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Central airway and peripheral lung structures in airway disease dominant COPD

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TAKE-HOME MESSAGE: This study shows that airway disease-dominant COPD, defined using central airway dimension on CT, is associated with a smaller central airway tree, less small airway dysfunction, and slower lung function decline than the emphysema-dominant COPD.

Author Contributions: NT, KS, KT, SS, and MS made contributions to the design of the study and the analysis and interpretation of data. HS and AO made substantial contributions to the CT data analyses. TO created software to analyse the airway structure and contributed to the analysis and interpretation of the data. SK, MN and TH made contributions to the design of the study and critically revised the manuscript for important intellectual content.

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Abstract (250 words)

The concept that the small airway is a primary pathological site for all COPD phenotypes has been challenged by recent findings that the disease starts from the central airways in COPD subgroups and that a smaller central airway tree increases COPD risk. This study aimed to examine whether the computed tomography (CT)-based airway disease-dominant (AD) subtype, defined using the central airway dimension, was less associated with small airway dysfunction (SAD) on CT, compared to the emphysema-dominant (ED) subtype**.**

COPD patients were categorized into mild, AD, ED, and mixed groups based on wall area percent (WA%) of the segmental airways and low attenuation volume percent in the Kyoto-Himeji (n=189) and Hokkaido COPD cohorts (n=93). The volume percent of SAD regions (SAD%) was obtained by nonrigidly registering inspiratory and expiratory CT.

The AD group had a lower SAD% than the ED group and similar SAD% to the mild group. The AD group had a smaller lumen size of airways proximal to the segmental airways and more frequent asthma history before age 40 years than the ED group. In multivariable analyses, while the AD and ED groups were similarly associated with greater airflow limitation, the ED, but not the AD group, was associated with greater SAD%, whereas the AD, but not the ED group, was associated with a smaller central airway size.

The CT-based AD COPD subtype might be associated with a smaller central airway tree and asthma history, but not with peripheral lung pathologies including small airway disease, unlike the ED subtype.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by limited airflow and causes morbidities and mortality worldwide [1]. Long-term exposure to noxious particles such as cigarette smoke induces structural alterations in both central large and peripheral small airways and parenchymal destruction that can be categorized into centrilobular emphysema (CLE), pareseptal emphysema (PSE), and panlobular emphysema [2, 3]. These pathological changes are combined heterogeneously in each patient, making it difficult to predict outcomes with simple assessments of each change.

Chest computed tomography (CT) is used to separately assess the airways and parenchyma and to identify airway disease-dominant (AD) and emphysema-dominant (ED) subtypes to account for the heterogeneous clinical manifestations [4-9]. While small airway disease, which is considered a main pathology of COPD [10-15], cannot be directly evaluated with CT due to the limited resolution, a finding by Nakano et al. [16] that the central airway dimension on CT reflects small airway disease on histology has rationalized CT assessments of central airways in patients with COPD.

The introduction of non-rigid registration of inspiratory and expiratory CT has enabled to localize regions with small airway dysfunction (SAD) [17]. Vasilescu et al. [18] showed that the SAD on CT is closely associated with the remodelling and loss of terminal bronchioles on microCT in COPD. Labaki et al. [19] showed that regions with SAD on CT are subsequently converted into emphysema after 5 years, supporting the concept that the small airway is a primary pathological site for all COPD phenotypes [11, 12, 14, 20]. However, this concept has been challenged by recent findings that the disease starts from the central airways in COPD subgroups [21] and that a smaller

central airway tree size relative to lung size, termed dysanapsis, is associated with greater COPD risk [22]. Moreover, a very recent microCT study showed that the terminal bronchioles were relatively preserved in paraseptal emphysema compared to in centrilobular emphysema[23].

We thus hypothesized that central airway disease might develop independently of peripheral lung disease in the AD subtype of COPD patients. For this goal, using two cohorts: the Kyoto-Himeji cohort and the Hokkaido COPD cohort [24-26], this study specifically aimed to prove that the classical CT-based AD subtype, defined using central airway dimension, would be less severe in the SAD compared with the ED subtype and have some distinct morphological and clinical features.

Methods

Study design: The details are provided in the online supplement. This study analysed the baseline data of a prospective observational study at the Kyoto University Hospital and Terada Clinic (Kyoto-Himeji cohort) and the cross-sectional and longitudinal data of the Hokkaido COPD cohort [24-26]. The Kyoto-Himeji cohort enrolled smokers aged ≥40 years with a smoking history of ≥10 pack-years but without a current diagnosis of asthma from April 2018 to April 2020; this study was approved by the Ethics Committee of Kyoto University (No.C1311) and registered with the University Hospital Medical Information Network (UMIN000028387). The Hokkaido COPD cohort study was approved by the Health Authority Research Ethics Committee of Hokkaido University School of Medicine (No.med02-001), and the inclusion and exclusion criteria are described elsewhere [24-26]. Patients with a prior history of asthma before

age 40 years were included in the Kyoto-Himeji cohort but not in the Hokkaido COPD cohort. Each participant provided written informed consent.

CT acquisitions: In the Kyoto-Himeji cohort, full inspiratory and end-tidal expiratory CT were acquired using an Aquilion Precision scanner at Kyoto University and an Aquilion lightning scanner at Terada Clinic (Canon Medical Systems, Otawara, Japan). Images with a 1 mm slice thickness were reconstructed using soft (FC13) and sharp (FC51) kernels for parenchymal and airway analysis. A phantom that mimicked the parenchyma and airways was scanned to confirm that both scanners provided consistent measurements (Online supplemental Figure S1 and S2). In the Hokkaido COPD cohort, full inspiratory and end-tidal expiratory CT were acquired using a Somatom plus Volume Zoom scanner (Siemens AG, Berlin, Germany), and images with a 1.25 mm slice thickness were reconstructed using standard (B30) and sharp (B60) kernels for parenchymal and airway analysis.

Analysis of CT images: Using SYNAPSE VINCENT software (FUJIFILM; Tokyo, Japan), the lung fields were automatically extracted. The volume percentage of regions showing CT values less than -950 HU to total lung volume on inspiratory CT (LAV%) was calculated to evaluate emphysema severity [25] based on a report showing that the threshold of -950 HU provides the strongest correlation between the extent of emphysematous change on CT and microscopically-measured emphysema severity [27]. Additionally, the expiratory lung images were nonrigidly registered onto the inspiratory lung images, and SAD was identified as voxels with CT values of -950 HU or more on the inspiratory CT and less than -856 HU on the registered expiratory CT based on a report showing that SAD regions defined using the thresholds of -950HU and -856HU on inspiratory and expiratory CT is closely associated with the pathological changes of

small airways on microCT [18]. The volume percentage of SAD to the total lung (SAD%) was calculated [17]. The lumen, wall area, and wall area percent (WA%) of the segmental right apical and posterior basal bronchus (RB1 and RB10) were measured, and averaged [28]. For comparisons between the CT-based subtypes, lumen and wall areas were normalized by body surface area (BSA). CLE and PSE were visually assessed based on the Fleischner Society classification system [3]. The inter-rater variability of two analysts (NT and HS) in identifying PSE and CLE was excellent (kappa = 0.85 and 0.81).

Pulmonary function and clinical features: Post-bronchodilator spirometry was performed. The predicted forced vital capacity (FVC) and predicted forced expiratory volume in one second (FEV_1) were calculated with the LMS method [29]. Respiratory symptoms were evaluated using the COPD Assessment Test (CAT) in the Kyoto-Himeji cohort. The St. George's Respiratory Questionnaire (SGRQ) [30] was administered, the annual decline in FEV_1 over 5 years was calculated with a mixed-effects linear model, and mortality over 10 years was evaluated in the Hokkaido cohort.

Statistics: The R statistical program was used [31]. Based on the inspiratory CT, the patients were categorized into 4 groups: (1) low WA% and low percentage of low attenuation volume (mild), (2) high WA% and low LAV% (AD), (3) low WA% and high LAV% (ED), and (4) high WA% and high LAV% (mixed). The LAV% cut-off was set as 10% to identify established emphysema [32, 33]. The WA% cut-off was set as 60% based on a previous report that showed the mean (SD) WA% in the right segmental airways of healthy non-smokers was 58.1 (2.2)% [34]. To explore whether the AD, ED, and mixed groups had additional, independent impacts on percent of predicted FEV_1 (%FEV_1), SAD%, and the mean lumen area of right main and intermedius bronchus

compared to the mild group, 3 multivariable linear regression models were constructed using the CT-based categories, age, sex, smoking-pack years, body mass index (BMI), and CT scanners as independent variables.

Results

Figure 1A shows that in the Kyoto-Himeji cohort, of the 256 patients initially screened, 15 were excluded due to abnormal CT findings unrelated to COPD and insufficient breath-holds during the expiratory CT scan. Fifty-two smokers who did not fulfil the diagnostic criteria of COPD were excluded, and a total of 189 patients were cross-sectionally analysed. Figure 1B shows that of the 279 patients included in the original report by Nishimura et al. [24] as the Hokkaido COPD cohort, this study cross-sectionally and longitudinally analysed 93 patients who underwent inspiratory and expiratory CT using the same scanner with fixed conditions at Hokkaido University Hospital. Table 1 shows the demographics of the two cohorts.

Figure 2A shows that 26%, 19%, 36%, and 19% of COPD patients in the Kyoto-Himeji cohort were categorized into the mild (WA%<60% and LAV%<10%), AD (WA%≥60% and LAV%<10%), ED (WA%<60% and LAV%≥10%), and mixed (WA%≥60% and LAV%≥10%) groups (n=50/36/68/35), the clinical characteristics of which are shown in Table 2. The AD group had a larger BMI than the ED and mixed groups and higher self-reported rates of a history of asthma before age of 40 years than the mild and ED groups. On the visual emphysema assessments, pure PSE CT findings were more frequent, and pure CLE and mixed CLE and PSE findings were less frequent in the AD group than in the ED group.

Figure 2B shows that the SAD% did not differ between the mild and AD groups,

whereas the SAD% was increased in the ED and mixed groups compared to that in the mild group. Figure 2C shows that the lumen area of the segmental airways was smaller in the AD group than in the mild and ED groups, whereas the wall area did not differ among groups. Figure 2D shows that the mean lumen area of more central airways, including the right main and intermedius bronchus, was smaller in the AD group than in the mild and ED groups. Online supplemental Figure S3 shows that the lumen areas of the segmental airways as well as those of airways proximal to the segmental airways were also smaller in the AD group than in the mild and ED groups even when comparing these lumen areas without adjustment and with adjustment by height. Online supplemental Figure S4 shows that CT inspiratory lung volume adjusted by the predicted value of total lung capacity was larger in the ED group than in the AD group while no difference was found between the mild and AD groups.

Table 3 shows that in multivariable linear regression models, $\%FEV_1$ was significantly and similarly lower in the AD and ED groups compared to the mild group. In contrast, SAD% did not differ between the AD and mild groups while SAD% was significantly higher in the ED group compared to the mild group. Moreover, the mean lumen area of right main and intermedius bronchus was significantly lower in the AD, but not in the ED group, compared to the mild group.

The results of the Kyoto-Himeji cohort were validated in the Hokkaido COPD cohort. Figure 3A shows that 9%, 13%, 44%, and 34% of COPD patients were categorized into the mild, AD, ED, and mixed groups (n=8/12/41/32), the clinical data of which are summarized in Table 4. The AD group had a larger BMI and tended to have higher rates of blood eosinophil count≥300/μl and atopy than the mild and ED groups while bronchodilator response did not differ between the AD and ED groups. Figure 3B

shows that SAD% did not differ between the mild and AD groups but was increased in the mixed group. Figure 3C shows that the lumen area of the segmental airways was lower in the AD group than in the mild and ED groups. Figure 3D shows that the annual decline in FEV_1 over 5 years was significantly smaller in the AD group than in the ED and mixed groups. Online supplemental Figure S5 shows that the mean lumen area of the right main and intermedius bronchus tended to be smaller in the AD group than in the other groups and that the survival rate did not differ between the mild and AD groups.

Discussion

By using CT-based subtyping, this study showed that the SAD in the AD group was less severe than that in the ED group and was similar to that in the mild group in the two cohorts. In the multivariable models, while both the AD and ED groups showed similar reduction in FEV_1, the AD group was associated with a smaller lumen of the main and intermedius bronchus, but not with SAD, whereas the ED group was associated with SAD, but not with the size of main and intermedius bronchus. These findings confirm the notion that small airway disease is a feature of the emphysema-dominant COPD [10, 13-15], and suggest for the first time that a smaller central airway size, but not small airway disease, is a feature of the CT-based AD COPD subtype.

A previous CT study by Park et al. [35] visually diagnosed subjects with wall thickening of the central airways without emphysema with “bronchial disease” and showed that the extent of small airway disease was milder in this bronchial disease subtype than in the moderate to severe centrilobular emphysema subtype. The present

data confirm and expand upon those findings by providing quantitative CT measurements of central airway dimensions to show that the SAD% was lower in the AD group than in the ED group.

Moreover, the lumen area of the segmental airway was decreased in the AD group compared to that in the mixed and ED groups, whereas the wall area did not differ between the groups. Furthermore, the lumen size of the right main and intermedius bronchus was smaller in the AD group than in the mild group, but the lung size did not differ between the two groups. These findings suggest that a small central airway tree for a given lung size, in other words, dysanapsis [22], may be a major feature of the AD subtype.

The Kyoto-Himeji cohort showed that a prior history of asthma before age of 40 years was more frequent in the AD group than in the other 3 groups. Additionally, the analysis of the Hokkaido COPD cohort, although that study did not include patients with a prior history of asthma, showed that asthma-like features such as a blood eosinophil count≥300/μl and atopy [26] were more frequent in the AD group than in the other groups. Diaz et al. showed that a smaller central airway size contributes to greater airflow limitation, even in never-smokers [36], and childhood-onset asthma is closely associated with a smaller central airway size in adult smokers [37]. These results suggest that the smaller airways in the AD subtype might be induced by a combination of native airway size and airway damage in childhood, such as from asthma, but a distinct response to cigarette smoke exposure in the airways and parenchyma in adulthood might also affect airway size.

The SAD% was greater in the ED and mixed groups compared to the mild and AD groups. On visual assessment, CLE findings (pure CLE or CLE+PSE) were

identified in more than 80% of the ED and mixed groups. These results suggest the notion that small airway disease is closely associated with the CLE-dominant COPD subtype [10, 13-15]. In contrast, the SAD% was lower in the AD group than in the ED group, and pure PSE was found in 22% and 3% of patients in the AD and ED groups, respectively. This supports the hypothesis that small airway disease is less involved in the pathogenesis of PSE than in that of CLE [23, 35] .

More patients in the ED and mixed groups used long-acting muscarinic antagonist (LAMA) than in the mild and AD groups (Table2). Since LAMA increases lumen areas of central airways [38], we performed additional sub-analysis of patients treated with LAMA and found that the main findings from all the patients (Table 3) were reproduced (online supplemental Table S1). This suggests that the influence of different rates of LAMA use on the present results is small.

In the Hokkaido COPD cohort, the annual decline in FEV_1 over 5 years was smaller in the AD group than in the ED and mixed groups. This is consistent with previous reports on the association of emphysema with a rapid decline in FEV_1 in COPD patients [24, 33]. Furthermore, the present data build upon the works from Smith et al. [22], who showed that COPD patients with dysanapsis were not associated with a rapid FEV_1 decline, and Hayden et al. [39], who showed that a history of asthma before COPD onset was associated with exacerbations but not with a rapid lung function decline in COPD.

Based on these findings, we propose the CT-based AD COPD subtype as a distinct entity that is morphologically characterized by a smaller central airway tree with less small airway disease, and is clinically characterized by an elevated BMI, more frequent asthma history and/or asthma-like features, and slower lung function decline.

Therefore, identifying the AD group using CT is clinically relevant to providing personalized management of the disease. Since approximately 50% of COPD patients have a reduced maximal lung function in younger age and a higher incidence of COPD despite a normal decline in FEV_1 [40], the present data raise the hypothesis that smaller airway trees may exist before COPD onset, increase COPD incidence, and can be a main driver for the development of the AD subtype even without an accelerated decline in lung function.

Several limitations need to be mentioned. First, the sample size of the two cohorts was relatively small. Since the original purpose of this study was not to characterize the AD group, the present analyses included less patients in the AD groups than in the ED group. While the main finding that the SAD% was lower in the AD group than in the ED group was successfully reproduced in the independent Hokkaido COPD cohort, a future cohort which would equally include patients in the AD and ED groups should be performed to verify the present findings. Second, this study did not include healthy non-smokers. We did not determine the specific cut-off values of LAV% and WA% for the present study to identify the AD and ED subtypes. Alternatively, we used an LAV% of 10% and WA% of 60% as the cut-offs based on previous papers [32-34]. Third, spirometric gating was not used during the CT scans. Alternatively, all the patients were carefully coached to hold the breath at full-inspiration and end-tidal expiration. Fourth, the proportion of males was over 90%. The generalizability of the present findings to female patients is unclear.

In conclusion, by using two independent cohorts, the present data suggest that the airway disease-dominant COPD, defined using central airway dimension on CT, is associated with a smaller central airway tree, but not with the small airway disease,

unlike the emphysema-dominant COPD. The use of CT-based categorization into the AD and ED subtypes to reflect distinct natural COPD histories may help establish personalized medicine approaches to managing the heterogeneous manifestations of this disease.

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Table 1. Demographics of the two cohorts

	Kyoto-Himeji Cohort	Hokkaido Cohort
N	189	93
Age (years)	73.3 (8.3)	69.6 (7.9)
Male (%)	94%	92%
Smoking pack-year	62.4 (31.4)	61.0 (28.1)
BMI (kg/m^2)	23.2 (3.6)	22.7 (3.2)
FEV_1/FVC (%)	52.3 (11.8)	52.4 (12.6)
%FEV_1 (%)	63.3 (22.9)	66.5 (19.4)
%FVC (%)	91.2 (22.3)	101.6 (14.5)
Ins-CT-LV (L)	5.9 (1.1)	5.3 (1.1)
Exp-CT-LV (L)	3.9 (1.0)	3.7 (1.1)
LAV% (%)	15.3 (12.9)	21.0 (12.4)
WA%-segmental (%)	58.7 (4.8)	59.4 (5.1)
WA%-subsegmental (%)	64.0 (3.5)	63.7 (4.4)
SAD% (%)	27.7 (11.9)	29.1 (11.5)

Data are expressed as the mean (SD). BMI = body mass index. FEV_1 = forced expiratory volume in 1 sec. FVC = forced vital capacity. Ins-CT-LV = total lung volume on inspiratory CT. Exp-CT-LV = total lung volume on expiratory CT. LAV% = low attenuation volume percent. WA% = wall area percent. SAD% = small airway dysfunction percent.

Table 2. Clinical characteristics of the CT-based airway disease and emphysema dominant phenotypes in patients with COPD in the Kyoto-Himeji Cohort

	Mild	AD	ED	Mixed
N	50	36	68	35
Age (years)	72.2 (8.6)	73.7 (8.8)	73.9 (8.0)	73.3 (8.1)
Male (%)	96%	97%	93%	91%
Smoking pack-year	56.8 (32.0)	57.0 (33.1)	68.0 (27.8)	65.3 (34.4)
BMI (kg/m^2)	24.2 (3.3)	25.0 (2.8)†	21.7 (3.4)	22.7 (4.1)
FEV_1/FVC (%)	60.9 (6.0)	56.9 (8.6)†	48.3 (11.3)	43.3 (11.7)
$\%FEV_1$ (%)	76.4 (16.4)	64.5 (16.0)	60.1 (24.8)	49.3 (23.5)
%FVC (%)	96.4 (18.7)	86.8 (17.4)	93.3 (24.7)	84.2 (24.9)
PSE only (%)	22%	22%†	3%	11%
CLE only (%)	12%	11%†	43%	23%
CLE+PSE (%)	6%	6%†	49%	57%
CAT	10.6 (7.3)	9.4 (5.9)	12.9 (8.4)	14.0 (8.8)
No. exacerbations/yr	0.4 (1.1)	0.2 (0.5)	0.3 (0.6)	0.4 (0.7)
Asthma <40 yrs (%)	2%	28%*†	6%	14%
Allergic rhinitis (%)	8%	22%	7%	6%
Hypertension (%)	52%	64%	56%	60%
DM (%)	14%	19%	15%	11%
IHD (%)	18%	25%	12%	17%
GERD (%)	16%	25%	12%	9%
LAMA use	48%	42%†	82%*	71%*
LABA use	54%	61%	76%	83%
ICS use	34%	53%	43%	63%

Patients were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed CT phenotypes. Data are expressed as the mean (SD). * $p<0.05$ compared to the mild group. † $p<0.05$ compared to the ED group. BMI

= body mass index. FEV_1 = forced expiratory volume in 1 sec. FVC = forced vital capacity. PSE = visual CT findings of paraseptal emphysema. CLE = visual CT findings of centrilobular emphysema. CAT = COPD assessment test (assessed in 181 patients). DM = diabetes mellitus. IHD = ischaemic heart disease. GERD = gastroesophageal reflux disease. LAMA = long-acting muscarinic antagonist. LABA = long-acting beta agonist. ICS = inhaled corticosteroid.

Table 3. Multivariable analyses to explore associations of the airway disease-dominant and emphysema-dominant phenotypes with airflow limitation, small airway dysfunction, and more proximal central airway lumen area in the Kyoto-Himeji cohort

Models	CT categories	Estimate	95%CI	P value
Model 1: %FEV_1	Mild	Ref		
	AD	-14.1	-22.7, -5.5	0.002
	ED	-11.3	-19.1, -3.6	0.004
	Mixed	-24.3	-33.1, -15.5	< 0.001
Model 2: SAD%	Mild	Ref		
	AD	-1.2	-5.8, 3.5	0.62
	ED	5.3	1.1, 9.4	0.01
	Mixed	9.7	4.9, 14.4	< 0.001
Model 3: Mean LA (Main + Intermedius)	Mild	Ref		
	AD	-17.1	-27.7, -6.5	0.002
	ED	0.7	-8.8, 10.2	0.88
	Mixed	-19.1	-29.9, -8.2	< 0.001

COPD patients in the Kyoto-Himeji cohort were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed groups based on wall area percent of the segmental bronchus (WA%) and low attenuation volume percent (LAV%) on inspiratory CT. Each multivariable linear regression model included the CT-categorization (Reference [Ref]: the mild group), age, sex, body mass index, smoking pack-year, and CT scanner as independent variables. 95% CI = 95% confidence interval. %FEV_1 = % of predicted forced expiratory volume in 1 sec (FEV_1). SAD% = small airway dysfunction. “Mean LA” indicates the mean lumen area (LA) of the airways proximal to the segmental airways, including the right main and intermedius bronchus.

Table 4. Clinical characteristics of the patients with the airway disease-dominant and emphysema-dominant phenotypes in the Hokkaido COPD Cohort

	Mild	AD	ED	Mixed
N	8	12	41	32
Age (years)	64.3 (2.8)	68.0 (2.2)	69.6 (1.2)	71.4 (1.4)
Male (%)	88%	92%	90%	97%
Smoking pack-year	57.9 (26.9)	61.1 (22.9)	62.4 (32.1)	59.8 (25.8)
BMI (kg/m^2)	22.1 (2.0)	26.3 (4.2)*†	21.7 (2.3)	22.7 (3.0)
FEV_1/FVC (%)	65.9 (9.1)	62.7 (5.5)†	53.1 (12.4)	44.3 (9.1)
%FEV_1 (%)	80.1 (1.2)	72.9 (11.2)	71.0 (20.1)	54.9 (16.5)
%FVC (%)	99.3 (12.3)	93.8 (9.6)†	107.2 (12.6)	98.0 (16.5)
SGRQ total	21.1 (10.6)	26.9 (16.8)	26.0 (17.1)	35.8 (17.3)
Chronic bronchitis	25%	17%	7%	6%
BDR (%)	13%	33%	29%	44%
Eos≥300/μl (%)	13%	33%	22%	25%
IgE, IU/ml	335.5 (673.8)	317.2 (494.7)	231.2 (862.4)	94.8 (128.6)
Atopy (%)	14%	33%	18%	10%
DM (%)	0%	8%	0%	0%
IHD (%)	0%	25%	7%	13%

Patients were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed CT phenotypes. Data are expressed as the mean (SD). * $p<0.05$ compared to the mild group. † $p<0.05$ compared to the ED group. BMI = body mass index. FEV_1 = forced expiratory volume in 1 sec. FVC = forced vital capacity. SGRQ = St. George's Respiratory Questionnaire. BDR = the presence of bronchodilator reversibility. Eos≥300/μl = blood eosinophil count ≥300/μl. DM = diabetes mellitus. IHD = ischaemic heart disease.

Figure legends

Figure 1. Patient inclusion flowchart

Patient inclusion flow charts for (A) the Kyoto-Himeji cohort and (B) the Hokkaido COPD cohort, for whom the present study analysed inspiratory and expiratory CT.

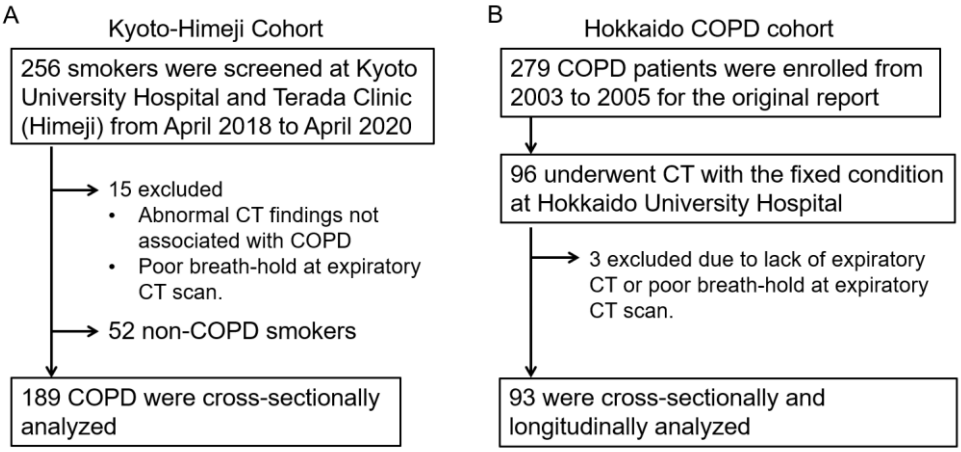
Figure 2. Small airway dysfunction in patients with the airway disease-dominant and emphysema-dominant phenotypes in the Kyoto-Himeji cohort

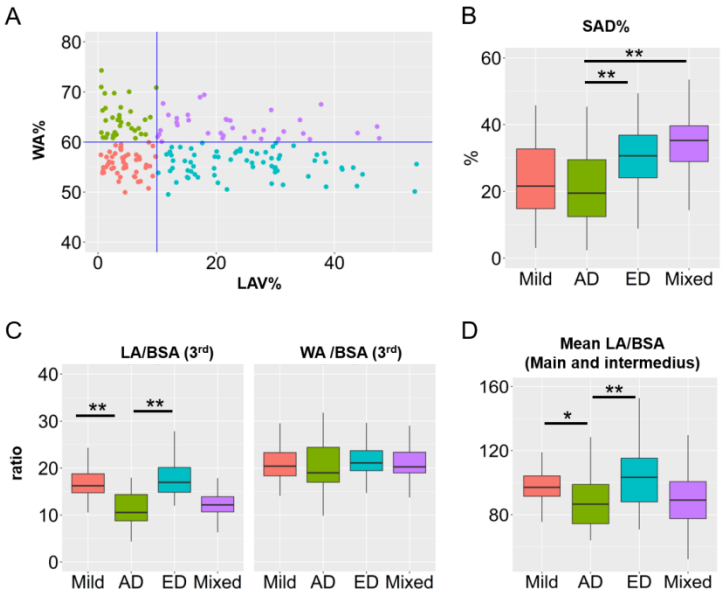
(A) COPD patients in the Kyoto-Himeji cohort were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed groups based on wall area percent of the segmental bronchus (WA%) and low attenuation volume percent (LAV%) on inspiratory CT. (B) Small airway dysfunction percent (SAD%) measured on a pair of inspiratory and expiratory CT scans and (C) Lumen area (LA) and wall area (WA) adjusted by body surface area (BSA) were compared between the groups. (D) The mean lumen area (LA) of the airways proximal to the segmental airways, including the right main and intermedius bronchus, was adjusted by BSA and compared. * and ** indicate $p<0.05$ and $p<0.005$, respectively, based on Tukey's multiple comparison tests.

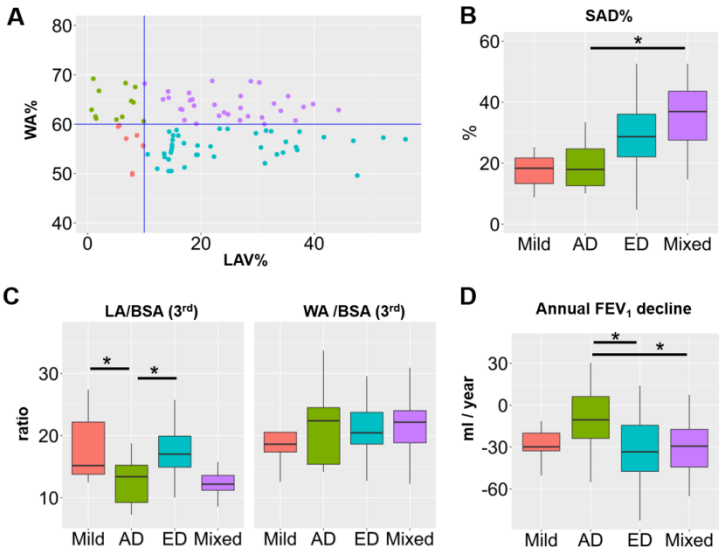
Figure 3. Small airway dysfunction and clinical longitudinal outcomes in patients with the airway disease-dominant and emphysema-dominant phenotypes in the Hokkaido COPD cohort

(A) COPD patients in the Hokkaido COPD cohort were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed CT subtypes. (B) Small airway dysfunction percent (SAD%) measured on a pair of inspiratory and expiratory

CT scans and (C) Lumen area (LA) and wall area (WA) adjusted by body surface area (BSA) were compared between the groups. (D) Annual change in forced expiratory volume in 1 sec (FEV_1) were compared among the 4 groups. * indicates $p<0.05$ from Tukey's multiple comparison tests.


A
Kyoto-Himeji Cohort
256 smokers were screened at Kyoto University Hospital and Terada Clinic (Himeji) from April 2018 to April 2020
15 excluded
• Abnormal CT findings not associated with COPD
• Poor breath-hold at expiratory CT scan.
52 non-COPD smokers
189 COPD were cross-sectionally analyzed
B
Hokkaido COPD cohort
279 COPD patients were enrolled from 2003 to 2005 for the original report
96 underwent CT with the fixed condition at Hokkaido University Hospital
3 excluded due to lack of expiratory CT or poor breath-hold at expiratory CT scan.
93 were cross-sectionally and longitudinally analyzed


A
WA%
LAV%
B
SAD%
%
Mild
AD
ED
Mixed
C
LA/BSA (3rd)
WA /BSA (3rd)
ratio
D
Mean LA/BSA
(Main and intermedius)


A
WA%
LAV%
B
SAD%
%
Mild
AD
ED
Mixed
C
LA/BSA (3rd)
WA /BSA (3rd)
ratio
D
Annual FEV1 decline
ml / year

Online supplement

Central airway and peripheral lung structures in airway disease dominant COPD

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3. Supplemental Table
- ✓ **Supplemental Table S1. Multivariable analyses to explore associations of the airway disease-dominant and emphysema-dominant phenotypes with airflow limitation, small airway dysfunction, and more proximal central airway lumen area in the Kyoto-Himeji cohort using data from patients who used long-acting muscarinic antagonist.**

4. References

1. Supplemental methods

1-1. Study design: This study used the baseline data of an ongoing prospective observational cohort study conducted at the Kyoto University Hospital in Kyoto and Terada Clinic in Himeji, Japan (Kyoto-Himeji cohort), as well as cross-sectional and longitudinal data of the Hokkaido COPD cohort study conducted in Hokkaido, Japan [1-3]. In the Kyoto-Himeji cohort, smokers aged ≥40 years with a history of ≥10 pack-years were enrolled between April 2018 and April 2020. The enrolled subjects underwent spirometry and a pair of full inspiratory and end-tidal expiratory chest CT scans during an exacerbation-free period. The exclusion criteria were as follows: (1) a history of other respiratory diseases, such as interstitial lung disease and lung cancer, (2) current primary diagnosis of asthma, (3) α1-antitrypsin deficiency, and (4) lung surgical resection. COPD was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. The Kyoto-Himeji cohort study was approved by the Ethics Committee of Kyoto University (approval No. C1311) and registered with the University Hospital Medical Information Network (UMIN000028387). In addition, the main findings from the Kyoto-Himeji cohort were validated using data from the Hokkaido COPD cohort. The Hokkaido COPD cohort was approved by the Health Authority Research Ethics Committee of Hokkaido University School of Medicine (approval No. med 02-001), and the inclusion and exclusion criteria were described elsewhere [1-3]. Subjects with a prior history of asthma before the age of 40 years were included in the Kyoto-Himeji cohort but not in the Hokkaido COPD cohort. Both the Kyoto-Himeji and the Hokkaido COPD cohort studies were performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from each participant. The collaborative analysis for these two independent cohorts was approved by the Ethics Committee of Kyoto University

(approval No. R2037).

1-2. CT acquisitions: In the Kyoto-Himeji cohort, whole-lung volumetric CT scans were acquired at full inspiration (TLC) and end-tidal expiration (FRC) using an Aquilion Precision scanner at Kyoto University and an Aquilion lightning scanner at Terada Clinic (Canon Medical Systems, Otawara, Japan). Participants were coached to hold their breath at full inspiration and end-tidal expiration during scanning. The scanning conditions of both scanners were as follows: 120 kVp, 0.5-s exposure time, and autoexposure control. Images with a 512×512 matrix and 1 mm slice thickness were generated using a soft reconstruction kernel (FC13) for parenchymal analysis and a sharp reconstruction kernel (FC51) for airway analysis. A phantom that mimicked the parenchyma and airways was also scanned using the two scanners. The results showed that both scanners provided consistent measurements of the given materials and tubes (Online supplementary Figure S1 and S2). In the Hokkaido COPD cohort, inspiratory (TLC) and expiratory (FRC) CT scans were acquired at Hokkaido University Hospital using a Somatom plus Volume Zoom scanner (Siemens AG, Berlin, Germany) with 140 kVp and 150 mA. Images with a 512×512 matrix and 1.25 mm slice thickness were generated using a standard reconstruction kernel (B30) for parenchymal analysis and a sharp reconstruction kernel (B60) for airway analysis.

1-3. Analysis of CT images: For both the Kyoto-Himeji and Hokkaido COPD cohorts, SYNAPSE VINCENT software (FUJIFILM; Tokyo, Japan) was used for parenchymal analyses [4], and custom-made software was used for airway analyses [5-7]. The lung fields were automatically extracted from inspiratory and expiratory CT scans. The

percent volume ratio of regions showing a signal less than -950 HU to total lung volume on inspiratory CT (LAV%) was calculated to evaluate emphysema severity [2, 4]. Additionally, the expiratory lung images were nonrigidly registered onto the inspiratory lung images, and SAD was identified as voxels with HU values of -950 HU or more on the inspiratory CT and less than -856 HU on the registered expiratory CT. The percent volume ratio of regions with SAD to the total lung volume (SAD%) was calculated [8, 9]. Furthermore, the lumen and wall areas were measured for each two-thirds portion of the right apical and lower posterior segmental bronchus (RB1 and RB10). Then, the wall area percent (WA%), defined as the percentage ratio of the wall area to the sum of the wall and lumen areas, was calculated for each segment and averaged. The lumen area of the right main and intermedius bronchi were measured. For comparisons between the CT-based subtypes, lumen and wall areas were normalized by body surface area (BSA) according to previous reports [5, 10]. CT inspiratory lung volume was adjusted by a predicted value of total lung capacity (TLC) that was calculated using the reference equation [11]. Furthermore, CLE and PSE were visually assessed based on the Fleischner Society classification system, in which the category of PSE included “absence”, “mild”, and “substantial” PSE, and the category of CLE included “absence”, “mild”, “moderate”, “confluent” and “advanced” CLE [12]. The inter-rater variability of the two analysts (NT and HS) was excellent (kappa = 0.85 and 0. 81 for PSE and CLE assessments). Substantial PSE and CLE were considered as the presence of PSE and CLE in this study. This study considered the lungs to be affected by PSE when “substantial” PSE was identified and to be affected by CLE when “moderate”, “confluent”, or “advanced” CLE was identified.

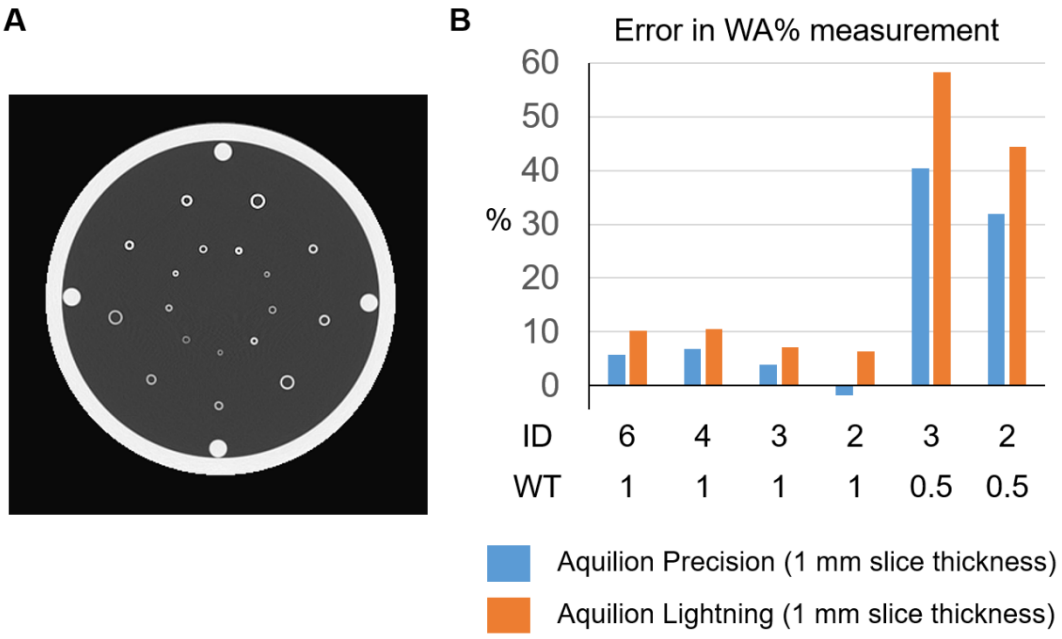
1-4. Pulmonary function and clinical features: Post-bronchodilator spirometry was performed using a Chestac-8900 (Chest M.I., Inc., Tokyo, Japan) in the Kyoto-Himeji cohort and a rolling seal Chestac-33 spirometer (Chest MI, Inc., Tokyo, Japan) in the Hokkaido COPD cohort. The predicted forced vital capacity (FVC) and predicted FEV_1 were calculated with the LMS method [13]. Respiratory symptoms were evaluated using the COPD Assessment Test (CAT) in the Kyoto-Himeji cohort. The St. George's Respiratory Questionnaire (SGRQ) [14] was administered and symptoms of chronic bronchitis and bronchodilator response defined as a change in FEV_1 ≥200 ml and ≥12% after inhalation of salbutamol were evaluated in the Hokkaido COPD cohort. Exacerbation was defined as the use of oral corticosteroids or antibiotics or the need for hospitalization because of worsening respiratory symptoms, and the number of exacerbations in the previous year before enrolment was recorded. Moreover, the annual decline in FEV_1 was calculated with a mixed-effects linear model using longitudinal data over 5 years, and mortality was evaluated using data over 10 years in the Hokkaido cohort study.

1-5. Statistics: The data are expressed as the mean (SD), unless otherwise indicated. Statistical analysis was performed with the R program [15]. Based on the LAV% and WA% on inspiratory CT, the subjects were categorized into 4 groups: (1) low WA% and low LAV% (mild), (2) high WA% and low LAV% (AD), (3) low WA% and high LAV% (ED), and (4) high WA% and high LAV% (mixed). The cut-off value for LAV% was set as 10% to identify subjects with established emphysema [16, 17]. The cut-off value for WA% was set as 60% based on a previous report that showed that the mean (SD) of WA% in right segmental airways of healthy non-smokers was 58.1 (2.2)% [18].

Continuous variables were compared among the 4 groups using Tukey's method. Interobserver variability in the visual categorization of PSE and CLE was assessed using the kappa score. To explore whether the AD, ED, and mixed groups had additional, independent impacts on percent of predicted FEV_1 (%FEV_1), SAD%, and the mean lumen area of right main and intermedius bronchus compared to the mild group, 3 multivariable linear regression models were constructed using the CT-based categories, age, sex, smoking-pack years, body mass index (BMI), and CT scanners as independent variables. These variables were selected based on a previous finding that in addition to demographic factors, the use of different CT scanners might affect lung structural measurements [19].

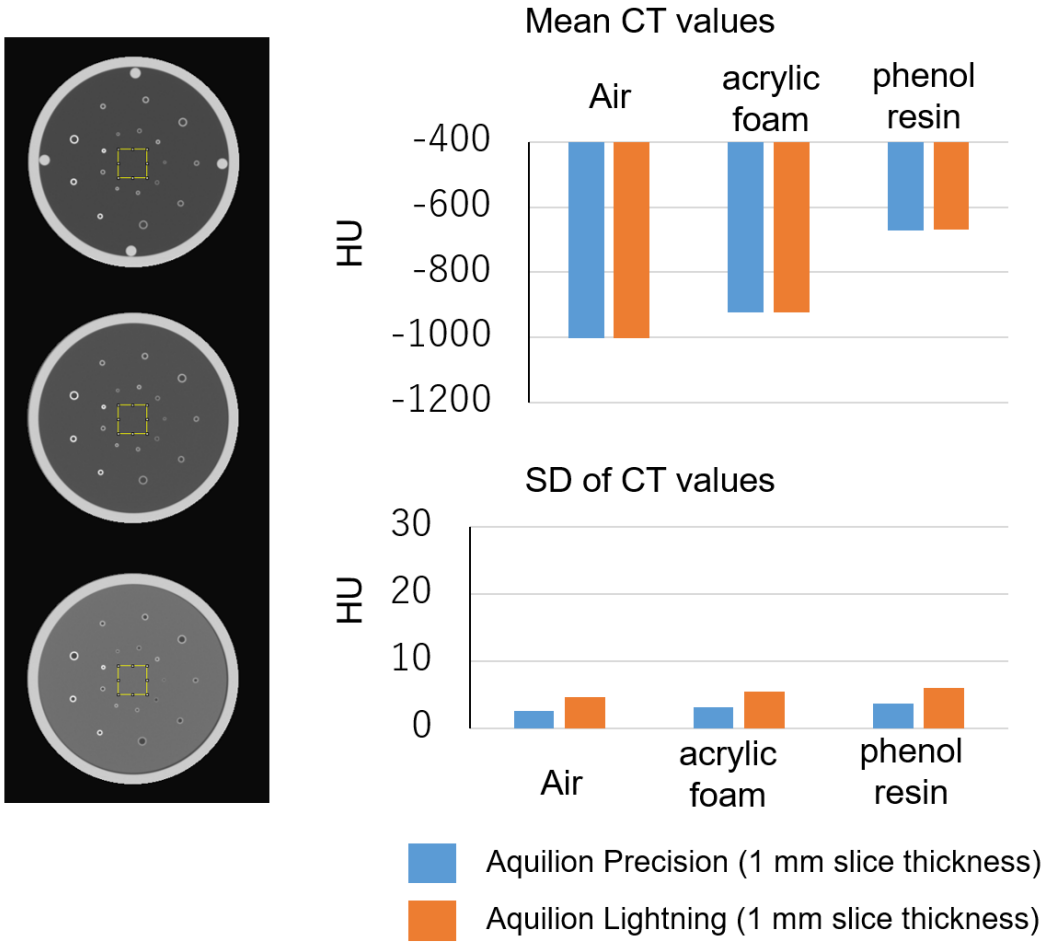
2. Supplemental Figures

Supplemental Figure S1. CT measurements of a phantom mimicking the airway



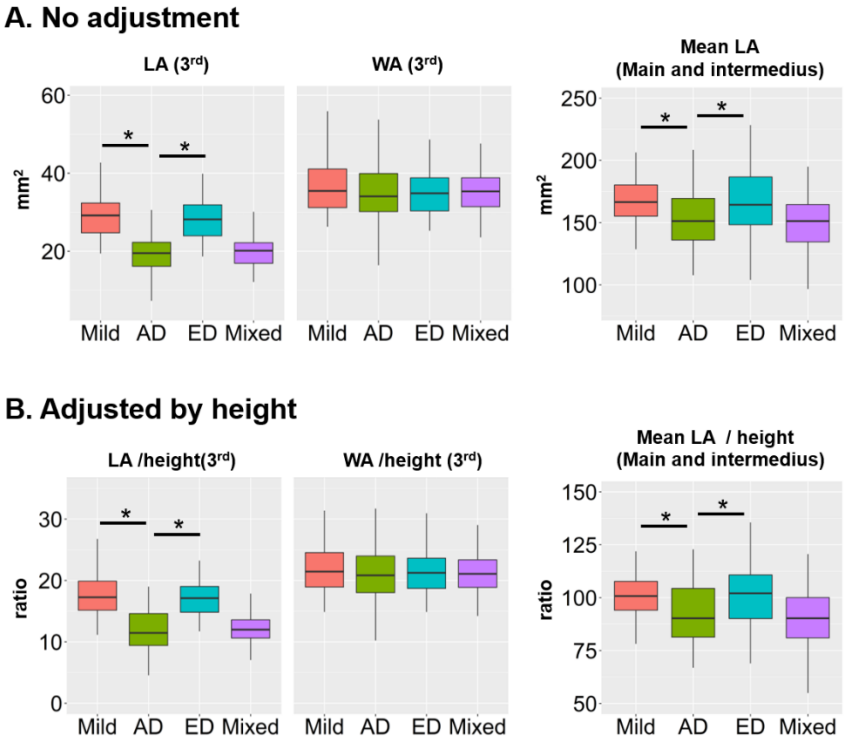
(A) An example of a CT scan of the phantom tubes. (B) The error in wall area percent (WA%) measurements was calculated by 100 * (measured WA% - real WA% of the tube)/(real WA% of the tube). ID and WT indicate the internal diameter and wall thickness of each tube. Aquilion Precision and Lightning devices were used in the Kyoto University Hospital and Terada Clinic, respectively. The error in WA% measurements was consistent in both scanners.

Supplemental Figure S2. CT measurements of a phantom mimicking the parenchyma



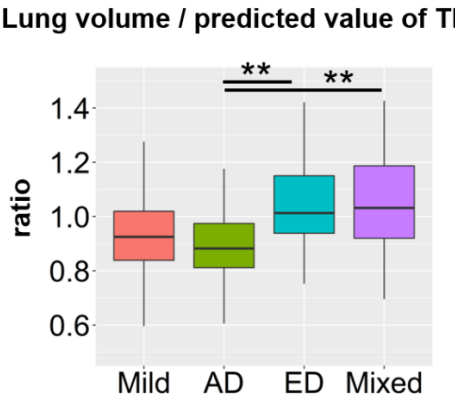
(A) Example CT scans of phantoms made of different materials (air, acrylic foam and phenol resin). (B) Mean and SD of the CT values in square regions of interest (ROIs). Aquilion Precision and Lightning devices were used in the Kyoto University Hospital and Terada Clinic, respectively. The mean (SD) CT values for the ROIs were consistent in both scanners.

Supplemental Figure S3. Comparisons of central airway dimensions with and without height adjustment in patients with the airway disease-dominant and emphysema-dominant phenotypes in the Kyoto-Himeji cohort



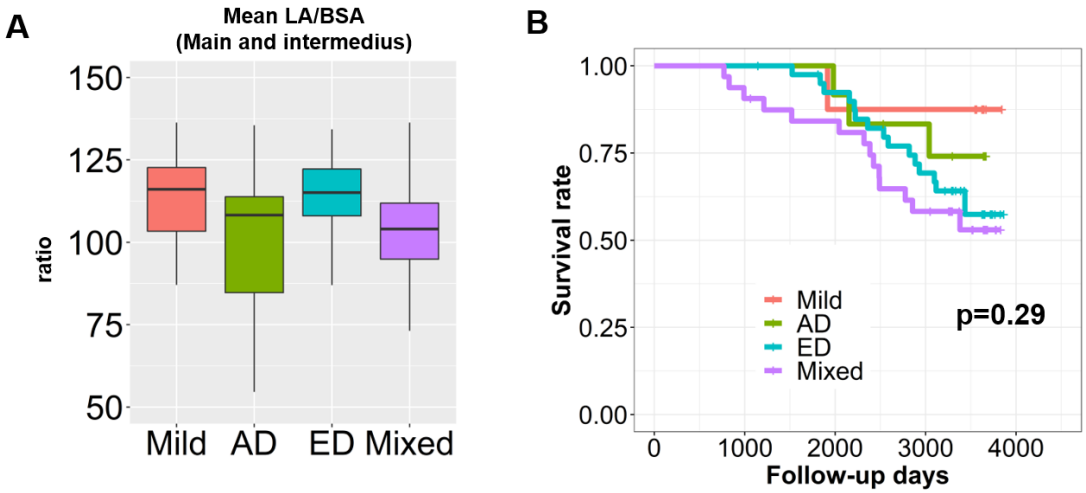
COPD patients in the Kyoto-Himeji cohort were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed groups based on wall area percent of the segmental bronchus (WA%) and low attenuation volume percent (LAV%) on inspiratory CT. (A) Non-adjusted lumen area (LA) and wall area (WA) of the segmental (3rd generation) airways and non-adjusted LA of the airways proximal to the segmental airways, including the right main and intermedius bronchus were compared between the groups. (B) The height-adjusted LA and WA of the 3rd generation airways and height-adjusted mean LA of the airways proximal to the 3rd generation airways were compared. * indicates $p<0.05$ based on Tukey's multiple comparison tests.

Supplemental Figure S4. Comparisons of lung volume between CT-based subtypes of COPD in the Kyoto-Himeji cohort



Lung volume was measured on inspiratory CT and adjusted by predicted value of total lung capacity. Lung volume/predicted value of TLC did not differ between the mild and airway-disease dominant (AD) groups, and was higher in the emphysema dominant (ED) and mixed groups.

Supplemental Figure S5. Mean lumen area of the right main and intermedius bronchus and long-term survival of patients with the airway disease-dominant and emphysema-dominant phenotypes in the Hokkaido COPD cohort



COPD subjects in the Hokkaido COPD cohort were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed CT subtypes. (A) The mean lumen area (LA) of the airways proximal to the segmental airways, including the right main and intermedius bronchi, were adjusted by body surface area (BSA) and compared among groups. (B) Ten-year survival was compared using the Kaplan-Meier curve estimates. The P value was obtained with the log-rank test.

3. Supplemental Table

Supplemental Table S1. Multivariable analyses to explore associations of the airway disease-dominant and emphysema-dominant phenotypes with airflow limitation, small airway dysfunction, and more proximal central airway lumen area in the Kyoto-Himeji cohort using data from patients who used long-acting muscarinic antagonist.

Models	CT categories	Estimate	95%CI	P value
Model 1: %FEV_1	Mild	Ref		
	AD	-14.8	-28.0, -1.6	0.03
	ED	-11.8	-22.5, -1.1	0.03
	Mixed	-28.6	-40.7, -16.5	< 0.001
Model 2: SAD%	Mild	Ref		
	AD	0.9	-6.0, 7.8	0.80
	ED	5.9	0.3, 11.5	0.04
	Mixed	10.1	3.7, 16.4	0.002
Model 3: Mean LA (Main + Intermedius)	Mild	Ref		
	AD	-20.8	-37.5, -4.2	0.01
	ED	-2.4	-16.0, 11.1	0.72
	Mixed	-23.9	-39.2, -8.6	0.002

COPD patients using long-acting muscarinic antagonist were categorized into mild (n=24), airway disease-dominant (AD, n=15), emphysema-dominant (ED, n=56), and mixed (n=25) groups. Each multivariable linear regression model included the CT-categorization (Reference [Ref]: the mild group), age, sex, body mass index, smoking pack-year, and CT scanner as independent variables. 95% CI = 95% confidence interval. %FEV_1 = % of predicted forced expiratory volume in 1 sec (FEV_1). SAD% = small airway dysfunction. “Mean LA” indicates the mean lumen area (LA) of the airways proximal to the segmental airways, including the right main and intermedius bronchus. Of note, the mean lumen area of right main and intermedius bronchus was significantly lower in the AD, but not in the ED group while SAD% was significantly higher in the ED group, but not in the AD group compared to the mild group.

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