



Lung function indices for predicting mortality in COPD

Afroditi K. Boutou^{1,2}, Dinesh Shrikrishna¹, Rebecca J. Tanner¹, Cayley Smith¹, Julia L. Kelly¹, Simon P. Ward¹, Michael I. Polkey¹ and Nicholas S. Hopkinson¹

Affiliations:

¹NIHR Respiratory Biomedical Research Unit at Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, UK.

²Respiratory Failure Unit, Papanikolaou General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Correspondence:

N.S. Hopkinson, NIHR Respiratory Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, Fulham Rd, London, SW3 6NP, UK.

E-mail: n.hopkinson@ic.ac.uk

ABSTRACT Chronic obstructive pulmonary disease (COPD) is characterised by high morbidity and mortality. It remains unknown which aspect of lung function carries the most prognostic information and if simple spirometry is sufficient.

Survival was assessed in COPD outpatients whose data had been added prospectively to a clinical audit database from the point of first full lung function testing including spirometry, lung volumes, gas transfer and arterial blood gases. Variables univariately associated with survival were entered into a multivariate Cox proportional hazard model.

604 patients were included (mean \pm SD age 61.9 ± 9.7 years; forced expiratory volume in 1 s $37 \pm 18.1\%$ predicted; 62.9% males); 229 (37.9%) died during a median follow-up of 83 months. Median survival was 91.9 (95% CI 80.8–103) months with survival rates at 3 and 5 years 0.83 and 0.66, respectively. Carbon monoxide transfer factor % pred quartiles (best quartile ($>51\%$): HR 0.33, 95% CI 0.172–0.639; and second quartile (51–37.3%): HR 0.52, 95% CI 0.322–0.825; *versus* lowest quartile ($<27.9\%$)), age (HR 1.04, 95% CI 1.02–1.06) and arterial oxygen partial pressure (HR 0.85, 95% CI 0.77–0.94) were the only parameters independently associated with mortality.

Measurement of gas transfer provides additional prognostic information compared to spirometry in patients under hospital follow-up and could be considered routinely.



@ERSpublications

Transfer factor not GOLD stage is the most powerful predictor of survival in patients with COPD

<http://ow.ly/mGmjG>

This article has supplementary material available from www.erj.ersjournals.com

Received: Sept 14 2012 | Accepted after revision: Jan 06 2013 | First published online: Jan 24 2013

Support statement: The study was supported by NIHR Respiratory Biomedical Research Unit at Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, UK.

Conflict of interest: None declared.

Copyright ©ERS 2013. ERJ Open articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 3.0.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem. Its prevalence, morbidity and mortality rates are increasing, and it is now the third leading cause of death worldwide [1]. However, survival rates vary widely between studies [2, 3], possibly due to different disease coding and the inclusion of COPD populations of varying severity. A range of pulmonary function tests is available to assess the severity of disease in COPD, including spirometry, gas transfer measurements, plethysmographic lung volumes and arterial blood gas analysis. The relative usefulness of these different measures remains unclear and in the context of finite healthcare resources it is important to establish whether they provide added value in the management of patients with this condition. In addition, where mortality is an end-point in clinical trials, it is important to be able to select or stratify patients appropriately in order that treatment effects can be determined accurately.

Several attempts have been made to identify potential predictors of survival among COPD patients. Since COPD has impacts beyond the lung [4, 5], the prognostic impact of both pulmonary and extrapulmonary factors has been investigated. Parameters of lung function and, particularly, forced expiratory volume in 1 s (FEV₁) [6, 7], age [8], sex [6, 7], body mass index (BMI) [9, 10], quadriceps strength [11], arterial blood gases [12, 13], lung volumes [14], gas transfer [15, 16], severity of dyspnoea [17], anaemia [18, 19], presence of comorbidities [20] and reduced physical activity or exercise capacity [21] are only some of the factors that have been studied. However, several of these studies have been conducted in specific COPD populations, such as selected patients with severe emphysema [2], patients using long-term oxygen treatment (LTOT) or noninvasive mechanical ventilation [6, 22, 23], and patients during or immediately after hospitalisation for a COPD exacerbation [7, 12, 24]. A limitation of these studies has been the generalisability of the population and the fact that in most studies a full range of lung function measures has not been compared [25]. Thus it has not been possible to draw definitive conclusions about the key lung function prognostic factors in COPD.

Against this background, data from a large cohort of COPD outpatients, who had undergone comprehensive lung function assessment and who had been prospectively entered into a clinical audit database, were analysed to establish whether spirometry, gas transfer or lung volumes wielded the most predictive power for survival.

Methods

Study population

Data on outpatients attending the hospital COPD clinic were entered prospectively onto a clinical audit database. These included pulmonary function test results, anthropometrics, treatments received and exacerbation rate. Data were extracted for individuals who had had their first full lung function testing, including arterial blood gas analysis, performed between February 1996 and October 2010. COPD diagnosis was clinically based on symptoms, radiology appearances and spirometry criteria, using an FEV₁ to forced vital capacity (FVC) ratio <0.7. Patients' treatment included inhaled β_2 -agonists, anticholinergics, oral theophyllines and inhaled steroids in various combinations. Exclusion criteria were evidence of chronic heart failure (New York Heart Association class III or IV), chronic renal failure, peripheral vascular disease or history of malignancy. The Royal Brompton, Harefield and National Heart and Lung Institute research ethics committee has ruled that ethical approval is not required for the retrospective analysis of routinely collected clinical data.

Study measurements

Spirometry, gas transfer and lung volumes assessed by body plethysmography were measured using a CompactLab System (Jaeger, Hoechberg, Germany). Quality control followed accepted guidelines, with carbon monoxide transfer factor (TLCO) gas analyser calibrations prior to each session, volume calibrations prior to each patient test and biological calibrations daily. Predicted values used are those of the European Coal and Steel Community [26]. Arterial oxygen (P_{aO_2}) and carbon dioxide (P_{aCO_2}) partial pressures were measured in arteriased earlobe capillary samples and arterio-alveolar oxygen gradient calculated. Arteriased capillary blood sampling is carried out routinely by our clinical physiologists and is better tolerated than an arterial puncture, while giving equivalent results [27]. For every patient, FEV₁, FVC, FEV₁/FVC ratio, total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and inspiratory capacity (IC)/TLC ratio were recorded. The values of TLCO were adjusted for haemoglobin concentration, according to previously published equations [28].

The annual exacerbation rate referred to the 12-month period prior to the patient's clinic attendance and was derived from a detailed medical history using an event-based definition; an increase in the patient's dyspnoea, cough and/or sputum beyond normal day-to-day variations, which required treatment with

antibiotics and or oral corticosteroids [29]. Survival, extracted from the central National Health Service, UK database was determined up to May 2011.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 17 for Windows XP. Data (including % predicted values) are presented as mean \pm SD. Exacerbation rate was treated *a priori* at the time of initial data entry as a categorical variable, separating the number of exacerbations into three groups: 0–1, 2–4 or >4 per year. Differences between survivors and non-survivors in demographic and clinical variables were assessed utilising the independent samples t-test or the Chi-squared model, where appropriate. The parameters found to be univariately associated with survival were subsequently entered in a multivariate Cox proportional hazard regression analysis model. Both FEV₁ and TLCO were entered in the survival analysis as categorical variables (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages and TLCO quartiles, respectively), as this methodology has been previously confirmed to better classify COPD patients with respect to survival [30, 31]. The Tukey–Hinges method was used to calculate the TLCO quartiles. Corresponding hazard ratios and 95% confidence intervals were calculated for each independent predictor. The median survival (with the corresponding 95% confidence intervals) and the overall survival rates were estimated using the Kaplan–Meier method. Correlation analysis was used to identify factors associated with PaO₂. A level of $p < 0.05$ was considered statistically significant.

Results

Study population

The study population consisted of 604 patients (380, or 62.9%, male and 224, or 37.1%, female), who had a mean age of 62 years. According to GOLD classification, most of the patients presented with severe or very severe disease (28.4% and 52.2%, respectively) and 17.1% of them were on LTOT. Approximately 85.5% of the patients were treated with inhaled steroids, 82.2% with long-acting inhaled β_2 -agonists and 63.4% with long acting anti-muscarinics. The demographic and clinical characteristics of the study population are presented in table 1.

Mortality

The mean \pm SD follow-up for the total population was 80 ± 49.8 months, while the median (95% CI) was 83.1 (6.6–210.8) months. 229 patients (37.9%) died during the follow-up period. Median (95% CI) survival for the total population was 91.9 (80.8–103) months and survival rates at 3 and 5 years were 0.83 and 0.66, correspondingly.

Predictors of survival

Table 2 presents the differences in patient characteristics between survivors and non-survivors. Survivors were younger ($p = 0.024$) with less severe disease (according to GOLD classification), presented with higher BMI ($p = 0.004$), FEV₁ % pred ($p < 0.001$), FVC % pred ($p < 0.001$), FEV₁/FVC ratio ($p < 0.001$), TLCO % pred ($p = 0.015$), IC/TLC % ($p < 0.001$) and PaO₂ at room air ($p = 0.001$), and a lower proportion received LTOT ($p < 0.001$), compared to non-survivors. Conversely, TLC % pred ($p = 0.015$), FRC % pred ($p < 0.001$), RV % pred ($p < 0.001$) and PaCO₂ ($p = 0.003$) were lower among the patients who were still alive at the end of the follow-up period. The following parameters were not associated with survival differences: sex, H⁺ concentration, arterio-alveolar gradient, smoking status and history (pack-years), and exacerbation rate.

When these univariate predictors were entered in a proportional Cox hazard model, the parameters which were found to predict mortality in the COPD population were age, TLCO % pred quartiles and PaO₂ (table 3). When the lowest TLCO quartile ($< 27.9\%$ pred) was used as reference, patients with TLCO $> 51\%$ pred and those with TLCO between 51 and 37.3% pred had significant lower mortality risk than those with TLCO $< 27.9\%$ pred. In addition, table 4 presents these results with TLCO % pred and FEV₁ % pred treated as continuous variables. Figure 1 presents the Kaplan–Meier survival curves, adjusted for age, PaO₂, GOLD stages, FVC % pred, FEV₁/FVC, TLC % pred, FRC % pred, IC/TLC, RV % pred, BMI and PaCO₂ for the four population groups, categorised by TLCO % pred quartiles. By contrast, figure 2 presents the Kaplan–Meier survival curves, adjusted for age, PaO₂, TLCO % pred quartiles, FVC % pred, FEV₁/FVC, TLC % pred, FRC % pred, IC/TLC, RV % pred, BMI and PaCO₂ for the four population groups categorised by GOLD stages. Figure E1 in the online data supplement shows receiver operating characteristic curves for survival prediction comparing TLCO % pred, FEV₁ % pred, IC/TLC and FEV₁/FVC ratio. TLCO % pred had the most predictive power with areas under the curve of 0.69, 0.67, 0.64 and 0.62 respectively.

Because oxygen therapy has an impact on survival in COPD, additional analyses were performed excluding patients on long-term oxygen. These are available in an online data supplement (tables E1 and E2). The results in this population were similar, with TLCO % pred again the strongest predictor of survival.

TABLE 1 Characteristics of the study population

Age years	61.9 ± 9.7
Sex %	
Male	62.9
Female	37.1
BMI kg·m⁻²	24.2 ± 5.3
FEV1 % pred	37 ± 18.1
FVC % pred	84.5 ± 22.4
FEV1/FVC	34.7 ± 12.3
GOLD classification %	
Stage I	2.3
Stage II	17.0
Stage III	28.4
Stage IV	52.2
TLC % pred	124.9 ± 18.4
RV % pred	205.1 ± 58.4
IC/TLC %	26.9 ± 8.8
FRC % pred	172.7 ± 38.5
Tlco % pred	40.8 ± 18
PaO₂ kPa	9.4 ± 1.4
PaCO₂ kPa	5.2 ± 0.9
Arterio-alveolar oxygen gradient kPa	5.1 ± 1.3
LTOT %	17.1
Current smokers %	13.2
Smoking history pack-years	43.8 ± 23
Exacerbations %	
0–1 per year	39.1
2–4 per year	42.7
>4 per year	18.2

Data are presented as mean ± SD, unless otherwise stated. n=604. BMI: body mass index; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung disease; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity; FRC: functional residual capacity; Tlco: carbon monoxide transfer factor; PaO₂: arterial oxygen partial pressure; PaCO₂: arterial carbon dioxide partial pressure; LTOT: long-term oxygen treatment.

Factors associated with PaO₂

All recorded demographic and clinical parameters were investigated to identify potential determinants of PaO₂. Correlation analysis revealed positive, but weak associations between PaO₂ and FEV1 %pred (r=0.25, p<0.001), Tlco % pred (r=0.29, p<0.001) and IC/TLC (r=0.23, p<0.001), and a moderate negative correlation between PaO₂ and PaCO₂ (r= -0.47, p<0.001). When these variables were entered in a multivariate regression analysis model, only PaCO₂ (beta= -0.45, p<0.001) and Tlco % pred (beta=0.28, p<0.001) were retained together explaining only 26% of the variance in PaO₂ values in the study population: PaO₂= -0.719 (PaCO₂)+0.018 (Tlco % pred)+12.431.

Discussion

The main finding of the present study was that, in stable outpatients with COPD, Tlco % pred and PaO₂, as well as younger age, were the only variables independently associated with survival. Staging according to the original GOLD criteria, other lung function parameters, anthropometric measures and exacerbation history did not yield any additional prognostic information.

Significance of the findings

The present paper compares different lung function parameters directly in a group of comprehensively assessed COPD patients. COPD is characterised by airflow obstruction due to a mixture of small airways disease and lung parenchymal destruction [29]. FEV1 and FEV1/FVC reflect the severity of airflow obstruction, while plethysmographic lung volumes represent the consequences of gas trapping and lung hyperinflation due to airflow obstruction and decreased lung elastic recoil. As the product of the transfer coefficient and alveolar volume, Tlco reflects both changes in functional lung volume and gas transport across the alveolar–capillary membrane and thus reflects the degree of parenchymal destruction and loss of pulmonary capillary bed, due to emphysema. In addition, the presence of processes that increase pulmonary venous pressure, such as in left heart failure, pulmonary oedema and mitral stenosis, could also result in a

TABLE 2 Differences between survivors and non-survivors

	Survivors	Non-survivors	p-value
Subjects n	375	229	
Age years	61.1 ± 10.1	63 ± 9.2	0.024
Sex %			
Male	62.4	63.8	NS
Female	37.6	36.2	
BMI kg·m⁻²	24.7 ± 5.3	23.4 ± 5.2	0.004
FEV₁ % pred	40.6 ± 18.8	30.9 ± 15	<0.001
FVC % pred	88.4 ± 22	78.2 ± 21.6	<0.001
FEV₁/FVC	36.4 ± 12.8	31.8 ± 11	<0.001
GOLD classification %			<0.001
Stage I	3.2	0.9	
Stage II	22.7	7.4	
Stage III	33	20.5	
Stage IV	41.1	71.2	
TLCO % quartiles			<0.001
Best quartile (>51)	31.3	13.9	
Quartile 2 (51–37.3)	29.1	18.3	
Quartile 3 (37.3–27.9)	22.2	29.3	
Quartile 4 (<27.9)	17.4	38.5	
TLCO % pred	44.7 ± 18.4	34.1 ± 15.2	<0.001
TLC % pred	123.4 ± 17	127.5 ± 20.5	0.015
FRC % pred	166.1 ± 35.3	184.4 ± 41.1	<0.001
RV % pred	195.6 ± 53.2	220.9 ± 63.1	<0.001
IC/TLC %	28.8 ± 8.6	23.5 ± 8	<0.001
PaO₂ kPa	9.6 ± 1.3	9.2 ± 1.6	0.001
PaCO₂ kPa	5.1 ± 0.7	5.4 ± 1	0.003
Arterio-alveolar oxygen gradient kPa	5 ± 1.3	5.1 ± 1.4	NS
LTOT %	11.0	27.1	<0.001
Smoking status %			
Never or ex-smokers	88.4	83.4	NS
Current smokers	11.6	16.6	
Smoking history pack-years	45.6 ± 25.1	41.1 ± 19.4	NS
Exacerbations %			
0–1 per year	40.3	37.1	
2–4 per year	40	47.2	NS
>4 per year	19.7	15.7	

Data are presented as mean ± SD, unless otherwise stated. BMI: body mass index; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung disease; TLCO: carbon monoxide transfer factor; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; IC: inspiratory capacity; PaO₂: arterial oxygen partial pressure; PaCO₂: arterial carbon dioxide partial pressure; LTOT: long-term oxygen treatment; NS: nonsignificant.

reduction in TLCO [32]. These effects of both pulmonary circulation abnormalities and possibly subclinical cardiac pathology on TLCO values could partially explain its superiority as a prognostic factor compared to FEV₁ or plethysmographic lung volumes.

To the authors' knowledge, this is the first study identifying TLCO % pred as an independent predictor of survival in a large, unselected general population of COPD outpatients. Although abnormal pulmonary function has long been considered as a predictor of mortality [3, 14, 25, 33–35], most studies in COPD have not assessed the impact of TLCO [18, 23, 36–39]. Two smaller studies have previously reported a correlation between transfer factor and survival in stable COPD patients but only in univariate and not multivariate analysis [15, 16]. MARTINEZ *et al.* [2] studied COPD patients who were randomised to the medical arm of the National Treatment Emphysema Trial (NETT) and found no association between TLCO % pred and survival. Although this was a larger population, it had been highly selected to meet the trial inclusion criteria for lung volume reduction surgery eligibility. Apart from these negative results, transfer factor has been identified as an independent predictor of survival in specific COPD subpopulations, such as patients receiving LTOT or noninvasive mechanical ventilation [40, 41].

TABLE 3 Predictors of mortality in the total chronic obstructive pulmonary disease population, according to the multivariate Cox regression analysis

	HR (95% CI)	p-value
Age years	1.034 (1.009–1.059)	0.007
PaO₂ kPa	0.860 (0.755–0.979)	0.023
Tlco % pred		0.006
Best quartile (>51)	0.332 (0.172–0.639)	0.001
Quartile 2 (51–37.3)	0.515 (0.322–0.825)	0.006
Quartile 3 (37.3–27.9)	0.711 (0.477–1.059)	0.093
Quartile 4 (<27.9)	Reference	
GOLD classification		0.125
Stage I	0.506 (0.087–2.94)	0.448
Stage II	0.407 (0.176–0.939)	0.035
Stage III	0.639 (0.408–1.002)	0.053
Stage IV	Reference	
FVC % pred	0.989 (0.969–1.010)	0.250
FEV₁/FVC	1.015 (0.994–1.037)	0.170
RV % pred	0.988 (0.975–1.051)	0.079
FRC % pred	1.023 (0.999–1.048)	0.057
TLC % pred	1.008 (0.976–1.041)	0.633
IC/TLC %	2.15 (0.37–3.293)	0.418
Paco₂ kPa	0.985 (0.796–1.218)	0.887
BMI kg·m⁻²	1.009 (0.970–1.036)	0.903

PaO₂: arterial oxygen partial pressure; Tlco; carbon monoxide transfer factor; GOLD: Global Initiative for Obstructive Lung disease; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; IC: inspiratory capacity; Paco₂: arterial carbon dioxide partial pressure; BMI: body mass index.

Arterial oxygen partial pressure breathing room air was also a strong predictor of survival in this cohort. This is consistent with the findings of several previous studies, in which PaO₂ values were positively associated with survival, both in COPD patients who were on LTOT [18, 23, 42] and those who were not [42]. Although some authors have failed to identify such an association in the past [8, 22], most of the latter studies were conducted in smaller, often non-general COPD populations and PaO₂ was sometimes measured on supplementary oxygen, which could explain discrepant findings. In the present dataset, only 26% of the variance in PaO₂ was explained by other lung function parameters. This supports the concept that PaO₂ reflects an integration of factors, including ventilation perfusion mismatch and cardiac output, neither of

TABLE 4 Predictors of mortality in the total chronic obstructive pulmonary disease population, according to the multivariate Cox regression analysis

	HR (95% CI)	p-value
Age years	1.030 (1.004–1.056)	0.021
PaO₂ kPa	0.851 (0.748–0.969)	0.015
Tlco % pred	0.971 (0.957–0.984)	<0.001
FEV₁ % pred	1.016 (0.974–1.060)	0.463
FVC % pred	0.977 (0.950–1.004)	0.090
FEV₁/FVC	0.988 (0.944–1.033)	0.582
RV % pred	0.987 (0.975–1.001)	0.055
FRC % pred	1.021 (0.998–1.045)	0.078
TLC % pred	1.011 (0.979–1.044)	0.507
IC/TLC %	2.009 (0.378–3.451)	0.628
Paco₂ kPa	0.991 (0.798–1.230)	0.932
BMI kg·m⁻²	1.006 (0.973–1.041)	0.710

Carbon monoxide transfer factor (Tlco) % pred and forced expiratory volume in 1 s (FEV₁) % pred entered the analysis as continuous variables. PaO₂: arterial oxygen partial pressure; FVC: forced vital capacity; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; IC: inspiratory capacity; Paco₂: arterial carbon dioxide partial pressure; BMI: body mass index.

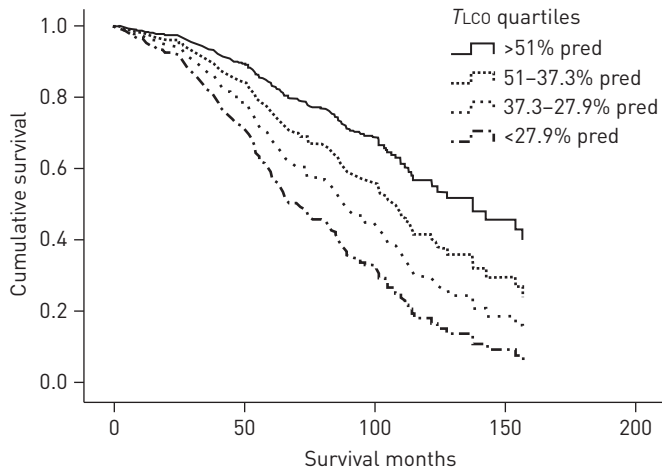


FIGURE 1 The Kaplan–Meier survival curves, adjusted for age, arterial oxygen partial pressure, Global Initiative for Chronic Obstructive Lung Disease classification, forced vital capacity (FVC) % pred, forced expiratory volume in 1 s to FVC ratio, total lung capacity (TLC) % pred, functional residual capacity % pred, inspiratory capacity to TLC ratio, residual volume % pred, body mass index and arterial carbon dioxide partial pressure for the four population groups, categorised by carbon monoxide transfer factor (TLCO) % pred quartiles.

which are well captured by conventional lung function measurements (airflow, lung volumes and gas transfer) but which may have implications for survival since cardiovascular morbidity and mortality is common in COPD [5].

Several parameters were not independently associated with survival in the current study. FEV₁ was higher among survivors, but this difference was significant only in the univariate analysis, indicating that TLCO is a better prognostic indicator. Although there are previous studies where FEV₁ was identified as a predictor of survival in COPD [3, 6, 43], several others have had findings similar to ours, since they failed to find such an association [9, 12, 24]. Furthermore, a recent review concluded that FEV₁ can probably predict mortality better as a component of the BODE (BMI, airflow obstruction, dyspnoea and exercise tolerance) index, than as an individual parameter [33]. CASANOVA *et al.* [14] identified the IC/TLC ratio (or “inspiratory fraction”) as a predictor of mortality in a study which included a large number of COPD outpatients; however, TLCO was not measured in that cohort. In the only study in which the prognostic value of IC/TLC was assessed in

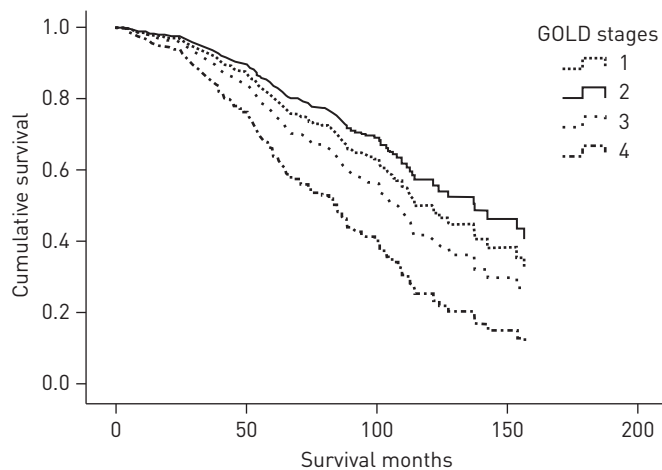


FIGURE 2 The Kaplan–Meier survival curves, adjusted for age, arterial oxygen partial pressure, carbon monoxide transfer factor % pred quartiles, forced vital capacity (FVC) % pred, forced expiratory volume in 1 s to FVC ratio, total lung capacity (TLC) % pred, functional residual capacity % pred, inspiratory capacity to TLC ratio, residual volume % pred, body mass index and arterial carbon dioxide partial pressure for the four population groups, categorised by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages. Survival only differed significantly between GOLD stage II and IV ($p=0.04$).

combination with transfer factor, $TLCO$ and not the inspiratory fraction was identified as an independent predictor of mortality [44], a finding which is confirmed by our results.

As in previous studies, older age was a predictor of reduced survival [11]. With a few exceptions [15, 22], this has been a consistent finding among both general COPD populations and COPD patients receiving LTOT [2, 17, 33, 40], though recently, of COPD phenotypes identified by cluster analysis, the one with the worst survival was younger patients with severe airflow limitation, a low BMI, frequent exacerbations and low rates of cardiovascular morbidities [45]. However, the most important finding regarding age in this study is that it can predict survival independently from the stage of the disease judged by the severity of airflow obstruction.

The present findings in COPD patients can also be considered in the light of data available from the general population suggesting that vital capacity rather than airflow obstruction is associated with mortality [46]. In a large population of people undergoing lung function for a wide range of indications, $TLCO$ was the most powerful predictor of survival [47]. This study also observed some variation in the predictive power of lung function parameters depending on the equation used to generate predicted values, though it is unlikely that this would have significantly altered the present findings.

Methodological issues

The study was based on prospectively collected comprehensive clinical data from patients under hospital care for management of their COPD. Other studies in this area have tended to measure only a limited selection of lung function tests (e.g. in the ECLIPSE trial gas transfer was not measured) [25, 35], to have had highly selected populations (e.g. the “medical” arm of the NETT trial) [2], or to include small cohorts only [11, 44]. The single centre approach has minimised bias regarding different patient populations and various measurement techniques that might have occurred in multicentre cohorts. Usual clinical practice was for patients to undergo routine comprehensive lung function assessment, including blood gas analysis, so it is unlikely that the results are biased by any specific indication for lung function testing.

The use of the UK National Health Service central data spine allowed us to establish the vital status of all participants. Data on cause of death were not available which might have allowed us to refine causal hypotheses linking lung function to mortality. As described above, an issue in previous studies of factors associated with survival in COPD has been one of the generalisability of the population. We studied a hospital clinic population likely to have a predominance of emphysema. This might have influenced the association between gas transfer measurements and survival, since there is an established correlation between emphysema severity and $TLCO$. Some caution is needed in extrapolating outcomes to patients with milder disease, but the findings are likely to be applicable to secondary care patients in general.

We chose to define exacerbations as episodes of worsening of disease sufficient to cause patients to seek medical assistance and receive a prescription for antibiotics. This definition can, to some extent, be criticised as dependent on behaviour but has the merit of incorporating an element of “clinical significance”. Techniques such as diary cards have been developed and this remains an area of controversy [48] but, to date, no consensus exists in the literature as to which is the “gold standard”. It seems unlikely that a different definition would have caused any systematic difference in the results obtained.

Patients were diagnosed with COPD on clinical grounds, including an FEV_1/FVC ratio of <0.7 . The lower limit of normal for this ratio is now considered to be a more reliable threshold for diagnosing airflow obstruction. However, since the fixed ratio was the one that was used when patients were being diagnosed initially and entered onto the COPD database it would be inappropriate to change this retrospectively. In addition, the relatively small number of patients with mild airflow obstruction, where the risk of misclassification is highest, makes this unlikely to jeopardise the findings of the study.

The present study compares the prognostic power of different lung function tests in predicting mortality. The Medical Research Council dyspnoea score was not recorded systematically so it is not possible to calculate the ADO (age, dyspnoea and obstruction) score or BODE score (the latter also requires a walking distance to be measured) and direct comparison is not possible [49].

In conclusion, in a large, general COPD outpatient population where a complete range of lung function testing had been applied, gas transfer provided the best prediction of survival, together with age and PaO_2 . Spirometry, although easy to perform and low-cost, cannot offer as much information as gas transfer, which is also superior to plethysmographic lung volume measurements. An argument can therefore be made for performing measures of gas transfer in routine practice for patients with COPD to provide them with the best prognostic information, and future classifications of COPD should include $TLCO$ and not rely merely on the severity of airflow obstruction. The results may also inform trial design, suggesting that gas transfer should also be used for stratification where therapies that are intended to influence mortality are to be tested.

Acknowledgements

We would like to thank the clinical physiologists in the lung function department at Royal Brompton Hospital, London, UK who performed the tests described in this paper.

References

- 1 Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
- 2 Martinez FJ, Foster G, Curtis JL, *et al.* Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am J Respir Crit Care Med* 2006; 173: 1326–1334.
- 3 Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Clin Chest Med* 1990; 11: 555–569.
- 4 Kelly JL, Elkin SL, Fluxman J, *et al.* Breathlessness and skeletal muscle weakness in patients undergoing lung health screening in primary care. *COPD* 2013; 10: 40–54.
- 5 Shrikrishna D, Hopkinson NS. Chronic obstructive pulmonary disease: consequences beyond the lung. *Clin Med* 2012; 12: 71–74.
- 6 Antonelli Incalzi R, Fuso L, De Rosa M, *et al.* Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 2794–2800.
- 7 Gudmundsson G, Gislason T, Lindberg E, *et al.* Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity. *Respir Res* 2006; 7: 109.
- 8 Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14–20.
- 9 Schols AM, Slangen J, Volovics L, *et al.* Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791–1797.
- 10 Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. *Chest* 2003; 123: 1460–1466.
- 11 Swallow EB, Reyes D, Hopkinson NS, *et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007; 62: 115–120.
- 12 Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; 124: 459–467.
- 13 Yildiz OA, Onen ZP, Sen E, *et al.* Predictors of long-term survival in patients with chronic obstructive pulmonary disease. *Saudi Med J* 2006; 27: 1866–1872.
- 14 Casanova C, Cote C, de Torres JP, *et al.* Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 591–597.
- 15 Solanes I, Casan P, Sangesin M, *et al.* Factores de riesgo de mortalidad en la EPOC [Risk factors for mortality in chronic obstructive pulmonary disease.] *Arch Bronconeumol* 2007; 43: 445–449.
- 16 Haruna A, Muro S, Nakano Y, *et al.* CT scan findings of emphysema predict mortality in COPD. *Chest* 2010; 138: 635–640.
- 17 Nishimura K, Izumi T, Tsukino M, *et al.* Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434–1440.
- 18 Chailleux E, Fauroux B, Binet F, *et al.* Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. *Chest* 1996; 109: 741–749.
- 19 Boutou AK, Karrar S, Hopkinson NS, *et al.* Anemia and survival in chronic obstructive pulmonary disease: a dichotomous rather than a continuous predictor. *Respiration* 2013; 85: 126–131.
- 20 Divo M, Cote C, de Torres JP, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155–161.
- 21 Waschki B, Kirsten A, Holz O, *et al.* Physical activity is the strongest predictor of all-cause mortality in patients with COPD. *Chest* 2011; 140: 331–342.
- 22 Gray-Donald K, Gibbons L, Shapiro SH, *et al.* Nutritional status and mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153: 961–966.
- 23 Dallari R, Barozzi G, Pinelli G, *et al.* Predictors of survival in subjects with chronic obstructive pulmonary disease treated with long-term oxygen therapy. *Respiration* 1994; 61: 8–13.
- 24 Almagro P, Calbo E, Ochoa de Echaguen A, *et al.* Mortality after hospitalization for COPD. *Chest* 2002; 121: 1441–1448.
- 25 Celli BR, Locantore N, Yates J, *et al.* Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 185: 1065–1072.
- 26 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
- 27 Zavorsky GS, Cao J, Mayo NE, *et al.* Arterial versus capillary blood gases: a meta-analysis. *Respir Physiol Neurobiol* 2007; 155: 268–279.
- 28 Clark EH, Woods RL, Hughes JM. Effect of blood transfusion on the carbon monoxide transfer factor of the lung in man. *Clin Sci Mol Med* 1978; 54: 627–631.
- 29 Rabe KF, Hurd S, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532–555.
- 30 Miller MR, Pedersen OF. New concepts for expressing forced expiratory volume in 1 s arising from survival analysis. *Eur Respir J* 2010; 35: 873–882.
- 31 Miller MR, Pedersen OF, Dirksen A. A new staging strategy for chronic obstructive pulmonary disease. *Int J Chron Obstr Pulmon Dis* 2007; 2: 657–663.
- 32 Hughes JMB, Pride NB. Examination of the carbon monoxide diffusing capacity (DICO) in relation to its Kco and Va components. *Am J Respir Crit Care Med* 2012; 186: 132–139.
- 33 Celli BR, Cote CG, Lareau SC, *et al.* Predictors of survival in COPD: more than just the FEV1. *Respir Med* 2008; 102: Suppl. 1, S27–S35.
- 34 Celli BR. Predictors of mortality in COPD. *Respir Med* 2010; 104: 773–779.

- 35 Vestbo J, Anderson W, Coxson HO, *et al.* Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008; 31: 869–873.
- 36 Budweiser S, Jorres RA, Riedl T, *et al.* Predictors of survival in COPD patients with chronic hypercapnic respiratory failure receiving noninvasive home ventilation. *Chest* 2007; 131: 1650–1658.
- 37 Bang KM, Gergen PJ, Kramer R, *et al.* The effect of pulmonary impairment on all-cause mortality in a national cohort. *Chest* 1993; 103: 536–540.
- 38 Coleta KD, Silveira LV, Lima DF, *et al.* Predictors of first-year survival in patients with advanced COPD treated using long-term oxygen therapy. *Respir Med* 2008; 102: 512–518.
- 39 Lima DF, Dela Coleta K, Tanni SE, *et al.* Potentially modifiable predictors of mortality in patients treated with long-term oxygen therapy. *Respir Med* 2011; 105: 470–476.
- 40 Pinto-Plata VM, Cote C, Cabral H, *et al.* The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004; 23: 28–33.
- 41 Dubois P, Machiels J, Smeets F, *et al.* CO transfer capacity as a determining factor of survival for severe hypoxaemic COPD patients under long-term oxygen therapy. *Eur Respir J* 1990; 3: 1042–1047.
- 42 MacNee W. Predictors of survival in patients treated with long-term oxygen therapy. *Respiration* 1992; 59: Suppl. 2, 5–7.
- 43 Domingo-Salvany A, Lamarca R, Ferrer M, *et al.* Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 680–685.
- 44 Moore AJ, Soler RS, Cetti EJ, *et al.* Sniff nasal inspiratory pressure *versus* IC/TLC ratio as predictors of mortality in COPD. *Respir Med* 2010; 104: 1319–1325.
- 45 Burgel PR, Roche N, Paillasseur JL, *et al.* Clinical COPD phenotypes identified by cluster analysis: validation with mortality. *Eur Respir J* 2012; 40: 495–496.
- 46 Burney PGJ, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. *Thorax* 2011; 66: 49–54.
- 47 Ward H, Cooper B, Miller MR. Validation of lung function prediction equations from patient survival data. *Eur Respir J* 2012; 39: 1181–1187.
- 48 Quint JK, Donaldson GC, Hurst JR, *et al.* Predictive accuracy of patient-reported exacerbation frequency in COPD. *Eur Respir J* 2011; 37: 501–507.
- 49 Puhan MA, Garcia-Aymerich J, Frey M, *et al.* Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009; 374: 704–711.