Online supplement

Central airway and peripheral lung structures in airway disease dominant COPD

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Contents

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.

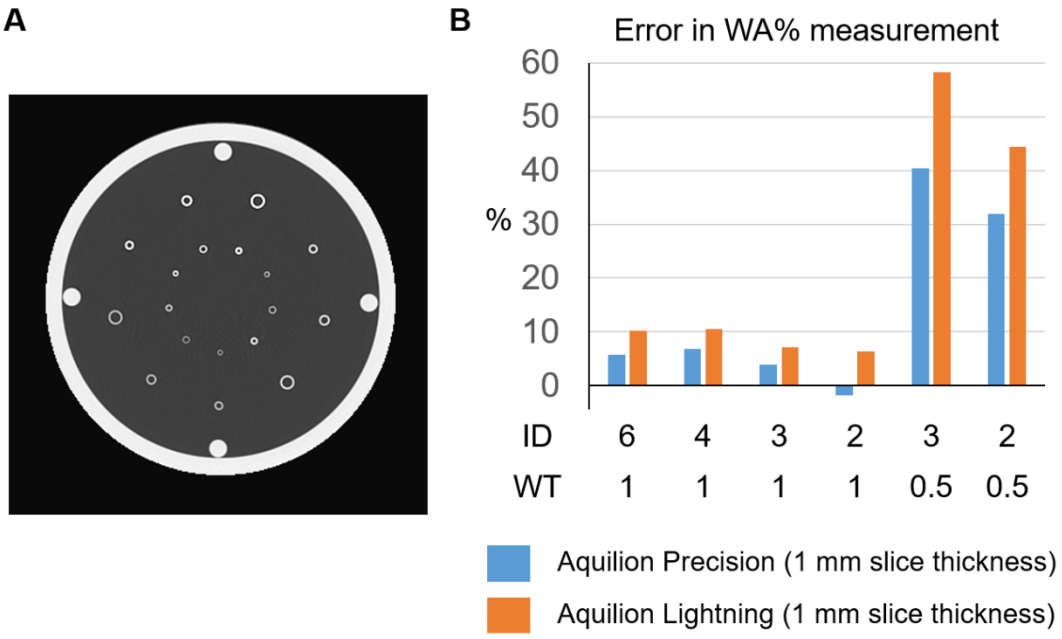
1-4. Pulmonary function and clinical features: Post-bronchodilator spirometry was performed using a Chestac-8900 (Chest M.I., Inc., Tokyo, Japan) in the Kyoto-Himeji cohort and a rolling seal Chestac-33 spirometer (Chest MI, Inc., Tokyo, Japan) in the Hokkaido COPD cohort. The predicted forced vital 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].

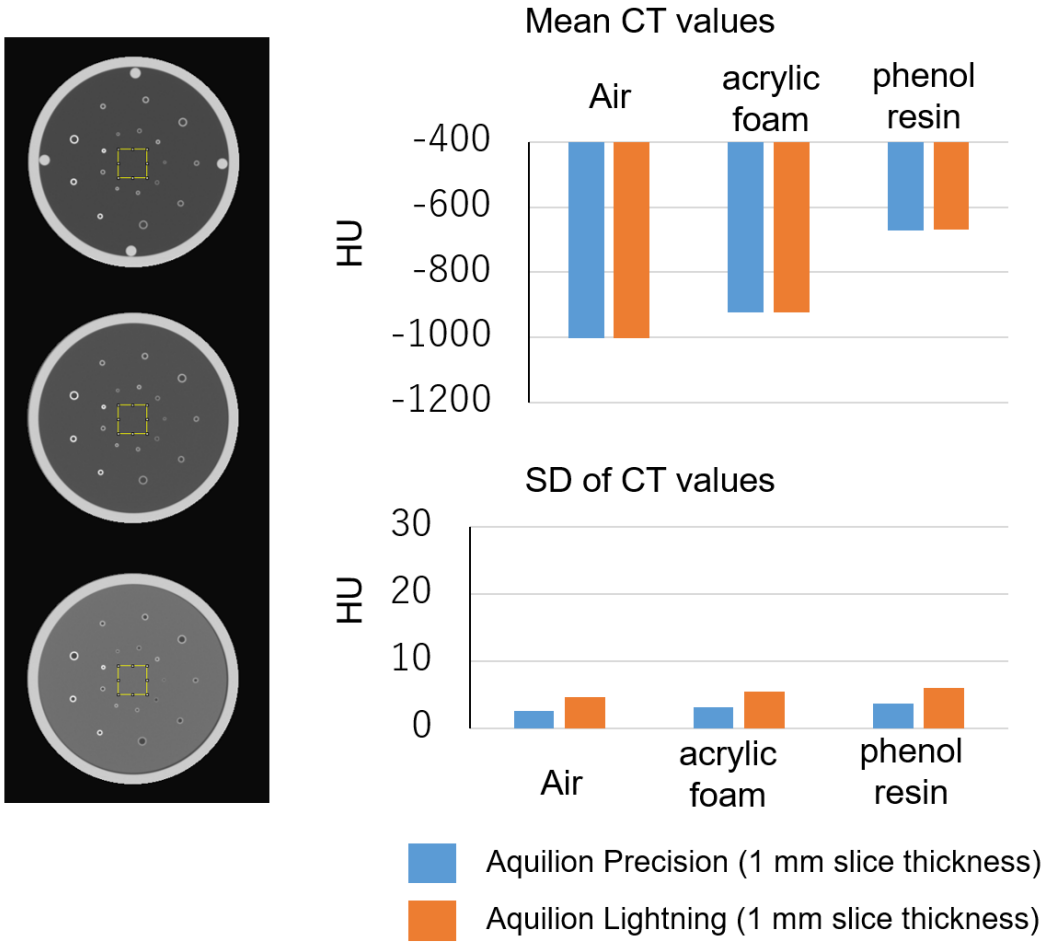
2. Supplemental Figures

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



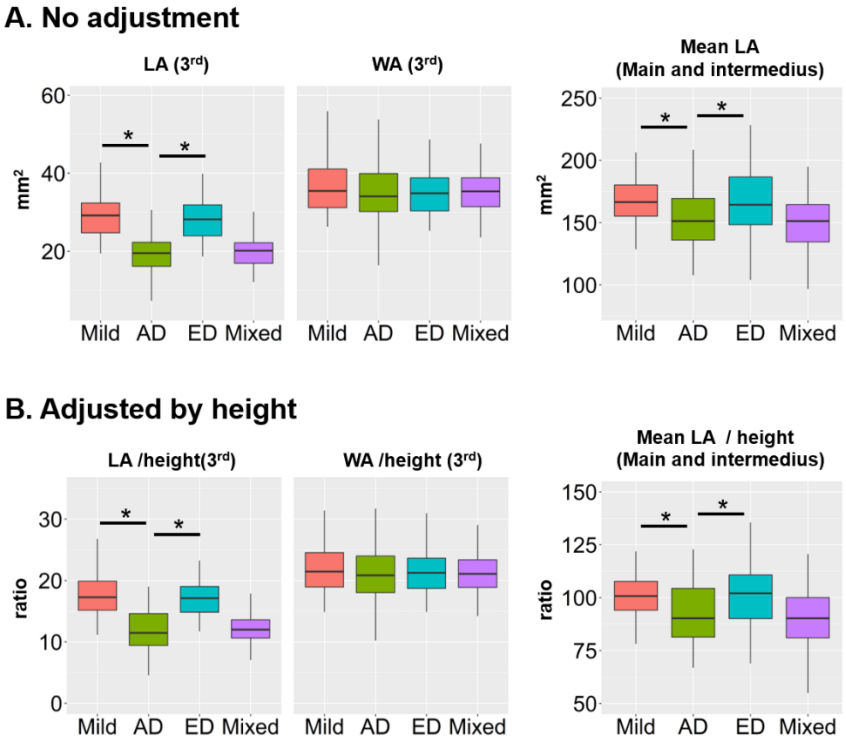
(A) An example of a CT scan of the phantom tubes. (B) The error in wall area percent (WA%) measurements was calculated by 100 * (measured WA% - real WA% of the tube)/(real WA% of the tube). ID and WT indicate the internal diameter and wall thickness of each tube. Aquilion Precision and Lightning devices 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



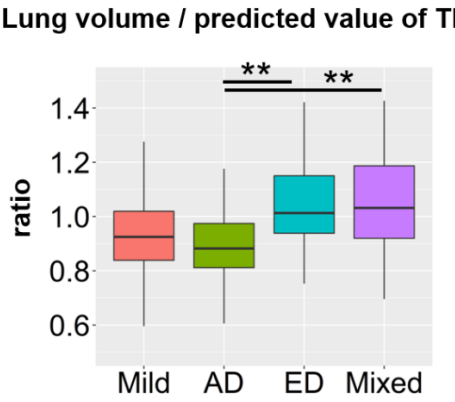
(A) Example CT scans of phantoms made of different materials (air, acrylic foam and phenol resin). (B) Mean and SD of the CT values in square regions of interest (ROIs). Aquilion Precision and Lightning devices were used in the Kyoto University Hospital and Terada Clinic, respectively. The mean (SD)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



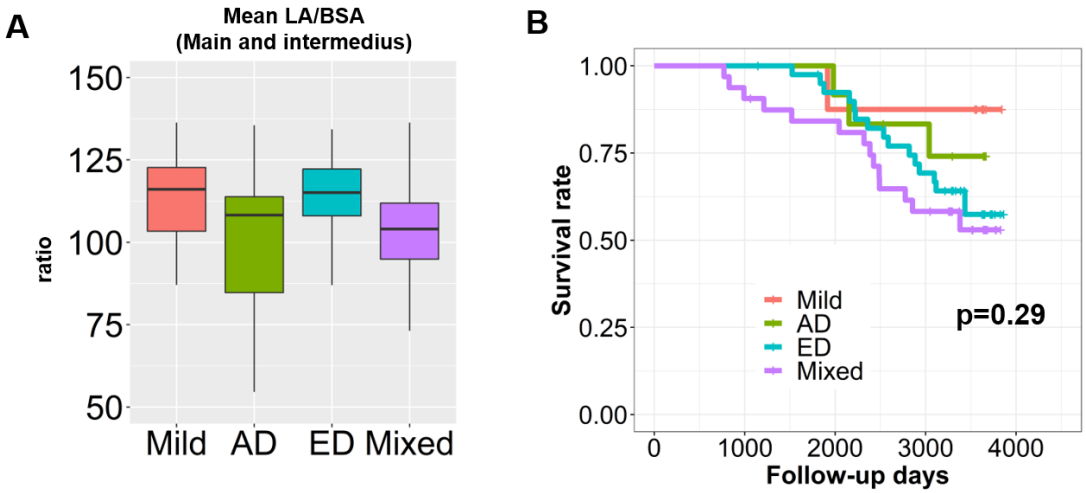
COPD patients in the Kyoto-Himeji cohort were categorized into mild, airway disease-dominant (AD), emphysema-dominant (ED), and mixed groups based on wall area percent of the segmental bronchus (WA%) and low attenuation volume percent (LAV%) on inspiratory CT. (A) Non-adjusted lumen area (LA) and wall 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.

4. References

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