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Lung function indices for predicting mortality in chronic obstructive pulmonary disease

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130 character summary: Diffusion capacity not GOLD stage is the most powerful predictor of survival in patients with COPD

Key Words COPD, Lung function, survival, hypoxia, gas transfer

ABSTRACT (193 words)

Background: Chronic Obstructive Pulmonary Disease (COPD) is characterized by high morbidity and mortality. It remains unknown which aspect of lung function carries the most prognostic information and if simple spirometry is sufficient.

Methods: 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, carbon monoxide diffusion capacity and arterial blood gases. Variables univariately associated with survival were entered into a multivariate Cox proportional hazard model.

Results: 604 patients were included (mean age 61.9±9.7 years, forced expiratory volume in 1 second 37±18.1 %predicted, 62.9% men); 229(37.9%) died during a median follow-up of 83 months. Median survival was 91.9(80.8-103) months with survival rates at 3 and 5 years 0.83 and 0.66, respectively. Carbon monoxide diffusion capacity %predicted quartiles [(best quartile (>51%): HR=: 0.33; 95% CI: 0.96-0. and second quartile (51-37.3%): HR=0.52, 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.

Conclusion: Measurement of diffusion capacity provides additional prognostic information compared to spirometry in patients under hospital follow-up and could be considered routinely.

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem worldwide. 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 various severity. A range of pulmonary function tests are 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 endpoint 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 extra-pulmonary factors has been investigated. Parameters of lung function and particularly forced expiratory volume in 1 second (FEV_1)[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 dyspnea[17], anemia[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 non-invasive mechanical ventilation[6, 22, 23] and patients during or immediately after hospitalization 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 that had been prospectively entered into a clinical audit database, were analyzed 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 FEV_1 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 III or IV), chronic renal failure, peripheral vascular disease or history of malignancy. The Royal Brompton, Harefield and NHLI 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 DLco gas analyzer 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] PaO_2 and $PaCO_2$ were measured in arterialized earlobe capillary samples and arterio-alveolar oxygen gradient (A-a gradient) calculated. Arterialized 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 FEV_1, FVC, FEV_1/FVC ratio, Total Lung Capacity (TLC), Functional Residual Capacity (FRC), Residual Volume (RV) and Inspiratory Capacity to TLC ratio (IC/TLC) were recorded. The values of carbon

monoxide diffusion capacity (DLco) 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 dyspnea, 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 NHS 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 are presented as mean value±1 standard deviation (SD) or as mean percent predicted value±1 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: a) 0-1/year, b) 2-4/year, c) >4/year. Differences between survivors and non-survivors in demographic and clinical variables were assessed utilizing 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 FEV_1 and DLco were entered in the survival analysis as categorical variables (GOLD stages and DLco 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 DLco quartiles. Corresponding hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each independent predictor. The median survival (with the corresponding 95% CIs) and the overall survival rates were estimated, using the Kaplan-Meier method. Correlation analysis was used to identify factors associated with PaO_2. 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 long term oxygen therapy (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 follow-up for the total population was 80±49.8 months, while the median was 83.1 (6.6-210.8) months. 229 patients (37.9%) died during the follow up period. Median 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), FEV_1 %predicted (p<0.001), FVC %predicted (p<0.001), FEV_1/FVC ratio (p<0.001), DLco %predicted (p=0.015), IC/TLC % (p<0.001) and PaO_2 at room air (p=0.001) and a lower proportion received LTOT (p<0.001), compared to non-survivors. Conversely, TLC %predicted (p=0.015), FRC %predicted (p<0.001), RV %predicted (p<0.001) and $PaCO_2$ (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, (A-a) gradient, smoking status, 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, DL_{CO} %predicted quartiles and PaO_2 (Table 3). When the lowest DLco %predicted quartile (<27.9) was used as reference, patients with DLco %predicted >51 and those with DLco %predicted between 51 and 37.3 had significant lower mortality risk than those with DLco %predicted <27.9. In addition, Table 4 presents these results with DLco %predicted and FEV_1 %predicted treated as continuous variables. Figure 1 presents the Kaplan Meier survival curves, adjusted for age, PaO_2, GOLD stages, FVC %predicted, FEV_1/FVC, TLC %predicted, FRC %predicted, IC/TLC, RV

%predicted, BMI and $PaCO_2$ for the four population groups, categorized by DLco %predicted quartiles. By contrast, Figure 2 presents the Kaplan Meier survival curves, adjusted for age, PaO_2, DLco %predicted quartiles, FVC %predicted, FEV_1/FVC, TLC %predicted, FRC %predicted, IC/TLC, RV %predicted, BMI and $PaCO_2$ for the four population groups categorized by GOLD stages. Figure E1 in the online supplement shows receiver operating curves, for survival prediction comparing DLco %predicted, FEV_1 %predicted, IC/TLC, and FEV_1/FVC ratio. DLco %predicted 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 supplement (Table E1, E2). The results in this population were similar, with DLco %predicted again the strongest predictor of survival.

Factors associated with PaO_2

All recorded demographic and clinical parameters were investigated to identify potential determinants of PaO_2. Correlation analysis revealed positive, but weak associations between PaO_2 and FEV_1 %predicted (r=0.25, p<0.001), DLco %predicted (r=0.29, p<0.001) and IC/TLC (r=0.23, p<0.001), and a moderate negative correlation between PaO_2 and $PaCO_2$ (r=-0.47, p<0.001). When these variables were entered in a multivariate regression analysis model, only $PaCO_2$ (beta=-0.45, p<0.001) and DLco %predicted (beta=0.28, p<0.001) were retained together explaining only 26% of the variance in PaO_2

values in the study population: PaO_2= -0.719 ($PaCO_2$) + 0.018 (DLco %predicted) + 12.431

DISCUSSION

The main finding of the present study was that in stable outpatients with COPD DLco %predicted and PaO_2 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 wield 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 characterized by airflow obstruction due to a mixture of small airways disease and lung parenchymal destruction.[29] FEV_1 and FEV_1/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 transfer coefficient (Kco) and alveolar volume (V_A), DLco 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 edema and mitral stenosis, could also result in a reduction in DLco.[32] These effects of both pulmonary circulation abnormalities and possibly sub-clinical cardiac pathology on DLco values, could partially explain its superiority as a prognostic factor compared to FEV_1 or plethysmographic lung volumes.

To the authors' knowledge, this is the first study identifying DLco %predicted 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 DLco[18, 23, 36-39]. Two smaller studies have previously reported a correlation between diffusion capacity and survival in stable COPD patients but only in univariate and not multivariate analysis[15, 16] Martinez *et al.* studied COPD patients who were randomized to the medical arm of the National Treatment Emphysema Trial (NETT) and found no association between DLco %predicted and survival.[2] 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 sub-populations, such as patients receiving LTOT or non-invasive mechanical ventilation.[40, 41]

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 where PaO_2 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 PaO_2 was sometimes measured on supplementary oxygen which could explain discrepant findings. In the present dataset only 26% of the variance in PaO_2 was explained by other lung function parameters. This supports the concept that PaO_2 reflects an integration of factors including ventilation perfusion mismatch and cardiac output, neither of 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. FEV_1 was higher among survivors, but this difference was significant only in the univariate analysis, indicating that DLco is a better prognostic indicator. Although there are previous studies where FEV_1 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 FEV_1 can probably predict mortality better as a component of the BODE index, than as an individual parameter.[33] Casanova *et al*. 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, DLco was not measured in that cohort.[14] In

the only study where the prognostic value of IC/TLC was assessed in combination with diffusion capacity, DLco 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,[11] older age was a predictor of reduced survival. 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, DLco 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 center approach has minimized bias regarding different patient populations and various measurement techniques that might have occurred in multicenter 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 DLco. 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 criticized as dependent on behavior 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 jeopardize the findings of the study.

The present study compares the prognostic power of different lung function tests in predicting mortality. MRC dyspnea score was not recorded systematically so it is not possible to calculate the ADO 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 DLco 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.

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REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Abdulhak AB, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FGR, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo J-P, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KMV, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope

CA, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh P-H, Yip P, Zabetian A, Zheng Z-J, Lopez AD, Murray CJL. 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. *The Lancet* 2012: 380(9859): 2095-2128.

2. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, DeCamp MM, Benditt J, Sciurba F, Make B, Mohsenifar Z, Diaz P, Hoffman E, Wise R, for the NETT Research Group. Predictors of Mortality in Patients with Emphysema and Severe Airflow Obstruction. *Am J Respir Crit Care Med* 2006: 173(12): 1326-1334.

3. Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Clinics in chest medicine* 1990: 11(3): 555-569.

4. Kelly JL, Elkin SL, Fluxman J, MI P, Soljak M, NS H. Breathlessness and skeletal muscle weakness in patients undergoing lung health screening in primary care. *COPD: Journal Of Chronic Obstructive Pulmonary Disease* 2013: 10(1).

5. Shrikrishna D, Hopkinson NS. Chronic obstructive pulmonary disease: consequences beyond the lung. *Clin Med* 2012: 12(1): 71-74.

6. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997: 10(12): 2794-2800.

7. Gudmundsson G, Gislason T, Lindberg E, Hallin R, Ulrik CS, Brondum E, Nieminen MM, Aine T, Bakke P, Janson C. 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(1): 14-20.

9. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998: 157(6 Pt 1): 1791-1797.

10. Chailleux E, Laaban J-P, 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(5): 1460-1466.

11. Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ, Moore AJ, Moxham J, Polkey MI. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007: 62(2): 115-120.

12. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003: 124(2): 459-467.

13. Yildiz OA, Onen ZP, Sen E, Gulbay BE, Kose K, Saryal S, Karabiyikoglu G. Predictors of long-term survival in patients with chronic

obstructive pulmonary disease. *Saudi medical journal* 2006: 27(12): 1866-1872.

14. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, Celli BR. Inspiratory-to-Total Lung Capacity Ratio Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2005: 171(6): 591-597.

15. Solanes I, Casan P, Sangenis M, Calaf N, Giraldo B, Guell R. [Risk factors for mortality in chronic obstructive pulmonary disease]. *Archivos de bronconeumologia* 2007: 43(8): 445-449.

16. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, Hirai T, Niimi A, Nishimura K, Chin K, Mishima M. CT scan findings of emphysema predict mortality in COPD. *Chest* 2010: 138(3): 635-640.

17. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002: 121(5): 1434-1440.

18. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. *Chest* 1996: 109(3): 741-749.

19. Boutou AK, Karrar S, Hopkinson NS, Polkey MI. Anemia and Survival in Chronic Obstructive Pulmonary Disease: A Dichotomous Rather than a Continuous Predictor. *Respiration* 2012.

20. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, Celli B, Group ftBC. Comorbidities and Risk of Mortality in Patients with Chronic Obstructive

Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine* 2012: 186(2): 155-161.

21. Waschki B, Kirsten A, Holz O, Müller K-C, Meyer T, Watz H, Magnussen H. Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD. *Chest* 2011: 140(2): 331-342.

22. Gray-Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996: 153(3): 961-966.

23. Dallari R, Barozzi G, Pinelli G, Merighi V, Grandi P, Manzotti M, Tartoni PL. Predictors of survival in subjects with chronic obstructive pulmonary disease treated with long-term oxygen therapy. *Respiration* 1994: 61(1): 8-13.

24. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality After Hospitalization for COPD. *Chest* 2002: 121(5): 1441-1448.

25. Celli BR, Locantore N, Yates J, Tal-Singer R, Miller BE, Bakke P, Calverley P, Coxson H, Crim C, Edwards LD, Lomas DA, Duvoix A, MacNee W, Rennard S, Silverman E, Vestbo J, Wouters E, Agustí A, Investigators ftE. Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine* 2012: 185(10): 1065-1072.

26. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. 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. *The European respiratory journal Supplement* 1993: 16: 5-40.

27. Zavorsky GS, Cao J, Mayo NE, Gabbay R, Murias JM. Arterial versus capillary blood gases: A meta-analysis. *Respiratory physiology & neurobiology* 2007: 155(3): 268-279.

28. Clark EH, Woods RL, Hughes JM. Effect of blood transfusion on the carbon monoxide transfer factor of the lung in man. *Clinical science and molecular medicine* 1978: 54(6): 627-631.

29. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. *Am J Respir Crit Care Med* 2007: 176(6): 532-555.

30. Miller MR, Pedersen OF. New concepts for expressing forced expiratory volume in 1 s arising from survival analysis. *European Respiratory Journal* 2010: 35(4): 873-882.

31. Miller MR, Pedersen OF, Dirksen A. A new staging strategy for chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease* 2007: 2(4): 657-663.

32. Hughes JMB, Pride NB. Examination of the Carbon Monoxide Diffusing Capacity (DlCO) in Relation to Its Kco and Va Components. *American Journal of Respiratory and Critical Care Medicine* 2012: 186(2): 132-139.

33. Celli BR, Cote CG, Lareau SC, Meek PM. Predictors of Survival in COPD: more than just the FEV1. *Respir Med* 2008: 102 Suppl 1: S27-35.

34. Celli BR. Predictors of mortality in COPD. *Respir Med* 2010: 104(6): 773-779.

35. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, Hagan G, Knobil K, Lomas DA, MacNee W, Silverman EK, Tal-Singer R, investigators obotE. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *European Respiratory Journal* 2008: 31(4): 869-873.

36. Budweiser S, Jorres RA, Riedl T, Heinemann F, Hitzl AP, Windisch W, Pfeifer M. Predictors of survival in COPD patients with chronic hypercapnic respiratory failure receiving noninvasive home ventilation. *Chest* 2007: 131(6): 1650-1658.

37. Bang KM, Gergen PJ, Kramer R, Cohen B. The effect of pulmonary impairment on all-cause mortality in a national cohort. *Chest* 1993: 103(2): 536-540.

38. Coleta KD, Silveira LV, Lima DF, Rampinelli EA, Godoy I. Predictors of first-year survival in patients with advanced COPD treated using long-term oxygen therapy. *Respir Med* 2008: 102(4): 512-518.

39. Lima DF, Dela Coleta K, Tanni SE, Silveira LV, Godoy I. Potentially modifiable predictors of mortality in patients treated with long-term oxygen therapy. *Respir Med* 2011: 105(3): 470-476.

40. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004: 23(1): 28-33.

41. Dubois P, Machiels J, Smeets F, Delwiche JP, Lulling J. CO transfer capacity as a determining factor of survival for severe hypoxaemic COPD patients under long-term oxygen therapy. *Eur Respir J* 1990: 3(9): 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, Garcia-Aymerich J, Alonso J, Felez M, Khalaf A, Marrades RM, Monso E, Serra-Batlles J, Anto JM. Health-related Quality of Life and Mortality in Male Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2002: 166(5): 680-685.

44. Moore AJ, Soler RS, Cetti EJ, Amanda Sathyapala S, Hopkinson NS, Roughton M, Moxham J, Polkey MI. Sniff nasal inspiratory pressure versus IC/TLC ratio as predictors of mortality in COPD. *Respir Med* 2010: 104(9): 1319-1325.

45. Burgel P-R, Roche N, Paillasseur J-L, Tillie-Leblond I, Chanez P, Escamilla R, Court-Fortune I, Perez T, Carré P, Caillaud D. Clinical COPD phenotypes identified by cluster analysis: validation with mortality. *European Respiratory Journal* 2012: 40(2): 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(1): 49-54.

47. Ward H, Cooper B, Miller MR. Validation of lung function prediction equations from patient survival data. *European Respiratory Journal* 2012: 39(5): 1181-1187.

48. Quint JK, Donaldson GC, Hurst JR, Goldring JJP, Seemungal TR, Wedzicha JA. Predictive accuracy of patient-reported exacerbation frequency in COPD. *European Respiratory Journal* 2011: 37(3): 501-507.

49. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Agustí AG, Gómez FP, Rodríguez-Roisín R, Moons KGM, Kessels AG, Held U. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *The Lancet* 2009: 374(9691): 704-711.

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
FEV_1 (%predicted)	37±18.1
FVC (%predicted)	84.5±22.4
FEV_1/FVC	34.7±12.3
GOLD classification (%)	
Stage I	2.3
Stage II	17.0
Stage III	28.4
Stage IV	52.2
TLC (%predicted)	124.9±18.4
RV (%predicted)	205.1±58.4
IC/TLC (%)	26.9±8.8
FRC (% predicted)	172.7±38.5
DLco (%predicted)	40.8±18
PaO_2 (KPa)	9.4±1.4
$PaCO_2$ (KPa)	5.2±0.9
(A-a) gradient (KPa)	5.1±1.3
LTOT (%)	17.1
Current smokers (%)	13.2
Pack-years	43.8±23
Exacerbations (%)	
0-1/year	39.1
2-4/year	42.7
>4/year	18.2

n=604. BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in 1 second; 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; DLco; Carbon Monoxide Transfer Factor; PaO_2: arterial Oxygen Partial Pressure; $PaCO_2$: arterial Carbon Dioxide Partial Pressure; (A-a) gradient: alveolar-arterial Oxygen gradient; LTOT: Long Term Oxygen Treatment

Table 2. Differences between survivors and non-survivors

	Survivors (n=375)	Non-survivors (n=229)	*p*
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*
FEV_1 %predicted	40.6±18.8	30.9±15	*<0.001*
FVC %predicted	88.4±22	78.2±21.6	*<0.001*
FEV_1/FVC	36.4±12.8	31.8±11	*<0.001*
GOLD classification (%)			
Stage I	3.2	0.9	*<0.001*
Stage II	22.7	7.4	
Stage III	33	20.5	
Stage IV	41.1	71.2	
DLco % quartiles			
Best quartile (>51)	31.3	13.9	*<0.001*
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	
DLco %predicted	44.7±18.4	34.1±15.2	*<0.001*
TLC %predicted	123.4±17	127.5±20.5	*0.015*
FRC %predicted	166.1±35.3	184.4±41.1	*<0.001*
RV %predicted	195.6±53.2	220.9±63.1	*<0.001*
IC/TLC %predicted	28.8±8.6	23.5±8	*<0.001*
PaO_2 (KPa)	9.6±1.3	9.2±1.6	*0.001*
$PaCO_2$ (KPa)	5.1±0.7	5.4±1	*0.003*

(A-a) 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	
Pack-years	45.6±25.1	41.1±19.4	NS
Exacerbations (%)			
0-1/year	40.3	37.1	
2-4/year	40	47.2	NS
>4/year	19.7	15.7	

BMI: Body Mass Index; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; RV: Residual Volume; IC: Inspiratory Capacity; DLco; Carbon monoxide diffusion capacity; PaO_2: arterial Oxygen Partial Pressure; $PaCO_2$: arterial Carbon Dioxide Partial Pressure; (A-a) gradient: alveolar-arterial Oxygen gradient; LTOT: Long Term Oxygen Treatment

Table 3. Predictors of mortality in the total COPD population, according to the multivariate Cox regression analysis.

	HR	95% CI	*p*
Age (years)	1.034	1.009-1.059	*0.007*
PaO_2 (KPa)	0.860	0.755-0.979	*0.023*
DLco %predicted			*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	reference	-
GOLD stages			*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	reference	-
FVC %predicted	0.989	0.969-1.010	*0.250*
FEV_1/FVC	1.015	0.994-1.037	*0.170*
RV %predicted	0.988	0.975-1.051	*0.079*
FRC %predicted	1.023	0.999-1.048	*0.057*
TLC %predicted	1.008	0.976-1.041	*0.633*
IC/TLC %	2.15	0.37-3.293	*0.418*
$PaCO_2$ (KPa)	0.985	0.796-1.218	*0.887*
BMI (kg/m^2)	1.009	0.970-1.036	*0.903*

PaO_2: arterial Oxygen Partial Pressure; DLco; Carbon Monoxide Diffusion Capacity; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; RV: Residual Volume; FRC: Functional Residual Capacity; TLC: Total Lung Capacity; IC: Inspiratory Capacity; $PaCO_2$: arterial Carbon Dioxide Partial Pressure; BMI: Body Mass Index

Table 4. Predictors of mortality in the total COPD population, according to the multivariate Cox regression analysis (DLco %predicted and FEV_1 %predicted entered the analysis as continuous variables)

	HR	95% CI	*p*
Age (years)	1.030	1.004-1.056	*0.021*
PaO_2 (KPa)	0.851	0.748-0.969	*0.015*
DLco %predicted	0.971	0.957-0.984	*<0.001*
FEV_1 %predicted	1.016	0.974-1.060	*0.463*
FVC %predicted	0.977	0.950-1.004	*0.090*
FEV_1/FVC	0.988	0.944-1.033	*0.582*
RV %predicted	0.987	0.975-1.001	*0.055*
FRC %predicted	1.021	0.998-1.045	*0.078*
TLC %predicted	1.011	0.979-1.044	*0.507*
IC/TLC %	2.009	0.378-3.451	*0.628*
$PaCO_2$ (KPa)	0.991	0.798-1.230	*0.932*
BMI (kg/m^2)	1.006	0.973-1.041	*0.710*

PaO_2: arterial Oxygen Partial Pressure; DLco; Carbon Monoxide Diffusion Capacity; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; RV: Residual Volume; FRC: Functional Residual Capacity; TLC: Total Lung Capacity; IC: Inspiratory Capacity; $PaCO_2$: arterial Carbon Dioxide Partial Pressure; BMI: Body Mass Index

FIGURE LEGENDS

Figure 1 The Kaplan Meier survival curves, adjusted for age, PaO_2, GOLD stages, FVC %predicted, FEV_1/FVC, TLC %predicted, FRC %predicted, IC/TLC, RV %predicted, BMI and $PaCO_2$ for the four population groups, categorized by DLco %predicted quartiles.

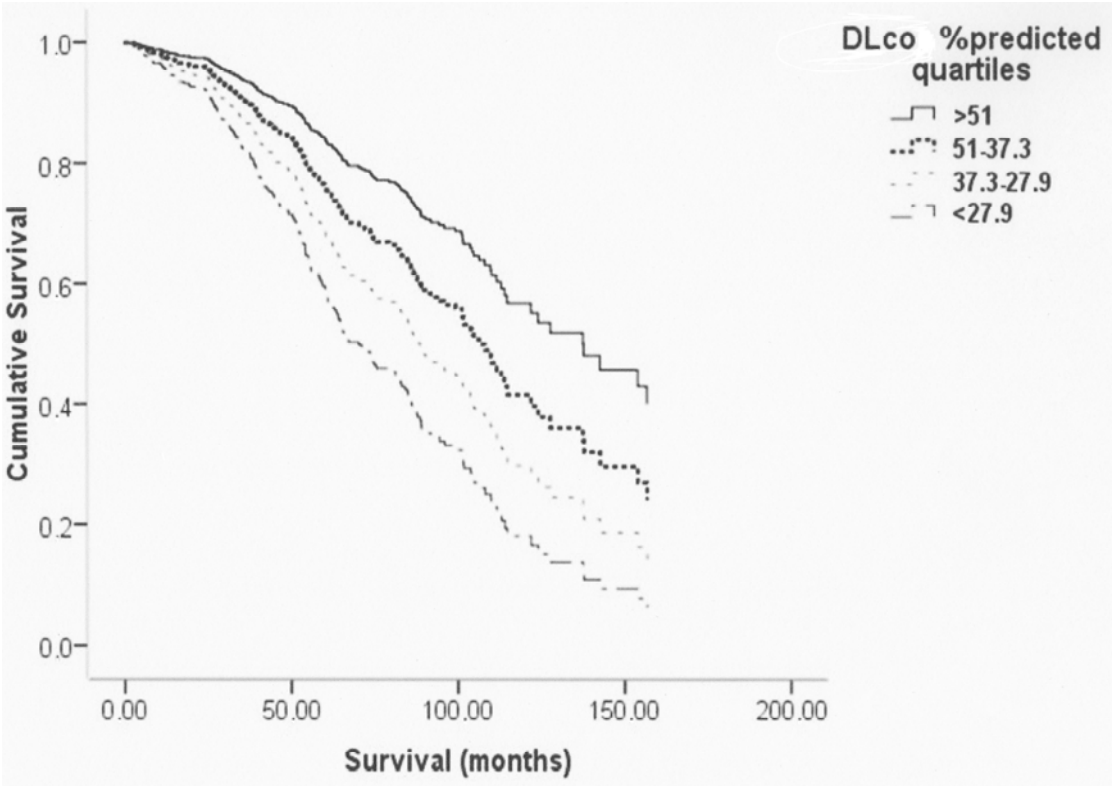
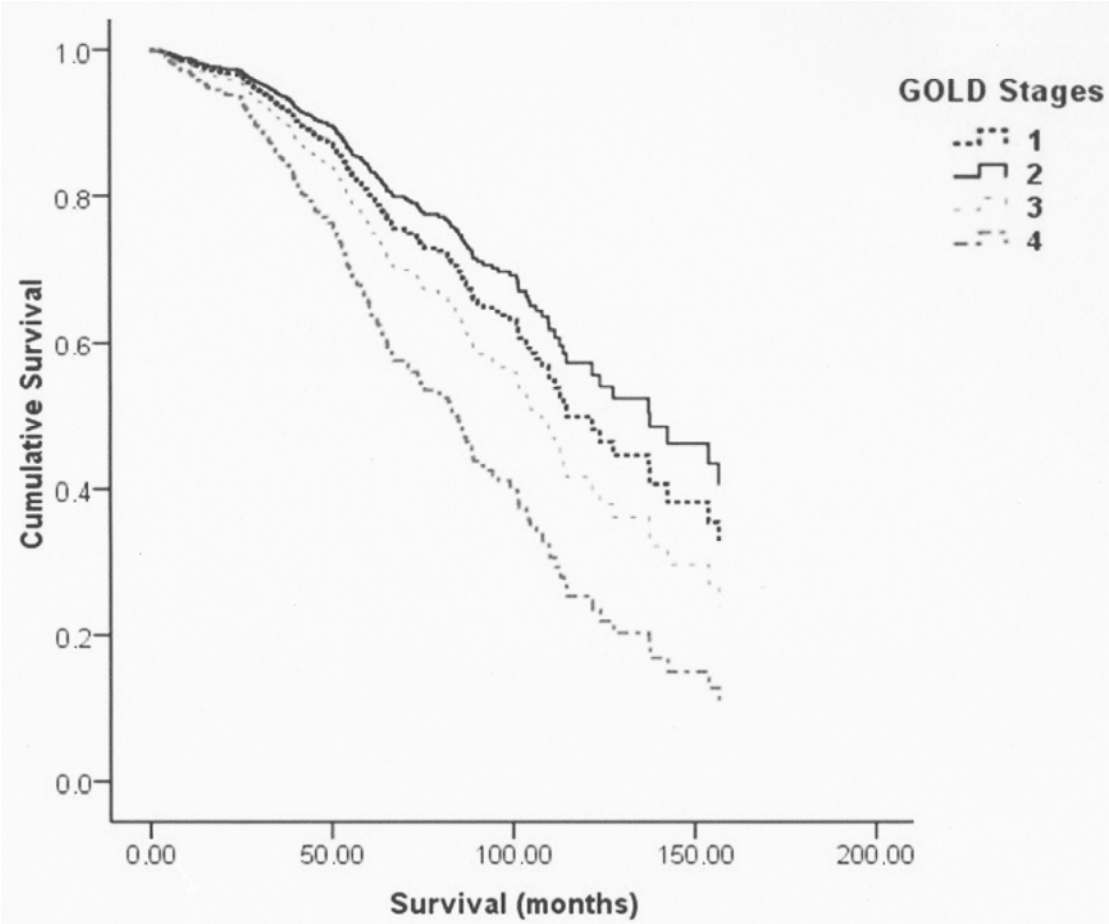


Figure 2 The Kaplan Meier survival curves, adjusted for age, PaO_2, DLco %predicted quartiles, FVC %predicted, FEV_1/FVC, TLC %predicted, FRC %predicted, IC/TLC, RV %predicted, BMI and $PaCO_2$ for the four population groups categorized by GOLD stages. Survival only differed significantly between GOLD stage II and IV (p=0.04).


GOLD Stages
1
2
3
4
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
50.00
100.00
150.00
200.00
Survival (months)