Markers of disease activity in COPD: an 8-year mortality study in the ECLIPSE cohort

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ABSTRACT
Rationale: There are no validated measures of disease activity in COPD. Since "active" disease is expected to have worse outcomes (*e.g.* mortality), we explored potential markers of disease activity in patients enrolled in the ECLIPSE cohort in relation to 8-year all-cause mortality.

Methods: We investigated 1) how changes in relevant clinical variables over time (1 or 3 years) relate to 8-year mortality; 2) whether these variables inter-relate; and 3) if any clinical, imaging and/or biological marker measured cross-sectionally at baseline relates to any activity component.

Results: Results showed that 1) after 1 year, hospitalisation for COPD, exacerbation frequency, worsening of body mass index, airflow obstruction, dyspnoea and exercise (BODE) index or health status (St George's Respiratory Questionnaire (SGRQ)) and persistence of systemic inflammation were significantly associated with 8-year mortality; 2) at 3 years, the same markers, plus forced expiratory volume in 1 s (FEV$_1$) decline and to a lesser degree computed tomography (CT) emphysema, showed association, thus qualifying as markers of disease activity; 3) changes in FEV$_1$, inflammatory cytokines and CT emphysema were not inter-related, while the multidimensional indices (BODE and SGRQ) showed modest correlations; and 4) changes in these markers could not be predicted by any baseline cross-sectional measure.

Conclusions: In COPD, 1- and 3-year changes in exacerbation frequency, systemic inflammation, BODE and SGRQ scores and FEV$_1$ decline are independent markers of disease activity associated with 8-year all-cause mortality. These disease activity markers are generally independent and not predictable from baseline measurements.

Introduction

COPD is a complex, heterogeneous disease that is a major cause of morbidity and mortality worldwide [1]. To address the complexity and heterogeneity of COPD in clinical practice, a strategy based on "treatable traits" was proposed [2].

Disease severity and disease activity are distinct attributes that are not necessarily correlated [3]. In COPD, severity has traditionally been expressed by forced expiratory volume in 1 s (FEV_1) as a proportion of its predicted value, because FEV_1 is a good predictor of exacerbations [4], healthcare cost [5] and mortality [6]. Several observational studies have defined prognostic measures that predict mortality in COPD better than FEV_1. In this context, the body mass index, obstruction, dyspnoea and exercise (BODE) index has been accepted as a valid multidimensional index to determine COPD severity [7]. By contrast, there are no validated measures in COPD for disease activity as have been developed in other diseases such as Crohn's disease [8], where the tools utilised are composite indices combining symptoms with laboratory values and/or functional limitation. Currently, the only reliable measures of disease activity in COPD are changes in subjective and/or objective measurements of disease severity. No biomarkers for cross-sectional measurement of disease activity have yet been established, although these would be useful [9–12].

ECLIPSE (NCT00292552) [13] was an observational, longitudinal study in which COPD patients were evaluated regularly for 3 years. In addition, survival status at 8 years after recruitment was obtained in an ECLIPSE subpopulation. ECLIPSE had multiple longitudinal assessments of variables related to disease severity, thereby offering a unique opportunity to investigate relationships between changes in those measures of disease and explore them as surrogate markers of disease activity in relation to a critical outcome, such as mortality [14].

We sought to investigate how changes in relevant variables over time (1 or 3 years) related to 8-year mortality, as a way to identify potential surrogate markers of disease activity; whether these components were inter-related, to help define the value of each of these components; and if any clinical, imaging and/ or biological marker measured at baseline related to any identified activity component.

Methods

ECLIPSE study design and ethics

The ECLIPSE study design and entry criteria have been published previously [13]. Briefly, participants with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II–IV COPD, plus smoking and non-smoking controls, were evaluated regularly for 3 years during the initial study period, and survival status was recorded for consenting participants at 8 years. ECLIPSE complied with the Declaration of Helsinki and was approved by ethics committees of participating centres. All participants provided written informed consent.

This study included only participants from the ECLIPSE study with COPD.

Measurements

Methods for ECLIPSE have been described previously [15–17]. Briefly, modified questionnaires of the American Thoracic Society, Medical Research Council and the St George's Respiratory Questionnaire (SGRQ) recorded patient-reported comorbidities, breathlessness and health-related quality of life. Moderate and severe exacerbations in the year before the study or during the 3-year study were also recorded.

Statistical analysis

Demographic characteristics are summarised as mean±SD or as percentages. The relationships between disease activity variables and mortality at 8 years were determined by categorising change from baseline to

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year 1, and to year 3 for variables known to relate to mortality. This included the following variables: FEV_1 decline; emphysema measured by quantitative computed tomography (CT) using the lowest 15th percentile density method (PD15); BODE index; frequent exacerbations (defined as two or more exacerbations per year); SGRQ total score; and the selected systemic biomarkers. Survival was evaluated to 8 years. Kaplan–Meier curves of individual clinical risk factors and biomarkers were analysed. Cox proportional hazards regression models were used to compare hazard ratios between change categories based on these clinical phenotypes, adjusting for baseline BODE, age and previous COPD hospitalisation. In addition, hazard ratios and 95% confidence intervals for survival to year 8 based on change are reported. Diagnostics for optimising model fit and predictive capability used Akaike's information criterion and the adequacy index, respectively [18]. Potential correlations between disease activity components (and with potential baseline markers) were explored using Spearman's ρ. All tests performed (SAS version 9.2; SAS Institute, Cary, NC, USA) were two-sided with a 0.05 significance level. All p-values were nominal; no adjustment was made for multiple comparisons, as the analyses were considered exploratory.

Results

Characteristics and survival of participants

Out of the 2164 original ECLIPSE COPD participants, 1934 (89%) were alive at end of the 3-year follow-up and potentially available for inclusion in the 8-year follow-up phase. A total of 211 participants had died and 19 were lost to follow-up (LTFU) at year 3. For the 8-year survival assessment, 1555 (80.4%) of the eligible subjects consented to and participated in the 8-year follow-up. Of these, 468 subjects died, 23 were LTFU at year 8 and 1064 were confirmed alive. Clinical and physiological characteristics of participants LTFU either due to administrative reasons (mainly due to a late protocol amendment, n=379) or unable to be accounted for at 8 years (n=42), were in between those of subjects alive and those dead at 8 years' follow-up (figure 1). Table 1 shows the baseline characteristics and clinical characteristics at year 3 for the 1555 participants who consented to participate in the 8-year follow-up, split by survival status at 8 years. Nonsurvivors were older, had more severe airflow limitation, reported more respiratory symptoms and worse health status, had a lower 6-min walk distance, more emphysema, a higher BODE score, more comorbidities and were more likely to have a COPD exacerbation history compared to survivors. Supplementary table E1 shows that patients that did not participate in the follow-up extension of ECLIPSE had baseline clinical characteristics that were in between that of those patients who died and those who survived in the 8-year study. A total of 679 COPD patients in ECLIPSE died over the 8-year period. The Kaplan–Meier estimate of probability of death over this period was 37%.
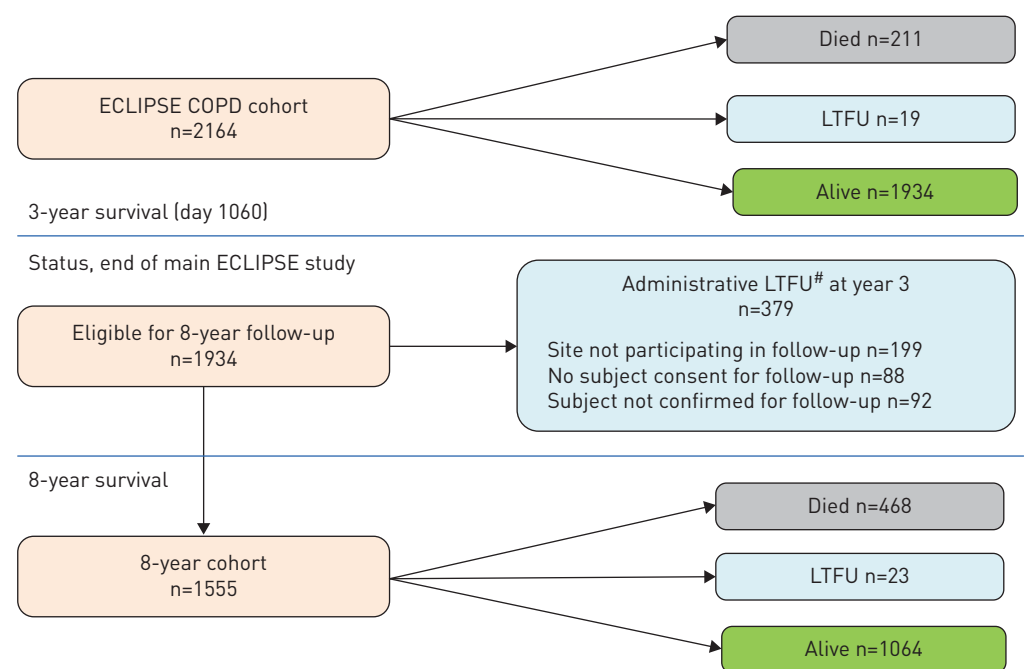

FIGURE 1 Consolidated Standards of Reporting Trials diagram of all subjects in the ECLIPSE COPD study. #: subjects or sites who stopped study participation or did not consent to 8-year survival status. LTFU: lost to follow-up.

TABLE 1 Demographic and clinical characteristics of participants with COPD in the ECLIPSE study, based on 8-year vital status

	Alive at year 8	Died by year 8	LTFU by year 8
Subjects n	1064	468	23
Baseline			
Age years	62±7	65±6	63±8
Male	62	72	43
Post-BD FEV_1 L	1.50±0.53	1.18±0.44	1.24±0.46
Post-BD FEV_1 % predicted	53±15	43±14	49±16
FEV_1/FVC ratio	0.47±0.11	0.40±0.10	0.42±0.09
GOLD II/III/IV %	56/37/7	30/50/20	35/61/4
GOLD 2017 A/B/C/D %	32/14/26/28	13/8/24/55	9/14/23/55
6MWD m	411±112	346±117	350±94
Emphysema PD15 $g \cdot L^{-1}$	57±27	44±24	32±25
BODE index	2.4±1.8	3.9±2.1	3.0±1.8
SGRQ total score	44±18	51±17	51±19
COPD hospitalisation history	11	21	22
Frequent exacerbation history	18	25	17
Cardiovascular history	30	39	9
Depression symptoms	22	25	30
Asthma history	23	22	26
Diabetes history	9	13	13
At year 3			
Post-BD FEV_1 L	1.42±0.55	1.07±0.44	1.11±0.37
Post-BD FEV_1 % predicted	50±16	39±14	44±14
FEV_1 decline during main study $mL \cdot year^{-1}$	32±45	42±40	45±40
6MWD m	405±122	327±129	321±109
Emphysema PD15 $g \cdot L^{-1}$	55±28	40±23	38±28
BODE index	2.6±2.0	4.4±2.2	3.8±1.8
SGRQ total score	43±19	54±19	55±20
COPD hospitalisation during main study	23	51	22
Frequent exacerbations, all 3 years of main study	8	20	13

Data are presented as mean±SD or %, unless otherwise stated. All comparisons between those alive and those who died by year 8 were statistically significant (p<0.05), excepting baseline depression and asthma history. LTFU: lost to follow-up; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walk distance; PD15: lowest 15th percentile of lung density; BODE: body mass index, obstruction, dyspnoea and exercise; SGRQ: St George's Respiratory Questionnaire.

Markers of disease severity and 8-year mortality

The baseline BODE index, a well-established marker of disease severity, was a good predictor of 8-year mortality risk (figure 2). We evaluated a panel of systemic biomarkers for their additive predictive ability for 8-year mortality risk by adding them to a base model with known markers of disease severity (BODE, age and COPD hospitalisation). Interleukin (IL)-6, neutrophils and surfactant protein D (SP-D) together improved the predictive capability of the model to predict 8-year mortality (optimising Akaike's information criteria among biomarker covariates). The base model of clinical covariates (BODE, age and COPD hospitalisation) provided 87% of the prognostic value of the full base plus biomarkers model (adequacy index=0.87).

Markers of disease activity and 8-year mortality

Table 2 presents the hazard ratios and 95% confidence intervals for risk of death for the variables of disease activity studied. Determined as change from baseline to the first year, hospitalisation for COPD, two or more exacerbations, ⩾1-unit worsening of BODE index or ⩾4-unit worsening of SGRQ total score and persistent elevation of inflammatory cytokines were all associated with increased risk of death. When determined over 3 years, the same variables, as well as FEV_1 decline, had a stronger association with risk of death at 8 years' follow-up. Change or decline in CT emphysema (PD15) showed weak association with risk of death at 1 year, which became nominally significant at 3 years.

Figures 3 and 4 show Kaplan–Meier estimates of survival at 8 years based on change in each of the variables determined from baseline to year 3 (table 2). Thresholds of 20 $mL \cdot year^{-1}$ and 40 $mL \cdot year^{-1}$ for
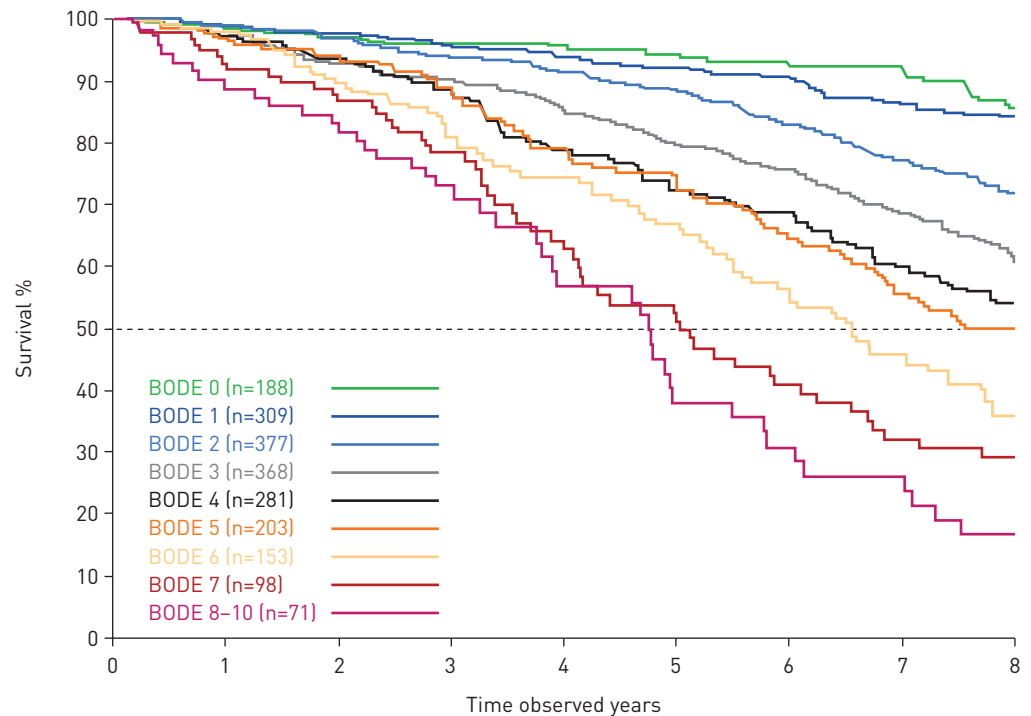
FIGURE 2 Kaplan–Meier curves for mortality at 8 years' follow-up, split by body mass index, obstruction, dyspnoea and exercise (BODE) index at baseline.

TABLE 2 Hazard ratios (HRs) for survival to year 8 based on markers of disease activity measured as change from baseline at the first year and the third year, respectively

	1-year change/event (n=2097)			3-year change/event (n=1555)		
	Subjects[#] n	HR (95% CI)	p-value	Subjects[#] n	HR (95% CI)	p-value
COPD hospitalisation						
No	1770	Reference group		1064	Reference group	
Yes	308	1.65 (1.34–2.02)	<0.001	487	1.95 (1.59–2.39)	<0.001
Frequent exacerbations[¶]						
No frequent exacerbations all years	1460	Reference group		1320	Reference group	
Frequent exacerbations all years	618	1.30 (1.09–1.54)	0.003	175	1.63 (1.27–2.10)	<0.001
Health status (SGRQ)						
⩾4 units improvement	675	0.94 (0.76–1.17)	0.606	444	0.96 (0.72–1.28)	0.796
−4–4 units change	630	Reference group		405	Reference group	
⩾4 units worse	526	1.37 (1.11–1.69)	0.004	538	1.58 (1.23–2.03)	<0.001
FEV$_1$ decline[+] mL·year^{-1}						
Per 20 mL·year^{-1} increment	1916	1.01 (1.00–1.02)	0.044	1555	1.14 (1.09–1.19)	<0.001
BODE index						
Improved	520	0.84 (0.67–1.07)	0.157	244	0.76 (0.54–1.08)	0.126
No change	623	Reference group		409	Reference group	
Worse	576	1.27 (1.02–1.58)	0.032	565	1.52 (1.17–1.97)	0.002
Persistent inflammation						
No markers	431	Reference group		[§]	[§]	
One marker	768	1.32 (1.03–1.71)	0.030			
⩾2 markers	220	1.48 (1.08–2.04)	0.016			
Emphysema PD15 decline[+] g·L^{-1}·year^{-1}						
Per 1 g·L^{-1}·year^{-1} increment	1556	1.00 (0.99–1.01)	0.078	1380	1.12 (1.00–1.24)	0.046

All models were adjusted for baseline age, baseline body mass index, obstruction, dyspnoea and exercise (BODE) index, and prior COPD hospitalisation. Year 1 change analyses reflect the original ECLIPSE cohort who remained in the study after year 1. Data for the 379 participants who did not consent for 8-year follow-up were censored at year 3, corresponding with the end of their original study participation. SGRQ: St George's Respiratory Questionnaire; FEV$_1$: forced expiratory volume in 1 s; PD15: lowest 15th percentile density method. [#]: number of participants with available data for the given parameter at the specified time point; [¶]: ⩾2 exacerbations per year; [+]: change from baseline used for year 1 analysis, rate of decline used for year 3 analysis; [§]: not all inflammatory markers were measured at year 3.
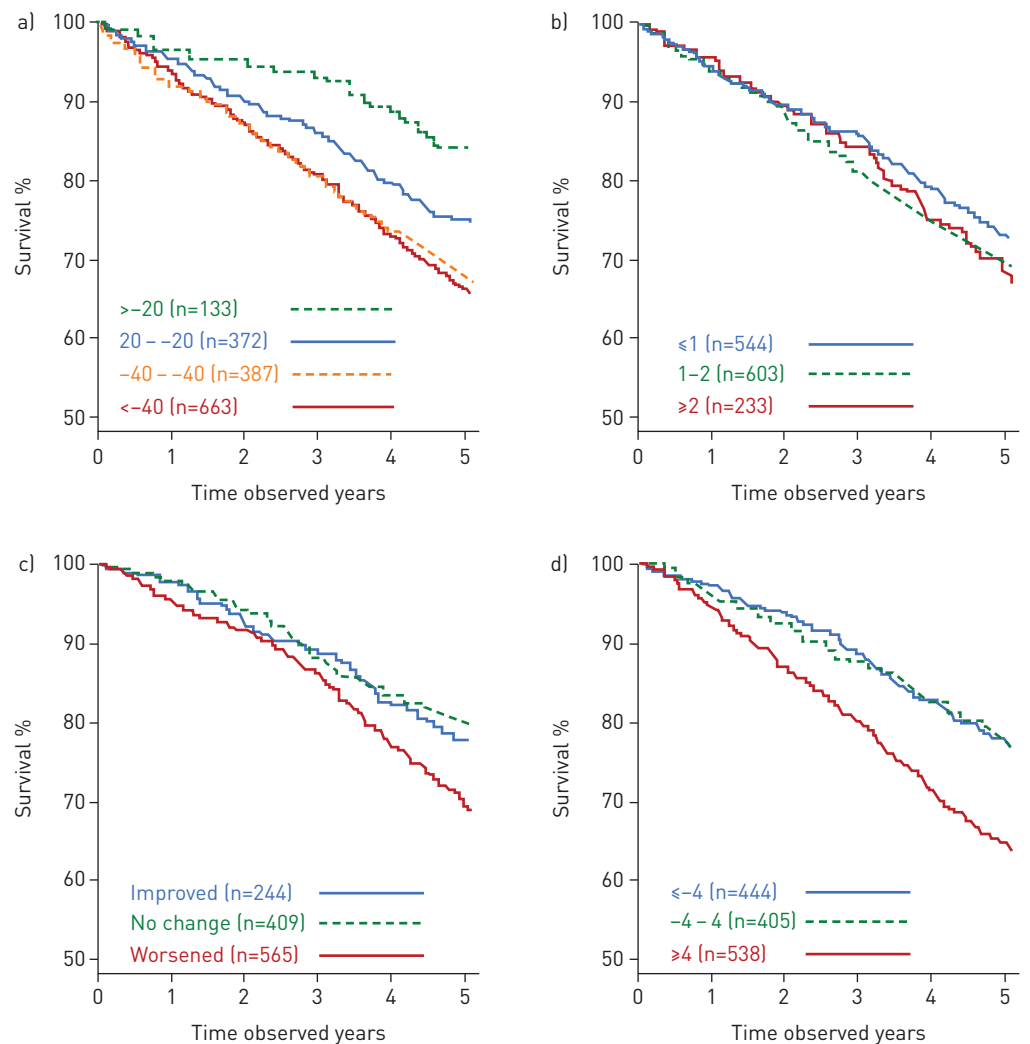
FIGURE 3 Kaplan–Meier curves for mortality from year 3 to year 8 for a) forced expiratory volume in 1 s decline (mL·year^{-1}); b) computed tomography decline (lowest 15th percentile density method) (g·L^{-1}·year^{-1}); c) body mass index, obstruction, dyspnoea, and exercise (BODE) index change; d) St George's Respiratory Questionnaire total score change.
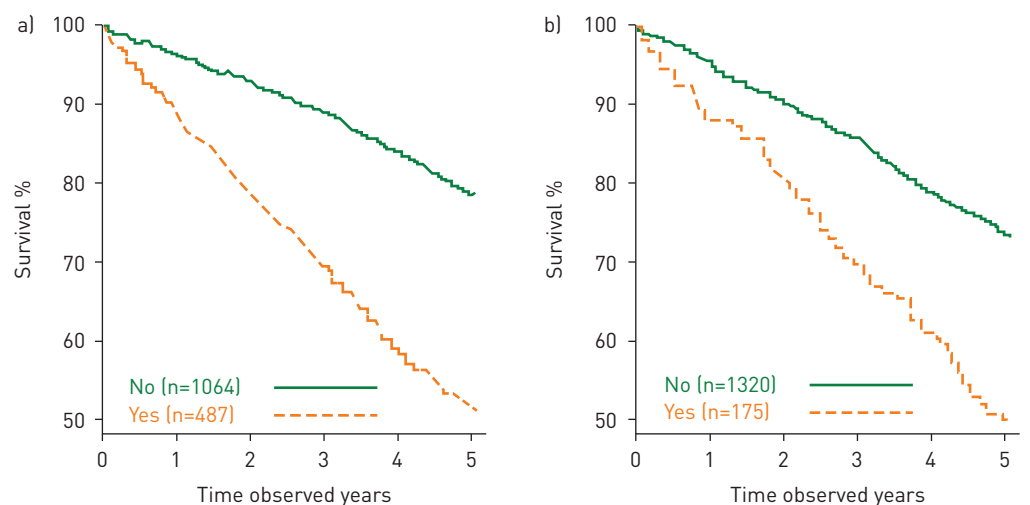

FIGURE 4 Kaplan–Meier curves for mortality from year 3 to year 8 for a) any COPD hospitalisation over 3 years; b) frequent exacerbations each year over 3 years.

FEV_1 decline were selected based on mean decline values for healthy never-smokers and smokers from the Framingham Offspring Cohort [19]; thresholds provided are not intended to suggest optimal decline thresholds. Probability of survival related to FEV_1 change was 84% for improvers (>20 mL·year^{-1} gain); 75% for the stable group (decline ±20 mL·year^{-1}); 67% for modest decliners (decline of 20–40 mL·year^{-1}); and 65% for substantial decliners (decline of >40 mL·year^{-1}).

Table 3 shows that changes in disease activity were independent of lung function severity, as the same variables were significant across GOLD severity grades (II/III). In patients with GOLD grade IV, only rate of FEV_1 decline and hospitalisations reached statistical significance at 8 years, but the number of patients in this stage was relatively small (n=173).

Table 4 presents a matrix correlation (Spearman's ρ-values) between the disease activity markers identified in table 2. Changes in single variables (FEV_1, exacerbations and hospitalisations, inflammatory biomarkers and CT (PD15)) were not related to each other. There were modest and expected relations between changes in some of these individual variables and multidimensional indices (BODE and SGRQ) that integrate some of them.

Supplementary table E2 shows that these disease activity components were mostly unrelated to any baseline, cross-sectional measure.

Discussion

This long-term analysis of the ECLIPSE COPD cohort had three main novel observations. Change over time (1 or 3 years) of a number of variables (including FEV_1 decline, COPD exacerbations, BODE index, SGRQ score and presence of persistent inflammation) significantly predicted risk of death at 8 years' follow-up, suggesting that these variables should be considered as surrogate markers of disease activity. Changes in these variables were, generally, independent of each other, indicating that the construct of disease activity (like the disease itself) is heterogeneous and complex. Finally, change over time cannot yet be predicted accurately from any cross-sectional measurement obtained at baseline. Collectively, these

TABLE 3 Clinical characteristics and disease activity profile over 3 years classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric severity stage (II/III/IV)

	Alive at year 8	Died by year 8	p-value, alive *versus* died
GOLD II at baseline			
Subjects	594	139	
FEV_1 decline mL·year^{-1}	−33±48	−52±45	<0.001
Emphysema (PD15) decline g·L^{-1}·year^{-1}	−1.1±1.1	−1.1±1.1	0.861
SGRQ total score change to year 3	−0.6±12.4	2.7±13.8	0.011
6MWD change to year 3	0±85	−12±89	0.221
BODE index change to year 3	0.5±1.2	0.9±1.4	0.001
Subjects with COPD hospitalisation %	16	40	<0.001
GOLD III at baseline			
Subjects	393	233	
FEV_1 decline mL·year^{-1}	−32±41	−41±39	0.014
Emphysema (PD15) decline g·L^{-1}·year^{-1}	−1.2±0.9	−1.3±0.9	0.143
SGRQ total score change to year 3	0.5±12.4	5.2±14.4	<0.001
6MWD change to year 3	−19±102	−54±101	<0.001
BODE index change to year 3	0.3±1.5	0.9±1.7	<0.001
Subjects with COPD hospitalisation %	30	53	<0.001
GOLD IV at baseline			
Subjects	77	96	
FEV_1 decline mL·year^{-1}	−16±42	−33±31	0.003
Emphysema (PD15) decline g·L^{-1}·year^{-1}	−1.2±0.9	−1.3±0.8	0.492
SGRQ total score change to year 3	−0.7±14.0	2.3±10.1	0.128
6MWD change to year 3	−37±102	−48±112	0.576
BODE index change to year 3	0.4±1.6	0.5±1.4	0.556
Subjects with COPD hospitalisation %	43	62	0.012

Data are presented as n or mean±SD, unless otherwise stated. Participants are divided by survival status 5 years later (year 8 of observation). FEV_1: forced expiratory volume in 1 s; PD15: lowest 15th percentile density method; SGRQ: St George's Respiratory Questionnaire; 6MWD: 6-min walk distance; BODE: body mass index, obstruction, dyspnoea and exercise.

TABLE 4 Correlations (Spearman's ρ) between different disease activity components

	Description of variable	FEV_1-1y	FEV_1-Decl	PD15-1y	PD15-Decl	BODE-1y	BODE-3y	HOSP-1y	HOSP-3y	FE-1y	FE-3y	SGRQ-1y	SGRQ-3y
FEV_1-1y	FEV_1 change, baseline to year 1	1.00											
FEV_1-Decl	FEV_1 decline, baseline to year 3	**0.39**	1.00										
PD15-1y	Emphysema (PD15) change, baseline to year 1	−0.02	0.03	1.00									
PD15-Decl	Emphysema (PD15) decline, baseline to year 3	0.04	0.08	**0.37**	1.00								
BODE-1y	BODE change, baseline to year 1	**−0.38**	−0.15	0.02	−0.01	1.00							
BODE-3y	BODE change, baseline to year 3	**−0.27**	**−0.43**	−0.02	−0.11	**0.47**	1.00						
HOSP-1y	COPD hospitalisation, year 1	−0.01	−0.06	−0.06	−0.04	0.06	0.08	1.00					
HOSP-3y	COPD hospitalisation, first 3 years	−0.08	−0.09	−0.08	−0.06	0.06	0.13	**0.63**	1.00				
FE-1y	Frequent exacerbations, year 1	−0.06	−0.03	−0.01	−0.05	0.07	0.06	**0.39**	**0.36**	1.00			
FE-3y	Frequent exacerbations, year 1, year 2 and year 3	−0.04	−0.03	0.04	−0.04	0.08	0.05	**0.28**	**0.30**	**0.58**	1.00		
SGRQ-1y	SGRQ change, baseline to year 1	−0.16	−0.08	0.04	−0.02	0.23	0.11	0.06	0.08	0.06	0.02	1.00	
SGRQ-3y	SGRQ change, baseline to year 3	−0.10	**−0.26**	0.04	−0.08	0.13	**0.32**	0.06	0.13	0.04	0.07	**0.46**	1.00
SysInfl	⩾2 inflammation markers, year 1	−0.01	0.00	0.01	0.07	−0.03	0.01	0.19	0.19	0.15	0.09	0.04	−0.02

(Absolute) correlations >0.25 are presented in bold. FEV_1: forced expiratory volume in 1 s; PD15: lowest 15th percentile density method; BODE: body mass index, obstruction, dyspnoea and exercise; SGRQ: St George's Respiratory Questionnaire.

findings could help to inform clinical directions for sequential measurements of the variables explored to develop therapies targeting disease progression.

Previous studies

Markers of disease severity in COPD in relation to their capacity to predict clinically relevant outcomes, such as mortality, have been widely studied [20–23]. Our results confirm the robustness of the observations made in the original BODE 3-year report [7], as the assessment of disease severity provided by the BODE index remains a good predictor of longer-term mortality even among those who survived for an initial 3-year observation period. The prognostic value of BODE is improved by complementing the information with the presence of older age and of hospitalisation, easily determined using electronic medical records. As was true at 3 years' follow-up [24], the systemic levels of neutrophils, IL-6 and SP-D were associated with increased risk of death at 8 years. The levels of these biomarkers provided 13% of the prognostic ability of the model when added to the base model of BODE index, age and COPD hospitalisation to predict risk of death at 8 years' follow-up. To our knowledge, the current study is the first to investigate the relationship of multiple candidates for surrogate markers of disease activity in a large, well-characterised cohort of COPD patients with varying degrees of disease severity followed long-term (8 years) and to validate them in relation to an important clinical outcome (all-cause mortality).

Interpretation of novel findings

This study provides three novel observations. First, changes from baseline to 1 year in frequency of COPD exacerbations, BODE index, SGRQ score, and presence of persistent inflammation related significantly to 8-year mortality. The relationship becomes even stronger when these changes are determined at 3 years. FEV_1 decline, and to a lesser degree CT emphysema decline, also show a relationship with the outcome. Collectively, these observations provide evidence that changes in these variables are surrogate markers of disease activity. It is important to note here that these longitudinal measurements (*i.e.* changes over time) of disease activity are different from their baseline values, which may or may not be markers of disease severity.

To our knowledge, although previous studies have associated FEV_1 decline to mortality with measurements made between 2- and 6-year intervals [25, 26], only one previous study [27] has determined how long it may take to characterise the value of the FEV_1 decline in shorter time spans and relate it to impact on outcome. The results of that study, along with this study, suggest a time span between 1 and 3 years. Furthermore, FEV_1 decline (and COPD hospitalisation) over 3 years were the only predictors in the limited number of patients with GOLD grade IV. These results are important because, with increased use of electronic medical records, it is feasible to identify these patients in daily clinical practice. Monitoring of lung function can help identify individuals at risk and further explore the mechanisms associated with decline to support the development of modifying therapies aimed at ameliorating disease progression.

For the first year of observation, the presence of exacerbations leading to hospitalisations was a significant predictor, extending the original 3-year findings in ECLIPSE [28] and in other studies [29] to 8-year follow-up; development of two or more moderate exacerbations over the same time frame also related to increased mortality. When disease activity measures were determined by changes from baseline to 3-year follow-up, results confirmed that hospitalisations for COPD and at least two exacerbations per year were important predictors of mortality, and hence a marker of disease activity. This establishes a practical timeline for targeted evaluation of therapies aimed at preventing these events [30].

Additionally, worsening of the BODE index and SGRQ total score after 1 year were predictors of 8-year risk of death. These findings are aligned with previous studies. CASANOVA *et al.* [27] demonstrated that 1-year changes in the BODE index were less variable and a better predictor of survival than changes in FEV_1 in 740 COPD patients followed over 5 years. In the National Emphysema Treatment Trial, changes in the BODE index at 1 year were significant predictors of 2- and 5-year survival in that cohort of patients with COPD [31]. Additionally, the SGRQ score is known to relate to mortality, with a 4-unit change representing its minimum clinically important difference [32, 33]. In the current study, worsening in the SGRQ of ⩾4 units at 1 year was associated with increased risk of death over the subsequent 7 years. When changes were considered over 3 years, worsening of the BODE index or SGRQ score became even stronger predictors of risk of death at 8 years' follow-up.

The association between persistent systemic inflammation (*i.e.* high levels of two or more inflammatory biomarkers in blood samples obtained in two sequential years) and increased risk of death in the ECLIPSE study has already been published [34], and is supported by results from our 8-year mortality analyses. However, we only observed a weak relationship between 1- and 3-year worsening of CT emphysema (PD15) with all-cause mortality. These observations do not suggest a lack of association between

CT-detected degree of emphysema (*i.e.* an assessment of disease severity) and risk of death, as previously documented [35, 36], but rather that the changes detected using the methods implemented in ECLIPSE are not as strong as other markers of disease activity. It is possible too that the impact of progression *via* quantitative CT is more informative in earlier COPD (GOLD I) or those at risk of COPD (former GOLD 0) rather than in patients who already have a significant amount of emphysema.

The other two novel observations of this study relate to the lack of correlation between most of the different variables identified here and 8-year mortality, and the inability of cross-sectional measurements determined at baseline to predict disease activity. The former indicates that the variables studies here are heterogeneous and complex, reflecting the construct of COPD itself. Results of this study show that many important and disease-relevant individual measurements need to be considered independently to assess disease activity. In clinical practice, these observations support a management strategy based on the proposed "treatable traits" approach [2]. The multidimensional BODE and SGRQ indices, as well as the frequency and severity of exacerbations, are more sensitive to reflect activity, but lack the specificity needed to provide personalised therapeutic approaches. As with different trajectories of lung function throughout life [37, 38], there may be different trajectories for the multiple dimensions affected by COPD reflected in different biomarkers. However, none of our multiple cross-sectional measurements determined at baseline were significantly related to any of the disease activity components we determined, subsequently highlighting the pressing need to identify and validate other biomarkers of disease activity.

Strengths and limitations

Important strengths of the study are that the ECLIPSE cohort was followed in a prospective clinical setting with well-characterised COPD patients suffering from a wide range of airflow limitation. Moreover, markers of disease severity and of disease activity (as determined by their dynamic change over time) were separately assessed as predictors of all-cause mortality.

The main limitation of this study is that the 8-year survival status assessment was implemented as a late protocol amendment, and as consent for participation was not available from all sites, 19.6% of eligible subjects required censoring at the end of year 3, primarily due to administrative reasons. However, the baseline characteristics of the patients censored in this group were intermediate between that of survivors and nonsurvivors, suggesting that they were representative of the patients included in the overall study. The baseline and year 3 characteristics of the 1555 participants who consented to the 8-year follow-up *versus* the 398 participants who were alive but did not consent to participate in the 8-year follow-up are provided in supplementary table E1. Overall, the nonparticipants had worse values in most clinical variables than those who participated in the study. However, the fact that change in those parameters that related to mortality were evident in patients with slightly milder disease further support the relevance of our findings. Another limitation of the data was the lack of adjudication of the cause of death, as performed in several prospective interventional trials [39–41]. A limited number of serum and blood biomarkers were evaluated and did not include recently described markers such as collagen and elastin turnover biomarkers [42], which could be of use in assessing different components of COPD disease activity. Finally, the ECLIPSE population was recruited by specialists, often at academic centres with expertise in clinical trials, and does not represents a population-based sample.

Conclusions

This 8-year follow-up of patients with COPD enrolled in the ECLIPSE study shows that changes over time (1 or 3 years) in FEV_1 decline, exacerbation frequency, BODE and SGRQ scores and systemic inflammation could be used as surrogate markers of disease activity that relate significantly to all-cause mortality after 8-years' follow-up. Different variables of disease components are independent of each other and cannot currently be predicted by cross-sectional measures.

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