, hospital databases and public registries, to determine dates and causes of deaths.

TABLE 1 Baseline characteristics for the analysed cohort and according to 2-year survival

	Analysed cohort	2-year survivors	2-year nonsurvivors	p-value [#]
Subjects n	549	506	43	
Age years	66.0 ± 11.4	65.8 ± 11.6	69.1 ± 8.7	0.066
Male	69.8 (383)	70.6 (357)	60.5 (26)	0.167
Caucasian	99.1 (544)	99.2 (502)	97.7 (42)	0.158
Current smoker	33.3 (183)	33.0 (167)	37.2 (16)	0.714
Pack-years	45.0 ± 31.1	45.0 ± 31.0	50.0 ± 21.2	<0.001
Body mass index kg·m⁻²	26.1 ± 5.4	26.2 ± 5.3	24.5 ± 5.3	0.051
mMRC dyspnoea score[†]	3 (2–3)	2 (2–3)	3 (2–4)	0.001
6-min walk distance m	390 ± 131	380 ± 108	305 ± 109	<0.001
BODE score	3 (1–4)	3 (1–4)	4 (2–7)	<0.001
BOD score⁺	2 (1–4)	2 (1–4)	3 (2–5)	<0.001
Comorbidities				
Arterial hypertension	51.4 (282)	51.0 (258)	55.8 (24)	0.663
Coronary arterial disease	23.7 (130)	22.9 (116)	32.6 (14)	0.192
Congestive heart failure	14.4 (79)	14.2 (72)	16.3 (7)	0.896
Myocardial infarction	9.3 (51)	9.9 (50)	2.3 (1)	0.170
Pulmonary hypertension	9.7 (53)	9.3 (47)	14.0 (6)	0.477
Malignancy	3.8 (21)	4.0 (20)	2.3 (1)	0.851
Diabetes mellitus	12.0 (66)	11.5 (58)	18.6 (8)	0.317
Renal failure	6.0 (33)	5.7 (29)	9.3 (4)	0.177
Adjusted Charlson score	4 (3–5)	4 (3–5)	4 (3–6)	0.038
GOLD grade				
II	50.8 (279)	51.2 (259)	46.5 (20)	0.738
III	34.1 (187)	34.2 (173)	32.6 (14)	
IV	15.1 (83)	14.6 (74)	20.9 (9)	
Post-bronchodilator FVC % pred	78.7 ± 23.9	77.8 ± 24.2	78.7 ± 20.5	0.994
Post-bronchodilator FEV₁ % pred	48.9 ± 18.3	49.4 ± 18.5	45.9 ± 16.8	0.234
Post-bronchodilator FEV₁/FVC %	48.3 ± 14.1	48.6 ± 14.2	44.7 ± 13.1	0.084
Pro-adrenomedullin nmol·L⁻¹	0.60 (0.48–0.79)	0.59 (0.48–0.78)	0.78 (0.51–1.20)	0.006
Procalcitonin µg·L⁻¹	0.08 (0.07–0.1)	0.08 (0.07–0.10)	0.09 (0.07–0.11)	0.019
Copeptin pmol·L⁻¹	8.8 (2.4–15.2)	8.6 (2.4–14.7)	10.9 (5.5–28.9)	0.033
Pro-atrial natriuretic peptide pmol·L⁻¹	82.0 (52.4–140.4)	80.8 (51.9–136.0)	109.9 (60.4–205.7)	0.018

Data are presented as mean ± SD, % (n) or median (interquartile range), unless otherwise stated. mMRC: modified Medical Research Council; BODE: body mass, airflow obstruction, dyspnoea, exercise capacity index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FVC: forced vital capacity; % pred: % predicted; FEV₁: forced expiratory volume in 1 s. [#]: 2-year survivors versus 2-year nonsurvivors. [†]: scores range, in increasing severity, from 0 to 4. ⁺: BOD comprises BODE without the exercise capacity measurement; the three BOD components are scored according to the same cut-offs as they are in BODE [2], therefore, the “BOD” index ranges, in increasing severity, from 0 to 7.

Statistics

Continuous variables are expressed as mean ± SD or median (interquartile range (IQR)), and discrete variables as n (%) or *vice versa*. Baseline characteristics were compared between survivors and nonsurvivors using the Mann–Whitney U-test or the t-test.

To establish the relationships with 1-year or 2-year all-cause mortality of pro-adrenomedullin or BODE variables, alone or combined, we created univariate and multivariable Cox proportional hazard regression models. Biomarker values were log-transformed to conform to the models’ linearity assumption between predictor and outcome [18]. Proportional hazard assumptions were tested for all modelled variables; results are given as hazard ratios with 95% confidence intervals and significance levels for Chi-squared (Wald) test. Hazard ratios were standardised to describe a one-quartile change in each analysed variable.

The C statistic, bootstrap-corrected for multivariable models, is given as a measure of accuracy in classifying patients regarding survival. The C statistic is equivalent to the area under the receiver-operating characteristics curve. Larger values denote greater accuracy: the null value is 0.5, the maximum 1.0.

Incremental discrimination from adding blood biomarkers to BODE or BOD is shown using the likelihood ratio Chi-squared test for nested models [18] and the net reclassification improvement [19], which summarises the correct change in risk categories (downwards for survivors and upwards for nonsurvivors) with a tested predictive method *versus* the reference method. All analyses utilised a two-sided p=0.05 for significance.

TABLE 2 Cox regression models to predict 1-year and 2-year all-cause mortality

	HR (95% CI)	p-value	C statistic	Model Chi-squared	p-value
1-year all-cause mortality					
Univariate					
BODE	3.30 (2.04–5.35)	<0.001	0.745	23.24	<0.001
BOD [#]	3.74 (1.90–7.34)	<0.001	0.690	15.25	<0.001
Pro-adrenomedullin	2.36 (1.67–3.35)	<0.001	0.691	19.28	<0.001
Multivariate					
BODE	3.18 (1.91–5.28)	<0.001			
BODE plus pro-adrenomedullin	2.18 (1.53–3.09)	<0.001	0.818	39.56	<0.001
BOD [#]	3.84 (1.92–7.66)	<0.001			
BOD [#] plus pro-adrenomedullin	2.35 (1.65–3.34)	<0.001	0.800	34.38	<0.001
2-year all-cause mortality					
Univariate					
BODE	2.53 (1.73–3.69)	<0.001	0.679	22.07	<0.001
BOD [#]	3.74 (1.90–7.34)	<0.001	0.649	15.26	<0.001
Pro-adrenomedullin	1.95 (1.45–2.62)	<0.001	0.635	16.73	<0.001
Multivariate					
BODE	2.42 (1.64–3.57)	<0.001			
BODE plus pro-adrenomedullin	1.80 (1.34–2.42)	0.001	0.750	35.72	<0.001
BOD [#]	2.81 (1.66–4.78)	0.001			
BOD [#] plus pro-adrenomedullin	1.91 (1.42–2.59)	<0.001	0.738	31.48	<0.001

For each variable, the hazard ratio (HR) is based on an increment of one-quartile. p-values compare variable with HR=1 or C statistics=0.5 (null hypothesis). BODE: body mass, airflow obstruction, dyspnoea, exercise capacity index. #: BOD comprises BODE without the exercise capacity measurement; the three BOD components are scored according to the same cut-offs as they are in BODE [2], therefore, the "BOD index" ranges, in increasing severity, from 0 to 7.

Results

549 (86.1%) of 638 PROMISE-COPD patients had complete biomarker and BODE variable data and were included in the analysis (fig. 1 and table 1). Enrollees excluded for missing biomarker measurements (n=25) did not differ from analysed patients in sex, race or BODE component values or score (data not shown).

Median (IQR) follow-up for the 549 analysed patients was 722 (395–762) days. After 2 years, 43 (7.8%) patients had expired; 26 (4.7%; 60.5% of deaths) during the first year and 17 (3.1%; 39.5% of deaths) during the second year. The commonest causes of mortality were respiratory insufficiency attributed to COPD (34.9%) and cardiovascular events (18.6%).

Table 1 compares baseline characteristics of 2-year survivors *versus* 2-year nonsurvivors. Collectively, these subgroups had similar demographics and airflow limitation, but nonsurvivors had higher BODE scores, a greater burden of comorbidities (reflected by the age-adjusted Charlson score) and significantly higher levels of pro-adrenomedullin and the other plasma biomarkers studied. Pro-adrenomedullin levels at all four stable visits increased over time (p=0.01) and with nonsurvivor status (p=0.0006). However, there was no difference between the slope of increase in survivors and nonsurvivors over time (p=0.516, mixed-effect model).

Table 2 presents results of Cox regression analyses involving 1-year and 2-year all-cause mortality. All variables tested provided superior accuracy regarding the former than the latter. For both outcomes, BODE was the most accurate predictor, followed by pro-adrenomedullin or BOD, and pro-adrenomedullin was the most discriminative blood biomarker studied.

The combination of each biomarker with BODE improved predictive power significantly compared to using BODE alone (online supplementary tables E1 and E2). The greatest accuracy was achieved with pro-adrenomedullin plus BODE (C statistic 0.818, p<0.001 for 1-year mortality; C statistic 0.750, p<0.001 for 2-year mortality). For 1-year mortality, adding pro-adrenomedullin to BODE resulted in a net correct reclassification (95% CI) of 25.1 (2.0–48.2)% of patients (p=0.03; added-value Chi-squared 16.31, p<0.0001) relative to using BODE alone. For 2-year mortality, there was a net correct reclassification of 12.3 (-4.1–28.8)% of patients (p=0.14; added-value Chi-squared 13.65, p=0.0002) for 2-year mortality.

TABLE 3 Cox regression model including the BODE components and pro-adrenomedullin to predict 2-year all-cause mortality

	Likelihood ratio Chi-squared	HR (95% CI)	p-value
Univariate model			
Body mass index	8.9	0.58 (0.40–0.83)	0.003
Post-bronchodilator FEV1 % pred	3.9	0.67 (0.46–1.00)	0.048
mMRC dyspnoea score	27.8	1.88 (1.49–2.38)	<0.001
6-min walk distance	23.5	0.45 (0.32–0.62)	<0.001
Pro-adrenomedullin	31.7	2.07 (1.61–2.66)	<0.001
Multivariate model			
Body mass index	8.5	0.56 (0.38–0.83)	0.004
Post-bronchodilator FEV1 % pred	0.3	1.15 (0.68–1.96)	0.596
mMRC dyspnoea score	2.2	1.28 (0.92–1.78)	0.140
6-min walk distance	7.5	0.6 (0.38–0.85)	0.006
Pro-adrenomedullin	13.0	1.77 (1.3–2.42)	<0.001

For each variable, the hazard ratio (HR) is based on an increment of one-quartile. BODE: body mass, airflow obstruction, dyspnoea, exercise capacity index; FEV1: forced expiratory volume in 1 s; % pred: % predicted; mMRC: modified Medical Research Council.

Pro-adrenomedullin plus BODE showed superior ability to forecast 1-year or 2-year nonsurvival compared to BODE alone. Adding pro-adrenomedullin to BODE produced a net correct reclassification index (95% CI) of 41.2 (15.6–66.8)% of patients ($p=0.0016$; added-value Chi-squared 19.13, $p<0.0001$) for 1-year mortality and 8.8 (-10.6–28.3)% of patients ($p=0.37$; added-value Chi-squared 16.22, $p<0.0001$) for 2-year mortality, relative to using BODE alone.

Considering all individual BODE components plus pro-adrenomedullin in a multivariable Cox regression model revealed that pro-adrenomedullin, body mass index, and 6MWD, in descending order of strength, contributed to 2-year survival prediction, but FEV1 % pred and dyspnoea score did not (table 3). Figure 2 shows dichotomised Kaplan–Meier 2-year survival curves based on optimised cut-offs for BODE (4 out of 10 points) and pro-adrenomedullin; online supplementary figure E1 depicts such curves for the other studied plasma biomarkers. The optimised pro-adrenomedullin cut-off was estimated at $0.75 \text{ nmol}\cdot\text{L}^{-1}$, reflecting 68.1% sensitivity and 70.7% specificity.

Based on optimised cut-offs for BODE, BOD (4 out of 7 points) and pro-adrenomedullin, we devised two combined mortality prediction indices, “BODE-A” and, for when 6MWD is unobtainable, “BOD-A”. Both have three categories, associated with an increasing 2-year mortality rate: low risk (clinical index and biomarker below respective cut-offs), intermediate risk (one of the clinical index or biomarker below cut-offs and the other at/above cut-offs) or high risk (both the clinical index and biomarker at/above cut-offs). These categories and their corresponding 2-year all-cause mortality rates and survival curves are presented in figure 3. To identify 2-year survivors, low-risk BODE-A status had 86.0% sensitivity and 44.5%

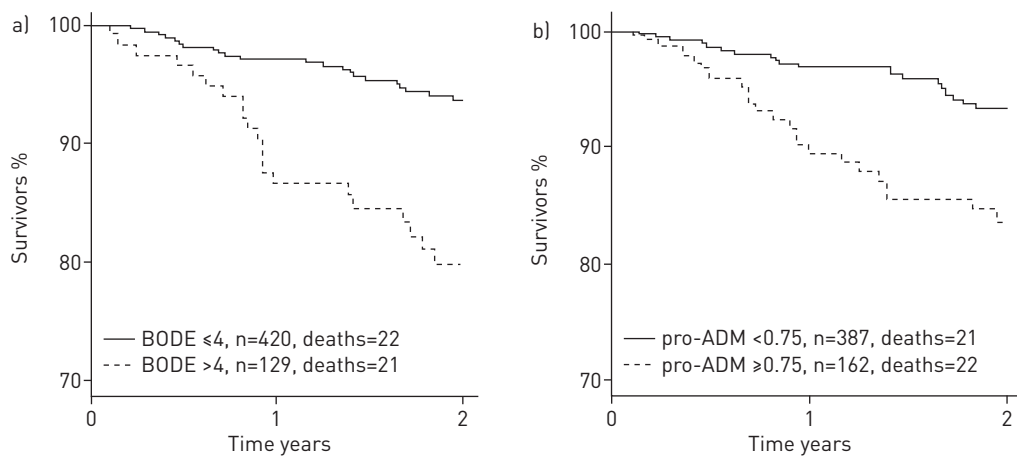


FIGURE 2 Dichotomised 2-year Kaplan–Meier survival curves based on optimised cut-offs for a) body mass, airflow obstruction, dyspnoea, exercise capacity index (BODE) (4 points) and b) pro-adrenomedullin (pro-ADM) ($0.75 \text{ nmol}\cdot\text{L}^{-1}$).

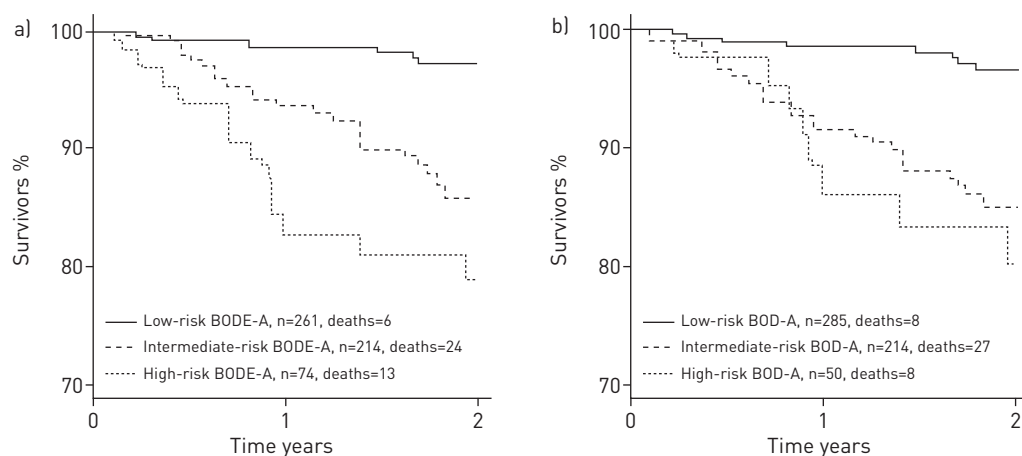


FIGURE 3 Kaplan–Meier 2-year survival curves by risk category according to a) the “BODE-A” index combining BODE (body mass, airflow obstruction, dyspnoea, exercise capacity) and pro-adrenomedullin or b) the “BOD-A” index combining BOD (body mass, airflow obstruction, dyspnoea) and pro-adrenomedullin. These indices, based on the optimised cut-offs for BODE (4 points), BOD (4 points) and pro-adrenomedullin ($0.75 \text{ nmol}\cdot\text{L}^{-1}$), each had three all-cause mortality risk categories: low (both BODE or BOD and pro-adrenomedullin below cut-offs), intermediate (either BODE or BOD and pro-adrenomedullin at or above cut-offs) and high (both BODE and BOD and pro-adrenomedullin at or above cut-offs). The three BOD components were scored according to the same cut-offs as in BODE [2].

specificity; low-risk BOD-A status had 81.4% sensitivity and 54.7% specificity. To identify 2-year nonsurvivors, high-risk BODE-A classification had 30.2% sensitivity and 87.9% specificity; high-risk BOD-A classification had 18.5% sensitivity and 91.7% specificity.

Notably, unavailable 6MWD data was informative in this study: compared to the 549 patients analysed, the 51 excluded for this cause had significantly higher 2-year mortality (7.8% versus 21.6%, $p=0.003$). In *post hoc* sensitivity analysis using a standard imputation method (HotDeck imputation) BODE accuracy increased. However, combined with BODE, pro-adrenomedullin continued to significantly improve 1-year and 2-year mortality prediction compared to using BODE alone (table 4). A second imputation method, using the worst possible BODE score for 6MWD, 3 points, in these 51 patients, produced similar results (data not shown).

Discussion

Interpretation of the findings

Pro-adrenomedullin as a mortality predictor

In this analysis of a well-characterised international cohort from the first multicentre study investigating the biomarker’s mortality prediction potential in COPD, pro-adrenomedullin was a powerful prognostic determinant in the stable disease state. Of plasma biomarkers that we studied, pro-adrenomedullin most accurately and significantly foretold 1-year and 2-year all-cause mortality. Moreover, pro-adrenomedullin forecasted these outcomes with similar accuracy as did BODE, and remained significantly associated with 2-year nonsurvival after adjustment for the BODE components. Hence, circulating pro-adrenomedullin itself potentially may be regarded as an independent multidimensional disease assessment tool in COPD.

Pro-adrenomedullin and BODE to predict mortality in COPD

To our knowledge, PROMISE-COPD was the first multicentre study primarily designed to investigate whether adding a systemic biomarker could enhance BODE prognostic power in COPD. We found that pro-adrenomedullin, used with BODE, indeed significantly improved 1-year and 2-year mortality prediction over that achieved by applying BODE alone. Importantly, for 1-year mortality, improvement occurred in every seventh patient ($p=0.02$). The incremental discrimination from combining pro-adrenomedullin with BODE in PROMISE-COPD at least equalled that from adding four circulating biomarkers to established clinical/laboratory risk factors in cardiovascular patients [20].

A much smaller, single-centre study [21] found in multivariable analysis that serum C-reactive protein and BODE independently predicted long-term all-cause mortality. However, the additive value of C-reactive protein in that investigation remains uncertain, as neither the C statistic, Cox analysis, nor the net reclassification improvement for the biomarker alone or combined with BODE were reported. Moreover, cardiovascular disease, shown to correlate with C-reactive protein levels, was not formally evaluated.

TABLE 4 Sensitivity analysis: Cox regression models to predict 1-year and 2-year all-cause mortality in patients with stable chronic obstructive pulmonary disease, with missing 6-min walk test data imputed (Hotdeck imputation)

	Likelihood ratio Chi-squared	p-value	C statistic
1-year mortality			
Univariate analysis			
Pro-adrenomedullin	24.38	<0.001	0.715
BODE	33.55	<0.001	0.759
BOD [#]	24.41	<0.001	0.714
Multivariate analysis			
Pro-adrenomedullin plus:			
BODE	53.33 [†]	<0.001	0.829
BOD [#]	46.82	<0.001	0.815
2-year mortality			
Univariate analysis			
Pro-adrenomedullin	26.98	<0.001	0.663
BODE	38.03	<0.001	0.711
BOD [#]	30.91	<0.001	0.688
Multivariate analysis			
Pro-adrenomedullin plus:			
BODE	59.46 ⁺	<0.001	0.771
BOD [#]	55.60	<0.001	0.764

Analysed cohort n=594 (549 with all data available plus the 45 (88.2%) out of 51 patients with missing 6-min walk distance but available pro-adrenomedullin data). p-values compare variables with the null hypothesis. BODE: body mass, airflow obstruction, dyspnoea, exercise capacity index. [#]: BOD comprises BODE without the exercise capacity measurement; the three BOD components are scored according to the same cut-offs as they are in BODE [2], therefore, the "BOD index" ranges, in increasing severity, from 0 to 7. [†]: for 1-year mortality prediction in this sensitivity analysis, value added of pro-adrenomedullin with BODE Chi-squared 19.78, p<0.001. ⁺: for 2-year mortality prediction in this sensitivity analysis, value added of pro-adrenomedullin with BODE Chi-squared 21.43, p<0.001.

Additionally, and notably, in the single-centre pro-adrenomedullin study, C-reactive protein was nonsignificant in predicting 2-year mortality after multivariable adjustment including pro-adrenomedullin [14].

Lately, an analysis from a large COPD cohort suggested that adding interleukin-6, or even interleukin-6 plus six other biomarkers to the BODE components and two additional clinical variables significantly improved mortality prediction compared to using the six clinical variables alone [7]. While this approach commendably aims to capture the complexity of a multidimensional disease, determining 13 variables may hamper applicability.

TABLE 5 Pathophysiological mechanisms supporting the role of adrenomedullin as a local and systemic anti-inflammatory factor, produced in response to chronic inflammation, infection or hypoxia in chronic obstructive pulmonary disease

Lipopolysaccharide, hypoxia and shear stress, encountered in conditions related to endothelial damage and infection, are associated with increased adrenomedullin levels

Adrenomedullin immunoreactivity has been reported in bronchial mucosa and glands and type II pneumocytes

Adrenomedullin is expressed by several immune system cells, including macrophages, monocytes and T-cells, in lymphoid organs, including the lung

Adrenomedullin downregulates serum and lung levels of a wide spectrum of inflammatory mediators [32], including:

- cytokines (tumour necrosis factor- α , interleukin (IL)-6, IL-1 β , IL-12 and interferon- γ)
- chemokines (macrophage inflammatory protein-2 and RANTES)
- serum amyloid A
- nitric oxide

Adrenomedullin upregulates systemic and local levels of the anti-inflammatory cytokine IL-10

Adrenomedullin inhibits neutrophil binding to vascular endothelial cells and subsequent neutrophil emigration in the lung

Adrenomedullin upregulates β -adrenergic agonist levels, a phenomenon observed in acute asthma and thought to represent a preventive mechanism against bronchoconstriction [31]

Hypoxia leads to adrenomedullin upregulation through the hypoxia inducible factor-1 pathway, which interacts with nuclear factor κ B to promote the expression of inflammatory genes [31, 33–35].

Pro-adrenomedullin as an alternative to the 6MWT for mortality prediction

The present analysis demonstrated that in stable COPD, baseline pro-adrenomedullin concentration plus the three “non-6MWD” BODE components more accurately predicted 1-year or 2-year mortality than did the original BODE including the 6MWD. This observation suggests that pro-adrenomedullin measurement may represent an alternative to the 6MWT for mortality prediction. Our multivariable analysis identified 6MWD as an independent 2-year nonsurvival predictor. Others found 6MWD to be valuable in prognosticating death and other adverse outcomes, besides its use for other important reasons, such as before-and-after treatment comparisons and to measure functional status in COPD [16, 22]. Although 6MWD proved to be independently associated with 2-year all-cause mortality in the multivariate analysis of all BODE components in our study, in contrast to the mMRC and FEV₁% pred, it has been tentatively excluded from the new “BOD-A” index. This apparent discrepancy can be justified only by fact that the 6MWD is irrefutably the most difficult item to be obtained clinically in the BODE grading system. Accordingly, the 6MWT has downsides posing barriers to BODE adoption [5, 6]: the test is relatively complex and time-consuming, and requires a 30-m track, a trained examiner certified in cardiopulmonary resuscitation with a minimum of an American Health Association-approved course in basic life support, and supplies and facilities for rapid medical emergency response. Additionally, the 6MWT may be burdensome for many patients, particularly the elderly, frail or those with musculoskeletal, neuromuscular or peripheral arterial disease [2, 23]. Indeed, previous attempts, such as the age, dyspnoea and airflow obstruction (ADO) score, have used a similar approach, *i.e.* refraining from the 6MWD and aiming to increase the applicability of COPD grading systems outside of the specialised respiratory medicine settings [23]. Recently, 6MWD has been shown to lack independent association with computed tomography (CT) density data in an unselected COPD population, thus portending that reduction in the distance walked in the 6MWT can be attributed, besides to lung parenchymal destruction caused by COPD itself, also to common comorbidities, such as cardiovascular and musculoskeletal disorders [24]. In this context, the fact that patients with musculoskeletal or neuromuscular disorders preventing walking at study inclusion were excluded from the study might have influenced our results. Conversely, the mMRC, which in our study did not independently correlate with mortality, remained an independent predictor only for the CT parameters related to the percentage of lung area with markedly reduced lung density values, *i.e.* reflecting the extent of emphysematous destructive changes. This confirms that dyspnoea perception is related to alveolar surface reduction, as assessed either by CT parameters or diffusing capacity of the lung for carbon monoxide [24, 25].

Notably, despite a musculoskeletal or neuromuscular disorder preventing walking being a study exclusion criterion, 8.0% of the PROMISE-COPD cohort had unavailable 6MWD values, by far the commonest grounds for ineligibility for the present analysis. Measuring a blood biomarker rather than 6MWD presumably would offer advantages of speed, simplicity, accessibility and possibly cost. Indeed, in Switzerland, estimated current 6MWT costs approach €40, while a pro-adrenomedullin determination is estimated to cost ~€15–25. Importantly, any such advantages need confirmation in a prospective, comparative study.

Pathophysiological basis for pro-adrenomedullin mortality prediction ability

Our observation that circulating pro-adrenomedullin independently predicts all-cause mortality in COPD patients even after adjusting for the BODE variables suggests that this adrenomedullin surrogate reflects COPD pathophysiological processes and predictive factors uncaptured, or suboptimally captured, by the BODE domains.

Inflammation-induced adrenomedullin expression has been reported in numerous tissues and *in vitro* models, including vascular endothelial cells, vascular smooth muscle cells, fibroblasts, neurons, macrophages and adipocytes, as well as undifferentiated mesenchymal stem cells and peripheral blood mononuclear cell-derived macrophages [12, 26–30]. Thus, in contrast to CALC I and CALC II products, such as procalcitonin, inflammation-related adrenomedullin production appears to occur ubiquitously in all cell types, independently of the differentiation state [12].

It is tempting, and supported by several observations [31–36] (table 5), to speculate that inflammation, infection and hypoxia upregulate production of adrenomedullin as an endogenous immunomodulatory factor, in an attempt to restore homeostasis in COPD. Interestingly, although adrenomedullin appears to be protective in animal models of infection, we found that elevated pro-adrenomedullin is associated with increased mortality in patients with COPD. Previous experimental work examining adrenomedullin in cardiovascular disease also found that adrenomedullin has beneficial properties [37], whereas clinical studies demonstrated that high levels of pro-adrenomedullin were associated with worse patient outcomes [38, 39]. Conceptually, this seeming dichotomy probably represents a “fire *versus* firefighter” epiphenomenon, where the proportional presence of firefighters at a fire reflects their protective, rather than causative, role [40]. Therefore, elevated pro-adrenomedullin levels seen with increased illness severity

and mortality might represent an endogenous, protective role for adrenomedullin [40], in an attempt to decrease inflammation, apoptosis and infection-induced organ damage [41, 42]. Henceforth, higher pro-adrenomedullin levels would reflect greater inflammatory stimuli or more pronounced systemic repercussions of the disease, possibly explaining this biomarker's predictive properties in COPD and other respiratory conditions, such as pneumonia, sepsis and dyspnoea with and without heart failure [40, 43–48].

Clinical and research implications of the findings

What are the possible clinical and research implications of our findings? Pro-adrenomedullin, BODE-A or BOD-A levels might help guide site-of-care decisions in ambiguous cases. In addition, at least theoretically, more accurately identifying COPD patients at higher death risk could facilitate aggressive yet selective early interventions to decrease or avert mortality and other adverse outcomes. Such interventions might include intensified follow-up, *e.g. via* telemonitoring, pharmacotherapy, noninvasive ventilation or pulmonary rehabilitation. Since patients with severe COPD generally require one to three hospitalisations annually, any effective early intervention potentially may considerably decrease healthcare resource consumption. Such an approach has been valuable in cardiovascular disease and was recently proposed for community-acquired pneumonia [49]. Interventional trials should be conducted of pro-adrenomedullin-aided site-of-care assignment or other clinical decision-making to clarify this biomarker's role in everyday COPD management [50]. Furthermore, application of pro-adrenomedullin, BODE-A, or BOD-A should be considered to identify at-risk patients for recruitment to placebo-controlled clinical trials of modalities to prolong survival in COPD, thereby increasing statistical power, decreasing sample size demands and speeding intervention development. Finally, it could be expected that pro-adrenomedullin levels would be differently upregulated beyond airflow limitation in different COPD phenotypes, *i.e.* according to the presence and severity of logistic process or distinctive comorbidities. Within this context, whether pro-adrenomedullin could be used to differentiate between the two main mechanisms of airflow obstruction in COPD, namely conductive airway inflammation and a parenchymal disruption [51, 52], perhaps giving the degree of arterial hypoxaemia, deserves further evaluation.

Strengths and limitations of the study

This study's strengths and weaknesses merit consideration. Among the former were the investigator-driven, multinational, multicentre, prospective design, and the standardised, comprehensive baseline patient assessment, including exercise capacity and novel blood biomarkers. Study limitations include the smaller cohort size relative to epidemiological studies, noninclusion of never-smokers, absence of standardised baseline lung CT and lack of a long-term, *e.g.* 5-year, follow-up confirming suggested cut-off values. Lastly, relatively low mortality may have under-powered the analysis to detect weak but statistically significant associations with death. Conversely, the low event rate most probably rendered conservative the findings regarding the significant predictive aptitude of pro-adrenomedullin, *i.e.* cohorts with higher mortality rates potentially might reveal stronger associations between pro-adrenomedullin and death than those reported here.

Conclusion

In summary, pro-adrenomedullin appears to be an accurate, significant and independent predictor of long-term all-cause mortality in patients with clinically stable COPD. In this setting, pro-adrenomedullin significantly improves 1-year or 2-year mortality prediction when combined with BODE, or with the three non-6MWT BODE components, compared to prognostication using BODE alone.

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