Emphysema and extrapulmonary tissue loss in COPD: a multi-organ loss of tissue phenotype

Bartolome R. Celli[1], Nicholas Locantore[2], Ruth Tal-Singer[2], John Riley[3], Bruce Miller[2], Jørgen Vestbo[4,5], Julie C. Yates[6], Edwin K. Silverman[1], Caroline A. Owen[1], Miguel Divo[1], Victor Pinto-Plata[7], Emiel F.M. Wouters[8], Rosa Faner[9] and Alvar Agusti[9,10] on behalf of the ECLIPSE Study Investigators[11]

Affiliations: [1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [2]GSK Research and Development, King of Prussia, PA, USA. [3]GSK Research and Development, Stevenage, UK. [4]Dept of Respiratory Medicine, Odense University Hospital, and Clinical Institute, University of Southern Denmark, Odense, Denmark. [5]Translational Medicine, Manchester Academic Health Sciences Centre, University Hospital South Manchester NHS Foundation Trust, Manchester, UK. [6]GSK Research and Development, Research Triangle Park, NC, USA. [7]Pulmonary and Critical Care Medicine Division, Baystate Medical Center, Springfield, MA, USA. [8]Dept of Respiratory Medicine, Maastricht University Medical Center, Maastricht, The Netherlands. [9]CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain. [10]Respiratory Institute, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain. [11]A full list of the ECLIPSE study investigators can be found in the Acknowledgements section.

Correspondence: Bartolome R. Celli, Pulmonary and Critical Care Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. E-mail: bcelli@copdnet.org

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ABSTRACT We tested whether emphysema progression accompanies enhanced tissue loss in other body compartments in 1817 patients from the ECLIPSE chronic obstructive pulmonary disease (COPD) cohort.

Clinical and selected systemic biomarker measurements were compared in subjects grouped by quantitative tomography scan emphysema quartiles using the percentage of low attenuation area (LAA%). Lowest and highest quartile patients had amino-acid metabolomic profiles. We related LAA% to 3 years decline in lung function (forced expiratory volume in 1 s (FEV_1)), body mass index (BMI), fat-free mass index (FFMI) and exacerbations, hospitalisations and mortality rates.

Participants with more baseline emphysema had lower FEV_1, BMI and FFMI, worse functional capacity, and less cardiovascular disease but more osteoporosis. Systemic C-reactive protein and interleukin-6 levels were similar among groups, but club cell protein 16 was higher and interleukin-8, surfactant protein D and soluble receptor for advanced glycation end product were lower with more emphysema. Metabolomics differed between extreme emphysema quartiles. Patients with more emphysema had accelerated FEV_1, BMI and FFMI decline and more exacerbations, hospitalisations and mortality.

COPD patients with more emphysema undergo excessive loss of pulmonary and extrapulmonary tissue, which is probably related to abnormal tissue maintenance. Because of worse clinical outcomes, we propose this subgroup be named the multi-organ loss of tissue (MOLT) COPD phenotype.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent respiratory symptoms and airflow limitation because of airway remodelling and/or alveolar emphysema [1]. For as yet unclear reasons, the presence and severity of emphysema varies markedly between COPD patients [2].

The pathological hallmark of emphysema is loss of lung tissue. Cross-sectional analyses have shown that emphysema is often associated with less tissue in other body compartments such as body mass index (BMI), skeletal muscle measured as a lower fat-free mass index (FFMI) [3, 4] as well as bone density (osteopenia and osteoporosis) [5, 6]. Likewise, longitudinal studies have identified that patients with emphysema have an accelerated loss of lung function [7, 8], as do patients with a low BMI [9]. The progression of emphysema over time, as shown by the decrease of lung density in computed tomography (CT) scans, is associated with lower levels of soluble receptor for advanced glycation end product (sRAGE) and surfactant protein D (SP-D), two molecular biomarkers related to lung tissue damage and regeneration [10, 11]. These observations, however, have never been conceptually interrelated.

We hypothesised that the progressive loss of lung tissue that characterises emphysema is indeed associated with the synchronous and also enhanced loss of tissue mass in several other body compartments because of generalised abnormal tissue maintenance and repair, and not just to inflammation [12]. We explored this hypothesis in the ECLIPSE study (a large cohort of COPD patients that was monitored over 3 years with clinical, functional and imaging variables) in combination with high-throughput technology assessment of blood biomarkers.

Methods

Study design

Details of the ECLIPSE study (ClinicalTrials.gov identifier number: NCT00292552; GSK study code: SCO104960) have been published previously [2, 13]. Briefly, ECLIPSE was an observational, controlled, longitudinal study where, after the baseline visit, participants were evaluated at 3 months, 6 months and then every 6 months for 3 years. Death was determined up to day 1060 of the study. ECLIPSE complies with the Declaration of Helsinki, and has been approved by the ethics committees of the participating centres. All participants signed their informed consent.

Participants

ECLIPSE studied 2164 COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II–IV) but the current analysis includes only those with full CT data (n=1817). Inclusion criteria were as follows: male/female aged 40–75 years, post-bronchodilator forced expiratory volume in 1 s (FEV_1) <80% of predicted and FEV_1/forced vital capacity (FVC) of $\leqslant$0.7; with a smoking history of $\geqslant$10 pack-years. Key exclusion criteria were the presence of a respiratory disorder other than COPD, other significant inflammatory diseases or a reported COPD exacerbation within 4 weeks of enrolment.

Measurements

Clinical characterisation

Dyspnoea was graded using the modified Medical Research Council (mMRC) score [14]; health status was measured with the COPD-specific St George's Respiratory Questionnaire (SGRQ-C) [15]. Exacerbations requiring treatment with antibiotics, oral corticosteroids and/or hospitalisation in the year prior to the study were also recorded. Comorbidities were self-reported and registered using the ATS-DLD-78 questionnaire. Nutritional status was assessed and corrected by anthropometrics using the BMI ($kg \cdot m^{-2}$) and the FFMI ($kg \cdot m^{-2}$) that was measured using bioelectrical impedance.

Functional measurements

Spirometry [16] and the 6-min walking distance (6MWD) test [17] were performed according to international guidelines. The BMI, airflow obstruction, dyspnoea and exercise capacity (BODE) index was calculated as previously reported [18].

CT scan quantification of emphysema

All subjects underwent a low-dose CT scan of the chest using multidetector-row scanners (GE Healthcare, Chicago, IL, USA or Siemens Healthcare GmbH, Erlangen, Germany) as described elsewhere [10]. All scans were evaluated centrally at the University of British Columbia, Canada. Emphysema was quantified

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as the percentage of lung CT voxels below a threshold of −950 Hounsfield units using the software Pulmonary Workstation 2.0 (VIDA Diagnostics, Iowa City, IA, USA). CT scans were repeated twice in most patients of the cohort, and the longitudinal follow-up showing worsening of emphysema was the result of a previous publication [10].

Circulating protein biomarkers

Details of the methods used to detect and quantify the concentration of circulating protein biomarkers have been published [19, 20]. In brief, whole blood was collected into tubes and was prepared by allowing the blood to clot at room temperature followed by centrifugation at 1500×*g*. Plasma (ethylenediaminetetraacetic acid (EDTA) anticoagulant) was obtained by centrifugation of vacutainer tubes at 2000×*g* for 10–15 min. Serum and plasma were stored at −80°C. Chemokine ligand 18 (CCL-18), SP-D, interleukin (IL)-8, IL-6, club cell secretory protein 16 (CC-16), tumour necrosis factor (TNF)-α and sRAGE were measured in serum. Fibrinogen and high-sensitivity C-reactive protein (CRP) were measured in plasma. All protein biomarkers were measured by validated immunoassays. Total white blood cells (WBCs) and neutrophil numbers were determined by an automated clinical laboratory method. All biomarkers were assessed at the baseline visit, with the exception of sRAGE, which was measured in samples from the year 1 visit.

Metabolomic analysis

An exploratory amino-acid metabolomic profile was performed in samples from 111 subjects (41 non-emphysematous and 77 emphysematous, as determined by CT scan) and 68 age- and gender-matched controls [20]. We compared the results of 15 belonging to the lowest and 32 to the highest emphysema quartile.

Statistical analysis

Results are presented as mean±SD, absolute value (%) or median (interquartile range (IQR)), as appropriate. Patients were stratified by quartiles of CT emphysema degree at recruitment. Differences amongst quartiles were tested using ANOVA for continuous variables, a Chi-squared test for categorical variables, non-parametric Kruskal–Wallis test for categorical variables. Three-year product-limit survival estimates were calculated using PROC LIFETEST. Because the analyses were exploratory, p-values were assessed at a nominal significance level of 0.05 without adjustment for multiplicity. All tests were performed using SAS version 9.1.3.

Results

Baseline characteristics

Clinical data

Figure 1 presents the CONSORT diagram of the study. Of the 2164 patients enrolled in ECLIPSE, 347 were excluded from this analysis because of lack of CT scan. We therefore report here the baseline results of 1817 patients (84%); 172 of them (9.5%) died during follow-up. The 347 patients excluded from the analysis because of incomplete CT data had similar demographics, lung function and walking capacity relative to those included in the study but had slightly worse BODE, SGRQ scores and oxygen saturation (data not shown). The metabolomic profile at recruitment was available in 47 patients from the extreme quartiles for analysis (figure 1).

Table 1 shows the main baseline characteristics of patients included in the study, stratified by CT emphysema quartiles. Patients with the most severe emphysema were thinner (BMI), and had worse FEV_1, 6MWD, oxygen saturation, dyspnoea, health status and BODE index. There were no differences in vital capacity, blood pressure or haemoglobin levels. Subjects with more emphysema reported a trend for higher smoking exposure but were more likely to be former smokers. They were also less likely to report a diagnosis of cardiovascular disease or diabetes or to be receiving treatment with statins, whereas a higher proportion reported osteoporosis and were on inhaled corticosteroids. Less than 2% of subjects were receiving oral corticosteroids in all quartiles.

Protein biomarker profile

WBC counts and the systemic inflammatory cytokines CRP and IL-6 did not differ among groups. Fibrinogen was minimally increased and IL-8 levels were significantly reduced in the more emphysematous subjects (table 1). By contrast, biomarkers associated with tissue damage and repair were significantly different between groups, so patients with more severe emphysema showed higher CC-16 and CCL-18 values and lower SP-D and sRAGE levels.

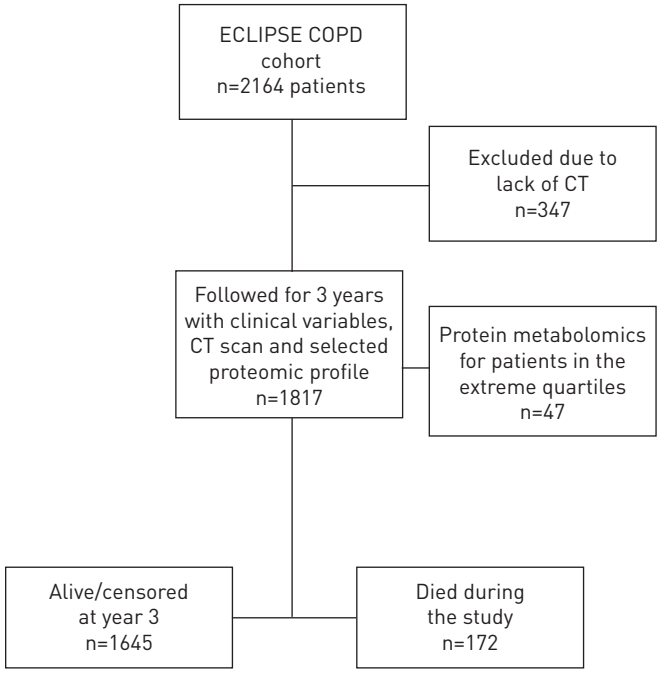

FIGURE 1 CONSORT diagram of the patients included in the study. COPD: chronic obstructive pulmonary disease; CT: computed tomography.

Metabolomic profile

The metabolomic profile in patients with the lowest emphysema quartile (Q1) displayed decreased serum creatine, glycine and N,N-dimethylglycine among other changes that have been associated with the degree of emphysema (table 2).

Outcomes during follow-up

As detailed in table 3 (and depicted graphically in figure 2), patients with more emphysema had an accelerated rate of decline in absolute values of both FEV_1 and BMI even though they started with significantly lower values at baseline (table 1). Table 4 and figure 2 show that more emphysematous patients also had a higher incidence of exacerbations, hospitalisations and mortality rate during follow-up.

Discussion

The results of this integrated analysis of the ECLIPSE cohort support the working hypothesis that patients with severe emphysema constitute a specific COPD subgroup characterised by an enhanced loss of tissue mass over time in several body organs, likely to be in relation to an abnormal tissue loss/repair capacity, as shown by the following observations. At baseline, patients with more severe emphysema had more airflow limitation, worse BODE index and worse health status but they also had: 1) lower BMI, lower FFMI (*i.e.* less muscle mass); 2) a higher prevalence of self-reported osteoporosis (*i.e.* less bone mass), but less cardiovascular disease and diabetes (two comorbidities that are generally related to low-grade systemic inflammation); and 3) specific alterations in cytokines associated with lung injury and repair, such as CC-16, CCL-18, SP-D and sRAGE, as well as a different metabolomic profile. Moreover, during follow-up these patients showed: 4) accelerated loss of FEV_1, BMI and FFMI despite having started from significantly lower values at the time of enrolment; and, finally, 5) more exacerbations, hospitalisations and higher mortality. All in all, the integration of these observations supports a defect in pulmonary and extrapulmonary tissue maintenance and repair in patients with severe emphysema with a direct impact on clinically relevant outcomes, such as exacerbations and death. We propose this subgroup of "imploding" COPD patients be named the multi-organ loss of tissue or MOLT phenotype.

Previous studies and novelty of observations

The original description of patients with emphysema characterised by being thin and barrel-chested was made close to 50 years ago [21, 22]. Previous cross-sectional studies have already shown that emphysema is often associated with low BMI, FFMI and osteoporosis [3, 5, 6, 23], whereas a few longitudinal studies reported that these patients have accelerated decline of lung density and function [7, 8, 10]. We therefore acknowledge that some of the observations reported here are not new. What is novel, though, is the integrated analysis of these findings over time and the inclusion in the analysis of biomarkers of tissue injury and repair. This comprehensive analytical approach supports the hypothesis that in patients with

TABLE 1 Baseline characteristics of patients stratified by quartiles of computed tomography emphysema severity

	Q1 LAA <7.5%	Q2 LAA 7.5–15%	Q3 LAA 15–25%	Q4 LAA ⩾25%	p-value
Subjects n	436	443	458	480	
Demographics					
Age years	62±8	63±7	64±6	64±7	**<0.001**
Male sex %	55	67	67	67	**<0.001**
Body mass index kg·m^{-2}	27±6	28±6	27±5	24±5	**<0.001**
Body mass index <21 kg·m^{-2} %	13	11	14	24	**<0.001**
Fat-free mass kg	53±13	53±13	51±13	48±12	**<0.001**
Fat-free mass index kg·m^{-2}	18.3±3.4	18.4±3.5	17.7±3.4	16.4±3.2	**<0.001**
Smoking exposure					
Pack-years	45±26	48±28	50±27	48±25	**0.044**
Current smoker %	56	40	31	21	**<0.001**
Symptoms					
mMRC dyspnoea score	1.4±1.0	1.6±1.1	1.8±1.0	1.9±1.0	**<0.001**
SGRQ total score	43±20	47±18	49±17	53±16	**<0.001**
Previous exacerbations per patient per year	0.69	0.81	0.95	1.09	**<0.001**
COPD hospitalisations per patient per year	0.14	0.21	0.21	0.27	**0.017**
Self-reported comorbidities %					
Cardiovascular disease	32	36	33	27	**0.024**
Chronic bronchitis	34	30	31	35	0.400
Osteoporosis	9	8	14	19	**<0.001**
Diabetes	12	12	10	5	**<0.001**
Reflux/heartburn	27	26	26	22	0.306
Medications %					
Inhaled corticosteroids	56	69	75	85	**<0.001**
Oral corticosteroids	<1	1	1	1	0.809
Statins	23	26	22	19	0.141
Physiology					
Heart rate beats per min	76±13	77±13	79±13	80±13	**<0.001**
Systolic blood pressure mmHg	133±19	134±20	134±18	131±18	0.076
Diastolic blood pressure mmHg	78±11	79±11	80±11	79±11	0.212
FEV_1 L	1.63±0.50	1.45±0.48	1.27±0.49	1.06±0.40	**<0.001**
FEV_1 % pred	59±13	52±14	46±14	38±13	**<0.001**
FVC L	3.00±0.89	3.08±0.84	3.07±0.95	3.02±0.95	0.507
FEV_1/FVC %	55±9	47±10	41±9	36±8	**<0.001**
Oxygen saturation %	95.2±2.6	94.5±3.3	94.4±3.1	94.2±2.9	**<0.001**
6MWD m	399±114	385±118	364±119	334±121	**<0.001**
BODE index	2.1±1.8	2.8±1.9	3.4±2.1	4.3±2.1	**<0.001**
Circulating blood					
Haematocrit %	0.43±0.04	0.44±0.04	0.44±0.04	0.44±0.04	0.081
Haemoglobin g·L^{-1}	145±13	146±14	146±13	147±12	0.099
White blood cell count 10^9·L^{-1}	8.1±2.5	7.8±2.2	7.9±2.5	7.8±2.2	0.124
Neutrophils 10^9·L^{-1}	5.3±2.1	5.1±1.9	5.3±2.3	5.2±1.9	0.379
Eosinophils 10^9·L^{-1}	0.23±0.20	0.22±0.15	0.22±0.15	0.21±0.15	0.225
Fibrinogen mg·dL^{-1}	433 (377–399)	441 (382–504)	454 (394–510)	453 (387–510)	**0.035**
CRP mg·L^{-1}	3.1 (1.5–7.7)	3.6 (1.6–7.3)	3.5 (1.7–7.3)	2.8 (1.3–6.3)	0.195
Interleukin-6 pg·mL^{-1}	2.0 (0.5–4.5)	2.1 (0.5–4.8)	2.2 (0.6–4.9)	1.8 (0.6–4.4)	0.637
Interleukin-8 pg·mL^{-1}	8.0 (3.8–15.4)	7.4 (3.5–13.7)	6.8 (3.5–11.6)	6.6 (3.2–11.8)	**0.007**
CC-16 ng·mL^{-1}	4.8 (3.1–6.6)	4.9 (3.4–6.9)	5.0 (3.7–6.8)	5.3 (3.7–7.1)	**0.008**
Surfactant protein D ng·mL^{-1}	129 (89–189)	122 (85–174)	117 (86–172)	115 (80–161)	**0.001**
sRAGE ng·mL^{-1}	1.4 (1.1–1.9)	1.3 (1.0–1.7)	1.2 (0.9–1.6)	1.0 (0.8–1.4)	**<0.001**
CCL-18 ng·mL^{-1}	100 (79–127)	104 (80–136)	111 (87–140)	105 (80–137)	**0.007**

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. LAA: low attenuation area; mMRC: modified Medical Research Council questionnaire; SGRQ: St George's Respiratory Questionnaire; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; 6MWD: 6-min walking distance; BODE: body mass index, airflow obstruction, dyspnoea and exercise capacity; CRP: C-reactive protein; CC-16: club cell secretory protein 16; sRAGE: soluble receptor for advanced glycation end product; CCL-18: chemokine ligand 18. Bold font highlights significant differences between groups (ANOVA).

TABLE 2 Comparison of amino-acid metabolomic profile in patients with the lowest (Q1) and highest (Q4) quartiles of computed tomography emphysema

	Q1 LAA <7.5%	Q4 LAA ⩾25%	p-value
Subjects n	15	32	
1-Methylhistidine	0.25 (0.04–0.89)	0.81 (0.60–1.03)	**0.021**
3-Methylhistidine	0.14 (0.07–0.93)	0.62 (0.23–1.68)	0.100
4-Hydroxyproline	44.0 (43.8–44.4)	11.7 (11.4–12.5)	**<0.001**
Aminoadipic acid	1.39 (1.05–1.58)	1.19 (0.93–1.37)	**0.045**
α-Aminobutyric acid	1.55 (1.16–1.71)	1.11 (0.87–1.31)	**0.008**
Alanine	1.17 (0.92–1.35)	0.95 (0.75–1.18)	0.164
Arginine	0.78 (0.65–0.84)	0.87 (0.74–0.94)	**0.013**
Asparagine	4.1 (4.0–4.2)	2.5 (2.4–2.6)	**<0.001**
Aspartic acid	1.42 (1.11–1.58)	1.22 (0.91–1.61)	0.264
β-Aminoisobutyric acid	0.77 (0.63–1.44)	1.04 (0.79–1.33)	0.538
Citrulline	1.43 (1.17–1.62)	1.28 (1.11–1.54)	0.451
Cystathionine	1.09 (0.61–1.26)	1.03 (0.41–1.37)	0.767
Cystine	1.80 (1.66–2.16)	1.49 (1.40–1.71)	**0.004**
γ-Aminobutyric acid	1.04 (0.86–1.25)	1.27 (1.00–1.52)	0.132
Glutamic acid	1.25 (1.19–1.50)	1.08 (0.84–1.28)	**0.032**
Glutamine	1.27 (1.16–1.43)	1.19 (1.13–1.29)	0.079
Glycine	3.5 (3.2–3.6)	1.7 (1.5–1.9)	**<0.001**
Glycine-proline	12.2 (12.0–12.6)	6.7 (6.1–7.3)	**<0.001**
Histidine	1.11 (0.94–1.21)	1.07 (0.91–1.14)	0.479
Isoleucine	1.20 (1.11–1.33)	1.11 (0.90–1.34)	0.087
Leucine	1.20 (1.08–1.40)	1.09 (0.88–1.39)	0.126
Lysine	0.85 (0.81–0.95)	0.92 (0.86–1.03)	0.349
Methionine	1.90 (1.55–2.33)	2.38 (2.03–2.83)	0.071
Ornithine	0.63 (0.32–0.74)	0.69 (0.55–0.78)	0.087
Phenylalanine	1.36 (1.31–1.45)	1.21 (1.07–1.34)	**<0.001**
Proline	0.98 (0.85–1.13)	0.95 (0.84–1.08)	0.616
Sarcosine	80.5 (80.3–80.7)	47.3 (47.1–47.8)	**<0.001**
Serine	0.46 (0.39–0.57)	0.67 (0.45–0.83)	**0.005**
Thiaproline	326 (322–330)	172 (169–173)	**<0.001**
Threonine	0.44 (0.22–0.67)	0.79 (0.53–1.01)	**0.023**
Tryptophan	4.5 (4.3–4.8)	2.9 (2.4–3.4)	**<0.001**
Tyrosine	1.11 (1.04–1.19)	1.04 (0.94–1.18)	0.273
Valine	0.81 (0.03–0.88)	0.88 (0.71–1.04)	0.220

Data are presented as median (interquartile range), unless otherwise stated. LAA: low attenuation area. Note: all subjects in this subset were male and were not current smokers. Bold font highlights significant differences between groups.

TABLE 3 Mean±SD change in FEV_1, BMI and FFMI in the patients classified by quartiles of severity of emphysema

	Q1 LAA <7.5%	Q2 LAA 7.5–15%	Q3 LAA 15–25%	Q4 LAA ⩾25%	p-value
Subjects n	436	443	458	480	
FEV_1 decline mL·year^{-1}	29±48	34±45	37±38	38±34	0.005
BMI change kg·m^{-2}	−0.1±2.1	−0.1±2.1	−0.3±2.2	−0.5±1.9	0.036
FFMI change kg·m^{-2}	−0.4±2.0	−0.5±2.4	−0.4±2.6	−0.3±2.3	0.699

LAA: low attenuation area; FEV_1: forced expiratory volume in 1 s; BMI: body mass index; FFMI: fat-free mass index.

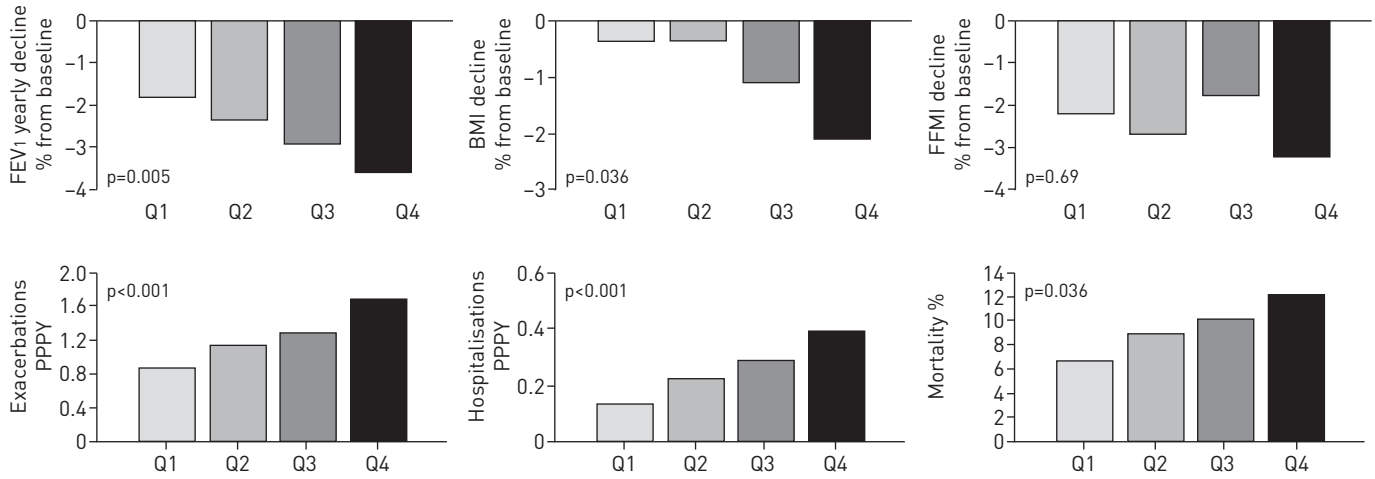

FIGURE 2 Longitudinal outcomes according to baseline quartiles of computed tomography (CT) emphysema. Emphysema severity was stratified using the percentage of low attenuation area quartiles, Q1 (lowest) to Q4 (highest). Upper panel: Forced expiratory volume in 1 s (FEV_1), body mass index (BMI) and fat-free mass index (FFMI) all decline as a percentage change from the baseline. Lower panel: Exacerbations and hospitalisations per patient per year (PPPY) and mortality (%) over the 3 years. For further explanations, see text.

severe emphysema, other extrapulmonary organs (*e.g.* adipose tissue, skeletal muscle, bone) suffer simultaneously the same "imploding or wasting" phenomena (*i.e.* loss of tissue mass) as the lung does.

Interpretation of findings

This hypothesis is supported by the following observations.

Lung physiology

More emphysematous patients had a much lower FEV_1 at baseline (table 1) and, nonetheless, lost lung tissue at a faster rate (table 3, figure 2). This observation differs from previous reports that showed that patients with higher FEV_1 at baseline lose more lung function than patients with lower FEV_1 [24, 25]. These discrepancies may be related to the fact that in those studies, patients were grouped by the baseline FEV_1 level only and not by their degree of emphysema, as we have done. In fact, in keeping with the results of our analysis, recent studies have also shown that the rate of FEV_1 decline in COPD is heterogeneous, and that a lower BMI and the presence of CT emphysema is associated with accelerated FEV_1 loss [7–9].

Comorbidity pattern

Comorbidities such as cardiovascular disease, diabetes, osteoporosis, lung cancer and anaemia are highly prevalent in COPD [26, 27] and contribute to poor outcomes [28, 29]. At baseline, we observed significant differences in the pattern of comorbidities present by the severity of emphysema, with the more emphysematous patients reporting less cardiovascular disease and diabetes (generally regarded as "inflammatory" comorbidities) but more osteoporosis and lower BMI and FFMI (clinical expressions of

TABLE 4 Longitudinal outcomes by quartiles of computed tomography emphysema extent at baseline

	Q1 LAA <7.5%	Q2 LAA 7.5–15%	Q3 LAA 15–25%	Q4 LAA ⩾25%	p-value
Subjects n	436	443	458	480	
COPD hospitalisations PPPY#	0.13	0.22	0.27	0.39	<0.001
COPD exacerbations PPPY#	0.86	1.14	1.28	1.69	<0.001
3-year survival % (95% CI)	93 (91–95)	91 (88–94)	90 (87–92)	88 (85–91)	0.036

LAA: low attenuation area; COPD: chronic obstructive pulmonary disease; PPPY: per patient per year. #: average number of events per year.

loss of bone, fat and skeletal muscle mass, respectively). Moreover, patients with more emphysema lost BMI at a higher rate and FFMI at a similar rate (table 3, figure 2) despite having lower baseline values (table 1).

Pattern of systemic inflammation

Systemic inflammation is often quoted as an important pathogenic mechanism of comorbidities in COPD [26, 30]. However, a previous analysis of the ECLIPSE cohort showed that not all COPD patients have evidence of systemic inflammation and that those who had it had a higher BMI and lower CT emphysema scores [31]. Here we expanded this previous analysis to include markers of lung tissue protection such as CC-16 and CCL-18 (which were higher in patients with more severe emphysema) and SP-D and sRAGE (which were lower in these same patients). By contrast, the reduced levels of SP-D in these same patients can reflect loss of lung tissue, whereas the low levels of sRAGE can be a surrogate marker of a reduced level of systemic inflammation in these patients (table 1) since sRAGE acts as a protective decoy by buffering inflammatory ligands, thus decreasing inflammatory injury [32].

Metabolomic pattern

Although the number of samples characterised metabolomically was small, the results clearly show that the pattern of patients with more severe emphysema was significantly distinct from that of patients with minimal emphysema (table 2). These observations are consistent with previous studies showing a reduction in branched chain amino acids in serum (as well as all amino acids in muscle biopsies) of emphysematous patients [20]. Likewise, they are consistent with previous reports of a suppressed whole-body protein and urea turnover after low-intensity exercise in patients with emphysema, while the exercise-induced anabolic response was maintained in non-emphysematous COPD patients and controls [33].

Relationship to outcomes

An important and novel component of this analysis is the investigation of observations made at baseline with changes occurring during follow-up. We noted that patients with more severe emphysema have more exacerbations and are more likely to be hospitalised and die within 3 years than patients without emphysema (table 3, figure 2). These observations are in keeping with one previous study that described a bi-modal pattern of exacerbations risk. Whereas patients with CT determined thickened airways had increased exacerbations, it also showed that patients with more emphysema also had increased risk of exacerbations compared with patients who fell in the middle for both airways thickness and emphysema [34]. Whether the cause or type of exacerbations is similar in both groups is unclear.

Taken together, our observations support the association of severe emphysema with excessive extrapulmonary tissue loss. Yet, determining the exact pathobiological mechanism(s) responsible for this COPD phenotype is not possible from our data, and further studies are needed to provide insight into the biological mechanisms that govern progressive loss of pulmonary and extrapulmonary tissue. However, it is of interest to note that we did not find differences in haemoglobin levels or white blood cell counts among the emphysema groups, suggesting that the wasting phenomenon is not affecting all organ body systems but rather some, all of which have a mesenchymal origin in common [35]. Likewise, the recent report of a B-cell signature in lung tissue of patients with emphysema may contribute to illuminate potential mechanisms of tissue loss, since wasting is also a common feature in B-cell-driven systemic diseases [36, 37].

Potential limitations

Our study has some potential limitations. First, the results only show associations and do not prove causality. Hence, findings will need to be replicated prospectively in a study powered to test these hypotheses. Second, we studied only a limited panel of biomarkers. However, we chose them based on previous reports and all of them can be measured in clinical practice. Third, comorbidities in the ECLIPSE study were self-reported and not objectively assessed; however, there is a good correlation between self-reported and objectively assessed comorbidities. Finally, mortality data refer to all-cause mortality since cause-specific mortality was not recorded in the study.

Conclusions

The results of this study indicate that COPD patients with severe emphysema undergo an excessive loss of tissue over time in several organs, including lungs, bones, skeletal muscle and adipose tissue. Proper identification of these patients is clinically relevant because they have more exacerbations, and are more likely to be hospitalised and die within 3 years than patients without this phenotype. We propose to name this subgroup the multi-organ loss of tissue (or MOLT) COPD phenotype.

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Steering Committee: H. Coxson (Canada), L. Edwards (GSK, USA), R. Tal-Singer (Co-chair, GSK, USA), D. Lomas (UK), W. MacNee (UK), E. Silverman (USA), C. Crim (GSK, USA), J. Vestbo (Co-chair, Denmark), J. Yates (GSK, USA).

Scientific Committee: A. Agusti (Spain), P. Calverley (UK), B. Celli (USA), C. Crim (GSK, USA), B. Miller (GSK, USA), W. MacNee (Chair, UK), S. Rennard (USA), R. Tal-Singer (GSK, USA), E. Wouters (The Netherlands), J. Yates (GSK, USA).

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