Disproportionally impaired diffusion capacity relative to airflow limitation in COPD

Naoya Tanabe[1*†], Chin Kook Rhee[2*], Susumu Sato[1], Shigeo Muro[1,3], Hiroshi Shima[1], Kazuya Tanimura[1], Ki-Suck Jung[4], Kwang Ha Yoo[5], Toyohiro Hirai[1]

[1] Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[2] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[3] Department of Respiratory Medicine, Nara Medical University, Nara, Japan

[4] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Medical Center, Hallym University College of Medicine, Anyang, Republic of Korea

[5] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea

*These two authors contributed equally to this study.

E-mail Addresses

Naoya Tanabe ntana@kuhp.kyoto-u.ac.jp

Chin Kook Rhee chinkook77@gmail.com

Susumu Sato ssato@kuhp.kyoto-u.ac.jp

Shigeo Muro smuro@naramed-u.ac.jp

Hiroshi Shima hirocima2469@kuhp.kyoto-u.ac.jp

Kazuya Tanimura kaztani@kuhp.kyoto-u.ac.jp

Ki-Suck Jung pulmoks@hallym.ac.kr

Kwang Ha Yoo khyou@kuh.ac.kr

Toyohiro Hirai t_hirai@kuhp.kyoto-u.ac.jp

†Corresponding author full contact details:

Name: Naoya Tanabe

Address: Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku,

Post code: 606-8507

City: Kyoto

Country: Japan

E-mail: ntana@kuhp.kyoto-u.ac.jp

Abstract (250/250)

Forced expiratory volume in 1 second (FEV_1) is a standard physiological index of chronic obstructive pulmonary disease (COPD), but reflects emphysema and vascular abnormalities less sensitively than diffusion capacity for carbon monoxide (D_{LCO}). This study tested whether a disproportionally impaired D_{LCO} relative to FEV_1 (FEV_1 z-score>-3 and D_{LCO} z-score≤-3) is a common functional COPD phenotype associated with distinct clinical and structural features and the prognosis of two cohorts. The cross-sectional analyses of the Korea COPD Subgroup Study (KOCOSS) cohort (multicenter study in Korea) included 743 males with COPD whose D_{LCO} was available. The cross-sectional and longitudinal analyses of the Kyoto University Cohort (single-center study in Japan) included 195 males with COPD who were prospectively followed for 10 years. A disproportionally impaired D_{LCO} relative to FEV_1 was observed in 29% and 31% of patients in the KOCOSS and Kyoto University cohorts, respectively. In the multivariable analysis, the disproportionally impaired D_{LCO} was associated with worse symptoms, shorter 6-minute walking distance, paraseptal and centrilobular emphysema on computed tomography, and reduced arterial oxygen and carbon dioxide pressures compared to the reference (FEV_1 z-score>-3 and D_{LCO} z-score>-3). In the multivariable Cox proportional hazard model, a higher long-term mortality was observed in the disproportionally impaired D_{LCO} group than in the reference group (hazard ratio [95% confidence interval] =3.09 [1.52-6.29]) and similar to the D_{LCO} z-score≤-3 and FEV_1 z-score≤-3 group. The disproportionally impaired D_{LCO} relative to FEV_1 is common and associated with

increased symptoms, emphysema, arterial blood gas abnormalities, and increased long-term mortality in patients with COPD.

Keywords: Chronic obstructive pulmonary disease, Emphysema, Airway, Computed tomography, Pulmonary function, Prognosis

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Declaration of interest statement

The authors report no conflicts of interest in this work.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide.[1] While the diagnosis of COPD is simply based on airflow limitation on spirometry,[2] spirometry is insufficient to capture the heterogeneous structural alterations underlying the clinical manifestations, including airway disease, emphysema, and vascular abnormalities.[3]

The single-breath lung diffusion capacity for carbon monoxide (D_{LCO}) is a noninvasive, repeatable physiological measure of the capacity of gas exchange in the alveolar space of the lungs.[4, 5] D_{LCO} is closely associated with emphysema measured on histology[6, 7] and computed tomography (CT)[8], as well as vascular abnormalities on CT.[9, 10, 11] Moreover, a lower D_{LCO} is associated with a lower arterial partial pressure of oxygen (PaO_2), exercise capacity, and poor prognosis in patients with COPD.[12, 13, 14] Even in smokers with normal spirometry, D_{LCO} may be decreased, and the decreased D_{LCO} is associated with more severe symptoms and impaired exercise capacity[15] and predicts the future development of COPD.[16] Furthermore, Balasubramanian et al.[17] recently proposed the categorization of patients with COPD based on a combination of forced expiratory volume in 1 second (FEV_1) on spirometry and D_{LCO}, and showed that an impaired D_{LCO} (≤50% of predicted) has negative effects on symptoms, exercise capacity, and exacerbation frequency, even in patients without a substantial reduction in FEV_1 (>50% of predicted). These findings suggest that functional phenotyping based on FEV_1 and D_{LCO} may improve clinical COPD management.

However, the detailed structure-function relationships and even long-term prognosis in relation to this phenotyping remain to be explored.

A disproportionally impaired D_{LCO} relative to FEV_1 was hypothesized to be a common functional phenotype associated with the distinct clinical manifestations, structural changes, and prognosis of COPD. This study aimed to identify patients with COPD presenting a disproportionally impaired D_{LCO} relative to FEV_1 in two observational cohorts: the Kyoto University Cohort (single-center study in Japan)[8, 18] and the Korea COPD Subgroup Study (KOCOSS) Cohort (multicenter study in Korea).[19, 20] Furthermore, this study tested whether this functional phenotype was associated with impairments in patient-reported outcomes and exercise capacity in the KOCOSS Cohort, and with a greater severity of emphysema on CT, abnormal arterial oxygen and carbon dioxide pressures, and increased long-term mortality in the Kyoto University Cohort.

Methods

Study design

The present study consisted of the following datasets from two independent cohorts: the cross-sectional data from the KOCOSS Cohort and the cross-sectional and longitudinal data from the Kyoto University Cohort. The KOCOSS Cohort was obtained from a multicenter prospective observational study conducted at 48 tertiary referral hospitals in the Republic of Korea beginning in 2011.[19, 20] The study protocol was approved by the Institutional Review Board of Konkuk University Medical Center (Institutional Review Board No. 177 KHH1010338), and all the hospitals obtained approval from the

Institutional Review Board committee. The Kyoto University Cohort is a single-center prospective observational study that has been conducted at the Kyoto University Hospital in Japan since 2006 using a single CT scanner with the fixed scanning conditions described below.[8, 18, 21] The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kyoto University (approval Nos. E182 and R1660-1). All participants in both the Kyoto University and KOCOSS cohorts provided written informed consent. The collaborative analysis of the two cohorts was further approved by the Ethics Committee of Kyoto University (approval No. R2033).

The inclusion criteria of the present study were as follows: (1) age 40-85 years with a smoking history of at least 10 pack-years, (2) a physician's diagnosis of COPD based on patient-reported respiratory symptoms and the presence of airflow limitation confirmed by a postbronchodilator FEV_1/forced vital capacity (FVC) ratio below the lower limit of normal (LLN), and (3) availability of postbronchodilator spirometry and D_{LCO}. D_{LCO} was adjusted by the blood hemoglobin level according to a previous report. [22] The LLN of FEV_1/FVC and z-scores and reference values of FEV_1 and FVC were obtained based on the "other" ethnic group data provided by the Global Lung Function Initiative (GLI) 2012. [23] The z-scores and reference values of D_{LCO} was also calculated using the GLI calculation system.[4] Patients with a history of lung resection surgery or other lung diseases, such as interstitial lung disease and those with alpha-1 antitrypsin

deficiency, were excluded. Because the majority (> 90%) of patients enrolled in the two cohorts were male, female patients were also excluded.

In the KCOSS Cohort, patient-reported outcomes, including the mMRC dyspnea scale, COPD assessment test (CAT), and St. George's Respiratory Questionnaire (SGRQ),[24, 25] and exercise capacity as assessed by the 6-minute walking distance (6MWD) were cross-sectionally evaluated.

In the Kyoto University Cohort, the residual volume (RV), RV to total lung capacity (TLC) ratio (RV/TLC), mMRC, emphysema and airway diseases on inspiratory CT and arterial blood gases measured in room air, including PaO_2 and partial pressure of carbon dioxide ($PaCO_2$) at baseline, were cross-sectionally evaluated. The CO transfer coefficient (Kco) that corresponds to D_{LCO} divided by alveolar volume (V_A) was also measured. Furthermore, longitudinal follow-up survival data available as of October 2019 from the Kyoto University Cohort were evaluated.

Chest CT

All subjects in the Kyoto University Cohort underwent full inspiratory CT with a peak kilovoltage of 120, a 0.5-second exposure time, and autoexposure control using an Aquilion 64 scanner (Cannon Medical; Tokyo, Japan). Images with a 0.5-mm slice thickness were reconstructed with a high spatial frequency algorithm (FC56). Using a SYNAPSE VINCENT volume analyzer (FUJIFILM Medical, Tokyo, Japan), the percentage of low attenuation regions less than -950 HU to the total lung regions (LAV%) was calculated to evaluate emphysema.[26, 27, 28] The wall area percentage (WA%), which was defined as the percentage of the wall area relative to the sum of the wall and lumen areas, was measured for the right apical and posterior basal segmental

bronchus and averaged to evaluate airway disease.[29, 30, 31] Mild and substantial paraseptal emphysema (PSE), and mild and substantial (moderate to advanced) centrilobular emphysema (CLE) were visually identified based on the Fleischner Society classification system.[32] The inter-rater variability of two pulmonologists (NT and HS) was excellent (kappa = 0.80 and 0.76 for the PSE and CLE evaluations). Substantial PSE and CLE were considered to indicate the presence of PSE and CLE in this study. In addition, the ratio of the pulmonary artery diameter to the aorta diameter (PA/Ao) was obtained by manually measuring the pulmonary and aorta diameters.[33]

Statistics

The data are reported as means ± SD, unless indicated otherwise. Statistical analyses were performed with the R program.[34] A p-value less than 0.05 was considered statistically significant. Based on the z-scores of FEV_1 and D_{LCO}, [35] the patients were categorized into the following 4 groups: (1) FEV_1 z-score > -3 and D_{LCO} z-score > -3 (reference), (2) FEV_1 z-score > -3 and D_{LCO} z-score ≤ -3 (disproportionally impaired D_{LCO}), (3) FEV_1 z-score ≤ -3 and D_{LCO} z-score > -3 (disproportionally impaired FEV_1), and (4) FEV_1 z-score ≤ -3 and D_{LCO} z-score ≤ -3 (mixed-impaired). Tukey's method was used to compare the variables among the 4 groups. Multivariable linear regression and Cox proportional hazard models were constructed and adjusted for age, height, weight, and smoking pack-years to examine the effects of the disproportionally impaired D_{LCO}, disproportionally impaired FEV_1, and mixed-impaired groups on the clinical measures and long-term outcome in comparison with the reference group. Furthermore, similar

analyses were performed by defining the 4 groups using a cut-off of 50% for the % of predicted FEV_1 and D_{LCO}.

Results

Figure 1 shows patient flowcharts for the two cohorts. In the KOCOSS Cohort, 743 male patients whose hemoglobin-adjusted D_{LCO} was available and FEV_1/FVC was below the LNN were included in the cross-sectional analysis. In the Kyoto University Cohort, of the 253 stable patients with COPD enrolled from January to December 2012, 195 male patients with an FEV_1/FVC below the LNN were included in the cross-sectional and longitudinal analyses. Table 1 shows the basic clinical data of the two cohorts.

As shown in Figure 2, approximately 47%, 30%, 5-10%, and 16% of the patients were categorized into the reference, disproportionally impaired D_{LCO}, disproportionally impaired FEV_1, and mixed-impaired groups in both cohorts, respectively (n=351/212/62/118 in the KOCOSS Cohort, and n=89/62/10/34 in the Kyoto University Cohort).

The cross-sectional analysis of the KOCOSS Cohort showed that age, smoking pack-years, mMRC≥2, CAT, and the SGRQ scores were higher while the BMI and 6-minute walking distance were lower in the disproportionally impaired D_{LCO} group, as shown in Table 2. In the multivariable analysis shown in Figure 3, compared to the reference group, the disproportionally impaired D_{LCO} was significantly associated with higher mMRC, CAT, and SGRQ scores and a lower 6MWD.

The cross-sectional analysis of the baseline data from the Kyoto University Cohort presented in Table 3 showed that age, an mMRC≥2, the prevalence of visual CT findings of CLE and PSE, and LAV% were higher while the PaO_2, and $PaCO_2$ were lower in the disproportionally impaired group than in the reference group. WA% and PA/Ao on CT did not significantly differ among the groups. In the multivariable analysis shown in Figure 4, the rates of both PSE and CLE were higher and PaO_2 and $PaCO_2$ were lower in the disproportionally impaired D_{LCO} group than in the reference group. In contrast, the rates of PSE and $PaCO_2$ in the disproportionally impaired FEV_1 and mixed-impaired groups did not significantly differ from those in the reference group.

Of the 195 male patients enrolled in the Kyoto University Cohort from 2006 to 2012, 52 had died as of October 2019. As shown in Figure 5A, the survival rate differed among the 4 groups. In Figure 5B, the percentages of respiratory disease-related deaths were 29, 36, 0, and 67% in the reference, disproportionally impaired D_{LCO}, disproportionally impaired FEV_1, and mixed-impaired groups, respectively. In the multivariable Cox proportional hazard model shown in Figure 5C, the disproportionally impaired D_{LCO} and mixed-impaired groups had similar effects on all-cause mortality (HR [95% confidence interval (CI)] = 3.09 [1.52-6.29] and 3.53[1.56-8.03], respectively), whereas the effect of the disproportionally impaired FEV_1 on all-cause mortality was not significant (HR [95% CI] = 0.91 [0.19-4.19]). The prognostic effect of the disproportionally impaired D_{LCO} was detected even after adjusting for LAV% (HR [95% CI] = 2.55 [1.21-5.34]).

Furthermore, additional analyses were performed using the % predicted FEV_1 and D_{LCO} to categorize patients into the 4 groups (see the online supplemental figures S1 and

S2). While the percentage of subjects with the disproportionally impaired D_{LCO}, defined using the z-scores of FEV_1 and D_{LCO}, was 29 and 31% in the KOCOSS and Kyoto University cohorts, the use of the % predicted value -based definition of this subtype (% of predicted $FEV_1 > 50\%$ and % of predicted $D_{LCO} \leq 50\%$) changed the percentages to 18% and 21% in the KOCOSS and Kyoto University cohorts, respectively. Nonetheless, the disproportionally impaired D_{LCO} relative to FEV_1 based on the % predicted value was significantly associated with an increase in MRC, CAT, and SGRQ scores in the KOCOSS cohort, and with increased odds ratio of the presence of PSE and CLE, lower PaO_2 and $PaCO_2$, and higher mortality in the Kyoto University Cohort.

Discussion

This study shows that a disproportionally impaired D_{LCO} relative to FEV_1 was common (approximately 30%) in patients with COPD in two cohorts from different countries. This functional subgroup presented an increased severity of symptoms, impaired quality of life and exercise capacity, greater PSE and CLE, and lower PaO_2 and $PaCO_2$ than the reference group. Furthermore, the longitudinal data collected over 10 years from the Kyoto University Cohort shows that this group exhibited a higher risk of long-term mortality. These findings highlight the clinical relevance of identifying a disproportionally impaired D_{LCO} relative to FEV_1 in COPD management.

D_{LCO} reflects emphysema more strongly than FEV_1 and predicts future emphysema progression and mortality.[12, 36] Nonetheless, FEV_1 on spirometry has been exclusively used in clinical practice and research fields until Balasubramanian et al.[17] recently showed the utility of categorizing patients with COPD based on a

combination of FEV_1 and D_{LCO}. The present data confirm and extend those previous findings by showing that the disproportionally impaired D_{LCO} is associated with worse patient-reported outcomes, an abnormal gas exchange, higher rates of PSE and CLE, and increased mortality rates in patients with COPD. In particular, the finding that the hazard ratio of mortality did not differ between the disproportionally impaired D_{LCO} and mixed-impaired groups is important, as it improves our ability to estimate the prognosis of patients with COPD.

The rates of both PSE and CLE were higher in the disproportionally impaired D_{LCO} group, while the rate of CLE, but not PSE, was higher in the disproportionally impaired FEV_1 and mixed-impaired groups than in the reference group. This result is consistent with a previous finding that a reduced in FEV_1 is associated with CLE, but not PSE.[37, 38, 39] A recent microCT study showed relatively milder small airway disease in PSE than CLE regions in explanted lungs from patients with COPD.[40] Collectively, the disproportionally impaired D_{LCO} might reflect more severe emphysema, particularly PSE, with relatively less damage to the airways in patients with COPD.

The disproportionally impaired D_{LCO} group showed a higher mortality than the reference group, even after adjusting for LAV%. An impaired diffusion capacity is associated with emphysema, pulmonary vascular abnormalities,[6, 9, 10, 11] and dysfunction of pulmonary microvascular perfusion,[41] even in patients with mild COPD. Therefore, the disproportionally impaired D_{LCO} might reflect pulmonary vascular dysfunction and might be associated with increased mortality independent of the emphysema severity.

The present data showing associations between the disproportionally impaired D_{LCO} and lower PaO_2 and $PaCO_2$, confirms a previous finding that the diffusion capacity is correlated with PaO_2.[12] Additionally, the data are the first to show that a lower D_{LCO} is associated with a lower $PaCO_2$ in patients with a relatively preserved FEV_1. This result is also consistent with a previous finding that differences in alveolar-arterial oxygen levels characterized by decreases in both $PaCO_2$ and PaO_2 precede chronic respiratory failure in patients with COPD.[13] Therefore, $PaCO_2$ may be decreased in the early stage of emphysema development and D_{LCO} impairment, and then become increased in the late stage of the disease to eventually cause chronic hypercapnic respiratory failure.

The use of two cohorts from Japan and Korea is an advantage of this study. The two cohorts consistently showed similar frequencies in the 4 groups, suggesting that the disproportionally impaired D_{LCO} relative to FEV_1 is commonly identified in patients with COPD. Interestingly, the percentage of this functional phenotype was higher than the value documented in a previous report from the COPDGene study.[17] The discrepancy might be due to the different severity between the studies as % of predicted FEV_1 in the previous study (70%) was higher than in the present two cohorts.

FEV_1/FVC decreases with age and may cause an overdiagnosis of COPD in elderly subjects.[35, 42, 43] Therefore, the present study defined the airflow limitation based on FEV_1/FVC < LNN, but not FEV_1/FVC < 0.7 (the Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria[2]). Indeed, as shown in Supplemental Figure S3, of 798 males with FEV_1/FVC <0.7 in the KOCOSS cohort, 55 males showed FEV1/FVC≥LLN, and age was higher in those with FEV_1/FVC ≥LNN than those with FEV_1/FVC <LLN.

This study has some limitations. First, although cardiac dysfunction and pulmonary hypertension may affect D_{LCO}, the present study did not examine the possible effects of these abnormalities using echocardiography and heart catheterization. However, PA/Ao, which is a good marker for pulmonary hypertension,[44] did not differ significantly between the four groups in this study. Second, the present study analyzed the data from male patients. Further studies are needed to confirm whether the findings from the present study are generalizable to female subjects.

Conclusion

In the present study, the data obtained from the Korean and Japanese cohorts show that a disproportionally impaired D_{LCO} relative to FEV_1 is a common functional phenotype in patients with COPD. The identification of this phenotype may improve our understanding of the various clinical manifestations of each individual and help non-invasively estimate the long-term prognosis of patients with COPD in daily practice.

References

1. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health. 2015 Dec;5(2):020415. doi: 10.7189/jogh.05-020415. PubMed PMID: 26755942; PubMed Central PMCID: PMCPMC4693508.
2. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J. 2017 Mar;49(3). doi: 10.1183/13993003.00214-2017. PubMed PMID: 28182564.
3. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet. 2004 Aug 21-27;364(9435):709-21. doi: 10.1016/S0140-6736(04)16900-6. PubMed PMID: 15325838.
4. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J. 2017 Sep;50(3). doi: 10.1183/13993003.00010-2017. PubMed PMID: 28893868.
5. Radovanovic D, Contoli M, Marco FD, et al. Clinical and Functional Characteristics of COPD Patients Across GOLD Classifications: Results of a Multicenter Observational Study. COPD. 2019 Aug;16(3-4):215-226. doi: 10.1080/15412555.2019.1659760. PubMed PMID: 31500459.
6. Gould GA, MacNee W, McLean A, et al. CT measurements of lung density in life can quantitate distal airspace enlargement--an essential defining feature of human emphysema. Am Rev Respir Dis. 1988 Feb;137(2):380-92. doi:

10.1164/ajrccm/137.2.380. PubMed PMID: 3341629.

7. Morrison NJ, Abboud RT, Muller NL, et al. Pulmonary capillary blood volume in emphysema. Am Rev Respir Dis. 1990 Jan;141(1):53-61. doi: 10.1164/ajrccm/141.1.53. PubMed PMID: 2297187.

8. Tanabe N, Muro S, Hirai T, et al. Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2011 Jun 15;183(12):1653-9. doi: 10.1164/rccm.201009-1535OC. PubMed PMID: 21471102.

9. Cho YH, Lee SM, Seo JB, et al. Quantitative assessment of pulmonary vascular alterations in chronic obstructive lung disease: Associations with pulmonary function test and survival in the KOLD cohort. Eur J Radiol. 2018 Nov;108:276-282. doi: 10.1016/j.ejrad.2018.09.013. PubMed PMID: 30396668.

10. Estepar RS, Kinney GL, Black-Shinn JL, et al. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. Am J Respir Crit Care Med. 2013 Jul 15;188(2):231-9. doi: 10.1164/rccm.201301-0162OC. PubMed PMID: 23656466; PubMed Central PMCID: PMCPMC3778757.

11. Matsuoka S, Washko GR, Yamashiro T, et al. Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. Am J Respir Crit Care Med. 2010 Feb 1;181(3):218-25. doi: 10.1164/rccm.200908-1189OC. PubMed PMID: 19875683; PubMed Central PMCID: PMCPMC2817812.

12. Boutou AK, Shrikrishna D, Tanner RJ, et al. Lung function indices for predicting mortality in COPD. Eur Respir J. 2013 Sep;42(3):616-25. doi:

10.1183/09031936.00146012. PubMed PMID: 23349449; PubMed Central PMCID: PMCPMC3759303.

13. Uemasu K, Sato S, Muro S, et al. Annual decline in arterial blood oxygen predicts development of chronic respiratory failure in COPD with mild hypoxaemia: A 6-year follow-up study. Respirology. 2019 Mar;24(3):262-269. doi: 10.1111/resp.13402. PubMed PMID: 30230650.

14. Santus P, Radovanovic D, Balzano G, et al. Improvements in Lung Diffusion Capacity following Pulmonary Rehabilitation in COPD with and without Ventilation Inhomogeneity. Respiration. 2016;92(5):295-307. doi: 10.1159/000448847. PubMed PMID: 27598467.

15. Kirby M, Owrangi A, Svenningsen S, et al. On the role of abnormal DL(CO) in ex-smokers without airflow limitation: symptoms, exercise capacity and hyperpolarised helium-3 MRI. Thorax. 2013 Aug;68(8):752-9. doi: 10.1136/thoraxjnl-2012-203108. PubMed PMID: 23604381.

16. Harvey BG, Strulovici-Barel Y, Kaner RJ, et al. Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. Eur Respir J. 2015 Dec;46(6):1589-1597. doi: 10.1183/13993003.02377-2014. PubMed PMID: 26541521; PubMed Central PMCID: PMCPMC4752006.

17. Balasubramanian A, MacIntyre NR, Henderson RJ, et al. Diffusing Capacity of Carbon Monoxide in Assessment of COPD. Chest. 2019 Dec;156(6):1111-1119. doi: 10.1016/j.chest.2019.06.035. PubMed PMID: 31352035.

18. Tanimura K, Sato S, Fuseya Y, et al. Quantitative Assessment of Erector Spinae Muscles in Patients with Chronic Obstructive Pulmonary Disease. Novel Chest

Computed Tomography-derived Index for Prognosis. Ann Am Thorac Soc. 2016 Mar;13(3):334-41. doi: 10.1513/AnnalsATS.201507-446OC. PubMed PMID: 26700501.

19. Lee JY, Chon GR, Rhee CK, et al. Characteristics of Patients with Chronic Obstructive Pulmonary Disease at the First Visit to a Pulmonary Medical Center in Korea: The KOrea COpd Subgroup Study Team Cohort. J Korean Med Sci. 2016 Apr;31(4):553-60. doi: 10.3346/jkms.2016.31.4.553. PubMed PMID: 27051239; PubMed Central PMCID: PMCPMC4810338.

20. Rhee CK, Kim JW, Hwang YI, et al. Discrepancies between modified Medical Research Council dyspnea score and COPD assessment test score in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:1623-31. doi: 10.2147/COPD.S87147. PubMed PMID: 26316736; PubMed Central PMCID: PMCPMC4541543.

21. Tanabe N, Sato S, Tanimura K, et al. Associations of CT evaluations of antigravity muscles, emphysema and airway disease with longitudinal outcomes in patients with COPD. Thorax. 2020 2020-08-31 00:00:00.

22. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005 Oct;26(4):720-35. doi: 10.1183/09031936.05.00034905. PubMed PMID: 16204605.

23. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. European Respiratory Journal. 2012;40(6):1324-1343. doi:

10.1183/09031936.00080312.

24. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992 Jun;145(6):1321-7. doi: 10.1164/ajrccm/145.6.1321. PubMed PMID: 1595997.

25. Choi JY, Yoon HK, Shin KC, et al. CAT Score and SGRQ Definitions of Chronic Bronchitis as an Alternative to the Classical Definition. Int J Chron Obstruct Pulmon Dis. 2019;14:3043-3052. doi: 10.2147/COPD.S228307. PubMed PMID: 31920301; PubMed Central PMCID: PMCPMC6941605.

26. Gevenois PA, De Vuyst P, de Maertelaer V, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med. 1996 Jul;154(1):187-92. doi: 10.1164/ajrccm.154.1.8680679. PubMed PMID: 8680679.

27. Shimizu K, Tanabe N, Tho NV, et al. Per cent low attenuation volume and fractal dimension of low attenuation clusters on CT predict different long-term outcomes in COPD. Thorax. 2020 Feb;75(2):116-122. doi: 10.1136/thoraxjnl-2019-213525. PubMed PMID: 31896733.

28. Shima H, Tanabe N, Sato S, et al. Lobar distribution of non-emphysematous gas trapping and lung hyperinflation in chronic obstructive pulmonary disease. Respir Investig. 2020 Jul;58(4):246-254. doi: 10.1016/j.resinv.2020.01.001. PubMed PMID: 32085990.

29. Oguma T, Hirai T, Niimi A, et al. Limitations of airway dimension measurement on images obtained using multi-detector row computed tomography. PLoS One.

2013;8(10):e76381. doi: 10.1371/journal.pone.0076381. PubMed PMID: 24116105; PubMed Central PMCID: PMCPMC3792973.

30. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med. 2000 Sep;162(3 Pt 1):1102-8. doi: 10.1164/ajrccm.162.3.9907120. PubMed PMID: 10988137.

31. Tanabe N, Oguma T, Sato S, et al. Quantitative measurement of airway dimensions using ultra-high resolution computed tomography. Respir Investig. 2018 Nov;56(6):489-496. doi: 10.1016/j.resinv.2018.07.008. PubMed PMID: 30392536.

32. Lynch DA, Austin JH, Hogg JC, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. Radiology. 2015 Oct;277(1):192-205. doi: 10.1148/radiol.2015141579. PubMed PMID: 25961632; PubMed Central PMCID: PMCPMC4613878.

33. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med. 2012 Sep 6;367(10):913-21. doi: 10.1056/NEJMoa1203830. PubMed PMID: 22938715; PubMed Central PMCID: PMCPMC3690810.

34. R Core Team. R: A Language and Environment for Statistical Computing. URL http://www.R-project.org/. 2015.

35. Quanjer PH, Pretto JJ, Brazzale DJ, et al. Grading the severity of airways obstruction: new wine in new bottles. Eur Respir J. 2014 Feb;43(2):505-12. doi: 10.1183/09031936.00086313. PubMed PMID: 23988764.

36. Mohamed Hoesein FA, Zanen P, van Ginneken B, et al. Association of the transfer

coefficient of the lung for carbon monoxide with emphysema progression in male smokers. Eur Respir J. 2011 Nov;38(5):1012-8. doi: 10.1183/09031936.00050711. PubMed PMID: 21565924.

37. Smith BM, Austin JH, Newell JD, Jr., et al. Pulmonary emphysema subtypes on computed tomography: the MESA COPD study. Am J Med. 2014 Jan;127(1):94 e7-23. doi: 10.1016/j.amjmed.2013.09.020. PubMed PMID: 24384106; PubMed Central PMCID: PMC3882898.

38. Araki T, Nishino M, Zazueta OE, et al. Paraseptal emphysema: Prevalence and distribution on CT and association with interstitial lung abnormalities. Eur J Radiol. 2015 Jul;84(7):1413-8. doi: 10.1016/j.ejrad.2015.03.010. PubMed PMID: 25868675; PubMed Central PMCID: PMCPMC4450117.

39. Park J, Hobbs BD, Crapo JD, et al. Subtyping COPD by Using Visual and Quantitative CT Imaging Features. Chest. 2020 Jan;157(1):47-60. doi: 10.1016/j.chest.2019.06.015. PubMed PMID: 31283919; PubMed Central PMCID: PMCPMC6965698.

40. Tanabe N, Vasilescu DM, Hague CJ, et al. Pathological Comparisons of Paraseptal and Centrilobular Emphysema in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2020 Sep 15;202(6):803-811. doi: 10.1164/rccm.201912-2327OC. PubMed PMID: 32485111.

41. Hueper K, Vogel-Claussen J, Parikh MA, et al. Pulmonary Microvascular Blood Flow in Mild Chronic Obstructive Pulmonary Disease and Emphysema. The MESA COPD Study. Am J Respir Crit Care Med. 2015 Sep 1;192(5):570-80. doi: 10.1164/rccm.201411-2120OC. PubMed PMID: 26067761; PubMed Central

PMCID: PMCPMC4595687.

42. Quanjer PH, Brazzale DJ, Boros PW, et al. Implications of adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. Eur Respir J. 2013 Oct;42(4):1046-54. doi: 10.1183/09031936.00195512. PubMed PMID: 23520323.

43. Kubota M, Kobayashi H, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respir Investig. 2014 Jul;52(4):242-50. doi: 10.1016/j.resinv.2014.03.003. PubMed PMID: 24998371.

44. Devaraj A, Wells AU, Meister MG, et al. Detection of pulmonary hypertension with multidetector CT and echocardiography alone and in combination. Radiology. 2010 Feb;254(2):609-16. doi: 10.1148/radiol.09090548. PubMed PMID: 20093532.

Tables

Table 1. Demographics of patients in the two cohorts

	KOCOSS	Kyoto University
N	743	195
Age (years)	68.9 (7.6)	69.9 (8.5)
Male (%)	100%	100%
Smoking pack-years	47.2 (24.2)	67.2 (34.7)
Height (cm)	165.4 (5.6)	164.5 (6.1)
Weight (kg)	62.8 (9.6)	59.8 (9.3)
Body mass index	22.9 (3.1)	22.1 (2.9)
FEV_1 (% predicted)	62.4 (19.2)	61.6 (19.7)
FVC (% predicted)	101.9 (19.2)	101.0 (18.4)
FEV_1 (z-score)	-2.2 (1.1)	-2.2 (1.1)
FVC (z-score)	0.1 (1.3)	0.0 (1.3)
FEV_1/FVC	0.48 (0.11)	0.48 (0.12)
D_{LCO} (% predicted)	58.1 (19.1)	58.0 (21.9)
D_{LCO} (z-score)	-3.0 (1.6)	-3.0 (1.9)
mMRC≥2 (%)	34%	25%

Data are reported as means (SD). FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. D_{LCO} = diffusion capacity for carbon monoxide. mMRC = modified MRC dyspnea scale.

Table 2. Clinical characteristics of the 4 groups in the KOCOSS Cohort

	Reference	Disproportionally impaired D_{LCO}	Disproportionally impaired FEV_1	Mixed-impaired	P
N	351	212	62	118	
Age (years)	69.0 (7.6)	70.4 (7.6)	65.7 (7.1) †	67.6 (7.3)	<0.01
Smoking PY	44.2 (22.7)	51.3 (25.6)†	45.3 (20.2)	49.4 (26.9)	<0.01
BMI	23.9 (2.8)	22.1 (3.0)†	23.3 (3.1)	21.2 (3.0)†	<0.01
FEV_1 (z-score)	-1.7 (0.8)	-1.9 (1.2)†	-3.4 (0.4)†	-3.6 (0.4)†	<0.01
FVC (z-score)	0.4 (1.1)	0.5 (1.1)	-1.0 (1.2)†	-0.9 (1.2)†	<0.01
D_{LCO} (z-score)	-1.8 (0.8)	-4.3 (1.2)†	-2.2 (0.7)†	-4.7 (1.2)†	<0.01
mMRC≥2 (%)	21%	34%†	55%†	59%†	<0.01
6MWD* (m)	431 (93)	404 (106)†	417 (77)	361 (108)†	<0.01
CAT*	12.9 (7.2)	15.6 (8.4)†	17.8 (7.4)†	19.6 (8.1)†	<0.01
SGRQ total*	27.2 (17.0)	40.4 (18.5)†	39.4 (18.5)†	44.6 (20.1)†	<0.01
Symptom*	35.9 (18.1)	48.3 (20.1)†	51.6 (19.9)†	49.7 (20.8)†	<0.01
Activity*	38.3(21.9)	52.9 (21.3)†	52.1 (22.3)†	59.3 (23.5)†	<0.01
Impact*	18.4 (17.7)	30.9 (20.9)†	28.3 (19.8)†	34.5 (22.1)†	<0.01

Data are presented as means (SD). All subjects were male. Smoking PY = smoking pack-years. BMI = body mass index. FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. RV/TLC = ratio of residual volume to total lung capacity. D_{LCO} = diffusion capacity for carbon monoxide. 6MWD = six-minute walking distance. CAT = COPD assessment test. SGRQ = St. George's Respiratory Questionnaire. Symptom, Activity, and Impact were the domains of the SGRQ score. * 6MWD, CAT, and SGRQ data were available for 641, 717, and 395 patients, respectively. P = p-value. † $p<0.05$ compared to the reference group based on Tukey's multiple comparison or multiple Fisher's exact tests followed by Bonferroni correction.

Table 3. Clinical characteristics of the 4 groups in the Kyoto University Cohort

	Reference	Disproportionally impaired D_{LCO}	Disproportionally impaired FEV_1	Mixed-impaired	P
N	89	62	10	34	
Age (years)	68.8 (9.0)	73.6 (6.4)†	67.5 (5.1)	66.9 (9.2)	<0.01
Smoking PY	65.2 (34.8)	72.6 (35.9)	70.4 (39.4)	61.7 (30.5)	0.43
BMI	23.0 (2.7)	21.6 (3.1)†	21.3 (2.4)	20.8 (2.7)†	<0.01
FEV_1 (z-score)	-1.6 (0.9)	-2.0 (0.8)†	-3.5 (0.4) †	-3.7 (0.6) †	<0.01
FVC (z-score)	0.3 (1.1)	0.4 (1.0)	-0.7 (1.4)†	-1.2 (1.2)†	<0.01
RV/TLC (%)	39.2 (6.4)	42.3 (7.9)†	48.0 (11.2)†	48.8 (6.1)†	<0.01
D_{LCO} (z-score)	-1.6 (0.9)	-4.2 (1.0)†	-1.7 (0.9)	-5.1 (1.5)†	<0.01
Kco (z-score)	-1.0 (1.2)	-3.5 (1.0)†	-1.1 (0.9)	-4.0 (1.5)†	<0.01
V_A/TLC (%)	81.8 (5.2)	78.4 (7.1)†	82.7 (7.4)	74.0 (7.4)†	<0.01
mMRC≥2 (%)	15%	32%†	10%	47%†	<0.01
PaO_2* (mmHg)	79.6 ()	74.0 (8.1)†	72.3 (9.2)	74.6 (7.3)†	<0.01
$PaCO_2$* (mmHg)	39.8 (3.5)	38.0 (3.7)†	42.4 (2.7)	40.2 (4.4)	<0.01
LAV% (%)	24.0 (6.8)	32.4 (6.9)†	31.4 (6.7)†	39.5 (8.2)†	<0.01
WA% (%)	59.7 (5.8)	60.3 (6.1)	61.3 (5.1)	59.1 (5.9)	0.68
PSE	35%	58%†	10%	53%	<0.01
CLE	29%	92%†	60%	94%†	<0.01
PA/Ao	0.77 (0.11)	0.76 (0.10)	0.77 (0.06)	0.80 (0.13)	0.51

Data are presented as means (SD). All subjects were male. Smoking PY = smoking pack-years. BMI = body mass index. FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. RV/TLC = ratio of residual volume to total lung capacity. D_{LCO} = diffusion capacity for carbon monoxide (CO). Kco = CO transfer coefficient. V_A/TLC = ratio of alveolar volume to total lung capacity. PaO_2 = partial pressure of oxygen. $PaCO_2$ = partial pressure of carbon dioxide. PSE = paraseptal emphysema. CLE = moderate to

severe centrilobular emphysema. LAV% = low attenuation volume percentage. WA% = wall area percentage. PA/Ao = diameter ratio of pulmonary artery to aorta. * PaO_2 and $PaCO_2$ data were available for 184 patients. P = p-value. † $p<0.05$ compared to the reference group based on Tukey's multiple comparison or multiple Fisher's exact tests followed by Bonferroni correction.

Figure Legends

Figure 1. Patient flow charts

A. The KOCOSS Cohort was cross-sectionally analyzed. B. The Kyoto University Cohort was cross-sectionally and longitudinally analyzed.

Figure 2. Distributions of FEV_1 and D_{LCO} in the two cohorts

A. KOCOSS Cohort. B. Kyoto University Cohort. Patients were categorized into 4 groups: (1) FEV_1 z-score > -3 and D_{LCO} z-score > -3 (reference, red), (2) FEV_1 z-score > -3 and D_{LCO} z-score ≤ -3 (disproportionally impaired D_{LCO}, green), (3) FEV_1 z-score ≤ -3 and D_{LCO} z-score > -3 (disproportionally impaired FEV_1, blue), and (4) FEV_1 z-score ≤ -3 and D_{LCO} z-score ≤ -3 (mixed-impaired, purple).

Figure 3. Associations of D_{LCO}, FEV_1, and both impairments with patient-reported outcomes and exercise capacity in a multivariable analysis of the KOCOSS cohort

Patients (n=743) were categorized into 4 groups: (1) FEV_1 z-score > -3 and D_{LCO} z-score > -3 (reference, n=351), (2) FEV_1 z-score > -3 and D_{LCO} z-score ≤ -3 (disproportionally impaired D_{LCO}, n=212), (3) FEV_1 z-score ≤ -3 and D_{LCO} z-score > -3 (disproportionally impaired FEV_1, n=62), and (4) FEV_1 z-score ≤ -3 and D_{LCO} z-score ≤ -3 (mixed-impaired, n=118). A dot with an error bar indicates the least square mean (LS mean) with the 95% CI. * $p<0.05$ compared to the reference group in the multivariable models. Each model was adjusted for age, pack-years of smoking, height and weight. 6MWD = six-minute walking distance. CAT = COPD assessment test. SGRQ = St. George's

Respiratory Questionnaire. * 6MWD, CAT, and SGRQ data were available for 641, 717, and 395 patients, respectively.

Figure 4. Associations of D_{LCO}, FEV_1, and both impairments with emphysema subtypes and arterial blood gases in a multivariable analysis of the Kyoto University Cohort

Patients (n=195) were categorized into 4 groups: (1) FEV_1 z-score > -3 and D_{LCO} z-score > -3 (reference, n=89), (2) FEV_1 z-score > -3 and D_{LCO} z-score ≤ -3 (disproportionally impaired D_{LCO}, n=62), (3) FEV_1 z-score ≤ -3 and D_{LCO} z-score > -3 (disproportionally impaired FEV_1, n=10), and (4) FEV_1 z-score ≤ -3 and D_{LCO} z-score ≤ -3 (mixed-impaired, n=34). (A) Odds ratio for the presence of paraseptal emphysema and centrilobular emphysema on CT. A dot with an error bar indicates the regression coefficient with the 95% CI. (B) Least square mean (LS mean) with the 95% CI for the partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$). * $p<0.05$ compared to the reference group in the multivariable models. Each model was adjusted for age, pack-years of smoking, height and weight. PaO_2 and $PaCO_2$ data were available for 184 patients.

Figure 5. Long-term survival of patients with COPD in the Kyoto University Cohort

(A) Kaplan-Meier curves of survival for the 4 groups: (1) FEV_1 z-score > -3 and D_{LCO} z-score > -3 (reference, n=89), (2) FEV_1 z-score > -3 and D_{LCO} z-score ≤ -3 (disproportionally impaired D_{LCO}, n=62), (3) FEV_1 z-score ≤ -3 and D_{LCO} z-score > -3 (disproportionally impaired FEV_1, n=10), and (4) FEV_1 z-score ≤ -3 and D_{LCO} z-score ≤ -

3 (mixed-impaired, n=34). (B) Causes of death. (C) Multivariable Cox proportional hazard models. A dot with an error bar indicates the hazard ratio with 95% CI. * $p<0.05$ compared to the reference group in the multivariable models. The model used for the upper panel included the group, age, pack-years of smoking, height, and weight as independent variables, and the model used for the lower panel included the group, age, pack-years of smoking, height, weight, and LAV% (a CT index of emphysema severity) as independent variables.

Figure 1

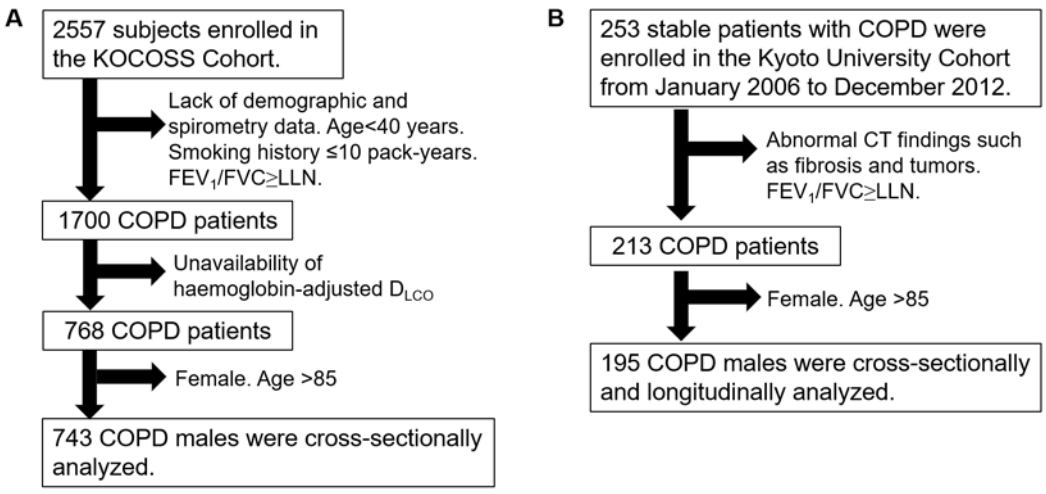

A
2557 subjects enrolled in the KOCOSS Cohort.
Lack of demographic and spirometry data. Age<40 years. Smoking history ≤10 pack-years. FEV1/FVC≥LLN.
1700 COPD patients
Unavailability of haemoglobin-adjusted DLCO
768 COPD patients
Female. Age >85
743 COPD males were cross-sectionally analyzed.
B
253 stable patients with COPD were enrolled in the Kyoto University Cohort from January 2006 to December 2012.
Abnormal CT findings such as fibrosis and tumors. FEV1/FVC≥LLN.
213 COPD patients
Female. Age >85
195 COPD males were cross-sectionally and longitudinally analyzed.

Figure 2

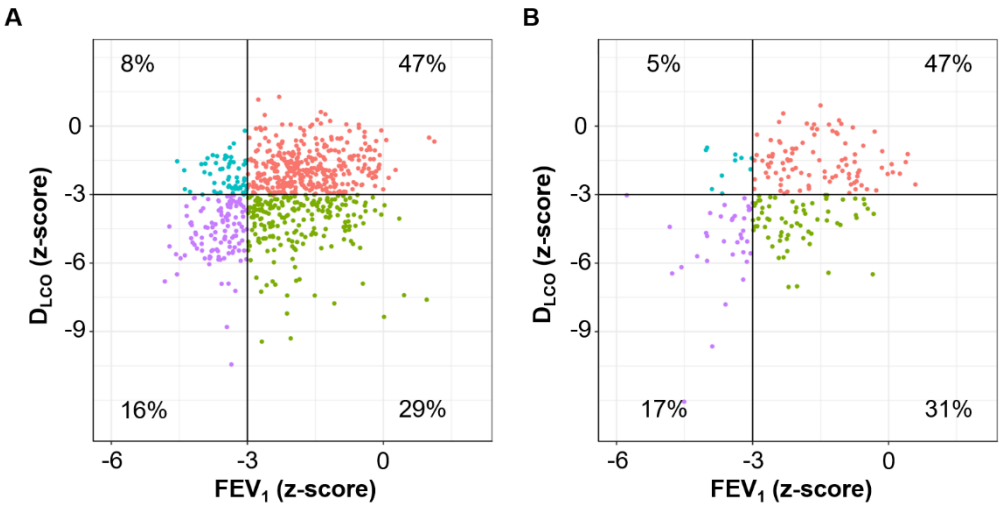

A
8%
47%
16%
29%
0
-3
-6
-9
-6
-3
0
D_{LCO} (z-score)
FEV_1 (z-score)
B
5%
47%
17%
31%
0
-3
-6
-9
-6
-3
0
D_{LCO} (z-score)
FEV_1 (z-score)

Figure 3

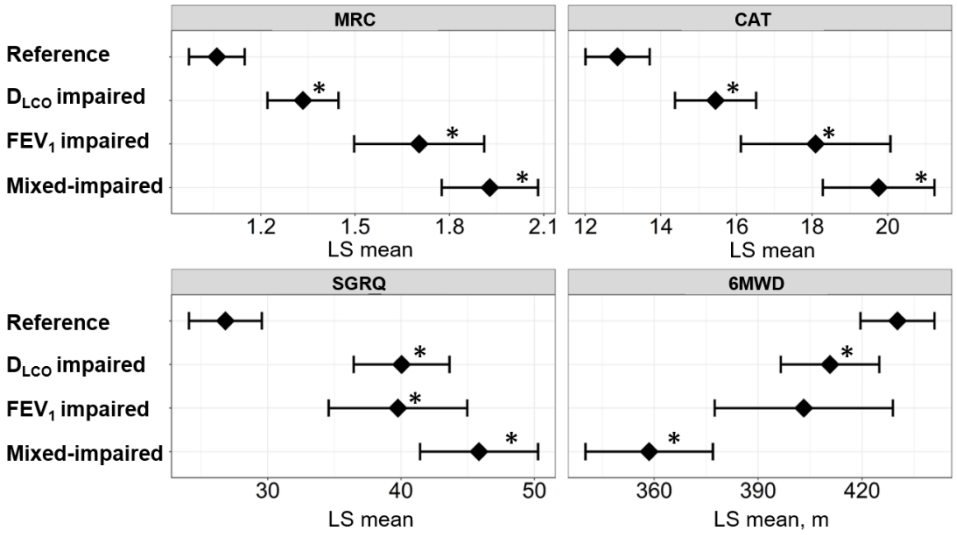

MRC
CAT
SGRQ
6MWD
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
1.2
1.5
1.8
2.1
12
14
16
18
20
30
40
50
360
390
420
LS mean
LS mean, m

Figure 4

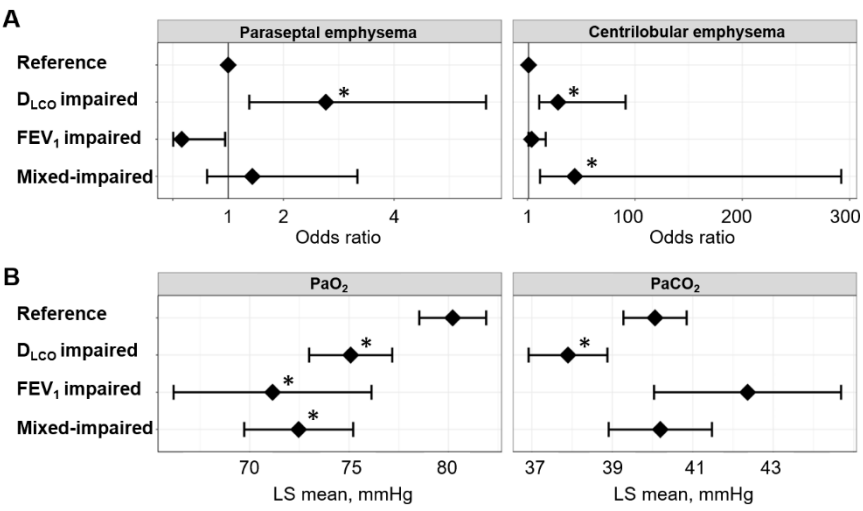
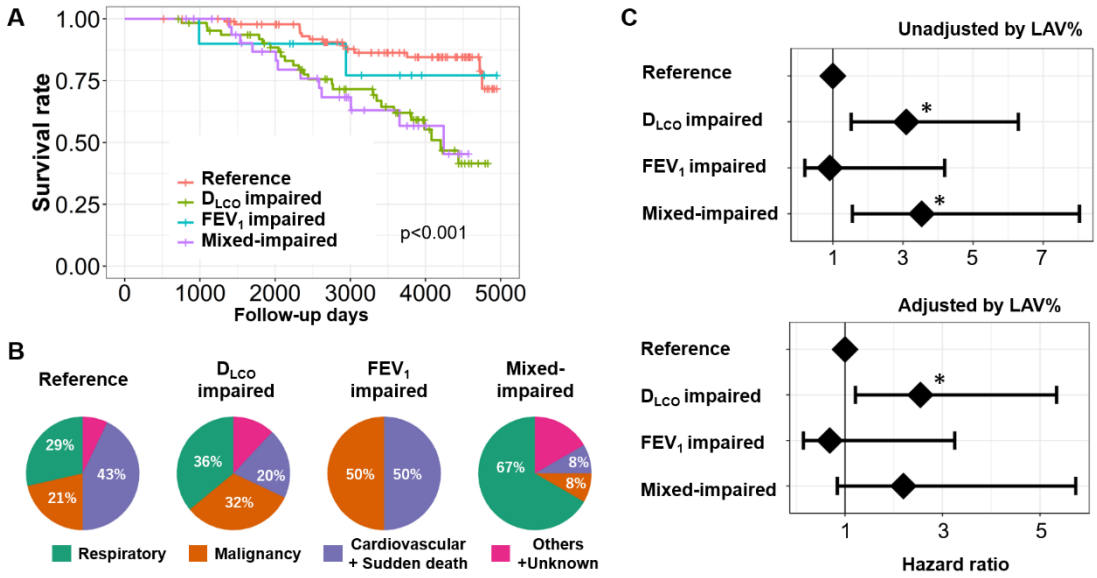

A
Paraseptal emphysema
Centrilobular emphysema
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
1
2
4
Odds ratio
1
100
200
300
Odds ratio
B
PaO2
PaCO2
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
70
75
80
LS mean, mmHg
37
39
41
43
LS mean, mmHg

Figure 5


A
1.00
0.75
0.50
0.25
0.00
Survival rate
0
1000
2000
3000
4000
5000
Follow-up days
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
p<0.001
B
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
29%
43%
21%
36%
20%
32%
50%
50%
67%
8%
8%
Respiratory
Malignancy
Cardiovascular + Sudden death
Others +Unknown
C
Unadjusted by LAV%
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
*
*
1
3
5
7
Adjusted by LAV%
Reference
DLCO impaired
FEV1 impaired
Mixed-impaired
*
1
3
5
Hazard ratio